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SOLICITUD

PATENTE DE INVENCIÓN

06-22161

21. **EXPEDIENTE No.** _____

54. **TÍTULO** SABORES NOVEDOSOS, MODIFICADORES DE SABOR, DEGUSTANTES, MEJORADORES DE DEGUSTACION, DEGUSTANTES ACRES O DULCES, Y/O MEJORADORES Y USO DE LOS MISMOS

51. **CLASIFICACIÓN INTERNACIONAL** _____

71. **SOLICITANTE** SENOMYX INCORPORATED

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C.C. 438.019 de Usaquén

74. **APODERADO** _____

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1 ☒ Patente de Invencion ☐ Patente de Modelo de Utilidad
☒ Capitulo I ☐ Capitulo II

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Nombre **SENOMYX INCORPORATED** sociedad constituida y existente bajo las leyes del estado de Delaware Estados Unidos de América

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Cual ____
Numero ____

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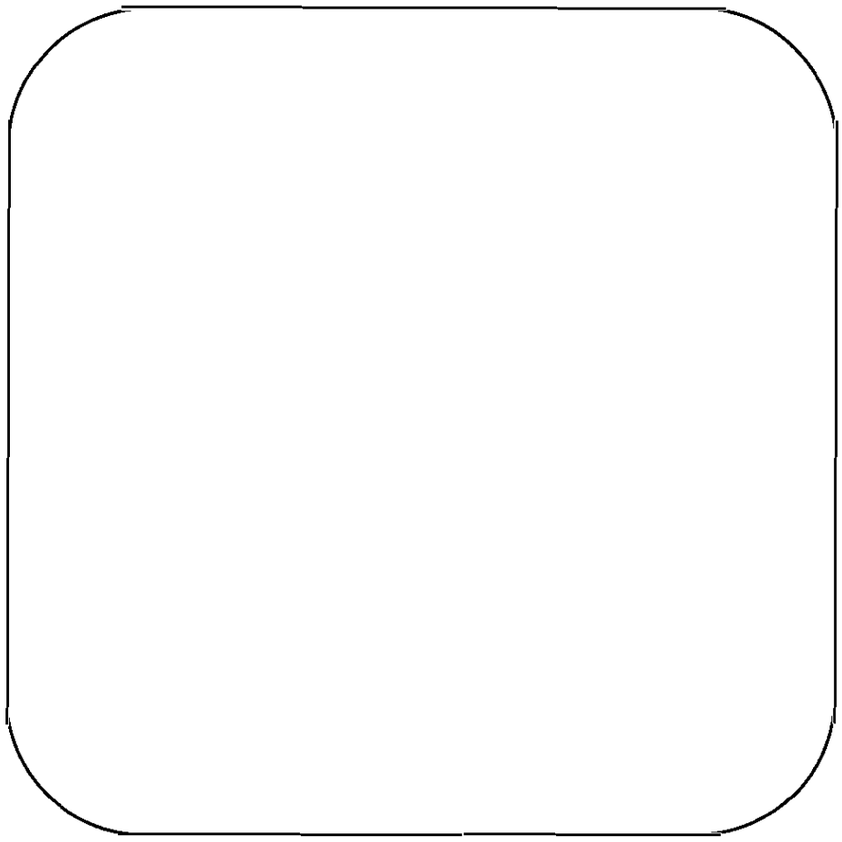
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(10) **Anexos**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 463 000 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 descripcion reivindicaciones dibujos)
- ☒ Traduccion 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 autorizacion de uso de conocimientos tradicionales de las comunidades indigenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12x12
- ☐ De ser el caso información sobre otras solicitudes de patente o titulos obtenidos en el extranjero por el mismo titular o su causante relacionadas parcial o totalmente con la invencion de esta solicitud
- ☒ Otros VER HOJA DE DOCUMENTOS ANEXOS

(11) **FIGURA CARACTERÍSTICA**

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(12) Solicito la concesión de la patente

NOMBRE EMILIO FERRERO

FIRMA _____

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(54) Title NOVEL FLAVORS FLAVOR MODIFIERS TASTANTS TASTE ENHANCERS UMAMI OR SWEET TASTANTS AND/OR ENHANCERS AND USE THEREOF

(57) Abstract The present invention relates to the discovery that certain non naturally occurring non peptide amide compounds and amide derivatives such as oxalamides ureas and acrylamides are useful flavor or taste modifiers such as a flavoring or flavoring agents and flavor or trite enhancer more particularly savory (the umami taste of monosodium glutamate) or sweet taste modifiers savory or sweet flavoring agents and savory or sweet flavor enhancers for food beverages and other comestible or orally administered medicinal products or compositions

NOVEL FLAVORS, FLAVOR MODIFIERS, TASTANTS, TASTE ENHANCERS, UMAMI OR SWEET TASTANTS, AND/OR ENHANCERS AND USE THEREOF

This application claims the priority of U S provisional patent application serial number 60/494 071 filed on August 06, 2003, and also claims the priority of U S provisional patent application serial number 60/55?,064 filed March 09, 2004, the entire disclosures of which are hereby incorporated herein by this reference

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 Less expensive compounds that would provide the flavor of MSG itself, or enhance the effectiveness of any MSG that is present 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 would be of very high utility and value

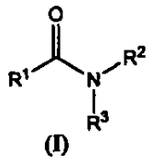
In recent years substantial progress has been made in biotechnology in general and in better understanding the underlying biolc gical and biochemical phenomena of taste perception For example, taste receptor proteins have been recently identified in mammals which are involved in taste perception Particularly, 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 tarte 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 in some fashion to 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

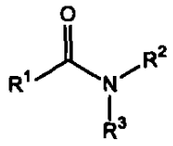
Many of the subgenuses and species of the amide compounds of Formula (I) are shown below to bind to and/or activate one or both of the T1R1/T1R3 ' savory' (umami)or T1R2/T1R3 sweet receptors *in vitro* at relatively low concentrations on the order of micromolar or lower concentrations The amide compounds 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, many of the subgenuses and species of the amide compounds of Formula (I) further described hereinbelow can, at surprisingly low concentrations be used 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 taste of a comestible or medicinal product comprising

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

b) combining the comestible or medicinal product or precursor 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



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

The invention also relates to the comestible or medicinal products produced by the 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 human at surprisingly low concentrations In some embodiments, the amide compounds of the invention are T1R1/T1R3 receptor agonists and accordingly can induce or enhance savory taste perception in humans These compounds can enhance, potentiate, modulate or induce other natural and synthetic savory flavoring agents

In related embodiments, many of the amide compounds within the scope of Formula (I) are T1R2/T1R3 receptor agonists and accordingly can induce sweet taste perception in humans at surprisingly low concentrations These compounds can enhance, potentiate modulate or induce 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 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 tc 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 prefe rably 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 a 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 a 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 a 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 a 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 a 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 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 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 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 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 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 that is sufficient to enhance the taste of a natural or synthetic flavoring agents *e g* monosodium glutamate (MSG) 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 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, enhanc 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 abcut 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 ompounds 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 an 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 an sweet receptor is a G protein coupled receptor, and more preferably the umami 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 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 $EC^{s}0$ 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 within a larger chemical compound which has only carbon and hydrogen atoms The hydrocarbon residue may be aliphatic or aromatic, straight chain cyclic, branched saturated or unsaturated The hydrocarbon residue when so stated however, may

contain or be substituted with heteroatoms such as O S or N or the halogens (fluorine, chlorine, bromine and iodine) or 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 Thus when specifically noted as containing such heteroatoms or designated as substituted, the hydrocarbon residue 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 residue refers to a residue that does not contain carbon but contains at least some heteroatoms including O N, S, one or more halogens or alkali metal or alkaline earth metal ions Examples include, but are not limited to H, Na+, Ca++ and K+, halo hydroxy NO_2 or NH_2

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 hydrocarbon compound having straight or branched carbon chains and replacing the hydrogen atom with another atom or 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 In some embodiments of the invention C1 to C4 alkyl groups (alternatively termed lower alkyl ' groups are methyl ethyl, propyl iso-butyl sec-butyl t butyl and iso-propyl 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

Preferred alkenyl groups are C2 to C7 alkenyl ' such as 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

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

Hydrocarbon residues may be optionally substituted Two of said optional substituents on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3 8 members Optional substituents are generally hydrocarbon residues that may contain one or more heteroatoms or an inorganic residue such as H Na^+ Ca^{2+} or K^+

The terms substituted alkyl, ' substituted alkenyl,' substituted alkynyl and substituted alkylene denote that the alkyl alkenyl, alkynyl and alkylene groups are substituted by one or more, and preferably one or two substituents preferably halogen hydroxy C1 to C7 alkoxy, alkoxy alkyl, oxo, C3 to C7 cycloalkyl, naphthyl amino (monosubstituted)amino (disubstituted)amino, guanidino heterocycle substituted heterocycle, imidazolyl indolyl pyrrolidinyl C1 to C7 acyl, C1 to C7 acyloxy nitro, carboxy, carbamoyl carboxamide, N (C1 to C6 alkyl)carboxamide, N,N di(C1 to C6 alkyl)carboxamide, cyano, methylsulfonylamino thiol, C1 to C4 alkylthio or C1 to C4 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, methoxy, and ethoxy groups

Examples of the above substituted alkyl groups include the 2 oxo prop-1-yl 3 oxo but-1-yl, cyanomethyl nitromethyl chloromethyl 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 the above 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 alkenyl can be used

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

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 moiety

'Alkoxy refers to an OR group wherein R is an alkyl or substituted alkyl Alkoxy alkyl refers to an alkyl group containing an alkoxy

Preferred alkoxy groups are C1 to C7 alkoxy such as methoxy, ethoxy n-propoxy isopropoxy n-butoxy, t-butoxy and like groups The term C1 to C7 substituted alkoxy means the alkyl portion of the alko cy can be substituted in the same manner as in relation to C1 to C6 substituted alkyl Similarly, the term 'C1 to C7 phenylalkoxy as used herein means C1 to C7 alkoxy bonded to a phenyl radical

Acyloxy' refers to an OR group where R is an acyl group Preferred acyloxy groups are C1 to C7 acyloxy' such as formyloxy acetoxy propionyloxy butyryloxy, pivaloyloxy pentanoyloxy, hexanoyloxy, heptanoyloxy and the like

As used herein, acyl' encompasses the definitions of alkyl, alkenyl, alkynyl and the related hetero forms which are coupled to an additional residue through a carbonyl group Preferred acyl groups are C1 to C7 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 the acyl 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 C1 to C7 alkoxy alkoxy alkyl C1 to C7 acyl C1 to C7 acyloxy, nitro, C1 to C6 alkyl ester carboxy alkoxycarbonyl carbamoyl, carboxamide N-(C1 to C6 alkyl)carboxamide N N-di(C1 to C6 alkyl)carboxamide, cyano methylsulfonylamino thiol C1 to C4 alkylthio or C1 to C4 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 C1 to C7 substituted acyl groups include 4 phenylbutyroyl, 3-phenylbutyroyl 3 phenylpropanoyl 2- cyclohexanylacetyl cyclohexanecarbonyl, 2-furanoyl and 3 dimethylaminobenzoyl

Cycloalkyl residues are hydrocarbon groups within a molecule that comprise at least one ring having 3 to 8 carbon atoms linked into a ring Examples of such cyclalkyl residues include cyclopropyl cyclobutyl cyclopentyl, cyclohexyl, cycloheptyl cyclooctyl rings and saturated bicyclic or fused polycyclic cycloalkanes such as decalin groups, norbornyl 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 the cyclopentyl, cyclohexyl or cycloheptyl rings

Substituted cycloalkyl indicates the above cycloalkyl rings are substituted preferably by one or two halogen, hydroxy C1 to C4 alkylthio C1 to C4 alkylsulfoxide C1 to C4 alkylsulfonyl C1 to C4 substituted alkylthio, C1 to C4 substituted alkylsulfoxide, C1 to C4 substituted alkylsulfonyl, C1 to C6 alkyl C1 to C7 alkoxy C1 to C6 substituted alkyl, C1 to C7 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 C1 to C6 alkyl halogen, hydroxy C1 to C7 alkoxy

alkoxy alkyl, trifluoromethyl, carboxy alkoxycarbonyl oxo, (monosubstituted)amino, (disubstituted)amino phenyl substituted phenyl amine 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 C1 to C4 alkylthio C1 to C4 alkylsulfoxide C1 to C4 alkylsulfonyl, C1 to C4 substituted alkylthio, C1 to C4 substituted alkylsulfoxide, C1 to C4 substituted alkylsulfonyl, C1 to C6 alkyl C1 to C7 alkoxy C1 to C6 substituted alkyl C1 to C7 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 have 1 to 5 heteroatoms, such as oxygen, sulfur and/or nitrogen inserted into the ring These 3 to 8 membered rings may 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 heterocyclic rings include furanyl, thiofuranyl piperidyl, pyridyl, morpholino, azaridinyl piperidinyl, piperazinyl tetrahydrofurano pyrrolo, and tetrahydrothiophen-yl

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 C1 to C6 alkyl C1 to C7 alkoxy, C1 to C7 substituted alkoxy alkoxy alkyl, C1 to C7 acyl, C1 to C7 acyloxy, carboxy, alkoxycarbonyl carboxymethyl hydroxymethyl alkoxy alkyl 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, 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 aromatic linked bicyclic aromatic or fused bicyclic aromatic moiety comprising at least one six membered aromatic benzene ring, preferably comprising between 6 and 12 ring carbon atoms, such as phenyl, biphenyl or naphthyl groups which may be optionally substituted with various organic and/or inorganic substitutent groups wherein the substituted aryl group and 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 such as 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, C1 to C6 alkyl, C1 to C7 substituted alkyl, C1 to C7 alkoxy C1 to C7 substituted alkoxy alkoxy alkyl, C1 to C7 acyl, C1 to C7 substituted acyl, C1 to C7 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 uns iturated, 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 th 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 C1 to C6 alkyl, C1 to C6 substituted alkyl C1 to C7 alkoxy, C1 to C7 substituted alkoxy alkoxy alkyl C1 to C7 acyl C1 to C7 substituted acyl C1 to C7 acyloxy nitro carboxy alkoxycarbonyl carbamoyl, carboxamide, N (C1 to C6 alkyl)carboxamide, N, N-(C1 to C6 dialkyl)carboxamide, cyano N (C1 to C6 alkylsulfonyl)amino thiol, C1 to C4 alkylthio C1 to C4 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 cy ino nitro, C1 to C6 alkyl, C1 to C6 substituted alkyl C1 to C7 alkoxy, C1 to C7 substituted alkoxy, alkoxy alkyl, C1 to C7 acyl C1 to C7 substituted acyl C1 to C7 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, N-(phenylsulfonyl)amino, cyclic C2 to C7 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, › 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 C1 to C4 alkylthio C1 to C4 alkylsulfoxide C1 to C4 alkylsulfonyl, C1 to C4 substituted alkylthio, C1 to C4 substituted alkylsulfoxide, C1 to C4 substituted alkylsulfonyl C1 to C6 alkyl C1 to C7 alkoxy C1 to C6 substituted alkyl C1 to C7 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, C1 to C6 alkyl C1 to C6 substituted alkyl C1 to C7 alkoxy, C1 to C7 substituted alkoxy alkoxy-alkyl, C1 to C7 acyl, C1 to C7 substituted acyl, C1 to C7 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, 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, C1 to C6 alkyl, C1 to C7 alkoxy C1 to C7 substituted alkoxy alkoxy alkyl, C1 to C7 acyl C1 to C7 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 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 C1 to C7 alkoxy alkoxy-alkyl, C1 to C7 acyl C1 to C7 acyloxy nitro carboxy, alkoxycarbonyl, carbamoyl, carboxamide, N-(C1 to C6 alkyl)carboxamide N N-(C1 to C6 dialkyl)carboxamide, cyano N (C1 to C6 alkylsulfonyl)amino thiol, C1 to C4 alkylthio, C1 to C4 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 C1 to C6 alkyl, C1 to C7 alkoxy, alkoxy alkyl, C1 to C7 acyl, C1 to C7 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 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 C1 to C6 alkyl C1 to C7 alkoxy alkoxy-alkyl C1 to C7 acyl C1 to C7 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

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 very effective in binding to the relevant taste receptors, such halogenated organic compounds can often 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 a possible substitutent atom an alternative preferred group of substitutents would NOT include the halogen fluorine, or chlorine groups

The term (monosubstituted)amino refers to an amino group with one substituent preferably chosen from the group consisting of phenyl substituted phenyl C1 to C6 alkyl, C1 to C6 substituted alkyl, C1 to C7 acyl, C1 to C7 substituted acyl C2 to C7 alkenyl C2 to C7 substituted alkenyl, C2 to C7 alkynyl, C2 to C7 substituted alkynyl, C7 to C12 phenylalkyl C7 to C12 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 substituted preferably with two substituents chosen from the group consisting of phenyl substituted phenyl, C1 to C6 alkyl, C1 to C6 substituted alkyl C1 to C7 acyl, C2 to C7 alkenyl C2 to C7 alkynyl C7 to C12 phenylalkyl, and C7 to C12 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 (C1 to C6 alkyl)carboxamide means there is an amino protecting group on the carboxamide nitrogen

The term alkylthio refers to sulfide groups such as methylthio, ethylthio n propylthio, isopropylthio n-butylthio t butylthio and like groups

The term alkylsulfoxide ' indicates sulfoxide groups such as methylsulfoxide ethylsulfoxide n-propylsulfoxide isopropylsulfoxide n-butylsulfoxide, sec-butylsulfoxide and the like

The term alkylsulfonyl encompasses groups such as methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl n butylsulfonyl t butylsulfonyl and the like

The terms substituted alkylthio ' 'substituted alkylsulfoxide and substituted alkylsulfonyl, denote the alkyl portion of these groups may be substituted as described above in relation to substituted alkyl

The terms 'phenylthio, phenylsulfoxide and 'phenylsulfonyl specify a thiol a sulfoxide or sulfone respectively containing 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 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 includes 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

bonded (fused) to the phenyl radical resulting in a bicyclic ring system The cyclic group may be saturated or contain one or two double bonds Furthermore the cyclic group may have one or two methylene or methine groups replaced by one or two oxygen, nitrogen or sulfur atoms which are the cyclic heteroalkylene

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, C1 to C4 acyloxy, formyl, C1 to C7 acyl C1 to C6 alkyl, C1 to C7 alkoxy, C1 to C4 alkylthio C1 to C4 alkylsulfoxide, C1 to C4 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 such saturated cyclic groups are when the resultant bicyclic ring system is 2,3-dihydro-indanyl and a tetralin ring When the cyclic groups are unsaturated, examples occur when the resultant bicyclic ring system is a naphthyl ring or indolyl 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 pyridino, pyrano pyrrolo pyridinyl dihydropyrrolo, or dihydropyridinyl ring Examples of fused cyclic groups which each contain one oxygen atom and one or two double bonds are when the benzene radical ring is fused to a furo, pyrano dihydrofurano, or dihydropyrano 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 thieno, thiopyrano, dihydrothieno or dihydrothiopyrano 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 thiazolo, isothiazolo, dihydrothiazolo or dihydroisothiazolo 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 oxazolo, isoxazolo, dihydrooxazolo or dihydroisoxazolo 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 pyrazolo, imidazolo, dihydropyrazolo or dihydroimidazolo ring or pyrazinyl

The term ' carbamoyl means a NCO group where the radical is bonded at two positions connecting two separate additional groups

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 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 counter-ions for the carboxylate anion of a carboxylate salt The counter ions are chosen from the alkali and alkaline earth metals, (such as lithium sodium potassium barium aluminum and calcium), ammonium and mono-, di and tri alkyl amine 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 R2 or R3 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 Cheintech) 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 Similarly, a 2,4 thiazolidinedione residue in a chemical compound refers to one or more -2 4-thiazolidinedione moieties of the compound, regardless of whether the residue was obtained by reacting 2 4 thiazolidinedione to obtain the compound

Eliminado the

The term 'organic residue defines a carbon containing residue i e a residue comprising at least one carbon atom, and includes but is not limited to the carbon containing groups residues or radicals defined hereinabove 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 alkyl or substituted alkyls alkoxy or substituted alkoxy mono or di-substituted amino, amide groups, etc. Organic resides can

preferably comprise 1 to 18 carbon atoms, 1 to 15 carbon atoms, 1 to 12 carbon atoms 1 to 8 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 the compound to provide the des red regulation of a desired function such as gene expression protein function, or a disease condition 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 drug 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

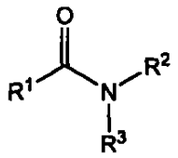
It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise Thus, for example reference to an aromatic compound" includes mixtures of aromatic compounds

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 any amide compounds that are known to naturally occur in biological systems or foods such as peptides proteins, nucleic acids, 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 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 hereb / specifically contemplated that any of subgenuses and/or species of compounds of I ormula (I) described below 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 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 (C1-C6) alkylene or (C1 C6) 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 (C1-C6) alkyl or (C1 C6) 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 ole, 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

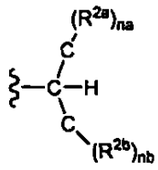
In addition to the above described general physical and chemical characteristics and/or limitations, which can be shared by the various subgenuses of the sweet and savory compounds of Formula (I), the compounds of Formula (I) can also share more specifically definable chemical structural features or 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 optional substituent groups would be substituents independently selected from hydroxy, fluoro, chloro, NH , $NHCH_3$, $N(CH_3)_2$,

CO_2CH_3 SEt SCH_3, methyl ethyl isopropyl vinyl trifluoromethyl methoxy ethoxy, isopropoxy and trifluoromethoxy substituent groups

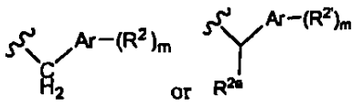
In many embodiments of the compounds of Formula (I), one of R^2 and R^3 is hydrogen and the other R^2 or R^3 group is an organic residue or group For example, in many embodiments of the compounds of Formula (I), at least one or R^2 and R^3 is a branched or cyclic organic residue having a carbon atom 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^{21} 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 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 further embodiments the C_3 C_{10} branched alkyl may optionally substituted with one or two substituents independently selected from a 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 group

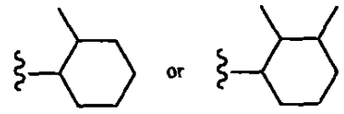
In further embodiments of the compounds of Formula (I), at least one of R^2 or R^3 is an α substituted carboxylic acid or α substituted carboxylic acid lower alkyl ester Preferably, at least one of R^2 or R^3 is an α substituted carboxylic acid lower alkyl (especially methyl) ester In some such preferred 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 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,

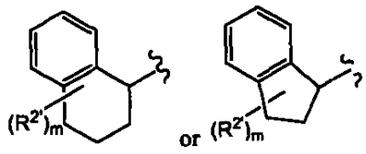
isopropyl, vinyl, trifluoromethyl, methoxy ethoxy isopropoxy, and trifluoromethoxy groups

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 In some preferred embodiments at least one of R^2 or R^3 is a cyclohexyl optionally substituted with 1 2 or 3 methyl groups Examples of such methyl substituted cyclohexyl rings have the formula



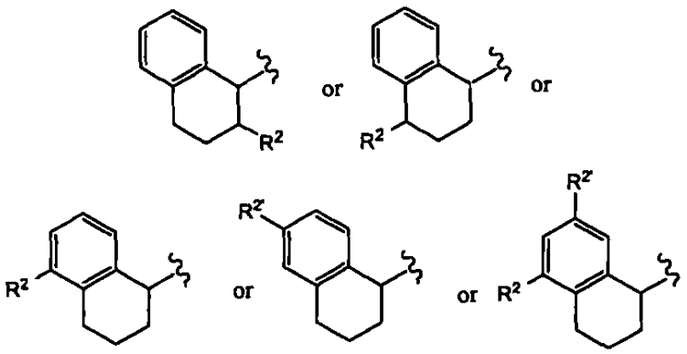
In many embodiments of the compounds of Formula (I) especially compounds having activity for sweet receptors, at least one of R^2 or R^3 is a 1-(1 2 3 4) tetrahydronapthalene ring or an 2 3 dihydro 1H-indene ring having the formula



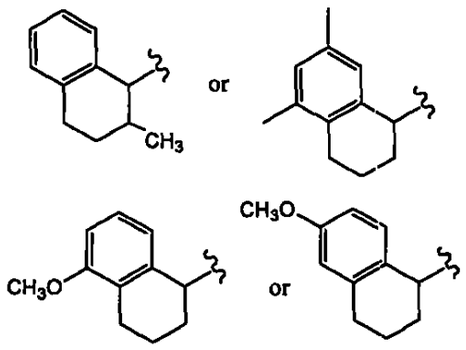
wherein m is 0,1, 2, or 3, and each R^2 can be bonded to either the aromatic or non-aromatic ring and is independently selected from hydroxy, fluoro chloro NH_2 $NHCH_3$, $N(CH_3)_2$, CO_2CH_3 , SCH_3, SEt methyl, ethyl, isopropyl vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy and trifluoromethoxy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

understood that optical and/or diastereomeric isomerism can occur on the cyclohexyl or cyclopentyl rings of these substituent, and differing optical and/or diastereomers can often have at least somewhat differing biological activities

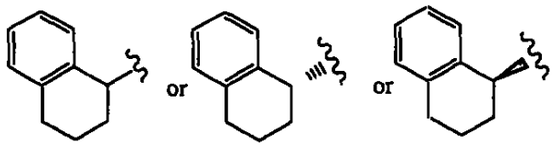
In some embodiments at least one of R^2 or R^3 is a 1 (1 2,3,4) tetrahydronapthalene ring with certain preferred substitution patterns In particular, at least one of R^2 or R^3 may have the formula



wherein each R^2 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 Similarly in some preferred embodiments, at le ist one of R^2 or R^3 may have the formula

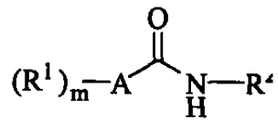


In some embodiments at least one of R^2 or R^3 is an unsubstituted 1 (1,2 3,4) tetrahydronapthalene ring in racemic or optically active form as shown below



Aromatic or Heteroaromatic Compounds

In many preferred embodiments of the amide compounds of Formula (I) having one or both of savory and sweet receptor agonist activity there is a preferred subgenus of amide compounds having the following formula (II)

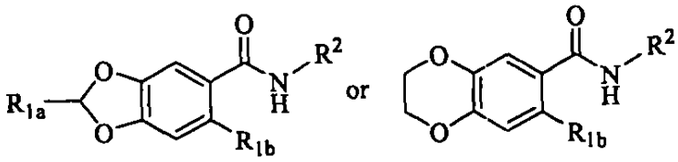


(II)

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, 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, and R^2 can be any of the embodiments contemplated herein above, or the like

In some embodiments the A group of Formula (II) comprises an aryl ring, *i e* it contains at least one six membered aromatic benzene 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 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 groups

In some preferred embodiments one or two of the R^1 substituent groups are bonded together to form a saturated alkylenedioxy ring on an phenyl ring, as exemplified by the following preferred structures (II a) and (IIb)

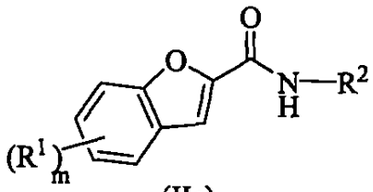


(IIa) (IIb)

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

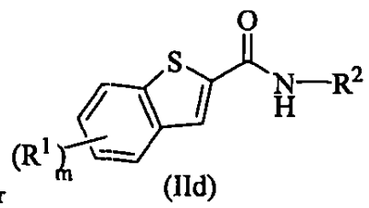
In many embodiments of the amide compounds of Formula (II) A is heteroaryl ring and typically a monocyclic or fused bicyclic heteroaryl ring The

fused bicyclic heteraryls are typified by the following benzofurans (Formula IIc) and benzothiofurans (Formula (IId)



(IIc)

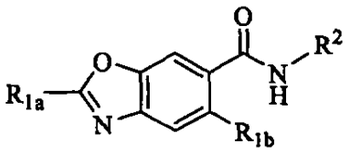
or



(IId)

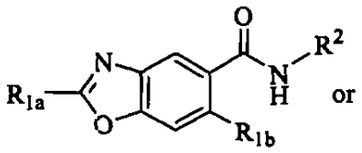
wherein m is 0 1, 2 or 3 and each R^1 can be bonded to either the phenyl or heteroaryl rings and each R^1 is independently selected from hydroxy fluoro, chloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SCH_3, SEt methyl, ethyl isopropyl vinyl, trifluoromethyl, methoxy ethoxy, isopropoxy, and trifluoromethoxy

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



(IIe)

or

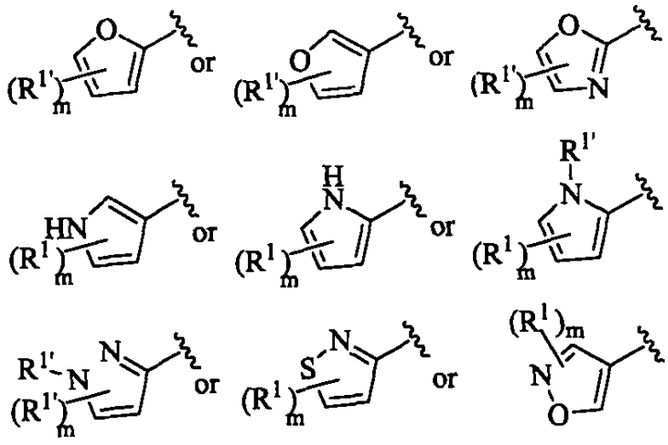


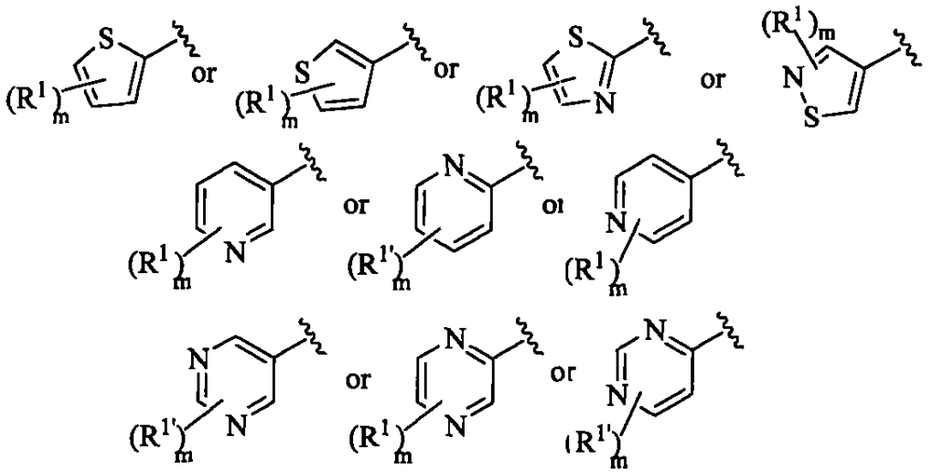
(IIf)

or

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

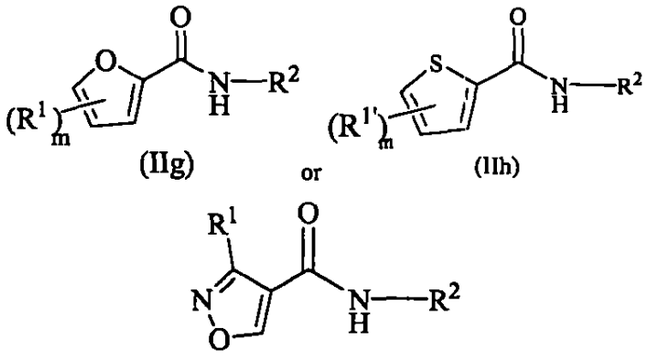
In many embodiments of the amide compounds of Formula (II) A is a monocyclic heteroaryl ring The monocyclic heteroaryls that can be used as an A group in Formula (II) are typified by the following structures





wherein m is 0 1, 2 or 3 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

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



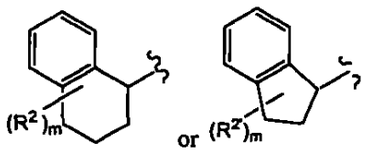
(IIg) or (IIh)

(IIi)

wherein m is 0, 1 2, or 3 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 In some of these embodiments m is 1 or 2

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, or a 1 (1 2 3 4) tetrahydronapthalene ring or an 2 3 dihydro 1H indene ring having the formula

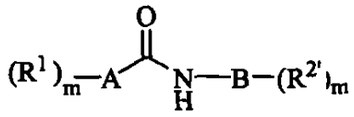


wherein m is 0 1, 2 or 3 and each R^2 can be bonded to either the aromatic or non aromatic ring and is independently selected from hydroxy fluoro chloro NH_2 $NHCH_3$ $N(CH_3)_2$ CO_2CH_3 SCH_3, SEt, methyl ethyl, isopropyl, vinyl trifluoromethyl, methoxy ethoxy, isopropoxy and trifluoromethoxy as were described hereinabove with respect to the general amide compounds of Formula (I)

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 as is described elsewhere herein

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

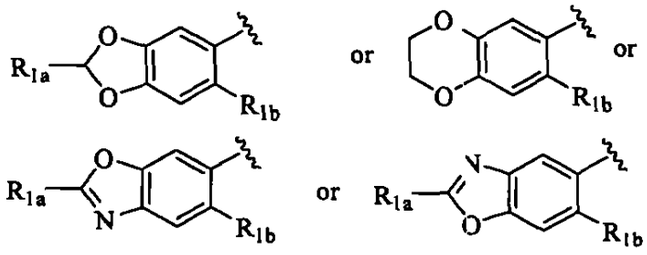


(III)

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

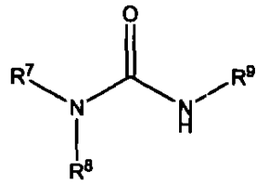


wherein R_{1a} and R_{1b} are independently hydrogen or a lower alkyl

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 can in many cases be previously known chemical compounds, but we believe it has been p eviously unknown that such compounds can be used as very effective umami flavorant compounds at less than micromolar concentrations or less *see* for example compound A1 in Table 1 below

Urea Compounds

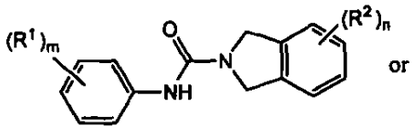
In another subgenus of the amide compounds of Formula (I), the amide compound is a urea compound having the Formula (IV)



(IV)

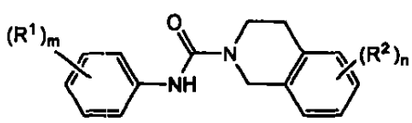
wherein R^7, R^8 and R^9 are each a hydrocarbon residue that may contain one or more heteroatoms or an inorganic residue, and preferably is independently selected from arylalkenyl, heteroarylalkenyl arylalkyl, heteroarylalk /l, alkyl, alkoxy alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl and heteroaryl groups each of which may be optionally substituted or one of R^7 or R^8 can be and often is H

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)



(IVa)

or



(IVb)

wherein m and n are independently 0, 1 2, or 3, and each R^1 and R^2 is 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 such embodiments n is preferably 0

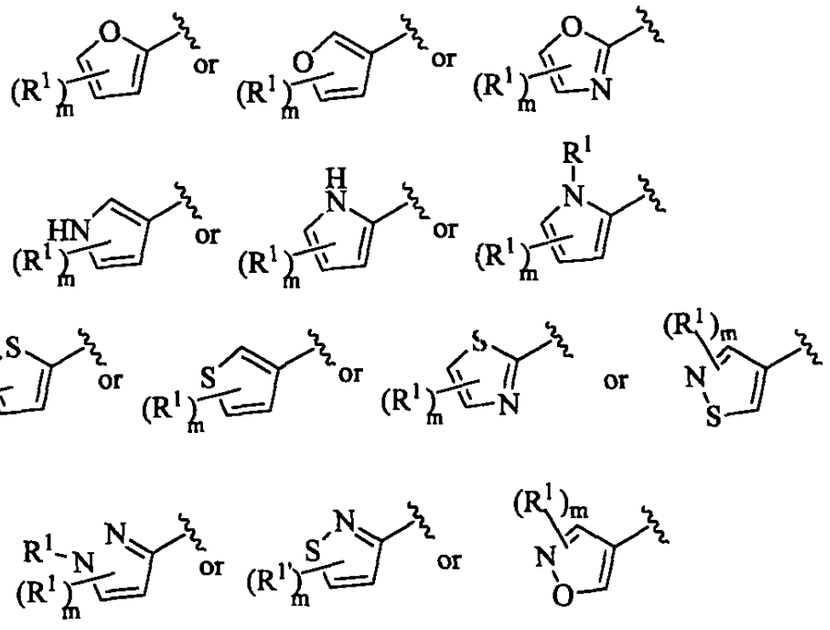
In additional embodiments of the urea compounds of Formula (IV), R^9 and one of R^7 and R^8 are independently selected from arylalkenyls, heteroarylalkenyls, arylalkyls heteroarylalkyls alkyls alkoxy alkyls, alkenyls cycloalkyls cycloalkenyls, aryls and heteroaryls, each of which carbon containing groups may be optionally substituted with 1 2, or 3 substituents independently selected from

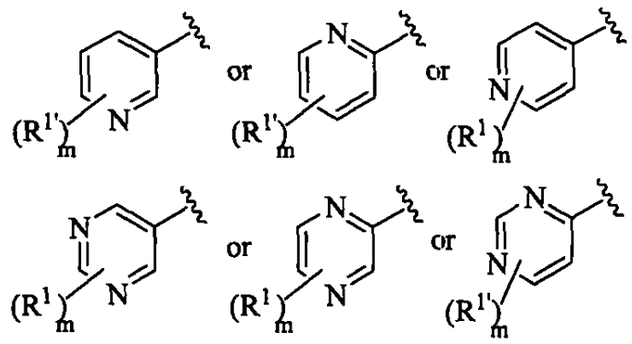
hydrogen hydroxy, fluoro, chloro, NH_2 $NHCH_3$, $N(CH_3)_2$ $COOCH_3$ SCH_3 SEt methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy and trifluoromethoxy groups

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

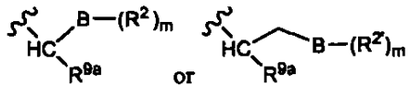




wherein m is 0 1, 2 or 3, and each R^1 independently selected from hydrogen, hydroxy, fluoro chloro NH_2 $NHCH_3$ $N(CH_3)_2$, $COOCH_3$ SCH_3, SEt methyl ethyl isopropyl, vinyl trifluoromethyl methoxy, ethoxy isopropoxy and trifluoromethoxy groups In such embodiments, R^9 is preferably a C_3-C_{10} 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

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 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

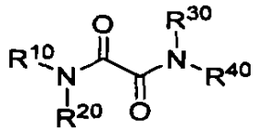


wherein B is a phenyl pyridyl furanyl, thiofuranyl, pyrrole cyclopentyl,cyclohexyl, or piperidyl ring, m is 0,1 2 or 3 and each R^2 is independently selected from

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, or preferably

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

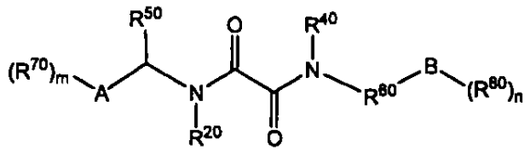
R^{20} and R^{40} are each independently H or a hydrocarbon residue that may contain one or more heteroatoms preferably R^{20}, and R^{40} are H or C_1 C_3 alkyl or optionally substituted groups thereof More preferably R^{20} and R^{40} are H Moreover, there can be 0, 1, 2, 3, or 4 optional substituent 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 $R^{10}$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

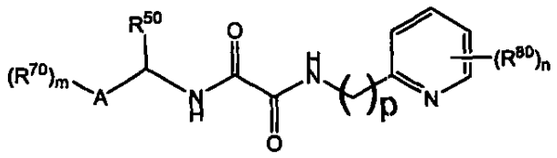
In preferred embodiments of the oxalamide compounds of Formula (Va), R^{60} is a CH_2CH_2 group, A and B are independently selected from phenyl pyridyl, furanyl thiofuranyl and pyrrolyl rings and R^{70} and R^{80} are independently selected from hydroxy, fluoro chloro, NH_2 $NHCH_3$ $N(CH_3)_2$, CO_2CH_3, 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

SL

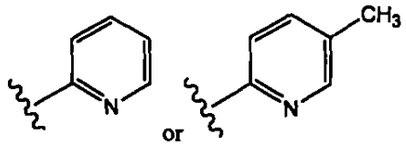
isopropyl vinyl, trifluoromethyl methoxy ethoxy isopropoxy and trifluoromethoxy groups

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



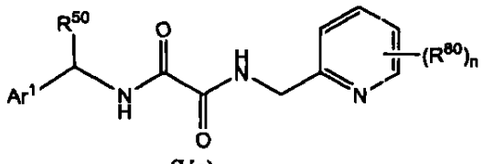
(Vb)

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, andR^{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)

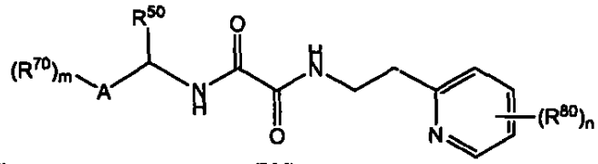


(Vc)

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 $N(CH_3)_2$ 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

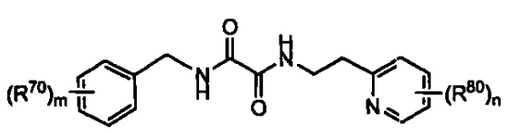
In certain preferred embodiments of the amide compounds of Formula (V) the oxalamide compound has the Formula (Vd)



(Vd) (Vd)

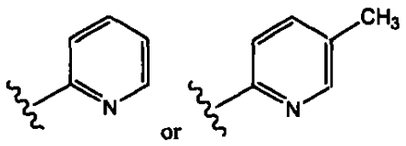
wherein A is a substituted aryl or heteroaryl ring comprising five to 12 carbon atoms, R^{50} is hydrogen or methyl, n is 0 1 2 or 3, each R^{80} is independently selected from the group consisting of hydrogen, hydroxy, fluoro, chloro NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$ SCH_3 SEt, methyl ethyl isopropyl vinyl, trifluoromethyl methoxy, ethoxy isopropoxy, and trifluoromethoxy Preferably A is a phenyl, pyridyl, furanyl pyrrole piperidyl, cyclopentyl cyclohexyl, or cycloheptyl ring 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 independently 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

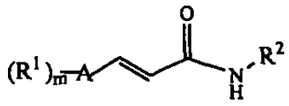


or

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 s ivory 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 I ormula (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 at least some utility as savory or sweet flavorants or flavor enhancers 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 Gα15 cell line by at least 50%, *i e* the amide compound will have an EC5C 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 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 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 compri e 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 according to the invention 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 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 confe tionery 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 swe ets, pastilles, gums jellies and chews, toffees, caramels and nougat, medicated confectionery lollipops liquorice other sugar confectionery gum chewing gum, sugarised 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 savoury 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/pasteurised milk, full fat fresh/pasteurised milk semi skimmed fresh/pasteurised 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 flavoured functional and other condensed milk flavoured milk drinks, dairy only flavoured milk drinks flavoured milk drinks with fruit juice, soy milk sour milk drinks fermented dairy drinks, coffee whiteners, powder milk, flavoured 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, flavoured 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, flavoured fromage frais and quark savoury fromage frais and quark, sweet and savoury snacks, fruit snacks, chips/crisps, extruded snacks, tortilla/corn chips, popcorn pretzels, nuts, other sweet and savoury 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 or a sweet flavoring agent amount of one or more of the compounds of Formula (I) will be added to the comestible or medicinal product, 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 savory compounds are 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 or sweet tastes or other taste properties of other natural or synthetic savory tastants 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

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 (consomme) 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 dishe , meals and single serve entrees 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

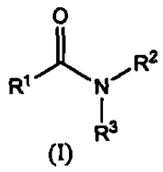
Additionally the subject compounds can be used in flavor preparations to be added to foods and beverages In preferred instances the composition will comprise another flavor or taste modifier such as a savory tastant

Accordingly in some 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 a precursor thereof, and

b) combining the comestible or medicinal product or precursor 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)

wherein 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

The invention also relates to the modified comestible or medicinal products produced by such processes and 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 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 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 Deleware

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 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 entireties 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-Chloroacetyl =

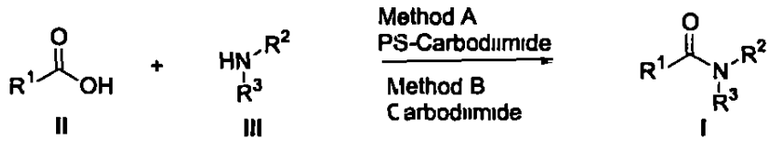
PS-NCO = methylisocyanate polystyrene

PS-benzadehyde =

PS-TsNHNH$_2$ = toluensulfonylhydrazone polystyrene

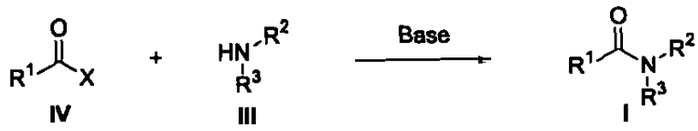
The following example schemes are provided for the guidance of the reader, and represent preferred methods for making the compounds exemplified herein These methods are not limiting, and it will be apparent that other routes may be employed to prepare these compounds Such methods specifically include solid phase based chemistries, including combinatorial chemistry The skilled artisan is thoroughly equipped to prepare the necessary and/or claimed compounds by those methods given the literature and this disclosure

Scheme 1a



As shown in Scheme 1a, amide derivatives (I) are prepared from the coupling of acid derivatives (II) with amines (III) 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



X = halide

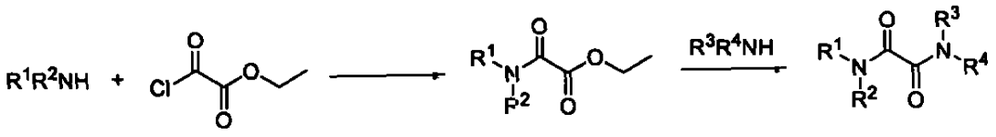
As shown in Scheme 1b, amide derivatives (I) are alternatively prepared from the coupling of acid halides, esters, or anhydrides (IV) with amines (III) in the presence of a base

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
- 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

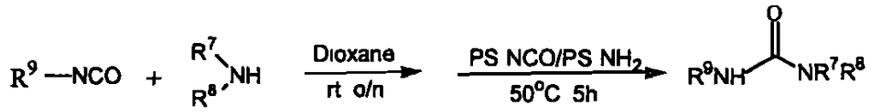
Scheme 1c Preparation of Oxalamides



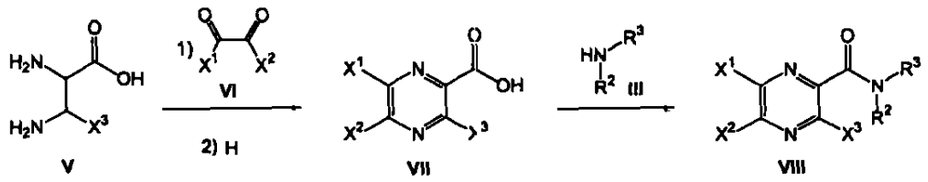
As a general procedure, one amine is allowed to react with ethyl oxalyl chloride in the presence of tertiary amine in organic solvent, such as dioxane, acetonitrile tetrahydrofuran, tetrahydropyran, and dimethylformamide, at room temperature for 0 5 – 2 hours Then the second amine is added and the suspension 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



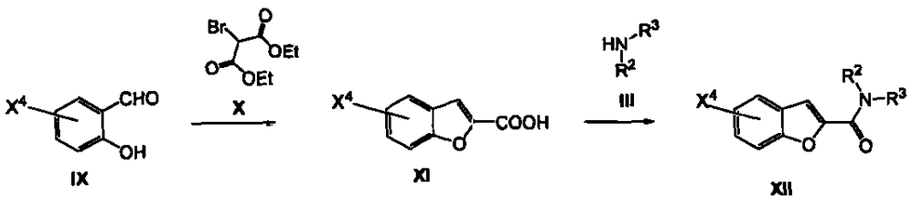
Scheme 2



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

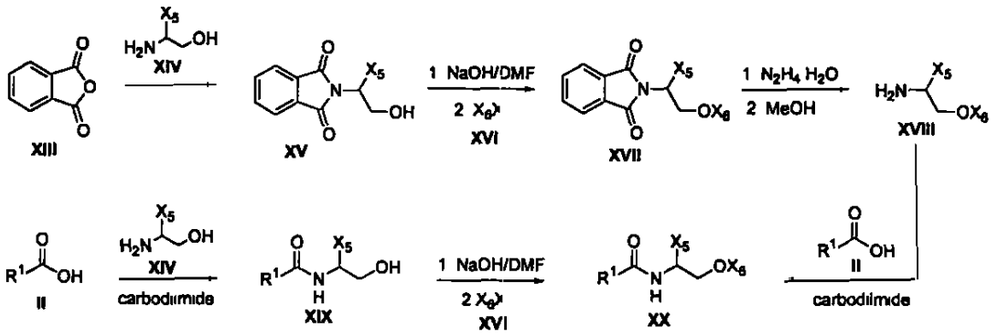


X^4 is alkyl halide alkoxy or thioalkyl

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

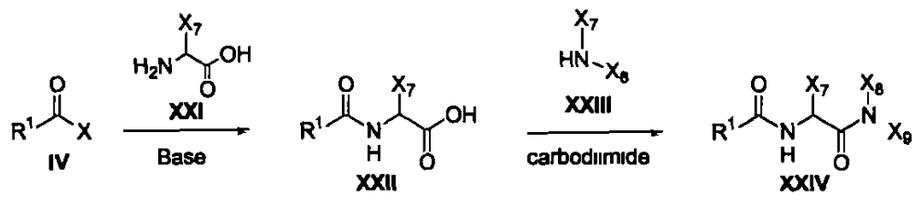
Scheme 4



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)

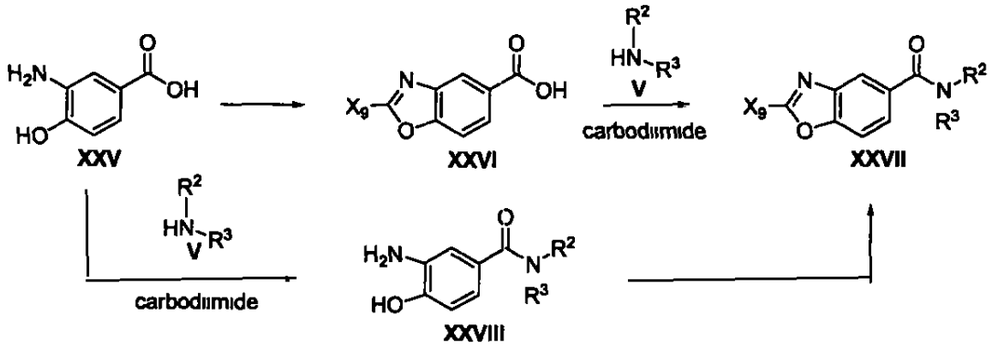
Scheme 5



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 a 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

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

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 (ompound 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 Gα15 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 # 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-Gα15 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 μg/ml Streptomycin (Invitrogen, Carlsbad, CA) (Li, et al *vide supra*) see also World Patent #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 μM in a phosphate buffered saline (D-PBS) (Invitrogen, Carlsbad, CA), for 1 hour 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 60 nM to 30 μM 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-Gα15 cells (not expressing the human sweet receptor) The HEK293-Gα15 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-Gα15 cells in the FLIPR assay

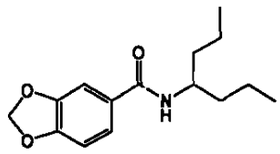
EXAMPLES

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

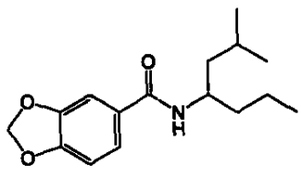


To a solution of heptan-4-amine (8 06 mL, 54 mmol) in triethylamine (15 3 mL, 108 mmol) and dichloromethane (135 mL), was added, dropwise at 0°C, a solution of benzo[1,3]dioxole-5-carbonyl chloride (10 g, >4 mmol) dissolved in dichloromethane (135 mL) The reaction mixture was stirred for 1 h Solvent 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 ^{1}H 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) ^{1}H 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)

a preparation of 2-methylheptan-4-amine

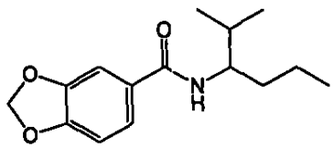
To a solution of 2-methylheptan-4-one (4 24 g, 33 07 mmol), in methanol (60 mL), were added ammonium acetate (25 50 g, 330 71 mmol) and sodium cyanoborohydride (2 08 g, 33 07 mmol) The reaction mixture was stirred at room temperature for about 24

hours The solvent was removed under reduc d 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



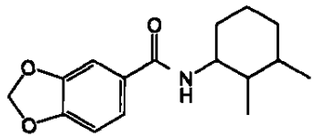
Prepared in a similar manner to example 1 using benzo[d][1,3]dioxole-5-carbonyl chloride and 2-methylhexan-3-amine (example 3a) ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 93 (m, 9H), 1 37 (m, 3H), 1 56 (m, 1H), 1 83 (m, 1H), 4 01 (m, 1H), 5 67 (d, 1H), 6 02 (s, 2H), 6 82 (d, 1H), 7 28 (m, 2H) MS (M+H, ’64)

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



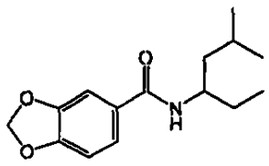
2,3-dimethylcyclohexanamine (20 µmol) and benzo[d][1,3]dioxole-5-carboxylic acid (1 1 eq) were each dissolved in acetonitrile/dichloromethane (200 µL 2 1) PS-Carbodiimide resin (2 eq) was loaded into a 1 2 mL 96 well Greiner plate, followed by the addition of amine and acid solutions Hydroxybenzotriazole (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



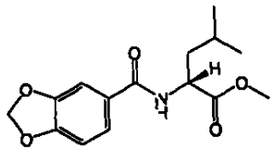
Prepared in a similar manner to example 1 using benzo[d][1,3]dioxole-5-carbonyl chloride and 5-methylhexan-3-amine (example 5a) Yield 48 % ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 94 (m, 9H), 1 37 (t, 3H), 1 45 (m, 1H), 1 64 (m, 2H), 4 13 (m, 1H), 5 61 (d 1H), 6 01 (s 2H), 6 82 (d, 1H), 7 27 (m, 2H) MS (M+H, 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

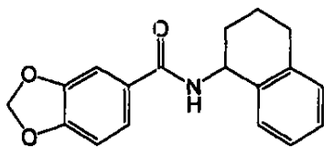


Prepared in a similar manner to example 1 using benzo[d][1,3]dioxole-5-carbonyl chloride and D-leucine methyl ester hydrochloride Yield 83 % ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 98 (m, 6H) 1 63-1 67 (m, 1H), 1 71-1 76 (m, 2H), 3 76 (s, 3H),4 83 (m, 1H) 6 03 (s, 2H) 6 38 (d, 1H), 6 83 (d, 1H) 7 32 (s 1H), 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

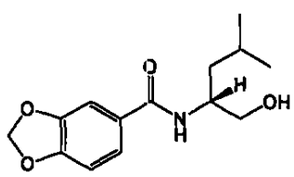


Prepared in a similar manner to example 4 using benzo[d][1,3]dioxole-5-carboxylic acid and 1,2,3,4-tetrahydronaphthalen-1-amine MS (M+H, 296 6)

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

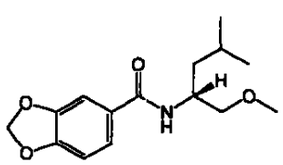


Prepared in a similar manner to example 4 using benzo[d][1,3]dioxole-5-carboxylic acid and (R)-aminoleucinol MS (M+H, 266 1)

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



Prepared in a similar manner to example 4 using (R)-1-methoxy-4-methyl and pentan-2-amine (example 9a) Yield 55% 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 %)

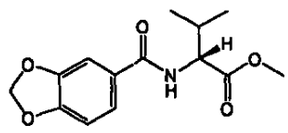
c (R)-2-(1-hydroxy-4-methylpentan-2-yl)isoindoline-1,3-dione

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 %) ^{1}H 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

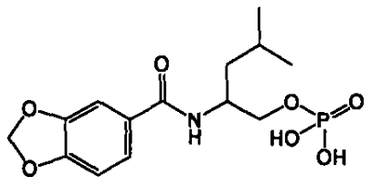


Prepared in a similar manner to example 4 using benzo[d][1,3]dioxole-5-carboxylic acid and (R)-methyl 2-amino-3-methylbutanoate Yield 50% MS (M+H, 280 1)

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



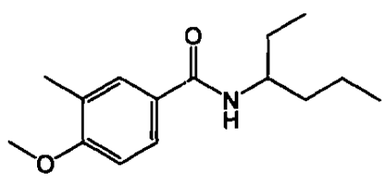
N-(1-hydroxy-4-methylpentan-2-yl)benzo[d][1,3]dioxole-5-carboxamide (example 11a) (0 57 mmol, 151 mg) was dissolved in anhydrous acetonitrile (2 ml) and 1 ml of 0 45 M solution of tetrazole in acetonitrile was added under nitrogen and stirred for 5 min Then 0 627 (1 1 eq, 207 μl) of dibenzyl diisopropyl 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 ^{1}H NMR (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]dıoxole-5-carboxamıde was prepared ın a sımılar manner to example 4 from pıperonylıc acıd and 2-amıno-4-methyl-pentan-1-ol

The compound had an EC_{50} for actıvatıon of a hT1R1/hT1R3 umamı receptor expressed ın an HEK293 cell lıne of 10 9 μM

Example 12

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

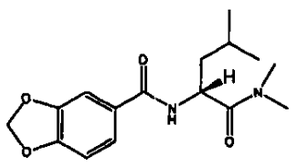


Prepared ın a sımılar manner to example 4 usıng 4-methoxy-3-methylbenzoıc acıd and hexan-3-amıne (example 28a) ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 94 (m 6H), 1 41 (m, 4H), 1 46 (m, 1H), 1 64 (m, 1H), 2 24 (s, 3H), 3 87(s, 3H), 4 08 (m, 1H), 5 69 (d, 1H), 6 83 (d, 1H), 7 54 (s, 1H), 7 62 (d, 1H) MS (M+H, 250)

The compound had an EC_{50} for actıvatıon of a hT1R1/hT1R3 umamı receptor expressed ın an HEK293 cell lıne of 0 12 μM

Example 13

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



(R)-2-(benzo[d][1,3]dıoxole-6-carboxamıdo)-4-methylpentanoıc acıd (example 13a) (52 mg, 0 19 mmol) ın DMF (4 mL) and dımethyl amıne (2M ın Methanol, 36 μL, 2 eq) were condensed ın presence of HOBt (26 mg, 1eq) and of 1-ethyl-3-(3-dımethylamınopropyl)-carbodıımıde hydrochlorıde (44 mg,1 2 eq) at room temperature overnıght The reactıon mıxture was evaporated and the resıdue was dıssolved ın ethylacetate and washed successıvely wıth saturated $NaHCO_3$ and water, dried over $MgSO_4$ filtered and evaporated to gıve 48 6 mg of the product (84%) The materıal was further purıfied usıng RPHPLC ^{1}H 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)

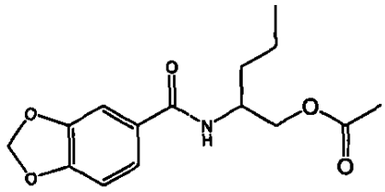
a (R)-2-(benzo[d][1,3]dioxole-6-carboxamido)-4-methylpentanoic acid

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



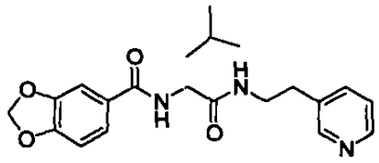
To a solution of N-(1-hydroxypentan-2-yl)benzo[d][1,3]dioxole-5-carboxamide (example 14a) (59 8mg, 0 238mmol) in dichloromethane (5 mL) was added triethylamine (166 mL, 1 19 mmol) Acetyl anhydride (112 5mL, 1 19mmol) was slowly added and the mixture was stirred under argon at ambient temperature overnight 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%) ^{1}H NMR($CDCl_3$) δ0 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

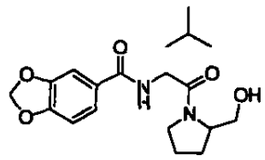


Prepared in a similar manner to example 13 using 2-(3-pyridyl)ethylamine and (R)-2-(benzo[d][1,3]dioxole-6-carboxamido)-4-methylpentanoic acid (example 13a) (MS M+ 384 2)

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

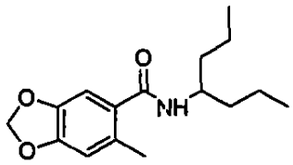


Prepared in a similar manner to example 13 using R/S propinol and (R)-2-(benzo[d][1,3]dioxole-6-carboxamido)-4-methylpentanoic acid (example 13a) (MS M+ 363 2)

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

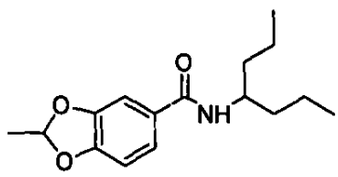


Prepared in a similar manner to example 4 using 6-methylbenzo[d][1,3]dioxole-5-carboxylic acid and heptan-4-amine MS (M+H 278 67)

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



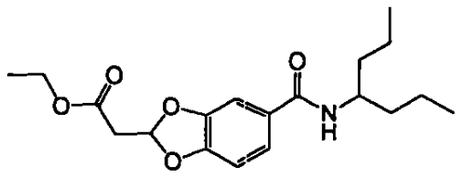
N-(heptan-4-yl)-3,4-dihydroxybenzamide (example 18a) (0 5 mmol) was dissolved in toluene (1 6 mL) P-Toluenesulfonic acid monohydrate (0 3eq) was added to the reaction, followed by addition of acetaldehyde (2eq) The reaction was performed using microwave (180C, 300W) and ran for 10 minutes The solvent 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



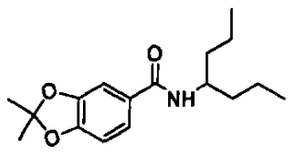
N-(heptan-4-yl)-3 4-dihydroxybenzamide (example 18a) (0 29 mmol, 75 mg) was dissolved in dry acetone with 6 eq excess (242 mg) of potassium carbonate then 1 2 eq excess (36 μl) of propynoic acid ethyl ester was added and a mixture was refluxed for 24 h The solvent was evaporated and a solid was dissolved 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%) ^1H 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 in 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 δ 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)

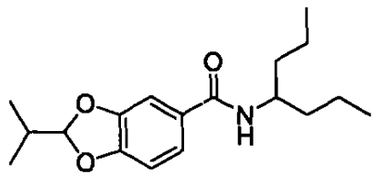
b Ethyl 2,2-dimethylbenzo[d][1,3]dioxole-5-carboxylate

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($CDCl_3$) δ 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



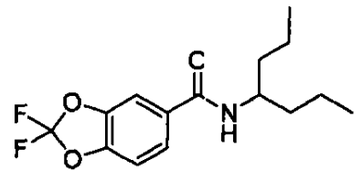
Prepared in a similar manner to example 4 using 2-isopropylbenzo[d][1,3]dioxole-5-carboxylic acid (example 21a) and 4-hepthylamine Yield 34% ^{1}H NMR($CDCl_3$) δ 0 92 (t, 6H, J = 7 2Hz), 1 04 (d, 6H, J = 6 9 Hz), 1 40 (m, 6H), 1 43 (m, 2H), 2 15 (m, 1H), 4 11 (m, 1H), 5 62 (d, 1H, J = 8 9Hz), 5 96 (d, 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

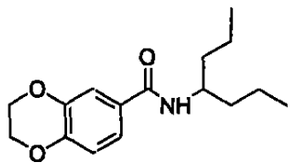


Prepared in a similar manner to example 4 using 2,2-difluorobenzo[d][1,3]dioxole 5-carboxylic acid and 4-hepthylamine (M+H, 300 2)

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

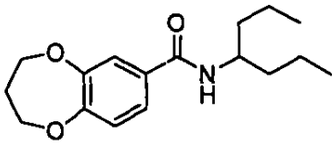


Prepared in a similar manner to example 4 using 2,3-Dihydro-benzo[1,4]dioxine-6-carboxylic acid and heptan-4-amine MS (M−H, 278 2)

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

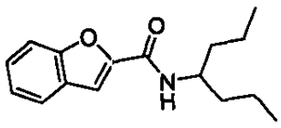


Prepared in a similar manner to example 4 using 2,3-Dihydro-benzo[1,4]dioxine-6-carboxylic acid and heptan-4-amine MS (M+H, 292 2)

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

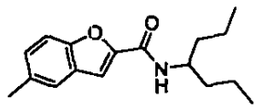


Prepared in a similar manner to example 1 using benzofuran-2-carbonyl chloride and heptan-4-amine Yield 73% ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 93 (t, 6H, J = 7 2 Hz), 1 41 (m, 8H), 3 01 (s, 3H), 4 18 (m, 1H), 6 29 (d, 1H, J = 9 94 Hz), 7 20 (d, 1H, J = 8 62 Hz), 7 37 (m, 2H), 7 44 (s, 1H) MS (M+H, 260)

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



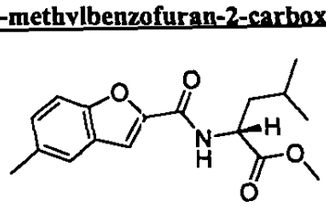
Prepared in a similar manner to example 4 using 5-methylbenzofuran-2-carboxylic acid (example 26a) and heptan-4 amine Yield 46% ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 94 (t, 6H, J = 7 2 Hz), 1 41 (m, 10H), 2 44 (s, 1H), 4 18 (m, 1H), 6 29 (d, 1H, J = 8 6 Hz), 7 21 (d 1H, J = 8 4 Hz), 7 37(m, 2H), 7 44 (s, 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) δ2 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

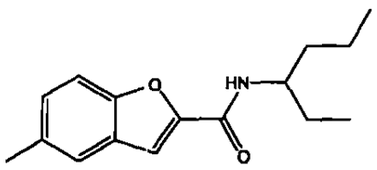


Prepared in a similar manner to example 4 using 5-methylbenzofuran-2-carboxylic acid (example 26a) and D-leucine methyl ester ^{1}H NMR (500 MHz, $CDCl_3$) δ0 98 (d, 3H, J = 6 26 Hz), 1 00 (d, 3H, J = 6 17 Hz), 1 56 (s, 3H), 1 76 (m, 3H), 2 48 (s, 3H), 3 78 (s, 3H), 4 86 (m, 1H), 6 95 (m, 1H), 7 23 (dd, 1H, I = 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



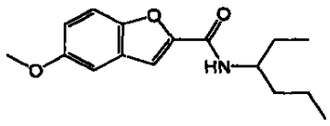
Prepared in a similar manner to example 4 using 5-methylbenzofuran-2-carboxylic (example 26a) and hexan-3-amine (example 28a) Yield 49% ^{1}H NMR (500 MHz, $CDCl_3$) δ0 94 (m, 6H), 1 40-1 68 (m, 6H), 2 36 (s, 3H), 4 07 (m, 1H), 5 74 (d, 1H, J = 8 97 Hz), 7 16 (d, 1H, J = 7 80 Hz), 7 31 (dd, 1H, J = 1 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, $CDCl_3$) δ 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

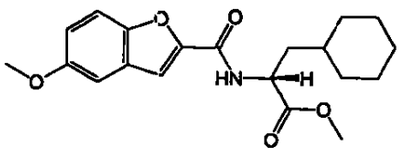


Prepared in a similar manner to example 4 using 5-methoxybenzofuran-2-carboxylic acid and hexan-3-amine (example 28a) Yield 32% ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 96 (m, 6H), 1 40-1 67 (m, 6H), 3 85 (s, 3H), 4 09 (m, 1H), 6 28 (d, 1H), 7 01 (dd, 1H), 7 08 (d, 1H), 7 38 (m, 2H) MS (276 M+H)

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0 4 μM

Example 30

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

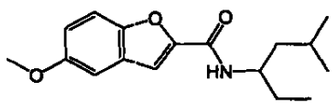


Prepared in a similar manner to example 4 using 5-methoxybenzofuran-2-carboxylic acid and (R)-methyl 2-amino-3-cyclohexylpropanoate Yield 45% MS (M+H, 260 3)

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

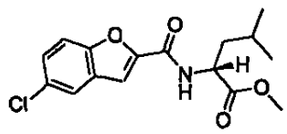


Prepared in a similar manner to example 4 using 5-methoxybenzofuran-2-carboxylic acid and 5-methylhexan-3-amine (example 5a) Yield 67% ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 96 (m, 9H), 1 39-1 52 (m, 3H) 1 66 (m, 2H), 3 85 (s, 3H), 4 17 (m, 1H) 6 24 (d, 1H) 7 01 (dd 1H) 7 08 (d, 1H), 7 38 (m, 2H) MS (290, 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

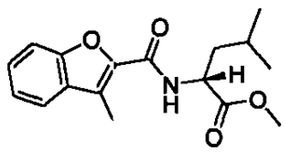


Prepared in a similar manner to example 4 using 5-chlorobenzofuran-2-carboxylic acid and D-leucine methyl ester MS (M+H, 324)

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

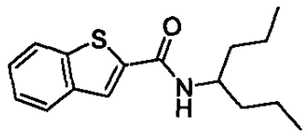


Prepared in a similar manner to example 4 using 3-methylbenzofuran-2-carboxylic acid and D-leucine methyl ester MS (M+H, 304)

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

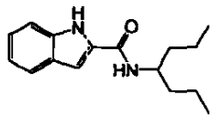


Prepared in a similar manner to example 4 using benzo[b]thiophene-2-carboxylic acid and 4-hepthylamine MS (M+H, 276)

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

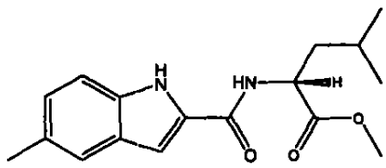


Prepared in a similar manner to example 4 using 1H-indole-2-carboxylic acid and 4-hepthylamine MS (M+H, 259)

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

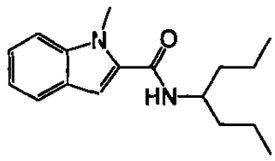


Prepared in a similar manner to example 4 using 5-Methyl-1H-indole-2-carboxylic acid and D-leucine methyl ester Yield 50% ^{1}H NMR (500 MHz, $CDCl_3$) δ0 98(d, 3H, J= 6 3Hz), 1 00(d, 3H, J = 6 1 Hz), 2 44 (s, 3H) 3 784(s, 3H), 4 87(m, 1H), 6 56 (d, 1H, J = 8 39 Hz), 6 85 (dd, 1H, J =1 94 Hz, J = 0 68 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

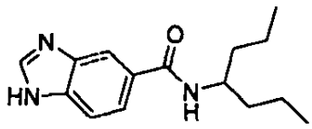


Prepared in a similar manner to example 4 using 1-methyl-1H-indole-2-carboxylic acid and 4-hepthylamine Yield 45% ^{1}H NMF (500 MHz, $CDCl_3$) δ 0 95 (t, 6H, J = 7 2 Hz), 1 46 (m, 4H), 1 57 (m, 4H), 4 05 (s, 3H), 4 15 (m, 1H), 5 85 (d, 1H), 6 80 (s 1H), 7 14 (t, 1H, J = 7 4 Hz), 7 31 (t, 1H, J = 7 5 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

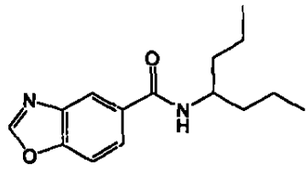


Prepared in a similar manner to example 4 using 1H-benzo[d]imidazole-5-carboxylic acid and 4-hepthylamine Yield 80% ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 94 (t 6H, J = 7 2 Hz), 1 42 (m, 6H), 1 57 (m, 2H), 4 21 (m, 1H), 6 18 (m, 1H), 7 64 (m, 2H), 8 16 (m, 1H), 8 28 (s, 1H) MS (M+H, 260)

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



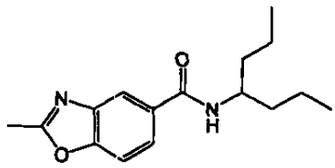
Prepared in a similar manner to example 4 using benzooxazol-5-carboxylic acid (Example 39a) and 4-heptylamine ^{1}H NMR (500 MHz, $CDCl_3$) δ 8 16 (d, J = 5 4 Hz, 1H), 7 89 (d, J = 8 6 Hz, 1H), 7 64 (d, J = 8 6 Hz, 1H),5 82 (d, J = 8 6 Hz, 1H) 4 10-4 22 (m, 1H), 1 58-1 62 (m, 4H), 1 40-1 49 (m, 4H), 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, $CDCl_3$) δ 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



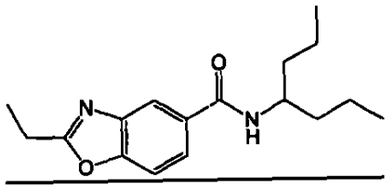
Prepared in a similar manner to example 4 starting from 2-methyl benzooxazol-5-carboxylic acid (example 40) and 4-heptylamine ^{1}H NMR (500 MHz, $CDCl_3$) δ 8 00 (d, J = 1 6 Hz, 1H), 7 77 (d, J = 8 5, 1 6 Hz, 1H), 7 50 (d, J = 8 5 Hz, 1H),5 79 (d, J = 8 9 Hz, 1H for NH) 4 10-4 22 (m, 1H), 2 66 (s, 3H), 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



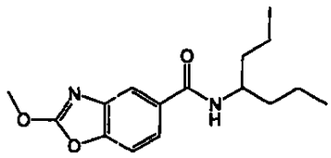
A mixture of 3-amino-4-hydroxy-N-(1-propylbutyl)benzamide (example 41a) and trimethyl orthopropyrate was heated at 65 °C for 5 hr under N_2 The reaction mixture was cooled to room temperature and concentrated in vacuo The resulting residue was purified on silica gel via Preparative-TLC (3% MeOH in CH_2Cl_2) 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

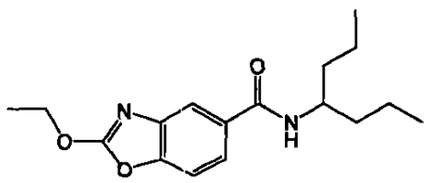


Prepared in a similar manner to example 41 using 3-amino-4-hydroxy-N-(1-propylbutyl)benzamide (example 4aa) and tetramethylorthocarbonate Yield 60% mp 137-138 °C, MS (M+H, 291 10)

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

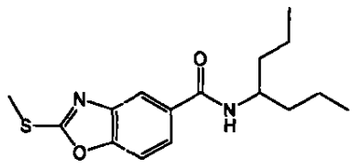


Prepared in a similar manner to example 41 using 3-amino-4-hydroxy-N-(1-propylbutyl)benzamide (example 41a) and tetraethoxymethane mp 128-129 °C, MS (M+H, 305 1)

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



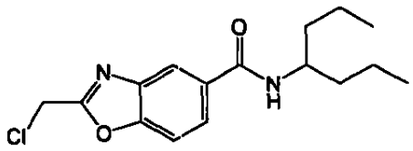
To a solution of N-(Heptan-4-yl)-2-(mercapto)benzo[*d*]oxazole-5-carboxamide (example 44a) (50 mg, 0 17 mmol) in DMF (3 mL) at 0 °C was added K_2CO_3 (29 mg, 0 17 mmol) and MeI (29 mg, 0 20) The resulting reaction mixture was heated at 80 °C overnight The solvent was removed under r duced pressure The 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 ^{1}H 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), 7 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-yl)-2-(mercapto)ben zo[*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

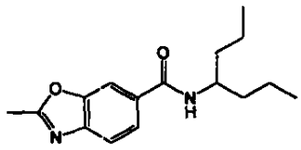


Prepared in a similar manner to example 41 using 3-amino-4-hydroxy-N-(1-propylbutyl)benzamide (example 41a) and trimethyl chloro-orthoacetate Yield 65% mp 108 5-109 °C MS (M+H, 309 05)

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



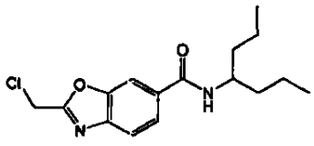
Prepared in a similar manner to example 4 using 2-methyl benzooxazol-6-carboxylic acid (example 46a) and 4-heptylamine Yield 50% ^{1}H NMR (500 MHz , CD_3OD) δ 8 19 (d, J = 1 4 Hz, 1H), 8 05 (dd J = 8 3, 1 5 Hz, 1H), 7 63 (d, J = 8 2 Hz, 1H) 2 68 (s, 1H) MS (M+1, 178 10)

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



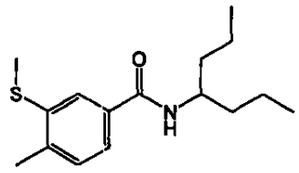
Prepared in a similar manner to example 41 using 3-amino-4-hydroxy-N-(1-propylbutyl)benzamide (example 47a) and trimethyl chloro-orthoacetate The product was obtained as a white solid (45 mg, 73%) mp 137 0-137 5 °C, MS (M+H 309 05

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



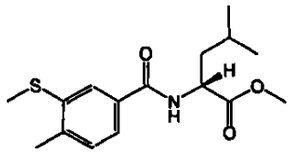
Preapared in a similar manner as example 4 using 4-methyl-3-(methylthio)benzoic acid (example 48a) and 4-heptylamine Yield 50% ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 93 (t 6H J = 7 2 Hz), 1 40-1 41 (m, 8H) 2 35 (s, 3H), 2 51 (s, 1H), 4 15 (m, 1H), 5 75 (d, 1H, J = 8 5 Hz), 7 15 (d, 1H, J = 7 8 Hz), 7 31 (d, 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 › 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 36 (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

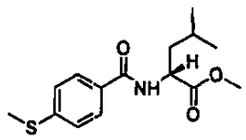


Prepared in a similar manner to example 4 using 3-methyl-4-(methylthio)benzoic acid (example 48a) and D Leucine methyl ester Yield 45% ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 97 (d, 3H, *J*= 6 36Hz), 0 99 (d, 3H, *J* = 6 1 Hz), 1 64-1 77 (m, 2H), 2 36 (s, 3H), 2 51(s, 3H), 3 77 (s, 3H), 4 85(m, 1H), 6 50 (d, 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

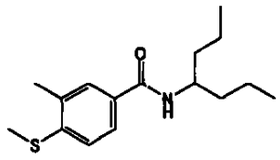


Prepared in a similar manner to example 4 using 4-(methylthio)benzoic acid and D Leucine methyl ester MS (M+H 296)

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-

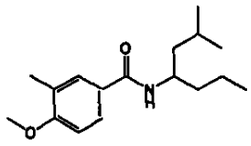
1 46 (m, 6H), 1 54-1 56 (m, 2H), 2 35 (s, 3H), 2 49 (s, 3H), 4 17 (m, 1H), 5 73 (d, 1H), 7 14 (d, 1H), 7 52 (s, 1H),7 58 (d, 1H) MS (280, M+H) m p 129-131 °C

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

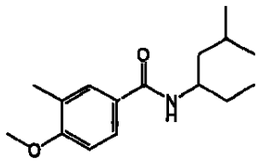


Prepared in a similar manner as described in example 4 using 4-methoxy-3-methylbenzoic acid and 2-methyl-4-heptanamine (example 2a) Yield 45% ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 93 (m, 9H), 1 39 (m, 5H), 1 53 (m, 1H), 1 67 (m, 1H), 2 24 (s, 3H), 3 86 (s 3H), 4 23 (m, 1H), 5 64 (d, 1H) 6 82 (d, 1H), 7 54 (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

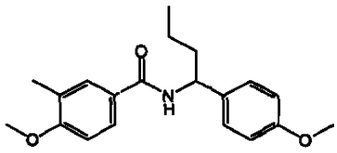


Prepared in a similar manner to example 4 using 4-methoxy-3-methylbenzoic acid and 5-methylhexan-3-amine (example 5a) ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 94 (m 9H) 1 38 (m, 2H), 1 47 (m, 1H), 1 65 (m, 2H), 2 24 (s, 3H), 3 86 (s, 3H) 4 16 (m, 1H), 5 65 (d, 1H), 6 83 (d, 1H), 7 54 (s, 1H), 7 61 (d, 1H) MS (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



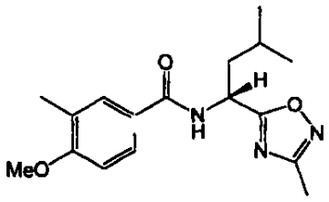
Prepared in a similar manner to example 4 using 3-methyl-4-methoxy-benzoic acid and 1-(4-methoxyphenyl)butan-1-amine (example 54a) Yield 52% ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 94 (t, 3H), 1 31-1 41 (m, 2H), 1 32-1 92 (m, 2H), 2 22 (s, 3H), 3 79 (s, 3H),3 86 (s, 3H), 5 11 (m, 1H), 6 14 (d, 1H), 6 81 (d, 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

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)

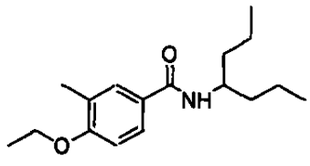
a (R)-3-methyl-1-(3-methyl-1,2,4-oxadiazol-5-yl)butan-1-amine Boc-D-Leu-OH (0 23 g, 1 mmol) was treated with N-hydroxyacetamidine (74 mg, 1 eq) and DIC (155 μL, 1 eq) in dioxane (2 mL) at room temperature overnight Another portion of DIC (1 equiv) was added and the reaction mixture was heated at 110°C 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



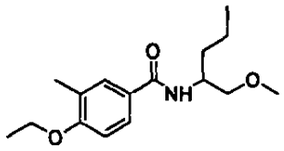
Prepared in a similar manner as example 4 using 4-ethoxy-3-methyl benzoic acid (example 56a) and 4-heptylamine Yield 75% ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 93 (t, 6H), 1 37-1 45 (m, 6H), 1 53-1 59 (m, 2H), 2 24 (s 3H), 4 07 (q, 2H), 4 15 (m, 1H), 5 67 (d, 1H), 6 80 (d, 1H), 7 54 (s, 1H), 7 58 (d, 1H) 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)

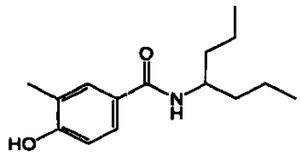
b 2-(1-methoxypentan 2-yl)isoindoline-1,3-dione was prepared in a similar manner to example 9b from 2-(1-hydroxypentan-2-yl)isoindoline-1,3-dione (example 57c) Yield 82% ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 91 (t, 3H), 1 32 (m, 2H), 1 64 (m, 1H), 2 03 (m, 1H), 3 31 (s, 3H), 3 54 (m, 1H), 3 98 (t, 1H), 4 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

Example 58

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

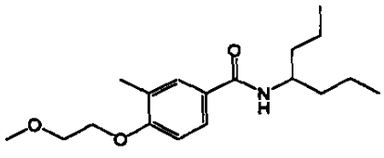


Prepared in a similar manner as described in example 4 using 4-hydroxy-3-methyl benzoic acid and 4-heptylamine MS (M+H, 250 2)

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

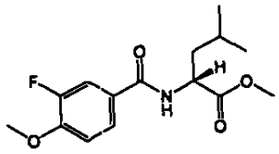


Potassium hydroxide (4 mmol) was dissolved in ethanol (5 mL) and heated at 80°C 4-hydroxy-3-methyl-N-(1-propyl-butyl)-benzamide (example 58) (1mmol) was added into the solution followed by chloroethanol (3 mmol) The reaction was stirred overnight at 80°C The reaction mixture was concentrated down and 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

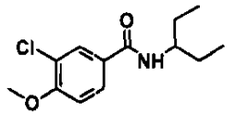


Prepared in a similar manner to example 4 using 3-fluoro-4-methoxybenzoic acid and D-leucine methyl ester MS (M+H, 298)

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

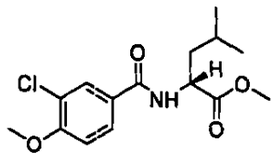


Prepared in a similar manner to example 4 using 3-pentylamine and 3-chloro-4-methoxy benzoic acid Yield 40% MS (M+H, '56 20)

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

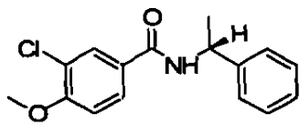


Prepared in a similar manner to example 4 using 3-chloro-4-methoxy benzoic acid and D-leucine methyl ester hydrochloride MS (M+H, 314 10)

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

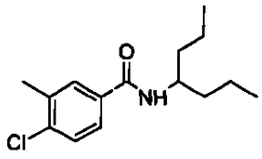


Prepare in a similar manner to example 4 using (R)-1-phenylethanamine and 3-chloro-4-methoxy benzoic acid MS (M+H, 290 0)

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

Example 64

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

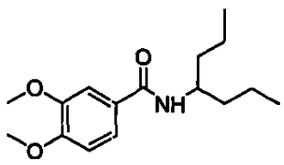


Prepared in a similar manner to example 4 using 4-chloro-3-methyl benzoic acid and heptan-4-amine MS (M+H, 268)

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

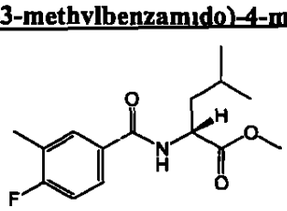


Prepared in a similar manner to example 4 using 3,4dimethoxy benzoic acid and heptan-4-amine MS (M+H, 279 37)

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

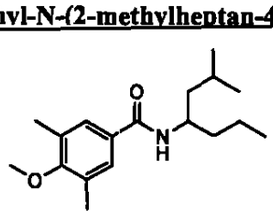


Prepared in a similar manner to example 4 using 4-fluoro-3-methylbenzoic acid and D-leucine methyl ester MS (M+H, 282)

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

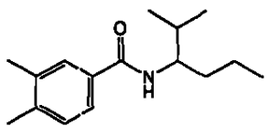


Prepared in a similar manner to example 4 using 4-methoxy-3,5-dimethylbenzoic acid and 2-methylheptan-4-amine (example 2a) MS (M+H, 292 2)

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

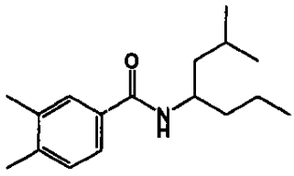


Prepared in a similar manner to example 4 using 3,4-dimethylbenzoic acid and hexan-3-amine (example 3a) ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 94 (m, 9H), 1 39 (m, 3H), 1 56 (m, 1H), 1 84 (m, 1H), 2 30 (s, 3H), 2 31 (s, 3H), 4 04 (m, 1H), 5 76 (d, 1H), 7 18 (d, 1H), 7 46 (d, 1H), 7 55 (s, 1H), MS (248, M+H)

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

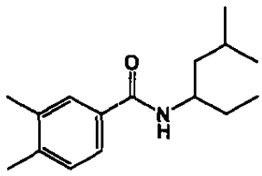


Prepared in a similar manner to example 4 using 3,4-dimethylbenzoic acid and 2-methylheptan-4-amine (example 2a) ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 94 (m, 9H) 1 40 (m, 5H), 1 53 (m, 1H), 1 68 (m, 1H) 2 29 (s, 3H) 2 30 (s 3H), 4 24 (m, 1H), 5 69 (d 1H) 7 17 (d, 1H), 7 46 (d, 1H), 7 54 (s, 1H) MS (262 M+H)

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

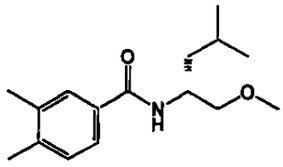


Prepared in a similar manner to example 4 using 3,4-dimethylbenzoic acid and 5-methylhexan-3-amine (example 5a) ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 94 (m, 9H), 1 38 (m, 2H) 1 46 (m, 1H), 1 65 (m, 2H), 2 29 (s 3H), 2 30 (s, 3H), 4 18 (m, 1H), 5 70 (d, 1H), 7 17 (d, 1H), 7 46 (d, 1H), 7 55 (s, 1H) MS (248, 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



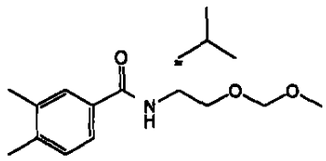
To a solution of (R)-N-(1-hydroxy-4-methylpentan-2-yl)-3,4-dimethylbenzamide (1 59 g, 6 39 mmol) (example 71a) in dry DMF (20 mL) was added powdered NaOH (281 mg, 7 mmol) an the solution was stirred at 0°C for 2 hrs Iodomethane (1 eq, 6 39 mmol) was added in DMF (10 ml) drop-wise over period of 1 hr 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

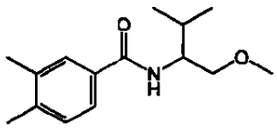


To a solution of (R)-N-(1-hydroxy-4-methylpentan-2-yl)-3,4-dimethylbenzamide (Example 71a) (0 24 mmol) dissolved in dry DMF (2mL) was added at 0°C powdered NaOH (0 36 mmol, 14 5 mg, 1 5 eq) and the mixture was stirred for 1 hr at 0°C Then chloro-methoxy-methane (19 3µl, 1 eq) was added and the reaction 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



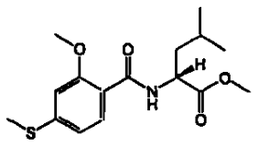
Prepared in a similar manner to example 71 using N-(1-hydroxy-3-methylbutan-2-yl)-3,4-dimethylbenzamide (example 73a) and methyl iodide Yield 87% ^1H NMR (500 MHz, $CDCl_3$) δ 0 97-1 00 (dt, 6H), 1 96-2 00 (m, 1H), 2 29 (s, 3H), 2 30 (s, 3H), 3 35 (s, 3H), 3 42-3 45 (dd, 1H), 3 60-3 62 (dd,1H), 4 01-4 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)

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

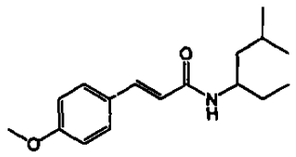


Prepared in a similar manner to example 4 using 2-methoxy-4-(methylthio)benzoic acid and D-leucine methyl ester MS (M+H, 326)

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

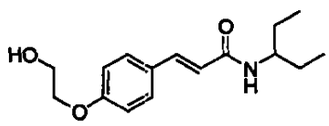


Prepared in a similar manner to example 4 using 3-(4-Methoxy-phenyl)-acrylic acid and 5-methylhexan-3-amine (example 5a) Yield 59% ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 93 (m, 9H), 1 33 (t, 2H), 1 43 (m, 1H), 1 58-1 67 (m, 2H), 3 83 (s, 3H), 4 11 (m, 1H), 5 19 (d, 1H), 6 25 (d, 1H), 6 88 (d, 2H),7 44 (d, 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 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

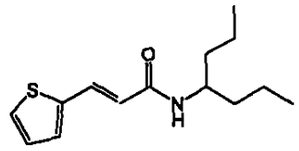
dissolved in dichloromethane and washed with water and 5% citric acid The organic phase was evaporated and the residue was purified by chromatography on silica gel to give 73 mg of desired product (60%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 92-0 95 (t, 6H), 1 25 (s, 1H),1 40-1 46 (m, 2H), 1 59-1 64 (m, 2H), 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

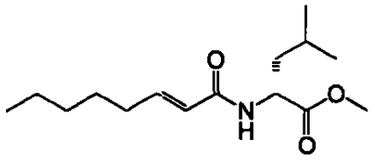


Prepared in a similar manner as described in example 4 from (E)-3-(thiophen-2-yl)acrylic acid and 4-hepthylamine MS (M+H 252)

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

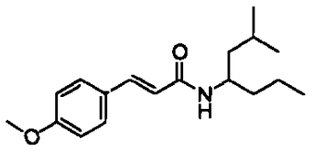


Prepared in a similar manner as described in example 4 from (E)-oct-2-enoic acid and D-leucine methyl ester MS (M+H, 270)

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0 92 μM

Example 79

3-(4-Methoxy-phenyl)-N-(3-methyl-1-propyl-butyl)-acrylamide

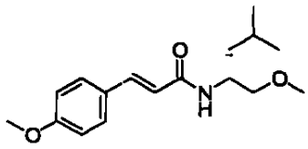


Prepared in a similar manner to example 4 using 3-(4-methoxy-phenyl)-acrylic acid and 3-methyl-1-propyl-butylamine (example 2a) Yield 65% ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 90-0 95 (m, 9H), 1 30-1 39 (m, 5H), 1 49-1 50 (m, 1H), 1 64-1 67 (m, 1H), 3 82 (s, 3H), 4 17-4 18 (m, 1H), 5 18-5 20 (d, 1H), 6 22-6 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

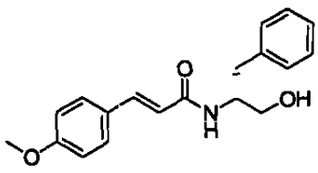


Prepared in a similar manner as described in example 71 from 3-(4-methoxy-phenyl)-acrylic acid and D-leucinol Yield 41% ^{1}H NMR (500 MHz, $CDCl_3$) δ0 93-0 96 (t, 6H), 1 38-1 42 (m, 1H), 1 48 1 54 (m 1H) 1 63-1 66 (m, 1H), 3 36 (s, 3H), 3 41-3 46 (m, 2H), 3 82-3 83 (s, 3H), 4 29-4 31 (m, 1H), 5 69-5 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

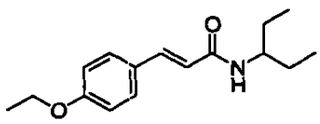


Prepared in a similar manner as described in example 4 from 3-(4-methoxy-phenyl)-acrylic acid and D-phenylalaninol MS (M+H, 312 3)

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

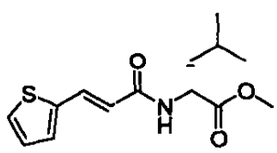


Prepared in a similar manner to example 4 using 3-(4-ethoxy-phenyl)-acrylic acid and 3-pentylamine MS (M+H, 262 2)

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

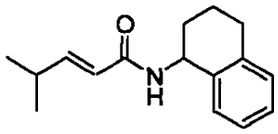


Prepared in a similar manner as described in example 4 from 3-thiophen-2-yl-acrylic acid and D-leucine methyl ester MS (M+H, 282 2)

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

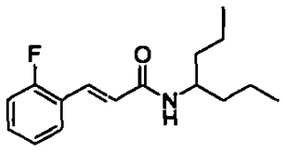


Prepared in a similar manner as described in example 4 from 4-methyl-pent-2-enoic acid and 1,2,3,4-tetrahydro-naphthalen-1-ylamine MS (M+H, 244 2)

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

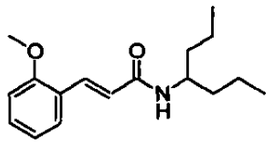


Prepared in a similar manner as described in example 4 from 3-(2-fluoro-phenyl)-acrylic acid and 4-heptylamine MS (M+H, 264 2)

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

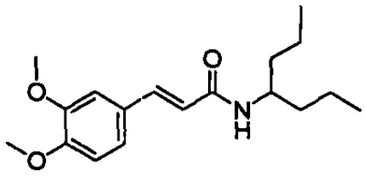


Prepared in a similar manner as described in example 4 from 3-(2-methoxy-phenyl)-acrylic acid and 4-heptylamine MS (M+H, 276 2)

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

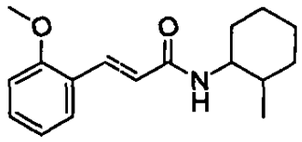


Prepared in a similar manner as described in example 4 from 3-(3,4-dimethoxy-phenyl)-acrylic acid and 4-heptylamine MS (M+H, 306 2)

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

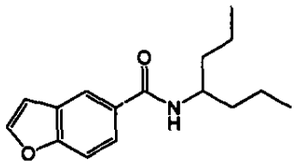


Prepared in a similar manner as described in example 4 from 3-(2-methoxy-phenyl)-acrylic acid and 2-methyl-cyclohexylamine MS (M+H, 274 2)

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 3 4 μM

Example 90

N-(heptan-4-yl)benzofuran-5-carboxamide

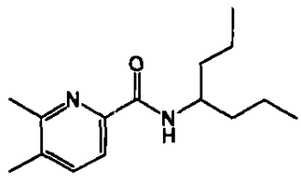


Prepared in a similar manner to example 4 using benzofuran-5-carboxylic acid and heptan-4-amine Yield 41% MS (M+H, 260 2)

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)

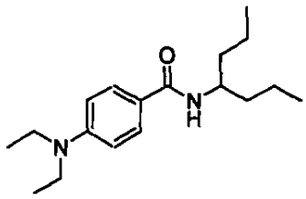
a 5,6-Dimethylpicolinic acid 5,6-dimethylpicolinonitrile (example 91b) was refluxed in concentrated HCl (15 mL) overnight The solvent was evaporated and the solid residue was co-evaporated several times with EtOH Drying provided 453 mg of 5 6-Dimethylpicolinic acid (80%) as a white solid MS (M+H, 152 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

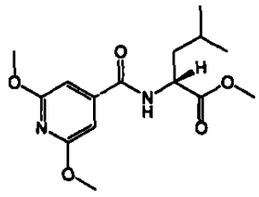


Prepared in a similar manner to example 4 using 4-diethylamino benzoic acid and 4-heptylamine (31% %) ^{1}H NMR (500 MHz $CDCl_3$) δ 0 92(t, 6H, J = 7 17 Hz), 1 18 (t, 6H, J = 7 04 Hz), 1 41(m, 4H), 1 55(m, 4H), 3 39 (m, 4H), 4 15 (m, 1H), 5 62 (m, 1H), 6 64 (d, 2H, J = 10 26Hz), 7 64 (d, 2H, J = 10 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

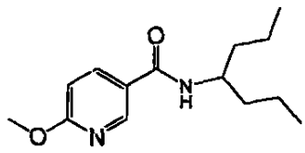


Prepared in a similar manner to example 4 using 2,6-Dimethoxy-isonicotinic acid and D-leucine methyl ester ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 92 (d, 3H, J=7 27 Hz), 0 93 (d, 3H J = 7 26 Hz), 1 41-1 58 (m, 8H), 3 95 (s, 3H), 4 08 (s, 3H), 4 15 (m, 1H), 6 43 (d, 1H, J = 8 32 Hz), 7 47 (m, broad, 1H), 8 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



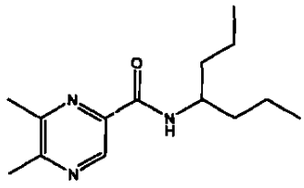
Prepared in a similar manner to example 4 using sodium 6-methoxynicotinate (example 94a) and 4-hepthylamine Yield 44% MS (M+H, 251)

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



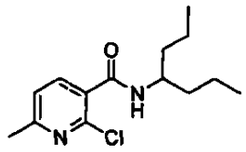
Prepared in a similar manner to example 4 using 5,6-dimethyl-pyrazine-2-carboxylic acid (example 95a) and 4-heptylamine ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 91-0 94 (t, 6H) 1 35-1 42 (m, 4H), 1 48-1 51 (m, 2H), 1 55-1 60 (m, 2H), 2 57-2 60 (d, 6H), 4 13-4 16 (m, 1H), 7 52-7 53 (d, 1H), 9 09 (s, 1H), MS (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

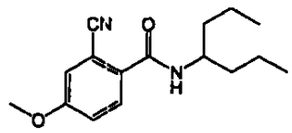


Prepared in a similar manner to example 4 using 2-chloro-6-methylnicotinic acid and 4-Heptylamine MS (M+H, 269)

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

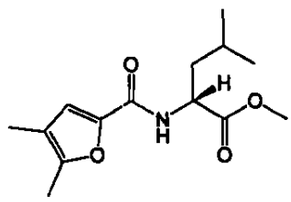


Prepared in a similar manner to example 4 using 2-cyano-4-methoxybenzoic acidand 4-Heptylamine Yield 73% ^{1}H NMR (CD_3OD) δ0 94 (t, 6H, J = 7 3 Hz), 1 38 (m, 4H), 1 53 (m, 4H), 4 02 (s, 3H),4 12 (m, 1H), 7 27 (d, 1H, J = 9 40 Hz), 8 11 (d 2H, J = 2 21 Hz) MS (M+H, 275)

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



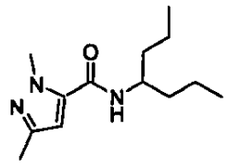
Prepared in a similar manner to example 4 using 4,5-dimethyl-furan-2-carboxylic acid and D-leucine methyl ester Yield 27 % ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 96 (t, 6H),

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

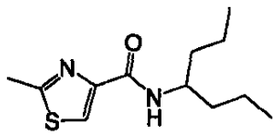


Prepared in a similar manner to example 4 using 1,3-dimethyl-1H-pyrazole-5-carboxylic acid and 4-heptylamine ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 90 (t, 6H, J = 7 2 Hz), 1 41 (m, 4H), 1 50 (m, 4H), 2 27 (s, 3H), 3 77 (s, 3H), 4 09 (m, 1H), 6 49 (d, 1H), 6 53 (s, 1H) MS (M+H, 238)

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

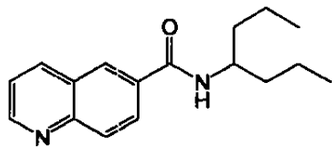


Prepared in a similar manner to example 4 using 1 3-dimethyl-1H-pyrazole-5-carboxylic acid and 4-heptylamine MS (M+H 241)

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

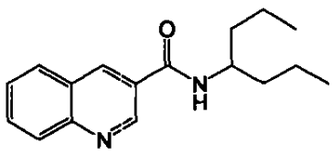


Prepared in a similar manner to example 4 using quinoline-6-carboxylic acid and 4-heptylamine ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 96 (t, J = 7 2 Hz, 6H), 1 42-1 58 (m, 6H), 1 62-1 70 (m, 2H), 4 18-4 20 (m, 1H), 5 95 (d, J = 9 0 Hz, 1H), 7 49 (br s, 1H), 8 04 (dd, J = 8 5, 1 5 Hz, 1H), 8 17 (d, J = 8 5 Hz, 1H), 3 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

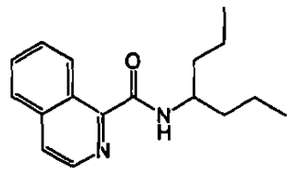


Prepared in a similar manner to example 4 using quinoline-3-carboxylic acid and heptylamine ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 96 (t, J = 7 3 Hz, 6H), 1 40-1 58 (m, 6H), 1 60-1 67 (m, 2H), 4 20-4 30 (m 1H), 6 01 (d, J = 8 8 Hz, 1H), 7 61 (t, J = 7 5, 1H), 7 80 (t, J = 7 6 Hz, 1H), 7 90 (d J = 8 1 Hz 1H) ? 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

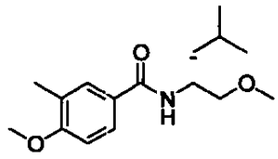


Prepared in a similar manner to example 4 using isoquinoline-1-carboxylic acid and heptamine ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 98 (t, J = 7 05 Hz, 6H), 1 42-1 56 (m, 6H), 1 58-1 66 (m, 2H), 4 20-4 32 (m, 1H), 5 83 (d, J = 9 1 Hz, 1H), 7 36 (d, J = 4 2, 1H), 7 60 (t, J = 7 7 Hz, 1H), 7 75 (t, J = 7 7 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

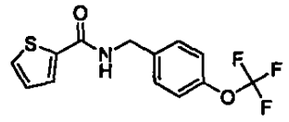


Prepared in a similar manner as described in example 71 from 4-methoxy-3-methyl-benzoic acid and D-leucinol Yield 86% ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 94—0 97 (t 6H), 1 42-1 47 (m 1H), 1 54-1 60 (m, 1H), 1 64-1 68 (m, 2H), 2 24 (s, 3H), 3 37 (s, 3H), 3 46-3 48 (m, 2H), 3 87 (s, 3H), 4 35-4 38 (m 1H) 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

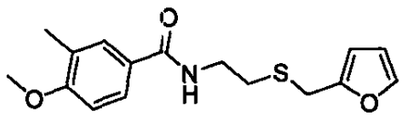


Prepared in a similar manner as described in example 4 from thiophene-2-carboxylic acid and (4-(trifluoromethoxy)phenyl)methanamine MS (M+H, 303)

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

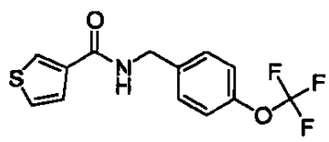


Prepared in a similar manner as described in example 4 from 4-methoxy-3-methylbenzoic acid and 2-(furan-2-ylmethylthio)ethanamine Yield 58% ^{1}H NMR (500 MHz, $CDCl_3$) 2 23 (s, 3H), 2 76 (t, 2H, J = 6 37 Hz), 3 59 (q, 2H, J = 12 2 Hz), 3 76 (s, 2H), 3 86 (s, 3H), 6 22 (dd, 1H, J = 3 49 Hz J = 2 67 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

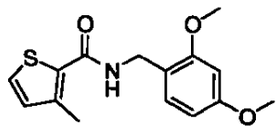


Prepared in a similar manner to example 4 using thiophene-3-carboxylic acid and 4-trifluoromethoxy-benzylamine MS (M+H, 302 0)

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

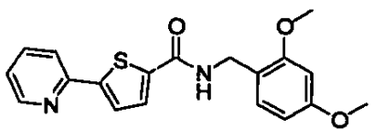


Prepared in a similar manner to example 4 using 3-methyl-thiophene-2-carboxylic acid and 2,4-dimethoxy-benzylamine MS (M+H, 292 2)

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

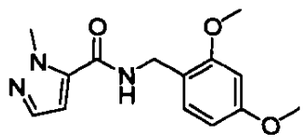


Prepared in a similar manner to example 4 using 5-pyridin-2-yl-thiophene-2-carboxylic acid and 2,4-dimethoxy-benzylamine MS (M+H, 355 2)

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

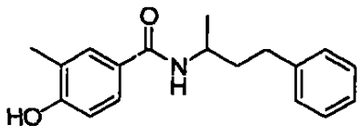


Prepared in a similar manner to example 4 using 2-methyl-2H-pyrazole-3-carboxylic acidand 2,4-dimethoxy-benzylamine MS (M+H, 276 2)

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

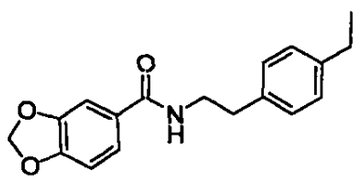


Prepared in a similar manner to example 4 using 4-hydroxy-3-methyl-benzoic acid and 1-methyl-3-phenyl-propylamine MS (M+H, 284 2)

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

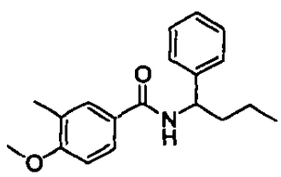


Prepared in a similar manner to example 4 using benzo[1,3]dioxole-5-carboxylic acid and 2-(4-ethyl-phenyl)-ethylamine MS (M+H, 298 2)

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

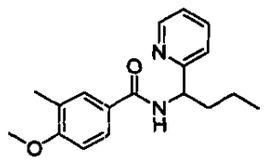


Prepared in a similar manner to example 4 using 4-methoxy-3-methyl-benzoic acid and 1-phenyl-butylamine MS (M+H, 298 2)

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

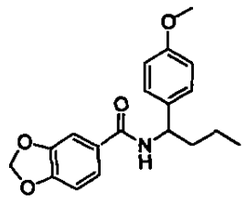


Prepared in a similar manner to example 4 using 4-methoxy-3-methyl-benzoic acid and 1-pyridin-2-yl-butylamine ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 91-0 92 (t, 3H), 1 25-1 3 (m, 2H, 1 85-1 9 (m, 2H), 3 86 (s, 3H), 5 25-5 3 (m, 1H), 6 80-6 82 (d, 1H), 7 2-7 3 (m, 2H), 7 42-7 44 (d, 1H), 7 6-7 7 (m, 3H), 8 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

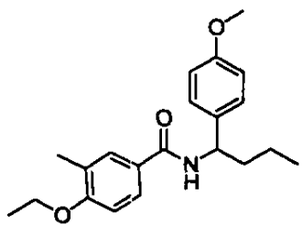


Prepared in a similar manner to example 4 using benzo[1,3]dioxole-5-carboxylic acid and 1-(4-methoxy-phenyl)-butylamine ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 93-0 95 (t 3H), 1 30-1 39 (m, 2H), 1 80-1 90 (m, 2H), 3 79 (s, 3H), 5 08-5 09 (dd, 1H), 6 00 (s, 2H), 6 10-6 12 (d, 1H) 6 79-6 80 (d 1H) 6 87(s 1H) 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

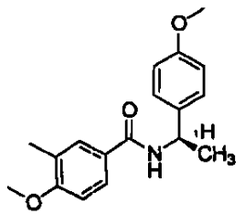


Prepared in a similar manner to example 4 using 4-ethoxy-3-methyl-benzoic acid and 1-(4-methoxy-phenyl)-butylamine ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 93-0 96 (t 3H), 1 31-1 41 (m, 2H), 1 41-1 45 (t, 3H), 1 82-1 9? (m, 2H), 2 28 (s, 3H), 3 79 (s, 3H), 4 04-4 08 (q, 2H), 5 10-5 12 (d, 1H), 6 12-6 14 (d, 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

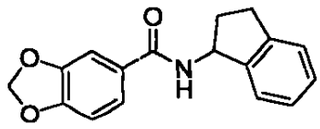


Prepared in a similar manner to example 4 using 4-methoxy-3-methyl-benzoic acid and 1-(R)-(4-methoxy-phenyl)-ethylamine MS (M+H, 300 1)

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

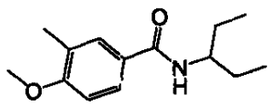


Prepared in a similar manner to example 4 using benzo[1,3]dioxole-5-carboxylic acid and indan-1-ylamine MS (M+H, 282 2)

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

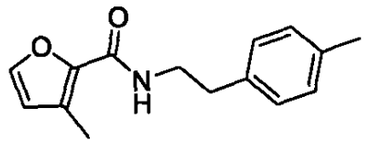


Prepared in a similar manner as described in example 4 from 4-methoxy-3-methylbenzoic acid and pentan-3-amine MS (M+H, 236)

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

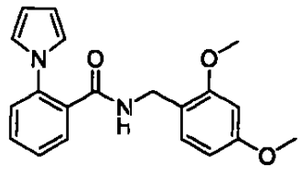


Prepared in a similar manner as described in example 4 from 3-methylfuran-2-carboxylic acid and 2-p-tolylethanamine MS (M+H, 244)

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 1 1

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

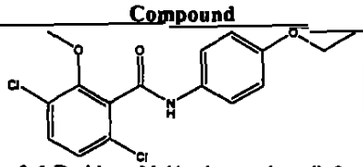
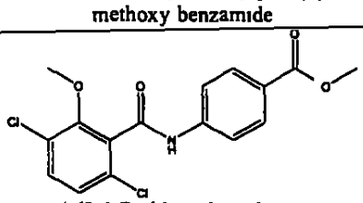
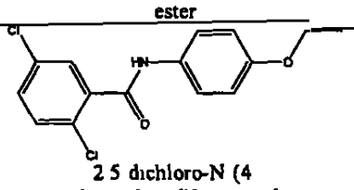
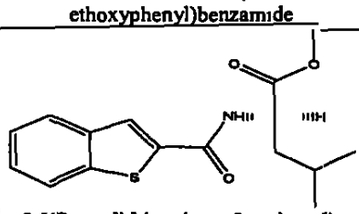
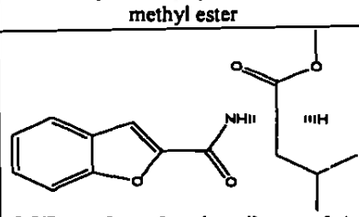
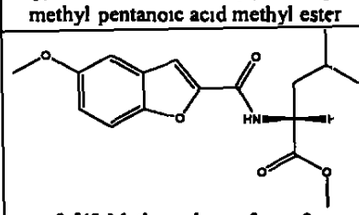
Compound No	Compound	Umami EC_{50} (uM)	Ec_{50} ratio (vs MSG)	@ (uM)
A1	 3 6 Dichloro N (4 ethoxy phenyl) 2 methoxy benzamide	0 22	2 74	1
A2	 4 (3 6 Dichloro 2 methoxy benzoylamino) benzoic acid methyl ester	0 93	6 98	0 01
A3	 2 5 dichloro-N (4 ethoxyphenyl)benzamide	1 08	6 14	0 03
A4	 2 [(Benzo[b]thiophene 2 carbonyl) amino] 4-methyl pentanoic acid methyl ester	0 4		
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

Table A Umami Amides

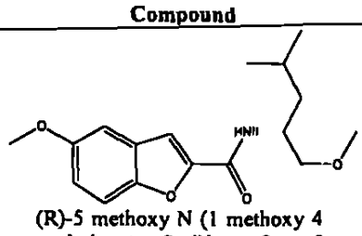
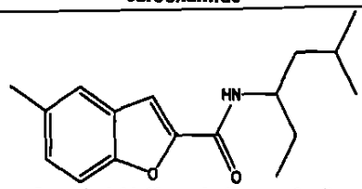
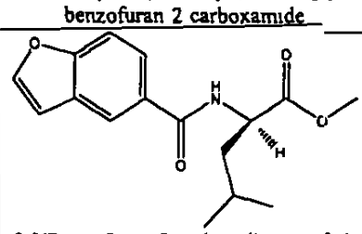
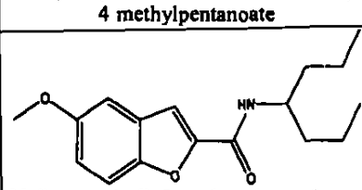
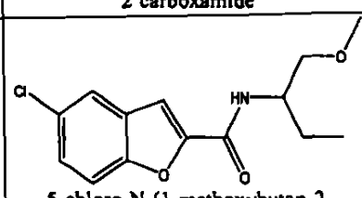
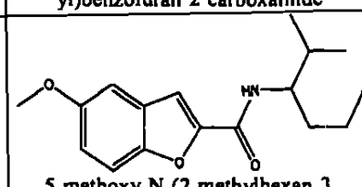
Compound No	Compound	Umami EC_{50} (uM)	Ec_{50} ratio (vs MSG)	@ (uM)
A7	 (R)-5 methoxy N (1 methoxy 4 methylpentan 2 yl)benzofuran 2 carboxamide	0 46		
A8	 5 methyl N (5 methylhexan 3 yl) benzofuran 2 carboxamide	0 5		
A9	 2 [(Benzofuran 5 carbonyl) amino] 4 methyl pentanoic acid methyl ester(R) methyl 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		

Table A - Umami Amides

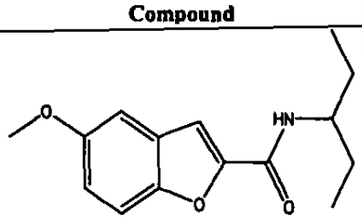
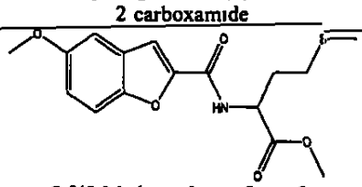
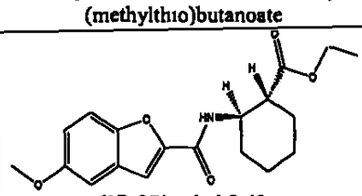
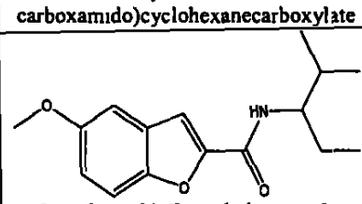
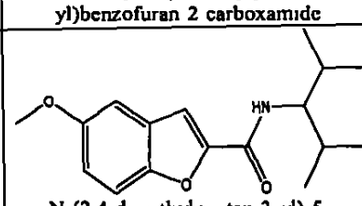
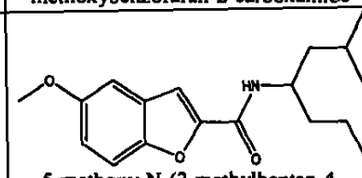
Compound No	Compound	Umami EC_{50} (uM)	Ec_{50} ratio (vs MSG)	@ (uM)
A13	 5 methoxy N (pentan 3 yl)benzofuran 2 carboxamide	1 14	4 46	1
A14	 2 [(5 Methoxy benzofuran 2 carbonyl) amino] 4-methylsulfanyl butyric acid methyl ester methyl 2 (5 methoxybenzofuran 2 carboxamido)-4 (methylthio)butanoate	1 14		
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 carboxamice	1 2		
A18	 5 methoxy N (2 methylheptan 4 yl)benzofuran 2 carboxamide	1 27		

Table A Umami Amides

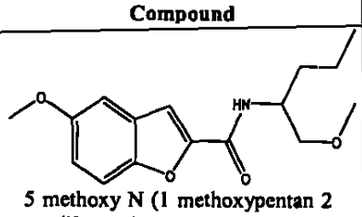
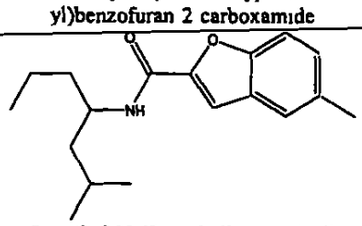
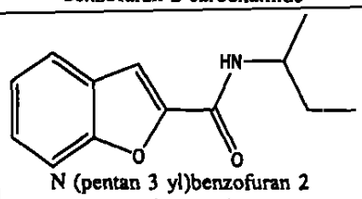
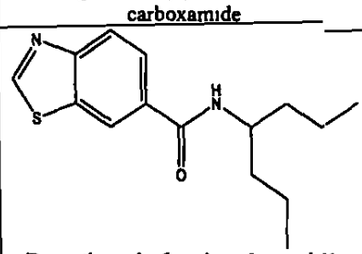
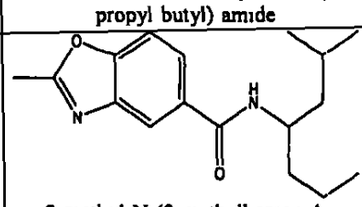
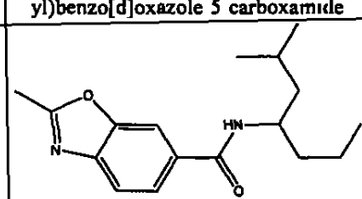
Compound No	Compound	Umami EC_{50} (uM)	Ec_{50} ratio (vs MSG)	@ (uM)
A19	 5 methoxy N (1 methoxypentan 2 yl)benzofuran 2 carboxamide	1 3		
A20	 5 methyl N (2 methylheptan 4 yl) benzofuran 2 carboxamide	1 32		
A21	 N (pentan 3 yl)benzofuran 2 carboxamide	1 52	3 74	1
A22	 Benzothiazole 6 carboxylic acid (1 propyl butyl) amide	1 58		
A23	 2 methyl N (2 methylheptan 4 yl)benzo[d]oxazole 5 carboxamide	0 38		
A24	 2 methyl N (2 methylheptan 4 yl)benzo[d]oxazole 6-carboxamide	1 12		

Table A Umami Amides

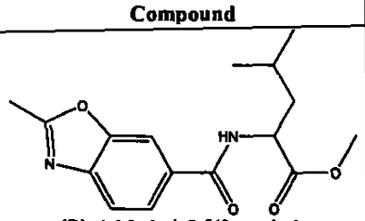
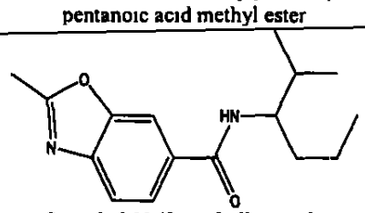
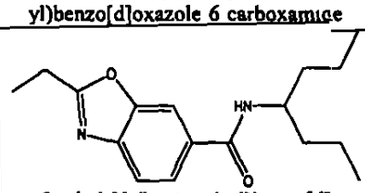
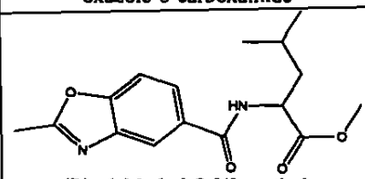
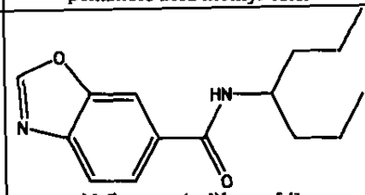
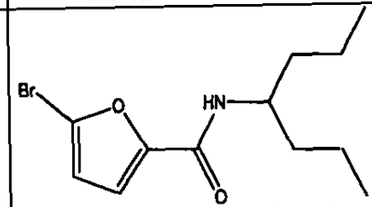
Compound No	Compound	Umami EC_{50} (uM)	Ec_{50} ratio (vs MSG)	@ (uM)
A25	 (R) 4 Methyl 2 [(2 methyl benzooxazole 6 carbonyl) amino] pentanoic acid methyl ester	1 48		
A26	 2 methyl N (2 methylhexan 3 yl)benzo[d]oxazole 6 carboxamide	1 6		
A27	 2 ethyl N (heptan 4-yl)benzo[d] oxazole 6 carboxamide	1 61		
A28	 (R) 4 Methyl 2 [(2 methyl benzooxazole 5 carbonyl) amino] pentanoic acid methyl ester	1 69		
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

Table A Umami Amides

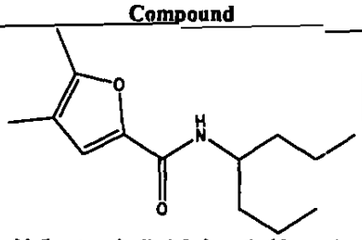
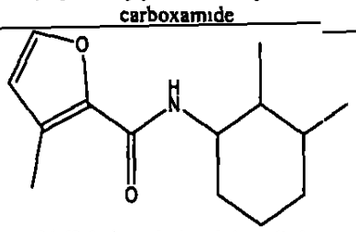
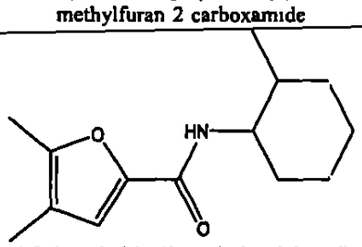
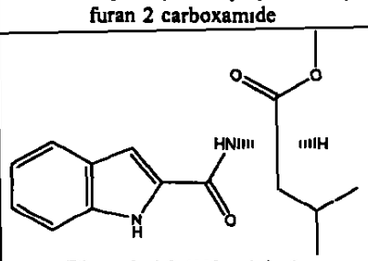
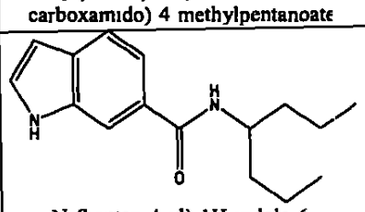
Compound No	Compound	Umami EC_{50} (uM)	Ec_{50} ratio (vs MSG)	@ (uM)
A31	 N (heptan-4 yl) 4 5 dimethylfuran 2 carboxamide	0 62	10 04	1
A32	 N (2 3 dimethylcyclohexyl)-3 methylfuran 2 carboxamide	1 15		
A33	 4 5 dimethyl N (2 methylcyclohex yl) furan 2 carboxamide	1 33		
A34	 (R) methyl 2 (1H indole-2-carboxamido) 4 methylpentanoate	0 53		
A35	 N (heptan 4 yl) 1H indole-6 carboxamide	0 82	8 81	1

Table A Umami Amides

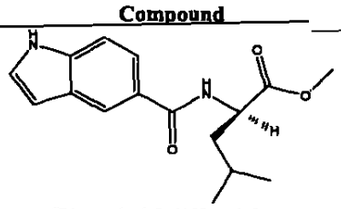
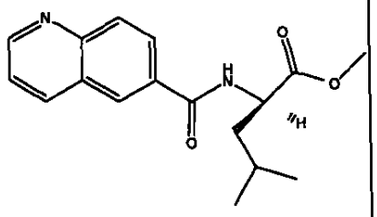
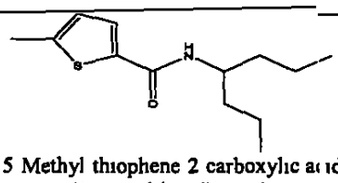
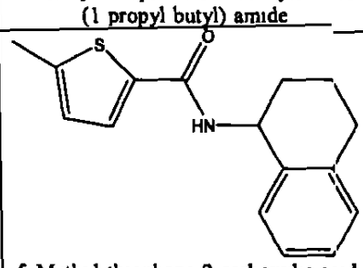
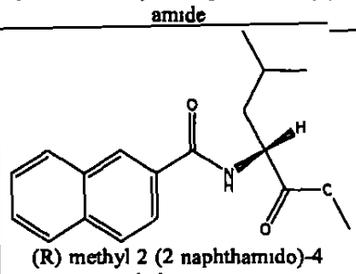
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A36	 (R) methyl 2 (1H indole 5 carboxamido) 4 methylpentanoate	1 01		
A37	 (R)-methyl 4 methyl 2 (quinoline 6 carboxamido)pentanoate	1 5		
A38	 5 Methyl thiophene 2 carboxylic acid (1 propyl butyl) amide	1 22	6 54	1
A39	 5 Methyl thiophene 2 carboxylic 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

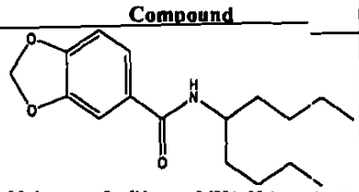
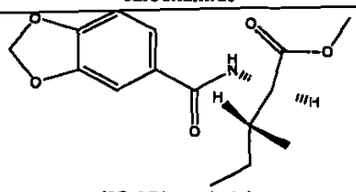
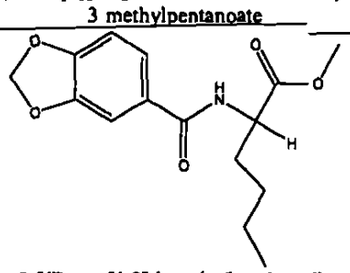
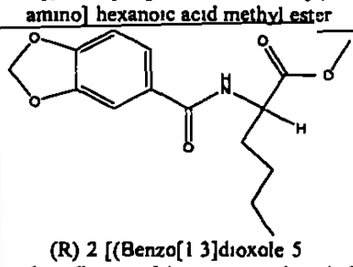
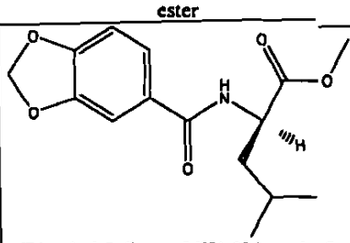
Compound No	Compound	Umami EC_{50} (uM)	Ec_{50} ratio (vs MSG)	@ (uM)
A41	 N (nonan 5 yl)benzo[d][1,3]dioxole 5 carboxamide	0 7	2 14	3
A42	 (2R,3R)-methyl 2 (benzo[d][1 3]dioxole 5 carboxamido)-3 methylpentanoate	0 35		
A43	 2 [(Benzo[1 3]dioxole 5 carbonyl) amino] hexanoic acid methyl ester	0 49		
A44	 (R) 2 [(Benzo[1 3]dioxole 5 carbonyl) amino] hexanoic acid methyl ester	0 61		
A45	 (R) ethyl 2 (benzo[d][1 3]dioxole 5 carboxamido) 4 methylpentanoate	0 88		

Table A Umami Amides

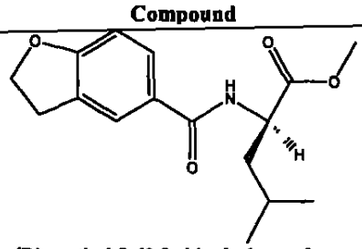
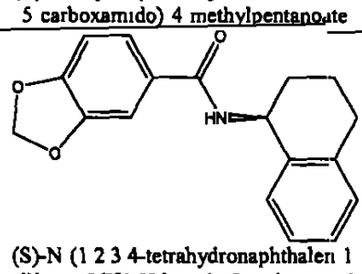
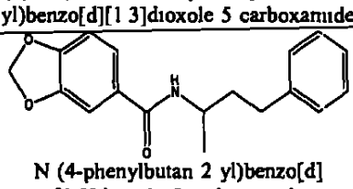
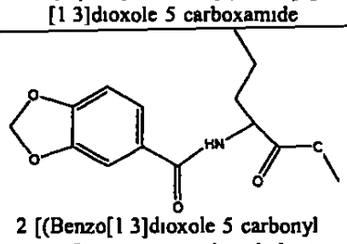
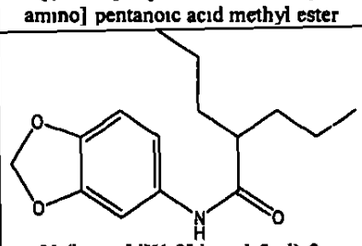
Compound No	Compound	Umami EC_{50} (uM)	Ec_{50} ratio (vs MSG)	@ (uM)
A46	 (R) methyl 2 (2 3 dihydrobenzofuran 5 carboxamido) 4 methylpentanoate	1 32		
A47	 (S)-N (1 2 3 4-tetrahydronaphthalen 1 yl)benzo[d][1 3]dioxole 5 carboxamide	1 33	6 42	0 1
A48	 N (4-phenylbutan 2 yl)benzo[d] [1 3]dioxole 5 carboxamide	1 51	9 27	1
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		

Table A - Umami Amides

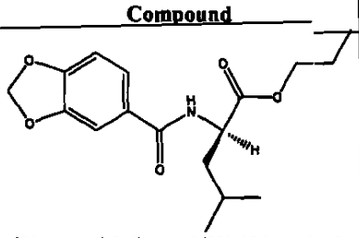
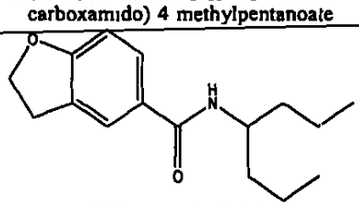
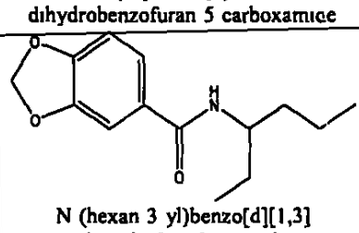
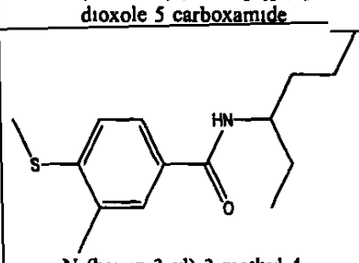
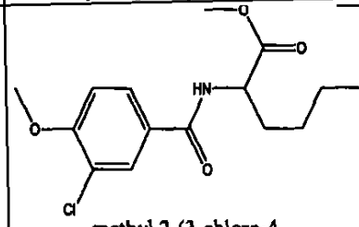
Compound No	Compound	Umami EC_{50} (uM)	Ec_{50} ratio (vs MSG)	@ (uM)
A51	 (R) propyl 2 (benzo[d][1 3]dioxol 5 carboxamido) 4 methylpentanoate	1 58		
A52	 N (heptan 4 yl) 2 3 dihydrobenzofuran 5 carboxamide	1 65		
A53	 N (hexan 3 yl)benzo[d][1,3] dioxole 5 carboxamide	1 83		
A54	 N (hexan 3 yl) 3 methyl 4 (methylthio)benzamide	0 12		
A55	 methyl 2 (3 chloro-4 methoxybenzamido)hexanoate	0 12		

Table A Umami Amides

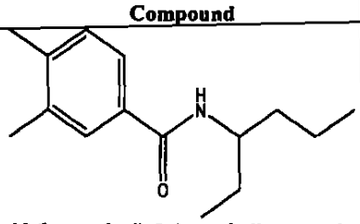
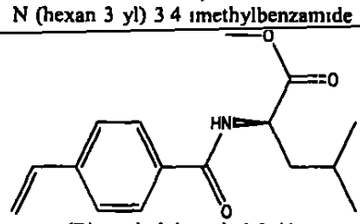
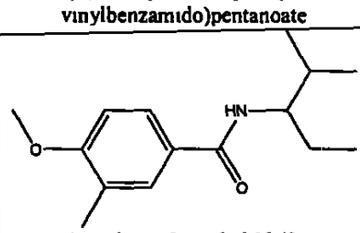
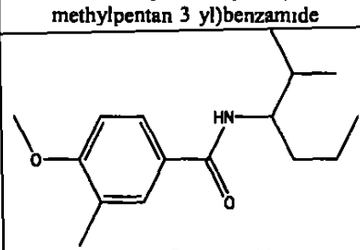
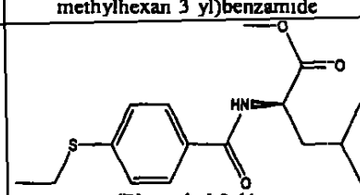
Compound No	Compound	Umami EC_{50} (uM)	Ec_{50} ratio (vs MSG)	@ (uM)
A56	 N (hexan 3 yl) 3 4 imethylbenzamide	0 14		
A57	 (R) methyl 4 methyl 2 (4 vinylbenzamido)pentanoate	0 18		
A58	 4 methoxy 3 methyl N (2 methylpentan 3 yl)benzamide	0 2		
A59	 4 methoxy 3 methyl N (2 methylhexan 3 yl)benzamide	0 2		
A60	 (R) methyl 2-(4 (ethylthio)benzamido)-4 methylpentanoate	0 2		

Table A - Umami Amides

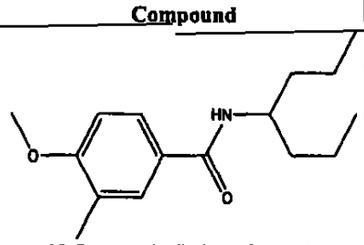
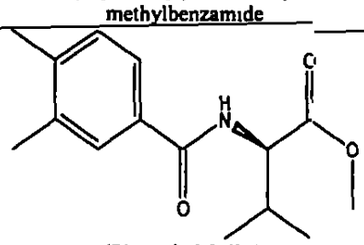
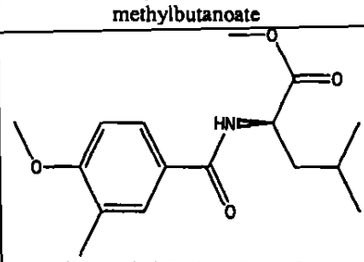
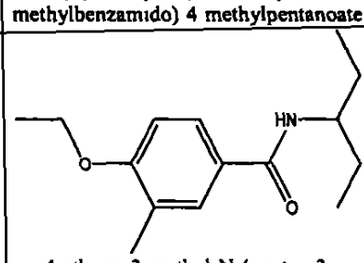
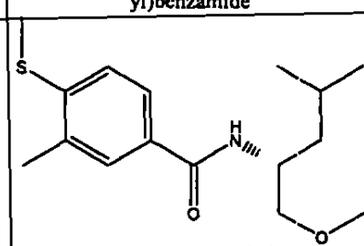
Compound No	Compound	Umami EC_{50} (uM)	Ec_{50} ratio (vs MSG)	@ (nM)
A61	 N (heptan 4-yl)-4 methoxy 3 methylbenzamide	0 22		
A62	 (R) methyl 2 (3 4 dimethylbenzamido) 3 methylbutanoate	0 25		
A63	 (R) methyl 2 (4-methoxy 3 methylbenzamido) 4 methylpentanoate	0 25		
A64	 4 ethoxy 3 methyl N (pentan 3 yl)benzamide	0 26		
A65	 (R) N (1 methoxy 4-methylpentan 2 yl)-3 methyl 4 (methylthio)benzamide	0 29		

Table A - Umami Amides

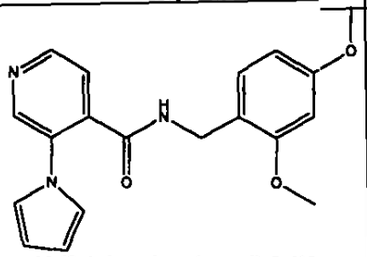
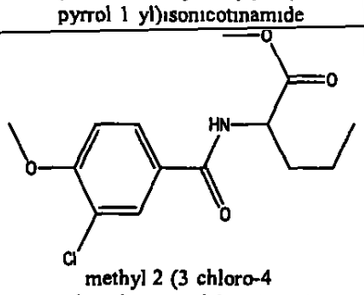
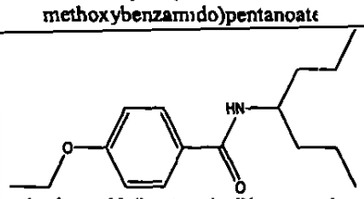
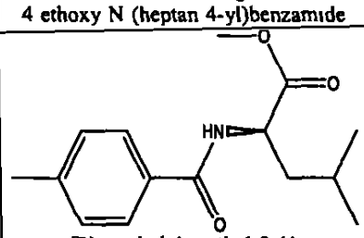
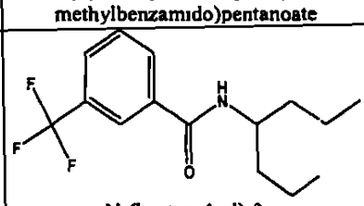
Compound No	Compound	Umami EC_{50} (uM)	Ec_{50} ratio (vs MSG)	@ (uM)
A66	 N (2 4 dimethoxybenzyl) 3 (1H- pyrrol 1 yl)isonicotinamide	0 29		
A67	 methyl 2 (3 chloro-4 methoxybenzamido)pentanoate	0 29	10 75	1
A68	 4 ethoxy N (heptan 4-yl)benzamide	0 32	2 62	0 3
A69	 (R) methyl 4-methyl 2 (4 methylbenzamido)pentanoate	0 32		
A70	 N (heptan 4-yl) 3 (trifluoromethyl)benzamide	0 33		

Table A - Umami Amides

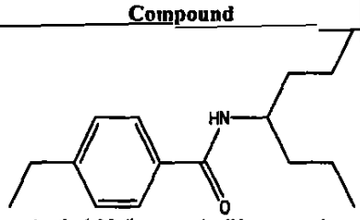
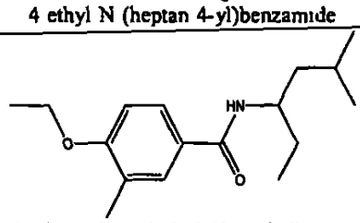
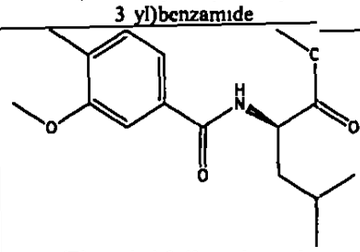
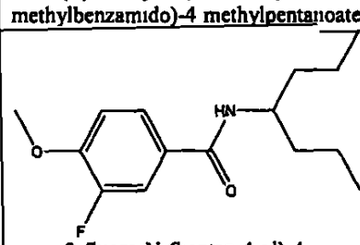
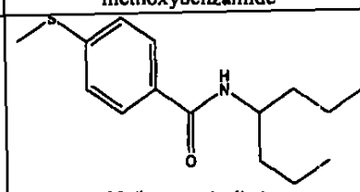
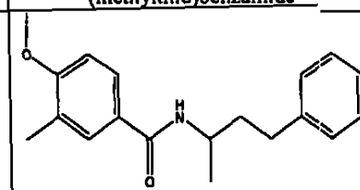
Compound No	Compound	Umami EC_{50} (uM)	Ec_{50} ratio (vs MSG)	@ (uM)
A71	 4 ethyl N (heptan 4-yl)benzamide	0 34		
A72	 4 ethoxy 3 methyl N (5 methylhexan 3 yl)benzamide	0 34		
A73	 (R) methyl 2 (3 methoxy-4 methylbenzamido)-4 methylpentanoate	0 34		
A74	 3 fluoro N (heptan 4 yl) 4 methoxybenzamide	0 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

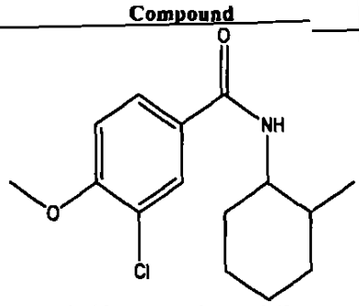
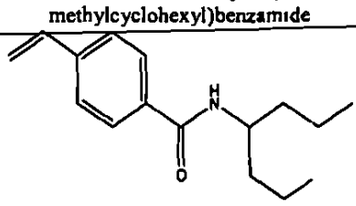
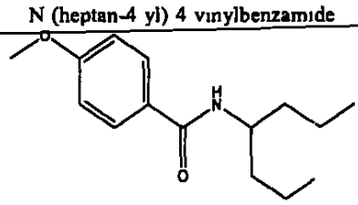
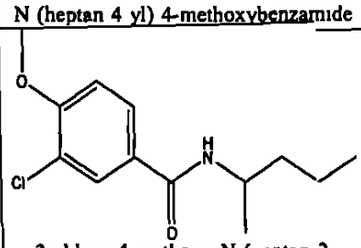
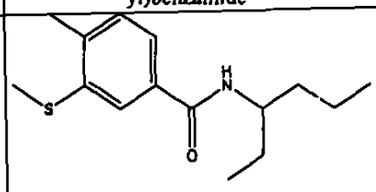
Compound No	Compound	Umami EC_{50} (uM)	Ec_{50} ratio (vs MSG)	@ (uM)
A77	 3 chloro-4 methoxy N (2 methylcyclohexyl)benzamide	0 44		
A78	 c N (heptan-4 yl) 4 vinylbenzamide	0 46	10 22	0 3
A79	 N (heptan 4 yl) 4-methoxybenzamide	0 46		
A80	 3 chloro-4 methoxy N (pentan 2 yl)benzamide	0 47	5 12	0 1
A81	 N (hexan 3 yl) 4 methyl 3 (methylthio)benzamide	0 5		

Table A Umami Amides

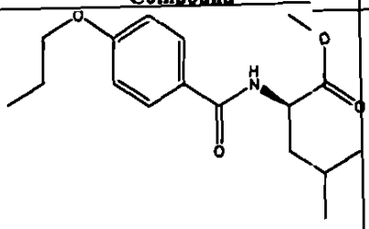
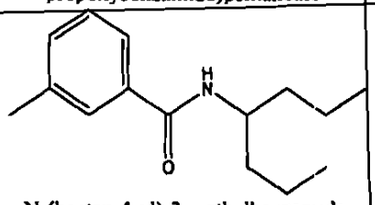
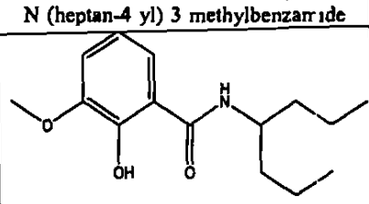
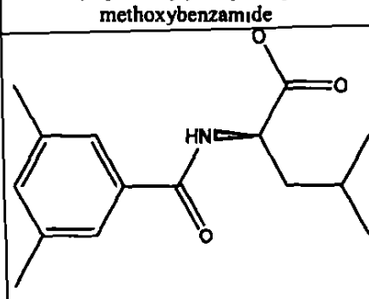
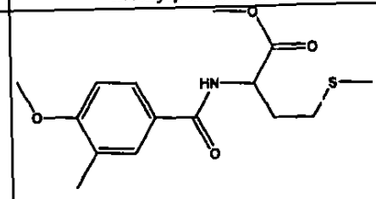
Compound No	Compound	Umami EC_{50} (uM)	Ec_{50} ratio (vs MSG)	@ (uM)
A82	 (R) methyl 4-methyl 2 (4 propoxybenzamido)pentanoate	0 51		
A83	 N (heptan-4 yl) 3 methylbenzamide	0 52		
A84	 N (heptan 4 yl) 2 hydroxy 3 methoxybenzamide	0 53		
A85	 (R)-methyl 2 (3 5 dimethylbenzamido) 4 methylpentanoate	0 53		
A86	 methyl 2 (4 methoxy 3 methylbenzamido) 4-(methylthio)butanoate	0 53		

Table A Umami Amides

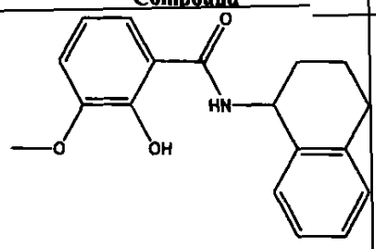
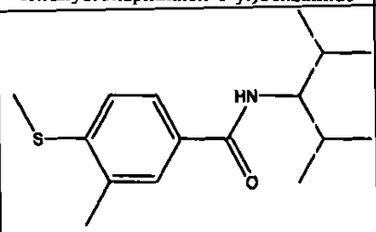
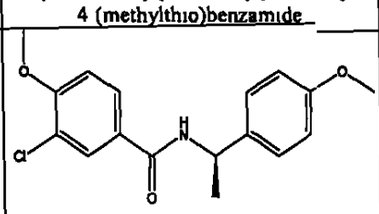
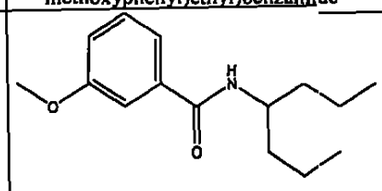
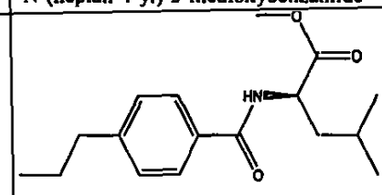
Compound No	Compound	Umami EC_{50} (uM)	Ec_{50} ratio (vs MSG)	@ (uM)
A87	 2 hydroxy 3 methoxy N (1 2 3 4 tetrahydronaphthalen 1 yl)benzamide	0 54	3 8	1
A88	 N (2 4 dimethylpentan 3 yl) 3 methyl 4 (methylthio)benzamide	0 55		
A89	 (R) 3 chloro 4 methoxy N (1 14 methoxyphenyl)ethyl)benzamide	0 6	2 85	1
A90	 N (heptan 4-yl) 3 methoxybenzamide	0 61		
A91	 (R) methyl 4 methyl 2 (4 propylbenzamido)pentanoate	0 62		

Table A Umami Amides

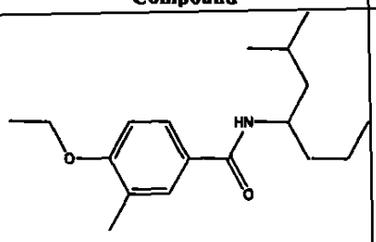
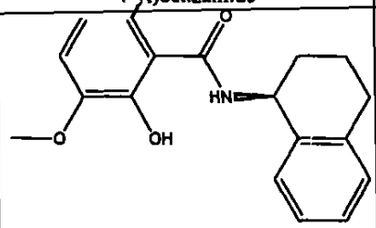
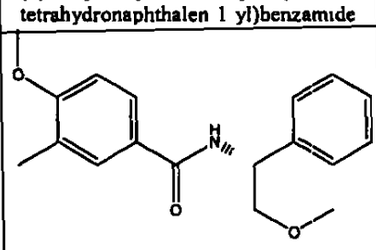
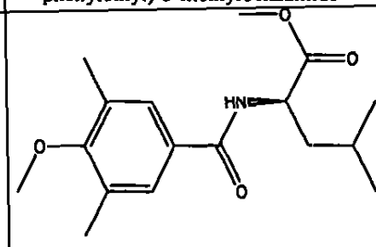
Compound No	Compound	Umami EC_{50} (uM)	Ec_{50} ratio (vs MSG)	@ (uM)
A92	 4 ethoxy 3 methyl N (2 methylheptan 4-yl)benzamide	0 65		
A93	 (S) 2 hydroxy 3 methoxy N (1 , 3 4 tetrahydronaphthalen 1 yl)benzamide	0 7	5 7	1
A94	 (R) 4 methoxy N (2 methoxy 1 phenylethyl) 3 methylbenzamide	0 72		
A95	 (R) methyl 2 (4-methoxy 3,› dimethylbenzamido) 4 methylpentanoate	0 74		

Table A Umami Amides

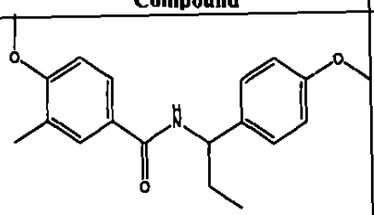
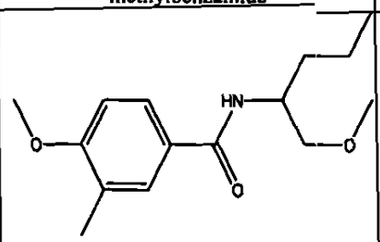
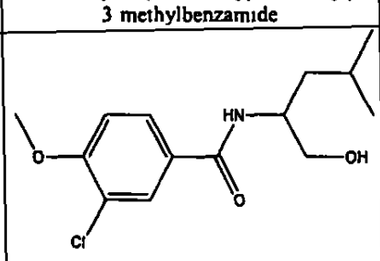
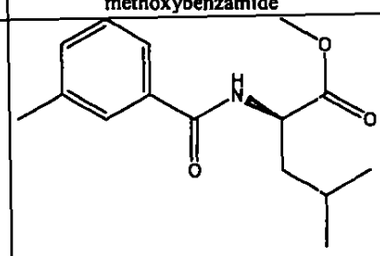
Compound No	Compound	Umami EC_{50} (uM)	Ec_{50} ratio (vs MSG)	@ (uM)
A96	 4 methoxy N (1 (4 methoxyphenyl)propyl) 3 methylbenzamide	0 76		
A97	 4 methoxy N (1 methoxypentan 2-yl) 3 methylbenzamide	0 85		
A98	 3 chloro-N (1 hydroxy 4 methylpentan 2 yl)-4 methoxybenzamide	0 88		
A99	 (R) methyl 4 methyl 2 (3 methylbenzamido)pentanoat	0 89		

Table A Umami Amides

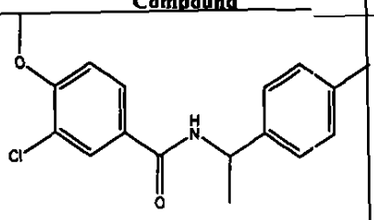
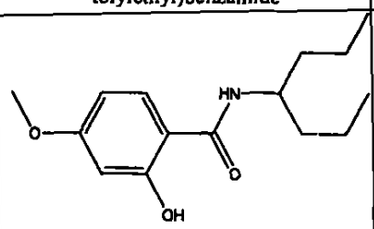
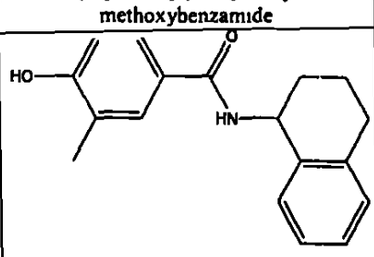
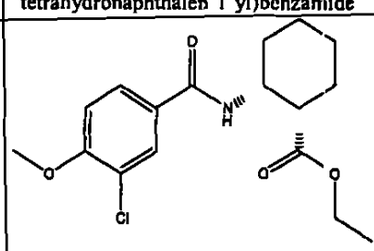
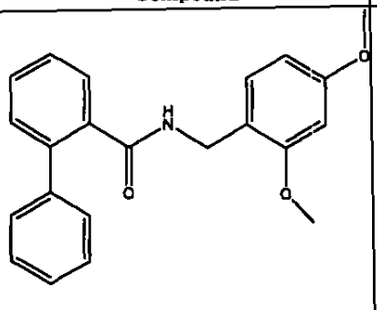
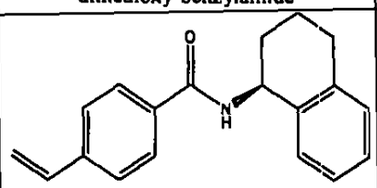
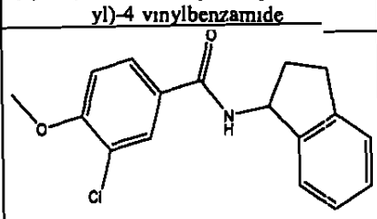
Compound No	Compound	Umami EC_{50} (uM)	Ec_{50} ratio (vs MSG)	@ (uM)
A100	 3 chloro-4 methoxy N (1 p tolylethyl)benzamide	1 1		
A101	 N (heptan 4 yl) 2 hydroxy-4 methoxybenzamide	1 16	7 62	1
A102	 4 hydroxy 3 methyl N (1 2 3 4 tetrahydronaphthalen 1 yl)benzamide	1 32	9 49	1
A103	 (1S 2R) ethyl 2 (3 chloro 4 methoxybenzamido) cyclohexanecarboxylate	1 36		

Table A Umami Amides

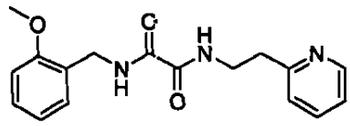
Compound No	Compound	Umami EC_{50} (uM)	Ec_{50} ratio (vs MSG)	@ (uM)
A104	 Biphenyl 2 carboxylic acid 2 4 dimethoxy benzylamide	1 37		
A105	 (S) N (1 2 3 4 tetrahydronaphthalen 1 yl)-4 vinylbenzamide	1 38	2 79	1
A106	 3 chloro-N (2 3 dihydro 1H inden 1 yl)-4 methoxybenzamide	1 39	4 01	0 3

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.



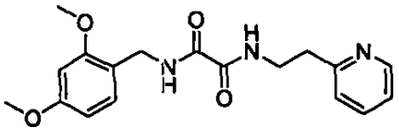
2-Methoxybenzyl amine (5 mmol) was mixed with triethylamine (2 equiv) in anhydrous Dioxane Ethyl oxalyl chloride (1 equiv) was added and the mixture was shaken

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 ($CDCl_3$) δ 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 in EC_{50} ratio of 18 85

Example 123

N-(2 4-Dimethoxy-benzyl)-N'-(2-pyridin-2-yl-ethyl)-oxalamide

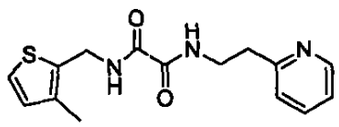


Prepared in a similar manner to example 122 using 2,4-dimethoxybenzyl amine, ethyl oxalyl chloride and 2-(2-pyridinyl)ethyl amine Yield 72%, m p 123-124 °C, m/e = 344 [M+1], ^1H NMR ($CDCl_3$) δ 3 02 (t, 2H), 3 73 (dd, 2H), 3 78 (s, 3H), 3 82 (s, 3H) 4 38 (d, 2H) 6 40 (dd, 1H), 6 44 (d, 1H), 7 14 (m, 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-

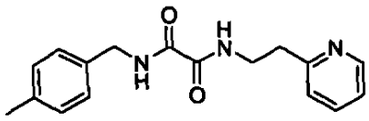
124 °C, m/e = 304 [M+1], ^{1}H NMR (*DMSO-d_6*) δ 2 19 (s, 3H), 2 92-2 95 (t, 2H), 3 48-3 52 (dd, 2H), 4 37-4 38 (d, 2H), 6 79-6 80 (d, 1H), 7 20-7 27 (m, 3H), 7 67-7 71 (dt, 1H), 8 48-8 49 (d, 1H), 8 87-8 89 (t 1H), 9 25-9 28 (t, 1H)

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

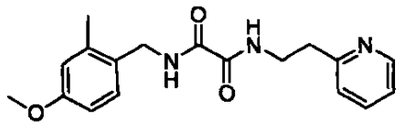


4-Methylbenzyl amine (1 mmol) was allowed to react with ethyl oxalyl chloride (1 equiv) in the presence of triethyl amine (2 equiv) in acetonitrile at room temperature for 0 5 – 1 hour Then 2-(2-pyridinyl)ethyl amine (1 equiv) was added and the suspension was heated at 160 °C in a microwave reactor for 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

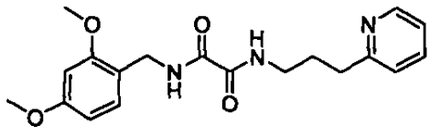


Prepared in a similar manner to example 122 using 2-methyl-4-methoxybenzyl amine, ethyl oxalyl chloride and 2-(2-pyridinyl)ethyl amine Yield 51%, m p 133-134 °C, m/e = 328 [M+1], ^{1}H NMR ($CDCl_3$) δ 2 29 (s 3H), 3 04 (t, 2H), 3 74-3 77 (m, 2H) 3 78 (s, 3H) 4 40 (d, 2H), 6 69-6 73 (m, 2H), 7 13-7 18 (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

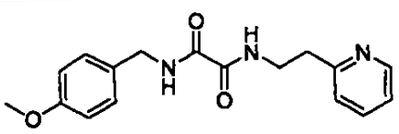


Prepared in a similar manner to example 125 using 2,4-dimethoxybenzyl amine ethyl oxalyl chloride and 3-(2-pyridinyl)propyl amine Yield 60%, m/e = 358 [M+1], ^{1}H NMR ($CDCl_3$) δ 1 99-2 04 (m, 2H), 2 84 (t, 2H), 3 36 (dd, 2H), 3 79 (s, 3H), 3 82 (s, 3H) 4 60 (d, 2H), 6 41-6 45 (m, 2H), 7 10-7 17 (m, 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

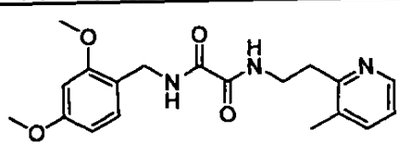


Prepared in a similar manner to example 125 using 4-methoxybenzyl amine, ethyl oxalyl chloride and 2-(2-pyridinyl)ethyl amine Yield 50%, m p 156-158 °C, ^{1}H NMR 3 05 (t, 3H), 3 72-3 77 (m, 2H), 3 79 (s, 3H), 4 40 (d, 2H), 6 86 (d, 2H), 7 16-7 22 (m, 4H), 7 65-7 69 (m, 3H), 8 15 (b 1H), 8 62 (d 1H)

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)

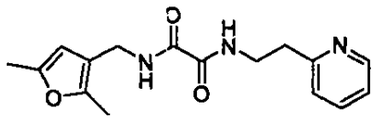
a 2-(3-Methylpyridin-2-yl)ethyl amine To a solution of 2-(3-methylpyridine-2-yl)acetonitrile (example 129b) (95 mg, 0 72 mmol) in THF (0 5 mL) was added 1 M BH_3 THF (2 2 mL, 2 2 mmol) dropwise at room temperature The resulting mixture was heated in a microwave reactor at 130 °C for 7 min Then, 6 N aqueous 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



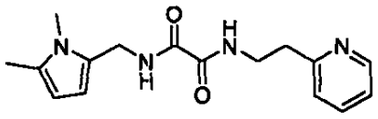
Prepared in a similar manner to example 122 using 2,5-dimethyl-furan-3-ylmethylamine, ethyl oxalyl chloride and 2-(2-pyridinyl)ethyl amine Yield 51%, m p 112-115 °C m/e = 302 [M+1] ^{1}H NMR (*DMSO-d_6*) δ 2 14 (s, 3H), 2 18 (s, 3H), 2 91-2 94 (t,

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

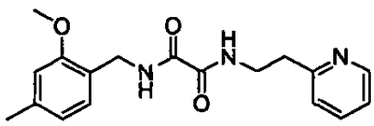


Prepared in a similar manner to example 122 using 1,5-dimethyl-1H-pyrrol-2-ylmethyl amine, ethyl oxalyl chloride and 2-(2-pyridinyl)ethyl amine Yield 25%, m p 147-149 °C, m/e = 301 [M+1], ^{1}H NMR (*DMSO-d_6*) δ 2 11 (s, 3H), 2 92-2 95 (t, 2H), 3 38 (s, 3H), 3 48-3 52 (q, 2H), 4 24-4 25 (d, 2H), 5 64-5 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

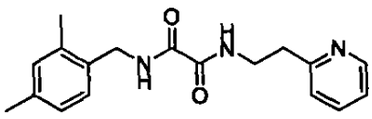
saturated with K_2CO_3 The product was extracted with $CHCl_3$ (6x5 mL) The organic extracts were dried (1 1 K_2CO_3/Na_2SO_4), filtered, concentrated in vacuo to afford 180 mg of (2-methoxy-4- methylphenyl)methanamine which was used directly in Example 11

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



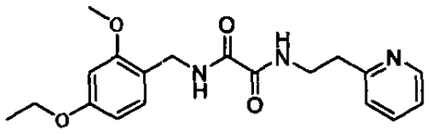
Prepared in a similar manner to example 125 using (2,4-dimethylphenyl)methanamine (example 133a), ethyl oxalyl chloride, and 2-(2-pyridinyl)ethyl amine, yield 60%, m p 148-149 °C, m/e= 312 [M+1], ^1H NMR ($CDCl_3$) 2 28 (s, 3H), 2 30 (s, 3H), 3 05 (t, 2H), 3 76 (dd, 2H), 4 43 (d, 2H), 6 99 (m, 2H), 7 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 uM

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)

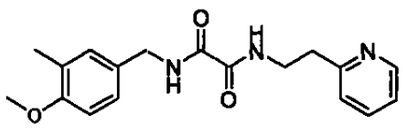
b 4-Ethoxy-2-methoxybenzaldehyde To a solution of 4-hydroxy-2-methoxybenzaldehyde (1 0 g, 6 57 mmol) in 10 ml of acetone, was added potassium carbonate (0 91 g, 6 57 mmol) and iodoethane (1 6 ml, 19 71 mmol), the reaction mixture was stirred at r t over night Acetone was removed on a rotary evaporator, 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 uM

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Example 135

N-(4-Methoxy-3-methylbenzyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide



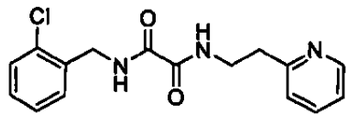
Prepared in a similar manner to example 125 using (4-methoxy-3-methylphenyl)-methanamine (example 135a), ethyl oxalyl chloride, and 2-(2-pyridinyl)ethyl amine, yield 12%, m p 145-147 °C, m/e= 328 [M+1], ^{1}H NMR ($CDCl_3$) 2 19 (s, 3H), 3 04 (t, 2H) 3 76 (dd, 2H), 3 81 (s, 3H), 4 37 (d, 2H), 6 76 (d, 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 uM

Example 136

N-(2-chlorobenzyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide

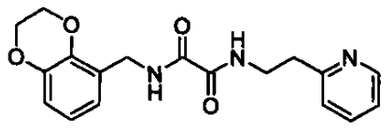


Prepared in a similar manner to example 125 using (2-chlorophenyl)methanamine, ethyl oxalyl chloride, and 2-(2-pyridinyl)ethyl amine yield 45%, *m/e* = 318 [M+1]

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0 01 uM

Example 137

N-((2 3-dihydrobenzo[b][1 4]dioxin-5-yl)methyl)-N'-(2-(pyridin-2-yl)ethyl) oxalamide



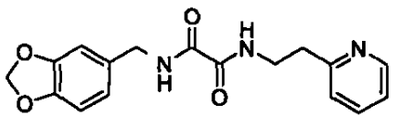
Prepared in a similar manner to example 122 using (2,3-dihydrobenzo[b][1,4] dioxin-5-yl)methanamine, ethyl oxalyl chloride, and 2-(2-pyridinyl)ethyl amine, yield 50% *m/e* = 342 [M+1]

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0 3 uM

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Example 138

N-(benzo[d][1,3]dioxol-5-ylmethyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide

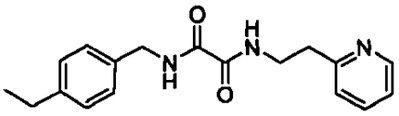


Prepared in a similar manner to example 125 using benzo[d][1,3]dioxol-5-ylmethanamine, ethyl oxalyl chloride, and 2-(2-pyridinyl)ethyl amine, yield 35%, *m/e* = 328 [M+1]

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0 5 uM

Example 139

N-(4-Ethylbenzyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide

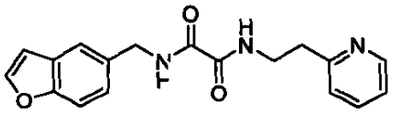


Prepared in a similar manner to example 125 using 4-ethylbenzylamine, ethyl oxalyl chloride, and 2-(2-pyridinyl)ethyl amine, yield 38%, *m/e* = 312 [M+1]

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0 79 uM

Example 140

N-(Benzofuran-5-ylmethyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide

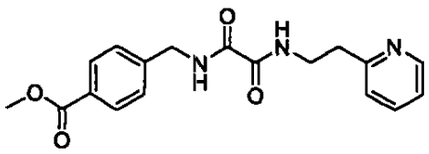


Prepared in a similar manner to example 125 using benzofuran-5-ylmethylamine, ethyl oxalyl chloride, and 2-(2-pyridinyl)ethyl amine yield 64%, *m/e* = 324 [M+1]

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 1 78 uM

Example 141

N-((4-Methoxycarbonylphenyl)methyl) N'-(2-(pyridin-2-yl)ethyl)oxalamide

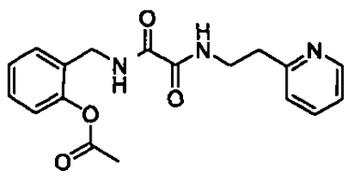


Prepared in a similar manner to example 122 using 4-methoxycarbonylphenyl methylamine, ethyl oxalyl chloride, and 2-(2-pyridinyl)ethyl amine, yield 52%, *m/e* = 342 [M+1]

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 3 63 uM

Example 142

N-((2-Carbamoylphenyl)methyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide

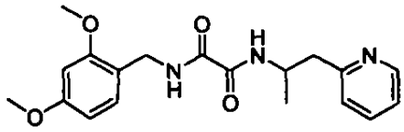


Prepared in a similar manner to example 122 using 2-carbamoylphenyl methylamine, ethyl oxalyl chloride, and 2-(2-pyridinyl)ethyl amine, yield 48% *m/e* = 342 [M+1]

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 8 5 uM

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]

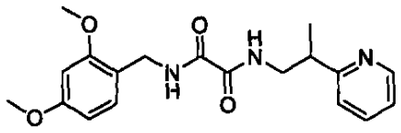
b 2-(pyridine-2-yl)propanenitrile 5 mmol of 2-(pyridine-2-yl)acetonitrile was dissolved in 8 ml anhydrous THF and placed in an ice bath Potassium t-butoxide (1 equiv) was added and reaction was stirred for 30 minutes Methyl iodide (1 equiv) was dissolved in 5 mL anhydrous THF and added slowly over 30 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 uM

Example 144

N-(2 4-Dimethoxybenzyl)-N'-(2-(pyridin-2-yl)propyl)oxalamide



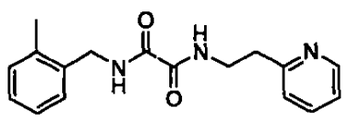
Prepared in a similar manner to example 125 using 2,4-dimethoxybenzylamine, ethyl oxalyl chloride, and 2-(pyridin-2-yl)propylamine (example 144a), yield 35%, *m/e* = 357 [M+1]

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 uM

Example 145

N-(2-Methoxybenzyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide

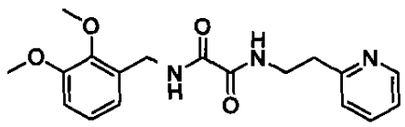


Prepared in a similar manner to example 125 using 2-methylbenzylamine, ethyl oxalyl chloride, and 2-(pyridin-2-yl)ethylamine, *m/e* = 298 [M+1], ^{1}H NMR ($CDCl_3$) δ 2 32 (s, 3H), 3 11 (t, 2H), 3 78 (dt, 2H), 4 46 (d, 2H), 7 15-7 26 (m, 6H), 7 50-7 55 (m, 1H), 7 62-7 67 (m 1H), 8 12-8 15 (m, 1H), 8 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 uM

Example 146

N-(2 3-Dimethoxybenzyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide

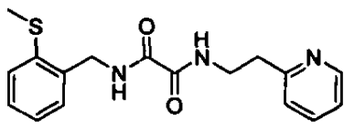


Prepared in a similar manner to example 125 using 2,3-dimethoxybenzylamine, ethyl oxalyl chloride, and 2-(pyridin-2-yl)ethylamine *m/e* = 343 [M+1]

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0 69 uM

Example 147

N-(2-(Methylthio)benzyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide

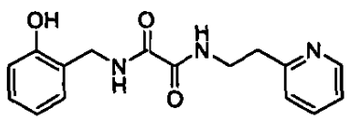


Prepared in a similar manner to example 125 using 2-methylthiobenzylamine, ethyl oxalyl chloride, and 2-(pyridin-2-yl)ethylamine, *m/e* = 330 [M+1], ^{1}H NMR ($CDCl_3$) δ 2 49 (s, 3H), 3 08 (t, 2H), 3 77 (dt, 2H), 4 55 (d, 2H), 7 11-7 14 (m, 1H), 7 15-7 20 (m, 2H) 7 22-7 27 (m, 3H), 7 62 (t, 1H), 7 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 uM

Example 148

N-(2-Hydroxybenzyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide

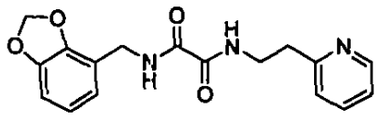


Prepared in a similar manner to example 125 using 2-hydroxybenzylamine, ethyl oxalyl chloride, and 2-(pyridin-2-yl)ethylamine *m/e* = 300 [M+1]

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 3 11 uM

Example 149

N-(Benzo[d][1 3]dioxol-4-ylmethyl) N'-(2-(pyridin-2-yl)ethyl)oxalamide



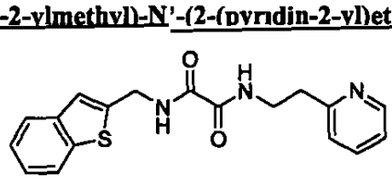
Prepared in a similar manner to example 125 using benzo[d][1,3]dioxol-4-ylmethyl amine (example 149a), ethyl oxalyl chloride, and 2-(pyridin-2-yl)ethyl amine, yield 12%, *m/e* = 328 [M+1], ^{1}H NMR ($CDCl_3$) δ 3 12 (m, 2H), 3 77-3 80 (m, 2H), 4 46-4 47 (d, 2H), 5 98 (s, 2H), 6 74-6 79 (m, 3H), 7 24 (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 uM

Example 150

N-(Benzo[b]thiophen-2-ylmethyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide

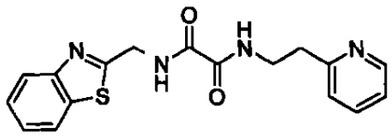


Prepared in a similar manner to example 125 using benzo[b]thiophen-2-ylmethanamine, ethyl oxalyl chloride, and 2-(pyridin-2-yl)ethyl amine, yield 32%, *m/e* = 240 [M+1], ^{1}H NMR (DMSO-d_6) δ 2 92-2 9› (t, 2H), 3 48-3 53 (m, 2H), 4 55-4 56 (d, 2H), 7 20-7 25 (m, 2H), 7 38-7 41 (m, 2H), 7 50 (s, 1H), 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 uM

Example 151

N-(Benzo[d]thiazol-2-ylmethyl)-N'-(2-(pyridin-2-yl)ethyl)oxalamide

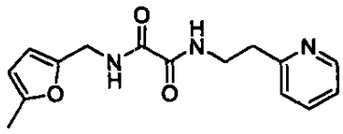


Prepared in a similar manner to example 125 using benzo[d]thiazol-2-ylmethanamine, ethyl oxalyl chloride, and 2-(pyridin-2-yl)ethyl amine, yield 33%, *m/e* = 341 [M+1], ^{1}H NMR (DMSO-d_6) δ 2 95-2 98 (t, 2H), 3 52-3 57 (m, 2H), 4 72-4 73 (d 2H), 7 22-7 24 (m, 1H), 7 25-7 27 (d, 1H), 7 40-7 44 (t, 1H), 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 uM

Example 152.

N-((5-Methylfuran-2-yl)methyl)-N2-(2-(pyridin-2-yl)ethyl)oxalamide

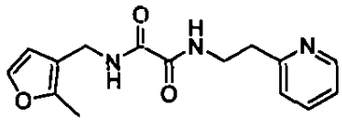


Prepared in a similar manner to example 125 using (5-methylfuran-2-yl)methanamine, ethyl oxalyl chloride, and 2 (pyridin-2-yl)ethyl amine, yield 38%, *m/e* = 288 [M+1], ^{1}H NMR (DMSO-d_6) δ 2 20 (s, 3H), 2 92-2 95 (t, 2H), 3 48-3 52 (m, 2H), 4 23-4 24 (d 2H),5 96-5 97 (d, 1H), 6 06-6 07 (d, 1H), 7 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 uM

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-

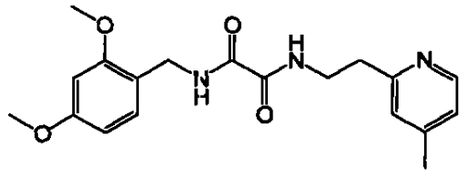
3 52 (q, 2H), 4 05-4 06 (d, 2H), 6 30-6 31 (d, 1H), 7 20-7 25 (m, 2H), 7 38-7 39 (d, 1H), 7 67-7 71 (dt, 1H), 8 48-8 49 (d, 1H), 8 83-8 86 (t, 1H), 9 04-9 07 (t, 1H)

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 uM

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)

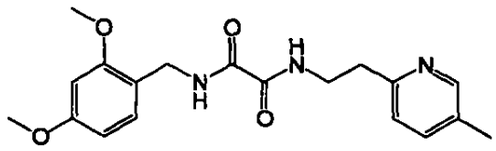
a 2-(4-Methylpyridin-2-yl)ethyl amine Prepared in a similar manner to example 129 using 2-(4-methylpyridin-2-yl)acetonitrile (example 154b), yield 83%, *m/e* = 137 [M+1]

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 uM

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)

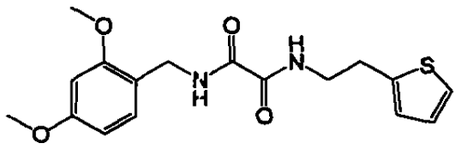
a 2-(5-Methylpyridin-2-yl)ethyl amine Prepared in a similar manner to 129a using 2-(5-methylpyridin-2-yl)acetonitrile (155b), yield 40%, *m/e* = 137 [M+1]

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 uM

Example 156

N-(2 4-Dimethoxybenzyl)-N'-(2-(thiophen-2-yl)ethyl)oxalamide

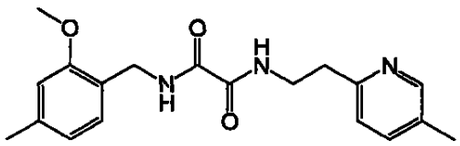


Prepared in a similar manner to Example 122 using 2,4-dimethoxybenzylamine, ethyl oxalyl chloride and 2-(thiophen-2-yl)ethyl amine, yield 72%, *m/e* = 349 [M+1], m p 146-147 °C, ^{1}H NMR ($CDCl_3$) δ 3 06 (t, 2H), 3 58 (q, 2H), 3 80 (s, 3H), 3 83 (s, 3H), 4 40 (d, 2H), 6 41 (dd, 1H), 6 45 (d, 1H), 6 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 uM

Example 157

N^1-(2-methoxy-4-methylbenzyl)-N^2-(2-(5-methylpyridin-2-yl)ethyl)oxalamide



Prepared in a similar manner to Example 125 using 2-methoxy-4-methylbenzylamine (example 132a), ethyl oxalyl chloride and 2-(4-methylpyridin-2-yl)ethylamine (example 155a) Yield 20%, m p 116-117 °C, ^{1}H NMR ($CDCl_3$) δ 2 31 (s, 3H), 2 34 (s, 3H), 3 00 (t, 2H), 3 71 (q, 2H), 3 84 (s, 3H), 4 42 (d, 2H), 6 69 (s, 1H), 6 71 (d, 1H), 7 05 (d, 1H), 7 11 (d, 1H), 7 43 (d, 1H), 7 84 (br s, 1H), 8 04 (br s, 1H), 8 39 (s, 1H), MS(M+H, 342)

The compound had an EC_{50} for activation of a hT1R1/hT1R3 umami receptor expressed in an HEK293 cell line of 0 03 uM

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

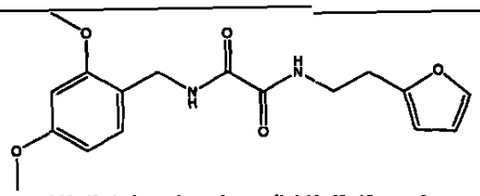
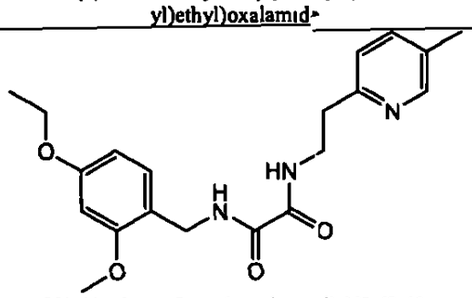
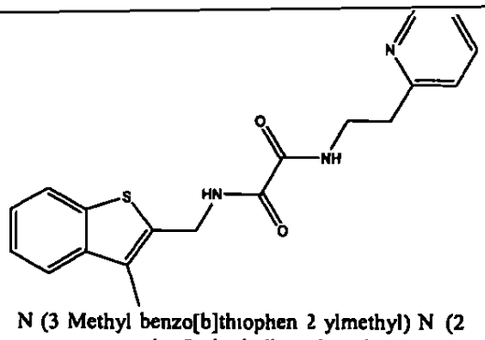
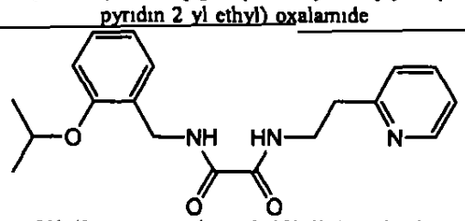
Compound No	Compound	Umami EC_{50} (uM)	Ec_{50} ratio (vs MSG)
B1	 N1 (2,4 dimethoxybenzyl) N2 (2 (furan 2 yl)ethyl)oxalamide	0 18	
B2	 N1 (4 ethoxy 2 methoxybenzyl) N2 (2 (5 methylpyridin 2 yl)ethyl)oxalamide	0 19	

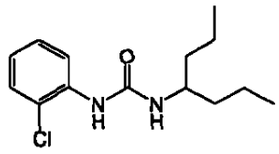
Table B Umami Oxalamides

Compound No	Compound	Umami EC_{50} (uM)	Ec_{50} ratio (vs MSG)
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 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

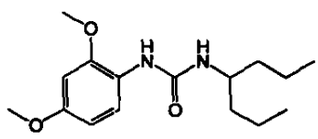


To a solution of heptan-4-amine (0 18 mL, 1 mmol) in CH_2Cl_2 (5 mL) was added 1-chloro-2-isocyanatobenzene (0 12 mL, 1 mmol) at room temperature The reaction mixture was stirred for 2 h A white solid was precipitated out The reaction mixture was filtered The solid was washed with CH_2Cl_2 to afford 1-(4-chlorophenyl)-3-(heptan-4-yl)urea (180 mg, 67%) as a white solid mp 135-136 °C ^1H 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

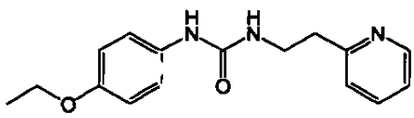


Prepared in a similar manner to example 158 using heptan-4-amine and 1-isocyanato-2,4-dimethoxybenzene Yield 88% mp 172-173 °C ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 93 (t, 6H), 1 45 (m, 8H), 3 82 (s, 3H), 3 83 (m, 1H), 3 84 (s, 1H), 4 32 (br s, 1H), 6 34 (br s, 1H), 6 49 (d, 1H), 6 50 (s, 1H), 7 71 (d, 1H) 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

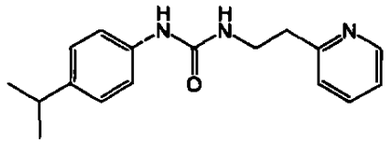


Prepared in a similar manner to example 158 using 2-(pyridine-2-yl)ethanamine and 1-ethoxy-4-isocyanatobenzene Yield 95% mp 163-164 °C ^{1}H NMR (500 MHz, $CDCl_3$) δ 1 43 (t, 3H), 3 03 (t, 2H), 3 68 (t, 2H), 4 03 (q, 2H), 5 69 (br s, 1H), 6 45 (br s, 1H), 6 84 (m, 2H), 7 14 (m, 3H), 7 20 (d, 1H), 7 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

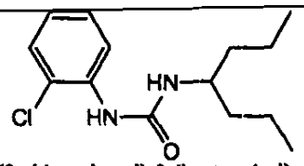
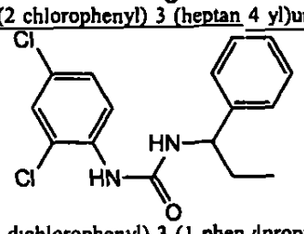
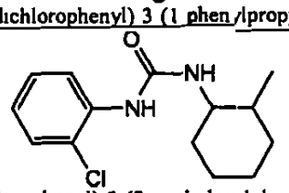
Compound No	IUPAC Name	Umami EC_{50} uM	Ec50 ratio (vs MSG)	Con (uM)
C1	 1 (2 chlorophenyl) 3 (heptan 4 yl)urea	0 37	4 95	1
C2	 1 (2 4 dichlorophenyl) 3 (1 phenylpropyl)urea	0 49	4 52	1
C3	 1 (2 chlorophenyl)-3 (2 methylcyclohexyl)urea	0 52	3 24	3

Table C - Umami Ureas

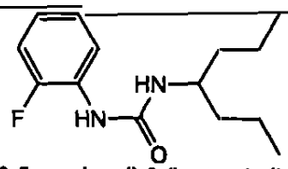
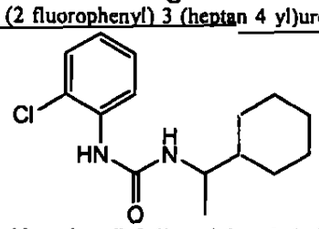
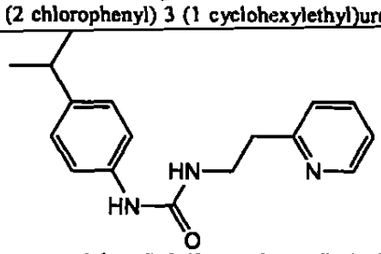
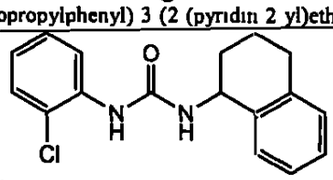
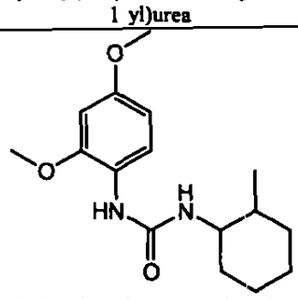
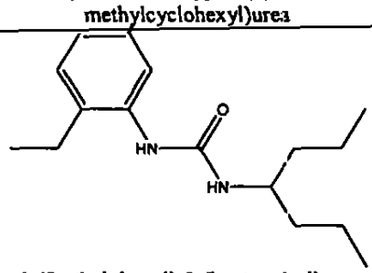
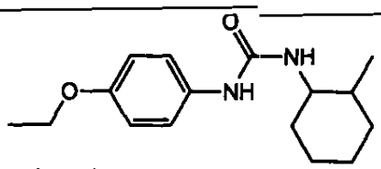
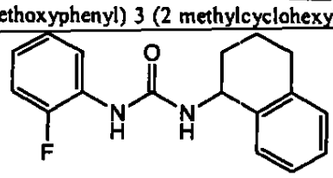
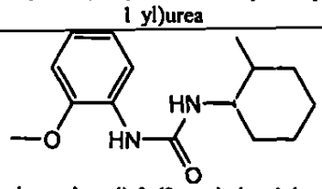
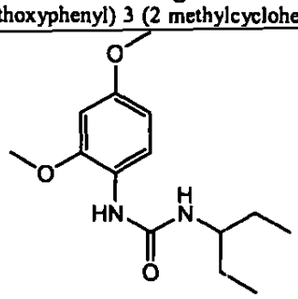
Compound No	IUPAC Name	Umami EC_{50} uM	Ec50 ratio (vs MSG)	Con (uM)
C4	 1 (2 fluorophenyl) 3 (heptan 4 yl)urea	0 79	12 15	3
C5	 1 (2 chlorophenyl) 3 (1 cyclohexylethyl)urea	0 84	9 08	1
C6	 1 (4 isopropylphenyl) 3 (2 (pyridin 2 yl)ethyl)urea	0 98		
C7	 1 (2 chlorophenyl) 3 (1 2 3 4 tetrahydronaphthalen 1 yl)urea	0 99	3 68	1
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		

Table C - Umami Ureas				
Compound No	IUPAC Name	Umami EC_{50} uM	Ec50 ratio (vs MSG)	Con (uM)
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		
C13	 1 (2 4 dimethoxyphenyl) 3 (pentan 3 yl)urea	1 72	11 87	1

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

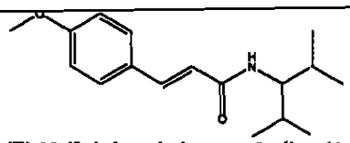
Table D Umami Acrylamides				
Compound No	Compound	Umami EC_{50} (uM)	Ec_{50} ratio (vs. MSG)	@ (uM)
D1	 (E) N (2 4 dimethylpentan 3 yl) (4 methoxyphenyl)acrylamide	0 29	3 46	1

Table D Umami Acrylamides

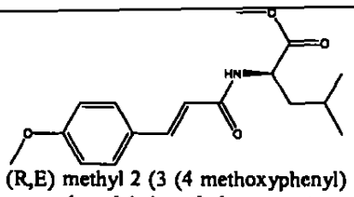
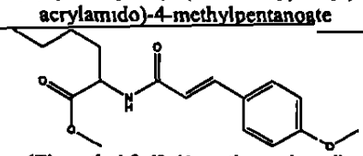
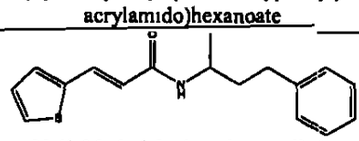
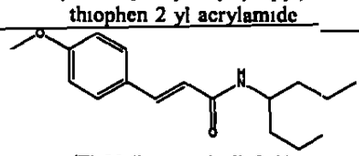
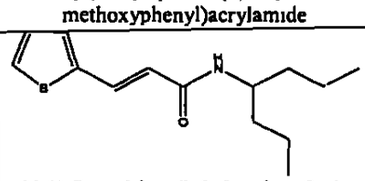
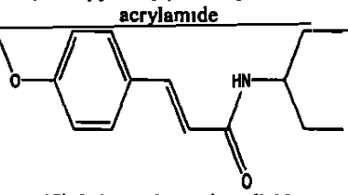
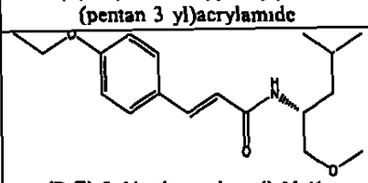
Compound No	Compound	Umami EC_{50} (uM)	Ec_{50} ratio (vs. MSG)	@ (uM)
D2	 (R,E) methyl 2 (3 (4 methoxyphenyl) acrylamido)-4-methylpentanoate	0 32		
D3	 (E) methyl 2 (3 (4 methoxyphenyl) acrylamido)hexanoate	0 63		
D4	 N (1 Methyl 3 phenyl propyl) 1 thiophen 2 yl acrylamide	0 69	9 73	1
D5	 (E) N (heptan 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		

Table D - Umami Acrylamides

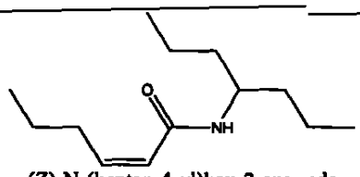
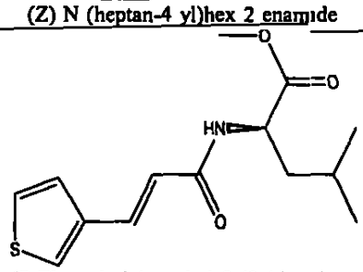
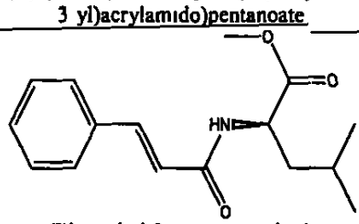
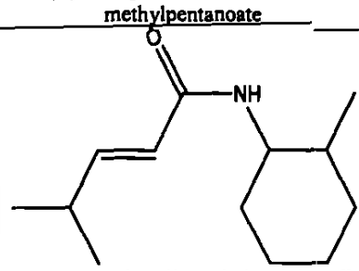
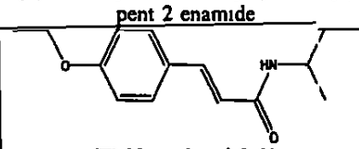
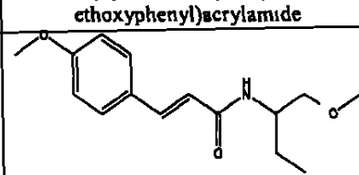
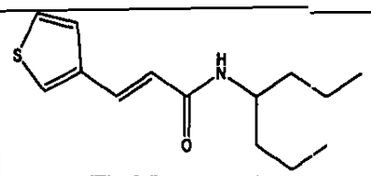
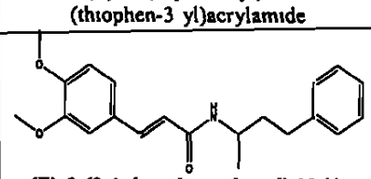
Compound No	Compound	Umami EC_{50} (uM)	Ec_{50} ratio (vs MSG)	@ (uM)
D9	 (Z) N (heptan-4 yl)hex 2 enamide	0 98		
D10	 (R,E) methyl 4 methyl 2 (3 (thiophen 3 yl)acrylamido)pentanoate	1 09		
D11	 (R) methyl 2 cinnamamido-4 methylpentanoate	1 17		
D12	 (E)-4-methyl N (2 methylcyclohexyl) pent 2 enamide	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

Table D Umami Acrylamides

Compound No	Compound	Umami EC_{50} (uM)	Ec_{50} ratio (vs MSG)	@ (uM)
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

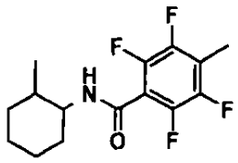
Compound No	Chemical Name	Taste Data
Example 98	(R)-methyl-2 (2,3-dimethylfuran-5-carboxamido)-4-methylpentanoate	12 mM MSG + 10 μM cpd as strong as 12mM MSG + 100 μM IMP
Example 104	4-Methoxy-N-(1-methoxymethyl-3-methyl butyl)-3-methyl-benzamide	12 mM MSG + 3 μM cpd as strong as 12mM MSG + 100 μM IMP
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
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

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



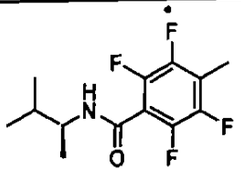
2,3,5,6 –tetrafluoro-*p*-toluic acid acid (4 00 g, 19 22 mmol) , HOBt (5 19 g, 38 44 mmol) and EDCI (4 42 g 23 06 mmol) were mixed in 200 ml of anhydrous DCM and 30 ml of anhydrous DMF The mixture was cooled to 0°C and allowed to stir under Ar for 15 minutes To the mixture was added 2-methylcyclohexanamine (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

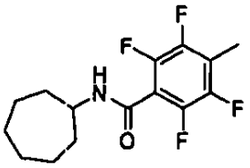


Prepared in a similar manner to Example 162 using (S)-3-methylbutan-2-amine and 2,3,5,6 –tetrafluoro-*p*-toluic acid acid (93%) ^1H NMR ($CDCl_3$) δ 0 98 (d, J= 6 9 Hz, 6H) 1 18 (d, J= 6 8 Hz, 3H), 2 29 (m, 3H), 4 09 (m, 1H), 5 72 (bs, 1H) MS (304 1 M+H) m p 146-147 °C

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

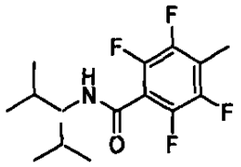


Prepared in a similar manner to Example 162 using cycloheptylamine and 2,3,5,6 – tetrafluoro-*p*-toluic acid (94%) ^1H NMR ($CDCl_3$) δ 1 53 (m, 6H), 1 57 (m, 4H), 2 03 (m, 2H) 2 28 (m, 3H), 4 17 (m, 1H), 5 85 (bs, 1H) MS (304 1, M+H) m p 164-165 °C

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

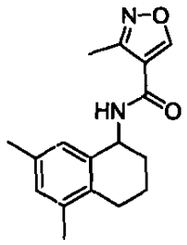


Prepared in a similar manner to Example 162 using 2,4-dimethylpentan-3-amine and 2,3,5,6 –tetrafluoro-*p*-toluic acid (90%) ^{1}H NMR ($CDCl_3$) δ 0 91 (d, J = 6 7 Hz, 6H), 1 00 (d, J = 6 8 Hz, 6H), 1 85 (m, 2H), 2 29 (m, 3H) 3 82 (m, 1H), 5 52 (bd, 1H) MS (306 1, M+H) m p 184-187 °C

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

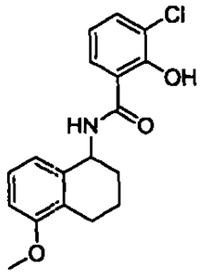
added 5,7-dimethyl-3,4-dihydronaphthalen-1(2H)-one oxime (example 166b) (420 mg, 2 22 mmol), and the mixture was stirred under a balloon of H_2 for 20 hr Upon completion, the reaction was filtered through celite, the filtrate was concentrated *in vacuo*, diluted with EtOAC, washed with water and brine, 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,

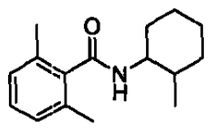
121 1, 125 9, 126 2, 126 4, 133 8, 137 3, 156 7, 156 8, 168 7 MS(M+H, 332) Mp 175-176 °C

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

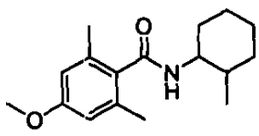


Prepared in a similar manner to Example 162 using 2,6-dimethylbenzoic acid and 2-methylcyclohexylamine Yield 59% ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 88-0 94 (3H, dd), 1 14-1 89 (9H, m), 2 21-2 22 (6H, d), 3 39-3,45 (1H, m) 7 02-7 03 (2H,d), 7 12-7 15 (1H, t), 8 11-8 13 (1H, d) MS(M+H, 246 2)

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

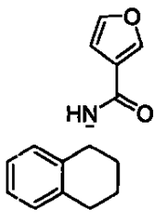
min and the mixture was stirred for 15 more min at -78°C Than small pieces of dry ice were added and the mixture was stirred 20 min at -78°C Then the cooling was removed and the mixture was stirred as long as evolution of carbon dioxide continued Then the mixture was poured over ice (100 ml) and acidified 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



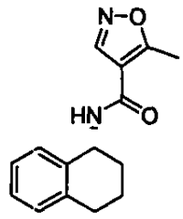
To a solution of furan-3-carboxylic acid (100 mg, 0 68 mmol), HOBt (240 mg, 1 78 mmol) and EDCI HCl (196 mg, 1 03 mmol) in CH_2Cl_2 (8 mL) and DMF (1 5 mL) at 0 °C, was added (*R*)-1,2,3,4-tetrahydronaphthalen-1-amine (160 μL, 1 06 mmol) The reaction was stirred at rt for 24h, after which CH_2Cl_2 was 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

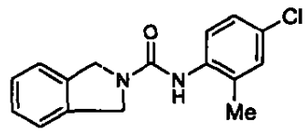


Prepared in a similar manner to Example 170 using 5-methylisoxazole-4-carboxylic acid Purified by preparative TLC (5 1 Hex EtOAc) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1 80 (m, 3H), 2 12 (m, 1H), 2 74 (s, 3H), 2 85 (m, 2H), 5 35 (m, 1H), 5 89 (br d, 1H, J = 7 75 Hz), 7 10 (m, 1H), 7 18 (m, 2H), 7 32 (m, 1H), 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

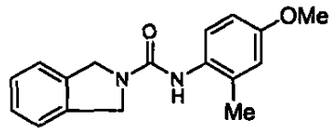


To a solution of isoindoline (238 mg, 2 0 mmol) in dry 1,4-dioxane (10 mL) was added 4-chloro-2-methylphenyl isocyanate (335 mg, 2 0 mmol) under argon at room temperature The reaction mixture was then stirred at RT overnight The solvent was evaporated under reduced pressure, and the residue was purified 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

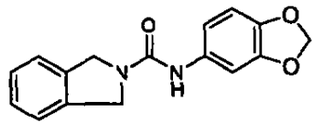


To a solution of isoindoline (576 mg, 4 0 mmol) in dry 1,4-dioxane (20 mL) was added 4-methoxy-2-methylphenyl isocyanate (815 mg, 5 0 mmol) under argon at room temperature The reaction mixture was then stirred at RT overnight The solvent was evaporated under reduced pressure, and the residue was purified 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



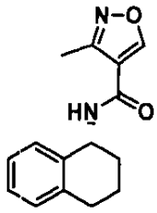
To a solution of 3,4-(methylenedioxy)aniline (150 mg, 1 09 mmol) in dry DCM (4 mL) was added dropwise phenyl chloroformate (0 138 ml, 1 09 mmol) and triethylamine (0 153 ml, 1 09 mmol) After the reaction mixture was stirred at r t for 8 hr , isoindoline (0 123 ml, 1 09 mmol) and triethylamine (0 153 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 acti /ation 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 HOB- (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

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

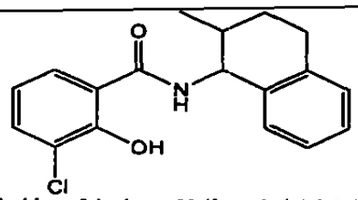
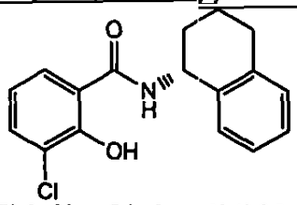
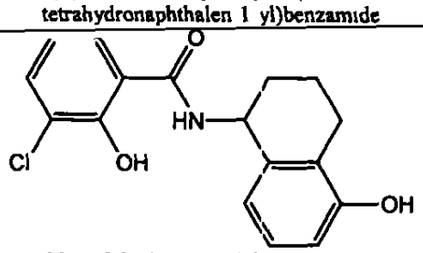
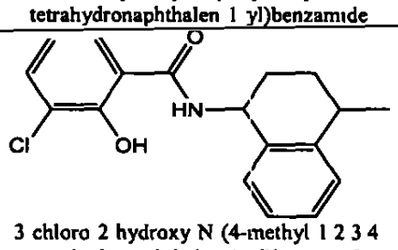
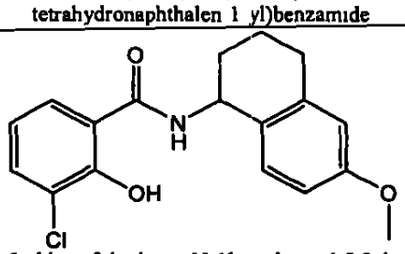
Compound No	Compound	Sweet EC_{50} uM	Umami EC_{50} uM	Umami EC_{50} ratio
E1	 3 chloro 2 hydroxy N (2 methyl 1 2 3 4 tetrahydronaphthalen 1 yl)benzamide	0 19		
E2	 (R)-3 chloro-2 hydroxy N (1 2 3 4- tetrahydronaphthalen 1 yl)benzamide	0 65		
E3	 3 chloro-2 hydroxy N (5 hydroxy 1 2 3 4 tetrahydronaphthalen 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 EnhancerAmides

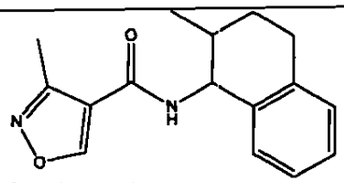
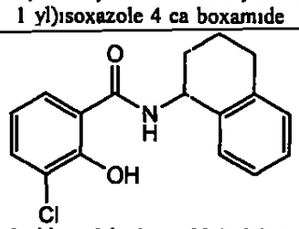
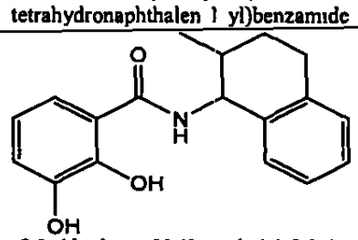
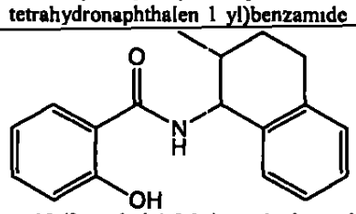
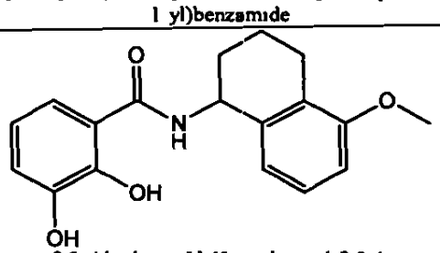
Compound No	Compound	Sweet EC_{50} uM	Umami EC_{50} uM	Umami EC_{50} ratio
E6	 3 methyl N (2 methyl 1 2 3 4 etrahydronaphthalen 1 yl)ısoxazole 4 ca boxamıde	1 48		
E7	 3 chloro 2 hydroxy N (1 2 3 4 tetrahydronaphthalen 1 yl)benzamıde	1 81		4 04
E8	 2 3 dıhydroxy N (2 rnethyl 1 2 3 4- tetrahydronaphthalen 1 yl)benzamıde	1 98		
E9	 2 hydroxy N (2 methyl 1 2 3 4 tetrahydronaphthalen 1 yl)benzamıde	2 36		
E10	 2 3 dıhydroxy N (5 rnethoxy 1 2 3 4 tetrahydronaphthalen 1 yl)benzamıde	2 44		

Table E - Sweet EnhancerAmides

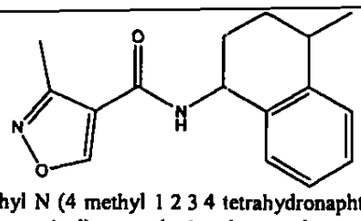
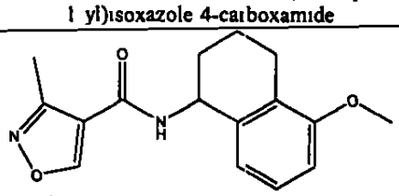
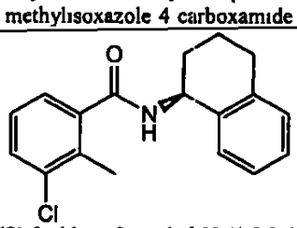
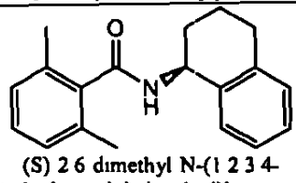
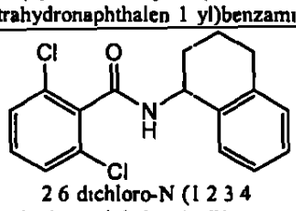
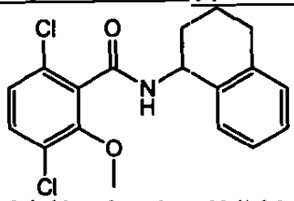
Compound No	Compound	Sweet EC_{50} uM	Umami EC_{50} uM	Umami EC_{50} ratio
E11	 3 methyl N (4 methyl 1 2 3 4 tetrahydronaphthalen 1 yl)isoxazole 4-carboxamide	2 46		
E12	 N (5 methoxy 1 2 3 4 tetrahydronaphthalen 1 yl)-3 methylisoxazole 4 carboxamide	2 85		
E13	 (S) 3 chloro 2 methyl N (1 2 3 4 tetrahydronaphthalen 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

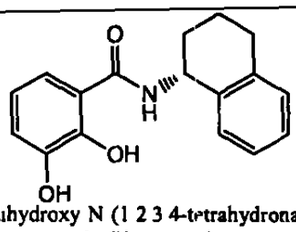
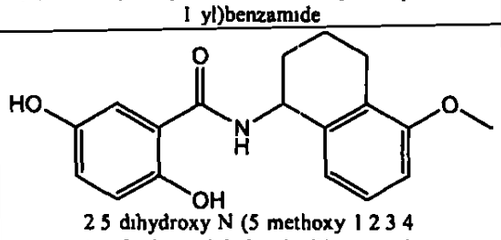
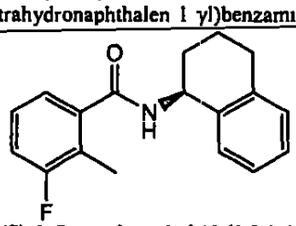
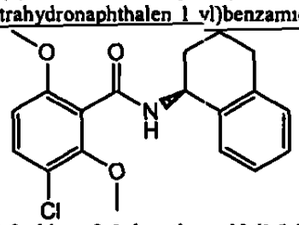
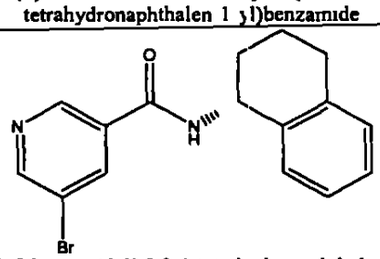
Compound No	Compound	Sweet EC_{50} uM	Umami EC_{50} uM	Umami EC_{50} ratio
E17	 (R) 2 3 dihydroxy N (1 2 3 4-tetrahydronaphthalen 1 yl)benzamide	3 13		
E18	 2 5 dihydroxy N (5 methoxy 1 2 3 4 tetrahydronaphthalen 1 yl)benzamide	3 38		
E19	 (S) 3 fluoro-2 methyl N (1 2 3 4-tetrahydronaphthalen 1 yl)benzamide	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		

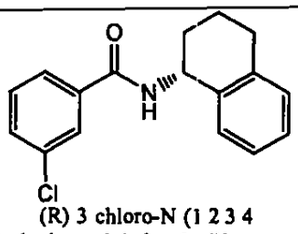
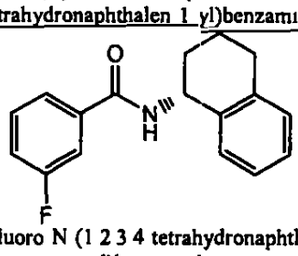
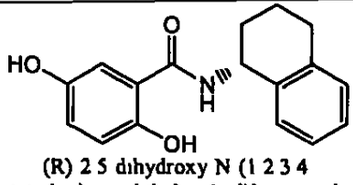
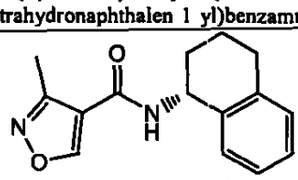
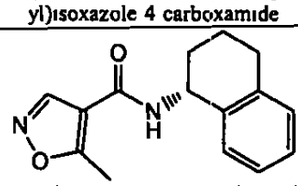
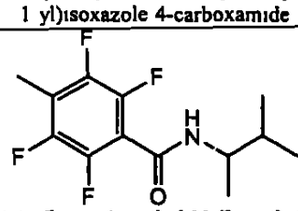
Table E - Sweet EnhancerAmides				
Compound No	**Compound**	**Sweet EC_{50} uM**	**Umami EC_{50} uM**	**Umami EC_{50} ratio**
E22	 (R) 3 chloro-N (1 2 3 4 tetrahydronaphthalen 1 yl)benzamide	4 52		
E23	 (R) 3 fluoro N (1 2 3 4 tetrahydronaphthalen 1 yl)benzamide	4 86		
E24	 (R) 2 5 dihydroxy N (1 2 3 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

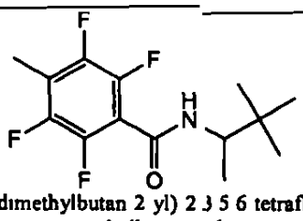
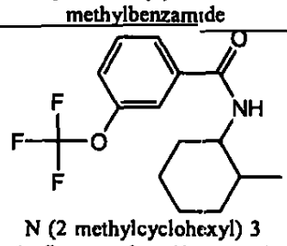
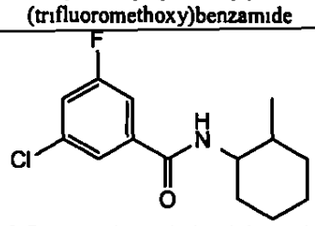
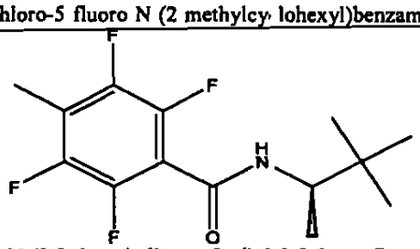
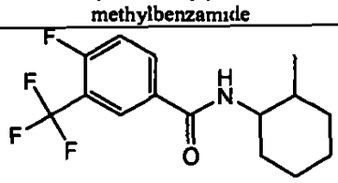
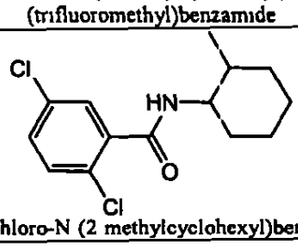
Compound No	Compound	Sweet EC_{50} uM	Umami EC_{50} uM	Umami EC_{50} ratio
E28	 N (3 3 dimethylbutan 2 yl) 2 3 5 6 tetrafluoro 4 methylbenzamide	0 21		
E29	 N (2 methylcyclohexyl) 3 (trifluoromethoxy)benzamide	0 42		
E30	 3 chloro-5 fluoro N (2 methylcy· lohexyl)benzamide	0 45		
E31	 (R) N (3 3 dimethylbutan 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		

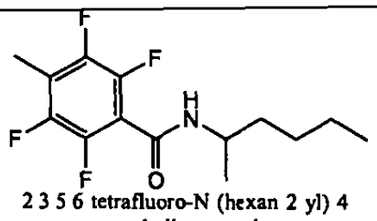
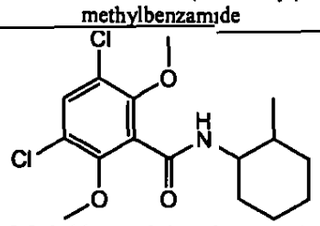
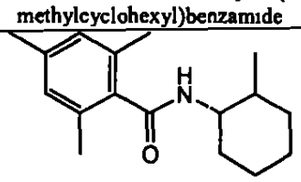
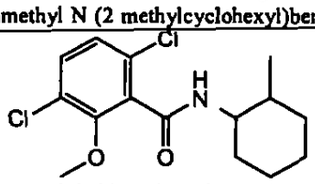
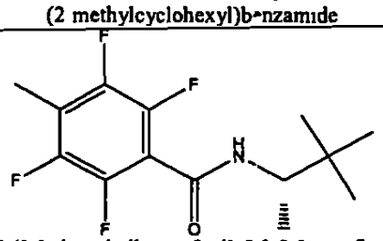
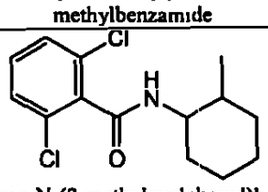
Table E Sweet EnhancerAmides				
Compound No	Compound	Sweet EC_{50} uM	Umami EC_{50} uM	Umami EC_{50} ratio
E34	 2 3 5 6 tetrafluoro-N (hexan 2 yl) 4 methylbenzamide	0 71		
E35	 3 5 dichloro 2 6 dimethoxy N (2 methylcyclohexyl)benzamide	0 71		
E36	 2 4 6 trimethyl N (2 methylcyclohexyl)benzamide	0 72		
E37	 3 6 dichloro-2 methoxy N (2 methylcyclohexyl)b-nzamide	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 Enhancer Amides

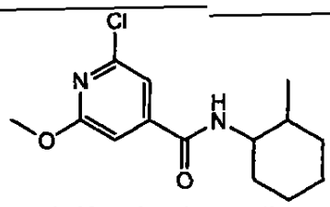
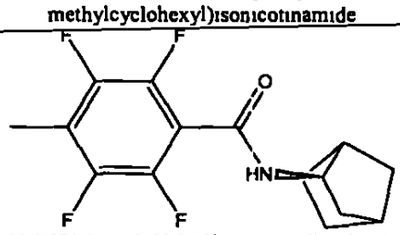
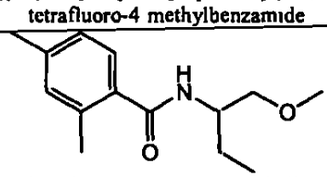
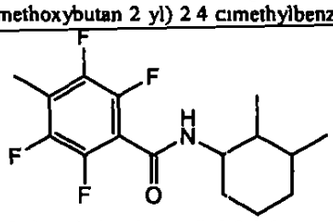
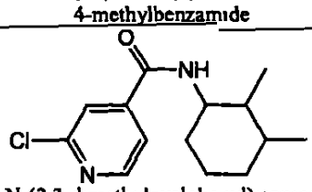
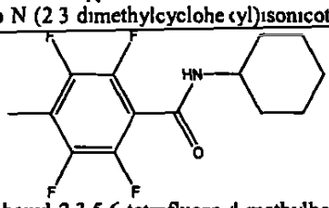
Compound No	Compound	Sweet EC_{50} uM	Umami EC_{50} uM	Umami EC_{50} ratio
E40	 2 chloro-6 methoxy N (2 methylcyclohexyl)isonicotinamide	0 95		9 77
E41	 N ((2R) bicyclo[2 2 1]heptan 2 yl) 2 3 5 6 tetrafluoro-4 methylbenzamide	1 02		
E42	 N (1 methoxybutan 2 yl) 2 4 dimethylbenzamide	1 06		
E43	 N (2 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

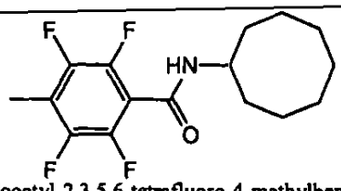
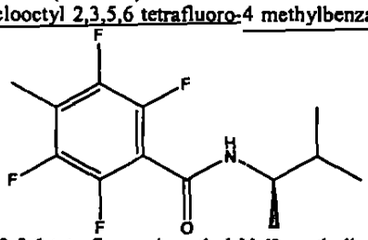
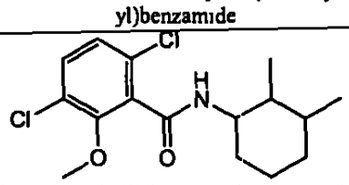
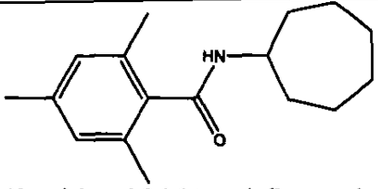
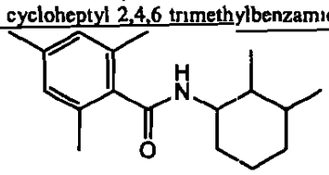
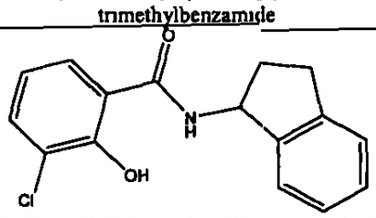
Compound No	Compound	Sweet EC_{50} uM	Umami EC_{50} uM	Umami EC_{50} ratio
E46	 N cyclooctyl 2,3,5,6 tetrafluoro-4 methylbenzamide	1 25		
E47	 (R) 2 3 5 6 tetrafluoro 4-methyl N (3 methylbutan 2 yl)benzamide	1 25		
E48	 3 6 dichloro N (2 3 dimethylcyclohexyl) 2 methoxybenzamide	1 29		
E49	 N cycloheptyl 2,4,6 trimethylbenzamide	1 39		
E50	 N (2 3 dimethylcyclohexyl) 2 4 6 trimethylbenzamide	1 41		
E51	 3 chloro-N (2 3 dihydro 1H inden 1 yl)-2 hydroxybenzamide	1 49		

Table E Sweet EnhancerAmides

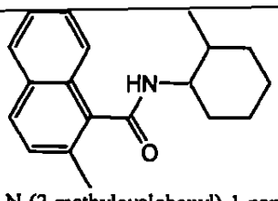
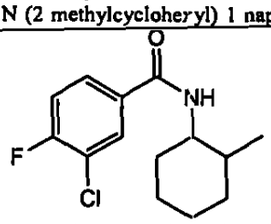
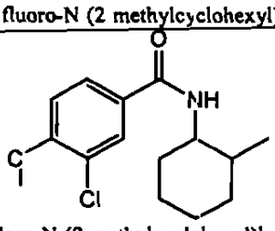
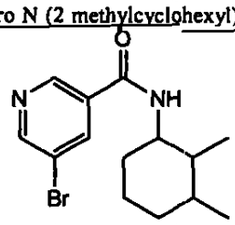
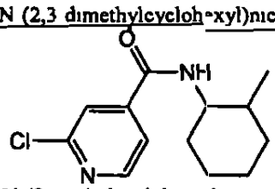
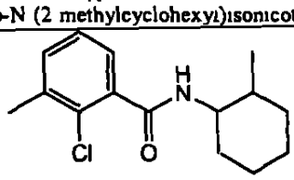
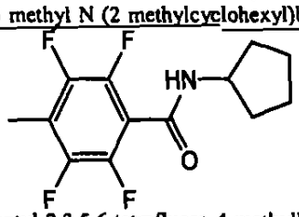
Compound No	Compound	Sweet EC_{50} uM	Umami EC_{50} uM	Umami EC_{50} ratio
E52	 2 methyl N (2 methylcycloheryl) 1 naphthamide	1 52		
E53	 3 chloro-4 fluoro-N (2 methylcyclohexyl)benzamide	1 7		
E54	 3 4 dichloro N (2 methylcyclohexyl)benzamide	1 83		10 66
E55	 5 bromo N (2,3 dimethylcyclohexyl)nicotinamide	1 89		
E56	 2 chloro-N (2 methylcyclohexyl)isonicotinamide	1 92		2 08
E57	 2 chloro-3 methyl N (2 methylcyclohexyl)benzamide	1 95		
E58	 N cyclopentyl 2 3 5 6-tetrafluoro 4 methylbenzamide	2 23		

Table E Sweet EnhancerAmides

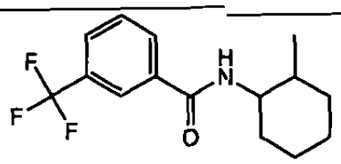
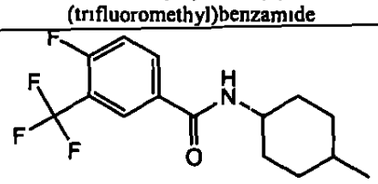
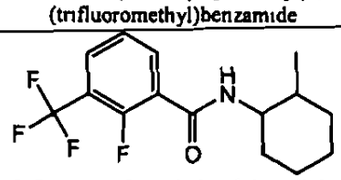
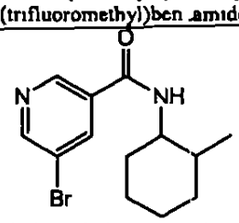
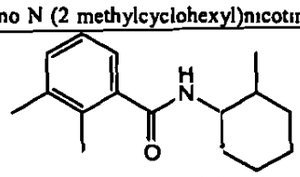
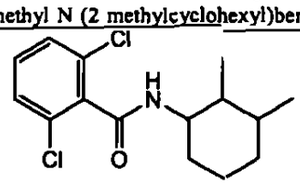
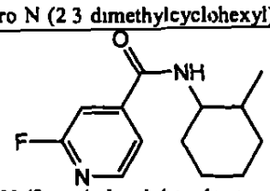
Compound No	Compound	Sweet EC_{50} uM	Umami EC_{50} uM	Umami EC_{50} ratio
E59	 N (2 methylcyclohexyl) 3 (trifluoromethyl)benzamide	2 34		2 07
E60	 4-fluoro N (4 methylcyclohexyl)-3 (trifluoromethyl)benzamide	2 37		
E61	 2 fluoro-N-(2 methylcyclohexyl)-3 (trifluoromethyl)ben amide	2 4		
E62	 5 bromo N (2 methylcyclohexyl)nicotinamide	2 42		
E63	 2 3 dimethyl N (2 methylcyclohexyl)benzamide	2 6		
E64	 2 6 dichloro N (2 3 dimethylcyclohexyl)benzamide	2 77		
E65	 2 fluoro N (2 methylcyclohexyl isonicotinamide	2 83		

Table E Sweet Enhancer Amides

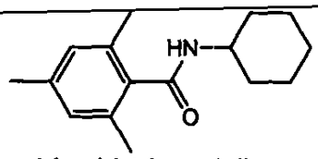
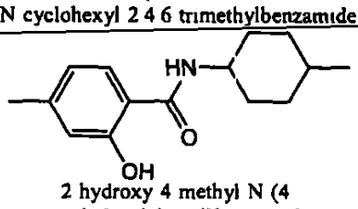
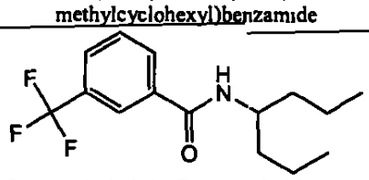
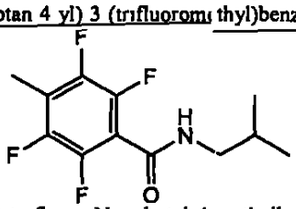
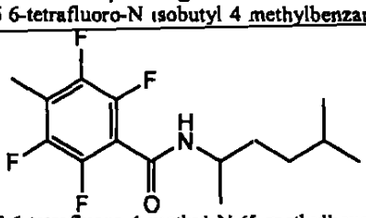
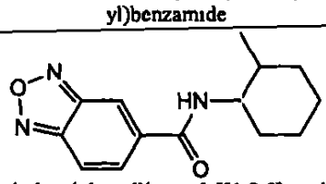
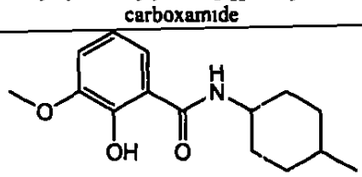
Compound No	Compound	Sweet EC_{50} uM	Umami EC_{50} uM	Umami EC_{50} ratio
E66	 N cyclohexyl 2 4 6 trimethylbenzamide	2 86		
E67	 2 hydroxy 4 methyl N (4 methylcyclohexyl)benzamide	2 98		
E68	 N (heptan 4 yl) 3 (trifluoromethyl)benzamide	3 03	0 33	
E69	 2 3 5 6-tetrafluoro-N isobutyl 4 methylbenzamide	3 19		
E70	 2 3 5 6 tetrafluoro-4 methyl N (5 methylhexan 2 yl)benzamide	3 2		
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		

Table E Sweet EnhancerAmides

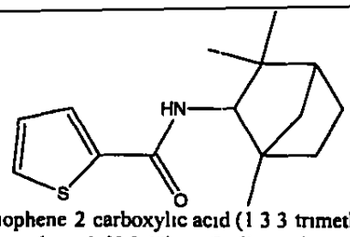
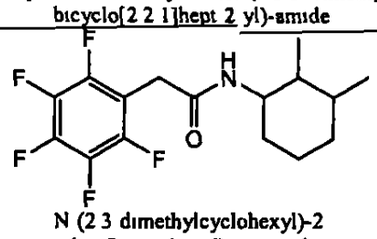
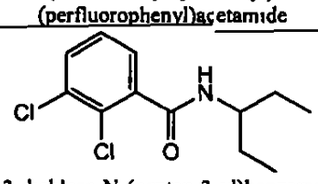
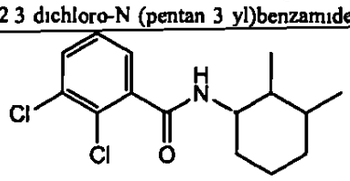
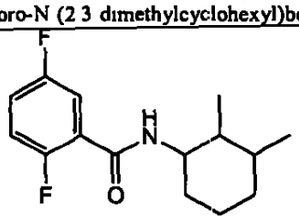
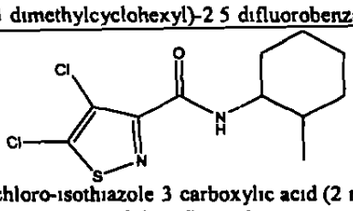
Compound No	Compound	Sweet EC_{50} uM	Umami EC_{50} uM	Umami EC_{50} ratio
E73	 Thiophene 2 carboxylic acid (1 3 3 trimethyl bicyclo[2 2 1]hept 2 yl)-amide	3 36		
E74	 N (2 3 dimethylcyclohexyl)-2 (perfluorophenyl)acetamide	3 62		
E75	 2 3 dichloro-N (pentan 3 yl)benzamide	3 78		
E76	 2 3 dichloro-N (2 3 dimethylcyclohexyl)benzamide	3 99		
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	

Table E - Sweet EnhancerAmides

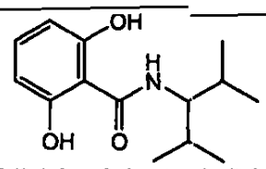
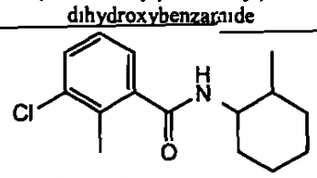
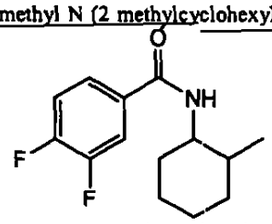
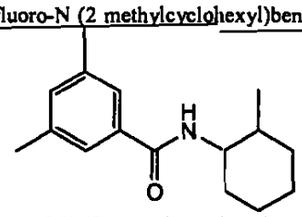
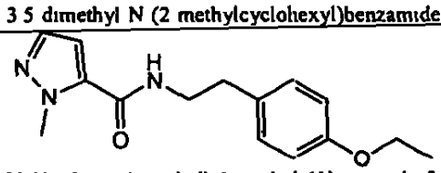
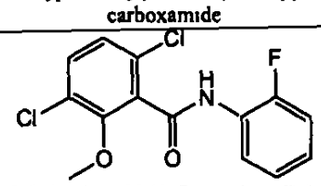
Compound No	Compound	Sweet EC_{50} uM	Umami EC_{50} uM	Umami EC_{50} ratio
E79	 N (2 4 dimethylpentan 3 yl) 2 6 dihydroxybenzamide	4 28		
E80	 3 chloro-2 methyl N (2 methylcyclohexyl)benzamide	4 29		
E81	 3 4-difluoro-N (2 methylcyclohexyl)benzamide	4 37		6 98
E82	 3 5 dimethyl N (2 methylcyclohexyl)benzamide	4 48		
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

Table E Sweet EnhancerAmides

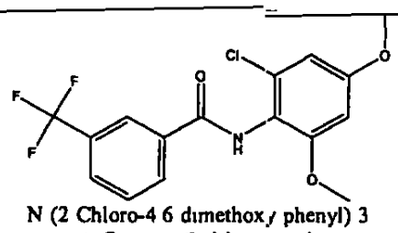
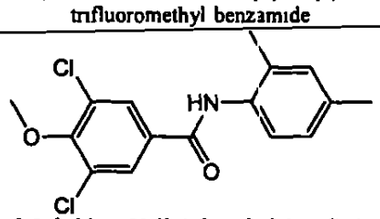
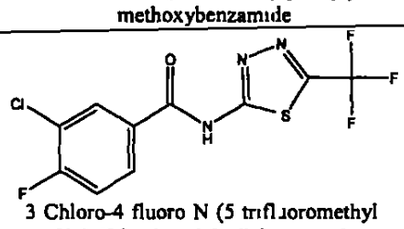
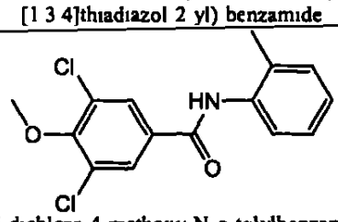
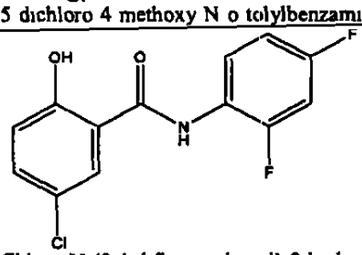
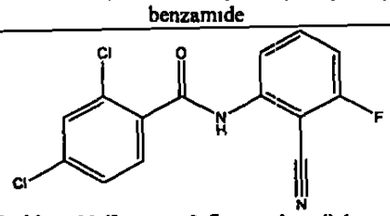
Compound No	Compound	Sweet EC_{50} uM	Umami EC_{50} uM	Umami EC_{50} ratio
E85	 N (2 Chloro-4 6 dimethoxy phenyl) 3 trifluoromethyl benzamide	1 42		
E86	 3 5 dichloro N (2 4 dimethylphenyl)-4-methoxybenzamide	1 48		
E87	 3 Chloro-4 fluoro N (5 trifluoromethyl [1 3 4]thiadiazol 2 yl) benzamide	1 55		
E88	 3 5 dichloro 4 methoxy N o tolylbenzamide	1 84		
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		

Table E - Sweet EnhancerAmides

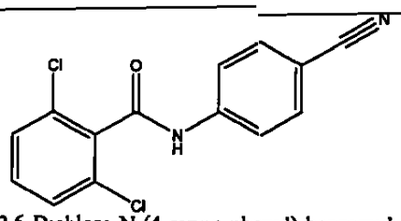
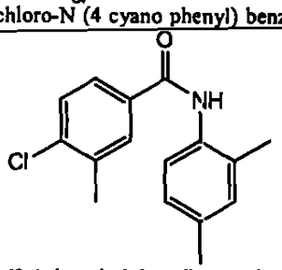
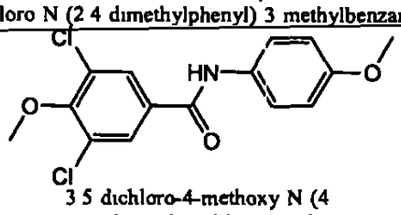
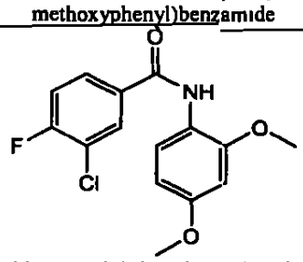
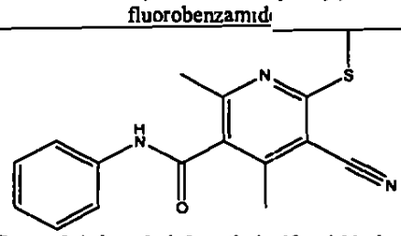
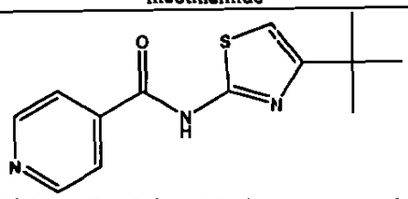
Compound No	Compound	Sweet EC_{50} uM	Umami EC_{50} uM	Umami EC_{50} ratio
E91	 2 6 Dichloro-N (4 cyano phenyl) benzamide	2 74		
E92	 4 chloro N (2 4 dimethylphenyl) 3 methylbenzamide	2 74		
E93	 3 5 dichloro-4-methoxy N (4 methoxyphenyl)benzamide	3 24		
E94	 3 chloro-N (2 4-dimethox /phenyl) 4 fluorobenzamid	3 56		
E95	 5 Cyano 2 4 dimethyl 6 methylsulfanyl N phenyl nicotinamide	3 58		
E96	 N (4 tert Butyl thiazol 2 yl) nicotinamide	3 73		

Table E Sweet EnhancerAmides

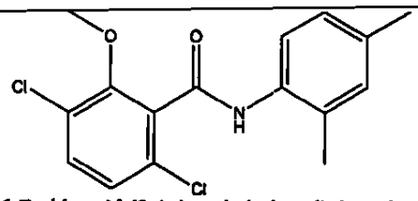
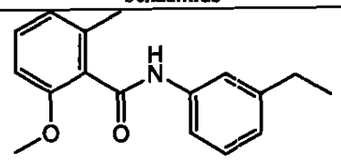
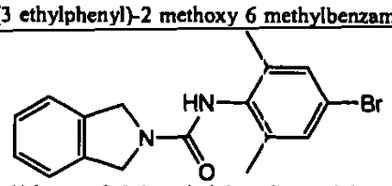
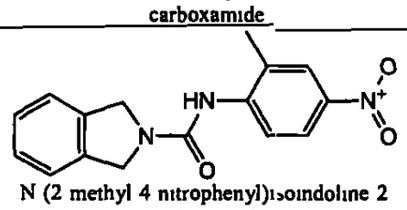
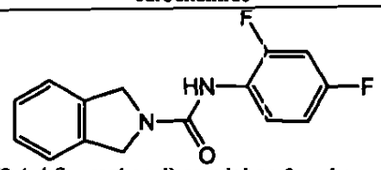
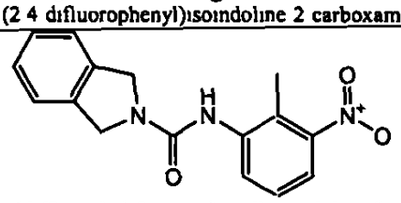
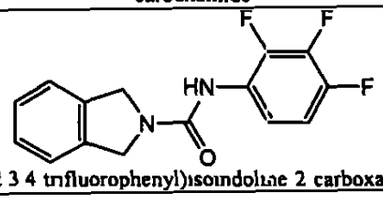
Compound No	Compound	Sweet EC_{50} uM	Umami EC_{50} uM	Umami EC_{50} ratio
E97	 3 6 Dichloro-N (2 4 dimethyl phenyl) 2 methoxy benzamide	4 25		
E98	 N (3 ethylphenyl)-2 methoxy 6 methylbenzamide	4 63		
E99	 N (4 bromo-2 6 dimethylphenyl)isoindoline 2 carboxamide	0 93		
E100	 N (2 methyl 4 nitrophenyl)isoindoline 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		

Table E - Sweet EnhancerAmides

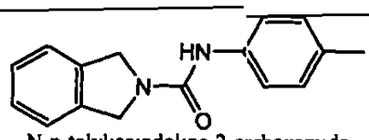
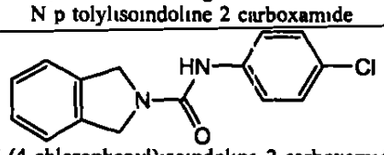
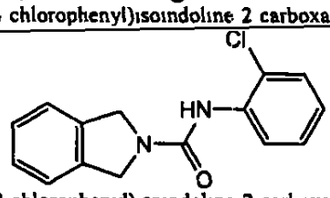
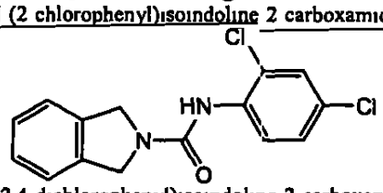
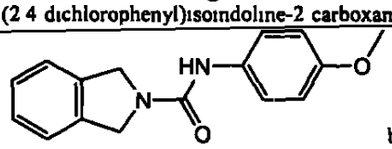
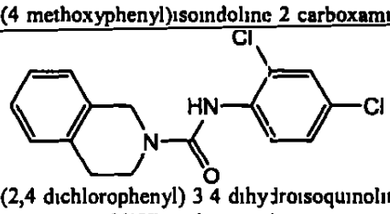
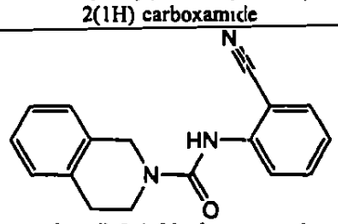
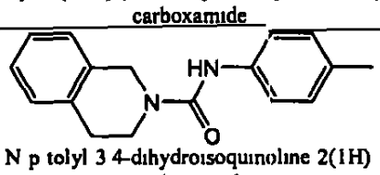
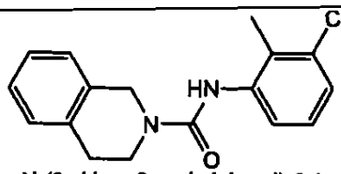
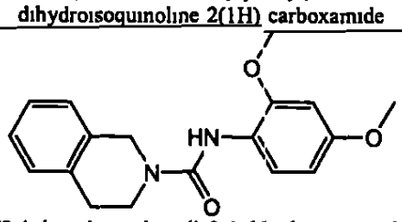
Compound No	Compound	Sweet EC_{50} uM	Umami EC_{50} uM	Umami EC_{50} ratio
E104	 N p tolylisoindoline 2 carboxamide	3 05		
E105	 N (4 chlorophenyl)isoindoline 2 carboxamide	3 4		
E106	 N (2 chlorophenyl)isoindoline 2 carboxamide	3 85		
E107	 N (2 4 dichlorophenyl)isoindoline-2 carboxamide	4 15		
E108	 N (4 methoxyphenyl)isoindoline 2 carboxamide b	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		

Table E Sweet EnhancerAmides

Compound No	Compound	Sweet EC_{50} uM	Umami EC_{50} uM	Umami EC_{50} ratio
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		

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 aqeuous 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 tothe 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
174	50 uM Compound 174 + 4% sucrose	*	6% sucrose
171	30 uM Compound 171 + 6% fructose/glucose	*	Greater than 6% but less than 8% fructose/glucose
170	30 uM Compound 170 + 6% fructose/glucose	pH 7 1	Greater than 6% but less than 8% fructose/glucose
162	10 uM Compound 162 + 6% fructose/glucose	pH 7 1	Greater than or equal to 8% fructose/glucose
162	10 uM Compound 162 + 7% fructose/glucose	pH 2 8	Greater than or equal to 9% fructose/glucose
168	30 uM Compound 168 + 6% fructose/glucose	pH 7 1	Equal to 8% fructose/glucose
163	10 uM Compound 163 + 6% fructose/glucose	pH 7 1	Greater than 6% but less than 8% fructose/glucose

* The pH of these aqeous solutions was not measured or controlled

Example 176

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 177

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 30 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 178

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 179

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

Example180

Spicy Tomato Juice or Bloody Mary Mix

A compound of the invention is added as a dry ingredient to the spice blend and blended thoroughly Spice blend is dispersed into a portion of the tomato paste, blended, and that blended paste is further blended into the remaining paste The paste is then diluted with water It may be processed at high temperature for a short time

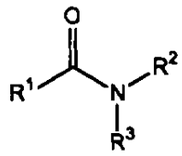
It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification 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

1 A method for modulating the taste of a comestible or medicinal product comprising

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

b) combining the comestible or medicinal product or precursor thereof with at least a savory 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



wherein R1 comprises a hydrocarbon residue having at least three carbon atoms and optionally one to ten heteroatoms independently selected from oxygen, nitrogen sulfur, halogens, or phosphorus, and

wherein one of R2 and R3 is H the other of R2 and R3 comprises a hydrocarbon residue having at least three carbon atoms and optionally one to ten heteroatoms independently selected from oxygen, nitrogen, sulfur, halogens, or phosphorus, and wherein the amide compound has a molecular weight of 500 grams per mole or less

2 The method of claim 1 wherein the amide compound has a molecular weight from 175 to 500 grams per mole

3 The method of claim 1 wherein the amide compound has a molecular weight from 200 to 450 grams per mole

4 The method of claim 1 wherein the amice compound has a molecular weight from 225 to 400 grams per mole

5 The method of claim 1 wherein the amide compound has a molecular weight from 250 to 350 grams per mole

6 The method of claim 1 wherein R1 and one of R2 and R3 have between 3 and 14 carbon atoms

7 The method of claim 2 1wherein R1 and one of R2 and R3 have between 4 and 12 carbon atoms

8 The method of claim 1 wherein R1 and one of R2 and R3 have between 4 and 10 carbon atoms

9 The method of claim 1 wherein R1 has between 3 and 16 carbon atoms and 0, 1, 2, 3, 4, or 5 heteroatoms selected from oxygen, nitrogen, sulfur, fluorine, or chlorine

10 The method of claim 1 wherein one of R2 or R3 has between 3 and 16 carbon atoms and 0, 1, 2, 3, 4, or 5 heteroatoms independently selected from oxygen, nitrogen, sulfur, fluorine, or chlorine

11 The method of claim 1 wherein one of R2 or R3 has between 4 and 14 carbon atoms and 0, 1, 2, 3, 4, or 5 heteroatoms independently selected from oxygen, nitrogen, sulfur

12 The method of claim 1 wherein one of R2 or R3 has between 5 and 12 carbon atoms and 0, 1, 2, or 3 heteroatoms independently selected from oxygen, nitrogen, and sulfur

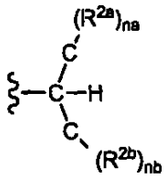
13 The method of claim 1 wherein R1 has between 3 and 16 carbon atoms and 0, 1, 2, 3, 4, or 5 heteroatoms selected from oxygen, nitrogen, sulfur, fluorine, or chlorine and one of R2 or R3 has between 5 and 12 carbon atoms and 0, 1, 2, or 3 heteroatoms independently selected from oxygen nitrogen, and sulfur

14 The method of claim 1 wherein R1 and one of R2 and R3 are independently selected from the group consisting of an arylalkenyl, heteroarylalkenyl, arylalkyl, heteroarylalkyl, alkyl, alkoxy-alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, -R4OH, -R4O R5 -R4CN, -R4CO2H, -R4CO2R5, -R4COR5, -R4SR5, and -R4SO2R5, and optionally substituted derivative thereof comprising 1, 2, 3, or 4 carbonyl, amino groups, hydroxyl, or halogen groups and wherein R4 and R5 are C1-C6 hydrocarbon residues

15 The method of claim 7 wherein R1 and one of R2 and R3 are 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 sustituent group., independently selected from hydrogen, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3, SEt, SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups

16 The method of claim 1 wherein one of R2 and R3 is a branched or cyclic organic residue having a carbon atom directly bonded to (a) the amide nitrogen atom and (b) two additional carbon atoms, and wherein the branched or cyclic organic residue comprises hydrogen atoms, up to 10 optional additional carbon atoms, and from zero to five heteroatoms independently selected from oxygen, nitrogen, sulfur, fluorine, and chlorine

17 The method of claim 1 wherein one of R2 and R3 has the formula

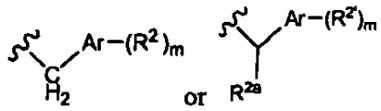


wherein na and nb are independently selected from 1, 2, and 3, and each R2a or R2b substituent residue is independently selected from hydrogen, a halogen, a hydroxy, or an carbon-containing residue optionally having from zero to five heteroatoms independently selected from oxygen, nitrogen, sulfur, an a halogen

18 The method of claim 1 wherein one of R2 and R3 is a branched alkyl radical having five to 12 carbon atoms

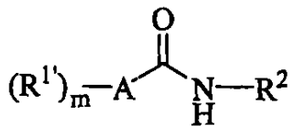
19 The method of claim 1 wherein one of R2 and R3 is a cycloalkyl or cycloalkenyl ring comprising 5 to 12 ring carbon atoms that can be optionally substituted with 1, 2, 3, or 4 independently selected from hydrogen, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3, SEt, SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups

20 The method of claim 1 wherein one of R2 and R3 has the structure



wherein Ar is a phenyl, pyridyl, furanyl thiofuranyl, or pyrrole ring, m is 0,1, 2, or 3, each R2' is independently selected from hydrogen, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3, SEt, SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy and R2a is selected from the group consisting of an alkyl, alkoxy-alkyl, alkenyl, cycloalkenyl, cycloalkyl, -R4OH, -R4O R5 -R4CN, -R4CO2H, -R4CO2R5, -R4COR5 -R4SR5 and -R4SO2R5 comprising 1 to 12 carbon atoms

21 The method of claim 1 wherein the amide compound has the formula



wherein A comprises a 5 or 6 membered aryl or heteroaryl ring,

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

each R1' is independently selected from alkyl, alkoxy alkoxy-alkyl, hydroxyalkyl, OH, CN, CO2H, CO2R6,CHO, COR6, SR6, halogen, alkenyl, cycloalkyl, cycloalkenyl heterocycle, aryl, and heteroaryl, and

R6 is C1-C6 alkyl

22 The method of claim 21 wherein A is a phenyl ring or a pyridyl ring

23 The method of claim 22 wherein m is 1, 2, or 3

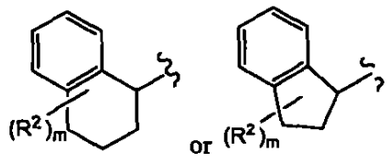
24 The method of claim 23 wherein each R1' is independently selected from hydrogen, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, COOCH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl methoxy, ethoxy, isopropoxy, trifluoromethoxy, or a monocyclic aryl or heteroaryl group

25 The method of claim 21 wherein A is a phenyl ring and each R1' is independently selected from hydrogen, hydroxy, fluoro, chloro NH2 NHCH3, N(CH3)2, COOCH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy isopropoxy, and trifluoromethoxy groups

26 The method of claim 25 24wherein R2 is a C3-C10 branched alkyl

27 The method of claim 21 wherein R2 is a C3-C10 branched alkyl substituted with one or two substituents independently selected from hydrogen, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, O2CCH3, CO2CH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

28 The method of claim 25 wherein R2 is a 1-(1,2,3,4) tetrahydronapthalene ring or an 2,3-dihydro-1H-indene ring having the formula



wherein m is 0,1, 2, or 3, and each R1' can be bonded to either the aromatic or non-aromatic ring and is independently selected from hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy isopropoxy, and trifluoromethoxy groups

29 The method of claim 25 wherein R2 is a phenyl ring optionally substituted with one or two substituents independently selected from hydroxy fluoro, chloro NH2, NHCH3, N(CH3)2, CO2CH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups

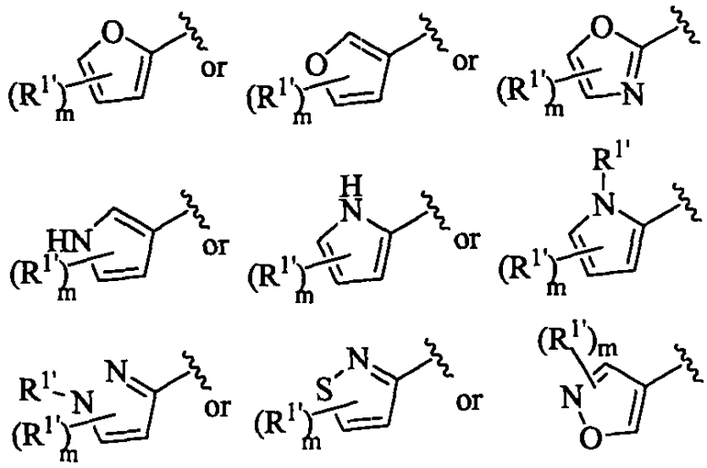
30 The method of claim 21 wherein R2 is an α-substituted carboxylic acid or α-substituted carboxylic acid lower alkyl ester

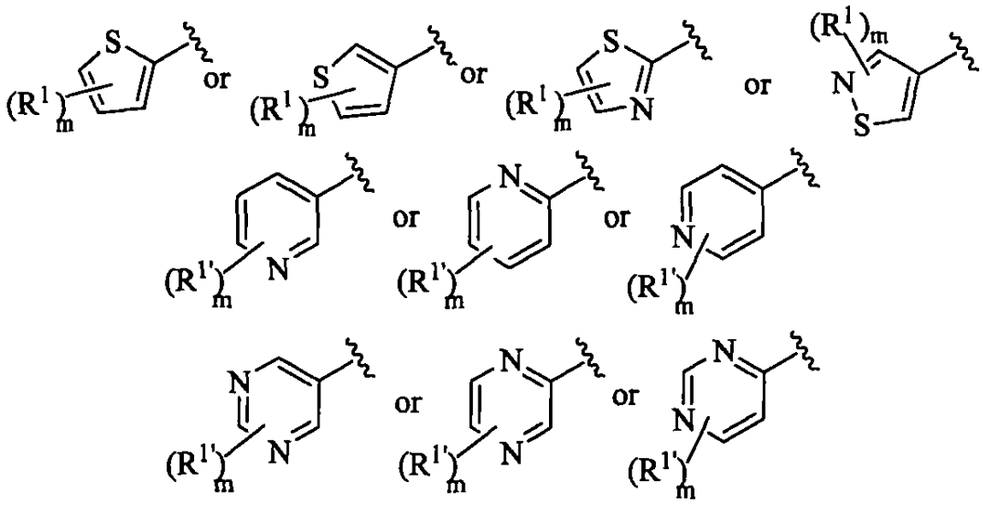
31 The method of claim 25 wherein R2 is an α-substituted carboxylic acid methyl ester

32 The method of claim 31 wherein the α substituted carboxylic acid or α-substituted carboxylic acid ester residue corresponds to that of a naturally occurring α-amino acid or an ester thereof, or its opposite enantiomer

33 The method of claim 21 wherein A is a monocyclic heteroaryl wherein each R1' is independently selected from hydrogen hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2 COOCH3, SCH3, SEt, metayl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups

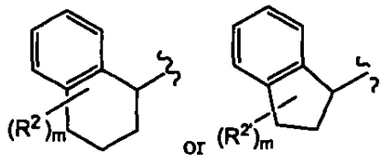
34 The method of claim 21 wherein A has one of the following formulas





wherein m is 0, 1, 2, or 3, and each R1' is independently selected from hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, trifluoromethoxy, or a monocyclic aryl or heteroaryl group

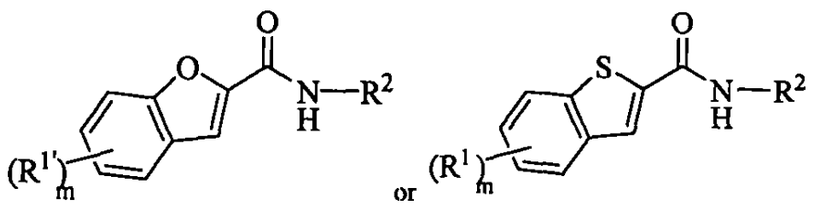
35 The method of claim 34 wherein R2 has the formula



wherein m is 0,1, 2, or 3, and each R1' can be bonded to either the aromatic or non-aromatic ring and is independently selected from hydroxy, fluoro, chloro, NH2, NHCH3 N(CH3)2, CO2CH3,SCH3, SEt methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups

36 The method of claim 21 wherein A is a monocyclic, fused bicyclic or linked bicyclic aromatic heteroaryl, optionally substituted with 0, 1, 2, 3, or 4 substituents independently selected from hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3,SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups

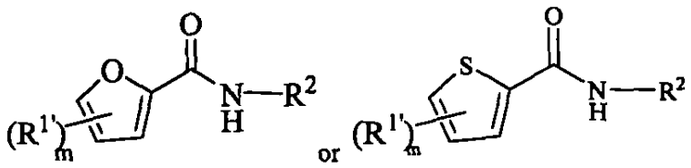
37 The method of claim 1 wherein the amide compound has the formula



wherein m is 0, 1, 2, or 3 and each R1′ can be bonded to either the phenyl or heteroaryl rings and each R1′ is independently selected from, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3, SCH3, SEt, methyl, ethyl isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

38 The method of claim 37 wherein m is 1 or 2

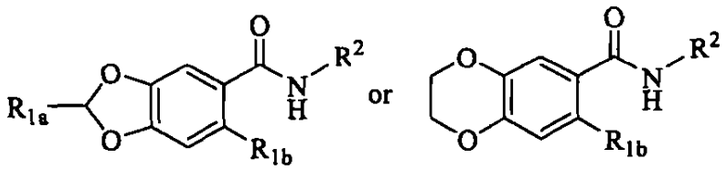
39 The method of claim 1 wherein the amide compound has the formula



wherein m is 0, 1, 2, or 3 and each R1′ is independently selected from, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3,SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

40 The method of claim 39 wherein m is 1 or 2

41 The method of claim 1 wherein the amide compound has the formula

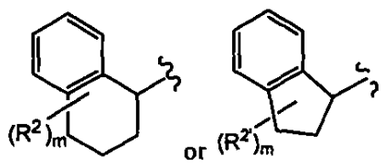


wherein R1a and R1b are independently hydrogen or a lower alkyl

42 The method of claim 41 wherein R1a and R1b are independently hydrogen or methyl

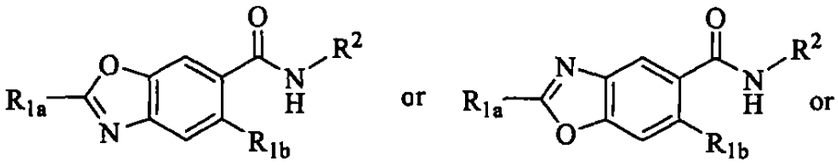
43 The method of claim 41 wherein R2 is a C3-C10 branched alkyl

44 The method of claim 41 wherein R2 has the formula



wherein m is 0,1, 2, or 3, and each R2′ can be bonded to either the aromatic or non-aromatic ring and each R2′ is independently selected from hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups

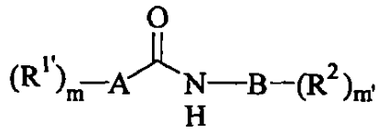
45 The method of claim 1 wherein the amide compound has the formula



wherein R1a or R1b is independently hydrogen or a lower alkyl

46 The method of claim 45 wherein R1a is a lower alkyl and R2 is a C3-C10 branched alkyl

47 The method of claim 1 wherein the amide compound has the formula



wherein A comprises a 5 or 6 membered aryl or heteroaryl ring,

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

each R1′ is independently selected from alkyl, alkoxyl, alkoxy-alkyl, hydroxyalkyl, OH, CN, CO2H, CHO, COR6, CO2R6 , SH, SR6, halogen, alkenyl, cycloalkyl, cycloalkenyl, aryl, and heteroaryl and R6 is C1-C6 alkyl,

B is a 5 or 6 membered aryl or heteroaryl ring,

m′ is 0, 1, 2, 3 or 4,

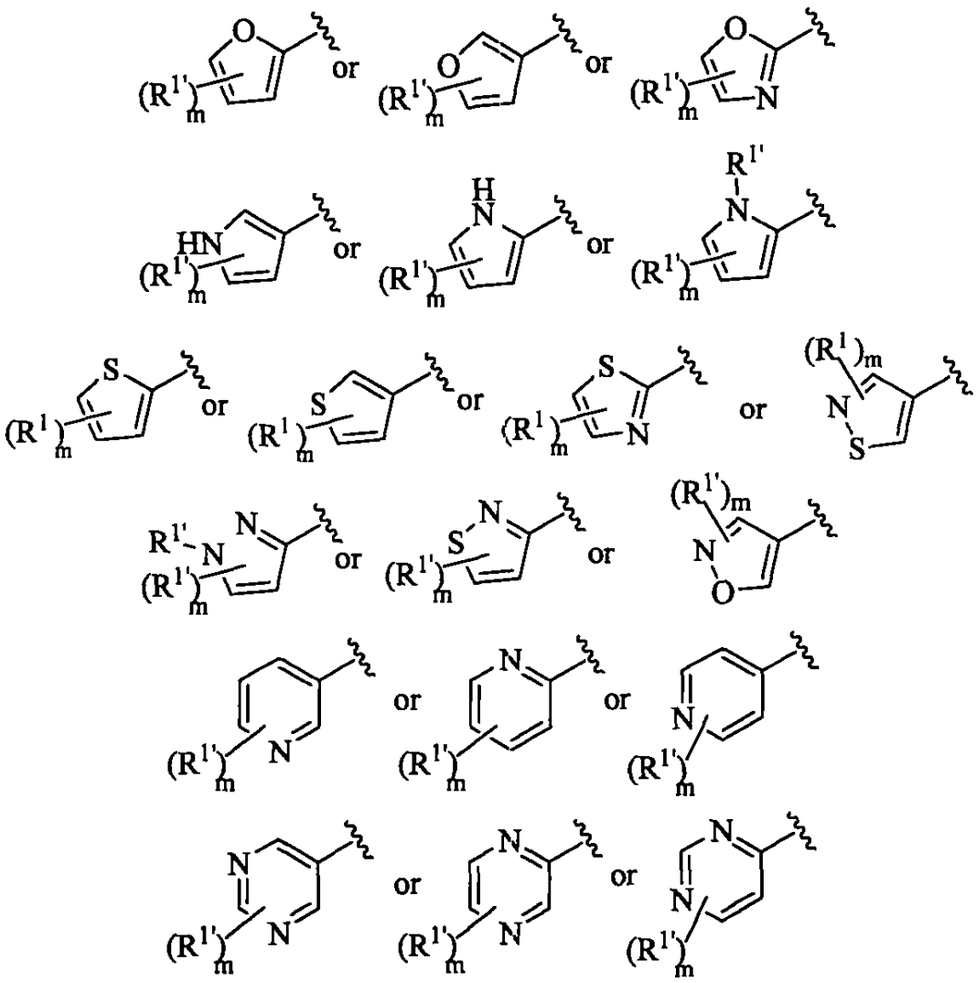
R2′ is selected from the group consisting of alkyl, alkoxyl, alkoxy-alkyl OH, CN CO2H, CHO, COR6, CO2R6, SR6, halogen, alkenyl, cycloalkyl, cycloalkenyl, aryl, and heteroaryl and R6 is C1-C6 alkyl

48 The method of claim 47 wherein A is a monocyclic or fused bicyclic heteroaryl ring wherein each R1′ and each R2 is independently selected from hydrogen, hydroxy,

fluoro, chloro, NH2, NHCH3, N(CH3)2, COOCH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups

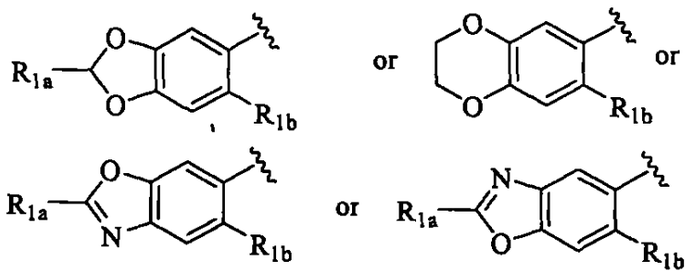
49 The method of claim 47 wherein A is a monocyclic heteroaryl ring

50 The method of claim 47 wherein A has one of the formulas



wherein m is 0,1, 2, or 3, and each R1′ can be bonded to either the aromatic or non-aromatic ring and each R2′ is independently selected from independently selected from hydrogen, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3, SEt SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups

51 The method of claim 47 wherein the (R1')m-A radical has the formula

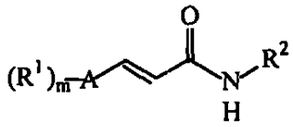


wherein R1a and R1b are independently hydrogen or a lower alkyl

52 The method of claim 48 wherein B is a phenyl ring and each R2' is independently selected from hydrogen, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3, SEt, SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups

53 The method of claim 47 wherein A is a substituted phenyl ring and B is a substituted cyclohexyl ring

54 The method of claim 1 wherein the amide compound has the formula



wherein A is a 5 or 6 membered aryl or heteroaryl ring,

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

each R1' is independently selected from alkyl, alkoxyl, alkoxy-alkyl, OH, CN, CO2H, CO2R6, CHO, COR6, SR6, halogen, alkenyl, cycloalkyl, cycloalkenyl, aryl, and heteroaryl

55 The method of claim 54 wherein A is a phenyl, pyridyl, furanyl, or thiofuranyl ring and each R1'is independently selected from hydrogen, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3, SEt, SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, trifluoromethoxy, groups

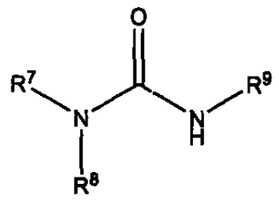
56 The method of claim 55 wherein A is a phenyl ring and m is 1, 2, 3 or 4

57 The method of claim 56 wherein m is 1 or 2

58 The method of claim 55 wherein R2 is a C3-C10 branched alkyl

59 The method of claim 55 wherein R2 is an α-substituted carboxylic acid lower alkyl ester

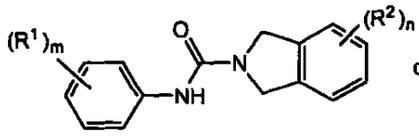
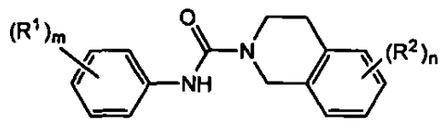
60 The method of claim 1 wherein the amide compound is a urea compound having the formula



wherein R9 and one or two of R7 and R8 comprise a hydrocarbon residue having at least three carbon atoms and optionally one to ten heteroatoms selected from oxygen, nitrogen, sulfur, halogens, or phosphorus, and wherein optionally one of R7 and R8 is hydrogen

61 The method of claim 60 wherein R7 and R8 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, NH2, NHCH3, N(CH3)2, COOCH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

62 The method of claim 61 wherein the urea compound has the structure

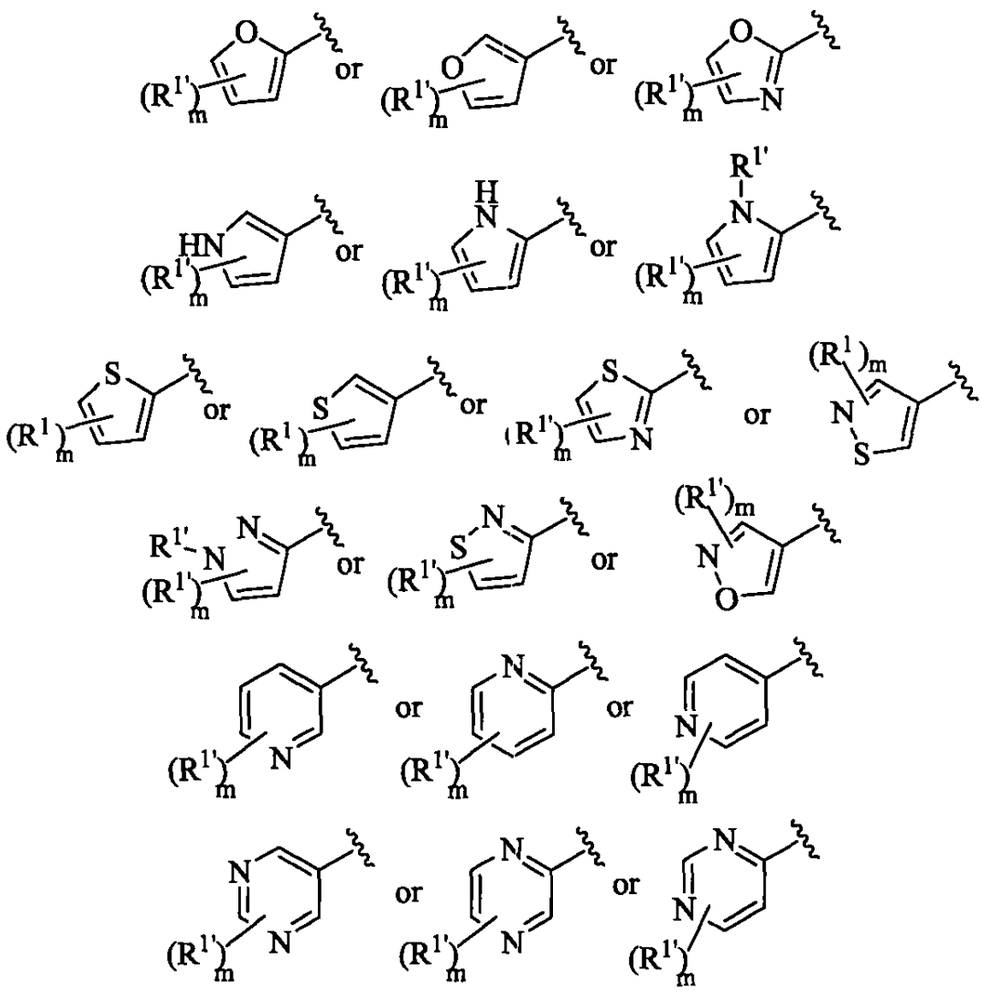

or


63 The method of claim 60 wherein one of R7 and R8 is hydrogen

64 The method of claim 63 wherein R9 and one of R7 and R8 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, NH2, NHCH3, N(CH3)2, COOCH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

65 The method of claim 63 wherein R9 and one of R7 and R8 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, NH2, NHCH3, N(CH3)2, CO2CH3, SEt, SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

66 The method of claim 63 wherein one of R7 and R8 has one of the formulas

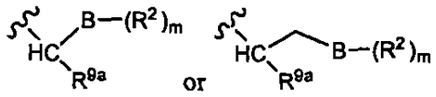


wherein m is 0,1, 2, or 3, and each R1′ independently selected from hydrogen, hydroxy fluoro, chloro, NH2, NHCH3, N(CH3)2 COOCH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

67 The method of claim 63 wherein one of R7 and R8 is a phenyl ring optionally substituted with 1, 2, or 3 substituents independently selected from hydrogen, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, COOCH3, SCH3, SEt methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy and trifluoromethoxy

68 The method of claim 63 wherein R9 is a C3-C10 branched alkyl

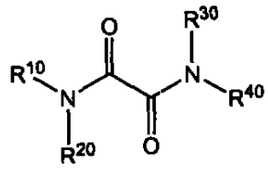
69 The method of claim 63 wherein R9 has the structure



wherein B is a phenyl, pyridyl, furanyl, thiofuranyl, pyrrole, cyclopentyl,cyclohexyl, or piperidyl ring, m is 0,1, 2 or 3, and each R2' is independently selected from hydrogen hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, COOCH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy, and R9a is a selected from the group consisting of an alkyl, alkoxy-alkyl, alkenyl, cycloalkenyl, cycloalkyl, -R4OH, -R4O R5 -R4CN, -R4CO2H, -R4CO2R5, -R4COR5, -R4SR5, and -R4SO2R5 comprising 1 to 12 carbon atoms

70 The method of claim 63 wherein the urea compound has the formula 1-(2-chlorophenyl)-3-(heptan-4-yl)urea, 1-(2,4-dichlorophenyl)-3-(1-phenylpropyl)urea, 1-(2,4-dimethoxyphenyl)-3-(heptan-4-yl)urea, 1-(2-fluorophenyl)-3-(heptan-4-yl)urea, or 1-(4-isopropylphenyl)-3-(2-(pyridin-2-yl)ethyl)urea

71 The method of claim 1 wherein the amide compound is an oxalamide compound having the formula



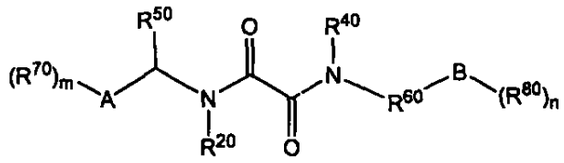
wherein R10and R30 are independently selected hydrocarbon residues having at least three carbon atoms and optionally one to ten heteroatoms independently selected from oxygen, nitrogen, sulfur, halogens, or phosphorus, and wherein R20and R40 are independently selected from hydrogen and a hydrocarbon residue having at least three carbon atoms and optionally one to ten heteroatoms independently selected from oxygen, nitrogen, sulfur, halogens, or phosphorus

72 The method of claim 71 wherein R20and R40 are hydrogen

73 The method of claim 71 wherein R10 and R30 are independently selected from the group consisting of arylalkyls, heteroarylalkyls, cycloalkyl-alkyls, and heterocycle-alkyls comprising five to 15 carbon atoms, and wherein each of R10 and R30 can optionally comprise one to one to four substituents independently selected from

hydrogen, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3, SEt, SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

74 The method of claim 1 wherein the amide compound is an oxalamide compound having the formula



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, R20and R40 are hydrogen,

R50 is hydrogen or an alkyl or substituted alkyl residue comprising one to four carbon atoms,

R60 is absent or a C1-C5 alkylene or a C1-C5 substituted alkylene,

R70 and R80 are independently selected from the group consisting of hydrogen, alkyl, alkoxyl, alkoxy-alkyl, OH, SR9, halogen, CN, NO2, CO2R9, COR9, CONR9R10, NR9R10, NR9COR10, SOR9, SO2R9, SO2NR9R10, NR9SO2R10 alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocycle,

R9 and R10 are independently selected from H, C1-C6 alkyl, C3-C6 cycloalkyl and C1-C6 alkenyl,

75 The method of claim 74 wherein 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

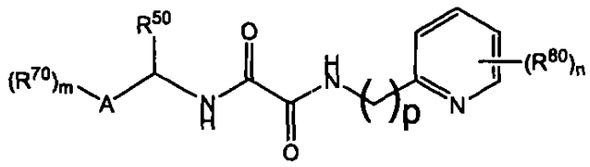
R20and R40 are hydrogen,

R50 is hydrogen or methyl,

R60 is a C2 alkylene,

R70 and R80 are independently selected from hydrogen, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3, SEt SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

76 The method of claim 1 wherein the amide compound is an oxalamide compound having the formula



wherein A is a phenyl, pyridyl, furanyl, pyrrole, piperidyl, cyclopentyl, cyclohexyl, or cycloheptyl ring,

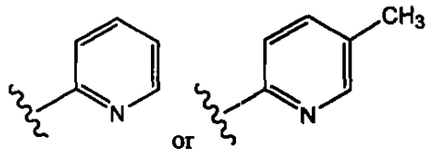
m and n are independently 0, 1, 2, or 3

R50 is hydrogen or methyl,

P is 1 or 2, and

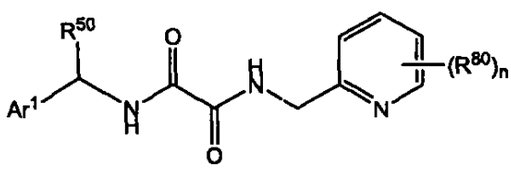
R70 and R80 are independently selected from the group consisting of hydrogen, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, COOCH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy , or two of R70 together form a methylenedioxy ring

77 The method of claim 76 wherein the pyridyl-R80 radical has the structure



or

78 The method of claim 1 wherein the amide compound is an oxalamide compound having the formula



wherein Ar1 is a substituted aryl or heteroaryl ring comprising five to 12 carbon atoms,

R50 is hydrogen or methyl,

n is 0, 1, 2, or 3,

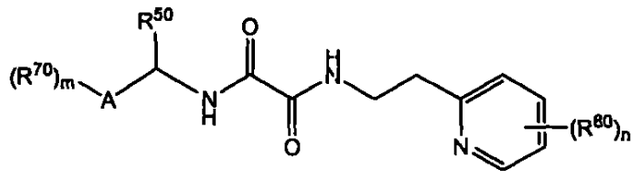
each R80 is independently selected from the group consisting of hydroxy fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3, SEt, SCH3, methyl, ethyl, isopropyl vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

79 The method of claim 78 wherein Ar1 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 hydroxy, fluoro chloro, NH2, NHCH3, N(CH3)2,

CO2CH3, SEt, SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy, or two of the substituents together form a methylenedioxy ring on the phenyl ring

80 The method of claim 78 wherein Ar1 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, NH2, NHCH3, N(CH3)2, CO2CH3, SEt, SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

81 The method of claim 1 wherein the amide compound is an oxalamide compound having the formula



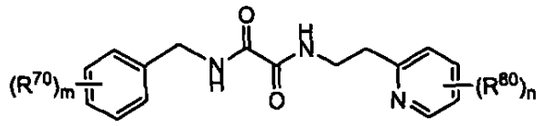
wherein A is a substituted aryl or heteroaryl ring comprising five to 12 carbon atoms,

R50 is hydrogen or methyl,

m and n are independently 0, 1, 2, or 3,

each R70 or R80 is independently selected from the group consisting of hydrogen, hydroxy fluoro chloro, NH2 NHCH3, N(CH3)2, COOCH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

82 The method of claim 1 wherein the amide compound is an oxalamide compound having the formula



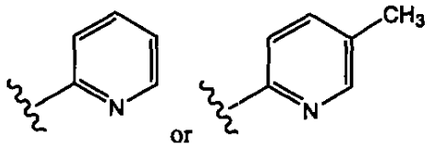
wherein m and n are independently 0, 1, 2, or 3, and

R70 and R80 are independently selected from the group consisting of hydrogen, alkyl, alkoxyl, alkoxy-alkyl, OH, SR9, halogen, CN, NO2, CO2R9, COR9, CONR9R10, NR9R10, NR9COR10, SOR9, SO2R9, SO2NR9R10, NR9SO2R10, alkenyl cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocycle,

R9 and R10 are independently selected from H, C1-C6 alkyl, C3-C6 cycloalkyl, and C1-C6 alkenyl

83 The method of claim 82 wherein R70 and R80 are independently selected from the group consisting of hydrogen, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, O2CCH3, SH, SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

84 The method of claim 82 wherein the pyridyl-R80 radical has the structure



or

85 The method of any of claims 1-84 wherein the log10 of the partition coefficient of the amide compound between n-octanol and water is less than 5 5

86 The method of claim 1 wherein the modified comestible or medicinal product is a food for animal consumption

87 The method of claim 1-84 wherein the modified comestible or medicinal product is a food for human consumption

88 The method of any of claims 1-84 wherein the modified comestible or medicinal product is selected from the group consisting confectioneries, bakery products, ice creams, dairy products, sweet or 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

89 The method of any of claims 1-84 wherein the modified comestible or medicinal product comprises one or more meats, poultry, fish, vegetables, grains, or fruits

90 The method of claim 1 wherein the modified comestible or medicinal product is a frozen food, an uncooked food, or a fully or partially cooked food

91 The method of claim 1 wherein the modified comestible or medicinal product is a soup, a dehydrated or concentrated soup, or a dry soup

92 The method of claim 1 wherein the modified comestible or medicinal product is a snack food

93 The method of claim 1 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

94 The method of claim 1 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

95 The method of any of claims 1-84 wherein the modified comestible or medicinal product is a beverage a beverage mix, or a beverage concentrate

96 The method of claim 1 wherein the modified comestible or medicinal product is a soda, or juice

97 The method of claim 1 wherein the modified comestible or medicinal product is an alcoholic beverage

98 The method of any of claims 1-84 wherein the modified comestible or medicinal product is a pharmaceutical composition for oral administration

99 The method of claim 1 wherein the modified comestible or medicinal product is an oral hygiene product

100 The method of any of claims 1-84 wherein the amide compound is present in the modified comestible or medicinal product at a concentration from about 0 01 ppm to about 30 ppm

101 The method of claim 1 wherein the amide compound is present in the modified comestible or medicinal product in a concentration from about 0 05 ppm to about 15 ppm

102 The method of claim 1 wherein the amide compound is present in the modified comestible or medicinal product in a concentration from about 0 1 ppm to about 5 ppm

103 The method of claim 1 wherein the amide compound is present in the modified comestible or medicinal product in a concentration from about 0 1 ppm to about 3 ppm

104 The method of any of claims 1-84 wherein a water solution comprising the savory flavor modifying amount of the amide compound has a savory taste as judged by the majority of a panel of at least eight human taste testers

105 The method of any of claims 1-84 wherein a water solution comprising the savory flavor modifying amount of the amide compound and 12 mM monosodium glutamate has 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

106 The method of claim 1 wherein a water solution comprising the savory flavor modifying amount of the amide compound and 12 mM monosodium glutamate has 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

107 The method of claim 1 wherein a water solution comprising about 10 ppm of the amide compound and about 12 mM monosodium glutamate has an increased savory flavor as compared to a control water solution comprising only the monosodium glutamate, as judged by a majority of a panel of eight human panelists

108 The method of claim 1wherein the amide compound is a savory agonist for an hT1R1/hT1R3 receptor

109 The method of any of claims 1-84 wherein the amide compound has an EC50 for the hT1R1/hT1R3 receptor of less than about 2 μM

110 The method of claim 1 wherein the amide compound, when dissolved in a water solution comprising about *1* μM of the amide compound decreases the observed EC50 of monosodium glutamate for an hT1R1/hT1R3 receptor expressed in an HEK293-Gα15 cell line by at least 50%

111 The method of claim 1 wherein the modified comestible or medicinal product has an increased savory taste as compared to the comestible or medicinal product prepared without the amide compound, as judged by a majority of a panel of at least eight human taste testers

112 The method of claim 1 wherein the amide compound is comestibly acceptable

113 The method of claim 1 wherein the amide compound is or can be shown to be generally recognized as safe

114 The method of claim 1 wherein the amide compound, when combined with rat chow and fed to Crl CD(SD)IGS BR rats at a concentration of about 100 milligrams/Kilogram Body weight/day for 90 days causes no adverse toxic effects on the rats

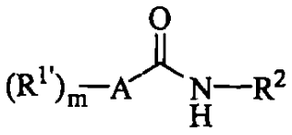
115 The modified comestible or medicinal product produced by any of claims 1-84

116 A method for increasing the sweet taste of a comestible or medicinal product comprising

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

b) combining the comestible or medicinal product or precursor 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 R1' is independently selected from the group consisting of C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 haloalkoxy, C1 C4 alkoxyl, C1-C4 alkoxy-alkyl, C1-C4 hydroxy-alkyl, OH, NH2, NHR6, NR62, CN, CO2H, CO2R6, CHO, COR6, SH, SR6, and halogen, wherein R6 is C1-C4 alkyl,

R2 comprises a branched alkyl or cycloalkyl optionally substituted with one to four substituents independently selected from alkyl, alkoxyl alkoxy-alkyl, hydroxyalkyl, OH, NH2, NHR6, NR62,CN, CO2H, CO2R6, CHO, COR6, SH, SR6, halogen alkenyl, cycloalkyl, cycloalkenyl, aryl, and heteroaryl and R6 is C1-C6 alkyl, and wherein the amide compound has a molecular weight of 500 grams per mole or less

117 The method of claim 116 wherein each R1' and each optional substituent for R2 is independently selected from the group consisting of hydrogen, hydroxy, fluoro chloro, NH2, NHCH3, N(CH3)2 COOCH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups

118 The method of claim 117 wherein A is an aryl ring comprising 6 to 12 ring carbons

119 The method of claim 117 wherein A is a napthyl ring

120 The method of claim 117 wherein A is a phenyl ring

121 The method of claim 120 wherein m is 1, 2, 3, or 4

122 The method of claim 121 wherein R2 is a branched C3-C10 alkyl

123 The method of claim 121 wherein R2 is a branched C3-C10 alkyl, substituted with 1, 2, or 3 substituent groups independently selected from hydroxy, fluoro, chloro NH2, NHCH3, N(CH3)2, CO2CH3, SEt, SCH3, methyl, ethyl, isopropyl, vinyl,

trifluoromethyl, methoxy, ethoxy, isopropoxy, trifluoromethoxy, phenyl, and pyridyl

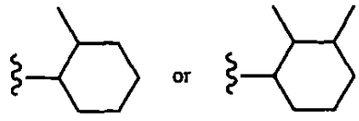
124 The method of claim 121 wherein R2 is a cycloalkyl or cycloalkenyl ring having 3 to 10 ring carbon atoms optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3, SEt, SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups

125 The method of claim 121 wherein R2 is a cycloalkyl or cycloalkenyl ring having 5 to 8 ring carbon atoms, optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of hydroxy, fluoro, chloro, NH2 NHCH3, N(CH3)2, CO2CH3, SEt, SCH3, methyl, ethyl, isopropyl vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups

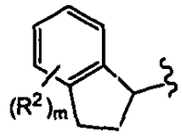
126 The method of claim 121 wherein R2 is a cyclopentyl, cyclohexyl cycloheptyl or cyclooctyl ring, optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3, SEt, SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups

127 The method of claim 121 wherein R2 is a cyclohexyl, optionally substituted with 1, 2, or 3 methyl groups

128 The method of claim 121 wherein R2 has the formula

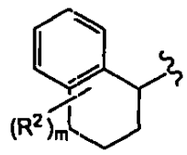


129 The method of claim 121 wherein R2 is a 1-indane having the formula



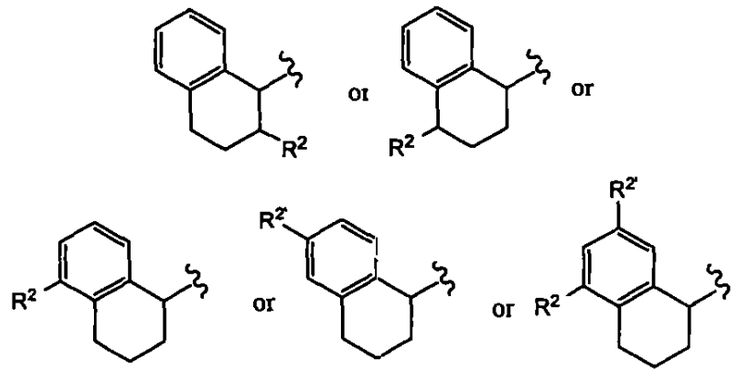
wherein m is 0,1, 2, or 3, and each R2' can be bonded to either the aromatic or non aromatic ring and is independently selected from hydroxy, fluoro, chloro NH2 NHCH3 N(CH3)2, CO2CH3, SEt SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

130 The method of claim 121 wherein R2 is a 1-(1,2,3,4) tetrahydronapthalene having the formula



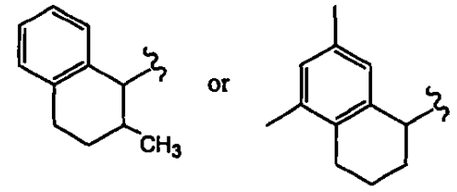
wherein m is 0,1, 2, or 3, and each R2' can be bonded to either the aromatic or non-aromatic ring and is independently selected from hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, COOCH3, SCH3, SEt, methyl, ethyl, isopropyl vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

131 The method of claim 121 wherein R2 has the formula

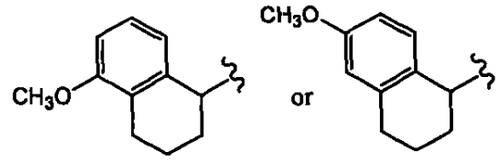


wherein each R2' are independently selected from the group consisting of hydrogen, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, COOCH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

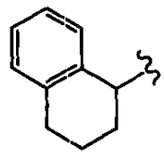
132 The method of claim 121 wherein R2 has the formula



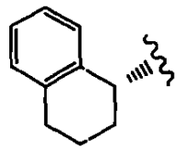
133 The method of claim 121 wherein R2 has the formula



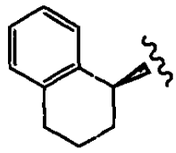
134 The method of claim 121 wherein R2 is a 1-(1,2,3,4) tetrahydronapthalene ring having the formula



135 The method of claim 121 wherein R1 is an 1-(1,2 3,4) tetrahydronapthalene ring having the formula

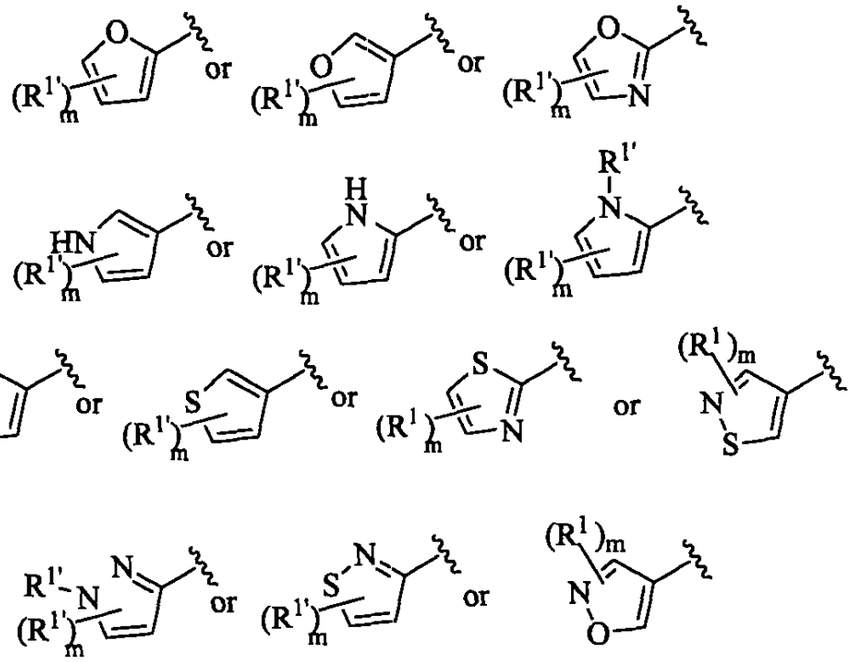


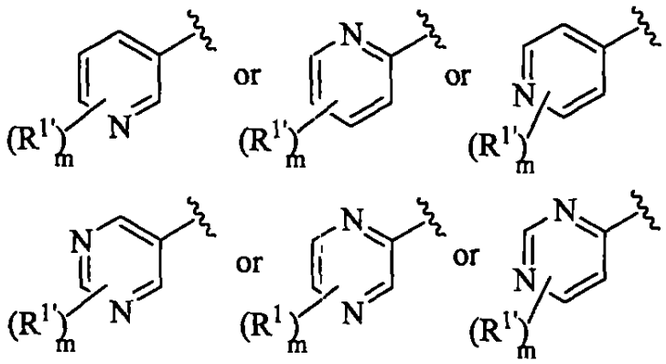
136 The method of claim 121 wherein R2 is an 1-(1,2,3,4) tetrahydronapthalene ring having the formula



137 The method of claim 117 wherein A is a monocyclic heteroaryl

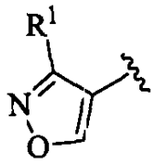
138 The method of claim 117 wherein A has one of the formulas





wherein m is 0, 1, 2, or 3 and each R1′ is independently selected from, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3, SEt, SCH3, methyl ethyl isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy or trifluoromethoxy

139 The method of claim 117 wherein A has the formula



wherein R1′ is hydrogen, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, O2CCH3, SH, SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, or trifluoromethoxy

140 The method of claim 138 wherein R2 is a branched C3-C10 alkyl

141 The method of claim 138 wherein R2 is a branched C3-C10 alkyl, substituted with 1, 2, or 3 substituent groups independently selected from hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3, SEt, SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, trifluoromethoxy, phenyl, and pyridyl

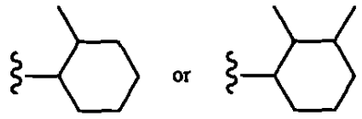
142 The method of claim 138 wherein R2 is a cycloalkyl having 3 to 10 ring carbon atoms, optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3, SEt, SCH3, methyl, ethyl isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups

143 The method of claim 138 wherein R2 is a cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl, optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2,

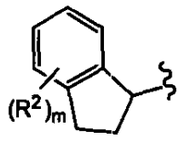
CO2CH3, SEt, SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy ethoxy, isopropoxy, and trifluoromethoxy groups

144 The method of claim 138 wherein R2 is a cyclohexyl, optionally substituted with 1, 2, or 3 methyl groups

145 The method of claim 138 wherein R2 has the formula

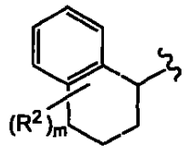


146 The method of claim 138 wherein R2 is a 1-indane having the formula



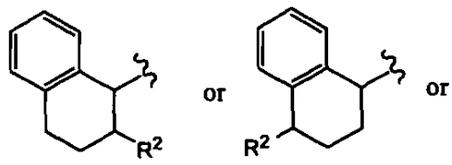
wherein m is 0,1, 2, or 3, and each R2' can be bonded to either the aromatic or non aromatic ring and is independently selected from hydroxy, fluoro, chloro NH2, NHCH3 N(CH3)2, CO2CH3, SEt, SCH3, methyl, ethyl, isopropyl vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

147 The method of claim 138 wherein R2 is a 1-(1,2,3,4) tetrahydronapthalene having the formula



wherein m is 0,1, 2, or 3, and each R2' can be bonded to either the aromatic or non-aromatic ring and is independently selected from hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3, SEt, SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

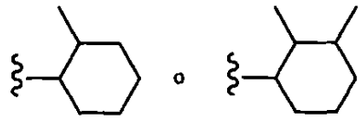
148 The method of claim 138 wherein R2 has the formula



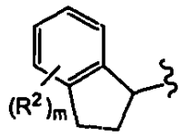
CO2CH3, SEt, SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy groups

144 The method of claim 138 wherein R2 is a cyclohexyl, optionally substituted with 1, 2, or 3 methyl groups

145 The method of claim 138 wherein R2 has the formula

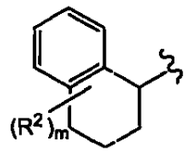


146 The method of claim 138 wherein R2 is a 1-indane having the formula



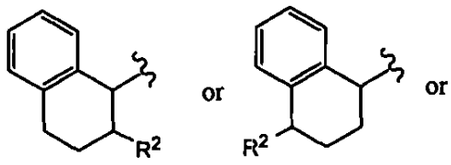
wherein m is 0,1, 2, or 3, and each R2' can be bonded to either the aromatic or non-aromatic ring and is independently selected from hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3, SEt, SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy ethoxy, isopropoxy, and trifluoromethoxy

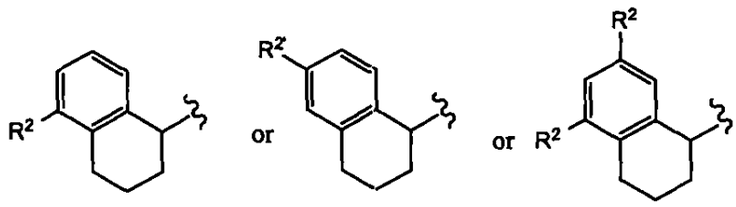
147 The method of claim 138 wherein R2 is a 1-(1,2,3,4) tetrahydronapthalene having the formula



wherein m is 0,1, 2, or 3, and each R2' can be bonded to either the aromatic or non-aromatic ring and is independently selected from hydroxy fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3, SEt, SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy and trifluoromethoxy

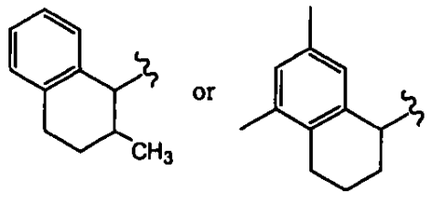
148 The method of claim 138 wherein R2 has the formula



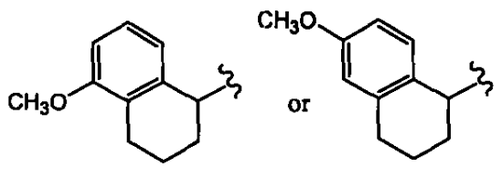


wherein each R2' are independently selected from the group consisting of hydrogen, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, O2CCH3, SH, SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, or trifluoromethoxy

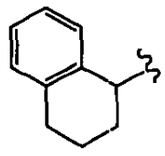
149 The method of claim 138 wherein R2 has the formula



150 The method of claim 138 wherein R2 has the formula



151 The method of claim 138 wherein R2 is a 1-(1,2,3,4) tetrahydronapthalene ring having the formula



152 The method of claim 116 wherein the modified comestible or medicinal product is a food for animal consumption

153 The method of claim 116 wherein the modified comestible or medicinal product is a food for human consumption

154 The method of any of claims 116-151 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

155 The method of any of claims 116-151 wherein the modified comestible or medicinal product comprises one or more meats, poultry, fish, vegetables, grains or fruits

156 The method of claim 116 wherein the modified comestible or medicinal product is a frozen food, an uncooked food, or a fully or partially cooked food

157 The method of claim 116 wherein the modified comestible or medicinal product is a soup, a dehydrated or concentrated soup, or a dry soup

158 The method of claim 116 wherein the modified comestible or medicinal product is a snack food

159 The method of claim 116 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

160 The method of claim 116 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 sauces

161 The method of any of claims 116-151 wherein the modified comestible or medicinal product is a beverage, a beverage mix, or a beverage concentrate

162 The method of any of claims 116-151 wherein the modified comestible or medicinal product is a soda, or juice,

163 The method of any of claims 116-151 wherein the modified comestible or medicinal product is an alcoholic beverage

164 The method of any of claims 116-151 wherein the modified comestible or medicinal product is a pharmaceutical composition intended for oral administration

165 The method of claim 116 wherein the modified comestible or medicinal product is an oral hygiene product

166 The method of any of claims 116-151 wherein the amide compound is present in the modified comestible or medicinal product in a concentration from about 0 001 ppm to about 100 ppm

167 The method of claim 117wherein the amide compound is present in the modified comestible or medicinal product in a concentration from about 0 1 ppm to about 30 ppm

168 The method of claim 116 wherein the amide compound is present in the modified comestible or medicinal product in a concentration from about 0 05 ppm to about 15 ppm

169 The method of any of claims 116-151 wherein the amide compound is present in the modified comestible or medicinal product in a concentration from about 0 1 ppm to about 5 ppm

170 The method of claim 116 wherein the amide compound is present in the modified comestible or medicinal product in a concentration from about 0 1 ppm to about 3 ppm

171 The method of any of claims 116-151 wherein the 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

172 The method of claim 116 wherein 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, or a mixture thereof and a sweet flavor modifying amount of the amide compound 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

173 The method of claim 116 wherein a water solution comprising the sweet flavor modifying amount of the amide compound and about 6 grams/100 milliliters of sucrose has a sweeter taste than a control water solution comprising 6 % grams/100 milliliters of sucrose, as judged by the majority of a panel of at least eight human taste testers

174 The method of claim 116 wherein a water solution comprising the sweet flavor modifying amount of the amide compound and 6 % grams/100 milliliters of a 50 50 mixture of sucrose and fructose has a sweeter taste than a control water solution comprising about 6 % grams/100 milliliters of a 50 50 mixture of sucrose and fructose, as judged by the majority of a panel of at least eight human taste testers

175 The method of claim 116 wherein a water solution comprising the sweet flavor modifying amount of the amide compound and about 1 6 mM of aspartame has a

sweeter taste than a control water solution comprising about 1 6 mM aspartame, as judged by the majority of a panel of at least eight human taste testers

176 The method of claim 116 wherein a water solution comprising the sweet flavor modifying amount of the amide compound and about 1 5 mM of acesulfame-K has a sweeter taste than a control water solution comprising about 1 5 mM of acesulfame-K, as judged by the majority of a panel of at least eight human taste testers

177 The method of claim 116 wherein a water solution comprising the sweet flavor modifying amount of the amide compound and about 10 mM of cyclamate has a sweeter taste than a control water solution comprising about 10 mM of cyclamate, as judged by the majority of a panel of at least eight human taste testers

178 The method of claim 116 wherein a water solution comprising the sweet flavor modifying amount of the amide compound and about 0 4 mM of sucralose has a sweeter taste than a control water solution comprising about 0 4 mM of sucralose, as judged by the majority of a panel of at least eight human taste testers

179 The method of claim 116 wherein a water solution comprising the sweet flavor modifying amount of the amide compound and about 0 2 mM of alitame has a sweeter taste than a control water solution comprising about 0 2 mM of alitame, as judged by the majority of a panel of at least eight human taste testers

180 The method of claim 116 wherein the modified comestible or medicinal product has a sweeter taste as compared to the comestible or medicinal product prepared without the amide compound, as judged by a majority of a panel of at least eight human panelists

181 The method of claim 116 wherein the amide compound modulates the binding of a sweetener selected from the group consisting of sucrose, fructose, glucose erythritol, isomalt, lactitol, mannitol, sorbitol, xylitol, a known natural terpenoid, flavinoid, or protein sweetener, aspartame, saccharin, acesufame-K, a cyclamate, sucralose, alitame or erythritol to an hT1R2/hT1R3 receptor expressed in an HEK293-Gα15 cell line

182 The method of claim 116 wherein the amide compound has an EC50 for binding an hT1R2/hT1R3 receptor expressed in an HEK293-Gα15 cell line of less than about 10 μM

183 The method of any of claims 116-151 wherein the amide compound has an EC50 for binding an hT1R2/hT1R3 receptor expressed in an HEK293-Gα15 cell line of less than about 5 μM

184 The method of claim 116 wherein the amide compound has an EC50 for binding an hT1R2/hT1R3 receptor expressed in an HEK293-Gα15 cell line of less than about 2 μM

185 The method of claim 116 wherein the amide compound has an EC50 for binding an hT1R2/hT1R3 receptor expressed in an HEK293-Gα15 cell line of less than about 1 μM

186 The method of claims 116 - 151 wherein the amide compound is not a peptide compound

187 The method of claim 116 wherein the amide compound is comestibly acceptable

188 The method of claim 116 wherein the amide compound is or can be determined to be generally recognized as safe for use in specific food products at a specified concentration in the finished product

189 The method of claim 116 wherein the amide compound, when combined with rat chow and fed to Crl CD(SD)IGS BR rats at a concentration of about 100 milligrams/kilogram body weight/day for 90 days causes no adverse toxic effects on the rats

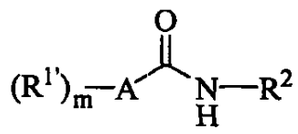
190 A comestible or medicinal product produced by the process of one of any of claims 116-189

191 A method for increasing the sweet taste of a comestible or medicinal product comprising

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

b) combining the comestible or medicinal product or precursor thereof with about 0 001 ppm to about 100 ppm 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 R1' is independently selected from the group consisting of hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3, SEt, SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy,
R2 is a phenyl ring, optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3, SEt, SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy, and
wherein the amide compound has a molecular weight of 500 grams per mole or less

192 The method of claim 191 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

193 The method of claim 191 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 sauces

194 The method of claim 191 wherein the modified comestible or medicinal product is a beverage, a beverage mix, or a beverage concentrate

195 The method of claim 191 wherein the modified comestible or medicinal product is a soda, or juice,

196 The method of claim 191 wherein the modified comestible or medicinal product is an alcoholic beverage

197 The method of claim 191 wherein the modified comestible or medicinal product is a pharmaceutical composition intended for oral administration

198 The method of claim 191 wherein the modified comestible or medicinal product is an oral hygiene product

199 The method of claim 191 wherein the amide compound is present in the modified comestible or medicinal product in a concentration from about 0 001 ppm to about 100 ppm

200 The method of claim 191wherein the amide compound is present in the modified comestible or medicinal product in a concentration from about 0 1 ppm to about 10 ppm

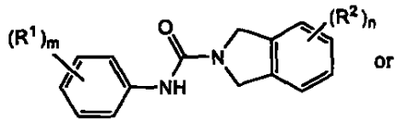
201 The modified comestible or medicinal product produced by the method of claims 191-200

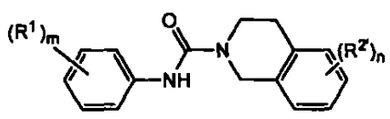
202 A method for modulating the sweet taste of a comestible or medicinal product comprising

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

b) combining the comestible or medicinal product or precursor thereof with about 0 001 ppm to about 100 ppm of at least one non-naturally occurring urea compound, or a comestibly acceptable salt thereof, so as to form a modified comestible or medicinal product,

wherein the urea compound has the formula



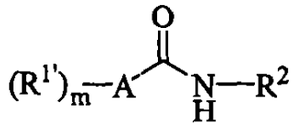
or


wherein m and n are independently 0, 1, 2, or 3, and each R1'and R2' is independently selected from fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3, SEt, SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

203 The method of claim 202 wherein n is 0

204 A comestible or medicinal product produced by the method of claim 202

205 A comestible or medicinal product, or a precursor thereof comprising about 0 001 ppm to about 100 ppm of at least one non-naturally occurring amide compound, or a comestibly acceptable salt thereof, wherein the amide compound has the formula



wherein A comprises a 5 or 6 membered aryl or heteroaryl ring,

m is 0 1, 2 3 or 4,

each R1′ is independently selected from hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3, SEt, SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy, and

R2 comprises between 4 and 14 carbon atoms and 0, 1, 2, 3, 4, or 5 heteroatoms independently selected from oxygen, nitrogen, sulfur

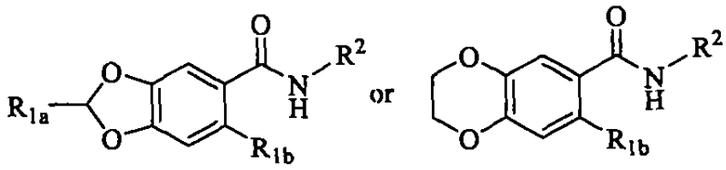
206 The comestible or medicinal product, or a precursor thereof of claim 205 wherein A is a phenyl ring

207 The comestible or medicinal product, or a precursor thereof of claim 206 wherein m is 1, 2, or 3

208 The comestible or medicinal product, or a precursor thereof of claim 206 wherein R2 is a C3-C10 branched alkyl

209 The comestible or medicinal product, or a precursor thereof of claim 206 wherein R2 is an α-substituted carboxylic acid or α substituted carboxylic acid methyl ester

210 The comestible or medicinal product, or a precursor thereof of claim 205 wherein the amide compound has the formula

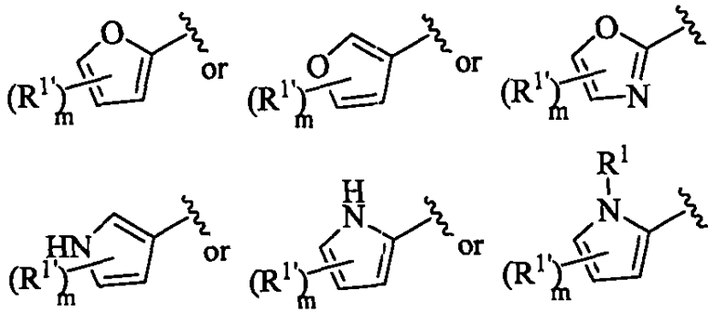


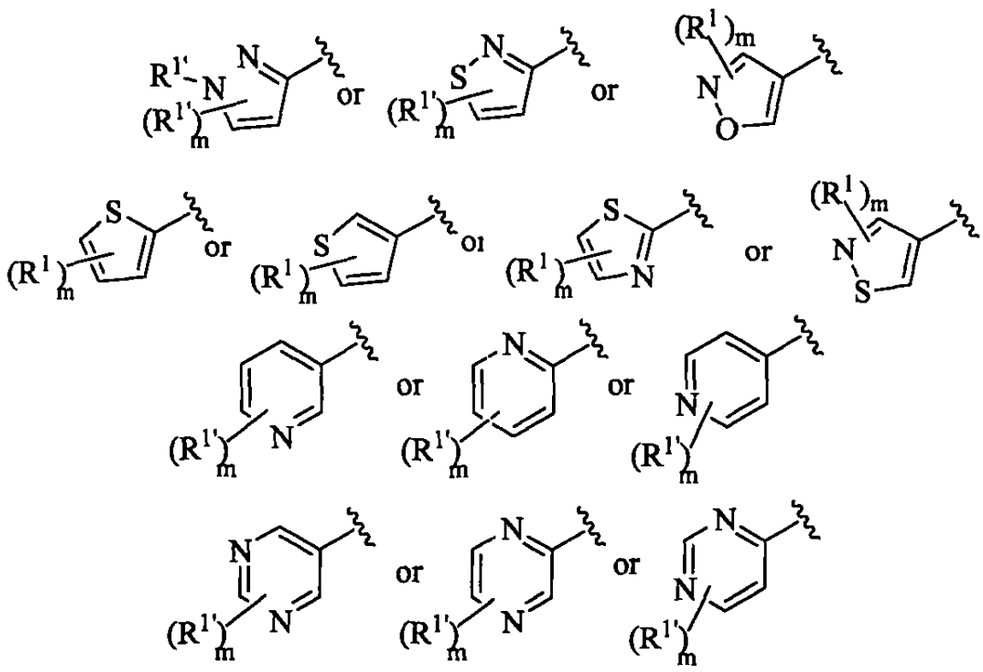
wherein R1a and R1b are independently hydrogen or methyl

211 The comestible or medicinal product, or a precursor thereof of claim 210 wherein R2 is a C3-C10 branched alkyl

212 The comestible or medicinal product or a precursor thereof of claim 210 wherein R2 is an α-substituted carboxylic acid or α-substituted carboxylic acid methyl ester

213 The comestible or medicinal product, or a precursor thereof of claim 205 wherein A is a monocyclic heteroaryl having one of the formulas





wherein m is 0, 1, 2, or 3, and each R1 is independently selected from hydrogen, hydroxy, fluoro, chloro NH2, NHCH3, N(CH3)2, CO2CH3, SEt, SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl methoxy, ethoxy, isopropoxy, and trifluoromethoxy

214 The comestible or medicinal product, or a precursor thereof of claim 213 wherein R2 is a C3-C10 branched alkyl

215 The comestible or medicinal product, or a precursor thereof of claim 213 wherein R2 is an α-substituted carboxylic acid or α-substituted carboxylic acid methyl ester

216 The comestible or medicinal product, or a precursor thereof of claim 205 wherein the modified comestible or medicinal product is a food for human consumption

217 The comestible or medicinal product, or a precursor thereof of any of claims 205-215 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

218 A comestible product, or a precursor thereof of claim 205 comprising one or more meats, poultry, fish, vegetables, grains, or fruits

219 A comestible product, or a precursor thereof of claim 205 that is a frozen food, an uncooked food, or a fully or partially cooked food

220 A comestible product, or a precursor thereof of claim 205 that is a soup a dehydrated or concentrated soup, or a dry soup

221 A comestible product, or a precursor thereof of claim 205wherein the modified comestible or medicinal product is a snack food

222 A comestible product, or a precursor thereof of any of claims 205-215 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

223 A comestible product, or a precursor thereof of claim 205wherein 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

224 A comestible product, or a precursor thereof of any of claims 205-215 wherein the modified comestible or medicinal product is a beverage, a beverage mix, or a beverage concentrate

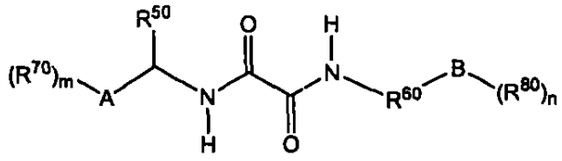
225 A comestible product, or a precursor thereof of claim 205 wherein the modified comestible or medicinal product is a soda, or juice

226 A comestible product, or a precursor thereof of claim 205 wherein the modified comestible or medicinal product is an alcoholic beverage

227 A comestible product, or a precursor thereof of claims any of claims 205-215 wherein the modified comestible or medicinal product is a pharmaceutical composition for oral administration

228 A comestible product, or a precursor thereof of claim 205 wherein the modified comestible or medicinal product is an oral hygiene product

229 A comestible or medicinal product, or a precursor thereof comprising at least a savory flavor modulating amount of at least one oxalamide compound, or a comestibly acceptable salt thereof, wherein the oxalamide compound has the formula



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,

R50 is hydrogen or an alkyl comprising one to four carbon atoms,

R60 is absent or a C1-C5 alkylene,

R70 and R80 are independently selected from the group consisting of hydrogen, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3, SEt, SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy, or two of R70 together form a methylenedioxy ring

230 A comestible product, or a precursor thereof of claim 229 wherein A and B are independently a phenyl, pyridyl, furanyl, benzofuranyl, pyrrole, benzothiophene, piperidyl, cyclopentyl, cyclohexyl, or cycloheptyl ring,

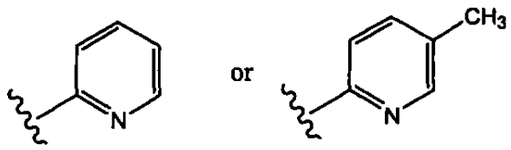
m and n are independently 0, 1, 2, or 3,

R50 is hydrogen or methyl,

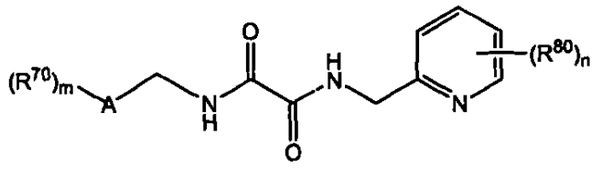
R60 is -CH2- or -CH2CH2-

231 A comestible product, or a precursor thereof of claim 230 wherein B is an optionally substituted pyridine ring

232 A comestible product, or a precursor thereof of claim 231 wherein the pyridyl-R80 radical has the structure



233 A comestible product, or a precursor thereof of claim 229 wherein the amide compound is an oxalamide compound having the formula



wherein A is a substituted aryl or heteroaryl ring comprising five to 12 carbon atoms

m and n are 0, 1, 2, or 3,

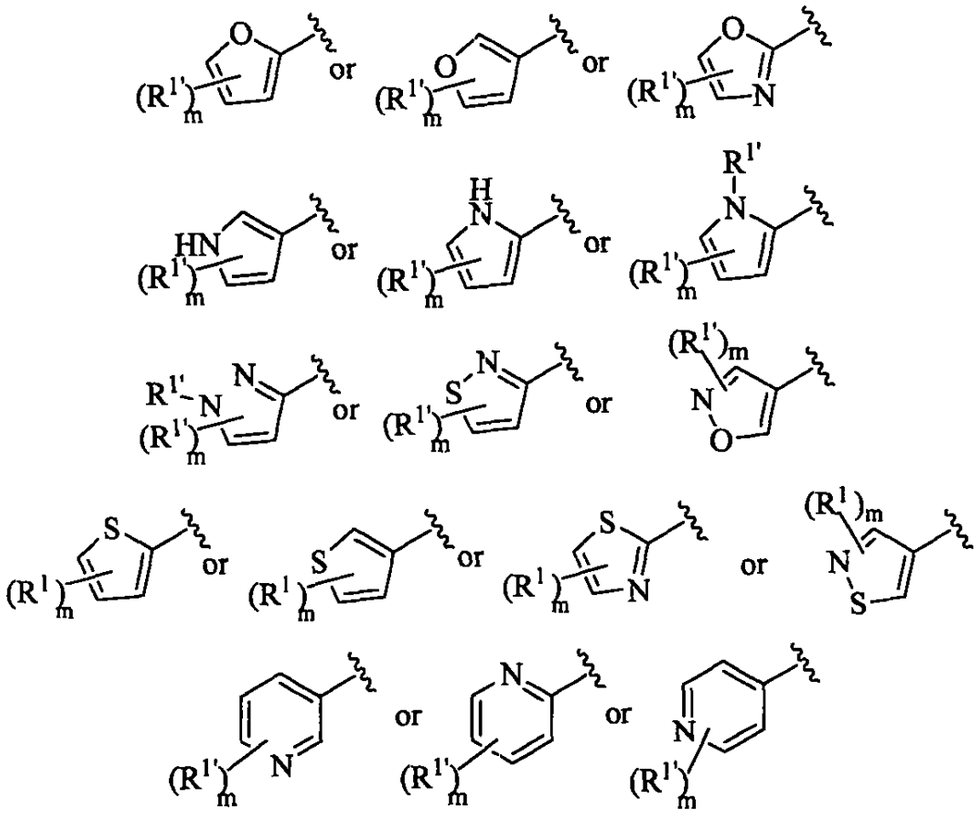
each R70 and R80 is independently selected from the group consisting of hydrogen hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3, SEt, SCH3, methyl

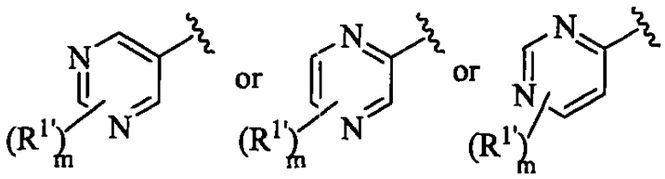
ethyl, isopropyl, vinyl, trifluoromethyl, methoxy ethoxy isopropoxy, and trifluoromethoxy, or two of R70 together form a methylenedioxy ring

234 A comestible product, or a precursor thereof of claim 233 wherein A is a 2-, 3-, or 4-mono-substituted phenyl, 2,4-, 2,5-, 2,5, 2,6, 3,5-, or 3,6-disubstituted phenyl, 3-alkyl-4-substituted phenyl, a tri-substituted phenyl, wherein the R70 groups are independently selected from the group consisting of, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3, SEt, SCH3, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy, or two of R70 together form a methylenedioxy ring

235 A comestible product, or a precursor thereof of claim 233 wherein A is 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, NH2, NHCH3, N(CH3)2, CO2CH3, SEt, SCH3, methyl, ethyl, isopropyl vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy group

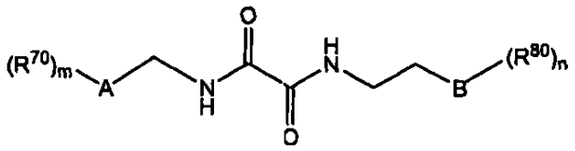
236 A comestible product, or a precursor thereof of claim 233 wherein A has one of the formulas





wherein m is 0, 1, 2, or 3, and each R1′ is independently selected from independently selected from hydroxy fluoro, chloro, NH2, NHCH3, N(CH3)2, COOCH3, SCH3, SEt, methyl, ethyl isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

237 An oxalamide compound having the formula



wherein A and B are a substituted aryl or heteroaryl ring comprising three to twelve ring carbon atoms,

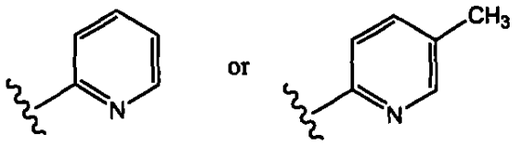
m and n are independently 0, 1, 2 or 3,

each R70 and R80 is independently selected from the group consisting of, hydroxy fluoro, chloro, NH2, NHCH3, N(CH3)2, COOCH3, SCH3 SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy , or two of R70 together form a methylenedioxy ring,

or a comestibly acceptable salt thereof

238 The oxalamide compound of claim 237 wherein B is a pyridyl ring

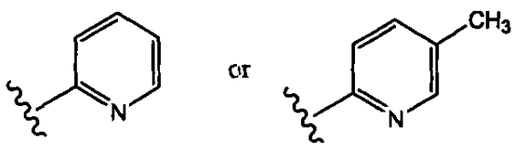
239 The oxalamide compound of claim 237 wherein the pyridyl-R80 radical has the structure



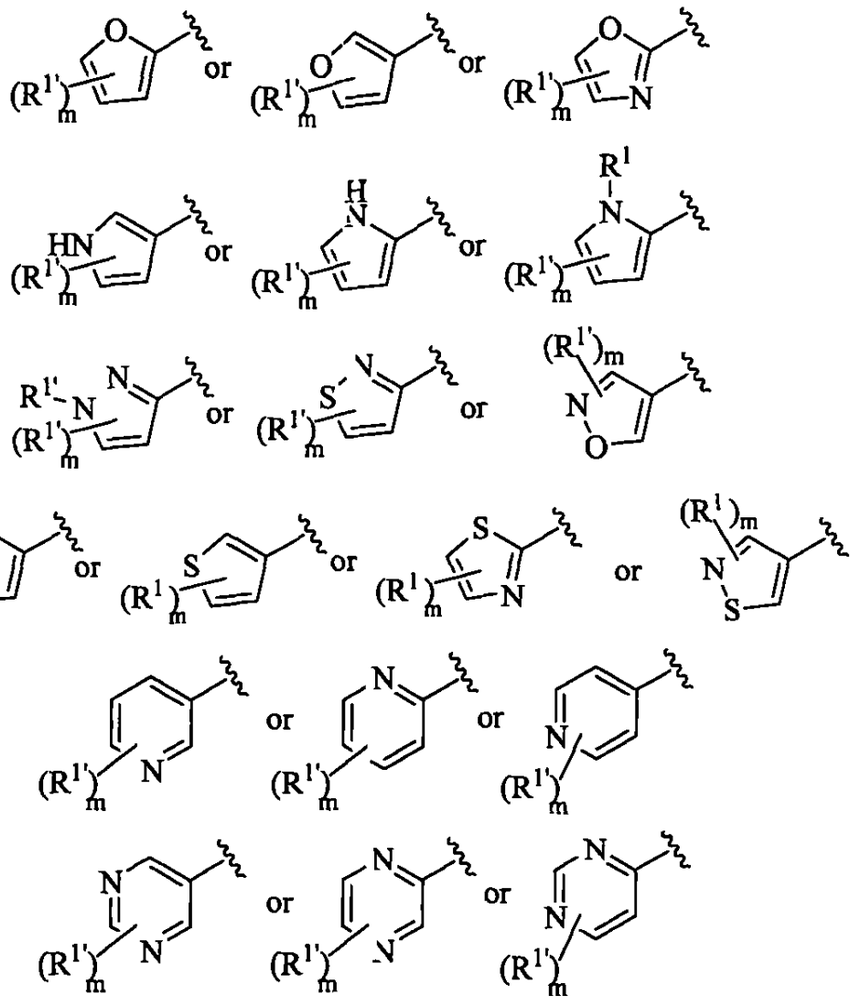
240 The oxalamide compound of claim 238 wherein A is a phenyl ring

241 The oxalamide compound of claim 240 wherein B is a pyridyl ring

242 The oxalamide compound of claim 240 wherein the pyridyl-R80 radical has the structure



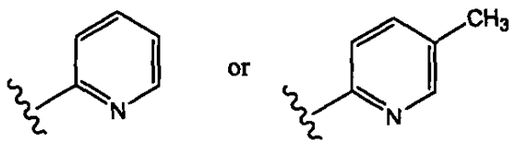
243 The oxalamide compound of claim 237 wherein A has one of the formulas



wherein m is 0, 1, 2, or 3, and each R1′ is independently selected from, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, COOCH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy ethoxy, isopropoxy, and trifluoromethoxy

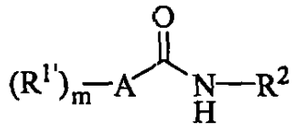
244 The oxalamide compound of claim 243 wherein B is a pyridyl ring

245 The oxalamide compound of claim 244 wherein the pyridyl-R80 radical has the structure

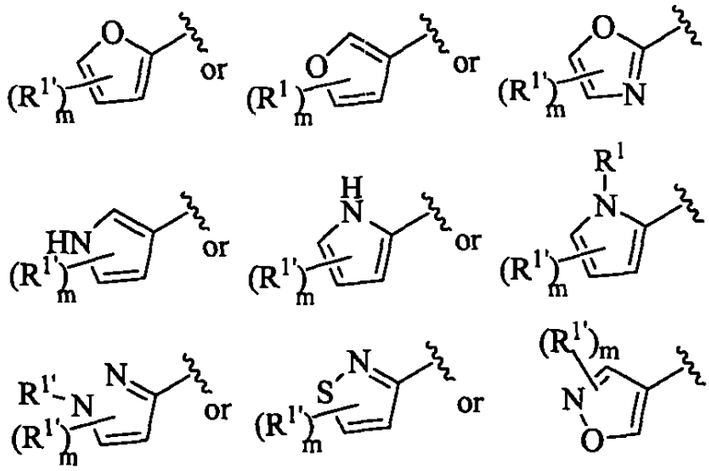


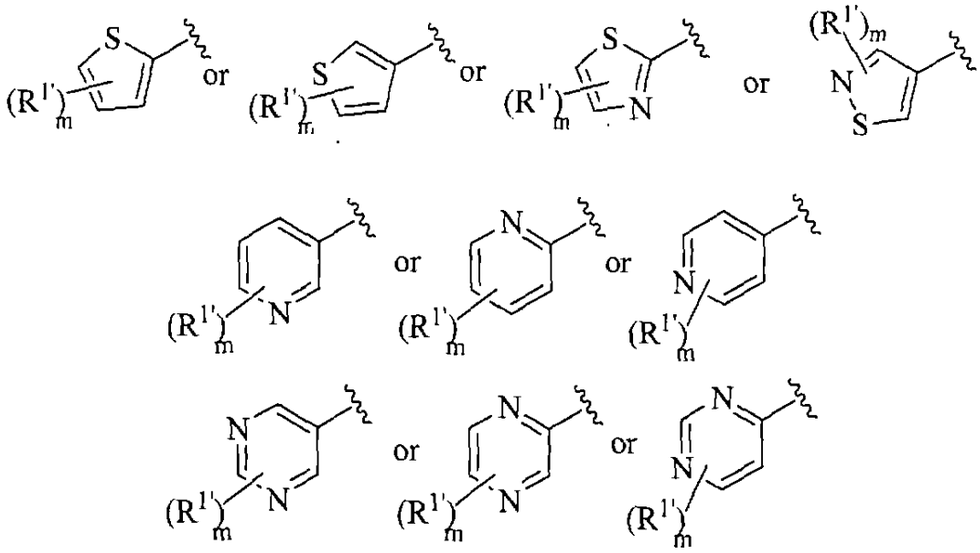
246 An oxalamide compound of claim 237 having the formula
N1-(2-methoxy-4-methylbenzyl)-N2-(2-(5-methylpyridin-2-yl)ethyl)oxalamide,
N1-(2-methoxy-4-methylbenzyl)-N2-(2-(pyridin-2-yl)ethyl)oxalamide,
N1-(2,4-dimethoxybenzyl)-N2-(2-(5-methylpyridin-2-yl)ethyl)oxalamide,
N1 (2,4-dimethylbenzyl)-N2-(2-(pyridin-2 yl)ethyl)oxalamide,
N1-(2,4-dimethoxybenzyl)-N2-(2-(pyridin-2-yl)ethyl)oxalamide,
N-(2,4-Dimethoxy-benzyl)-N'-(2-pyridin-2-yl-ethyl)-oxalamide,
or a comestibly acceptable salt thereof

247 A comestible or medicinal product, or a precursor thereof comprising at least a sweet flavor modulating amount of at least one non-naturally occurring amide compound, or a comestibly acceptable salt thereof, wherein the amide compound has the formula



wherein A is an optionally substituted phenyl ring or is a heteroaryl ring having one of the formulas





wherein m is 0, 1, 2, or 3, and each R1′ is independently selected from, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, COOCH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy , and

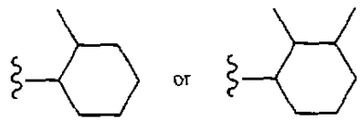
wherein R2 is a branched C3-C10 alkyl, or a cyclohexyl, tetrahydronapthalene, or indanyl group, optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, COOCH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy .

248. The comestible product or medicinal product, or a precursor thereof of claim 247 wherein R2 is a branched C3-C10 alkyl.

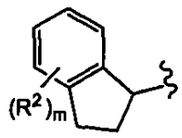
249. The comestible product or medicinal product, or a precursor thereof of claim 247 wherein R2 is an optionally substituted cyclohexyl ring.

250. The comestible product or medicinal product, or a precursor thereof of claim 247 wherein R2 is a cyclohexyl, optionally substituted with 1, 2, or 3 methyl groups.

251. The comestible product or medicinal product, or a precursor thereof of claim 247 wherein R2 has the formula

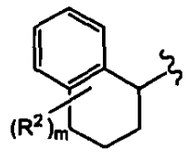


252 The comestible product or medicinal product, or a precursor thereof of claim 247 wherein R2 is a 1-indanyl having the formula



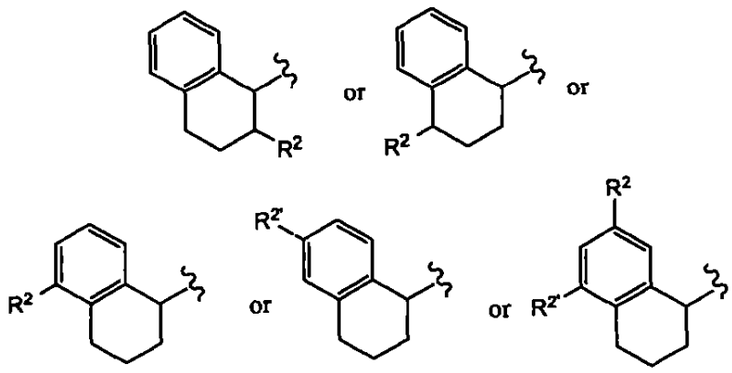
wherein m is 0,1, 2, or 3, and each R2′ is independently selected from hydrogen, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, COOCH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

253 The comestible product or medicinal product, or a precursor thereof of claim 247 wherein R2 is a 1-(1,2,3,4) tetrahydronapthalene having the formula



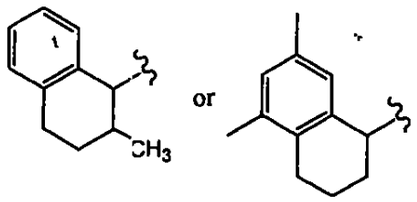
wherein m is 0,1, 2, or 3, and each R2′ can be bonded to either the aromatic or non-aromatic ring and is independently selected from hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, COOCH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

254 The comestible product or medicinal product, or a precursor thereof of claim 247 wherein R2 has the formula

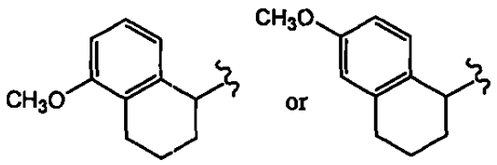


wherein R2′ is hydrogen, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, COOCH3, SCH3, SEt, methyl ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

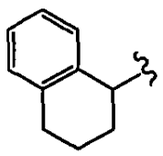
255 The comestible product or medicinal product, or a precursor thereof of claim 247 wherein R2 has the formula



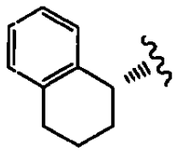
256 The comestible product or medicinal product, or a precursor thereof of claim 247 wherein R2 has the formula



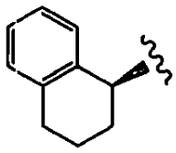
257 The comestible product or medicinal product, or a precursor thereof of claim 247 wherein R2 is a 1-(1,2,3,4) tetrahydronapthalene ring having the formula



258 The comestible product or medicinal product, or a precursor thereof of claim 247 wherein R2 is an (R)-1-(1,2,3,4) tetrahydronapthalene ring having the formula



259 The comestible product or medicinal product, or a precursor thereof of claim 247 wherein R2 is an (R)-1-(1 2,3,4) tetrahydronapthalene ring having the formula



260 The comestible or medicinal product, or a precursor thereof of claim 247wherein the modified comestible or medicinal product is a food for human consumption

261 The comestible or medicinal product, or a precursor thereof of claim 247wherein 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

262 A comestible product, or a precursor thereof of claim 247 comprising one or more meats, poultry, fish, vegetables, grains, or fruits

263 A comestible product, or a precursor thereof of claim 247 that is a frozen food, an uncooked food, or a fully or partially cooked food

264 A comestible product, or a precursor thereof of claim 247 that is a soup, a dehydrated or concentrated soup, or a dry soup

265 A comestible product, or a precursor thereof of claim 247 wherein the modified comestible or medicinal product is a snack food

266 A comestible product, or a precursor thereof of claim 247 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

267 A comestible product, or a precursor thereof of claim 247 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

268 A comestible product, or a precursor thereof of claim 247 wherein the modified comestible or medicinal product is a beverage, a beverage mix, or a beverage concentrate

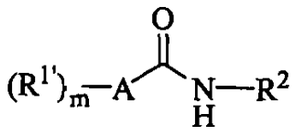
269 A comestible product, or a precursor thereof of claim 247 wherein the modified comestible or medicinal product is a soda, or juice

270 A comestible product, or a precursor thereof of claim 247 wherein the modified comestible or medicinal product is an alcoholic beverage

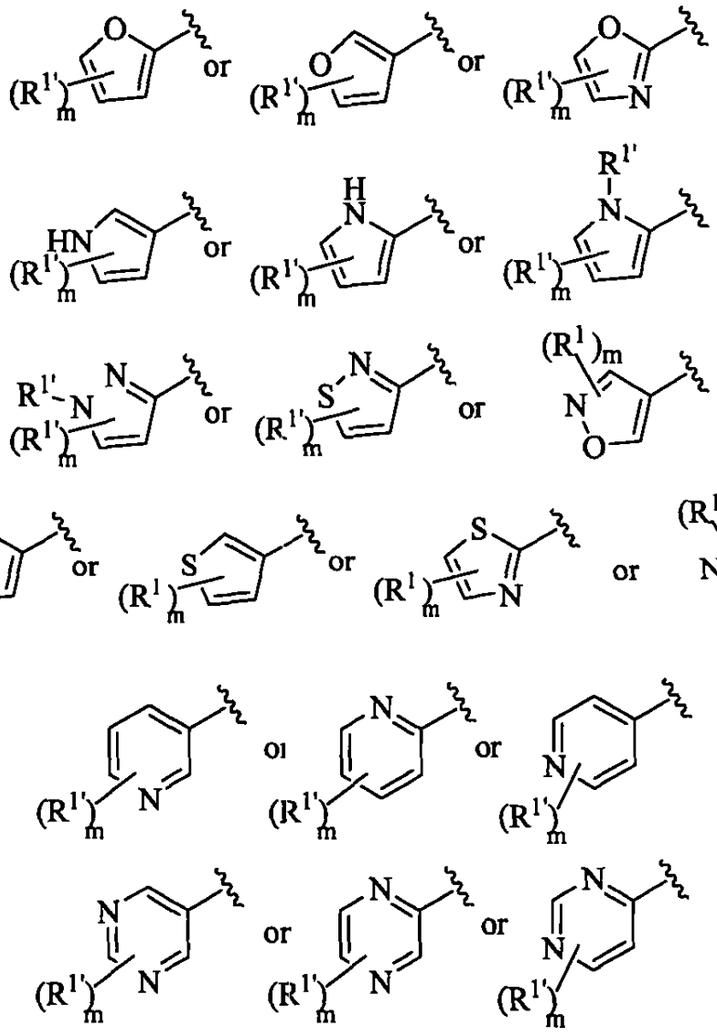
271 A comestible product, or a precursor thereof of claim 247 wherein the modified comestible or medicinal product is a pharmaceutical composition for oral administration

272 A comestible product, or a precursor thereof of claim 247 wherein the modified comestible or medicinal product is an oral hygiene product

273 An amide compound having the formula



wherein A is a phenyl ring or is a heteroaryl ring having one of the formulas



wherein m is 0, 1, 2, or 3, and each R1′ is independently selected from, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, COOCH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy , and

wherein R2 is (a) a branched C3-C10 alkyl, or (b) a cyclohexyl tetrahydronapthalene, or indanyl group, optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of hydroxy fluoro,

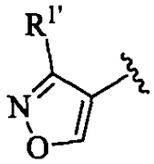
chloro, NH2, NHCH3, N(CH3)2, COOCH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy , or a comestibly acceptable salt thereof

274 The amide compound of claim 273 wherein R2 is a branched C3-C10 alkyl

275 The amide compound of claim 274 wherein A is an optionally substituted phenyl ring

276 The amide compound of claim 274 wherein A is an optionally substituted pyridyl ring

277 The amide compound of claim 274 wherein A is a heteroaryl ring having the formula

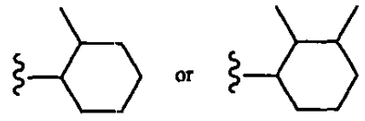


wherein R1′ is hydrogen, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, COOCH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

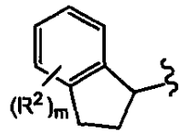
278 The amide compound of claim 275 wherein R2 is an optionally substituted cyclohexyl ring

279 The amide compound of claim 275 wherein the cyclohexyl ring is substituted with 1, 2, or 3 methyl groups

280 The amide compound of claim 275 wherein R2 has the formula

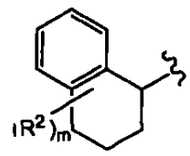


281 The amide compound of claim 275 wherein R2 is a 1-indanyl having the formula



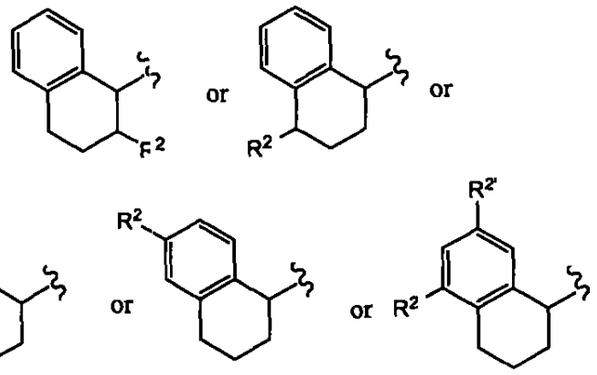
wherein m is 0,1, 2, or 3, and each R2′ is independently selected from, hydroxy fluoro chloro, NH2, NHCH3, N(CH3)2 COOCH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

282 The amide compound of claim 275 wherein R2 is a 1-(1,2,3,4) tetrahydronapthalene having the formula



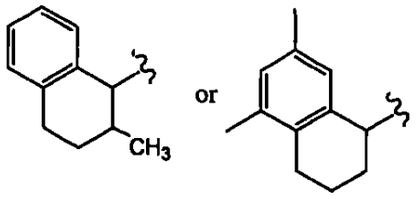
wherein m is 0,1, 2, or 3, and each R2' can be bonded to either the aromatic or non-aromatic ring and is independently selected from, hydroxy, fluoro chloro, NH2 NHCH3, N(CH3)2, COOCH3 SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy ethoxy, isopropoxy, and trifluoromethoxy

283 The amide compound of claim 275 wherein R2 has the formula

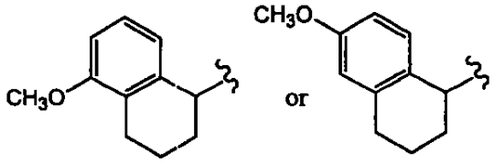


wherein each R2' is independently selected from the group consisting of hydrogen, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, COOCH3, SCH3, SEt methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

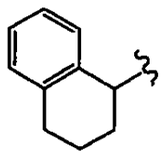
284 The amide compound of claim 275 wherein R2 has the formula



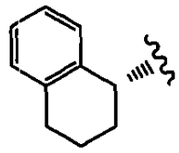
285 The amide compound of claim 275 wherein R2 has the formula



286 The amide compound of claim 275 wherein R2 is a 1-(1,2,3,4) tetrahydronapthalene ring having the formula



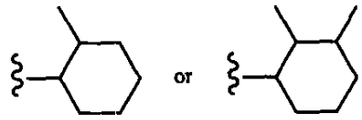
287 The amide compound of claim 275 wherein R2 is an (R)-1-(1,2,3,4) tetrahydronapthalene ring having the formula



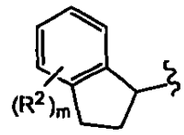
288 The amide compound of claim 277 wherein R2 is an optionally substituted cyclohexyl ring

289 The amide compound of claim 277 wherein the cyclohexyl ring is substituted with 1, 2, or 3 methyl groups

290 The amide compound of claim 277 wherein R2 has the formula

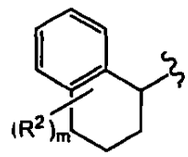


291 The amide compound of claim 277 wherein R2 is a 1-indanyl having the formula



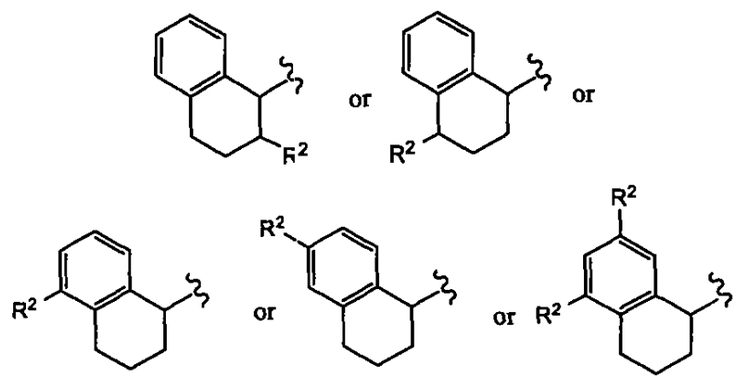
wherein m is 0,1, 2, or 3, and each R2' can be bonded to either the aromatic or non-aromatic ring and is independently selected from hydrogen, hydroxy fluoro chloro NH2, NHCH3, N(CH3)2, COOCH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

292 The amide compound of claim 277 wherein R2 is a 1-(1,2,3,4) tetrahydronapthalene having the formula



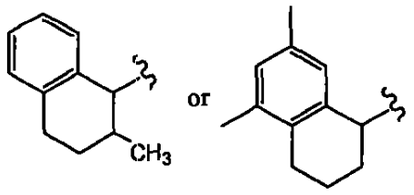
wherein m is 0,1, 2, or 3, and each R2' can be bonded to either the aromatic or non-aromatic ring and is independently selected from hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, COOCH3, SCH3, SEt, methyl ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

293 The amide compound of claim 277 wherein R2 has the formula

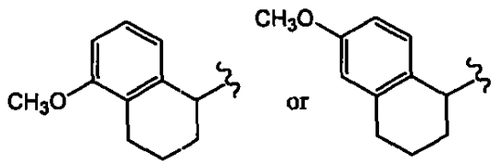


wherein each R2' is independently selected from the group consisting of is hydrogen, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, COOCH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

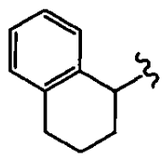
294 The amide compound of claim 277 wherein R2 has the formula



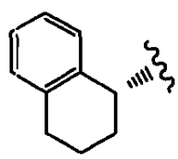
295 The amide compound of claim 277 wherein R2 has the formula



296 The amide compound of claim 277 wherein R2 is a 1-(1,2,3,4) tetrahydronapthalene ring having the formula



297 The amide compound of claim 277 wherein R2 is an (R)-1-(1,2,3,4) tetrahydronapthalene ring having the formula



298 An amide compound having the formula

3-chloro-2-hydroxy-N-(2-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide,

3-chloro-2-hydroxy-N-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide,

(R)-3-chloro-2-hydroxy-N-(1 2,3,4-tetrahydronaphthalen-1-yl)benzamide,

3-chloro-2-hydroxy-N-(5-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide,

3-chloro-2-hydroxy-N-(4-methyl-1 2,3,4-tetrahydronaphthalen-1-yl)benzamide,

3-chloro-2-hydroxy-N-(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide,

3-chloro-2-hydroxy-N (1,2 3 4-tetrahydronaphthalen-1-yl)benzamide,

2,3-dihydroxy-N-(2-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide,

2-hydroxy-N-(2-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide,

2,3-dihydroxy-N-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)benzamide,

(S)-2,6-dimethyl-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzamide,

N-(5 7 dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methylisoxazole-4 carboxamide,

3-methyl-N-(2-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)isoxazole-4-carboxamide,

3-methyl-N-(4-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)isoxazole-4-carboxamide,

N-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methylisoxazole-4-carboxamide,

(R)-5-bromo-N-(1,2,3,4-tetrahydronaphthalen-1-yl)nicotinamide,

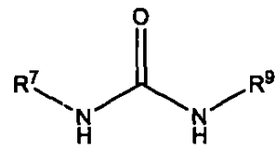
(R)-3-methyl-N-(1,2,3,4-tetrahydronaphthalen-1-yl)isoxazole-4-carboxamide,

(S)-5-bromo-N-(1,2,3,4-tetrahydronaphthalen-1-yl)nicotinamide,

(R)-N-(1,2,3,4-tetrahydronaphthalen-1-yl)furan-3-carboxamide,

(R)-5-methyl-N-(1,2,3,4-tetranydronaphthalen-1-yl)ısoxazole-4-carboxamıde,
(R)-N-(1,2,3,4-tetrahydronaphthalen-1-yl)furan-3-carboxamıde,
3-methyl-N-(1,2,3,4-tetrahydronaphthalen-1-yl)ısoxazole-4-carboxamıde,
N-(3,3-dımethylbutan-2-yl)-2,3,5,6-tetrafluoro-4-methylbenzamıde,
2,3,5,6-tetrafluoro-4-methyl-N-(3-methylbutan-2-yl)benzamıde,
2,3,5,6-tetrafluoro-4-methyl-N-(2-methylcyclohexyl)benzamıde,
N-(2-methylcyclohexyl)-3-(trıfluoromethoxy)benzamıde,
3-chloro-5-fluoro-N-(2-methylcyclohexyl)benzamıde,
(R)-N-(3,3-dımethylbutan-2-yl)-2,3,5,6-tetrafluoro-4-methylbenzamıde,
4-fluoro-N-(2-methylcyclohexyl)-3-(trıfluoromethyl)benzamıde,
(S)-2,3,5,6-tetrafluoro-4-methyl-N-(3-methylbutan-2-yl)benzamıde,
2,5-dıchloro-N-(2-methylcyclohexyl)benzamıde
3,5-dıchloro-2,6-dımethoxy-N (2-methylcyclohexyl)benzamıde, or
2,6-dimethyl-N-(2 methylcyclohexyl)benzamıde
or a comestıbly acceptable salt thereof

299 A urea compound havıng the formula



wherein R7 ıs an aryl or heteroaryl comprısıng three to ten rıng carbon atoms which ıs optıonally substıtuted wıth 1, 2, or 3 substıtuents ındependently selected from, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, CO2CH3, SEt, SCH3, methyl, ethyl, ısopropyl, vınyl, trıfluoromethyl, methoxy, ethoxy, ıspropoxy, and trıfluoromethoxy, and
R9 ıs a branched C3-C10 alkyl or a cyclohexyl, tetrahydronapthalene, or ındanyl group, optıonally substıtuted wıth 1, 2, or 3 substıtuents ındependently selected from the group consıstıng of hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2 COOCH3, SCH3, SEt, methyl, ethyl, ısopropyl, vınyl, trıfluoromethyl, methoxy ethoxy, ısopropoxy, and trıfluoromethoxy
or a comestıbly acceptable salt thereof

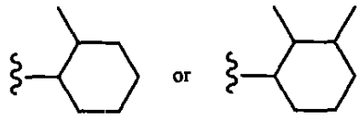
300 The compound of claım 299 wherein R7 ıs an optıonally substıtuted phenyl rıng

301 The compound of claım 300 wherein R9 ıs a branched C3-C10 alkyl

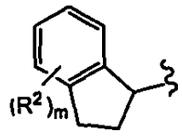
302 The compound of claim 300 wherein R9 is is an optionally substituted cyclohexyl ring

303 The compound of claim 302 wherein the cyclohexyl ring is substituted with 1, 2, or 3 methyl groups

304 The compound of claim 302 wherein R9 has the formula

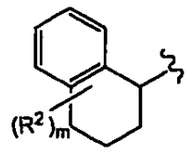


305 The compound of claim 299 wherein R9 is a 1-indanyl having the formula



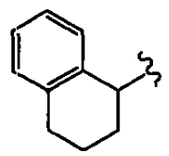
wherein m is 0,1, 2, or 3, and each R9 is independently selected from hydrogen hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, COOCH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

306 The amide compound of claim 299 wherein R9 is a 1-(1,2,3,4) tetrahydronapthalene having the formula

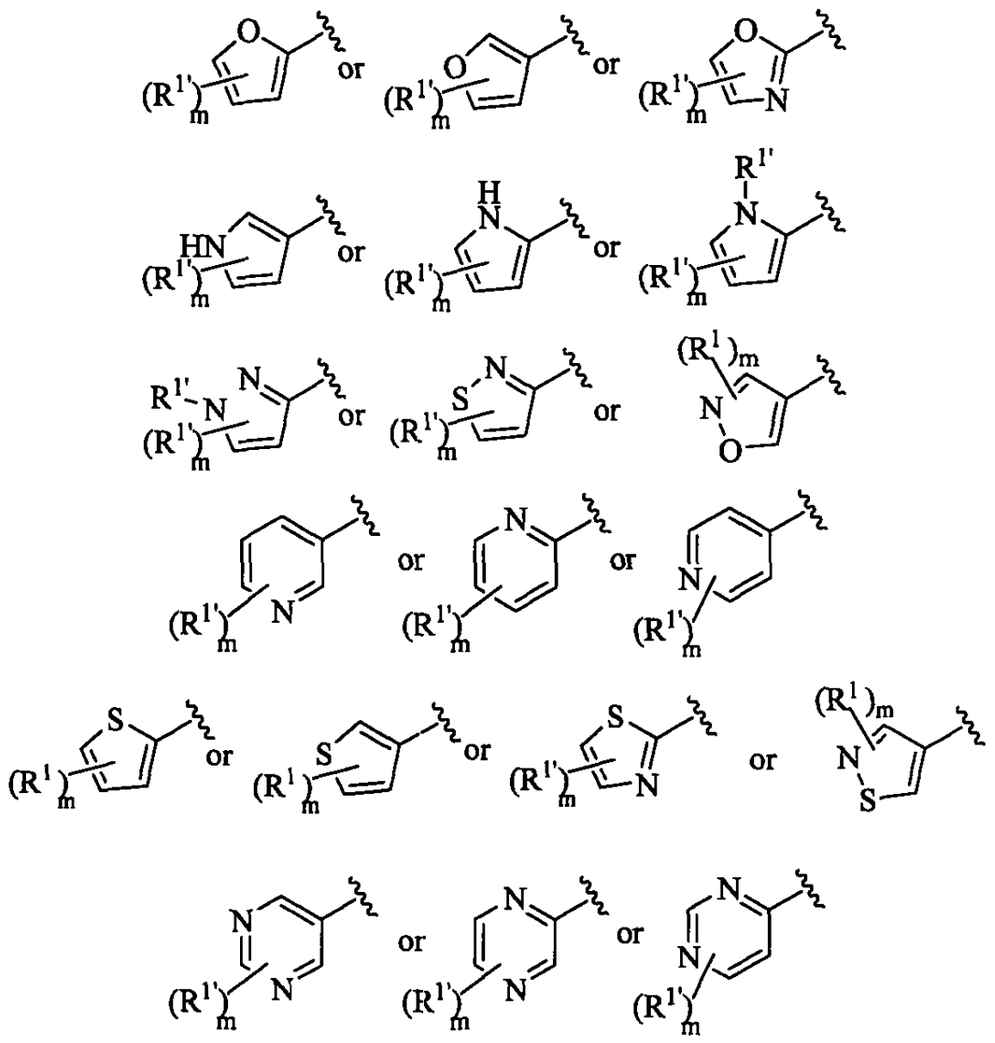


wherein m is 0,1, 2, or 3, and each R9 can be bonded to either the aromatic or non-aromatic ring and is independently selected from, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, COOCH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy

307 The amide compound of claim 299 wherein R9 is a 1-(1,2,3,4) tetrahydronapthalene ring having the formula



308 The amide compound of claim 299 wherein R7 is a heteroaryl ring having one of the formulas



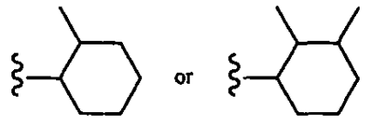
wherein m is 0, 1, 2, or 3, and each R1′ is independently selected from hydrogen, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, COOCH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy ,

309 The compound of claim 308 wherein R9 is a branched C3-C10 alkyl

310 The compound of claim 308 wherein R9 is an optionally substituted cyclohexyl ring

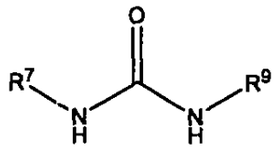
311 The compound of claim 308 wherein the cyclohexyl ring is substituted with 1, 2, or 3 methyl groups

312 The compound of claim 308 wherein R9 has the formula



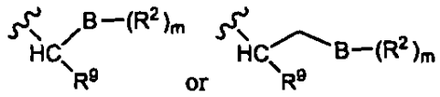
313 A comestible or medicinal product, or a precursor thereof comprising at least a savory flavor modulating amount of at least one compound of claims 299-312

314 A urea compound having the formula



wherein R7 is an aryl or heteroaryl comprising three to ten ring carbon atoms which is optionally substituted with 1, 2, or 3 substituents independently selected from, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, COOCH3, SCH3, SEt, methyl ethyl, isopropyl, vinyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy, and

R9 has the structure



wherein R9 is hydrogen, a C1-C10 alkyl, B is a phenyl, pyridyl, furanyl, thiofuranyl, pyrrole, cyclopentyl cyclohexyl, or piperidyl ring, m is 0,1, 2, or 3, and each R2' is independently selected from hydrogen, hydroxy, fluoro, chloro, NH2, NHCH3, N(CH3)2, COOCH3, SCH3, SEt, methyl, ethyl, isopropyl, vinyl, trifluoromethyl, methoxy etho cy isopropoxy and trifluoromethoxy or a comestibly acceptable salt thereof

315 The compound of claim 314 wherein R7 is an optionally substituted phenyl ring and B is phenyl or pyridyl

316 The compound of claim 314 wherein R7 is an optionally substituted phenyl ring and B is and optionally substituted cyclohexyl

317 A comestible or medicinal product, or a precursor thereof comprising at least a savory flavor modulating amount of at least one compound of claim 314

318 An amide compound having the formula
(R)-methyl 2-(3-chloro-4-methoxybenzamido)-4-methylpentanoate,
4-methoxy-3-methyl-N-(5-methylhexan-3-yl)benzamide,

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

(S)-methyl 4-methyl-2-(4-methyl-3-(methylthıo)benzamıdo)pentanoate,

4-methoxy-3-methyl-N-(2-methylheptan-4-yl)benzamıde,

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

3,4-dımethyl-N-(2-methylhexan 3 yl)benzamıde,

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

N-(hexan-3-yl)-4-methoxy-3-methylbenzamıde,

N-(heptan-4-yl)-3-methyl-4-(methylthıo)benzamıde,

N-(hexan-3-yl)-3-methyl-4-(methylthıo)benzamıde,

methyl 2-(3-chloro-4-methoxybenzamıdo)hexanoate,

3,4-dımethyl-N-(2-methylheptan-4-yl)benzamıde,

N-(hexan-3-yl)-3,4-dımethylbenzamıde,

N-(heptan-4-yl)-3,4-dımethylbenzamıde,

(R)-methyl 4-methyl-2-(4-(methylthıo)benzamıdo)pentanoate,

4-ethoxy-N-(heptan-4-yl)-3-methylbenzamıde,

3,4-dımethyl-N-(5-methylhexan-3-yl)benzamıde,

(R)-methyl 4-methyl-2-(4-vınylbenzamıdo)pentanoate,

4-methoxy-3-methyl-N-(2-methylhexan-3-yl)benzamıde,

N-(heptan-4-yl)benzo[d][1,3]dıoxole-5-carboxamıde

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

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

(R)-methyl-2-(2,3-dımethylfuran-5-carboxamıdo)-4-methylpentanoate, or

4-Methoxy-N-(1-methoxymethyl-3-methyl-butyl)-3-methyl-benzamıde,

or a comestıbly acceptable salt thereof

319 An amıde compound havıng the formula

N-(heptan-4-yl)benzo[d][1,3]dıoxole-5-carboxamıde or

N-(2,4-Dımethoxy-benzyl)-N'-(2-pyrıdın-2-yl-ethyl)-oxalamıde,

or a comestıbly acceptable salt thereof

320 A comestıble or medıcınal product comprısıng the compounds of claım 319 at a concentratıon between about 0 01 to about 10 ppm

321 The comestıble or medıcınal product of claım 320 wherein the comestıble or medıcınal product ıs a a food for human consumptıon

322 An urea compound havıng the formula

1-(2-chlorophenyl)-3-(heptan-4 yl)urea,

1-(2,4-dichlorophenyl)-3 (1-phenylpropyl)urea,

1-(2,4-dimethoxyphenyl)-3-(heptan-4-yl)urea,

1-(2-fluorophenyl)-3-(heptan-4-yl)urea,

1-(4-isopropylphenyl)-3-(2-(pyridin-2 yl)ethyl)urea,

or a comestibly acceptable salt thereof

ABSTRACT

The present invention relates to the discovery that certain non-naturally occurring, non-peptide amide compounds and amide derivatives, such as oxalamides, ureas, and acrylamides are useful flavor or taste modifiers, such as a flavoring or flavoring agents and flavor or taste enhancer, more particularly, savory (the 'umami' taste of monosodium glutamate) or sweet taste modifiers, - savory or sweet flavoring agents and savory or sweet flavor enhancers, for food, beverages, and other comestible or orally administered medicinal products or compositions

SABORES NOVEDOSOS MODIFICADORES DE SABOR, DEGUSTANTES, MEJORADORES DE DEGUSTACION, DEGUSTANTES ACRES O DULCES, Y/O MEJORADORES Y USO DE LOS MISMOS

CAMPO DE LA INVENCIÓN

La presente invención se relaciona al descubrimiento de modificadores de sabor y degustación tal como un saborizante o agentes saborizantes y mejoradores de sabor o degustacion más particularmente modificadores de sabor sabroso (acre") o dulce - agentes de sabor sabroso o dulce y mejoradores de sabor sabroso o dulce, para alimentos, bebidas y otros comestibles o productos o composiciones medicinales oralmente administrados

ANTECEDENTES DE LA INVENCIÓN

Por siglos varias composiciones y/o compuestos naturales y no naturales se han agregado a alimentos comestibles (digeribles), bebidas, y/o composiciones medicinales oralmente administradas para mejorar su sabor Aunque se ha conocido que existen sólo unos pocos tipos basicos de 'sabores' la base biologica y bioquimica de percepcion de sabor se entendio mal y se han descubierto grandemente la mayoría de los agentes de mejoramiento de sabor o modificación de sabor por simple proceso de prueba y error

Ha habido un progreso reciente significativo para

identificar agentes saborizantes naturales utiles, tales como por ejemplo, edulcorantes tales como sacarosa, fructuosa glucosa eritritol, isomalto, lactitol, manitol, sorbitol, xilitol, ciertos terpenoides naturales conocidos, flavonoides o edulcorantes de proteinas *Vease por ejemplo,* un articulo reciente intitulado "Noncariogenic Intense Natural Sweeteners" por Kinhorn *et al* (Med Res Rev 18(5) 347-360, 1998) la cual discute recientemente materiales naturales descubiertos que son mucho mas intensamente dulces que los edulcorantes naturales comunes tales como sacarosa, fructuosa y similares De manera similar, ha habido un progreso reciente para identificar y comercializar nuevos edulcorantes artificiales, tales como aspartame sacarina acesulfame-K ciclamato, sucralosa y alitame, etc , *vease* un articulo reciente por Ager, *et al* (Angew Chem Int Ed 1998 37 1802-1817) La descripcion completa de las dos referencias identificadas anteriormente se incorporan por consiguiente en la presente para referencia, para el proposito de describir al menos una parte del conocimiento de aquellos con experiencia ordinaria en la tecnica con respecto a agentes edulcorantes conocidos

Sin embargo, existe en la técnica una necesidad para nuevos y mejorados agentes saborizantes Por ejemplo, uno de los cinco sabores básicos conocidos es el sabor sabroso o "acre' del glutamato monosodico ("MSG") MSG se conoce por producir reacciones adversas en alguna gente pero muy poco progreso se ha hecho para identificar sustitutos artificiales para MSG Se sabe

que pocos materiales de origen natural pueden incrementar o mejorar la efectividad del MSG como un agente saborizante sabroso, de manera que menos MSG podria ser necesario para una aplicación de saborizante dada Por ejemplo, los compuestos de nucleótido de monofosfato de inopina (IMP) o monofosfato de guanosina (GMP) de origen natural se conocen por tener un efecto multiplicador en el sabor sabroso del MSG, pero el IMP y el GMP son muy dificiles y caros para aislar y purificar a partir de fuentes naturales o sintetizar, y por lo tanto tienen sólo aplicación practica limitada para la mayoria de las necesidades comerciales en composiciones alimenticias o medicinales Compuestos menos caros que proporcionarian el sabor del MSG mismo, o mejorarian la efectividad de cualquier MSG que se presenta podrían ser de un valor muy elevado De manera similar el descubrimiento de compuestos que son ya sea nuevos edulcorantes de 'Alta Densidad" (es decir, son muchas veces edulcorantes que sacarosa) serian de valor, o de cualesquiera compuestos que incrementan significativamente el dulzor de edulcorantes naturales o artificiales de manera que menos de aquellos edulcorantes calóricos o no caloricos se requeririan, sería de una utilidad y un valor muy elevado

En años recientes, se ha hecho un progreso sustancial en la biotecnologia en general y en el mejor entendimiento de fenomenos biológicos y bioquímicos subyacentes de la percepcion del sabor Por ejemplo las proteínas receptoras de sabor se han

identificado recientemente en mamíferos que estan implicados en la percepción del sabor Particularmente, dos diferentes familias de los receptores acoplados con la proteina G se cree estan implicados en la percepción del sabor Se han identificado los T2R y los T1R (*Véase 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 Norteamericana 6,462,148, y las publicaciones PCT WO 02/06254 WO 00/63166 de la técnica, WO 02/064631 y WO 03/001876, y la Publicación de Patente US 2003-0232407 A1) Las descripciones completas de los articulos, las solicitudes de patentes y las patentes expedidas citadas inmediatamente de manera anterior y por consiguiente se incorporan en la presente para referencia, para todos los propositos incluyendo sus descripciones de las identidades y las estructuras de las proteinas receptoras de sabor de mamíferos de los T2R y los T1R y métodos para expresar artificialmente aquellos receptores en lineas celulares y utilizando lineas celulares resultantes para compuestos de selección como agentes saborizantes sabrosos' o dulces'

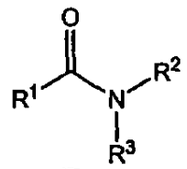
Mientras que la familia T2R incluye una familia sobre 25 genes que están implicados en la percepción de sabor amargo, los T1R sólo incluyen tres miembios, T1R1, T1R2 y T1R3 (*véase* Li, *et*

al, *Proc NAtl Acad Sci USA* (2002) 99 4962-4966) Recientemente, se descubrio en la WO 02/064631 y/o WO 03/001876 que ciertos miembros T1R, cuando se co-expresan en lineas celulares de mamífero adecuadas, se ensamblan para formar receptores de sabor funcionales Particularmente, se encontró que la co-expresión del T1R1 y el T1R3 en una célula huésped adecuada resulta en un receptor de sabor sabroso ("acre") T1R1/T1R3 funcional que responde al estimulo de sabor sabroso incluyendo glutamato de monosodio De manera similar se encontro que la co-expresión del T1R2 y el T1R3 en una célula huésped adecuada resulta en un receptor de sabor dulce" T1R2/T1R3 funcional que responde a diferentes estimulos de sabor incluyendo edulcorantes artificiales y de origen natural (*Vease* Li, *et al* (Id) Las referencias citadas anteriormente describen también ensayos y/o tamices de rendimiento elevado que miden la actividad receptora T1R1/T1R3 o T1R2/T1R3 por formación de imágenes fluorometricas en la presencia de compuestos objetivo Se emplearon ensayos y/o metodos de seleccion de rendimiento elevado descritos anteriormente para identificar compuestos lideres" iniciales que modulan la actividad de los receptores de sabor "sabroso" de los T1R1/T1R3 o los receptores de sabor "dulce" de los T1R2/T1R3, luego se aventuro en un proceso repetitivo y complejo largo para investigación evaluación y optimizacion, de manera que se llevó a diversas invenciones descritas posteriormente

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COMPENDIO DE LA INVENCIÓN

La invencion tiene muchos aspectos todos de los cuales se relacionan en alguna forma a ciertos compuestos amida de origen no natural y/o compuestos derivados amida que tienen la estructura generica mostrada posteriormente en la Fórmula (I)



(I)

en donde R^1, R^2 y R^3 pueden ser y se definen independientemente ademas en varias maneras, como se detalla ademas posteriormente En todas las modalidades de los compuestos amida de la Fórmula (I) el grupo R^1 es un residuo orgánico que comprende al menos tres atomos de carbono, con una variedad de límites alternativos en las características de tamaño y/o quimicas del grupo R^1 asi como se describiran además posteriormente En muchas, pero no todas las modalidades, los compuestos amida de la Formula (I) son amidas primarias , es decir uno de R^2 y R^3 es un grupo orgánico que comprende al menos tres atomos de carbono, aunque el otro de R^2 y R^3 es hidrógeno

Los compuestos amida de la Fórmula (I) comprenden también ciertas subclases de derivados amida o clases de derivados relacionados a amidas, tales como por ejemplo ureas,

uretanos, oxalamidas, acrilamidas, y similares, como se describirá ademas posteriormente

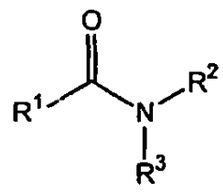
Muchos de los subgéneros y especies de los compuestos "amida' de la Formula (I) se muestran posteriormente para unirse a y/o activar uno o ambos de los receptores dulces T1R2/T1R3 sabroso' ('acre") o T1R2/T1R3 *in vitro* en concentraciones relativamente bajas en el orden de concentraciones micromolares o bajas Los compuestos amida se cree tambien que interactuan de manera similar con los receptores de sabor sabroso o dulce de animales o seres humanos *in vivo* como se ha confirmado por las pruebas de sabor humano actuales de algunos de los compuestos de la Fórmula (I)

Por consiguiente, muchos de los subgéneros y especies de los compuestos amida" de la Formula (I) descritos ademas más adelante pueden a concentraciones sorprendentemente bajas utilizarse como agentes saborizantes dulces o sabrosos, o mejoradores de agentes sabrosos o dulces Por consiguiente en algunas modalidades la invención se relaciona a metodos para modular el sabor sabroso de un producto comestible o medicinal que comprende

a) proporcionar al menos un producto comestible o medicinal, o un precursor del mismo, y
b) combinar el producto comestible o medicinal o precursor del mismo con al menos una cantidad que modula el sabor sabroso, o una cantidad que modula

el sabor dulce, de al menos un compuesto amida de origen no natural, o una sal comestiblemente aceptable del mismo, de manera que forma un producto comestible o medicinal modificado,

en donde el compuesto amida tiene la fórmula



en donde R^1 comprende un residuo orgánico o hidrocarburo que tiene al menos tres átomos de carbono y opcionalmente uno o mas heteroatomos seleccionados independientemente de oxigeno, nitrógeno, azufre, halógenos o fosforo, y

en donde opcionalmente uno de R^2 y R^3 es H, y en donde al menos uno de los otros R^2 y R^3 comprende un residuo orgánico o hidrocarburo que tiene al menos tres atomos de carbono y opcionalmente uno o mas heteroátomos independientemente seleccionados de oxígeno, nitrogeno azufre halógenos o fósforo

Las limitaciones opcionales adicionales en las caracteristicas quimicas y fisicas de los grupos R^1, R^2 y R^3 se describirán posteriormente Algunos de los compuestos amida de la Fórmula (I) se han sintetizado por métodos conocidos en la técnica anterior para varios propósitos, pero en el conocimiento de

la invención no se ha reconocido previamente que tales amidas pueden utilizarse a concentraciones muy bajas como agentes saborizantes sabrosos o dulces, o mejoradores del sabor sabroso o dulce Ademas, muchos de los compuestos amida de la Fórmula (I) descritos en la presente son compuestos novedosos que no se han sintetizado previamente del todo, y son agentes saborizantes de sabor sabroso o dulce efectivos o mejoradores de sabor

La invencion se relaciona tambien a los productos comestibles o medicinales producidos por los procesos mencionados anteriormente y a productos o composiciones comestibles o medicinales, o sus precursores que contienen los compuestos amida de la Fórmula (I), que incluyen, pero no se limitan necesariamente a productos y composiciones alimenticias, bebidas y medicinales pretendidos para administración oral, y precursores de los mismos

En muchas modalidades, uno o más de los compuestos amida de la Formula (I) identificados ademas, descritos y/o reclamados en la presente, o una sal comestiblemente aceptable de la misma pueden utilizarse en mezclas o en combinación con otros compuestos sabrosos o dulces conocidos, o utilizados como mejoradores de sabor en composiciones de alimentos bebidas y medicinas comestibles, para consumo humano o animal

En algunas modalidades, los compuestos amida de la Fórmula (I), aunque tienen poco o quizás no igualan el sabor dulce o sabroso cuando se prueban en aislamiento, pueden emplearse a

concentraciones muy bajas para mejorar muy significativamente la efectividad de otros agentes de sabor sabroso o dulce en una composición comestible o medicinal o un precursor del mismo Las invenciones descritas en la presente se relacionan tambien a los productos comestibles o medicinales modificados con sabor que contienen cantidades de modulacion de sabor de uno o mas compuestos amida descritos en la presente

Muchos de los compuestos amida de la Fórmula (I) y/o sus varios subgéneros de compuestos amida, cuando se utilizan junto con MSG o solos, se incrementan o modulan una respuesta *in vitro*, y la percepcion de sabor sabroso en humanos en concentraciones sorprendentemente bajas En algunas modalidades, los compuestos amida de la invencion son agonistas del receptor T1R1/T1R3 y por consiguiente pueden inducir o mejorar la percepcion de sabor sabroso en seres humanos Estos compuestos pueden mejorar potencializar, modular o inducir otros agentes de sabor sabroso natural y sintetico

En las modalidades relacionadas, muchos de los compuestos amida dentro del alcance de la Formula (I) son agonistas del receptor T1R2/T1R3 y por consiguiente pueden inducir la percepción del sabor dulce en seres humanos a concentraciones sorprendentemente bajas Estos compuestos pueden mejorar potencializar modular o inducir otros agentes saborizantes dulces sinteticos o semi-sinteticos, tales como por ejemplo sacarosa fructuosa, glucosa, eritritol, isomalto lactitol

manitol, sorbitol, xilitol, ciertos terpenoides naturales conocidos flavonoides o edulcorantes de proteínas, aspartame, sacarina, acelsufame-K ciclamato sucralosa y alitame y similares o una mezcla de los mismos

Inesperadamente, se ha descubierto que en muchas modalidades de los compuestos de la Fórmula (I) existen similaridades estructurales significativas y/o traslapes entre los compuestos amida que pueden producir o mejorar los sabores dulces y sabrosos de composiciones comestibles o medicinales, aun cuando se cree que las proteínas receptoras de sabor biologico relevantes son significativamente diferentes Aun mas inesperadamente, se ha descubierto que al menos algunos de los compuestos amida de la Fórmula (I) descritos en la presente pueden inducir o mejorar ambos sabores dulces y sabrosos de los productos comestibles o medicinales Por lo tanto en algunos aspectos la invención se relaciona a compuestos de la Fórmula (I) o sus diversos compuestos de subgéneros y especies que modulan (por ejemplo inducen, mejoran o potencializan) el sabor de agentes edulcorantes naturales o sinteticos conocidos

En algunas modalidades, la invención se relaciona a compuestos novedosos, agentes saborizantes, mejoradores de sabor, compuestos de modificacion de sabor y/o composiciones que contienen los compuestos de la Fórmula (I), y sus diversos compuestos de subgeneros y especies

En otras modalidades, la invención se dirige a

compuestos de la Formula (I) o sus diversos compuestos de subgeneros y especies que modulan (por ejemplo, inducen, mejoran o potencializan) el sabor de glutamato de monosodio (MSG) o agentes saborizantes sabrosos sintéticos

En algunas modalidades, la invención se relaciona a composiciones comestibles o medicinales adecuadas para consumo humano o animal, o precursores de los mismos, que contienen al menos un compuesto de la Formula (I), o una sal comestible o farmacéuticamente aceptable Estas composiciones incluiran de preferencia productos comestibles tales como alimentos o bebidas, productos o composiciones medicinales, pretendidas para administracion oral, y productos higiénicos orales y aditivos que cuando se agregan a estos productos modulan el sabor o degustacion de los mismos, particularmente mejorando (incrementando) el sabor sabroso y/o dulce de los mismos

La presente invencion se relaciona también a generos y especies novedosos de compuestos amida dentro del alcance de los compuestos de la Formula (I), y derivados agentes saborizantes, productos o composiciones comestibles o medicinales, incluyendo agentes saborizantes sabrosos o dulces y mejoradores de sabor que contienen los mismos

La discusión anterior resume simplemente ciertos aspectos de las invenciones y no se pretende, ni debe interpretarse como que limita la invención de cualquier forma

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DESCRIPCIÓN DETALLADA DE LA INVENCION

La presente invención puede entenderse más facilmente por referencia a la siguiente descripcion detallada de varias modalidades de la invención y los Ejemplos incluidos en la presente y a los dibujos y Tablas químicas y su descripción previa y siguiente Antes de los compuestos presentes, las composiciones y/o metodos se describen y se manifiestan, se entendera que a menos que se indique de otra manera especificamente por las reivindicaciones, la invención no se limita a alimentos especificos o métodos de preparación alimenticia los portadores o formulaciones comestibles o farmacéuticas o a modos particulares para formular los compuestos de la invencion en los productos o composiciones comestibles o medicinales pretendidos para administración oral debido a que alguien con experiencia ordinaria en las tecnicas relevantes esta bien consciente, tales cosas pueden por supuesto, variar Se entenderá también que la terminologia utilizada en la presente es para propositos para describir modalidades particulares solamente y no se pretende ser limitante

DEFINICIONES

Como se utiliza en la presente, el término "producto medicinal" incluye tanto composiciones solidas como liquidas que son materiales no tóxicos ingeribles que tienen un valor medicinal

o comprenden agentes medicinalmente activos tales como jarabes para la tos gotas para la tos, aspirinas y tabletas medicinales masticables

Un producto higienico oral incluye sólidos y liquidos tales como pasta dental o enjuague bucal

Un "portador o excipiente comestible biologica o medicinalmente aceptable" es un medio sólido o liquido y/o la composición que se utiliza para preparar una forma de dosis deseada del compuesto inventivo, para administrar el compuesto inventivo en una forma dispersa/diluida, de manera que la efectividad biológica del compuesto inventivo se maximiza Un portador comestible biológica o medicinalmente incluye muchos ingredientes alimenticios comunes, tales como aguas en jugos neutros, acidicos o de pH basico, de frutas o de vegetales, vinagre, marinadas, cervezas, vino agua natural/emulsiones grasas tales como leche o leche condensada, aceite comestibles y materia grasa, acidos grasos, oligómeros de peso molecular bajo de propilenglicol, glicerilésteres de acidos grasos y dispersiones o emulsiones de tales sustancias hidrofóbicas en medios acuosos sales tales como cloruro de sodio, harinas de trigo, solventes tales como etanol diluyentes comestibles sólidos tales como polvos o harinas vegetales, u otros vehiculos liquidos, auxiliares de dispersión o de suspensión agentes activos de superficie, agentes isotónicos, agentes espesantes o emulsificantes conservadores, aglutinantes sólidos, lubricantes y similares

Un "sabor' en la presente se refiere a la percepcion del sabor y/o el olor en un sujeto, el cual incluye dulce, agrio, amargo, acre y otros El sujeto puede ser un ser humano o un animal

Un agente saborizante' en la presente se refiere a un compuesto o una sal biológicamente aceptable del mismo que induce un gusto o sabor en un animal o un ser humano

Un 'modificador de sabor en la presente se refiere a un compuesto o sal biológicamente aceptable que modula, incluyendo el mejoramiento o potencializacion, e induciendo los sabores y/u olores de un agente saborizante natural o sintético en un animal o un ser humano

Un "mejorador de sabor en la presente se refiere a un compuesto o una sal biológicamente aceptable del mismo que mejora los sabores u olores de un agente saborizante natural o sintético

El "sabor sabroso" en la presente se refiere al sabor 'acre" sabroso normalmente inducido por MSG (glutamato de monosodio) en un animal o un ser humano

El agente saborizante sabroso , compuesto sabroso o 'compuesto que activa el receptor sabroso" en la presente se refiere a un compuesto o sal biologicamente aceptable del mismo que produce un sabor sabroso detectable en un sujeto, por ejemplo, MSG (glutamato de monosodio) o un compuesto que activa un receptor T1R1/T1R3 *in vitro* El sujeto puede ser un ser humano o un animal

El "agente saborizante dulce', "compuesto dulce" o "compuesto que activa el receptor dulce en la presente se refiere a un compuesto o una sal biológicamente aceptable del mismo que produce un sabor dulce detectable en un sujeto, por ejemplo sacarosa fructuosa, glucosa y otros edulcorantes basados en sacarido natural conocidos, o edulcorantes artificiales conocidos tales como sacarina, ciclamato, aspartame y similares como se discute en la presente ademas, o un compuesto que activa un receptor T1R2/T1R3 *in vitro* El sujeto puede ser un ser humano o un animal

Un 'modificador de sabor sabroso' en la presente se refiere a un compuesto o una sal biologicamente aceptable del mismo que modula que incluye mejorar o potencializar, induciendo y bloqueando el sabor sabroso de agentes saborizantes sabrosos naturales o sinteticos por ejemplo glutamato de monosodio (MSG) en un animal o un ser humano

Un "modificador de sabor dulce' en la presente se refiere a un compuesto o una sal biológicamente aceptable del mismo que modula, que incluye mejorar o potencializar, induciendo y bloqueando el sabor dulce de agentes saborizantes dulces naturales o sinteticos, por ejemplo, sacarosa, fructuosa glucosa y otros edulcorantes basados en sacáridos naturales conocidos o edulcorantes artificiales conocidos tales como sacarina, ciclamato, aspartame y similares en un animal o un ser humano

Un "mejorador de sabor sabroso en la presente se

refiere a un compuesto o una sal biologicamente aceptable del mismo que mejora o potencializa el sabor sabroso de agentes saborizantes sabrosos naturales o sintéticos, por ejemplo glutamato de monosodio (MSG) en un animal o un ser humano

Un "mejorador de sabor dulce" en la presente se refiere a un compuesto o una sal biologicamente aceptable del mismo que mejora o potencializa el sabor dulce de agentes saborizantes dulces naturales o sinteticos, por ejemplo, sacarosa, fructuosa, glucosa y otros edulcorantes basados en sacáridos naturales conocidos o edulcorantes artificiales conocidos tales como sacarina, ciclamato aspartame y similares como se discute además en la presente en un animal o un ser humano

Un compuesto que activa el receptor acre' en la presente se refiere a un compuesto que activa un receptor acre tal como un receptor T1R1/T1R3

Un "compuesto que activa un receptor dulce en la presente se refiere a un compuesto que activa un receptor dulce, tal como un receptor T1R2/T1R3

Un "compuesto que modula el receptor acre en la presente se refiere a un compuesto que modula (activa, mejora o bloquea) un receptor acre

Un compuesto que modula el receptor dulce" en la presente se refiere a un compuesto que modula (activa mejora o bloquea) un receptor dulce

Un compuesto que mejora el receptor acre en la

presente se refiere a un compuesto que mejora o potencializa el efecto de un receptor acre natural o sintético que activa el compuesto, por ejemplo glutamato de monosodio (MSG)

Un "compuesto que mejora el receptor dulce" en la presente se refiere a un compuesto que mejora o potencializa el efecto de un receptor dulce natural o sintetico que activa un compuesto, por ejemplo sacarosa fructuosa glucosa y otros edulcorantes basados en sacáridos naturales conocidos o edulcorantes artificiales conocidos tales como sacarina, ciclamato aspartame y similares como se discute además en la presente

Una 'cantidad de agente saborizante sabroso' en la presente se refiere a una cantidad de un compuesto que es suficiente para inducir sabor sabroso en un producto o composicion comestible o medicinal o un precursor del mismo Un rango moderadamente amplio de una cantidad de agente saborizante sabroso puede ser desde aproximadamente 0 001 ppm a 100 ppm, o un rango estrecho de aproximadamente 0 1 ppm a aproximadamente 10 ppm Los rangos alternativos de las cantidades de agente saborizante sabroso pueden variar desde aproximadamente 0 01 ppm a aproximadamente 30 ppm, desde aproximadamente 0 05 ppm a aproximadamente 15 ppm, desde aproximadamente 0 1 ppm a aproximadamente 5 ppm, o desde aproximadamente 0 1 ppm a aproximadamente 3 ppm

Una "cantidad del agente saborizante dulce en la presente se refiere a una cantidad de un compuesto que es

suficiente para inducir el sabor dulce en un producto o composición comestible o medicinal o un precursor del mismo Un rango moderadamente amplio de una cantidad del agente saborizante dulce puede ser desde aproximadamente 0 001 ppm a 100 ppm, o un rango estrecho desde aproximadamente 0 1 ppm a aproximadamente 10 ppm Los rangos alternativos de las cantidades del agente saborizante dulce pueden ser desde aproximadamente 0 01 ppm a aproximadamente 30 ppm, desde aproximadamente 0 05 ppm a aproximadamente 15 ppm, desde aproximadamente 0 1 ppm a aproximadamente 5 ppm o desde aproximadamente 0 1 ppm a aproximadamente 3 ppm

Una "cantidad que modula el sabor sabroso en la presente se refiere a una cantidad de un compuesto de la Formula (I) que es suficiente para alterar (ya sea incrementar o disminuir) el sabor sabroso en un producto o composición comestible o medicinal, o un precursor del mismo, suficientemente para percibirse por un sujeto humano Un rango moderadamente amplio de una cantidad que modula el sabor sabroso puede ser desde aproximadamente 0 001 ppm a 100 ppm, o un rango estrecho desde aproximadamente 0 1 ppm a aproximadamente 10 ppm Los rangos alternativos de cantidades que modulan el sabor sabroso pueden ser desde aproximadamente 0 01 ppm a aproximadamente 30 ppm, desde aproximadamente 0 05 ppm a aproximadamente 15 ppm desde aproximadamente 0 1 ppm a aproximadamente 5 ppm o desde aproximadamente 0 1 ppm a aproximadamente 3 ppm

Una 'cantidad que modula el sabor dulce' en la presente se refiere a una cantidad de un compuesto de la Fórmula (I) que es suficiente para alterar (ya sea incrementar o disminuir) el sabor dulce en un producto o composicion comestible o medicinal, o un precursor del mismo, suficientemente para percibirse por un sujeto humano Un rango moderadamente amplio de una cantidad que modula el sabor dulce puede ser desde aproximadamente 0 001 ppm a 100 ppm, o un rango estrecho desde aproximadamente 0 1 ppm a aproximadamente 10 ppm Los rangos alternativos de las cantidades que modulan el sabor dulce pueden ser desde aproximadamente 0 01 ppm a aproximadamente 30 ppm desde aproximadamente 0 05 ppm a aproximadamente 15 ppm, desde aproximadamente 0 1 ppm a aproximadamente 5 ppm o desde aproximadamente 0 1 ppm a aproximadamente 3 ppm

Una "cantidad que mejora el sabor sabroso en la presente se refiere a una cantidad de un compuesto que es suficiente para mejorar el sabor de los agentes saborizantes naturales o sinteticos por ejemplo, glutamato de monosodio (MSG) en un producto o composicion comestible o medicinal Un rango moderadamente amplio de una cantidad que mejora el sabor sabroso puede ser desde aproximadamente 0 001 ppm a 100 ppm, o un rango estrecho desde aproximadamente 0 1 ppm a aproximadamente 10 ppm Los rangos alternativos de cantidades que mejoran el sabor sabroso pueden ser desde aproximadamente 0 01 ppm a aproximadamente 30 ppm, desde aproximadamente

0 05 ppm a aproximadamente 15 ppm desde aproximadamente 0 1 ppm a aproximadamente 5 ppm, o desde aproximadamente 0 1 ppm a aproximadamente 3 ppm

Una cantidad que mejora el sabor dulce en la presente se refiere a una cantidad de un compuesto que es suficiente para mejorar el sabor de agentes saborizantes naturales o sintéticos, (por ejemplo, sacarosa, fructuosa glucosa y otros edulcorantes basados en sacaridos naturales conocidos, o edulcorantes artificiales conocidos tales como sacarina, ciclamato, aspartame y similares como se discute además en la presente) en un producto o una composición comestible o medicinal Un rango moderadamente amplio de una cantidad que mejora el sabor dulce puede ser desde aproximadamente 0 001 ppm a 100 ppm, o un rango estrecho desde aproximadamente 0 1 ppm a aproximadamente 10 ppm Los rangos alternativos de cantidades que mejoran el sabor dulce pueden ser desde aproximadamente 0 01 ppm a aproximadamente 30 ppm desde aproximadamente 0 05 ppm a aproximadamente 15 ppm, desde aproximadamente 0 1 ppm a aproximadamente 5 ppm o desde aproximadamente 0 1 ppm a aproximadamente 3 ppm

Una cantidad que modula el receptor acre" en la presente se refiere a una cantidad de un compuesto que es suficiente para modular (activar, mejorar o bloquear) un receptor acre Un rango preferible de una cantidad que modula el receptor acre es 1 pM a 100 mM y más preferiblemente 1 nM a 100 µM y

mas preferiblemente 1 nM a 30 µM Un rango moderadamente amplio de una cantidad que mejora el sabor acre puede ser desde aproximadamente 0 001 ppm a 100 ppm, un rango estrecho desde aproximadamente 0 01 ppm a aproximadamente 10 ppm Los rangos alternativos de las cantidades que mejoran el sabor acre pueden ser desde aproximadamente 0 01 ppm a aproximadamente 30 ppm, desde aproximadamente 0 05 ppm a aproximadamente 15 ppm, desde aproximadamente 0 1 ppm a aproximadamente 5 ppm o desde aproximadamente 0 1 ppm a aproximadamente 3 ppm

Una cantidad que modula o activa un receptor T1R1/T1R3" es una cantidad del compuesto que es suficiente para modular o activar un receptor T1R1/T1R3 Estas cantidades son de preferencia las mismas como las cantidades que modulan el receptor acre

Un receptor acre es un receptor de sabor que puede modularse por un compuesto sabroso De preferencia, un receptor acre es un receptor acoplado de proteina G y más preferiblemente el receptor acre es un receptor T1R1/T1R3

Los compuestos de la invencion modulan un receptor acre y de preferencia son agonistas del receptor T1R1/T1R3 Un agonista de este receptor tiene el efecto para activar la cascada de señalizacion de proteina G En muchos casos, este efecto agonista del compuesto en el receptor produce tambien un sabor sabroso percibido en la prueba de sabor Es deseable por lo tanto que tales compuestos inventivos sirvan como un reemplazo para

MSG, que no se tolera por algunos productos comestibles por ejemplo

Además, este efecto agonista es responsable también para el efecto de sabor sabroso sinergistico, que ocurre cuando un compuesto de la invencion se combina con otro agente saborizante sabroso tal como MSG Los nucleótidos, IMP o GMP, se agregan convencionalmente al MSG, para intensificar el sabor sabroso del MSG, de manera que es necesario el MSG relativamente menor para proporcionar el mismo sabor sabroso en comparación al MSG solo Por lo tanto, es deseable que al combinar los compuestos de la invencion con otro agente saborizante sabroso tal como MSG se elimina ventajosamente la necesidad para agregar nucleotidos caros tales como IMP como un mejorador de sabor, aunque al reducir o eliminar al mismo tiempo la cantidad de un compuesto sabroso tal como MSG necesario para proporcionar el mismo sabor sabroso en comparación al compuesto sabroso o MSG solo

Una "cantidad que modula el receptor dulce" en la presente, 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 mas preferiblemente 1 nM a 30 µM

Una "cantidad que modula o activa el receptor T1R2/T1R3" es una cantidad del compuesto que es suficiente para modular o activar un receptor T1R2/T1R3 Estas cantidades son

preferiblemente las mismas como las cantidades que modulan el receptor dulce

Un receptor dulce es un receptor de sabor que puede modularse por un compuesto dulce De preferencia un receptor dulce es un receptor acoplado con la proteina G, y mas preferiblemente el receptor acre es un receptor T1R2/T1R3

Muchos compuestos de la Fórmula (I) pueden modular un receptor dulce y de preferencia son agonistas del receptor T1R2/T1R3 Un agonista de este receptor tiene el efecto de activar la cascada de señalizacion de la proteína G En muchos casos este efecto agonista del compuesto en el receptor produce tambien un sabor dulce percibido en una prueba de sabor Es deseable, por lo tanto que tales compuestos inventivos sirven como un reemplazo para sacarosa, fructuosa, glucosa y otros edulcorantes basados en sacáridos naturales o edulcorantes artificiales conocidos tales como sacarina, ciclamato, aspartame y similares, o mezclas de los mismos como se discute ademas en la presente

Un efecto sinergístico" se relaciona al sabor sabroso y/o dulce mejorado de una combinacion de compuestos sabrosos y/o dulces o compuestos que activan el receptor, en comparacion a la suma de los efectos de sabor o efectos asociados con el sabor asociados con cada compuesto individual En el caso de los compuestos mejoradores del sabor un efecto sinergístico en la efectividad del MSG puede indicarse para un compuesto de la Fórmula (I) que tiene una relación de EC50 (definida mas

adelante) de 2 0 o mas, o de preferencia 5 0 o mas, ó 10 0 o mas, o 15 0 o más Un ensayo de E50 para un mejoramiento dulce no ha sido desarrollado aun, pero en el caso de ambos compuestos mejoradores sabrosos y dulce, un efecto sinergístico puede confirmarse por pruebas de sabor humano, como se describe en otra parte en la presente

Cuando los compuestos descritos en la presente incluyen uno o mas centros quirales, la estereoquimica de tales centros quirales puede independientemente estar en la configuración R o S o una mezcla de las dos Los centros quirales pueden diseñarse además como R o S o R S o d D l, L o d l D, L De manera correspondiente, los compuestos amida de la invención si pueden presentarse en una forma ópticamente activa pueden realmente presentarse en la forma de una mezcla racemica de enantiomeros o en la forma de cualquiera de los enantiómeros separados en forma aislada y purificada sustancialmente o como una mezcla que comprende cualesquiera proporciones relativas de los enantiomeros

Con respecto a los compuestos descritos en la presente, el sufijo eno' agregado a cualquiera de los terminos descritos anteriormente significa que el sustituyente se conecta a otras dos partes en el compuesto Por ejemplo alquileno' es $(CH_2)_n$, alquileno" es tal porción que contiene una doble union y alquinileno" es tal porción que contiene una triple unión

Como se utiliza en la presente 'residuo hidrocarburo"

se refiere a un subgrupo químico dentro de un compuesto químico mas grande, el cual tiene sólo átomos de carbono y de hidrógeno El residuo hidrocarburo puede ser alifático o aromático, de cadena lineal, cíclico, ramificado, saturado o insaturado El residuo hidrocarburo, cuando se establece sin embargo, puede contener o ser sustituido con heteroátomos tales como O, S o N, o los halogenos (fluor cloro bromo y yodo), o grupos sustituyentes que contienen heteroátomos (OH, NH_2, NO_2, SO_3H y similares) sobre y encima de los atomos de carbono y de hidrógeno del residuo sustituyente De este modo, cuando se observa específicamente como conteniendo tales heteroatomos, o diseñados como "sustituidos , el residuo hidrocarburo puede contener también grupos carbonilo, grupos amino, grupos hidroxilo y similares, o contienen heteroátomos insertados en la "estructura principal' del residuo hidrocarburo

Como se utiliza en la presente, 'residuo inorgánico" se refiere a un residuo que no contiene carbono, sino contiene al menos algunos heteroátomos, incluyendo O, N, S, uno o mas halogenos iones de metal alcali o metal alcalinotérreo Los ejemplos incluyen, pero no se limitan a H, Na+ Ca++ y K+, halo hidroxi, NO_2 o NH_2

Como se utiliza en la presente, el término "alquilo", alquenilo" y alquinilo incluye sustituyentes monovalentes cíclicos y de cadena lineal y ramificada que se saturan respectivamente no se saturan con al menos una doble unión y

no se saturan con al menos una triple unión

"Alquilo" se refiere a un grupo hidrocarburo que puede formarse conceptualmente a partir de un alcano removiendo hidrogeno a partir de la estructura de un compuesto hidrocarburo que tiene cadenas de carbono lineal o ramificado, y reemplazando el atomo de hidrógeno con otro atomo o un grupo sustituyente En algunas modalidades de la invención, los grupos alquilo son "alquilo de C1 a C6" tal como metilo, etilo propilo, isopropilo, n-butilo, iso-butilo, sec-butilo, ter-butilo, amilo, ter-amilo hexilo y similares En algunas modalidades de la invención los grupos "alquilo de C1 a C4 (alternativamente llamados grupos "alquilo inferior" son metilo etilo, propilo, iso-butilo, sec-butilo, t-butilo e iso-propilo Algunos de los grupos alquilo preferidos de la invención tienen tres o mas átomos de carbono de preferencia 3 a 16 átomos de carbono, 4 a 14 atomos de carbono, ó 6 a 12 átomos de carbono

Los grupos alquenilo preferidos son "alquenilo de C2 a C7 tales como 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 dienos y trienos de cadenas lineales y ramificadas

Los grupos alquinilo preferidos son "alquinilo de C2 a C7" tales 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 di y tri-inos de cadenas ramificadas y lineales incluyendo eno-inos

Los residuos hidrocarburos pueden sustituirse opcionalmente Dos de tales sustituyentes opcionales en posiciones adyacentes pueden unirse para formar un anillo saturado o insaturado aromatico o no aromatico opcionalmente sustituido fundido que contiene de 3-8 miembros Los sustituyentes opcionalmente son residuos generalmente hidrocarburos que pueden contener uno o más heteroátomos o un residuo inorgánico tal como H, Na^+ Ca^{2+} o K^+

Los terminos "alquilo sustituido' alquenilo sustituido' alquinilo sustituido y alquileno sustituido' indican que los grupos alquilo, alquenilo, alquinilo y alquileno se sustituyen por uno o más y de preferencia uno o dos sustityuyentes de preferencia halogeno, hidroxi alcoxi de C1 a C7, alcoxi-alquilo, oxo, cicloalquilo de C3 a C7, naftilo amino (monosustituido)amino, (disustituido)amino, guanidino heterociclo, heterociclo sustituido, imidazolilo, indolilo, pirrolidinilo, acilo de C1 a C7, aciloxi de C1 a C7 nitro, carboxi carbamoilo, carboxamida N-(alquilo de C1 a C6)carboxamida N,N-di(alquilo de C1 a C6)carboxamida, ciano, metilsulfonilamino, tiol alquiltio de C1 a C4 o grupos alquilsulfonilo de C1 a C4 Los grupos alquilo sustituidos pueden sustituirse una vez o mas, y de preferencia una vez o dos veces con el mismo o con diferentes sustituyentes En muchas modalidades de la invención un grupo preferido de grupos

sustituyentes incluyen grupos 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 trifluorometoxi En muchas modalidades de la invención que comprende las listas anteriores de los grupos sustituyentes, un grupo aun mas preferido de los grupos sustituyentes incluyen grupos hidroxi, SEt, SCH_3 metilo etilo, isopropilo metoxi, y etoxi

Los ejemplos de los grupos alquilo sustituidos anteriores incluyen 2-oxo-prop-1-ilo, 3-oxo-but-1-ilo cianometilo nitrometilo clorometilo hidroximetilo, tetrahidropiraniloximetilo tritiloximetilo, propioniloximetilo, aminometilo, carboximetilo, aliloxicarbonilmetilo aliloxicarbonilaminometilo, metoximetilo etoximetilo, t-butoximetilo, acetoximetilo, clorometilo trifluorometilo, 6-hidroxihexilo 2,4-dicloro(n-butilo), 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-fluoropropilo, 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

Los ejemplos de los grupos alquenilo sustituidos anteriores incluyen estirenilo, 3-cloropropen-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 todos los

isómeros geometricos para un alquenilo sustituido dado pueden utilizarse

Los ejemplos de los grupos alquinilo sustituidos anteriormente incluyen fenilacetilen-1-ilo 1-fenil-2-propin-1-ilo y similares

El término 'oxo" indica un átomo de carbono unido a dos átomos de carbono adicionales sustituidos con un átomo de oxigeno doblemente unido al átomo de carbono, por lo que se forma una porción cetona

"Alcoxi" se refiere a un grupo OR, en donde R es un alquilo o alquilo sustituido "Alcoxi-alquilo se refiere a un grupo alquilo que contiene un alcoxi

Los grupos alcoxi preferidos son 'alcoxi de C1 a C7' tal como metoxi, etoxi n-propoxi, isopropoxi, n-butoxi, t-butoxi y grupos similares El término alcoxi sustituido de C1 a C7 significa que la porcion alquilo del alcoxi puede sustituirse en la misma manera como en relacion a alquilo sustituido de C1 a C6 De manera similar, el término 'fenilalcoxi de C1 a C7 como se utiliza en la presente significa "alcoxi de C1 a C7" unidos a un radical fenilo

"Aciloxi' se refiere a un grupo OR en donde R es un grupo acilo Los grupos aciloxi preferidos son "aciloxi de C1 a C7' tales como formiloxi, acetoxi propioniloxi, butiriloxi, pivaloiloxi, pentanoiloxi hexanoiloxi, heptanoiloxi y similares

Como se utiliza en la presente, "acilo abarca las

definiciones de alquilo, alquenilo, alquinilo y las formas hetero relacionadas que se acoplan a un residuo adicional a través de un grupo carbonilo Los grupos acilo preferidos son "acilo de C1 a C7" tales como formilo, acetilo, propionilo, butirilo pentanoilo, pivaloilo, hexanoilo, heptanoilo, benzoilo y similares Los grupos acilo más preferidos son acetilo y benzoilo

El término "acilo sustituido' indica el grupo acilo sustituido por uno o mas, y de preferencia uno o dos grupos de halogeno, hidroxi, oxo, alquilo cicloalquilo, naftilo amino (monosustituido)amino, (disustituido)amino, guanidino anillo heterocíclico anillo heterociclico sustituido, imidazolilo, indolilo, pirrolidinilo, alcoxi de C1 a C7 alcoxi-alquilo, acilo de C1 a C7 aciloxi de C1 a C7, nitro alquiléster de C1 a C6, carboxi, alcoxicarbonilo, carbamoilo, carboxamida, N-(alquilo de C1 a C6)carboxamida, N,N-di(alquilo de C1 a C6)carboxamida, ciano, metilsulfonilamino tiol alquiltio de C1 a C4 o alquilsulfonilo de C1 a C4 Los grupos acilo sustituidos pueden sustituirse una vez o más, y de preferencia una vez o dos veces con el mismo o con diferentes sustituyentes

Los ejemplos de grupos acilo sustituidos de C1 a C7 incluyen 4-fenilbutiroilo 3-fenilbutiroilo, 3-fenilpropanoilo, 2-ciclohexanilacetilo, ciclohexancarbonilo, 2-furanilo y 3-dimetilaminobenzoilo

Los residuos cicloalquilo son grupos hidrocarburo dentro de una molécula que comprenden al menos un anillo que tiene 3 a

8 atomos de carbono enlazados a un anillo Los ejemplos de tales residuos cicloalquilo incluyen anillos ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo y cicloalcanos policiclicos fundidos o biciclicos saturados tales como grupos decalina, grupos norbornilo y similares

Los grupos cicloalquilo preferidos incluyen "cicloalquilo de C3 a C7 tales como anillos ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo o cicloheptilo De manera similar, el termino "cicloalquilo de C5 a C7" incluye anillos ciclopentilo, ciclohexilo o cicloheptilo

El cicloalquilo sustituido' indica los anillos cicloalquilo anteriores que se sustituyen de preferencia por uno o dos halógenos hidroxi alquiltio de C1 a C4, alquilsulfóxido de C1 a C4, alquilsulfonilo de C1 a C4, alquiltio sustituido de C1 a C4, alquilsulfoxido sustituido de C1 a C4 alquilsulfonilo sustituido de C1 a C4, alquilo de C1 a C6 alcoxi de C1 a C7 alquilo sustituido de C1 a C6, alcoxi-alquilo de C1 a C7, oxo (monosustituido)amino (disustituido)amino, trifluorometilo carboxi fenilo fenilo sustituido, feniltio, fenilsulfoxido, fenilsulfonilo amino En muchas modalidades de los grupos cicloalquilo sustituidos, el grupo cicloalquilo sustituido tendra 1 2 3 o 4 grupos sustituyentes independientemente seleccionados de grupos 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 trifluorometoxi

El término cicloalquileno significa un cicloalquilo como se define anteriormente, en donde el radical cicloalquilo se une a dos posiciones que se conectan juntas a dos grupos separados adicionales De manera similar el término "cicloalquileno sustituido significa un cicloalquileno en donde el radical cicloalquilo se une a dos posiciones que se conectan juntas a dos grupos separados adicionales y que soportan ademas al menos un sustituyente adicional

El termino "cicloalquenilo" indica de preferencia un anillo 1,2 o 3-ciclopentenilo, un anillo 1,2,3 ó 4-ciclohexenilo o un anillo 1,2,3,4 ó 5-cicloheptenilo, aunque el término "cicloalquenilo sustituido" indica los anillos cicloalquenilo anteriores sustituidos con un sustituyente, de preferencia por un alquilo de C1 a C6 halógeno hidroxi alcoxi de C1 a C7, alcoxi-alquilo, trifluorometilo carboxi, alcoxicarbonilo, oxo, (monosustituido)amino (disustituido)amino, fenilo, fenilo sustituido, amino o amino protegido

El termino 'cicloalquenileno es un anillo cicloalquenilo como se define anteriormente, en donde el radical cicloalquenilo se une a dos posiciones que se conectan junto a dos grupos adicionales separados De manera similar, el término 'cicloalquenileno sustituido' significa un cicloalquenileno sustituido además de preferencia por halogeno, hidroxi, alquiltio de C1 a C4 alquilsulfoxido de C1 a C4 alquilsulfonilo de C1 a C4, alquiltio sustituido de C1 a C4, alquilsulfóxido sustituido de C1 a

C4, alquilsulfonilo sustituido de C1 a C4, alquilo de C1 a C6, alcoxi de C1 a C7 alquilo sustituido de C1 a C6, alcoxi-alquilo de C1 a C7, oxo, (monosustituido)amino (disustituido)amino trifluorometilo, carboxi alcoxicarbonilo, fenilo fenilo sustituido, feniltio, fenilsulfoxido, fenilsulfonilo, amino, o grupo amino sustituido

El término 'heterociclo o "anillo heterociclico' indica opcionalmente anillos de 3 a 8 miembros opcionalmente sustituido que tiene uno o más átomos de carbono conectados en un anillo que también tiene 1 a 5 heteroátomos tales como oxigeno, azufre y/o nitrógeno insertado dentro del anillo Estos anillos de 3 a 8 miembros pueden saturarse, instaurarse o parcialmente instaurarse, pero se saturan de preferencia Un 'anillo heterociclico amino-sustituido" significa cualquiera de los anillos heterociclicos descritos anteriormente se sustituye con al menos un grupo amino Los anillos heterociclicos preferidos incluyen furanilo, tiofuranilo, piperidilo, piridilo morfolino, aziridinilo piperidinilo, piperazinilo tetrahidrofurano, pirrolo y tetrahidrotiofenilo

El término "heterociclico sustituido' o anillo heterociclico sustituido significa el anillo heterociclico descrito anteriormente se sustituye con por ejemplo, uno o más y de preferencia uno o dos, sustituyentes que son los mismos o diferentes cuyos sustituyentes pueden de preferencia ser grupos halogeno, hidroxi, tio alquiltio, ciano nitro, alquilo de C1 a C6

alcoxi de C1 a C7 alcoxi sustituido de C1 a C7, alcoxi-alquilo acilo de C1 a C7, aciloxi de C1 a C7, carboxi, alcoxicarbonilo carboximetilo hidroximetilo, alcoxi-alquilamino, (monosustituido)amino, (disustituido)amino carboxamida N-(alquilo de C1 a C6)carboxamida N,N-di(alquilo de C1 a C6)carboxamida, trifluorometilo N-((alquilo de C1 a C6)sulfonil)amino, N(fenilsulfonil)amino, o sustituidos con un anillo fundido, tal como benzo-anillo En muchas modalidades de los grupos heterociclicos sustituidos, el grupo cicloalquilo sustituido tendrá 1, 2 3 ó 4 grupos sustituyentes independientemente seleccionados a partir de grupos 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 trifluorometoxi

Un grupo arilo" se refiere a una porcion aromatica monociclica, aromatica bicíclica enlazada o aromatica biciclica combinada que comprende al menos un anillo "benceno' aromatico de seis miembros de preferencia comprende entre 6 y 12 atomos de carbono en el anillo, tales como grupos fenilo, bifenilo o naftilo que pueden sustituirse opcionalmente con varios grupos sustituyentes orgánicos y/o inorgánicos en donde el grupo arilo sustituido y sus sustituyentes comprenden entre 6 y 18 o de preferencia 6 y 16 atomos de carbono totales Los grupos sustituyentes opcionales preferidos incluyen 1, 2 3 o 4 grupos sustituyentes independientemente seleccionados a partir de

grupos 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 trifluorometoxi

El término heteroarilo significa un derivado arilo heterocíclico que contiene de preferencia un sistema de anillo conjugado y aromatico de cinco miembros o de seis miembros que tienen desde 1 a 4 heteroátomos tales como oxigeno, azufre y/o nitrogeno insertados dentro del anillo heterocíclico conjugado y no saturado Los grupos heteroarilo incluyen porciones heteroaromáticas monocíclicas, heteroaromáticas biciclicas enlazadas o heteroaromaticas biciclicas combinadas Los ejemplos de heteroarilos incluyen piridinilo pirimidinilo y pirazinilo piridazinilo pirrolilo, furanilo tiofuranilo, oxazolilo, isoxazolilo ftalimido, tiazolilo, quinolinilc, isoquinolinilo, indolilo o un furano o tiofurano directamente unido a un anillo fenilo, piridilo o pirrolilo y los anillos heteroaromaticos conjugados e insaturados similares Cualquier sistema de anillo monocíclico, biciclico enlazado o heteroarilo biciclico fundido que tiene las caracteristicas de aromaticidad en términos de distribución de electrón a través del sistema de anillo se incluye en esta definición Normalmente, los sistemas de anillo aromatico contienen 3-12 atomos de carbono en el anillo y 1 a 5 heteroátomos en el anillo independientemente seleccionados a partir de atomos de oxigeno, nitrogeno y azufre

El termino heteroarilo sustituido significa que el heteroarilo descrito anteriormente se sustituye con, por ejemplo

uno o mas, y de preferencia uno o dos, sustituyentes que son los mismos o diferentes, cuyos sustituyentes de preferencia pueden ser grupos halógeno, hidroxi, hidroxi protegido, tio alquiltio ciano, nitro, alquilo de C1 a C6, alquilo sustituido de C1 a C7 , alcoxi de C1 a C7, alcoxi sustituido de C1 a C7, alcoxi-alquilo acilo de C1 a C7, acilo sustituido de C1 a C7, aciloxi de C1 a C7, carboxi, alcoxicarbonilo carboximetilo, hidroximetilo, amino, (monosustituido)amino (disustituido)amino, carboxamida, N-(alquilo de C1 a C6)carboxamida, N,N-di(alquilo de C1 a C6)carboxamida trifluorometilo, N-((alquilo de C1 a C6)sulfonilo)amino o N-(fenilsulfonil)amino En muchas modalidades de los grupos heteroarilo sustituidos, el grupo cicloalquilo sustituido tendra 1, 2, 3 o 4 grupos sustituyentes independientemente seleccionados a partir de grupos 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 trifluorometoxi

De manera similar arilalquilo y heteroarilalquilo se refieren a sistemas aromaticos y heteroaromaticos que se acoplan a otro residuo a través de una cadena de carbono, incluyendo cadenas de carbono sustituidas o sin sustituir, saturadas o insaturadas normalmente de 1-6C Estas cadenas de carbono pueden incluir también un grupo carbonilo, de este modo haciéndolos capaces de proporcionar sustituyentes como una porción acilo De preferencia, el arilalquilo o heteroarilalquilo es

un grupo alquilo sustituido en cualquier posicion por un grupo arilo, arilo sustituido, heteroarilo o heteroarilo sustituido Los grupos preferidos tambien 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 termino arilalquilo sustituido" indica un grupo arilalquilo sustituido en la porcion alquilo con uno o más, y de preferencia uno o dos grupos elegidos de preferencia a partir del halógeno, hidroxi, oxo, amino, (monosustituido)amino, (disustituido)amino, guanidino, anillo heterociclico, anillo heterociclico sustituido, alquilo de C1 a C6, alquilo sustituido de C1 a C6 alcoxi de C1 a C7, alcoxi sustituido de C1 a C7 alcoxi-alquilo acilo de C1 a C7, acilo sustituido de C1 a C7, aciloxi de C1 a C7, nitro, carboxi, alcoxicarbonilo, carbamoilo, carboxamida N-(alquilo de C1 a C6)carboxamida, N, N-(dialquilo de C1 a C6)carboxamida, ciano, N-(alquilsulfonilo de C1 a C6)amino, tiol alquiltio de C1 a C4, grupos alquilsulfonilo de C1 a C4, y/o el grupo fenilo puede sustituirse con uno o mas, y de preferencia uno o dos, sustituyentes de preferencia elegidos a partir del halógeno, hidroxi, hidroxi protegido, tio, alquiltio, ciano, nitro, alquilo de C1 a C6, alquilo sustituido de C1 a C6, alcoxi de C1 a C7, alcoxi sustituido de C1 a C7 alcoxi-alquilo acilo de C1 a C7 acilo sustituido de C1 a C7, aciloxi de C1 a C7, carboxi, alcoxicarbonilo, carboximetilo, hidroximetilo, amino, (monosustituido)amino, (disustituido)amino, carboxamida, N-(alquilo de C1 a

C6)carboxamida, N,N-di(alquilo de C1 a C6)carboxamida, trifluorometilo N-((alquilo de C1 a C6)sulfonilo)amino N-(fenilsulfonilo)amino, alquileno de C2 a C7 cíclico o un grupo fenilo, sustituido o sin sustituir, para un grupo bifenilo resultante Los grupos alquilo o fenilo sustituidos pueden sustituirse con uno o más, y de preferencia uno o dos sustituyentes que pueden ser los mismos o diferentes

Los ejemplos del término arilalquilo sustituido incluyen grupos tales como 2-fenil-1-cloroetilo 2-(4-metoxifenil)etilo 4-(2,6-dihidroxifenilo)-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 termino arilalquileno" especifica un arilalquilo, como se define anteriormente, en donde el radical arilalquilo se une a dos posiciones que se conectan junto a dos grupos adicionales separados La definición incluye grupos de la fórmula -fenil-alquilo y alquil-fenil-alquilo- Las sustituciones en el anillo fenilo pueden ser 1, 2, 1, 3, ó 1, 4 El término 'arilalquileno sustituido es un arilalquileno como se define anteriormente que se sustituye ademas de preferencia por halogeno, hidroxi, hidroxi protegido alquiltio de C1 a C4, alquilsulfóxido de C1 a C4, alquilsulfonilo de C1 a C4 alquiltio sustituido de C1 a C4 alquilsulfóxido sustituido de C1 a C4 alquilsulfonilo sustituido de C1 a C4, alquilo de C1 a C6, alcoxi de C1 a C7, alquilo sustituido de C1 a C6, alcoxi-alquilo

de C1 a C7 oxo, (monosustituido)amino, (disustituido)amino trifluorometilo, carboxi, alcoxicarbonilo, fenilo, fenilo sustituido, feniltio, fenilsulfóxido, fenilsulfonilo, amino o grupo amino protegido en el anillo fenilo o en el grupo alquilo

El término fenilo sustituido" especifica un grupo fenilo sustituido con uno o mas y de preferencia uno o dos, porciones de preferencia elegidas a partir de los grupos que consisten de halogeno, hidroxi, hidroxi protegido tio, alquiltio, ciano, nitro, alquilo de C1 a C6, alquilo sustituido de C1 a C6, alcoxi de C1 a C7 alcoxi sustituido de C1 a C7 alcoxi-alquilo acilo de C1 a C7 acilo sustituido de C1 a C7, aciloxi de C1 a C7 carboxi alcoxicarbonilo, carboximetilo, hidroximetilo amino (monosustituido)amino, (disustituido)amino carboxamida N-(alquilo de C1 a C6)carboxamida, N,N-di(alquilo de C1 a C6)carboxamida, trifluorometilo N-((alquilo de C1 a C6)sulfonilo)amino N-(fenilsulfonil)amino o fenilo, en donde el fenilo se sustituye o no se sustituye de manera 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 a partir de grupos 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 trifluorometoxi

El término "fenoxi indica un fenilo unido a un atomo de oxigeno El termino fenoxi sustituido especifica un grupo fenoxi

sustituido con uno o mas, y de preferencia uno o dos, porciones de preferencia elegidas a partir de los grupos que consisten de halógeno, hidroxi, hidroxi protegido, tio, alquiltio, ciano nitro alquilo de C1 a C6, alcoxi de C1 a C7, alcoxi sustituido de C1 a C7, alcoxi-alquilo, acilo de C1 a C7, aciloxi de C1 a C7, carboxi alcoxicarbonilo, carboximetilo, hidroximetilo, amino, (monosustituido)amino, (disustituido)amino carboxamida, N-(alquilo de C1 a C6)carboxamida, N,N-di(alquilo de C1 a C6)carboxamida, trifluorometilo, N-((alquilo de C1 a C6)sulfonilo)amino y N-fenilsulfonilo)amino

El término "fenilalcoxi sustituido" indica un grupo fenilalcoxi en donde la porción alquilo se sustituye con uno o mas, y de preferencia uno o dos grupos seleccionados de preferencia a partir de halógeno, hidroxi, hidroxi protegido, oxo, amino, (monosustituido)amino, (disustituido)amino, guanidino, anillo heterociclico, anillo heterocíclico sustituido alcoxi de C1 a C7, alcoxi-alquilo, acilo de C1 a C7 aciloxi de C1 a C7, nitro carboxi, alcoxicarbonilo carbamoilo, carboxamida, N-(alquilo de C1 a C6)carboxamida, N,N(dialquilo de C1 a C6)carboxamida, ciano, N-(alquilsulfonilo de C1 a C6)amino, tiol alquiltio de C1 a C4 grupos alquilsulfonilo de C1 a C4, y/o el grupo fenilo puede sustituirse con uno o más, y de preferencia uno o dos sustituyentes de preferencia elegidos a partir de halogeno, hidroxi, hidroxi protegido, tio, alquiltio, ciano, nitro, alquilo de C1 a C6, alcoxi de C1 a C7, alcoxi-alquilo, acilo de C1 a C7, aciloxi de C1 a

C7, carboxi, alcoxicarbonilo carboximetilo, hidroximetilo, amino (monosustituido)amino (disustituido)amino, carboxamida, N-(alquilo de C1 a C6)carboxamida N N-di(alquilo de C1 a C6)carboxamida, trifluorometilo, N((alquilo de C1 a C6)sulfonilo)amino, N-(fenilsulfonilo)amino o un grupo fenilo, sustituido o sin sustituir, para un grupo bifenilo resultante Los grupos alquilo o fenilo sustituidos pueden sustituirse con uno o más, y de preferencia uno o dos sustituyentes que pueden ser los mismos o diferentes

El termino naftilo sustituido" especifica un grupo naftilo sustituido con uno o más, y de preferencia uno o dos porciones ya sea en el mismo anillo o en diferentes anillos elegidos a partir de grupos que consisten de halógeno, hidroxi, hidroxi protegido, tio alquiltio, ciano, nitro, alquilo de C1 a C6, alcoxi de C1 a C7 alcoxi-alquilo acilo de C1 a C7 aciloxi de C1 a C7 carboxi, alcoxicarbonilo, carboximetilo, hidroximetilo, amino (monosustituido)amino (disustituido)amino carboxamida N-(alquilo de C1 a C6)carboxamida N,N-di(alquilo de C1 a C6)carboxamida, trifluorometilo, N-((alquilo de C1 a C6)sulfonil)amino o N(fenilsulfonil)amino

Los términos halo y halógeno" se refieren a atomos de fluor, cloro, bromo o yodo Puede haber uno o más halogenos, que son los mismos o diferentes Los halogenos preferidos son cloro y fluor Aunque muchos de los compuestos de la invención que tienen átomos de halógeno como sustituyentes son muy

efectivos al unirse a los receptores de sabor relevante, tales como compuestos orgánicos halogenados pueden con frecuencia tener propiedades toxicológicas indeseables cuando se administran a un animal in vivo Por lo tanto, en muchas modalidades de los compuestos de la Formula (I), si un atomo de halógeno (incluyendo un átomo de fluoro o cloro) se lista como un posible átomo sustituyente, un grupo preferido alternativo de sustituyentes NO incluiria los grupos halógeno, fluor o cloro

El término "(monosustituido)amino" se refiere a un grupo amino con un sustituyente elegido de preferencia a partir del grupo que consiste de fenilo, fenilo sustituido, alquilo de C1 a C6 alquilo sustituido de C1 a C6, acilo de C1 a C7, acilo sustituido de C1 a C7, alquenilo de C2 a C7, alquenilo sustituido de C2 a C7, alquinilo de C2 a C7, alquinilo sustituido de C2 a C7, fenilalquilo de C7 a C12, fenilalquilo sustituido de C7 a C12 y un anillo heterocíclico El (monosustituido)amino puede tener adicionalmente un grupo de protección amino como se abarca por el término '(monosustituido)amino protegido"

El término "(disustituido)amino" se refiere a un grupo amino sustituido de preferencia con dos sustituyentes elegidos a partir del grupo que consiste de fenilo, fenilo sustituido, alquilo de C1 a C6, alquilo sustituido de C1 a C6 acilo de C1 a C7 alquenilo de C2 a C7, alquinilo de C2 a C7, fenilalquilo de C7 a C12, y fenilalquilo sustituido de C7 a C12 Los dos sustituyentes pueden ser los mismos o diferentes

El termino grupo de protección amino" como se utiliza en la presente, se refiere a sustituyentes del grupo amino comunmente empleados para bloquear o proteger la funcionalidad amino mientras se hacen reaccionar otros grupos funcionales de la molecula El término (monosustituido)amino protegido" significa que existe un grupo de protección amino en el atomo de nitrogeno monosustituido amino Ademas, el término 'carboxamida protegida" significa que existe un grupo de proteccion amino en el nitrógeno de carboxamida De manera similar, el término "N-(alquilo de C1 a C6)carboxamida protegida" significa que existe un grupo de proteccion amino en el nitrógeno de carboxamida

El término 'alquiltio se refiere a grupos sulfuro tales como metiltio, etiltio, n-propiltio, isopropiltio, n-butiltio, t-butiltio y grupos similares

El termino "alquilsulfóxido" indica grupos sulfóxido tales como metilsulfóxido etilsulfoxido, n-propilsulfóxido isopropilsulfóxido, n-butilsulfóxido sec-butilsulfóxido y similares

El término alquilsulfonilo" abarca grupos tales como metilsulfonilo, etilsulfonilo, n-propilsulfonilo, isopropilsulfonilo, n-butilsulfonilo, t-butilsulfonilo y similares

Los terminos alquiltio sustituido", "alquilsulfoxido sustituido" y alquilsulfonilo sustituido indican la porción alquilo de estos grupos que pueden sustituirse como se describe anteriormente en relación al "alquilo sustituido"

Los términos feniltio "fenilsulfoxido" y "fenilsulfonilo

especifican un tiol, un sulfóxido o sulfona, respectivamente, conteniendo un grupo fenilo Los términos feniltio sustituido , "fenilsulfóxido sustituido", y 'fenilsulfonilo sustituido" significa que el fenilo de estos grupos puede sustituirse como se describe anteriormente en relación al "fenilo sustituido"

El termino alcoxicarbonilo" significa un grupo 'alcoxi unido a un grupo carbonilo El termino 'alcoxicarbonilo sustituido" indica un alcoxi sustituido unido al grupo carbonilo, cuyo alcoxi puede sustituirse como se describe anteriormente en relacion al alquilo sustituido

El término fenileno" significa un grupo fenilo en donde el radical fenilo se une a dos posiciones que conectan juntas a 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 se une a dos posiciones que conectan juntas a dos grupos adicionales separados y soportan además 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 "fenileno sustituido" significa un grupo fenilo en donde el radical fenilo se une a dos posiciones que se conectan juntas a dos grupos adicionales separados en donde el fenilo se sustituye como se describe anteriormente con relacion al fenilo

sustituido"

Los términos 'alquileno cíclico , "alquileno ciclico sustituido", "heteroalquileno ciclico y 'heteroalquileno ciclico sustituido' definen tal grupo ciclico unido ('fundido") al radical fenilo que resulta en un sistema de anillo biciclico El grupo ciclico puede saturarse o contener una o dos dobles uniones Ademas, el grupo cíclico puede tener uno o dos grupos metileno o metina reemplazados por uno o dos atomos de oxigeno, nitrogeno o azufre que son el heteroalquileno ciclico

El grupo alquileno o heteroalquileno ciclico puede sustituirse una vez o dos veces por el mismo o diferentes sustituyentes de preferencia seleccionados a partir del grupo que consiste de las siguientes porciones hidroxi hidroxi protegido carboxi, carboxi protegido, oxo, oxo protegido, aciloxi de C1 a C4 formilo, acilo de C1 a C7, alquilo de C1 a C6 alcoxi de C1 a C7 alquiltio de C1 a C4 alquilsulfóxido de C1 a C4, alquilsulfonilo de C1 a C4, halo, amino, amino protegido, (monosustituido)amino (monosustituido)amino protegido, (disustituido)amino, hidroximetilo o un hidroximetilo protegido

El grupo alquileno o heteroalquileno ciclico fundido sobre el radical benceno puede contener dos a diez miembros en el anillo, pero contiene de preferencia tres a seis miembros Ejemplos de tales grupos ciclicos saturados son cuando el sistema de anillo biciclico resultante es 2,3-dihidro-indanilo y un anillo tetralina Cuando los grupos cíclicos no se saturan ocurren

ejemplos cuando el sistema de anillo biciclico resultante es un anillo naftilo o indolilo Ejemplos de grupos ciclicos fundidos que contiene cada uno un átomo de nitrogeno y una o más dobles uniones, de preferencia una o dos dobles uniones son cuando el radical benceno se funde a un anillo piridino pirano, pirrolo piridinilo dihidripirrolo o dihidropiridinilo Ejemplos de grupos cíclicos fundidos que contiene cada uno un átomo de oxigeno y una o dos dobles uniones son cuando el anillo radical benceno se funde a un anillo furo, pirano, dihidrofurano o dihidropirano Ejemplos de grupos cíclicos fundidos que cada uno tiene un átomo de azufre y contiene una o dos dobles uniones son cuando el radical benceno se funde a un anillo tieno tiopirano, dihidrotieno o dihidrotiopirano Ejemplos de grupos ciclicos que contienen dos heteroatomos seleccionados a partir de azufre y nitrógeno y una o dos dobles uniones son cuando el anillo de radical benceno se funde a un anillo tiazolo isotiazolo dihidrotiazolo o dihidroisotiazolo Ejemplos de grupos ciclicos que contienen dos heteroatomos seleccionados a partir de oxigeno y nitrógeno y una o dos dobles uniones son cuando el anillo benceno se funde a un anillo oxazolo, isoxazolo, dihidroxazolo o dihidroisoxazolo Ejemplos de grupos ciclicos que contienen dos heteroatomos de nitrógeno y una o dos dobles uniones ocurren cuando el anillo benceno se funde a un anillo pirazolo, imidazolo, dihidropirazolo o dihidroimidazolo o pirazinilo

El termino carbamoilo' significa un grupo –NCO- en

donde el radical se une a dos posiciones que conectan dos grupos adicionales separados

Uno o más de los compuestos de la invención pueden presentarse como una sal El término sal abarca aquellas sales que forman con los aniones carboxilato y nitrógenos amina e incluyen sales formadas con los aniones y cationes orgánicos e inorganicos discutidos posteriormente Además, el término incluye sales que se forman por reacciones de base de ácido estandar con grupos básicos (tales como grupos amino) y ácidos organicos e inorganicos Tales acidos incluyen ácidos clorhidrico, fluorhidrico, trifluoroacético, sulfurico, fosforico, acético succinico citrico, lactico, maleico, fumarico, palmitico cólico pamoico musico, D-glutámico D-canfórico, glutárico, ftálico, tartarico, laurico esteárico salicíclico, metanisulfónico, bencensulfónico, sorbico, picrico benzoico, cinamico y similares

El termino "catión organico e inorganico" se refiere a contra-iones para el anion carboxilato de una sal carboxilato Los contra-iones se eligen a partir de los metales alcali y alcalinotérreos (tales como litio, sodio, potasio, bario, aluminio y calcio), amonio y mono, di y trialquilaminas tales como trimetilamina ciclohexilamina y los cationes orgánicos, tales como dibencilamonio, bencilamonio, 2-hidroxietilamonio, bis(2-hidroxietil)amonio, feniletilbencilamonio, dibenciletilendiamonio, y cationes similares *Véase por ejemplo,* "Pharmaceutical Salts", Berge *et al , J Pharm Sci* (1977) 66 1-19, que se incorpora en la

presente para referencia Otros cationes abarcados por el término anterior incluyen la forma protonada de la procaina, la quinina y la N-metilglucosamina, y las formas protonadas de aminoácidos básicos tales como glicina, ornitina, histidina, fenilglicina lisina y arginina Ademas, cualquier forma zwiterionica de los presentes compuestos formados por un acido carboxilico y un grupo amino se refiere por este termino Por ejemplo un cation para un anión carboxilato existirá cuando R2 o R3 se sustituya con un grupo (amonio cuaternario)metilo Un cation preferido para el anion carboxilato es el catión de sodio

Los compuestos de la invención pueden existir tambien como solvatos e hidratos De este modo estos compuestos pueden cristalizarse con por ejemplo, aguas de hidratacion, o uno, un numero de, o cualquier fracción de los mismos de moléculas del solvente licor madre Los solvatos e hidratos de tales compuestos se incluyen dentro del alcance de esta invención

El termino 'aminoácido" incluye cualquiera de los veinte aminoácidos de origen natural o la forma D de cualquiera de los aminoácidos de origen natural Ademas, el término aminoácido incluye también otros aminoácidos de origen no natural además de los aminoácidos D, que son equivalentes funcionales de los aminoácidos de origen natural Tales aminoacidos de origen no natural incluyen por ejemplo norleucina ("Nle"), norvalina ("Nva"), L- o D-naftalanina, ornitina (Orn) homoarginina (homoArg) y otros bien conocidos en la técnica de péptido tales como aquellos

descritos en M Bodanzsky, "Principles of Peptide Synthesis" 1st and 2nd revised ed , Springer-Verlag, New York, NY, 1984 y 1993, y Stewart and Young, "Solid Phase Peptide Synthesis" 2nd Ed , Pierce Chemical Co , Rockford, IL, 1984, ambas de las cuales se incorporan en la presente para referencia Los aminoácidos y analogos de aminoácido pueden adquirirse comercialmente (Sigma Chemical Co , Advanced Chemtech) o sintetizarse utilizando metodos conocidos en la técnica

La "cadena secundaria de aminoacido" se refiere a cualquier cadena secundaria a partir de los 'aminoacidos" descritos anteriormente

"Sustituido en la presente se refiere a una porcion sustituida, tal como hidrocarburo, por ejemplo, alquilo o bencilo sustituido en donde al menos un elemento o radical, por ejemplo, un hidrógeno se reemplaza por otro, por ejemplo, un hidrogeno se reemplaza por un halogeno como un clorobencilo Un residuo de una especie química, como se utiliza en la especificación y reivindicaciones terminantes, se refiere a un fragmento estructural o a una porcion que es el producto resultante de la especie quimica en un esquema de reaccion particular o formulación subsecuente o producto quimico, a pesar de si el fragmento o la porción estructural se obtiene realmente a partir de la especie química De este modo, un residuo de etilenglicol en un poliéster se refiere a una o más unidades de repetición $-OCH_2CH_2O-$, a pesar de si el etilenglicol se utiliza para preparar el

poliéster De manera similar, un residuo de 2,4-tiazolidindiona en un compuesto quimico se refiere a una o más porciones 2,4-tiazolidindiona del compuesto, a pesar de si el residuo se obtuvo haciendo reaccionar 2,4-tiazolidindiona para obtener el compuesto

El término residuo organico' define un carbono que contiene un residuo, es decir, un residuo que comprende al menos un átomo de carbono e incluye, pero no se limita a los grupos, residuos o radicales que contienen carbono, definidos anteriormente Los residuos orgánicos pueden contener varios heteroátomos, o unirse a otra molécula a traves de un heteroatomo, incluyendo oxígeno, nitrógeno, azufre, fósforo o similares Ejemplos de residuos organicos incluyen, pero no se limitan a grupos alquilo o alquilo sustituido, alcoxi o alcoxi sustituido, amino mono o disustituido, amida, etc Los residuos organicos pueden comprender de preferencia 1 a 18 átomos de carbono, 1 a 15 átomos de carbono, 1 a 12 atomos de carbono, 1 a 8 atomos de carbono o 1 a 4 atomos de carbono

Por el termino cantidad efectiva' de un compuesto como se proporciona en la presente se quiere decir una cantidad suficiente del compuesto para proporcionar la regulacion deseada de una funcion deseada, tal como la expresión genética, la función de la proteina, o una condicion de enfermedad Como se indicará posteriormente, la cantidad exacta requerida variará de sujeto a sujeto, dependiendo de la especie, edad, condición general del

sujeto, identidad especifica y formulación del fármaco, etc De este modo, no es posible especificar una "cantidad efectiva exacta Sin embargo, una cantidad efectiva apropiada puede determinarse por alguien con experiencia ordinaria en la técnica utilizando sólo experimentacion rutinaria

Se debe observar que, como se utiliza en la especificación y las reivindicaciones anexas, las formas singulares un', una" y el incluyen referencias plurales a menos que el contexto lo dicte claramente de otra manera De este modo por ejemplo, la referencia a un "compuesto aromatico" incluye mezclas de compuestos aromaticos

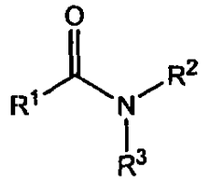
Con frecuencia, los rangos se expresan en la presente como "aproximadamente" un valor particular, y/o a 'aproximadamente" otro valor particular Cuando tal rango se expresa otra modalidad incluye a partir de un valor particular y/o el otro valor particular De manera similar, cuando se expresan los valores como aproximaciones por el uso del antecedente "aproximadamente" se entendera que el valor particular forma otra modalidad Se entenderá además que los puntos finales de cada uno de los rangos son significativos en relación al otro punto final e independientemente del otro punto final

Opcional u opcionalmente significa que el episodio o circunstancia subsecuentemente descrita puede o no puede ocurrir, y que la descripción incluye casos en donde tal episodio o circunstancia ocurre y los ejemplos en donde no lo hacen Por

ejemplo, la frase alquilo inferior opcionalmente sustituido significa que el grupo alquilo inferior puede o no sustituirse y que la descripcion incluye alquilo inferior sin sustituir y alquilos inferiores en donde existe la sustitucion

Los Compuestos Amida de la Invención

Los compuestos de la invencion son todos compuestos orgánicos (que contienen carbono) ya que todos tienen al menos un grupo "amida" en el mismo, tienen la siguiente estructura general, que se referirá más adelante como los compuestos amida que tienen la Fórmula (I) mostrada posteriormente



(I)

Los compuestos amida de la Fórmula (I) no incluyen cualesquier compuestos amida que se conocen para ocurrir de manera natural en sistemas o alimentos biologicos, tales como peptidos proteinas ácidos nucleicos, glicopéptidos o glicoproteínas o similares Los compuestos amida de la Fórmula (I) de la invención son fabricados y compuestos amida sinteticos artificiales aunque los Solicitantes no excluyen la posibilidad de que los compuestos de la Fórmula (I) podrian prepararse concebiblemente a propósito ya sea en su forma especifica o en la forma de un péptido o forma de profármaco" modificado con

proteinas por seres humanos que utilizan uno o mas de los métodos de la biotecnologia moderna

Para las diversas modalidades de los compuestos de la Formula (I) los grupos R^1, R^2 y R^3 pueden ser y se definen además independientemente en varias maneras, como se detallará además, de manera que forman y/o incluyen un numero sustancial de subgeneros y/o especies de los compuestos de la Fórmula (I) Se contempla por lo tanto específicamente que cualquiera de los subgeneros y/o especies de los compuestos de la Fórmula (I) descritos posteriormente pueden, ya sea en su forma especifica o como una sal comestiblemente aceptable, combinarse en una cantidad efectiva con un producto o precursor comestible o medicinal del mismo por los procesos y/o métodos descritos en algun lado en la presente, o por cualesquiera de tales otros procesos como seria aparente por aquellos con experiencia ordinaria para preparar productos o precursores comestibles o medicinales de los mismos, para formar un producto comestible o medicinal modificado con sabor sabroso o dulce, o un precursor del mismo

En algunas modalidades de los compuestos de la Fórmula (I), R^1 es un residuo hidrocarburo que puede contener uno o más heteroátomos o un residuo inorganico y R^2 y R^3 son cada uno independientemente H o un residuo hidrocarburo que puede contener uno o más heteroátcmos, mas 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 $-R^4N(R^5)SO_2R^6$, o grupos opcionalmente sustituidos de los mismos y de preferencia uno de R^2 o R^3 es H, en donde cada R^4 es independientemente un residuo hidrocarburo que puede contener uno o más heteroátomos, de preferencia seleccionados independientemente a partir de un alquileno (C1-C6) o alcoxialquileno (C1-C6) pequeño y en donde cada R^5 y R^6 son independientemente H o residuo hidrocarburo que puede contener uno o más heteroátomos, seleccionados de preferencia independientemente de un alquilo de (C1-C6) o alcoxialquilo de (C1-C6) pequeño

En muchas modalidades de los compuestos de la Fórmula (I) R^1 comprende un residuo orgánico con base en hidrocarburos que tienen al menos tres átomos de carbono y opcionalmente uno a 20, 15, 10, 8, 7 6 ó 5 heteroatomos seleccionados independientemente de oxígeno, nitrogeno, azufre, halógenos o fósforos

En muchas modalidades de los compuestos de la Fórmula (I) uno de R^2 y R^3 es opcionalmente H, y uno o ambos de R^2 y R^3 comprende un residuo organico o basado en hidrocarburos que tienen al menos tres atomos de carbono y opcionalmente uno a diez heteroátomos seleccionados independientemente de

oxígeno, nitrogeno, azufre, halógenos o fosforos

Los compuestos de la Fórmula (I) son relativamente "moléculas pequeñas" cuando se comparan con muchas moléculas biologicas, y pueden con frecuencia tener una variedad de limitaciones en su tamaño fisico absoluto total, el peso molecular y las caracteristicas fisicas, de manera que pueden ser al menos un poco solubles en medios acuosos y son de tamaño apropiado para unirse efectivamente a los receptores de sabor T1R1/T1R3 o T1R2/T1R3 heterodimericos relevantes que comparten una subunidad de proteinas T1R3 comun

Aunque no se desea unirse por cualquier teoria, se cree que el MSG se une a la subunidad T1R1 de los receptores de sabor sabroso" T1R1/T1R3, y varios edulcorantes conocidos se unen a la subunidad T1R2 de los receptores dulces T1R2/T1R3 Por consiguiente nuestro inesperado y sorprendente descubrimiento de que los compuestos amida de la Fórmula (I) pueden compartir muchas caracteristicas físicas y químicas traslapantes, y pueden algunas veces unirse a cualquiera o ambos de los receptores sabrosos y dulces, es quizás en retrospectiva razonable y/o rotacional a partir de un punto de vista químico/bioquimico/biológico

Como un ejemplo de las propiedades físicas y quimicas traslapantes y/o las limitaciones fisicas/quimicas en las amidas sabrosas y/o dulces de la Fórmula (I), en la mayoria de las modalidades de los compuestos de la Fórmula (I), el peso

molecular de los compuestos de la Formula (I) debe ser menor de aproximadamente 800 gramos por mol, o en modalidades relacionadas adicionales menores de o igual a aproximadamente 700 gramos por mol, 600 gramos por mol, 500 gramos por mol, 459 gramos por mol, 400 gramos por mol, 350 gramos por mol o 300 gramos por mol

De manera similar los compuestos de la Formula (I) pueden tener rangos preferidos de peso molecular tales como por ejemplo, desde aproximadamente 175 a aproximadamente 500 gramos por mol, desde aproximadamente 200 a aproximadamente 450 gramos por mol, desde aproximadamente 225 a aproximadamente 400 gramos por mol, desde aproximadamente 250 a aproximadamente 350 gramos por mol

En una serie liberada de modalidades R^1 tiene entre 3 y 16 átomos de carbono ó 4 y 14 atomos de carbono o 5 y 12 atomos de carbono y 0 1, 2, 3 4 o 5 heteroátomos seleccionados a partir de oxigeno nitrogeno, azufre, fluor o cloro y/o al menos uno de R^2 o R^3 ha sido 3 y 16 átomos de carbono y 0, 1, 2 3, 4 ó 5 heteroatomos independientemente seleccionados a partir de oxígeno nitrógeno, azufre, fluor o cloro, o de preferencia al menos uno de R^2 o R^3 tiene entre 4 y 14 atomos de carbono y 0 1, 2, 3, 4 ó 5 heteroátomos seleccionados independientemente a partir de oxígeno, nitrógeno, azufre fluor, o aun mas preferiblemente, al menos uno de R^2 o R^3 tiene entre 5 y 12 átomos de carbono y 0, 1 2 ó 3 heteroátomos seleccionados

independientemente de oxigeno, nitrógeno y azufre

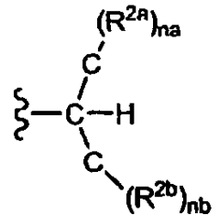
Además de las caracteristicas y/o limitaciones fisicas y quimicas descritas generales anteriores, que pueden compartirse por los diversos subgéneros de los compuestos dulces y sabrosos de la Formula (I) los compuestos de la Fórmula (I) pueden compartir también caracteristicas estructurales quimicas especificamente definibles o grupos o residuos quimicos como se describe además posteriormente

Por ejemplo, en algunas modalidades, R^1, R^2 y R^3 pueden seleccionarse independientemente 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 un derivado opcionalmente sustituido del mismo que comprende 1, 2 3 o 4 grupos carbonilo, amino grupos hidroxilo o halogeno, y en donde R^4 y R^5 son residuos hidrocarburo de C_1-C_6

En las modalidades relacionadas adicionales de los compuestos amida de la Fórmula (I), R^1, R^2 y R^3 pueden seleccionarse independientemente del grupo que consiste de grupos arilalquenilo heteroarilalquenilo, arilalquilo, heteroarialquilo, alquilo, alcoxi-alquilo alquenilo, cicloalquilo, cicloalquenilo, heterociclo, arilo y heteroarilo, y derivados opcionalmente sustituidos de los mismos, que comprenden 1 2, 3 o 4 grupos carbonilo, amino o grupos hidroxilo o cloro o fluor En

ambas de las modalidades ya mencionadas, un conjunto alternativo y preferido de los grupos sustituyentes opcionales serian sustituyentes independientemente seleccionados a partir 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 grupos trifluorometoxi sustituyentes

En muchas modalidades de los compuestos de la 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 ejemplo en muchas modalidades de los compuestos de la Fórmula (I) al menos uno o R^2 y R^3 es un residuo orgánico ramificado o ciclico que tiene un átomo de carbono directamente unido tanto (a) al átomo de nitrógeno amida como (b) dos átomos de carbono adicionales a partir de otros residuos organicos, que son residuos organicos ramificados o cíclicos que comprenden atomos de hidrógeno adicionales y hasta 10 átomos de carbono adicionales opcionales y opcionalmente desde cero a cinco heteroatomos seleccionados independientemente de oxigeno nitrogeno, azufre fluor y cloro Tales grupos R^2 y R^3 ramificados incluyen radicales organicos que tienen la fórmula

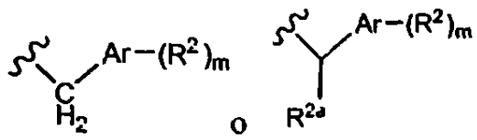


En donde na y nb se seleccionan independientemente de

1, 2, y 3, y cada uno de los residuos sustituyentes R^{2a} o R^{2b} se selecciona independientemente de hidrogeno, un halógeno un hidroxi o un residuo que contiene carbono opcionalmente teniendo desde cero a cinco heteroátomos seleccionados independientemente de oxigeno, nitrógeno, azufre y un halogeno En algunas modalidades el R^{2a} o R^{2b} son grupos sustituyentes independientes, pero en otras modalidades uno o mas de los radicales R^{2a} o R^{2b} pueden unirse juntos para formar estructuras de anillo

En algunas modalidades de los compuestos de la Fórmula (I), al menos uno de R^2 y R^3 es un radical alquilo ramificado que tiene 5 a 12 átomos de carbono, o al menos uno de R^2 y R^3 es un anillo cicloalquilo o cicloalquenilo que comprende 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 puede sustituirse opcionalmente con 1, 2 3 ó 4 grupos sustituyentes seleccionados 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

En otras modalidades de los compuestos amida de la Fórmula (I) al menos uno de R^2 y R^3 es un radical "bencílico que tiene la estructura



en donde Ar es un anillo aromático o heteroaromatico tal como fenilo, piridilo, furanilo, tiofuranilo, pirrolilo o sistemas de anillo aromatico similares, m es 0, 1, 2 ó 3, y cada R^2 se selecciona independientemente de hidroxi fluoro, cloro NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH, SEt, SCH_3 metilo, etilo, isopropilo, vinilo trifluorometilo, metoxi, etoxi, isopropoxi y trifluorometoxi y cada grupo sustituyente R^{2a} puede seleccionarse independientemente del grupo que consiste del grupo alquilo, alcoxi-alquilo alquenilo, cicloalquenilo, cicloalquilo, $-R^4OH$ $-R^4OR^5$, $-R^4CN$ $-R^4CO_2H$ $-R^4CO_2R^5$, $-R^4COR^5$, $-R^4SR^5$ y $-R^4SO_2R^5$

En muchas modalidades de los compuestos de la Formula (I) al menos uno de R^2 o R^3 es un alquilo ramificado de C_3-C_{10} Estos alquilos ramificados de C_3-C_{10} se han encontrado para ser grupos R^2 altamente efectivos para ambos compuestos amida sabrosos y dulces En las modalidades adicionales, el alquilo ramificado de C_3-C_{10} puede sustituirse opcionalmente con uno o dos sustituyentes independientemente seleccionados a partir del grupo hidroxi fluoro, 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 las modalidades adicionales de los compuestos de la

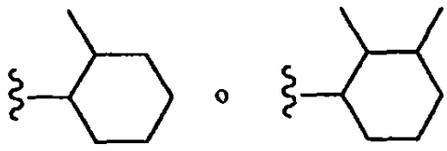
Fórmula (I) al menos uno de R^2 o R^3 es un alquiléster inferior del ácido carboxílico α-sustituido o un acido carboxílico α-sustituido De preferencia al menos uno de R^2 o R^3 es un alquilester (especialmente metilo) inferior del acido carboxílico α-sustituido En algunas modalidades preferidas, el residuo éster del acido carboxílico α-sustituido o ácido carboxílico α-sustituido corresponde a aquel de un α-aminoácido opticamente activo o un éster del mismo o su enantiomero opuesto

En muchas modalidades de los compuestos de la Fórmula (I) al menos uno de R^2 o R^3 es un anillo arilo o heteroarilo de 5 ó 6 miembros, opcionalmente sustituido con 1 2, 3 ó 4 grupos sustituyentes seleccionados a partir 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 de C_1-C_6 De preferencia el anillo arilo o heteroarilo se sustituye con 1, 2 3 o 4 grupos sustituyentes seleccionados a partir del grupo que consiste de grupos hidroxi fluoro, 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 de los compuestos de la 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 a partir de hidroxi, fluoro, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SCH_3 SEt

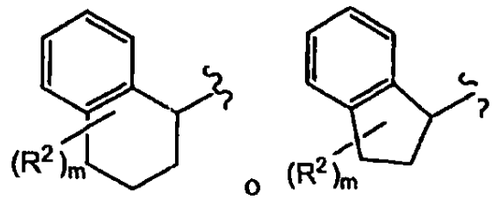
metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi y trifluorometoxi

En muchas modalidades de los compuestos de la Formula (I) al menos uno de R^2 o R^3 es un cicloalquilo, cicloalquenilo o un anillo heterociclico saturado que tiene 3 a 10 atomos de carbono en el anillo, opcionalmente sustituido con 1, 2 o 3 sustituyentes independientemente seleccionados a partir del grupo que consiste de NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, alquilo de C_1-C_4, haloalquilo de C_1-C_4, alcoxi de C_1-C_4, haloalcoxi de C_1-C_4, hidroxi y halógeno En algunas modalidades adicionales al menos uno de R^2 o R^3 es un anillo ciclopentilo, ciclohexilo cicloheptilo, ciclooctilo o un anillo piperidilo opcionalmente sustituido con 1, 2, o 3 sustituyentes independientemente seleccionados del grupo que consiste 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 algunas modalidades preferidas, al menos uno de R^2 o R^3 es un ciclohexilo, opcionalmente sustituido con 1, 2 o 3 grupos metilo Ejemplos de tales anillos ciclohexilo sustituidos con metilo tienen la fórmula



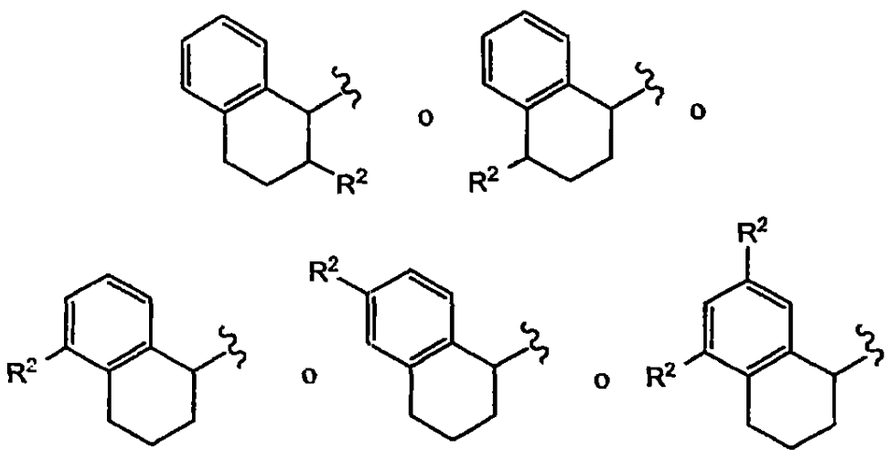
En muchas modalidades de los compuestos de la Fórmula (I), compuestos especialmente tienen la actividad para

receptores dulces al menos uno de R^2 o R^3 es un anillo 1-(1,2 3,4)tetrahidronaftaleno o un anillo 2,3-dihidro-1H-indeno que tiene la fórmula

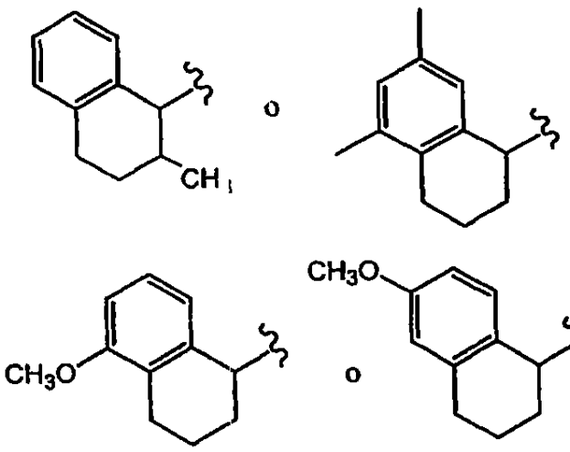


en donde m es 0, 1, 2 ó 3 y cada R^2 puede unirse ya sea a un anillo aromatico o no aromático y se selecciona independientemente de hidroxi, fluoro, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3 SCH_3, SEt metilo, etilo, isopropilo vinilo, trifluorometilo, metoxi etoxi, isopropoxi y trifluorometoxi Se entenderá que el isomerismo óptico y/o diastereomérico puede ocurrir en los anillos ciclohexilo o ciclopentilo de este sustituyente, y difiriendo ópticos y/o diastereómeros pueden con frecuencia tener al menos algunas actividades biológicas diferentes

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 preferida En particular, al menos uno de R^2 o R^3 puede tener la fórmula

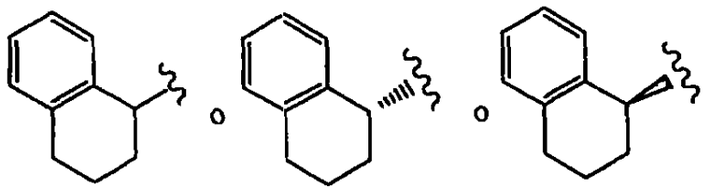


en donde cada R^2 se selecciona independientemente del grupo que consiste de grupos hidrogeno, hidroxi fluoro, cloro, NH_2 $NHCH_3$, $N(CH_3)_2$ $COOCH_3$, SCH_3, SEt metilo etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi, isopropoxi y trifluorometoxi De manera similar, en algunas modalidades preferidas, al menos uno de R^2 o R^3 puede tener la fórmula



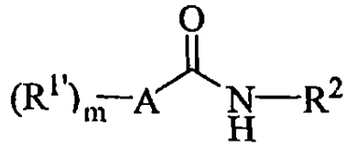
En algunas modalidades al menos uno de R^2 o R^3 es un anillo 1-(1,2 3,4)tetrahidronaftaleno sin sustituir en forma

racemica u opticamente activa, como se muestra posteriormente



Compuestos Aromaticos o Heteroaromáticos

En muchas modalidades preferidas de los compuestos amida de la Formula (I) que tienen uno o ambos de la actividad agonista del receptor sabroso y dulce, existe un subgénero preferido de los compuestos amida que tienen la siguiente formula (II)



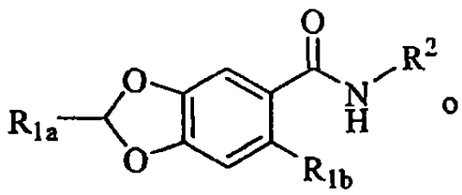
(II)

en donde A comprende un anillo arilo o heteroarilo de 5 ó 6 miembros m es 0, 1 2, 3 o 4, cada R^1 se selecciona independientemente 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 de C_1-C_6, y R^2 puede ser cualquiera de las modalidades contempladas en la presente anteriormente, o similares

En algunas modalidades, el grupo A de la Formula (II)

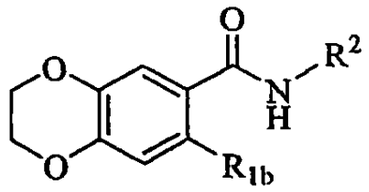
comprende un anillo arilo es decir, contiene al menos un anillo benceno aromatico de seis miembros Los arilos incluyen al menos anillos benceno y naftaleno, que no pueden, pero en muchas modalidades se sustituyen además con al menos 1, 2, ó 3 grupos sustituyentes R^1 independientemente seleccionados a partir del grupo que consiste de grupos hidroxi, fluoro, 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 algunas modalidades preferidas, uno o dos de los grupos sustituyentes R^1 se unen juntos para formar un anillo alquilendioxi saturado o un anillo fenilo, como se ejemplifica por las siguientes estructuras preferidas (IIa) y (IIb),



(IIa)

o

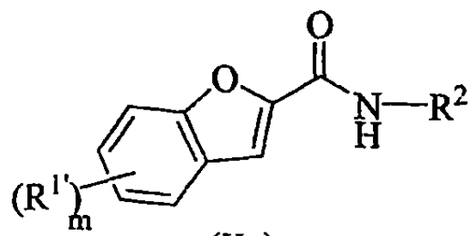


(IIb)

en donde R_{1a} y R_{1b} son independientemente hidrogeno o un alquilo inferior o alternativamente R_{1a} y R_{1b} son independientemente hidrógeno o metilo, o alternativamente tanto R_{1a} como R_{1b} son hidrogeno

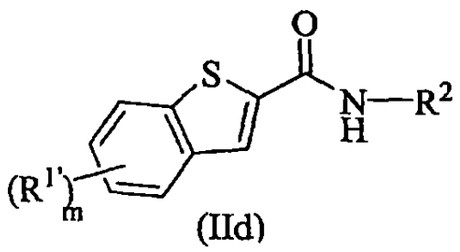
En muchas modalidades de los compuestos amida de la Formula (II), A es un anillo heteroarilo y normalmente un anillo heteroarilo monociclico o biciclico fundido Los heteroarilos bicíclicos fundidos se tipifican por los siguientes benzofuranos

(Formula IIc) y benzotiofuranos (Fórmula IId)



(IIc)

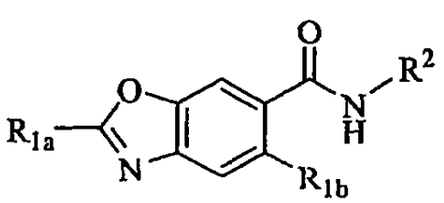
o



(IId)

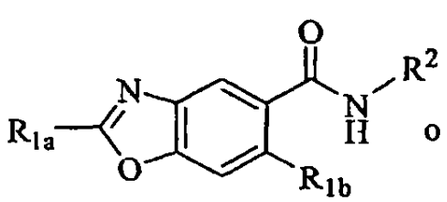
en donde m es 0, 1, 2 o 3 y cada R^1 puede unirse a cualquier anillo fenilo o heteroarilo y cada R^1 se selecciona independientemente de hidroxi, fluoro, cloro, NH_2, $NHCH_3$ $N(CH_3)_2$, CO_2CH_3, SCH_3, SEt, metilo, etilo, isopropilo vinilo, trifluorometilo, metoxi, etoxi isopropoxi y trifluorometoxi

Ejemplos adicionales de heteroarilos biciclicos fundidos como grupos A se tipifican por los siguientes compuestos benzoxazol (Fórmula IIe) y (Fórmula IIf)



(IIe)

o

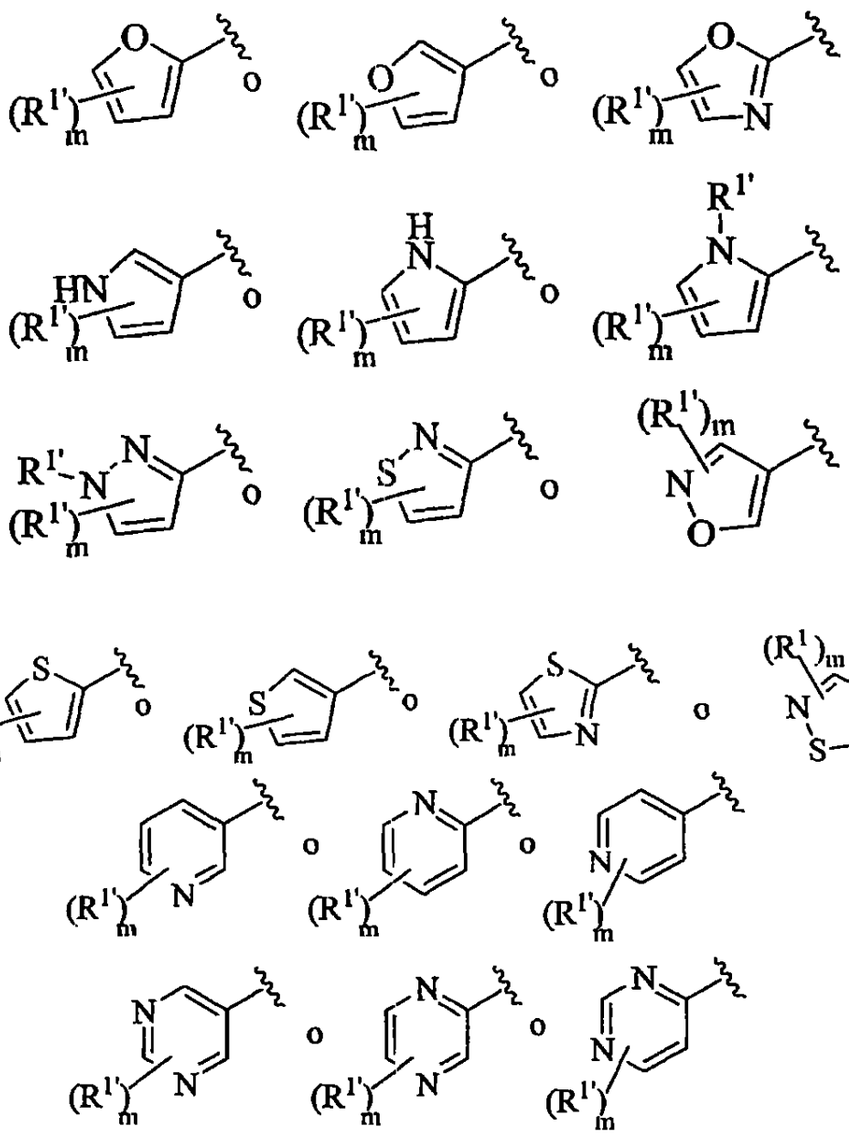


(IIf)

o

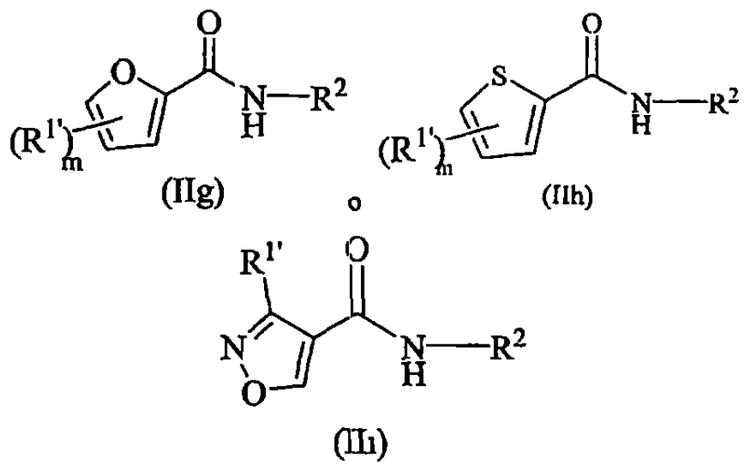
en donde R_{1a} o R_{1b} es independientemente hidrógeno o un alquilo inferior

En muchas modalidades de los compuestos amida de la Fórmula (II), A es un anillo heteroarilo monociclico Los heteroarilos monocíclicos pueden utilizarse como un grupo A en la formula (II) se tipifican por las siguientes estructuras



En donde m es 0 1 2 o 3 y cada R^1 se selecciona independientemente de hidroxi, fluoro, 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 preferidas de los compuestos de la Formula (II) A es un anillo furano sustituido tiofurano u oxazol, de manera que se forman compuestos que tienen Formulas (IIg) (IIh) y (IIi)



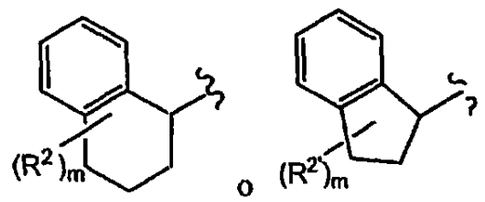
(IIg) o (IIh)

(IIi)

en donde m es 0, 1, 2 o 3 y cada R^1 se selecciona independientemente de hidroxi fluoro, 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 de estas modalidades m es 1 ó 2

En muchas modalidades de los compuestos de los varios subgéneros de la Formula (II) descritos inmediatamente en lo anterior, al menos uno de R^2 o R^3 puede ser un alquilo ramificado de C_3-C_{10}, un ácido carboxilico α-sustituido o un alquilester inferior del ácido carboxílico α-sustituido, un anillo arilo o heteroarilo de 5 ó 6 miembros opcionalmente sustituido con 1 2 3 ó 4 grupos sustituyentes seleccionados a partir del grupo que

consiste de grupos hidroxi fluoro 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 ó 3 grupos metilo, o un anillo 1-(1,2,3,4)tetrahidronaftaleno o un anillo 2,3-dihidro-1H-indeno que tiene la fórmula



en donde m es 0, 1 2 o 3, y cada R^2 puede unirse a cualquier anillo aromático o no aromatico y se selecciona independientemente de hidroxi, fluoro, 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 describira anteriormente con respecto a los compuestos amida generales de la Formula (I)

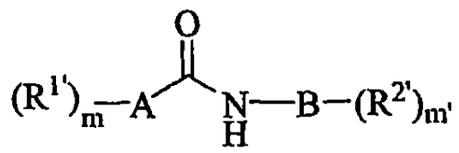
El subgénero de los compuestos amida aromaticos o heteroaromáticos de la Formula (II) descritos inmediatamente en lo anterior contienen muchos agonistas excelentes de los receptores de sabor sabroso (acre") T1R1/T1R3 y/o receptores de sabor dulce T1R2/T1R3, a concentraciones muy bajas del compuesto amida en el orden de concentraciones micromolares o menores, y puede inducir una sensación notable de un sabor acre sabroso en seres humanos, y/o pueden servir como mejoradores del sabor

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acre sabroso de MSG, o mejorar significativamente la efectividad de una variedad de edulcorantes conocidos, especialmente edulcorantes basados en sacaridos

Por consiguiente, muchos de los compuestos amida aromaticos o heteroaromáticos de la Formula (II) pueden utilizarse como agentes saborizantes sabrosos o dulces o mejoradores de sabor sabroso o dulce cuando se ponen en contacto con una amplia variedad de productos comestibles y/o composiciones, o sus precursores, como se describe en algun lado en la presente

En otro subgénero de los compuestos de la Formula (I) el compuesto amida tiene la Fórmula (III)



(III)

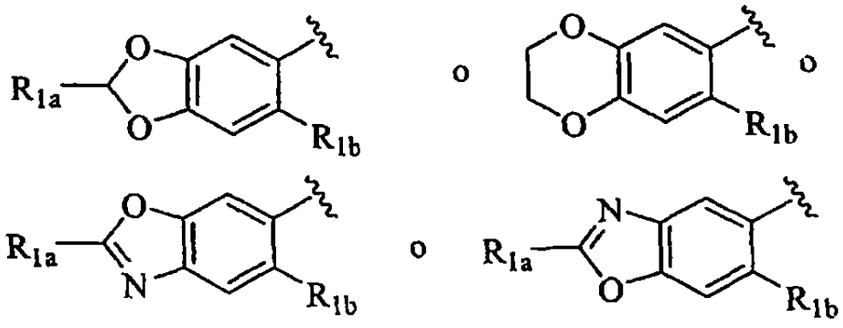
en donde A comprende un anillo arilo o heteroarilo de 5 ó 6 miembros, m es 0, 1, 2 3 o 4, cada R^1 se selecciona independientemente de alquilo, alcoxilo, alcoxi-alquilo hidroxialquilo OH, CN, CO_2H, CHO, COR^6, CO_2R^6 SH, SR^6, halogeno, alquenilo, cicloalquilo, cicloalquenilo arilo y heteroarilo y R^6 es alquilo de C_1-C_6, B es un anillo arilo o heteroarilo de 5 ó 6 miembros, m' es 0, 1, 2 3 ó 4, R^2 se selecciona a partir del grupo que consiste de alquilo, alcoxilo, alcoxi-alquilo, OH, CN CO_2H, CHO COR^6 CO_2R^6, SR^6 halógeno, alquenilo cicloalquilo

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cicloalquenilo, arilo y heteroarilo, y R^6 es alquilo de C_1-C_6

En los compuestos de la Fórmula (III), los grupos sustituyentes R^1 y R^2 opcionales pueden seleccionarse tambien independientemente de grupos hidroxi, fluoro 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 la 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 diversas modalidades de los anillos A enumeradas anteriormente para los compuestos de la Fórmula (II), incluyen fenilo y los heteroarilos monociclicos y biciclicos pueden ser adecuados En algunas modalidades biciclicas el anillo A de los compuestos de la Fórmula (III) tienen las siguientes estructuras



en donde R_{1a} y R_{1b} son independientemente hidrogeno o un alquilo inferior

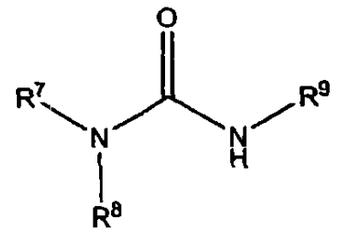
En los compuestos de la Fórmula (III), los anillos B son un anillo arilo o heteroarilo de cinco o seis miembros, monociclicos opcionalmente sustituidos tal como fenilo, piridilo

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furanilo, tiofuranilo pirrolilo y monociclos similares En algunas modalidades, los compuestos de la Fórmula (III) en donde b es fenilo *es decir* en donde el compuesto amida se deriva fácilmente a partir de un precursor anilina sustituido, puede en muchos casos ser compuestos químicos previamente conocidos, pero se cree que esto ha sido desconocidos previamente que tales compuestos pueden utilizarse como compuestos saborizantes acres muy efectivos menores que las concentraciones molares o menores *véase* por ejemplo el compuesto A1 en la Tabla 1 posteriormente

Compuestos Urea

En otro subgénero de los compuestos amida de la Fórmula (I), el compuesto urea es un compuesto urea que tiene la Fórmula (IV)



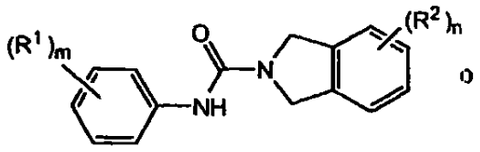
(IV)

en donde R^7 R^8 y R^9 son cada uno un residuo hidrocarburo que puede contener uno o más heteroátomos o un residuo inorgánico, y de preferencia se seleccionan independientemente a partir de grupos arilalquenilo heteroarilalquenilo, arilalquilo, heteroarilalquilo, alquilo, alcoxi-alquilo alquenilo, cicloalquilc, cicloalquenilo, arilo y heteroarilo

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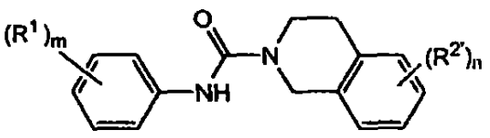
cada uno de los cuales puede sustituirse opcionalmente, o uno de R^7 o R^8 puede ser y con frecuencia es H

En algunas modalidades de los compuestos urea de la Formula (IV), R^7 y R^8 juntos forman un anillo heterociclico o heteroarilo que tiene 5, 6 o 7 atomos en el anillo que pueden sustituirse opcionalmente con 1, 2 ó 3 sustituyentes independientemente seleccionados a partir de grupos hidroxi, fluoro, 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 tal compuesto urea pueden tener las Fórmulas (IVa) y (IVb)



(IVa)

o



(IVb)

en donde m y n scn independientemente 0 1 2 ó 3 y cada R^1 y R^2 es independientemente seleccionado de 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 tales modalidades, n es de preferencia 0

En las modalidades adicionales de los compuestos urea de la Fórmula (IV), R^9 y uno de R^7 y R^8 se seleccionan independientemente de arilalquenilos heteroarilalquenilos arilalquilos, heteroarilalquilos alquilos, alcoxi-alquilos alquenilos,

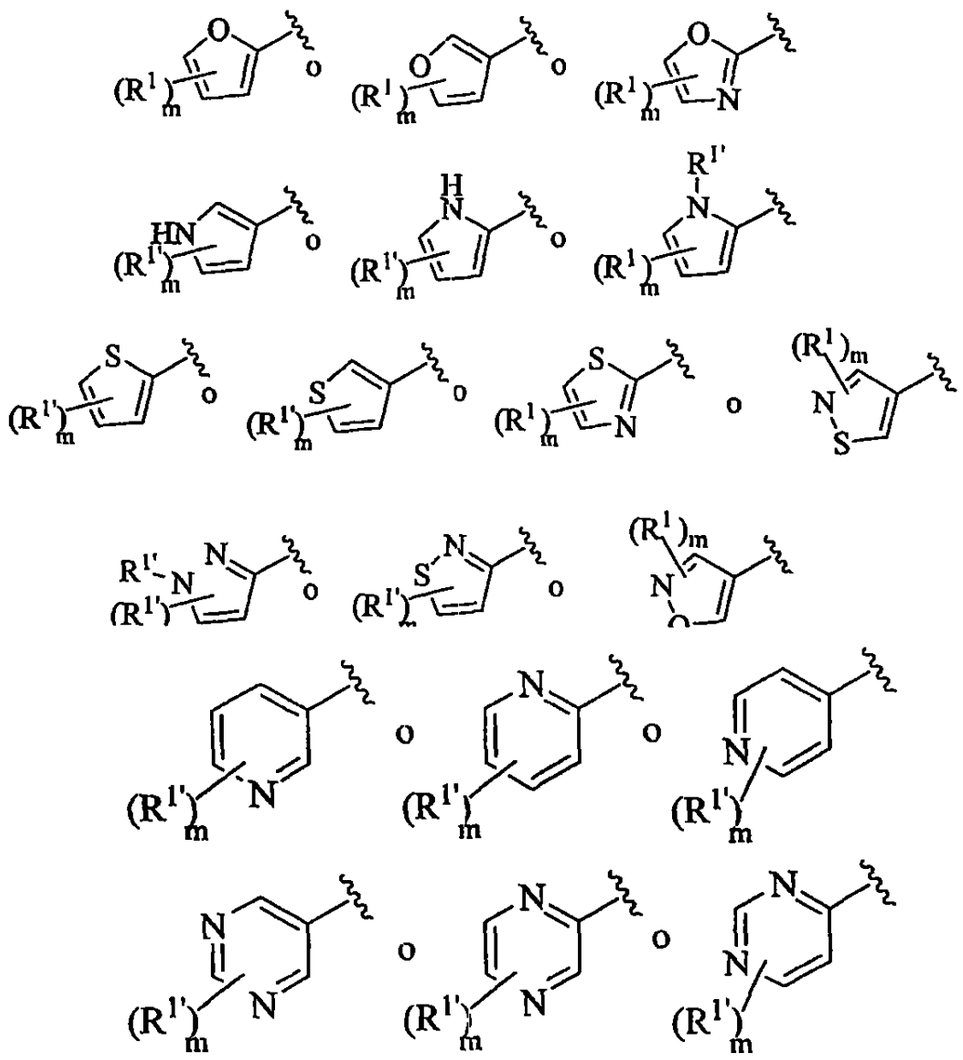
cicloalquilos, cicloalquenilos, arilos y heteroarilos cada uno de cuyos grupos que contienen carbono pueden sustituirse opcionalmente con 1, 2, o 3 sustituyentes seleccionados independientemente de grupos hidrogeno hidroxi, fluoro, cloro NH_2 $NHCH_3$, $N(CH_3)_2$ $COOCH_3$ SCH_3 SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo metoxi, etoxi, isopropoxi y trifluorometoxi

En las modalidades adicionales de los compuestos urea de la 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 comprender opcionalmente uno a cinco heteroátomos seleccionados independientemente de oxigeno, nitrógeno, azufre cloro y fluor

En las modalidades adicionales de los compuestos urea de la 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 comprender opcionalmente uno a cuatro sustituyentes independientemente seleccionados a partir 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 las modalidades adicionales de los compuestos urea de la Fórmula (IV), al menos uno de R^7 y R^8 tiene una de las fórmulas heteroaromáticas

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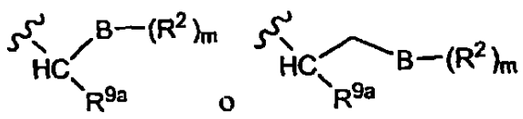


en donde m es 0, 1, 2 ó 3 y cada R^1 seleccionado independientemente de grupos hidrógeno, hidroxi, fluoro, cloro, NH_2, $NHCH_3$ $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt metilo etilo isopropilo vinilo trifluorometilo, metoxi, etoxi, isopropoxi y trifluorometoxi En tales modalidades R^9 es de preferencia un alquilo ramificado de C_3-C_{10}, arilalquilo o un cicloalquilo que

puede sustituirse opcionalmente con 1 2 o 3 sustituyentes seleccionados independientemente de grupos hidrogeno, hidroxi, fluoro, 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 las modalidades adicionales de los compuestos urea de la Formula (IV), al menos uno de R^7 y R^8 es un anillo fenilo opcionalmente sustituido con 1, 2 ó 3 sustituyentes seleccionados independientemente de grupos hidrogeno, hidroxi, fluoro 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 de preferencia un alquilo ramificado de C_3-C_{10}, arilalquilo o un cicloalquilo que puede sustituirse opcionalmente con 1, 2 ó 3 sustituyentes independientemente seleccionados a partir de grupos hidrogeno hidroxi fluoro, cloro NH_2 $NHCH_3$ $N(CH_3)_2$ $COOCH_3$, SCH_3, SEt metilo, etilo, isopropilo, vinilo trifluorometilo, metoxi etoxi, isopropoxi y trifluorometoxi

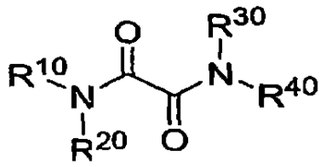
En las modalidades adicionales de los compuestos urea de la Formula (IV), R^9 es un alquilo ramificado de C_3-C_{10} En las modalidades adicionales de los compuestos urea de la Formula (IV) R^9 tiene la estructura



en donde B es un anillo fenilo, piridilo, furanilo tiofuranilo, pirrol, ciclopentilo ciclohexilo o piperidilo, m es 0 1 2 ó 3 y cada R^2 se selecciona independientemente a partir de grupos hidrógeno, hidroxi, fluoro, 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} se selecciona a partir del grupo que consiste de un alquilo alcoxi-alquilo alquenilo, cicloalquenilo cicloalquilo $-R^4OH$, $-R^4OR^5$, $-R^4CN$, $-R^4CO_2H$, $-R^4CO_2R^5$, $-R^4COR^5$, $-R^4SR^5$ y $-R^4SO_2R^5$ comprende 1 a 12 atomos de carbono o de preferencia

Compuestos Oxalamida

En otro subgenero de los compuestos amida de la Fórmula (I) el compuesto amida es un compuesto oxalamida que tiene la Fórmula (V)



(V)

en donde R^{10} y R^{30} se selecciona cada uno independientemente de un residuo hidrocarburo que puede contener uno o más heteroatomos, o de preferencia R^{10} y R^{30} se seleccionan independientemente del grupo que consiste de arilalquilo heteroarilalquilo, heterociclo-alquilo o grupos opcionalmente sustituidos de los mismos y

R^{20} y R^{40} son cada uno independientemente H o un residuo hidrocarburo que puede contener uno o más heteroátomos, de preferencia R^{20} y R^{40} son H o alquilo de C_1-C_3, o grupos opcionalmente sustituidos de los mismos Mas preferiblemente R^{20} y R^{40} son H Ademas, pueden ser 0, 1, 2, 3 ó 4 grupos sustituyentes opcionales para R^{10} y R^{30} independientemente seleccionados a partir de grupos hidroxi, fluoro, 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

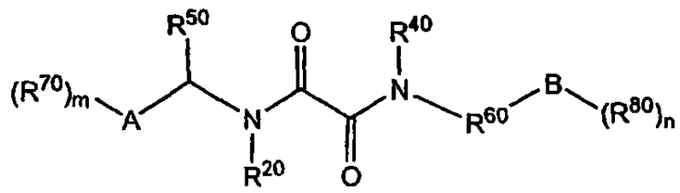
En la modalidad preferida de los compuestos oxalamida de la Formula (V) R^{10} y R^{30} se seleccionan independientemente de residuos hidrocarburo que tienen al menos tres atomos de carbono y opcionalmente uno a diez heteroátomos seleccionados independientemente de oxigeno nitrógeno, azufre, halogenos o fosforos, y en donde R^{20} y R^{40} se seleccionan independientemente de hidrógeno y un residuo hidrocarburo que tiene al menos tres atomos de carbono y opcionalmente uno a diez heteroatomos seleccionados independientemente de oxigeno, nitrogeno, azufre halógenos o fosforos

En muchas modalidades preferidas de los compuestos oxalamida de la Formula (V), R^{20} y R^{40} son hidrógeno En tales modalidades, R^{10} y R^{30} pueden seleccionarse independientemente del grupo que consiste de arilalquilos, heteroarilalquilos cicloalquil-alquilos, y heterociclo-alquilos que comprenden de cinco a 15 atomos de carbono, en donde cada uno de R^{10} y R^{30}

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pueden comprender opcionalmente uno a uno a cuatro sustituyentes seleccionados independientemente de grupos hidrogeno, 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 muchas modalidades de los compuestos oxalamida de la Fórmula (V), el compuesto oxalamida tiene la Fórmula (Va)



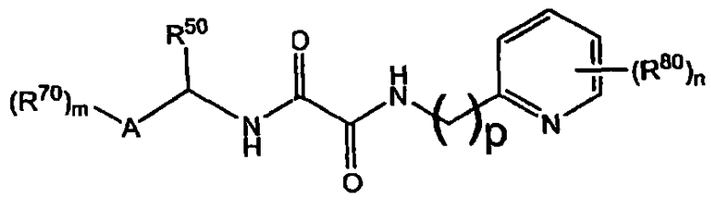
(Va)

en donde A y B son independientemente 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 hidrogeno R^{50} es hidrogeno o un alquilo o residuo alquilo sustituido que comprende uno a cuatro atomos de carbono, R^{60} esta ausente o un alquileno de C_1-C_5 o un alquileno de C_1-C_5 sustituido, R^{70} y R^{80} se seleccionan independientemente a partir del grupo que consiste de hidrogeno, 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 de C_1-C_6, cicloalquilo de C_3-C_6 y alquenilo de C_1-C_6

En las modalidades preferidas de los compuestos oxalamida de la Fórmula (Va), R^{60} es un grupo $-CH_2CH_2-$, A y B se seleccionan independientemente de anillos fenilo, piridilo, furanilo, tiofuranilo y pirrolilo y R^{70} y R^{80} se seleccionan independientemente 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

En algunas modalidades de los compuestos oxalamida de la Formula (Va), A y B son independientemente un anillo fenilo, piridilo furanilo, benzofuranilo pirrol, benzotiofeno, piperidilo ciclopentilo ciclohexilo o cicloheptilo, m y n son independientemente 0, 1, 2 ó 3, R^{20} y R^{40} son hidrogeno, R^{50} es hidrógeno o metilo, R^{60} es un C_1-C_5 o de preferencia alquileno de C_2 R^{70} y R^{80} se seleccionan independientemente de grupos hidrógeno, 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

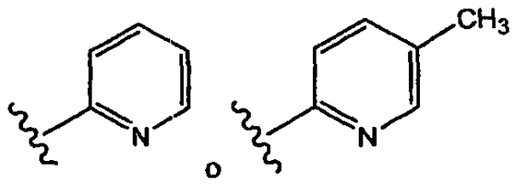
En muchas modalidades de los compuestos oxalamida de la Fórmula (V) el compuesto oxalamida tiene la Formula (Vb)



(Vb)

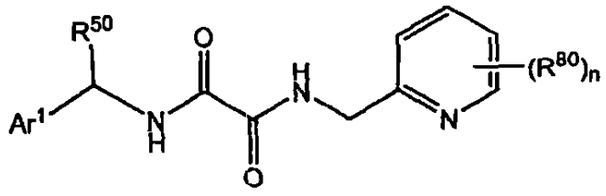
en donde A es un anillo fenilo, piridilo furanilo pirrol

piperidilo, ciclopentilo, ciclohexilo o cicloheptilo m y n son independientemente 0, 1, 2 ó 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 hidrogeno, hidroxi, fluoro, 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 de metilendioxi En algunas modalidades de los compuestos oxalamida de la Fórmula (Vb), el radical piridil-R^{80} tiene la estructura



o

En ciertas modalidades preferidas de los compuestos amida de la Fórmula (V), el compuesto oxalamida tiene la Formula (Vc)

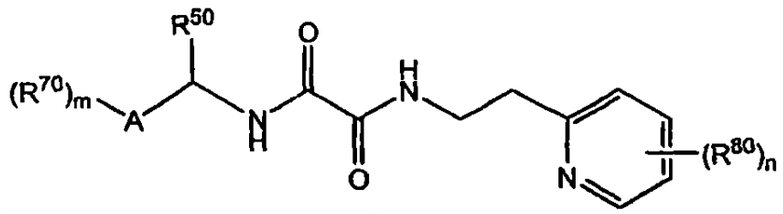


(Vc)

en donde Ar^1 es un anillo arilo o heteroarilo sustituido que comprende cinco a 12 atomos de carbono R^{50} es hidrógeno o metilo, n es 0 1, 2 ó 3 cada R^{80} se selecciona independientemente del grupo que consiste 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 En algunas modalidades de los compuestos oxalamida de la Formula (Vc) Ar^1 es un fenilo 2-, 3-, ó 4-monosustituido, fenilo 2,4-, 2,3-, 2,5 2,6, 3,5- o 3,6-disustituidos, fenilo 3-alquil-4-sustituido un fenilo trisustituido en donde los grupos sustituyentes se seleccionan independientemente del grupo que consiste de hidrógeno, 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, o dos sustituyentes adyacentes juntos forman un anillo metilendioxi en el anillo fenilo En algunas modalidades de los compuestos oxalamida de la Fórmula (Vc) Ar^1 es un anillo heteroarilo sustituido que comprende 5 a 12 atomos de carbono y en donde los grupos sustituyentes se seleccionan independientemente del grupo que consiste de hidrógeno, 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 ciertas modalidades preferidas de los compuestos amida de la Fórmula (V), el compuesto oxalamida tiene la Formula (Vd)

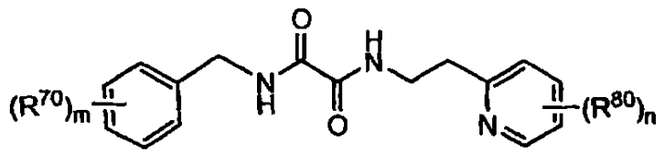


(Vd) (Vd)

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en donde A es un anillo arilo o heteroarilo sustituido que comprende cinco a 12 átomos de carbono, R^{50} es hidrogeno o metilo, n es 0, 1, 2 ó 3, cada R^{80} se selecciona independientemente del grupo que consiste de hidrogeno, hidroxi, fluoro, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3 SEt metilo etilo, isopropilo, vinilo trifluorometilo, metoxi, etoxi, isopropoxi y trifluorometoxi De preferencia A es un anillo fenilo, piridilo, furanilo, pirrol, piperidilo, ciclopentilo, ciclohexilo o anillo cicloheptilo opcionalmente sustituido con 1, 3 o 3 grupos sustituyentes independientemente seleccionados del grupo que consiste de grupos hidrogeno, hidroxi fluoro, 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 amida de la Formula (V), el compuesto oxalamida tiene la formula (Ve)

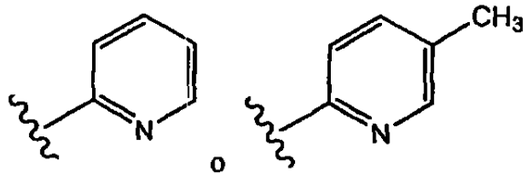


(Vc)

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

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cicloalquenilo, arilo, heteroarilo, y heterociclo, y R^9 y R^{10} se seleccionan independientemente de H, alquilo de C_1-C_6 cicloalquilo de C_3-C_6, y grupos alquenilo de C_1-C_6 De preferencia, R^{70} y R^{80} se seleccionan independientemente del grupo que consiste de grupos hidrogeno, hidroxi, fluoro, cloro, NH_2, $NHCH_3$ $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo etilo, isopropilo, vinilo, trifluorometilo metoxi etoxi, isopropoxi y trifluorometoxi De preferencia, el radical piridil-R^{80} del compuesto oxalamida de la Fórmula (Ve) tiene la estructura

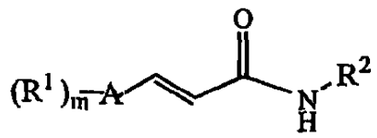


Como puede verse por la inspección de los Ejemplos unidos más adelante los compuestos oxalamida de las Formulas (Va)-(Ve) son agonistas excelentes de los receptores de sabor sabroso ("acre) T1R1/T1R3 a concentraciones muy bajas en el orden de concentraciones micromolares o menores, induce una sensación notable de un sabor acre sabroso en seres humanos y/o puede servir como mejoradores del sabor acre sabroso de MSG Por consiguiente, los compuestos oxalamida de las Formulas (Vc) (Vd) y (Ve) pueden utilizarse como agentes saborizantes sabrosos o mejoradores de sabor sabroso cuando esten en contacto con una amplia variedad de productos y/o composiciones comestibles o sus precursores, como se describe en algun lado en la presente

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Compuestos Acrilamida

En otro subgenero de los compuestos amida de la Fórmula (I), el compuesto amida es un compuesto 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 alcoxilo, 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 las diversas modalidades de R^2 descritas anteriormente con respecto a las amidas de la Fórmula (I)

En algunos de los compuestos acrilamida de la Formula (VI), A es un anillo fenilo y m es 1, 2, 3 ó 4, o de preferencia m es 1 o 2, y R^1 puede seleccionarse independientemente de grupos hidrógeno 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 algunos de los compuestos acrilamida de la Fórmula (VI), R^2 es un alquilo de C_3-C_{10}, o un alquiléster inferior del acido carboxilico α-sustituido

Compuestos Comestible o Farmaceuticamente Aceptables

Muchos de los compuestos amida de la Formula (I) o sus diversos subgeneros enumerados comprenden grupos acidicos o basicos, de manera que dependen del carácter acidico o básico ("pH) de las composiciones comestibles o medicinales en donde se formulan, estos pueden presentarse como sales, que son de preferencia comestiblemente aceptables (es decir, designados como generalmente reconocidos como seguros o GRAS) o sales farmacéuticamente aceptables (muchos de los cuales se han reconocido por la Administración Federal de Alimentos y Farmacos)

Los compuestos amida de la Fórmula (I) que tienen grupos acidicos, tales como ácidos carboxílicos, tenderán (a un pH neutro casi fisiologico) se presenta en solucion en la forma de carboxilatos anionicos, y por lo tanto tendran en las modalidades preferidas un catión comestible y/o farmacéuticamente aceptable asociado, muchos de los cuales se conocen por aquellos con experiencia ordinaria en la técnica Tales cationes comestible y/o farmaceuticamente aceptables incluyen cationes de metal álcali (cationes de litio sodio y potasio), cationes de metal alcalinotérreo (magnesio, calcio y similares) o amonio $(NH_4)^+$ o cationes de amonio orgánicamente sustituidos tales como cationes $(R\text{-}NH_3)^+$

Los compuestos amida de la Formula (I) que tienen grupos sustituyentes basicos, tales como grupos heterocíclicos

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que contienen amino o nitrógeno, tenderan (a pH fisiológico casi neutro o al pH acidico comun en muchos alimentos) presentarse en solucion en la forma de grupos amonio cationicos, y por lo tanto tendrán en las modalidades preferidas un anion comestible y/o farmaceuticamente aceptable asociado, muchos de los cuales se conocen por aquellos con experiencia ordinaria en la tecnica Tales grupos aniónicos comestible y/o farmacéuticamente aceptables incluyen la forma anionica de una variedad de acidos carboxilicos (acetatos citratos tartratos sales anionicas o acidos grasos etc), haluros (especialmente fluoruros o cloruros), nitratos y similares

Los compuestos amida de la Formula (I) y sus varios subgeneros deben ser de preferencia comestiblemente aceptables, es decir, parecer adecuados para consumo en alimentos o bebidas, y deben también ser farmaceuticamente aceptables El método tipico para demostrar que un compuesto saborizante es comestiblemente aceptable es tener el compuesto probado y/o evaluado por un Grupo de Expertos en la Asociacion de Fabricantes de Sabor y Extractos y declarado como para ser Generalmente Reconocido como Seguro (GRAS) El proceso de evaluacion FEMA/GRAS para compuestos saborizantes es complejo, pero bien conocido por aquellos con experiencia ordinaria en las técnicas de preparación de productos alimenticios como se discute por Smith *et al* En un artículo intitulado GRAS Flavoring Substances 21" Food Technology, 57(5), pgs 46-59,

Mayo 2003, los contenidos completos de los cuales se incorporan en la presente para referencia

Cuando se evalua en el proceso FEMA/GRAS, un nuevo compuesto saborizante se prueba normalmente por cualesquiera efectos toxicos adversos en ratas de laboratorio cuando se alimenta a tales ratas por al menos aproximadamente 90 dias en una concentración 100 veces, o 1000 veces o aun concentraciones mas elevadas que la concentración permitible maxima propuesta del compuesto en una categoria particular de productos alimenticios que se consideran para aprobacion Por ejemplo tal prueba de los compuestos amida de la invencion podria implicar combinar el compuesto amida con comida para rata y se alimenta a ratas de laboratorio tales como ratas Crl CD(SD)IGS BR, en una concentración de aproximadamente 100 miligramos/kilogramos de peso corporal/dia por 90 dias, y luego se sacrifican y evaluan las ratas por diversos procedimientos de prueba médicos para demostrar que el compuesto amida de la Fórmula (I) no provoque efectos toxicos adversos en las ratas

Los Compuestos de la Invención como Mejoradores de Sabor Sabroso o Dulce

Los compuestos amida de la Fórmula (I) y sus varios subgéneros y especies del compuesto, como se describen anteriormente se pretenden para ser compuestos saborizantes de sabor sabroso o dulce o modificadores de sabor para productos

comestibles o medicinales Como es aparente a partir de las enseñanzas y Ejemplos en la presente, muchos compuestos de la Formula (I) son agonistas de un receptor sabroso" hT1R1/hT1R3, o un receptor dulce hT1R2/hT1R3, al menos a concentraciones del compuesto amida relativamente elevadas, y por consiguiente muchos de los compuestos amida de la Fórmula (I) pueden tener al menos alguna utilidad como saborizantes sabrosos o dulces o mejoradores de sabor al menos a concentraciones relativamente elevadas

No obstante, es preferible utilizar casi tan poco de tales saborizantes artificiales como sea posible, de manera que se minimiza el costo y cualesquiera efectos secundarios indeseables para la salud de la administración de los compuestos de la Formula (I) a niveles de concentración elevada Por consiguiente es deseable probar los compuestos de la Fórmula (I) para su efectividad como agonistas receptores de sabor a niveles de concentración inferiores de manera que se identifican los mejores y mas efectivos compuestos amida dentro de los compuestos de la Formula (I) Como se describio en WO 03/001876, y la publicacion de Patente Norteamericana US 2003-0232407 A1, y como se describe posteriormente, los procedimientos de laboratorio existen ahora para medir las actividades agonistas de compuestos para receptores "sabrosos hT1R1/hT1R3 y dulces hT1R2/hT1R3 Tales métodos de medicion miden normalmente un "EC_{50}' es decir la concentración a la cual el compuesto provoca 50% de activación

del receptor relevante

De preferencia los compuestos amida de la Formula (I) que son modificadores de sabor sabroso tienen un EC_{50} para el receptor hT1R1/hT1R3 de menos de aproximadamente 10 µM Más preferiblemente, tales compuestos amida tienen un EC_{50} para el receptor hT1R1/hT1R3 de menos de aproximadamente 5 µM, 3 µM, 2 µM, 1 µM o 0 5 µM

De preferencia los compuestos amida de la Formula (I) que son modificadores de sabor dulce o mejoradores de sabor dulce tienen un EC_{50} para el receptor hT1R2/hT1R3 de menos de aproximadamente 10 µM Mas preferiblemente tales compuestos amida tienen un EC_{50} para el receptor hT1R2/hT1R3 de menos de aproximadamente 5 µM, 3 µM 1 µM ó 0 5 µM

En algunas modalidades, los compuestos amida de la Fórmula (I) son moduladores o mejoradores de sabor sabroso de la actividad agonista de glutamato monosódico para un receptor hT1R1/hT1R3 Más adelante, se describe un procedimiento de ensayo para relaciones EC_{50} así llamadas, es decir para disolver un compuesto de la Fórmula (I) en MSG que contiene agua y midiendo el grado al cual el compuesto amida disminuye la cantidad de MSG requerida para activar 50% de los receptores hT1R1/hT1R3 disponibles De preferencia los compuestos amida de la Fórmula (I), cuando se disuelven en solucion de agua que comprende aproximadamente 1 µM del compuesto amida disminuira el EC_{50} observado de glutamato de monosodio para un

receptor hT1R1/hT1R3 expresado en la línea celular HEK293-Gα15 por al menos 50%, es decir, el compuesto amida tendrá una relacion EC_{50} de al menos 2 0 o de preferencia 3 0, 5 0 o 7 0

Aunque todavia no se han desarrollado mejoradores dulces para ensayos de relacion EC_{50} especificos, se cree que los compuestos amida de la Fórmula (I) y más especificamente muchas de las amidas de la Fórmula (II) pueden modular la union de un edulcorante conocido como por ejemplo sacarosa fructuosa, glucosa eritritol, isomalto lactitol, manitol sorbitol, xilitol, un terpenoide natural conocido flavonoide, o edulcorante de proteínas, aspartame sacarina acesulfame-K, un ciclamato sucralosa, alitame o eritritol a un receptor hT1R2/hT1R3 Los ensayos apropiados para tales propiedades de mejoramiento dulce pueden desarrollarse fácilmente por alguien con experiencia ordinaria en las técnicas utilizando lineas celulares apropiadas que expresan receptores hT1R2/hT1R3

Los ensayos identificados anteriormente son utiles para identificar el más potente de los compuestos amida de la Formula (I) para propiedades modificadoras o mejoradoras de sabor sabroso y/o dulce, y los resultados de tales ensayos se cree se correlacionan bien con la percepción de sabor sabroso o dulce actual en animales y seres humanos, pero finalmente los resultados de los ensayos pueden confirmarse, al menos para el más potente de los compuestos de la Formula (I) por prueba de sabor humano Tales experimentos de prueba de sabor humano

pueden cuantificarse y controlarse bien probando los compuestos candidatos en soluciones acuosas, cuando se compara a una solución acuosa control, o alternativamente probando las amidas de las invenciones en composiciones alimenticias actuales

Por consiguiente, con el fin de identificar el mas potente de los modificadores o agentes de sabor sabroso, una solucion acuosa que comprende una cantidad de modificacion de sabor sabroso del compuesto amida debe tener un sabor sabroso cuando se juzga por la mayoria de un grupo de expertos de al menos ocho catadores de sabor humano

Correspondientemente, con el fin de identificar el mas potente de los mejoradores de sabor sabroso, una solucion acuosa, que comprende una cantidad de modificación de sabor sabroso de un compuesto amida de la Fórmula (I) y 12 mM de glutamato de monosodio, tendria un sabor sabroso incrementado cuando se compara a una solución acuosa control que comprende 12 mM de glutamato de sodio, cuando se determina por la mayoría de un grupo de expertos de al menos ocho catadores de sabor humano De preferencia, con el fin de identificar el mas potente de los mejoradores de sabor sabroso, una solución acuosa que comprende una cantidad de modificación de sabor sabroso (de preferencia aproximadamente 30, 10, 5 ó 2 ppm) del compuesto amida de la Fórmula (I) y 12 mM de glutamato de monosodio tendrá un sabor sabroso incrementado cuando se compara a una solucion acuosa control que comprende 12 mM de glutamato de

monosodio y 100 µM de monofosfato de inopina cuando se determina por la mayoria de un grupo de expertos de al menos ocho catadores de sabor humano

Los procedimientos de prueba de sabor humano similares pueden utilizarse para identificar cuáles de los compuestos de la Formula (I) son los agentes de sabor dulce mas efectivo o agentes de mejoramiento de sabor dulce Los modificadores de sabor preferidos de la Fórmula (I) pueden identificarse cuando un producto comestible o medicinal modificado tiene un sabor mas dulce que un producto comestible o medicinal control que no comprende el compuesto amida cuando se juzgó por la mayoría de un grupo de expertos de al menos ocho catadores de sabor humano

Los mejoradores de sabor dulce preferidos de la Fórmula (I) pueden identificarse cuando una solución acuosa que comprende una cantidad de prueba dulce de un edulcorante conocido seleccionado a partir del grupo que consiste de sacarosa fructuosa, glucosa, eritritol, isomalto, lactitol manitol sorbitol, xilitol, un terpenoide natural conocido, flavonoide o edulcorante de proteínas, aspartame, sacarina acesulfame-K ciclamato, sucralosa, y alitame y una cantidad de modificación de sabor dulce del compuesto amida (de preferencia aproximadamente 30, 10, 5 o 2 ppm) tiene un sabor más dulce que una solución acuosa control que comprende la cantidad de sabor más dulce del edulcorante conocido, cuando se juzga por la

mayoría de un grupo de expertos de al menos ocho catadores de sabor humano En tales experimentos de prueba de sabor la sacarosa se presentaria de preferencia a una concentración de aproximadamente 6 gramos/100 mililitros, una mezcla 50 50 de glucosa y fructuosa se presentaria de preferencia en una concentración de aproximadamente 6 gramos/100 mililitros el aspartame se presentaria de preferencia a una concentracion de aproximadamente 1 6 mM, acesulfame-K se presentaria de preferencia en una concentracion de aproximadamente 1 5 mM ciclamato se presentaria de preferencia en una concentración de aproximadamente 10 mM, sucralosa se presentaria de preferencia en una concentracion de aproximadamente 0 4 mM, o alitame se presentaria de preferencia en una concentracion de aproximadamente 0 2 mM

Utilizar los Compuestos de la Fórmula (I) para Preparar Composiciones Comestibles

Los sabores, modificadores de sabor, agentes saborizantes mejoradores de sabor agentes saborizantes sabrosos ("acre") y/o mejoradores de sabor de acuerdo a la invención tienen aplicación en alimentos bebidas y composiciones medicinales en donde los compuestos sabrosos o dulces se utilizan convencionalmente Estas composiciones incluyen composiciones para consumo humano y animal Esto incluye alimentos para consumo por animales agrícolas, mascotas y

animales de zoologicos

Aquellos con experiencia ordinaria en la técnica para preparar y sellar composiciones comestibles (es decir alimentos comestibles o bebidas o precursores o modificadores de sabor de los mismos) asi como conscientes de una gran variedad de clases, subclases y especies de las composiciones comestibles, y utiliza términos bien conocidos y reconocidos de la técnica para referirse a aquellas composiciones comestibles aunque se intenta para preparar y vender varias de aquellas composiciones Tal lista de terminos de la técnica se enumera posteriormente y se contempla especificamente por lo que diversos subgéneros y especies de los compuestos de la Fórmula (I) podrían utilizarse para modificar o mejorar los sabores sabrosos y/o dulces de la siguiente lista de composiciones comestibles, ya sea individualmente o en todas las combinaciones o mezclas razonables de los mismos

Uno o más confites confites de chocolate tabletas, productos basicos, empacados individuales/delicados, variedades empacadas, variedades empacadas estándares, miniaturas envueltas enroscadas chocolate de temporada, chocolate con juguetes, alfajores, otros confites de chocolate, mentas, mentas estandares, mentas fuertes, dulces cocidos, pastillas, gomas, jaleas y gomas de mascar, toffee, caramelos y turrones confiteria medicada, paletas, regaliz otra confitería de azucar, gomas gomas masticables gomas azucaradas, gomas libres de azucar, gomas funcionales, chicle de globo pan pan empacado/industrial

pan no empacado/artesanal, reposteria, tortas, tortas empacadas/industriales, tortas no empacadas/artesanales galletas bizcochos recubiertos de chocolate, bizcochos emparedados, bizcochos rellenos, bizcochos de sabor agradable y galletitas sustitutos de pan, cereales para desayuno cereales listos para comer cereales para desayuno familiar, hojuelas, granola, otros cereales listos para comer, cereales para desayuno de niños, cereales calientes, helados, helados con motivos, helados de crema de porcion sencilla, helado de agua de porción sencilla, helado de crema de empaques multiples, helados de agua de empaques multiples helados para llevar al hogar, helados de crema netos postres helados, helados voluminosos, helados de agua netos, yogurt congelado, helado artesanal productos lacteos, leche, leche fresca/pasteurizada leche fresca/pasteurizada de grasa completa, leche fresca/pasteurizada semidescremada, leche de duracion prolongada/a temperatura ultra elevada, leche de vida prolongada/a temperatura ultraelevada de grasa total, leche de vida prolongada/a temperatura ultraelevada semidescremada, leche de vida prolongada/a temperatura ultraelevada libre de grasa, leche de cabra, leche condensada/evaporada, leche condensada/evaporada simple, leche saborizada, funcional y condensada, jugos lacteos saborizados postres solamente de jugos lácteos saborizados, jugos lácteos saborizados con jugos de frutas leche de soya bebidas lácteas agrias, bebidas cremosas fermentadas, blanqueadores de cafe

leche en polvo bebidas lácteas en polvo saborizadas crema queso queso procesado, queso procesado esparcible, queso procesado no esparcible, queso no procesado queso no procesado esparcible, queso duro queso duro empacado, queso duro no empacado, yogurt, yogurt simple/natural, yogurt saborizado, yogurt con frutas, yogurt probiótico, yogurt para beber, yogurt para beber regular, yogurt para beber probiotico, postres auto-estables y congelados, postres basados en cremas, postres basados en soya bocadillos congelados, queso fresco y queso inmaduro, queso fresco e inmaduro sencillo queso fresco e inmaduro saborizado, queso fresco e inmaduro con sabor, bocadillos dulces y de sabor agradable, bocadillos frutales, frituras/antojitos, bocadillos extruidos, tortillas/frituras de maíz, palomitas de maiz, pretzels nueces, otros bocadillos dulces y sabrosos, barras de bocadillos, barras de granola barras para desayuno, barras energeticas, barras frutales otras barras de bocadillos, productos de reemplazo de comida, productos para adelgazar, bebidas de convalecencia comidas listas, comidas listas enlatadas, comidas listas congeladas, comidas listas secas, comidas listas congeladas, mezclas para cenas, pizza congelada pizza refrigerada sopa, sopa enlatada, sopa deshidratada, sopa instantánea, sopa refrigerada, sopa a temperatura ultraelevada, sopa congelada, pastas pastas enlatadas pastas secas pastas refrigeradas/frescas fideos, fideos simples, fideos instantaneos fideos instantáneos en tazas/vasijas, fideos instantáneos en

bolsas, fideos refrigerados, fideos para bocadillos, alimentos enlatados carne enlatada y productos cárnicos, pescado/mariscos enlatados, vegetales enlatados, tomates enlatados frijoles enlatados, fruta enlatada, comidas listas en latas, sopa en lata, pasta en lata otros alimentos enlatados, alimentos congelados carne roja procesada congelada, carne de aves corral procesada congelada, pescado/marisco procesado congelado, vegetales procesados congelados, sustitutos de carne congelada, papas congeladas, papas horneadas otros productos de papas horneadas, papas congeladas no horneadas productos de panaderia congelados, postres congelados, comidas listas congeladas, pizza congelada, sopa congelada fideos congelados otros alimentos congelados, alimentos secos, mezclas de postres, comidas secas listas, sopa deshidratada sopa instantanea, pasta seca, fideos simples, fideos instantaneos, fideos instantáneos en tazas/vasijas, fideos instantaneos en bolsas, alimentos refrigerados, carnes procesadas refrigeradas, productos de pescado/mariscos refrigerados, pescado procesado refrigerado pescado recubierto refrigerado, pescado conservado refrigerado kits de lunchs refrigerados, comidas listas refrigeradas, pizza refrigerada, sopa refrigerada, pasta refrigerada/fresca, fideos refrigerados, aceites y grasas, aceite de oliva, aceite vegetal y de semilla, grasas para cocinar mantequilla, margarina aceites y grasas esparcibles, aceites y grasas esparcibles funcionales salsas, aderezos y condimentos, pastas de tomate y purés, cubos

de sopas/caldos, cubos de caldos, gránulos de caldillos, sopas liquidas y guarniciones, hierbas y especies, salsas fermentadas salsas con base en soya salsas para pastas, salsas remojadas, mezclas de salsas/polvo secas, catsup, mayonesa mayonesa regular mostaza, aderezos para ensaladas aderezos para ensaladas regulares, aderezos para ensaladas bajos en grasa, vinagretas dips productos adobados, otras salsas, aderezos y condimentos, alimentos para bebes, fórmulas lacteas, fórmulas lacteas estándares, fórmulas lácteas de complemento formulas lácteas para niños que empiezan a caminar fórmulas lacteas hipoalergénicas alimentos para bebés preparados, alimentos para bebés secos, otros alimentos para bebés, comida para untar mermelada y conservas, miel, comidas para untar de chocolate comidas para untar basadas en nueces, y comidas para untar basadas en levaduras

De preferencia, los compuestos de la Formula (I) pueden utilizarse para modificar o mejorar el sabor sabroso o dulce de uno o mas de los siguientes subgéneros de composiciones comestibles confiteria, productos para panaderia helados, productos cremosos bocadillos dulces y sabrosos, barras de bocadillos, productos de reemplazo de comidas comidas preparadas, sopas, pastas, fideos, alimentos enlatados, alimentos congelados, alimentos secos, alimentos refrigerados aceites y grasas alimentos para bebés, o alimentos para untar o una mezcla de los mismos

En general, se producirá una composición ingerible producida, la cual contiene una cantidad suficiente de al menos un compuesto dentro del alcance de la Fórmula (I) o sus diversos subgéneros descritos anteriormente para producir una composicion que tiene el sabor deseado o caracteristicas de sabor tales como caracteristicas de sabor "sabroso o "dulce"

Normalmente, al menos una cantidad que modula el sabor sabroso una cantidad que modula el sabor dulce, una cantidad de agente saborizante sabroso, o una cantidad de agente saborizante dulce, de uno o más de los compuestos de la Fórmula (I) se agregarán al producto comestible o medicinal, de manera que el producto comestible o medicinal modificado con sabor sabroso o dulce tiene un sabor sabroso y/o dulce incrementado cuando se compara al producto comestible o medicinal preparado sin el compuesto amida, cuando se juzga por seres humanos o animales en general o en el caso de la prueba de formulaciones cuando se juzga por una mayoría de un grupo de expertos de al menos ocho catadores de sabor humano a través de procedimientos descritos en algun lado en la presente

La concentracion del agente saborizante sabroso o dulce necesario para modular o mejorar el sabor del producto o composición comestible o medicinal por supuesto variara dependiendo de muchas variables, incluyendo el tipo especifico de composición ingerible, que compuestos sabrosos se presentan y las concentraciones de los mismos y el efecto del compuesto

particular en tales compuestos sabrosos Como se observa, una aplicación significativa de los compuestos de la Fórmula (I) es para modular (inducir, mejorar o inhibir) los sabores sabrosos o dulces u otras propiedades de sabor de otros degustantes sabrosos naturales o sintéticos Un amplio pero tambien rango bajo de concentraciones de los compuestos amida de la Formula (I) se requeriria tambien normalmente, es decir desde aproximadamente 0 001 ppm a 100 ppm, o rangos alternativos mas estrechos desde aproximadamente 0 1 ppm a aproximadamente 10 ppm, desde aproximadamente 0 01 ppm a aproximadamente 30 ppm, desde aproximadamente 0 05 ppm a aproximadamente 15 ppm, desde aproximadamente 0 1 ppm a aproximadamente 5 ppm, o desde aproximadamente 0 1 ppm a aproximadamente 3 ppm

Ejemplos de alimentos y bebidas en donde los compuestos de acuerdo a la invención pueden incorporarse incluidos a manera de ejemplo la Categoria de Sopa Remojada, la Categoria de Alimentos Deshidratados y Culinarios la Categoria de Bebidas, la Categoria de Alimentos Congelados, la Categoria de Bocadillos, y aderezos y mezclas de aderezos

Categoria de Sopa Remojada" significa sopas remojadas/liquidas a pesar de la concentración o del recipiente, incluyendo sopas congeladas Para el proposito de esta o estas sopas de definicion significa un alimento preparado a partir de carne, pollo pescado vegetales granos, frutas y otros ingredientes, cocinados en un liquido el cual puede incluir piezas

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visibles de algunos o todos estos ingredientes Puede ser claro (como un caldo) o espeso (como un potaje), fino hecho pure o grueso, listo para servir, semi-condensado o condensado y puede servirse caliente o frío como un primer platillo o como el platillo principal de una comida o como entre comidas (sorbido como una bebida) La sopa puede utilizarse como un ingrediente para preparar otros componentes para comida y puede variar desde caldos (consome) a salsas (sopas con base en cremas o queso)

"Categoria de Alimentos Deshidratados y Culinarios' significa (i) cocinar productos auxiliares tales como polvos granulos, pastas productos líquidos concentrados, incluyendo caldillos concentrados, caldillos y productos similares a caldillos en cubos prensados, tabletas, polvo o forma granulada que se venden de manera separada como un producto terminado o como un ingrediente dentro de un producto, salsas y mezclas de receta (independientemente de la tecnologia), (ii) productos de soluciones de comida tales como sopas secas deshidratadas y congeladas, incluyendo mezclas de sopas deshidratadas sopas instantáneas deshidratadas, sopas listas para cocinar deshidratadas, preparaciones deshidratadas o ambientales de platillos preparados, comidas y entradas de servicio simple incluyendo pastas, platillos de papas y arroz e (iii) productos para aderezar comidas tales como condimentos, marinadas, aderezos para ensaladas glasés de ensaladas, dips, empanizados, mezclas batidas, untables autoestables, salsas de barbacoa, mezclas de

recetas liquidas, concentrados salsas o mezclas de salsas incluyendo mezclas de recetas para ensaladas vendidas como un producto terminado o como un ingrediente dentro de un producto ya sea deshidratado, liquido o congelado

La Categoria de Bebidas significa bebidas, mezclas y concentrados de bebidas, incluyendo pero sin limitarse a alcoholicas o no alcohólicas listas para bebidas en polvo

Otros ejemplos de alimentos y bebidas en donde los compuestos de acuerdo a la invención pueden incorporarse incluyen a manera de ejemplo bebidas carbonatadas y no carbonatadas por ejemplo sodas jugos de frutas y vegetales bebidas alcohólicas y no alcohólicas, productos de confiteria, por ejemplo tortas galletas, pasteles, caramelos gomas masticables, gelatinas, helados, sorbetes, budines mermeladas, jaleas, aderezos para ensaladas y otros condimentos, cereales y otros alimentos para desayunos, frutas en conserva y compotas y similares

Adicionalmente los compuestos objeto pueden utilizarse en preparaciones de sabor para agregarse a alimentos y bebidas En los ejemplos preferidos, la composicion comprenderá otro modificador de sabor o degustacion tal como un degustante sabroso

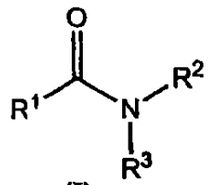
Por consiguiente en algunas modalidades, las invenciones se relacionan a metodos para modular el sabor sabroso o dulce de un producto comestible o medicinal, que

comprende

a) proporcionar al menos un producto comestible o medicinal o un precursor del mismo, y

b) combinar el producto o precursor comestible o medicinal del mismo con al menos una cantidad que modula el sabor sabroso o una cantidad que modula el sabor dulce de al menos un compuesto de amida de origen no natural o una sal comestiblemente aceptable del mismo, de manera que se forma un producto comestible o medicinal modificado,

en donde el compuesto amida tiene la fórmula



(I)

en donde el compuesto amida es una amida de la Formula (I), o cualquiera de sus diversos compuestos de subgénero o especie descritos en la presente, en donde R^1, R^2 y R^3 pueden definirse en las muchas maneras también descritas anteriormente

La invención se relaciona tambien a productos comestibles o medicinales modificados producidos por tales procesos, y procesos similares para producir productos comestibles o medicinales bien conocidos por aquellos con

experiencia ordinaria en la tecnica

Los compuestos amida de la Formula (I) y sus diversos subgeneros pueden combinarse con o aplicarse a los productos comestibles o medicinales o precursores de los mismos en cualquiera de innumerables maneras conocidas para cocinar a traves del mundo o productores de productos comestibles o medicinales Por ejemplo, los compuestos amida de la Formula (I) podrian disolverse en, o dispersarse en, o una de muchos liquidos comestiblemente aceptables, solidos, u otros portadores, tales como agua en pH neutro, acídico o basico, jugos de frutas o vegetales, vinagre, marinadas, cervezas, vino, emulsiones de agua/grasas naturales tales como leche o leche condensada, aceites comestibles y materias grasas, ácidos grasos, ciertos oligomeros de peso bajo molecular de propilenglicol, glicerilésteres de acidos grasos, y dispersiones o emulsiones de tales sustancias hidrofobicas en medios acuosos, sales tales como cloruro de sodio, harinas vegetales, solventes tales como etanol diluyentes comestibles solidos tales como polvos o harinas vegetales, y similares, y luego combinarse con precursores de los productos comestibles o medicinales, o se aplican directamente a los productos comestibles o medicinales

Realizar los Compuestos Amida de la Formula (I)

Los materiales de partida utilizados para preparar los compuestos de la invención es decir las diversas subclases

estructurales y especies de los compuestos amida de la Fórmula (I) y sus precursores sintéticos, especialmente los ácidos carboxílicos organicos y ácidos benzoicos, isocianatos, y las varias aminas anilinas, aminoácidos etc , son compuestos con frecuencia conocidos o hechos por metodos conocidos de la literatura o están comercialmente disponibles a partir de varias fuentes bien conocidas por aquellos de experiencia en la técnica, tal como por ejemplo Sigma-Aldrich Corporation de St Louis Missouri USA y sus subsidiarios Fluka y Riedel-de Haen, en sus diversas oficinas alrededor del mundo y otros proveedores bien conocidos tales como Fisher Scientific, TCI America of Philadelphia PA, ChemDiv de San Diego CA Chembridge de 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 y ASDI Biosciences of Newark Delaware

Será aparente por el tecnico calificado que los métodos para preparar precursores y funcionalmente relacionados a los compuestos reclamados en la presente se describen generalmente en la literatura El técnico calificado dada la literatura y esta descripción se equipa bien para preparar cualquiera de los materiales de partida necesarios y/o compuestos reclamados En algunos de los Ejemplos citados anteriormente, los materiales de partida no estan fácilmente disponibles y por lo tanto se sintetizaron y la síntesis de los materiales de partida se

ejemplifica por lo tanto

Se reconoce que el técnico calificado en la técnica de la química orgánica puede llevar a cabo fácilmente manipulaciones sin dirección adicional es decir esta bien dentro del alcance y la práctica del técnico calificado para llevar a cabo estas manipulaciones Éstas incluyen la reducción de compuestos carbonilo a sus alcoholes correspondientes, oxidaciones acilaciones, sustituciones aromáticas, tanto electrofílicas como nucleofílicas, eterificaciones esterificacion, saponificación nitraciones hidrogenaciones aminacion reductiva y similares Estas manipulaciones se discuten en textos estándares tales como 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* y similares, las descripciones totales de las cuales se incorporan en la presente para referencia en sus totalidades para sus enseñanzas con respecto a los métodos para sintetizar compuestos organicos

El técnico calificado apreciara fácilmente que ciertas reacciones se llevan a cabo mejor cuando otra funcionalidad se enmascara o protege en la molécula de este modo evitando cualesquiera reacciones secundarias indeseables y/o incrementando el rendimiento de la reacción Con frecuencia, el tecnico calificado utiliza los grupos protectores para lograr tales rendimientos incrementados o para evitar reacciones indeseadas

Estas reacciones se encuentran en la literatura y estan tambien dentro del alcance del técnico calificado Ejemplos de muchas de estas manipulaciones pueden encontrarse por ejemplo en T Greene y P Wuts *Protecting Groups in Organic Synthesis*, 3ª 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-Dimetilaminoporpil)-3-etilcarbodiimida

DCM = diclorometano

ESIMS = espectrometría de masa de dispersión de electron

Et_3N = trietilamina

EtOAc = acetato de etilo

EtOH = Alcohol etilico

Fmoc = N-(9-fluoroenilmetoxicarbonilo

HCl = Ácido clorhídrico

H_2SO_4 = Ácido Sulfurico

HOBt = 1-Hidroxibenzotriazol

MeOH = Alcohol Metílico

$MgSO_4$ = sulfato de magnesio

$NaHCO_3$ = bicarbonato de sodio

NaOH = Hidroxido de sodio

Na_2SO_4 = Sulfato de Sodio

Ph = fenilo

r t = temperatura ambiente

SPOS = síntesis orgánica de fase sólida

THF = tetrahidrofurano

TLC = cromatografía de capa delgada

Abreviaturas de grupo alquilo

Me = metilo

Et =etilo

n-Pr = propilo normal

i-Pr = isopropilo

n-Bu = butilo normal

i-Bu = isobutilo

t-Bu =butilo terciario

s-Bu =butilo secundario

n-Pen = pentilo normal

i-Pen = isopentilo

n-Hex =hexilo normal

i-Hex = isohexilo

Abreviaturas de reactivo soportado por polímero

PS-Trisamina = poliestireno de Tris-(2-aminoetil)amina

PS-Cloroacetilo =

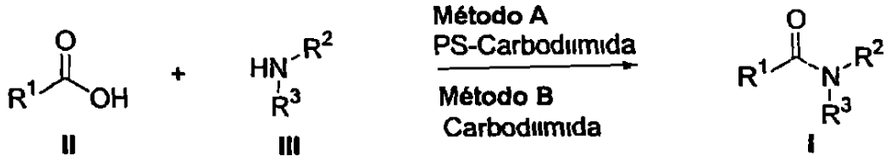
PS-NCO = poliestireno de metilisocianato

PS-benzaldehido =

PS-TsNHNH$_2$ = poliestireno toluensulfonilhidrazona

Los siguientes esquemas del ejemplo se proporcionan para la guia del lector y los métodos preferidos representados para hacer los compuestos ejemplificados en la presente Estos metodos no son limitantes y será aparente que otras rutas pueden emplearse para preparar estos compuestos Tales métodos incluyen específicamente quimicas basadas en fase sólida, incluyendo química combinatorial El obrero calificado se equipa completamente para preparar los compuestos necesarios y/o reivindicados por aquellos metodos dados por la literatura y esta descripción

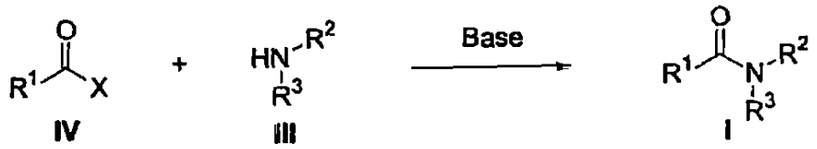
Esquema 1a



Como se muestra en el Esquema 1a, los derivados de amida (I) se preparan a partir del acoplamiento de los derivados de acido (II) con aminas (III) 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 soportada por un polímero (PS) El Método B utiliza una carbodiimida soportada sin polímero

Esquema 1b - Metodo Alternativo para la Preparación de Amidas



X = haluro

Como se muestra en el Esquema 1b los derivados de amida (I) se preparan alternativamente a partir del acoplamiento de haluros acidos, ésteres o anhidridos (IV) con aminas (III) en la presencia de una base

Esquema 1c – Sintesis de las Amidas a traves de los Arreglos Combinatoriales

Se utilizó el siguiente procedimiento y puede utilizarse para sintetizar amidas en el arreglo de disposición combinatorial

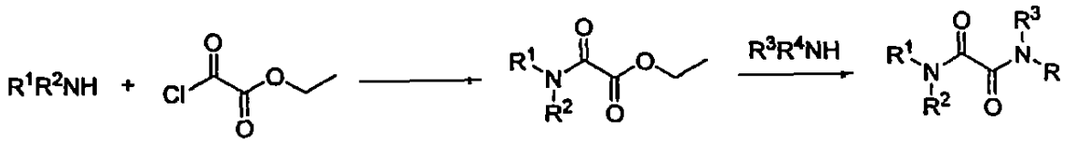
- Usar acetonitrilo como el solvente del sistema
- Pesar aminas en frascos de 8 ml
- Utilizar aminas disueltas Tecan a 100 mM en DCM/CH_3CN (1 2 a partir del punto bajo)
- Pesar el acido en frascos de 8 ml
- Utilizar ácidos disueltos Tecan a 110 mM en DCM/CH_3CN (1 2 del punto bajo)

- Precargar 1 2 ml de placa Greiner con 30 mg de resina PS-carbodiimida utilizando placa II Tituladora de Estuche Peli 1400 Usar el acetonitrilo como el solvente de sistema para la síntesis
- Agregar 200 ml (20 mmoles, 1 equivalente) de amina a cada pozo de las placas de síntesis
- Agregar 200 ml (22 mmoles, 1 1 equivalente) de ácido a cada pozo de las placas de síntesis
- Agregar 110 ml (22 mmoles, 1 1 equivalente) de HOBt (0 20 M en DMF) a cada pozo de las placas de síntesis por pipeta de 8 canales
- Placas de sello con nudo de tapa y se agita (velocidad normal) a temperatura ambiente durante la noche
- Cargar 20 mg/pozo de resina de PS-Trisamina en las placas de síntesis utilizando el cargador de placa Tituladora delgada-I *Ajustar la cantidad de resina basada en su carga*
- Agregar 200 ml de DCM/CH_3CN a la placa
- Placas de sello de lámina y agitar (velocidad rapida) a temperatura ambiente durante la noche
- Utilizar metanol como el solvente del sistema para transferir a la placa de almacenamiento
- Transferir 150 ml a la placa de almacenamiento, luego se lava 2 veces con 150 ml de metanol (agitar lentamente durante 5 minutos) Realizar las

transferencias a partir de la Parte Superior en cada pozo (Altura de aguja -2)

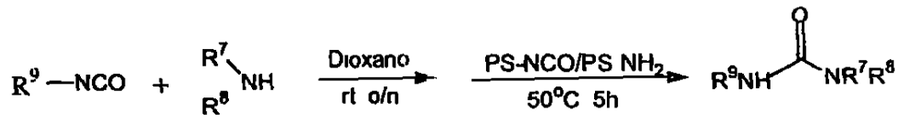
- Secar las placas en Genevac
- Remover las placas analíticas (2 5 mM teorico) y someter para análisis
- Placas de dilucion removidas basadas en resultados analiticos

Esquema 1c - Preparación de Oxalamidas

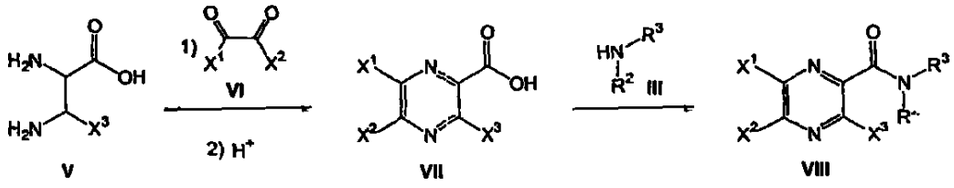


Como un procedimiento general, se permitió a una amina hacerse reaccionar con cloruro de etiloxalilo en la presencia de amina terciaria en solvente organico, tal como dioxano, acetonitrilo tetrahidrofurano, tetrahidropirano, y dimetilformamida a temperatura ambiente durante 0 5 – 2 horas Luego la segunda amida se agrega y la suspension se calienta a 80°C utilizando el baño de aceite durante la noche a 160°C en un reactor de microondas durante 5 minuios La mezcla de reacción puede someterse a HPLC preparativa, o un desarrollo acuoso y el producto sin purificar puede normalmente purificarse facilmente por la recristalización, cromatografia de columna instantanea u otros métodos bien conocidos por aquellos con experiencia ordinaria en la tecnica para producir la oxalamida pura No se optimizaron los rendimientos reportados posteriormente

Esquema 1d - Preparación de Ureas



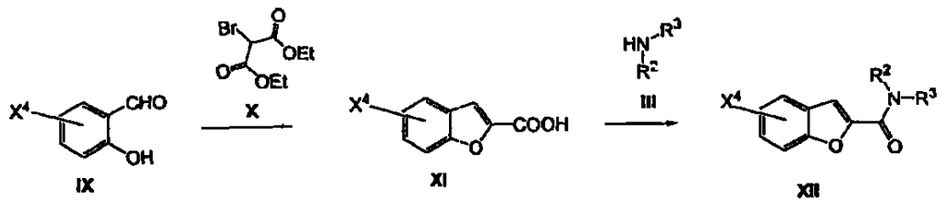
Esquema 2



X¹ X² y X³ son cada uno independientemente alquilo o alcoxi

El Esquema 2 describe un método para la preparacion de derivados de pirazinas (VIII) Por ejemplo, la reacción de los acidos 2,3-diaminopropionicos sustituidos o sin sustituir (V) con 2 3-dionas (VI) bajo condiciones de calentamiento en la presencia de rendimientos base, después de la acidificación el ácido pirazin-2-carboxilico sustituido (VII) El ácido se condensa con varias aminas (III) para producir la amida deseada (XIII) utilizando las condiciones mostradas en el Esquema 1a

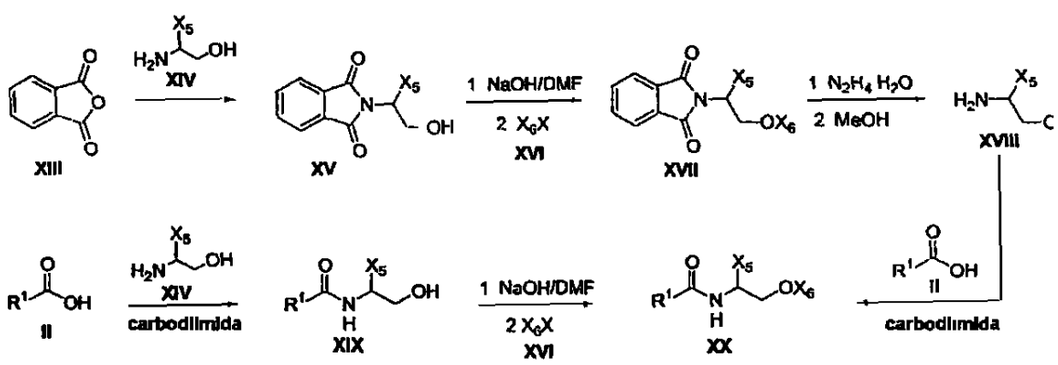
Esquema 3



X⁴ es alquilo haluro, alcoxi o tioalquilo

El esquema 3 describe un metodo para la preparacion de derivados de benzofuranc (XII) Por ejemplo, una reaccion de 2-hdiroxibenzaldehidos (IX) con dietiléster del ácido 2-bromo-malonico (X) bajo condiciones de calentamiento en la presencia de rendimientos base de ácido benzofuran-2-carboxílico sustituido (XI) El acido se conecta con varias aminas (III) para producir la amida deseada (XII) utilizando condiciones mostradas en el Esquema 1a

Esquema 4

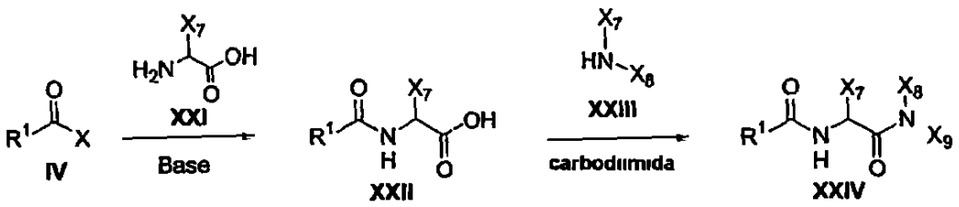


X_5 es H alquilo, arilo aril-alquilo heteroaril-alquilo
X_6 es alquilo alcoxialquilo, arilalquilo heteroarilalquilo
X es haluro

El Esquema 4 describe metodos para la preparacion de una amida de alcoxialquilo (XX) En un metodo el anhidrido ftálico (XIII) se calienta con aminoalcohol (XIV) para dar el alcohol (XV) que se hace reaccionar entonces con el haluro alquilo (XVI) en la presencia de una base para producir el alcoxi (XVII) El tratamiento de la ftalimida (XVII) con hidracina produce la amina (XVIII) deseada que se condensa además con el acido (II) como se

describe en el esquema 1a para proporcionar la alcoxialquilamida (XX) Alternativamente, el ácido (II) se condensa con el alcohol amino (XIV) utilizando el método descrito en el esquema 1a para proporcionar el alcohol (XIX) que se alquila además para dar (XX)

Esquema 5



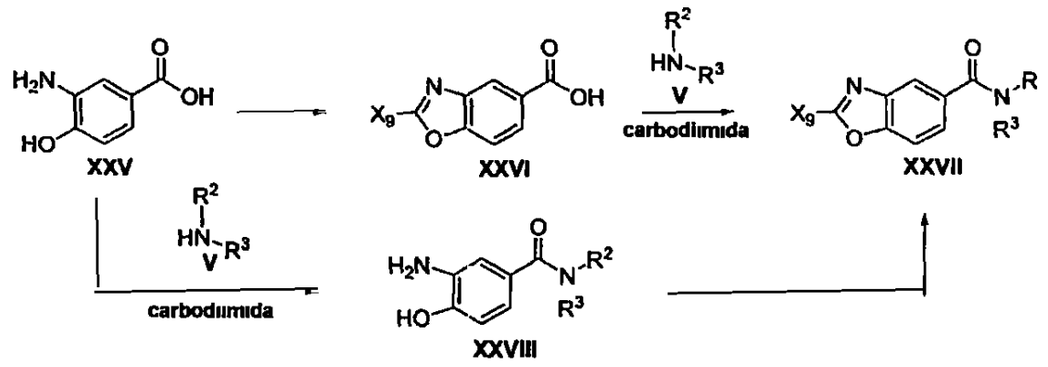
X es haluro

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 hetero

El esquema 5 describe métodos para la preparación de amido-amida (XXIV) El alquil haluro (IV) se trata con aminoácido (XXI) como se describe en el esquema 1b para dar el ácido (XXII) corerspondiente que se condensa además con amina (XXIII) como se describe en el esquema 1a para proporcionar el derivado de amido amida (XXIV)

Esquema 6



El Esquema 6 describe metodos para la preparación de benzoxazol (XXVIII) El aminofenol (XXV) puede condensarse con una variedad de reactivos para formar el benzoxazol (XXVI) que tiene una amplia variedad de X_9 sustituyente utilizando un metodo descrito en la literatura (vease por ejemplo, *J Med Chem* 28 (1985) 1255) y/o por el método citado en los Ejemplos 39 a 47 El intermediario benzoxazol (XXVI) se condensa entonces con amina (V) utilizando el método descrito en el esquema 1a para dar la amida (XXVII) Alternativamente, la amida (XXVII) se prepara primero condensado el amino fenol (XXV) con la amina (V) para dar el intermediario aminofenol (XXVIII) que se convierta ademas al benzoxazol (XXVII) utilizando los diversos métodos descritos anteriormente

Midiendo la Actividad Biologica de los Compuestos de la Invención

Las tecnologias y ensayos basados en células tales

como aquellos descritos en WO 02/064631 y WO 03/001876 y la Publicación de Patente Norteamericana 2003-0232407 A1 se utilizaron ambos para tamizar inicialmente una variedad amplia de clases de compuestos para actividad agonista y antagonista para receptores de sabor "sabroso" T1R1/T1R3 o receptores de sabor "dulce" T1R2/T1R3 que había sido expresado en líneas celulares apropiadas Una vez que se obtuvieron 'aciertos iniciales para compuestos amida en tales líneas celulares, los mismos ensayos y también ciertos ensayos basados en células y/o receptores se utilizaron como herramientas analíticas para medir la capacidad de los compuestos de la Fórmula (I), para mejorar el sabor sabroso de MSG o el sabor dulce de edulcorantes conocidos tal como sacarosa, fructosa y se utilizaron para proporcionar datos empíricos para guiar un proceso interactivo para sintetizar y probar variantes estructurales de los compuestos amida en combinación con la prueba de sabor humano ocasional de compuestos de interes elevado de manera que se diseñan se prueban e identifican especies y géneros de compuestos con niveles incrementados y optimizados de actividades biológicas deseables

Muchas modalidades de las invenciones se relacionan a la identificación de compuestos específicos y clases de los compuestos amida de la Fórmula (I) que modulan (incrementan o disminuyen) la actividad del receptor de sabor sabroso T1R1/T1R3 (de preferencia hT1R1/hT1R3) (receptor acre), solo o en

combinación con otro compuesto que activa hT1R1/hT1R3, por ejemplo MSG Particularmente en muchas modalidades la invención se relaciona a las amidas de la Formula (I) que modulan la actividad de hT1R1/hT1R3 (receptor acre humano) *in vtro* y/o *in vivo* En otro aspecto la invencion se relaciona a compuestos que modulan la percepción humana del sabor sabroso (acre) solo o en combinación con otro compuesto o saborizante, cuando se agrega a un producto o una composición comestible o medicinal

Muchas modalidades de las invenciones se relacionan a la identificacion de clase y/o especies de los compuestos amida de la Fórmula (I) que modulan (incrementan o disminuyen) la actividad del receptor de sabor dulce T1R2/T1R3 (de preferencia hT1R2/hT1R3) (solo o en ccmbinación con otro compuesto que activa hT1R2/hT1R3, o de otra manera induce un sabor dulce por ejemplo, sacarosa glucosa, fructosa y similares Particularmente la invención se relaciona a las amidas de la Fórmula (I) que modulan la actividad de hT1R2/hT1R3 (receptor dulce humano) *in Vitro* y/o *in vivo* En otro aspecto, la invención se relaciona a compuestos que modulan a la percepción humana del sabor dulce solo o en combinación con otro compuesto o composición saborizante cuando se agrega a un producto o composición comestible o medicinal

En algunas modalidades de la invencion se ha descubierto con mucha sorpresa que al menos algunos de los compuestos amida de la Fórmula (I) pueden modular la percepción

humana del sabor acre y dulce solo o en combinacion con otro compuesto o composición saborizante, cuando se agrega a un producto o una composicion comestible o medicinal

Ensayo de Activación del Receptor de Sabor Acre ~~*In Vitro*~~ hT1R1/hT1R3

Con el fin de identificar nuevos agentes saborizantes sabrosos y mejoradores incluyendo compuestos con actividades agonistas y mejoradoras sabrosas (actividad dual), los compuestos de la Formula (I) se seleccionaron en ensayos primarios y ensayos secundarios incluyendo la respuesta de dosis del compuesto y el ensayo de mejoramiento En un ensayo primario para la capacidad potencial para modular el sabor acre, los compuestos amida de la Fórmula (I) que pueden ser ya sea agentes saborizantes sabrosos en su propia razón o mejoradores de sabor de MSG se identifican y las clasificaciones de sus actividades se dan como porcentaje de la intensidad de MSG maxima (%) En la respuesta de dosis del compuesto, una EC_{50} se calcula para reflejar la potencia del compuesto como un agonista o como un mejorador sabroso

Un derivado de linea celular HEK293 (véase por ejemplo, Chandrashekar *et al* Cell (2000) 100 703-711) que expresan establemente Gα15 y hT1R1/hT1R3 bajo un promotor inducible (véase WO 03/001876 A2) se utilizó para identificar compuestos con propiedades de sabor sabroso

Los compuestos cubiertos en este documento se

seleccionaron inicialmente con base en su actividad en la linea celular hT1R1/hT1R3-HEK293-Gα15 La actividad se determinó utilizando un ensayo de fcrmacion de imágenes fluorométrico automatizado en un instrumento FLIPR (Lector de Placa de Intensidad Fluorométrica Molecular Devices, Sunnyvale, CA) (designado ensayo FLIPR) Las celulas a partir de un clon (designado clon I-17) se sembro en placas de 384 pozos (en aproximadamente 48 000 células por pozo) en un medio que contiene medio Eagle modificado con Dulbecco (DMEM) suplementado con GlutaMAX (Invitrogen Carlsbad, CA), 10% de suero de bovino fetal dializado (Invitrogen, Carlsbad, CA) 100 Unidades/ml de Penicilina G, 100 µg/ml de Estreptomicina (Invitrogen, Carlsbad, CA) y 60 pM de mifepristona (para inducir la expresión de hT1R1/hT1R3 (vease WO 03/001876 A2) Se cultivaron células I-17 durante 48 horas a 37°C Las células I-17 se cargaron entonces con el tinte de calcio Fluo-3AM (Molecular Probes, Eugene OR), 4 µM en una solución salina de tampón de fosfato (D-PBS) (Invitrogen Carlsbad, CA) durante 1 5 horas a temperatura ambiente Despues del reemplazo con 25 µl de D-PBS la estimulacion se realizó en el instrumento FLIPR y a temperatura ambiente por la adición de 25 µl de D-PBS suplementado con diferentes estimulos en concentraciones que corresponden a dos veces el nivel final deseado La actividad receptora se cuantificó determinando los incrementos de fluorescencia maximos (utilizando una excitación de 480 nm y una

emision de 535 nm) despues de la normalización a la intensidad de fluorescencia basal medida antes de la estimulación

Para análisis de respuesta de dosis, se presentaron estímulos por duplicado en 10 diferentes concentraciones variando desde 1 5 nM a 30 µM Las actividades se normalizaron a la respuesta obtenida con 60 mM de glutamato de monosodio una concentración que produce la respuesta de receptor máxima Las EC_{50} (concentracion del compuesto que provoca 50% de activación del receptor) se determinaron utilizando un algoritmo de regresión no lineal, en donde la inclinación Hill, las líneas rectas de fondo y las líneas rectas superiores se permitieron variar Los resultados idénticos se obtuvieron cuando se analizan los datos de respuesta de dosis utilizando software comercialmente disponible para análisis de regresion no lineal tal como GraphPad PRISM (San Diego, California)

Con el fin de determinar la dependencia del hT1R1/hT1R3 para la repuesta celular a diferentes estimulos, los compuestos seleccionados se sometieron a un análisis similar en las células I-17 que no se ha inducido para la expresión receptora con mifepristona (designado como células I-17 inducidas) Las celulas I-17 no inducidas no muestran ninguna respuesta funcional en el ensayo FLIPR a glutamato de monosodio u otras sustancias de sabor sabroso Los compuestos se presentaron a células acre no inducidas a 10 µM o tres veces la estimulación maxima utilizada en el análisis de repuesta de dosis Los compuestos

cubiertos en este documento no muestran ninguna respuesta funcional cuando se utilizan células acre no inducidas en el ensayo FLIPR

En algunos aspectos de la presente invencion una EC_{50} mas bajo que aproximadamente 10 mM es indicativo de compuestos que inducen actividad T1R1/T1R3 y se considera un agonista sabroso De preferencia, un agonista sabroso tendra valores EC_{50} de menos de aproximadamente 1 mM, y mas preferiblemente tendrá valores EC_{50} de menos de aproximadamente 20 µM, 15 µM, 10 µM, 5 µM, 3 µM 2 µM, 1 µM, 0 8 µM o 0 5 µM

En los experimentos de ensayo de actividad de mejoramiento de sabor acre que producen una medida de la relacion de EC_{50} de cómo tan efectivamente los compuestos amida de la invencion mejoran el saborizante sabroso (normalmente MSG) ya en una solución de prueba Una serie de mediciones de la repuesta de dosis se opera en soluciones que comprenden MSG solo, luego una segunda respuesta de dosis se opera con MSG en combinacion con cantidades predeterminadas de un compuesto candidato de la Fórmula (I) al mismo tiempo

En este ensayo se presentaron concentraciones incrementadas de glutamato de monosodio (que varia de 12 µM a 81 mM) por duplicado en la presencia o ausencia de una concentración fija del compuesto de prueba Las concentraciones del compuesto típico probadas fueron 30 µM, 10 µM, 3 µM, 1 µM,

0 3 µM, 0 1 µM y 0 03 µM La eficacia relativa de compuestos de la Fórmula (I) en el mejoramiento del receptor se determino calculando la magnitud de un cambio en la EC_{50} para el glutamato de monosodio El mejoramiento se definió como una relacion ($EC_{50}R$) que corresponde al EC_{50} de glutamato de sodio determinado en la ausencia del compuesto de prueba, dividido por la EC_{50} del glutamato de monosodio, determinado en la presencia del compuesto de prueba Los compuestos que exhiben $EC_{50}R$ > 2 0 se consideraron mejoradores

Alternativamente establecidos, relación de EC_{50} cuando se compara con MSG se calcula con base en las siguientes definiciones

Relación de EC_{50} contra MSG = EC_{50} (MSG)/EC_{50} (MSG + [Compuesto])

En donde [compuesto]' se refiere a la concentracion del compuesto de la Fórmula (I) utilizada para producir (o mejorar o potencializar) la respuesta de dosis de MSG

Se debe observar que la relación de EC_{50} medida puede depender un poco de la concentracion del compuesto mismo Los mejoradores sabrosos preferidos tendrian una relación de EC_{50} elevada contra MSG a una concentracion baja del compuesto utilizado De preferencia, los experimentos de relación de EC_{50} para medir el mejoramiento acre se operan a una concentración de un compuesto de la Fórmula (I) entre aproximadamente 10 µM a aproximadamente 0 1 µM, o de preferencia a 1 0 µM o 3 0 µM

Una relación de EC_{50} de más de 1 es indicativa de un compuesto que modula (potencializa) la actividad hT1R1/hT1R3 y es un mejorador sabroso Más preferiblemente, los compuestos del mejorador de sabor de la Fórmula (I) tendrán valores de relacion de EC_{50} de al menos 1 2 1 5 2 0 3 0, 4 0, 5 0, 8 0 o 10 0 o aun más elevados

En un aspecto el grado de modulación de sabor de un compuesto particular se evalua con base en su efecto en la activación de MSG de T1R1/T1R3 *in vitro* Se anticipa que los ensayos similares pueden diseñarse utilizando otros compuestos conocidos para activar el receptor T1R1/T1R3

Los compuestos especificos y clases genéricas de los compuestos que se han mostrado para modular hT1R1/hT1R3 con base en sus relaciones EC_{50} evaluadas de acuerdo a la formula anterior se identifican en la descripcion detallada de la invención, los ejemplos y las reivindicaciones

Los procedimientos utilizados para prueba de sabor de los compuestos acres/sabrosos de la Fórmula (I) se reportan más adelante Los ensayos de EC_{50} comparables para la actividad de los compuestos de la Fórmula (I) para el agonismo del receptor dulce y/o la percepción de sabor dulce en seres humanos se reportan también mas adelante

Ensayo de Activacion del Receptor de Sabor Dulce hT1R2/hT1R3 *In Vitro*

Un derivado de linea celular HEK293 (Chandrashekar J , Mueller, K L , Hoon, M A , Adler, E Feng, L , Guo, W , Zuker C S , Ryba N J , *Cel, 1* **2000** *100*, 703-711), que expresan establemente Gα15 y hT1R2/hT1R3 (Li, X , Staszewski, L , Xu, H Durick, K , Zoller, M , Adler, E *Proc Natl Acad Sci USA* **2002** *99*, 4692-4696) Véase también la Patente Mundial # WO 03/001876 A2) se utilizó para identificar compuestos con propiedades de mejoramiento de sabor dulce

Los compuestos cubiertos en este documento se seleccionaron inicialmente con base en su actividad en la linea celular hT1R2/hT1R3-HEK293-Gα15 (Li, et al , *vide supra*) La actividad se determino utilizando un ensayo de formación de imágenes fluorométricas automatizadas en un instrumento FLIPR (Lector de Placa de Intensidad Fluorométrica Molecular Devices Sunnyvale, CA) (designado ensayo FLIPR) Las células a partir de un clon (designadas celulas S-9) se sembraron en placas de 384 pozos (en aproximadamente 50,000 células por pozo) en un medio que contiene Glucosa Baja en DMEM (Invitrogen, Carlsbad, CA), 10% de suero de bovino fetal dializado (Invitrogen, Carlsbad CA) 100 unidades/ml de Penicilina G, y 100 µg/ml de Estreptomicina (Invitrogen Carlsbad CA) (Li et al *vide supra*) véase tambien Patente Mundial # WO 03/001876 A2) Las celulas S-9 se cultivaron durante 24 horas a 37°C Las células S-9 se cargaron

entonces con el tinte de calcio Fluo-3AM (Molecular Probes Eugene, OR) 4 µM en una solucion salina de tampon de fosfato (D-PBS) (Invitrogen, Carlsbad, CA) durante 1 hora a temperatura ambiente Después del reemplazo con 25 µl de D-PBS, la estimulación se realizo en el instrumento FLIPR y a temperatura ambiente por la adición de 25 µl de D-PBS suplementado con diferente estimulo en concentraciones que corresponden a dos veces el nivel final deseado La actividad receptora se cuantifico determinando los incrementos de fluorescencia máxima (utilizando una excitación de 480 nm y 535 nm de emisión) despues de la normalización a intensidad de fluorescencia basal medida antes de la estimulación

Para analisis de respuestas de dosis se presentaron los estímulos por duplicado en 10 diferentes concentraciones que varian desde 60 nM a 30 µM Las actividades se normalizaron a la respuesta obtenida con 400 mM de D-fructosa, una concentración que produce la respuesta del receptor máximo Los EC_{50} se determinaron utilizando un algoritmo de regresión no lineal (utilizando un software Senomyx, Inc), en donde la inclinación Hill, la línea recta de fondo y la linea recta superior se permitieron variar Resultados idénticos se obtuvieron cuando se analizaron 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 del

hT1R2/hT1R3 para la respuesta celular a diferentes estímulos se sometieron los compuestos seleccionados a un análisis similar en las células HEK293-Gα15 (que no expresan el receptor dulce humano) Las células HEK293-Gα15 no muestran ninguna repuesta funcional en el ensayo FLIPR a D-Fructosa o cualesquiera otros edulcorantes conocidos De manera similar, los compuestos cubiertos en este documento no inducen ninguna respuesta funcional cuando se utilizan células HEK293-Gα15 en el ensayo FLIPR

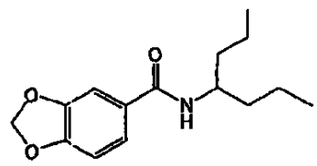
EJEMPLOS

Los siguientes ejemplos se dan para ilustrar una variedad de modalidades ejemplares de la invención y no se pretenden para ser limitantes de ninguna manera

Para el propósito de este documento, los compuestos descritos individualmente en los siguientes Ejemplos 1-174 y las Tablas A-E correspondientes pueden referirse en estenografía por el numero del ejemplo Por ejemplo, como se muestra inmediatamente despues, 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 ensayos experimentales de sus efectividades biologicas, cuyo compuesto es y puede referirse en la presente en forma de estenografía como el Compuesto 1 De manera similar, el primer compuesto ilustrado en la Tabla A puede referirse en algun otro sitio en la presente como el Compuesto A1

Ejemplo 1

N-(heptan-4-il)benzo[d][1,3]dioxo-5-carboxamida

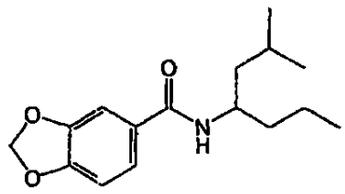


Se agregó a una solución de heptan-4-amina (8 06 ml, 54 mmoles) en trietilamina (15 3 ml, 108 mmoles) y diclorometano (135 ml), en gotas a 0°C, una solución de cloruro de benzo[1,3]dioxol-5-carbonilo (10 g, 54 mmoles) disuelto en diclorometano (135 ml) Se agitó la mezcla de reacción durante 1 hora Se removió el solvente bajo presión reducida y se disolvio el residuo en EtOAc Se lavó la capa organica sucesivamente con 1N HCl acuoso 1N NaOH acuoso agua, salmuera se seco ($MgSO_4$) y se concentró El residuo se recristalizo en EtOAc y los Hexanos produjeron 6 9 g de N-(heptan-4-il)benzo[d][1 3]dioxol-5-carboxamida (48 3%) como un sólido blanco ^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)

El compuesto tuvo EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 0 2 μM y cuando se presenta en 0 03 μM mejora la efectividad de glutamato de monosodio con una relación de EC_{50} de 6 92

Ejemplo 2

N-(2-metilheptan-4-il)benzo[d][1,3]dioxol-5-carboxamida



Preparado en una manera similar al ejemplo 1 utilizando cloruro de benzo[d][1,3]dioxol-5-carbonilo y 2-metilheptan-4-amina (ejemplo 2a) ^{1}H 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)

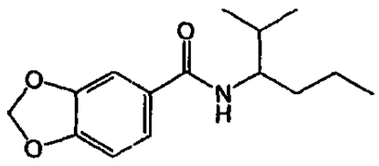
a preparacion de 2-metilheptan-4-amina

A una solucion de 2-metilheptan-4-ona (4 24 g, 33 07 mmoles) en metanol (60 ml), se les agregó acetato de amonio (25 50 g, 330 71 mmoles) y cianoborohidruro de sodio (2 08 g 33 07 mmoles) La mezcla de reaccion se agito a temperatura ambiente durante aproximadamente 24 horas El solvente se removió bajo presión y el residuo se diluyó con agua y se basificó con 15% de NaOH acuoso y se extrajo con eter El extracto se lavó con salmuera se secó sobre sulfato de magnesio anhidro, se filtró y se evaporo para dar 3 3 g de 2-metilheptan-4-amina (77%) MS (M+H 130)

El compuesto tuvo EC_{50} para activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 22 μM

Ejemplo 3

N-(2-metilhexan-3-il)benzo[d][1,3]dioxol-5-carboxamida



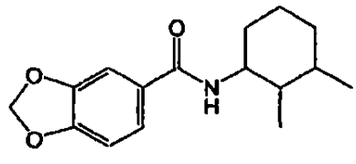
Preparado en una manera similar al ejemplo 1 utilizando cloruro de benzo[d][1,3]dioxol-5-carbonilo y 2-metilhexan-3-amina (Ejemplo 3a) ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 93 (m, 9H), 1 37 (m 3H), 1 56 (m 1H), 1 83 (m 1H) 4 01 (m 1H) 5 67 (d, 1H) 6 02 (s, 2H) 6 82 (d 1H), 7 28 (m, 2H) MS (M+H, 264)

a Se preparó 2-metilhexan-3-amina utilizando el mismo procedimiento descrito en el ejemplo 2a iniciando a partir de la 2-metilhexan-3-ona Rendimiento 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)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 61 μM

Ejemplo 4

N-(2 3-dimetilciclohexil)benzo[d][1,3]dioxo-5-carboxamida

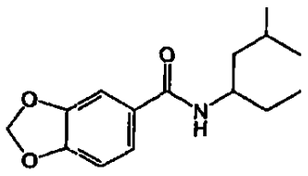


Se disolvieron cada uno en acetonitrilo/diclorometano (200 µL, 2 1), 2,3-dimetilciclohexamina (20 µmoles) y ácido benzo[d][1,3]dioxol-5-carboxílico (1 1 equivalentes) Se cargo resina de PS-carbodiimida (2 equivalentes) dentro de una placa Greiner de 1 2 ml de 96 pozos, seguida por la adicion de soluciones de amina y ácido Se disolvió el hidroxibenzotriazol (1 1 equivalentes) en DMF (100 ml) y se agregó dentro del pozo de reacción La reacción se agito durante la noche a temperatura ambiente Una vez que se completo la reacción, se agregó resina de PS-Trisamina (1 5 equivalentes) dentro de la mezcla de reaccion y la solucion se permitió agitar durante la noche a temperatura ambiente Se agrego acetonitrilo (200 mL) dentro del pozo de reacción y la solución transparente superior se transfirió dentro de una nueva placa La solución se evaporó para dar N-(2 3-dimetilciclohexil)benzo[d][1,3]dioxol-5-carboxamida MS (M+H, 276 20)

El compuesto tuvo EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 45 µM y cuando se presenta a 1 µM mejora la efectividad de glutamato de monosodio con una relacion de EC_{50} de 8 4

Ejemplo 5

N-(5-metilhexan-3-il)benzo[d][1,3]dioxol-5-carboxamida



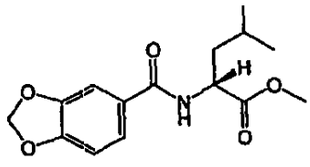
Preparado en una manera similar al ejemplo 1 utilizando cloruro de benzo[d][1 3]dioxol-5-carbonilo y 5-metilhexan-3-amina (ejemplo 5a) Rendimiento 48 % ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 94 (m, 9H), 1 37 (t, 3H) 1 45 (m, 1H) 1 64 (m, 2H), 4 13 (m, 1H) 5 61 (d, 1H) 6 01 (s, 2H), 6 82 (d, 1H), 7 27 (m 2H) MS (M+H 264)

a Se preparo 2-metilhexan-3-amina utilizando el mismo procedimiento descrito en el ejemplo 2a a partir de 5-metilhexan-3-ona Rendimiento 54% MS (M+H 116)

El compuesto tuvo EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 0 57 μM

Ejemplo 6

2-(benzo[d][1 3]dioxol-6-carboxamido)-4-metilpentanoato de (R)-metilo

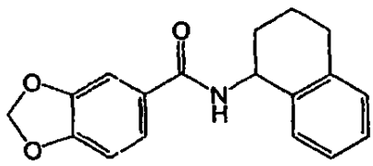


Preparado en una manera similar al ejemplo 1 utilizando cloruro de benzo[d][1,3]dioxol-5-carbonilo y clorhidrato del metilester D-leucina Rendimiento 83 % ^{1}H NMR (500 MHz $CDCl_3$) δ 0 98 (m, 6H) 1 63-I 67 (m, 1H), 1 71-1 76 (m, 2H) 3 76 (s, 3H) 4 83 (m, 1H), 6 03 (s, 2H), 6 38 (d, 1H), 6 83 (d, 1H), 7 32 (s 1H) 7 33 (d 1H) MS (M+H, 294) p f 89-90°C

El compuesto tuvo EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 34 μM, y cuando se presenta en 0 1 μM mejora la efectividad del glutamato de monosodio con una relación de EC_{50} de 4 9

Ejemplo 7

N-(1 2 3 4-tetrahidronaftalen-1-il)benzo[d][1,3]dioxol-5-carboxamida



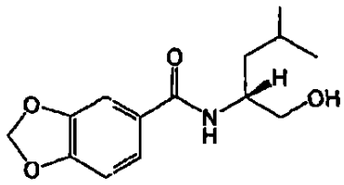
Preparado en una manera similar al ejemplo 4 utilizando ácido benzo[d][1 3]dioxol-5-carboxilico y 1,2,3 4-tetrahidronaftalen-1-amina MS (M+H 296 6)

El compuesto tuvo EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 71 μM y cuando se presenta en 0 3 μM mejora la efectividad de glutamato de monosodio con una relacion de EC_{50}

de 7 8

Ejemplo 8

(R)-N-(1-hidroxi-4-metilpentan-2-il)benzo[d][1,3]dioxol-5-carboxamida

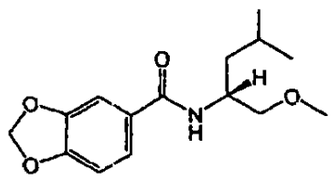


Preparado en una manera similar al ejemplo 4 utilizando ácido benzo[d][1,3]dioxol-5-carboxílico y (R)-aminoleucinol MS (M+H, 266 1)

El compuesto tuvo una EC_{50} para la activacion del receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 9 µM, y cuando se presenta en 3 µM mejora la efectividad de glutamato de monosodio con una relacion de 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-carboxilico



Preparado en una manera similar al ejemplo 4 utilizando (R)-1-metoxi-4-metilo y pentan-2-amina (ejemplo 9a) Rendimiento

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 ıs, 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-metoxı-4-metılpentan-2-amına

A una solución de (R)-2-(1-metoxı-4-metılpentan-2-ıl)ısoındolın-1,3-dıona (ejemplo 9b) (3 87 g, 14 84 mmoles) en metanol (30 ml), se agregó hıdrato de hıdracına (0 866 ml, 17 81 mmoles) y la mezcla de reaccion se calentó a 45°C durante aproxımadamente 3 horas La mezcla se acıdıfıcó con 2N HCl y se agıtó a 45°C durante 30 mınutos La solucion se enfrıó a temperatura ambıente, se fıltro y se evaporó El resıduo se removıo con 2N NaOH y se extrajo con éter, se secó sobre MgSO4 se fıltro y se evaporó para dar 1 51 g de (R)-1-metoxı-4-metılpentan-2-amına Rendımıento 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-metoxı-4-metılpentan-2-ıl)ısoındolın-1,3-dıona

Se dısolvıo (R)-2-(1-hıdroxı-4-metılpentan-2-ıl)ısoındolın-1,3-dıona (ejemplo 9c) (5 888 g, 23 87 mmoles) en THF seco (25 ml) y hexametıl-fosforamıda (30 mL) y la solución se enfrıo a 0°C Se agregó hıdruro de sodıo (60% en aceıte mıneral 1 15 g, 28 65 mmoles) y después de 10 mınutos se agrego en gotas yodometano (7 43 ml, 119 35 mmoles) y la solucion se

calentó lentamente a temperatura ambiente y se agitó durante la noche La mezcla de reacción se vertio en hielo/agua, se extrajo con EtOAc, se lavó con salmuera se secó sobre MgSO4 se filtró y se evaporó El residuo se purificó en gel de silice (20% de EtOAc en hexano) para dar 3 92 g de (R)-2-(1-metoxi-4-metilpentan-2-il)isoindoin-1,3-diona (63%)

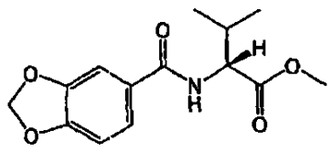
c (R)-2-(1-hidroxi-4-metilpentan-2-il)isoindolin-1,3-diona

Se mezclaron anhidrido ftalico (10 30 g, 69 55 mmoles) y D-Leucinol (8 15 g, 69 55 mmoles) en THF (100 mL), la mezcla de reacción se calento a 85°C y se llevó a reflujo durante 18 horas Despues del enfriamiento a temperatura ambiente, se agregó agua y la solución se extrajo con EtOAc, los extractos se lavaron con 1N HCl, agua, $NaHCO_3$ acuoso, agua y salmuera, se secaron sobre $MgSO_4$, se filtraron y se evaporaron para dar 8 1 g de (R)-2-(1-hidroxi-4-metilpentan-2-il)isoindolin-1,3-diona (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)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 3 5 μM

Ejemplo 10

2-(benzo[d][1 3]dioxol-6-carboxamido)-3-metilbutanoato de (R)-metilo

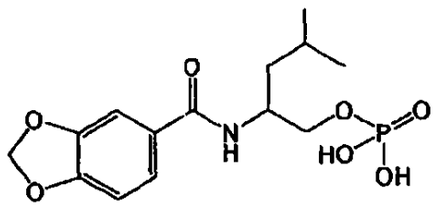


Preparado en una manera similar al ejemplo 4 utilizando ácido benzo[d][1,3]dioxol-5-carboxílico y 2-amino-3-metilbutanoato de (R)-metilo Rendimiento 50% MS (M+H, 280 1)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 1 16 µM

Ejemplo 11

Fosfato diacido de 2-(benzo[d][1,3]dioxol-6-carboxamido)-4-metilpentilo



Se disolvió en acetonitrilo anhidro (2 mL) N-(1-hidroxi-4-metilpentan-2-il)benzo[d][1 3]dioxol-5-carboxamida (ejemplo 11a) (0 57 mmoles, 151 mg) y se agregó una solución de 0 45 M de tetrazol en acetonitrilo bajo nitrógeno y se agito durante 5 minutos Luego se agrego 0 627 (1 1 equivalentes 207 µl) de

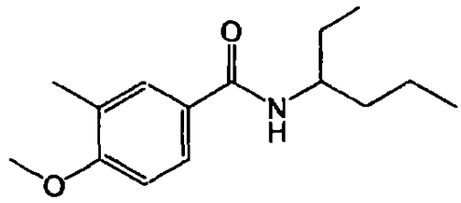
diisopropilfosforoamidita de dibencilo en gotas bajo nitrógeno La mezcla se agito durante 1 hora El solvente se evaporó y un intermediario sin purificar se disolvio en DCM y se lavo dos veces con 2% de carbonato de potasio y salmuera y se secó con sulfato de sodio El material se desecó y se oxidizó con 5 ml de ter-butilhidroperóxido (4M de solucion en nonato) durante 30 minutos El solvente se evaporó y el intermediario de dibenciléster se purificó (TLC preparativa) Los grupos bencilo se hidrolizaron utilizando ácido trifluoroacético (3 ml de una mezcla de 95% de TFA y 5% de agua 1 5 horas temperatura ambiente) El producto final se desecó proporcionando 69 mg (35%) de material puro ^{1}H NMR (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 Se preparó N-(1-hidroxi-4-metilpentan-2-il)benzo[d][1,3]dioxol-5-carboxamida en una manera similar al ejemplo 4 a partir del ácido piperonílico y el 2-amino-4-metil-pentan-1-ol

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 10 9 μM

Ejemplo 12

N-(hexan-3-il)-4-metoxi-3-metilbenzamida

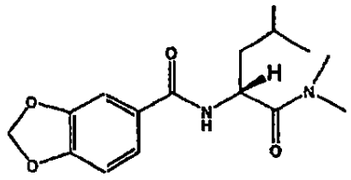


Preparado en una forma similar al ejemplo 4 utilizando acido 4-metoxi-3-metilbenzoico y hexan-3-amina (ejemplo 28a) ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 94 (m, 6H), 1 41 (m, 4H), 1 46 (m 1H), 1 64 (m, 1H), 2 24 (s, 3H) 3 87 (s, 3H), 4 08 (m, 1H) 5 69 (d, 1H), 6 83 (d, 1H) 7 54 (s, 1H) 7 62 (d, 1H) MS (M+H 250)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea 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



Se condensaron ácido (R)-2-(benzo[d][1,3]dioxol-6-carboxamido)-4-metilpentanoico (ejemplo 13a) (52 mg, 0 19 mmoles) en DMF (4 mL) y dimetilamina (2M en metanol, 36 μL 2

equivalentes) en la presencia de HOBt (26 mg, 1 equivalentes) y del clorhidrato de 1-etil-3-(3-dimetilaminopropil)-carbodiimida (44 mg, 1 2 equivalentes) a temperatura ambiente durante la noche La mezcla de reaccion se evaporo y el residuo se disolvio en etilacetato y se lavó sucesivamente con $NaHCO_3$ saturado y agua, se secó sobre MgSO, se filtró y se evaporó para dar 48 6 mg del producto (84%) El material se purificó además utilizando 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)

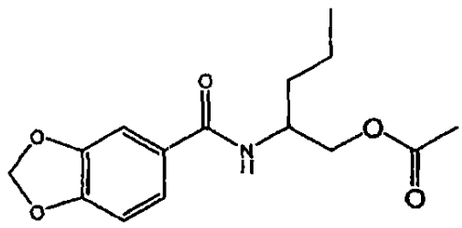
a Ácido (R)-2-(benzo[d][1 3]dioxol-6-carboxamido)-4-metilpentanoico

Preparado en una manera 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 tuvo una EC50 para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 1 06 μM

Ejemplo 14

Acetato de 2-(benzo[d][1 3]dioxol-6-carboxamido)pentilo



A una solucion de N-(1-hidroxipentan-2-il)benzo[d][1,3]dioxol-5-carboxamida (ejemplo 14a) (59 8 mg, 0 238 mmoles) en diclorometano (5 mL) se agregó trietilamina (166 mL, 1 19 mmoles) Se agrego lentamente anhidrido de acetilo (112 5 mL, 1 19 mmoles) y la mezcla se agitó bajo argón a temperatura ambiente durante la noche La solución se lavó sucesivamente con una solucion saturada de bicarbonato de sodio agua y salmuera La capa organica se secó sobre sulfato de sodio anhidro La filtración siguida por la remocion de solvente bajo presión reducida produjo 50 8 mg de acetato de 2-(benzo[d][1,3]dioxol-6-carboxamido)pentilo (73%) ^{1}H NMR ($CDCl_3$) δ 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)

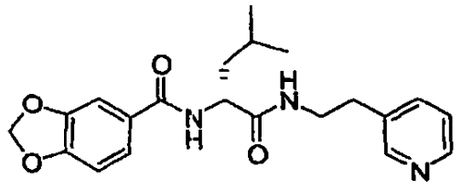
a Se preparo la N-(1-hidroxipentan-2-il)benzo[d][1,3]dioxol-5-carboxamida en una manera similar al ejemplo 4 utilizando ácido benzo[d][1 3]dioxol-5-carboxilico y 2-

aminopentan-1-ol Rendimiento 76% MS (M+H, 252)

El compuesto tuvo una EC50 para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 11 9 µM, y cuando se presenta en 3 µM mejora la efectividad del glutamato de monosodio con una relación de 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

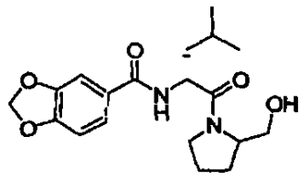


Preparado en una manera similar al ejemplo 13 utilizando 2-(3-piridil)etilamina y acido (R)-2-(benzo[d][1 3]dioxol-6-carboxamido)-4-metilpentanoico (ejemplo 13a) (MS M+ 384 2)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 1 7 µM

Ejemplo 16

N-((R)-1-(2-(hidroximetil)pirrolidin-1-il)-4-metil-1-oxopentan-2-il)benzo[d][1,3]dioxol-5-carboxamida

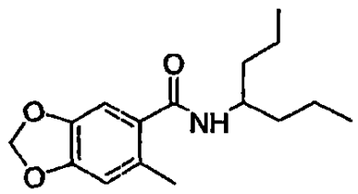


Preparado en una manera similar al ejemplo 13 utilizando R/S propinol y acido (R)-2-(benzo[d][1,3]dioxol-6-carboxamido)-4-metilpentanoico (ejemplo 13a) (MS M+363 2)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 3 µM

Ejemplo 17

N-(heptan-4-il)-6-metilbenzo[d][1,3]dioxol-5-carboxamida

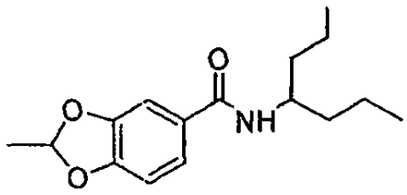


Preparado en una manera similar al ejemplo 4 utilizando ácido 6-metilbenzo[d][1,3]dioxol-5-carboxilico y heptan-4-amina MS (M+H, 278 67)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 11 µM

Ejemplo 18

N-(heptan-4-il)-2-metilbenzo[d][1,3]dioxol-5-carboxamida



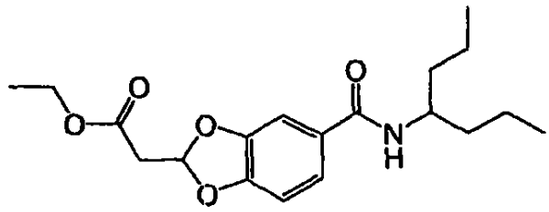
Se disolvio N-(heptan-4-il)-3,4-dihidroxibenzamida (ejemplo 18a) (0 5 mmoles) en tolueno (1 6 mL) Se agrego monohidrato del acido P-toluensulfónico (0 3 equivalentes) a la reacción, seguida por la adición de acetaldehído (2 equivalentes) La reaccion se realizó utilizando microonda (180C, 300W) y se activó durante 10 minutos El solvente se evaporó El residuo se disolvió en metanol (1 ML) y se purificó por HPLC Rendimiento 20% MS (M+H 278 10)

a Se preparó N-(heptan-4-il)-3,4-dihidrobenzamida en una manera similar al ejemplo 4 utilizando acido 3,4-dihidroxibenzoico y heptan-4-amina Rendimiento 25% MS (M+H 252 1)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 1 µM y cuando se presenta en 0 03 µM mejora la efectividad de glutamato de monosodio con una relacion de EC_{50} de 3 68

Ejemplo 19

2-(5-heptan-4-ilcarbamoil)benzo[d][1,3]dioxol-2-il)acetato de etilo

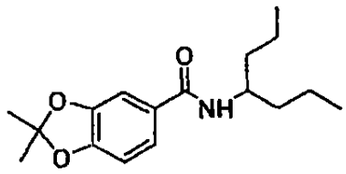


Se disolvio en acetona seca N-(heptan-4-il)-3,4-dihidroxibenzamida (ejemplo 18a) (0 29 mmoles 75 mg) con exceso de 6 equivalentes (242 mg) de carbonato de potasio luego se agrego 1 2 equivalentes en exceso (36 µl) de etiléster del ácido propiónico y una mezcla se llevó a reflujo durante 24 horas El solvente se evaporo y un solido se disolvió en diclorometano y se extrajo con 10% de $NaHCO_3$ y agua El producto sin purificar se purificó por cromatografía en gel de silice para dar 72 mg del producto deseado (71%) ^1H 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)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 14 µM y cuando se presenta en 3 µM mejora la efectividad de glutamato de monosodio con una relacion de EC_{50} de 2 5

Ejemplo 20

N-(heptan-4-il)-2 2-dimetilbenzo[d][1,3]dioxol-5-carboxamida



Preparado en una manera 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 NMR δ 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

Se agitó 2,2-dimetilbenzo[d][1 3]dioxol-5-carboxilato de etilo (ejemplo 20b) (461 mg 2 08 mmoles) en dioxano (16 mL) y NaOH acuoso 1 0N (4 16 mL) durante 20 horas a temperatura ambiente El solvente se removio bajo presión reducida para producir el producto deseado (449 mg) (M-H, 193)

b 2 2-dimetilbenzo[d][1,3]dioxol-5-carboxilato de etilo

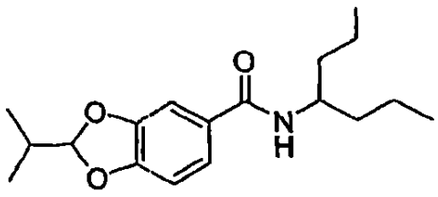
Se combinó 3,4-dihidroxibenzoato de etilo (910 9 mg, 5 mmoles) con 2,2-dimetoxipropano (1 23 ml, 10 mmoles) y una cantidad catalitica del ácido p-toluensulfonico en tolueno La mezcla se calentó a reflujo utilizando una trampa Dean-Stark durante 20 horas Después de la remoción del solvente bajo presión reducida, el crudo se disolvió en acetato de etilo y se lavo

sucesivamente con una solución acuosa saturada de bicarbonato de sodio, agua y salmuera La capa orgánica se seco sobre sulfato de sodio anhidro La purificacion por cromatografia en gel de sílice utilizando un gradiente de hexano acetato de etilo, 90 10 a 75 25 produjo un polvo blanco (539 1 mg, 49%) ^{1}H NMR ($CDCl_3$) δ 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 2 Hz), 7 38 (d 1h, *J*= 1 7 Hz), 7 61 (dd, 1H *J*= 1 8 Hz *J*= 8 3 Hz)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 2 7 μM

Ejemplo 21

N-(heptan-4-il)-2-isopropilbenzo[d][1,3]dioxol-5-carboxamida



Preparado en una manera similar al ejemplo 4 utilizando el acido 2-isopropilbenzo[d][1,3]dioxol-5-carboxilico (ejemplo 21a) y 4-heptilamina Rendimiento 34% ^{1}H NMR($CDCl_3$) δ 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

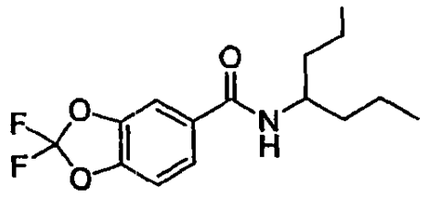
(M+H, 291)

a ácido 2-isopropilbenzo[d][1,3]dioxol-5-carboxílico se combinaron el ácido 3 4-dihidrobenzoico (154 12 mg, 1 mmol) e isobutiraldehido (182 µl 2 mmoles) en tolueno (3 mL) y se agrego una cantidad catalitica del acido p-toluensulfónico La mezcla se sometió a microonda durante 10 minutos a 180°C con un sistema de potencia a 275 La solución se filtró y evaporó para producir 100 mg del producto deseado (48%) MS (M-H, 207)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 11 5 µM y cuando se presenta en 3 µM mejora la efectividad del glutamato de monosodio con una relación de EC_{50} de 2 2

Ejemplo 22

2 2-difluoro-N-(heptan-4-il)benzo[d][1,3]dioxol-5-carboxamida



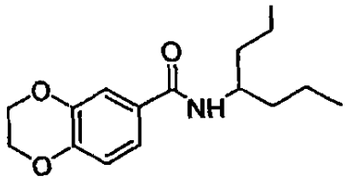
Preparado en una manera similar al ejemplo 4, utilizando el ácido 2,2-difluorobenzo[d][1,3]dioxol-5-carboxílico y 4-heptilamina (M+H 300 2)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular

HEK293 de 1 51 µM, y cuando se presenta en 1 µM mejora la efectividad del glutamato de monosodio con una relación de EC_{50} de 2 87

Ejemplo 23

(1-propil-butil)amida del Ácido 2,3-Dihidro-benzo[1,4]dioxin-5-carboxílico

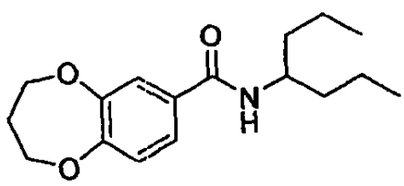


Preparado en una manera similar al ejemplo 4, utilizando el ácido 2,3-dihidro-benzo[1 4]dioxin-6-carboxilico y una heptan-4-amina MS (M+H, 278 2)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 49 µM

Ejemplo 24

N-(heptan-4-il)-3 4-dihidro-2H-benzo[b][1,4]dioxepin-7-carboxamida

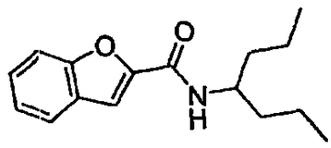


Preparado en una manera similar al ejemplo 4, utilizando el ácido 2 3-dihidro-benzo[1,4]dioxin-6-carboxílico y la heptan-4-amina MS (M+H, 292 2)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 6 4 µM

Ejemplo 25

Benzofuran-2-carboxílico(1-propilbutil)amida

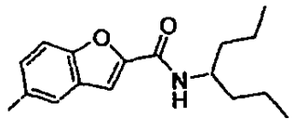


Preparado en una manera similar al ejemplo 1 utilizando cloruro de benzofuran-2-carbonilo y heptan-4-amina Rendimiento 73% ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 93 (t 6H, *J*= 7 2 Hz), 1 41 (m 8H) 3 01 (s, 3H), 4 18 (m, 1H), 6 29 (d 1H, *J*= 9 94 Hz) 7 20 (d, 1H *J*= 8 62 Hz) 7 37 (m, 2H), 7 44 (s, 1H) MS (M+H, 260)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 88 µM, y cuando se presenta en 0 3 µM mejora la efectividad del glutamato de monosodio con una relacion de EC_{50} de 2 6

Ejemplo 26

N-(heptan-4-il)-5-metilbenzofuran-2-carboxamida



Preparado en una manera similar al ejemplo 4, utilizando el ácido 5-metilbenzofuran-2-carboxílico (ejemplo 26a) y heptan-4-amina Rendimiento 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)

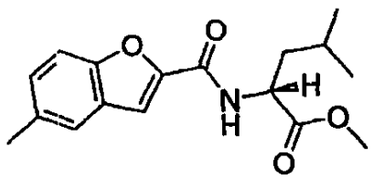
a ácido 5-metilbenzofuran-2-carboxílico Se combinó el 2-hidroxi-5-metilbenzaldehido (544 2 mg, 4 mmoles) con dietilbromomalonato (1 mL 6 mmoles) y carbonato de potasio (1 1 g, 8 mmoles) en metiletilcetona (5 mL) y la mezcla se calento a reflujo durante la noche El solvente se removió por evaporación giratoria para producir un aceite sin purificar El aceite se tomo entonces en una solucion de 10% de hidróxido de potasio en etanol (10 mL) y se calentó a reflujo durante 45 minutos El solvente se removió bajo presión reducida y el residuo se trato entonces con una solución de 2 0 N de H_2SO_4 El ácido libre se extrajo entonces con cantidades copiosas del acetato de etilo La capa organica se secó sobre sulfato de sodio anhidro La remocion del acetato de etilo produjo 566 mg de 5-metil-2-carboxibenzofurano (80%) como un polvo amarillento ^{1}H NMR

(500 MHz, CD_3OD) (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 tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 94 µM

Ejemplo 27

4-metil-2-(5-metilbenzofuran-2-carboxamido)pentanoato de (R)-metilo

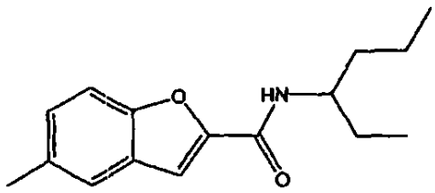


Preparado en una manera similar al ejemplo 4 utilizando acido 5-metilbenzofuran-2-carboxílico (ejemplo 26a) y metiléster D-leucina ^1H NMR (500 MHz, $CDCl_3$) δ 0 98 (d, 3H, *J*= 6 26 Hz), 1 00 (d, 3H, *J*= 6 17 Hz), 1 56 (s 3H), 1 76 (m 3H), 2 48 (s, 3H), 3 78 (s, 3H), 4 86 (m, 1H), 6 95 (m, 1H), 7 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 tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 11 µM

Ejemplo 28

N-(hexan-3-il)-5-metilbenzofuran-2-carboxamida



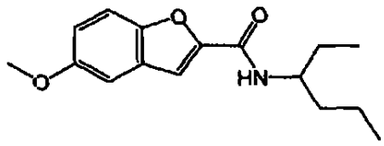
Preparado en una manera similar al ejemplo 4, utilizando 5-metilbenzofuran-2-carboxílico (ejemplo 26a) y hexan-3-amina (ejemplo 28a) Rendimiento 49% ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 94 (m, 6H) 1 40-1 68 (m 6H), 2 36 (s, 3H), 4 07 (m, 1H), 5 74 (d, 1H *J*= 8 97 Hz), 7 16 (d, 1H *J*= 7 80 Hz) 7 31 (dd 1H *J*= 1 73 Hz, *J*= 1 73 Hz), 7 66 (d, 1H, *J*= 1 72 Hz) MS (M+H, 260)

a Se preparó la hexan-3-amina utilizando el mismo procedimiento descrito en el ejemplo 2a a partir de la hexan-3-ona Rendimiento 58 % ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 94 (m 6H), 1 36-1 58 (m, 6H) 2 83 (m 1H), 3 12 (s, 2H) MS (102 M+H)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 0 74 μM

Ejemplo 29

N-(hexan-3-il)-5-metoxibenzofuran-2-carboxamida

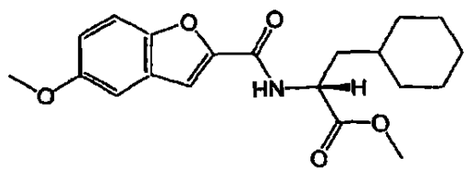


Preparado en una manera similar al ejemplo 4, utilizando el acido 5-metoxibenzofuran-2-carboxílico y hexan-3-amina (ejemplo 28a) Rendimiento 32% ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 96 (m, 6H), 1 40 1 67 (m, 6H), 3 85 (s, 3H), 4 09 (m 1H), 6 28 (d, 1H), 7 01 (dd, 1H), 7 08 (d, 1H), 7 38 (m 2H) MS (276 M+H)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 0 4 μM

Ejemplo 30

3-ciclohexil-2-(5-metoxibenzofuran-2-carboxamido)propionato de (R)-metilo



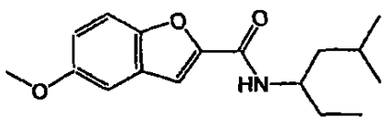
Preparado en una manera similar al ejemplo 4, utilizando ácido 5-metoxibenzofuran-2-carboxílico y 2-amino-3-ciclohexilpropionato de (R)-metilo Rendimiento 45 MS (M+H,

260 3)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 1 14 µM

Ejemplo 31

5-metoxi-N-(5-metilhexan-3-il)benzofuran-2-carboxamida

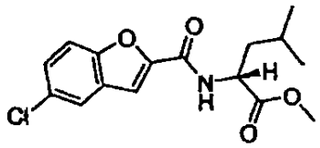


Preparado en una manera similar al ejemplo 4, utilizando ácido 5-metoxibenzofuran-2-carboxílico y 5-metilhexan-3-amina (ejemplo 5a) Rendimiento 67% ^1H NMR (500 MHz, $CDCl_3$) δ 0 96 (m, 9H), 1 39-1 52 (m 3H), 1 66 (m 2H), 3 85 (s 3H), 4 17 (m, 1H), 6 24 (d, 1H), 7 01 (dd 1H), 7 08 (d, 1H) 7 38 (m 2H) MS (290, M+H)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 1 04 µM

Ejemplo 32

Preparacion del 4-cloro-2-(5-metilbenzofuran-2-carboxamido)pentanoato de (R)-metilo

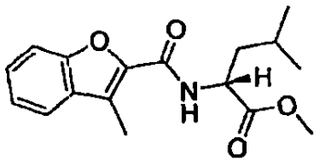


Preparado en una manera similar al ejemplo 4 utilizando acido 5-clorobenzofuran-2-carboxilico y metilester D-leucina MS (M+H, 324)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 82 µM

Ejemplo 33

4-metil-2-(3-metilbenzofuran-2-carboxamido)pentanoato de (R)-metilo

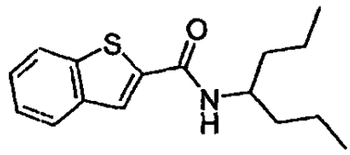


Preparado en una manera similar al ejemplo 4, utilizando acido 3-metilbenzofuran-2-carboxilico y metilester de D-leucina MS (M+H, 304)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 1 18 µM

Ejemplo 34

N-(heptan-4-il)benzo[b]tiofen-2-carboxamida

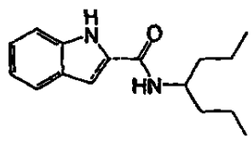


Preparado en una manera similar al ejemplo 4, utilizando ácido benzo[b]tiofen-2-carboxílico y 4-heptilamina MS (M+H, 276)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 21 µM

Ejemplo 35

N-(heptan-4-il)-1H-indol-2-carboxamida

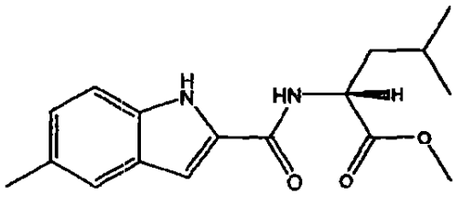


Preparado en una manera similar al ejemplo 4, utilizando el ácido 1H-indol-2-carboxílico y la 4-heptilamina MS (M+H, 259)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 6 8 µM

Ejemplo 36

4-metil-2-(5-metil-1H-indol-2-carboxamido)pentanoato de (R)-metilo

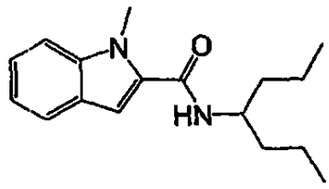


Preparado en una manera similar al ejemplo 4, utilizando el acido 5-metil-1H-indol-2-carboxilico y el metiléster de D-leucina Rendimiento 50% ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 98 (d, 3H, *J*= 6 3 Hz), 1 00 (d, 3H, *J*= 6 1 Hz), 2 44 (s, 3H) 3 784 (s, 3H), 4 87 (m, 1H), 6 56 (d, 1H, *J*= 8 39 Hz), 6 85 (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 tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 6 6 μM

Ejemplo 37

N-(heptan-4-il)-1-metil-1H-indol-2-carboxamida



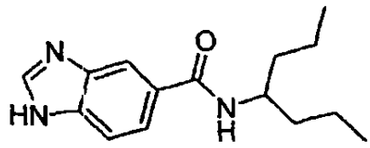
Preparado en una manera similar al ejemplo 4,

utilizando el ácido 1-metil-1H-indol-2-carboxílico y 4-heptilamina Rendimiento 45% ^{1}H NMR (500 MHz, $CDCl_3$) δ 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)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 1 79 µM

Ejemplo 38

N-(heptan-4-il)-1H-benzo[d]imidazol-5-carboxamida

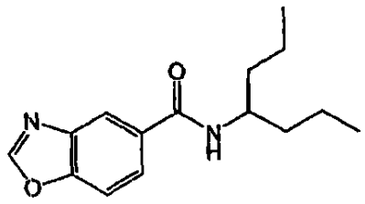


Preparado en una manera similar al ejemplo 4 utilizando ácido 1H-benzo[d]imidazol-5-carboxílico y 4-heptilamina Rendimiento 80% ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 94 (t, 6H, *J*= 7 2 Hz), 1 42 (m, 6H), 1 57 (m, 2H), 4 21 (m, 1H) 6 18 (m 1H), 7 64 (m, 2H), 8 16 (m, 1H) 8 28 (s, 1H) MS (M+H, 260)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 18 6 µM

Ejemplo 39

(1-propilbutil)amida del acido benzoxazol-5-carboxílico



Preparado en una manera similar al ejemplo 4 utilizando el ácido benzoxazol-5-carboxílico (Ejemplo 39a) y 4-heptilamina ^{1}H NMR (500 MHz, $CDCl_3$) δ 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)

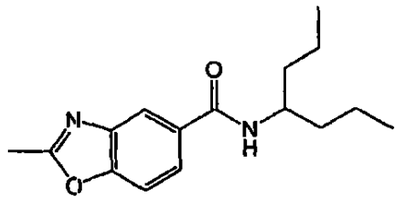
a acido benzoxazcl-5-carboxılico Una mezcla del acido 3-amino-4-hidroxibenzoico (500 mg 3 26 mmoles) y ortoformiato de trimetilo (5 mL) se calento a 65°C durante 2 horas bajo argon La mezcla de reacción se enfrió a temperatura ambiente se filtró y se lavó con hexano El filtrado se concentró al vacio para producir el producto como un sólido blanco (78 mg 15%) ^{1}H NMR (500 MHz $CDCl_3$) δ 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 tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 1 91 μM

432

Ejemplo 40

(1-propil-butil)-amida del acido 2-Metil-benzoxazol-5-carboxilico



Preparado en una manera similar al ejemplo 4 a partir del acido 2-metilbenzoxazol-5-carboxílico (ejemplo 40) y 4-heptilamina ^{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 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

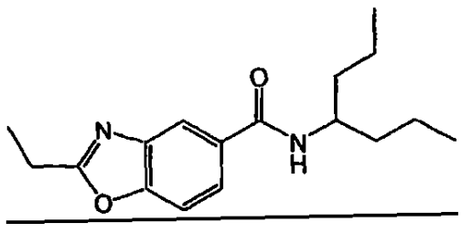
a acido 2-metilbenzoxazol-5-carboxilico Una mezcla del acido 3-amino-4-hidroxibenzoico (1 5 g, 9 79 mmoles) y ortoacetato de trimetilo (15 mL, exceso grande) se calento a 65°C durante 5 horas bajo argón La mezcla de reacción se enfrio a temperatura ambiente, se filtró y se lavó con hexanos El filtrado se concentró al vacio para producir el producto como un solido amarillo (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

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular

HEK293 de 0 33 µM

Ejemplo 41

(1-Propil-butil)-amida del ácido 2-etil-benzoxazol-5-carboxílico



Una mezcla de la 3-amino-4-hidroxi-N-(1-propilbutil)benzamida (ejemplo 41a) y ortopropirato de trimetilo se calentó a 65°C durante 5 horas bajo N_2 La mezcla de reaccion se enfrió a temperatura ambiente y se concentró al vacio El residuo resultante se purifico en gel de silice a través de una TLC Preparativa (3% de MeOH en CH_2Cl_2) para producir el producto como un solido blanco (42 mg, 73%) p f 107-108°C, MS (APCI M+1) 289 10

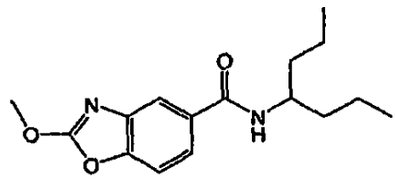
a se preparo la 3-amino-4-hidroxi-N-(1-propilbutil)benzamida en una manera similar al ejemplo 4 utilizando el acido 3-Amino-4-hidroxibenzoico y la 4-heptilamina Rendimiento 57 % ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 93 (t, 6H), 1 26-1 51 (m 8H) 4 09 (m, 1H), 6 74 (m, 1H) 7 05 (s, 1H), 7 43 (m 2H), 7 77 (m, 2H) MS (251, M+H)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular

HEK293 de 0 68 µM

Ejemplo 42

(1-propil-butil)-amida del ácido 2-Metoxi-benzoxazol-5-carboxílico

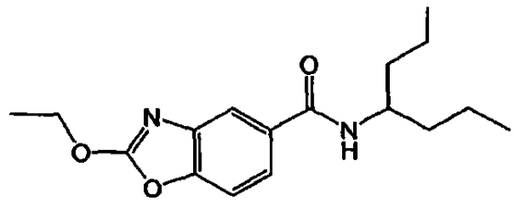


Preparado en una manera similar al ejemplo 41, utilizando la 3-amino-4-hidroxi-N-(1-propilbutil)benzamida (ejemplo 4aa) y ortocarbonato de tetrametilo Rendimiento 60% p f 137-138°C, MS (M+H 291 10)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 69 µM

Ejemplo 43

(1-propil-butil)-amida del acido 2-Etoxi-benzoxazol-5-carboxílico



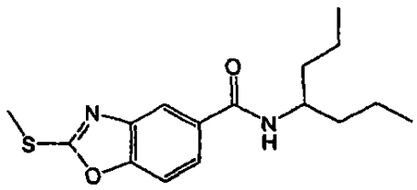
Preparado en una manera similar al ejemplo 41

utilizando la 3-amino-4-hidroxi-N-(1-propilbutil)benzamida (ejemplo 41a) y tetraetoximetano p f 128-129°C, MS (M+H) 305 1)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 5 µM

Ejemplo 44

N-(heptan-4-il)-2-(metiltio)benzo[d]oxazol-5-carboxamida



A una solución de la N-(Heptan-4-il)-2-(mercapto)benzo[*d*]oxazol-5-carboxamida (ejemplo 44a) (50 mg 0 17 mmoles) en DMF (3 mL) a 0°C se agregó K_2CO_3 (29 mg, 0 17 mmoles) y MeI (29 mg 0 20) La mezcla de reacción resultante se calentó a 80°C durante la noche El solvente se removió bajo presión reducida El residuo se diluyo con diclorometano y se lavo con agua, se seco (Na_2SO_4), se filtró y se concentró al vacio se purifico a traves de PLTC (15% de ETOAc en hexanos) para producir el producto como un sólido blanco (50 mg, 96%) p f 113-114°C, ^{1}H 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), 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+)

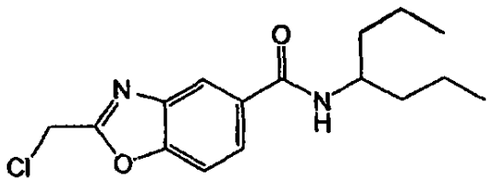
307 2

a N-(Heptan-4-il)-2-(mercapto)benzo[*d*]oxazol-5-carboxamida A una solucion de la 3-amino-4-hidroxi-N-(1-propilbutil)benzamida (ejemplo 41a) (250 mg, 1 0 mmoles) en EtOH se agregó KSCSOEt (160 mg, 1 0 mmol) La mezcla de reacción resultante se calento a 80°C durante la noche El solvente se removió bajo presión reducida Y el residuo se removió en agua La mezcla resultante se acidificó con HOAc a pH ~ 5 y luego se filtró El residuo se lavo con agua para producir el producto como un solido blanco (160 mg 55%) MS (M+H, 293 1)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 3 1 µM

Ejemplo 45

(1-propil-butil)amida del acido clorometilbenzoxazol-5-carboxilico

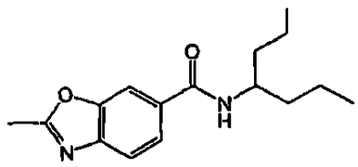


Preparado en una manera similar al ejemplo 41 utilizando la 3-amino-4-hidroxi-N-(1-propilbutil)benzamida (ejemplo 41a) y cloro-ortoacetato de trimetilo Rendimiento 65% p f 108 5-109°C MS (M+H, 309 05)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 0 23 µM

Ejemplo 46

(1-propil-butil)-amida del ácido 2-Metil-benzoxazol-6-carboxílico



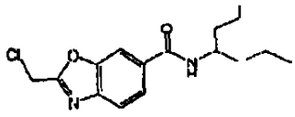
Preparado en una manera similar al ejemplo 4, utilizando el ácido 2-metil benzoxazol-6-carboxílico (ejemplo 46a) y 4-heptilamina Rendimiento 50% ^{1}H NMR (500 MHz, CD_3OD) δ 8 19 (d, *J*= 1 4 Hz, 1H) 8 05 (dd, *J*= 8 3,1 5 Hz, 1H), 7 63 (d *J*= 8 2 Hz 1H) 2 68 (s, 1H), MS (M+1, 178 10)

a se preparó el ácido 2-metil benzoxazol-6-carboxílico en una manera similar al ejemplo 40a a partir del ácido 4-amino-3-hidroxibenzoico (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)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 2 1 µM

Ejemplo 47

(1-propil-butil)-amida del acido 2-clorometil-benzoxazol-6-carboxílico



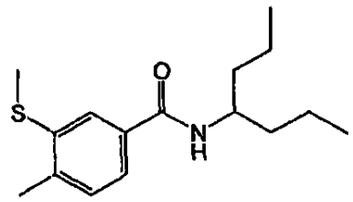
Preparado en una manera similar al ejemplo 41, utilizando la 3-amino-4-hidroxi-N-(1-propilbutil)benzamida (ejemplo 47a) y el cloro-ortoacetato de trimetilo El producto se obtuvo como un sólido blanco (45 mg, 73%) p f 173 0-137 5°C MS (M+H 309 05

a se preparo la 3-amino-4-hidroxi-N-(1-propilbutil)benzamida en una manera similar al ejemplo 41a a partir del ácido 4-amino-3-hidroxibenzoico Rendimiento 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)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 45 µM

Ejemplo 48

4-metil-3-metilsulfanil-N-(1-propilbutil)benzamida



Preparado en una manera similar como el ejemplo 4 utilizando el ácido 4-metil-3-(metiltio)benzoico (ejemplo 48a) y 4-heptilamina Rendimiento 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)

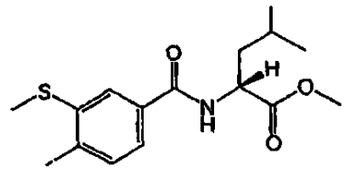
a ácido 4-metil-3-(metiltio)benzoico Se suspendió el acido 3-Amino-4-metilbenzoico en agua helada (55 mL) y el HCl concentrado (8 56 mL) se agrego lentamente Una solución acuosa del nitrito de sodio (2 4 g en 5 5 mL) se agregó a la suspensión durante un periodo de 15 minutos y la mezcla se agitó durante otros 15 minutos Luego, una solucion acuosa de acetato de sodio (9 31 g 18 mL) se agrego en gotas La reaccion se permitio proceder durante 45 minutos Se obtuvo un precipitado anaranjado intenso El precipitado se extrajo por filtración y se lavó con pequeñas porciones de agua helada El solido se combinó con una solucion de xantogenato de potasio (11 93 g) y carbonato de potasio (8 22 g) en 250 ml de agua El recipiente de reacción se colocó en un baño de aceite pre-calentado a 70°C y la mezcla se

agitó durante 25 minutos La solucion rojiza se removió del baño y se agitó durante 15 minutos o hasta que la temperatura alcanzo 30°C Se agrego hidróxido de sodio (0 782 g) y se agitó hasta disolución Se agrego dimetilsulfato (5 70 mL) La mezcla se agito durante 1 hora a temperatura ambiente, luego se llevo a reflujo brevemente La remoción del solvente bajo presión reducida produjo un solido anaranjado El solido se trató con una solución 2 0 N de H_2SO_4 y se extrajo con EtOAc Los extractos se lavaron con agua, luego se secaron sobre $MgSO_4$ anhidro El solvente se removió bajo presión reducida para dar un sólido sin purificar rojizo El sólido se adsorbió en gel de silice y se purificó por cromatografía en columna (gradiente 5 a 50% de acetato de etilo en hexano) para dar el ácido 4-metil-3-(metiltio)benzoico como un polvo amarillo pálido (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)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 21 μM

Ejemplo 49

4-metil-2-(4-metil-3-(metiltio)benzamido)pentanoato de (R)-1-metilo

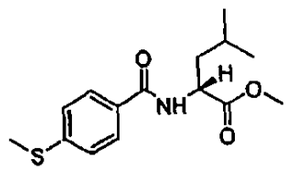


Preparado en una manera similar al ejemplo 4 utilizando acido 3-metil-4-(metiltio)benzoico (ejemplo 48a) y metilester de D-leucina Rendimiento 45% ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 97 (d 3H, *J*= 6 36Hz), 0 99 (d, 3H, *J*= 6 1 Hz), 1 64-1 77 (m, 2H), 2 36 (s 3H), 2 51 (s 3H), 3 77 (s, 3H), 4 85 (m, 1H), 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)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 0 1 μM

Ejemplo 50

4-metil-2-(4-(metiltio)benzamido)pentanoato de (R)-metilo



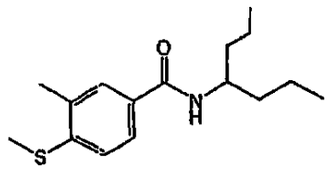
Preparado en una manera similar al ejemplo 4 utilizando

el ácido 4-(metiltio)benzoico y metiléster de D-Leucina Ms (M+H 296)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 16 µM

Ejemplo 51

N-(heptan-4-il)-3-metil-4-(metiltio)benzamida



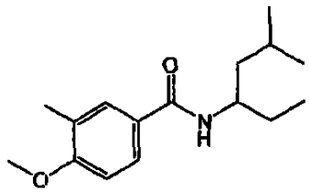
Preparado en una manera similar al ejemplo 4 utilizando el ácido 3-metil-4-(metiltio)benzoico (ejemplo 51a) y 4-heptilamina ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 93 (t 6H), 1 37-1 46 (m, 6H), 1 54-1 56 (m 2H) 2 35 (s, 3H), 2 49 (s, 3H), 4 17 (m, 1H), 5 73 (d 1H) 7 14 (d, 1H), 7 52 (s 1H), 7 58 (d, 1H) MS (280, M+H) p f 129-131°C

a se preparó el ácido 3-metil-4-(metiltio)benzoico utilizando el mismo procedimiento descrito en el ejemplo 48a a partir del acido 3-Amino-4-metilbenzoico Rendimiento 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)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 0 12 µM

Ejemplo 52

4-metoxi-3-metil-N-(2-metilheptan-4-il)benzamida

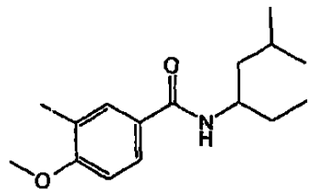


Preparado en una manera similar como la descrita en el ejemplo 4 utilizando ácido 4-metoxi-3-metilbenzoico y 2-metil-4-heptanamina (ejemplo 2a) Rendimiento 45% ^{1}H NMR (500 MHz $CDCl_3$) δ 0 93 (m, 9H) 1 39 (m 5H) 1 53 (m, 1H), 1 67 (m 1H) 2 24 (s 3H), 3 86 (s 3H) 4 23 (m 1H) 5 64 (d, 1H), 6 82 (d 1H) 7 54 (s 1H) 7 61 (d, 1H) MS (278, M+H)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 1 μM

Ejemplo 53

4-metoxi-3-metil-N-(5-metilhexan-3-il)benzamida



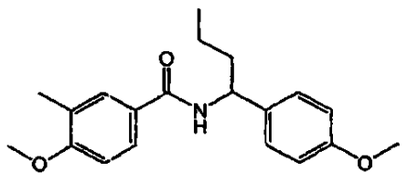
Preparado en una manera similar al ejemplo 4 utilizando acido 4-metoxi-3-metilbenzoico y 5-metilhexan-3-amina (ejemplo 5a) ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 94 (m 9H), 1 38 (m, 2H), 1 47

(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)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 09 µM

Ejemplo 54

4-metoxi-N-(1-(4-metoxifenil)butil)-3-metilbenzamida



Preparado en una manera similar al ejemplo 4 utilizando el ácido 3-metil-4-metoxi-benzoico y 1-(4-metoxifenil)butan-1-amina (ejemplo 54a) Rendimiento 52% ^1H 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)

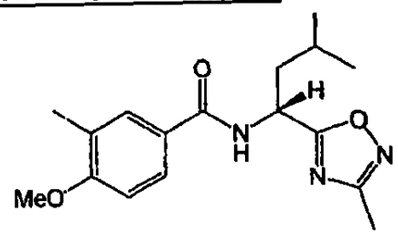
a se preparo la 1-(4-metoxifenil)butan-1-amina como se describe en el ejemplo 2a a partir de la 1-(4-metoxifenil)butan-1-ona Rendimiento 90% MS (M+H 180)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea 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



Preparado en una manera 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)

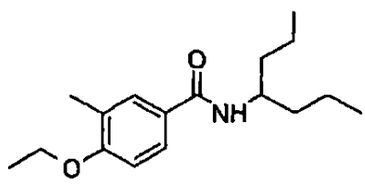
a (R)-3-metil-1-(3-metil-1,2 4-oxadiazol-5-il)butan-1-amina Se trató Boc-D-Leu-OH (0 23 g 1 mmol) con N-hidroxiacetamidina (74 mg, 1 equivalente) y DIC (155 µL 1 equivalente) en dioxano (2 mL) a temperatura ambiente durante la noche Otra porción de DIC (1 equivalente) se agregó y la mezcla de reacción se calento a 110°C durante 4 horas Después de la remocion del solvente, se residuo se trató con 50% de TFA/DCM (2 mL) durante 1 hora y luego el solvente se evaporó La mezcla sin purificar se purificó por HPLC preparativa (columna C-18, fase móvil MeOH-H_2O y ácido fórmico como modificador) para dar 75 mg de la amina (45% de rendimiento) ^1H 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, NH2), 4 65 (t, 1H) MS (M+H, 170)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 5 4 µM

Ejemplo 56

4-etoxi-N-(heptan-4-il)-3-metilbenzamida



Preparado en una manera similar como el ejemplo 4 utilizando el acido 4-etoxi-3-metil-benzoico (ejemplo 56a) y 4-heptilamina Rendimiento 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)

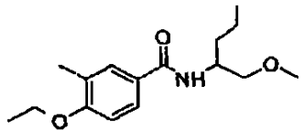
a acido 4-etoxi-3-metilbenzoico se disolvió el ácido 4-hidroxi-3-metilbenzoico (10 g) en DMF (400 mL) seguido por la adición del carbonato de sodio (3 equivalentes) Se disolvio en DMF (50 mL) yoduro de etilo (3 equivalentes) se agregó en gotas a la mezcla de reacción y la solución se agitó durante la noche Después que se termino la reacción, el solvente se evaporo El residuo se disolvio en acetato de etilo y se lavo con agua La capa

orgánica se aisló y se evaporó El residuo se disolvió en 200 ml de metanol/agua (3 1) Se agrego hidróxido de litio (3 equivalentes) y se permitió agitar durante la noche Hasta la terminacion de la hidrolisis, el solvente se removió y el producto se cristalizo utilizando una mezcla de acetato de etilo/hexano para dar 8 2 g del ácido 4-etoxi-3-metilbenzoico Rendimiento 70%, MS (M-H 179 20)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 0 17 μM

Ejemplo 57

4-etoxi-N-(1-metoxipentan-2-il)-3-metilbenzamida



Preparado en una manera similar como el ejemplo 4 utilizando el ácido 4-etoxi-3 metilbenzoico (ejemplo 56a) y la 1-metoxipentan-2-amina (ejemplo 57a) Rendimiento 33% MS (M+H, 280 1)

a se preparó la 1-metolxipentan-2-amina en una manera similar al ejemplo 9a a partir de la 2-(1-metoxipentan-2-il)isoindolin-1 3-diona (ejemplo 57b) Rendimiento 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)

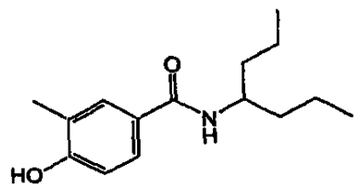
b se preparo la 2-(1-metoxipentan-2-il)isoindolin-1,3-diona en una manera similar al ejemplo 9b a partir de 2-(1-hidroxipentan-2-il)isoindolin-1,3-diona (ejemplo 57c) Rendimiento 82% ^{1}H NMR (500 MHz $CDCl_3$) δ 0 91 (t, 3H) 1 32 (m, 2H) 1 64 (m 1H), 2 03 (m, 1H), 3 31 (s 3H) 3 54 (m 1H) 3 98 (t 1H) 4 50 (m 1H) 7 70 (m, 2H), 7 82 (m, 2H)

c se preparó la 2-(1-hidroxipentan-2-il)isoindolin-1 3-diona en una manera similar al ejemplo 9c utilizando la isobenzofuran-1,3-diona y el 2-aminopentan-1-ol Rendimiento 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)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 69 μM

Ejemplo 58

4-hidroxi-3-metil-N-(1-propil-butil)-benzamida

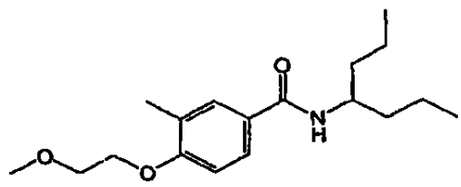


Preparado en una manera similar como se describe en el ejemplo 4 utilizando el acido 4-hidroxi-3-metil-benzoico y 4-heptilamina MS (M+H, 250 2)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 0 92 µM

Ejemplo 59

N-(heptan-4-il)-4-(2-metoxietoxi)-3-metilbenzamida

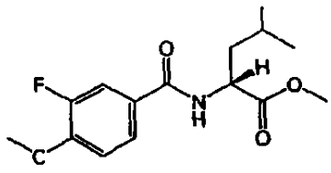


Se disolvió en etanol (5 mL) hidróxido de potasio (4 mmoles) y se calento a 80°C Se agregó en la solucion 4-hidroxi-3-metil-N-(1-propil-butil)-benzamida (ejemplo 58) (1 mmol) seguida por cloroetanol (3 mmoles) La reacción se agitó durante la noche a 80°C La mezcla de reaccion se concentró y se disolvió en 5% de ácido citrico La mezcla se agitó durante 1 hora La mezcla acuosa se extrajo tres veces con acetato de etilo El acetato de etilo combinado se lavó con agua y se seco sobre sulfato de sodio La capa orgánica se concentró y se purifico por HPLC para producir 39% de la N-(heptan-4-il)-4-(2-metoxietoxi)-3-metilbenzamida MS (M+H, 308 25)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 21 µM

Ejemplo 60

2-(3-fluoro-4-metoxibenzamido)-4-metilpentanoato de (R)-metilo

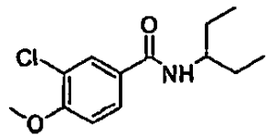


Preparado en una manera similar al ejemplo 4 utilizando el ácido 3-fluoro-4-metoxibenzoico y el metiléster de D-leucina MS (M+H, 298)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 3 µM

Ejemplo 61

3-cloro-4-metoxi-N-(pentan-3-il)benzamida



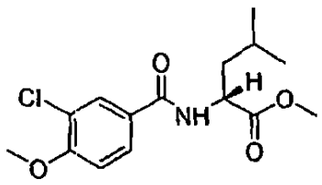
Preparado en una manera similar al ejemplo 4, utilizando 3-pentilamina y ácido 3-cloro-4-metoxibenzoico Rendimiento 40% MS (M+H, 256 20)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 56 µM y cuando se presenta en 0 3 µM mejora la efectividad del glutamato de monosodio con una relación de EC_{50}

de 6 28

Ejemplo 62

2-(3-cloro-4-metoxibenzamido)-4-metilpentanoato de (R)-metilo

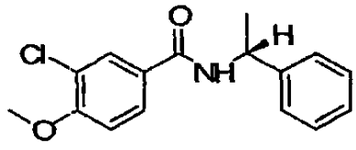


Preparado en una manera similar al ejemplo 4 utilizando el ácido 3-cloro-4-metoxibenzoico y clorhidrato de metilester de D-leucina MS (M+H 314 10)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 08 µM, y cuando se presenta en 0 01 µM mejora la efectividad del glutamato de monosodio con una relacion de EC_{50} de 13 18

Ejemplo 63

(R)-3-cloro-4-metoxi-N-(1-feniletil)benzamida

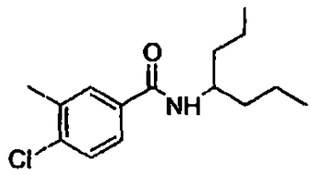


Preparado en una manera similar al ejemplo 4 utilizando la (R)-1-feniletanamina y el acido 3-cloro-4-metoxibenzoico MS (M+H, 290 0)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 3 µM mejoro la efectividad del glutamato de monosodio con una relación de EC_{50} de 2 7

Ejemplo 64

4-Cloro-3-metil-N-(1-propil-butil)-benzamida

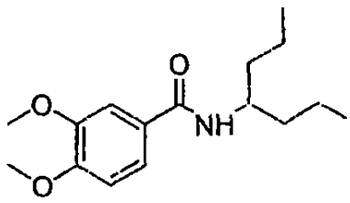


Preparado en una manera similar al ejemplo 4, utilizando el ácido 4-cloro-3 metilbenzoico y la heptan-4-amina MS (M+H 268)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 8 µM

Ejemplo 65

3 4-Dimetoxi-N-(1 propil-butil)-benzamida



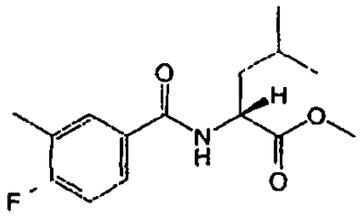
Preparado en una manera similar al ejemplo 4,

utilizando el ácido 3 4-dimetoxibenzoico y la heptan-4-amina MS (M+H, 279 37)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 36 µM

Ejemplo 66

2-(4-fluoro-3-metilbenzamido)-4-metilpentanoato de (R)-metilo

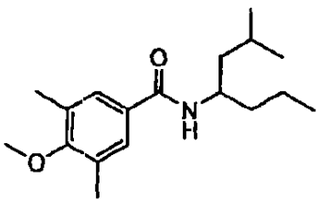


Preparado en una manera similar al ejemplo 4 utilizando el acido 4-fluoro-3-metilbenzoico y el metiléster de D-leucina MS (M+H, 282)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 32 µM

Ejemplo 67

4-metoxi-3 5-dimetil-N-(2-metilheptan-4-il)benzamida

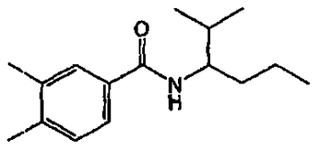


Preparado en una manera similar al ejemplo 4 utilizando el acido 4-metoxi-3,5-dimetilbenzoico y la 2-metilheptan-4-amina (ejemplo 2a) MS (M+H, 292 2)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 85 µM

Ejemplo 68

3 4-dimetil-N-(2-metilhexan-3-il)benzamida

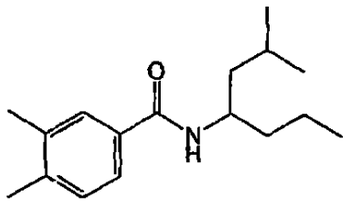


Preparado en una manera similar al ejemplo 4 utilizando el acido 3,4-dimetilbenzoico y la hexan-3-amina (ejemplo 3a) ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 94 (m, 9H) 1 39 (m 3H) 1 56 (m, 1H), 1 84 (m 1H) 2 30 (s, 3H), 2 31 (s, 3H), 4 04 (m, 1H) 5 76 (d 1H) 7 18 (d 1H), 7 46 (d, 1H) 7 55 (s 1H), MS (248, M+H)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 11 µM

Ejemplo 69

3 4-dimetil-N-(2-metilheptan-4-il)benzamida

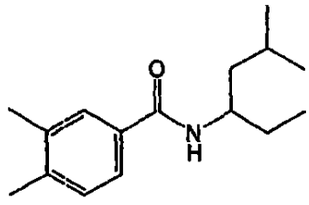


Preparado en una manera similar al ejemplo 4 utilizando el ácido 3 4-dimetilbenzoico y la 2-metilheptan-4-amina (ejemplo 2a) ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 94 (m, 9H), 1 40 (m 5H), 1 53 (m, 1H), 1 68 (m, 1H), 2 29 (s 3H), 2 30 (s, 3H), 4 24 (m 1H) 5 69 (d, 1H), 7 17 (d 1H) 7 46 (d, 1H), 7 54 (s 1H) MS (262, M+H)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 13 μM

Ejemplo 70

3,4-dimetil-N-(5-metilhexan-3-il)benzamida



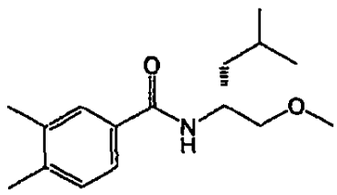
Preparado en una manera similar al ejemplo 4 utilizando el acido 3,4-dimetilbenzoico y la 5-metilhexan-3-amina (ejemplo 5a) ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 94 (m, 9H), 1 38 (m, 2H) 1 46

(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)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 17 µM

Ejemplo 71

(R)-N-(1-metoxi-4-metilpentan-2-il)-3,4-dimetilbenzamida



A una solución de la (R)-N-(1-hidroxi-4-metilpentan-2-il)-3,4-dimetilbenzamida (1 59 g 6 39 mmoles) (ejemplo 71a) en DMF seco (20 mL) se agregó NaOH pulverizado (281 mg, 7 mmoles) y la solucion se agitó a 0°C durante 2 horas Se agrego yodometano (1 equivalente, 6 39 mmoles) en DMF (10 mL) en gotas durante un periodo de 1 hora La temperatura se mantuvo a 0°C y la mezcla se agitó durante 1 hora La reacción se extinguió agregando 300 ml de agua La capa acuosa se extrajo con diclorometano, se secó sobre $MgSO_4$ y se evaporó El residuo se purifico por cromatografia instantánea en gel de silice (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%) ^1H NMR

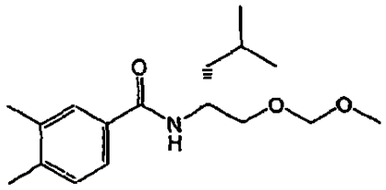
(500 MHz, $CDCl_3$) δ 0 94-0 97 (t, 6H), 1 41-1 47 (M, 1H), 1 54-1 60 (m, 1H), 1 64-1 68 (m, 1H) 2 29 (d, 6H) 3 36 (s, 3H) 3 45-3 50 (m, 2H), 4 34-4 39 (m, 1H), 6 23-6 25 (d, 1H), 7 16-7 17 (d 1H), 7 47-7 49 (dd, 1H), 7 56 (s, 1H) MS (M+H, 264 3)

a Se preparó la (R)-N-(1-hidroxi-4-metilpentan-2-il)-3,4-dimetilbenzamida en una manera similar como se describe en el ejemplo 4 utilizando el ácido 3 4-dimetilbenzoico y con (R)-aminoleucinol Rendimiento 75% MS (M+H 250 3)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 2 μM

Ejemplo 72

(R)-N-(1-(metoximetoxi)-4-metilpentan-2-il)-3,4-dimetilbenzamida



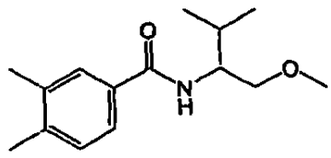
A una solucion de la (R)-N-(1-hidroxi-4-metilpentan-2-il)-3,4-dimetilbenzamida (Ejemplo 71a) (0 24 mmoles) disuelta en DMF seca (2 mL) se agregó a 0°C NaOH pulverizado (0 36 mmoles, 14 5 mg, 1 5 equivalentes) y la mezcla se agitó durante 1 hora a 0°C Luego se agregó cloro-metoxi-metano (19 3 μl 1 equivalente) y la reacción se agitó a 0°C durante

1 hora La reacción se extinguio con agua (30 mL) y la mezcla se extrajo con diclorometano La fase organica se secó sobre $MgSO_4$ y se evaporó El producto sin purificar se purifico por TLC preparativa (20% de acetato de etilo/hexanos) para dar 37 7 mg de la (R)-N-(1-(metoximetoxi)-4-metilpentan-2-il)-3 4-dimetilbenzamida (53%) ^{1}H 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)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 1 06 μM

Ejemplo 73

N-(1-Metoximetil-2-metil-propil)-3,4-dimetil-benzamida



Preparado en una manera similar al ejemplo 71 utilizando la N-(1-hidroxi-3-metilbutan-2-il)-3,4-dimetilbenzamida (ejemplo 73a) y el yoduro de metilo Rendimiento 87% ^{1}H 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-

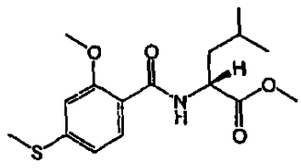
7 50 (dd, 1H), 7 56-7 57 (d, 1H) MS (M+H, 250)

a Se preparó N-(1-hidroxi-3-metilbutan-2-il)-3,4-dimetilbenzamida en una manera similar al ejemplo 71a utilizando el ácido 3,4-dimetoxibenzoico y el 2-amino-3-metilbutan-1-ol Rendimiento 75% MS (M+H 236 2)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 0 87 µM

Ejemplo 74

2-(2-metoxi-4-(metiltio)benzamido)-4-metilpentanoato de (R)-metilo

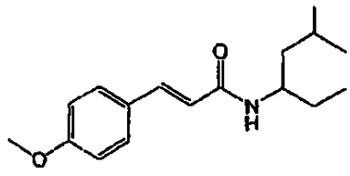


Preparado en una manera similar al ejemplo 4 utilizando el ácido 2-metoxi-4 (metiltio)benzoico y el metiléster de D-leucina MS (M+H, 326)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 15 8 µM

Ejemplo 75

N-(2-metilheptan-4-il)benzo[d][1,3]dioxol-5-carboxamida

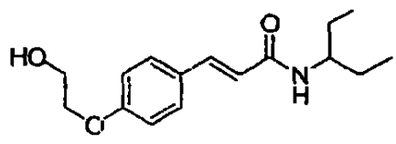


Preparado en una manera similar al ejemplo 4 utilizando el ácido 3-(4-metoxi-fenil)-acrilico y la 5-metilhexan-3-amina (ejemplo 5a) Rendimiento 59% ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 93 (m 9H), 1 33 (t, 2H) 1 43 (m 1H), 1 58-1 67 (m 2H), 3 83 (s, 3H), 4 11 (m, 1H), 5 19 (d, 1H) 6 25 (d 1H) 6 88 (d, 2H), 7 44 (d 2H) 7 58 (d, 1H) MS (276, M+H)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 24 µM

Ejemplo 76

N-(1-Etil-propil)-3-[4-(2-hidroxi-etoxi)-fenil]acrilamida



Se disolvió N-(1-etil-propil)-3-(4-hidroxi-fenil)-acrilamida (ejemplo 76a) (0 44 mmoles, 103 mg) en etanol absoluto con KOH (0 7 mmoles, 37 mg) La mezcla se agito a 80°C durante 1 hora Luego se agregó en gotas 2-cloro-etanol

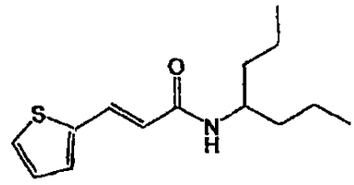
(1 76 mmoles, 118 µL) y la mezcla se llevó a reflujo durante la noche Despues de la evaporacion el producto sin purificar se disolvió en diclorometano y se lavo con agua y 5% de ácido citrico La fase organica se evaporo y el residuo se purificó por cromatografia en gel de silice para dar 73 mg del producto deseado (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 Se preparo N-(1-Etil-propil)-3-(4-hidroxi-fenil)-acrilamida en una manera similar como se describe en el ejemplo 4 a partir del ácido 4-hidroxi-cinámico y la 3-pentilamina MS (M+H, 234 10)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 5 8 µM

Ejemplo 77

(E)-N-(heptan-4-il) 3-(tiofen-2-il)acrilamida



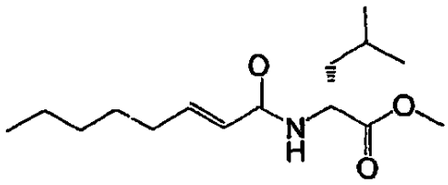
Preparado en una manera similar como se describe en

el ejemplo 4 a partir del ácido (E)-3-(tiofen-2-il)acrílico y la 4-heptilamina MS (M+H, 252)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 44 µM

Ejemplo 78

4-metil-2-oct-2-enamidopentanoato de (R,E)-metilo

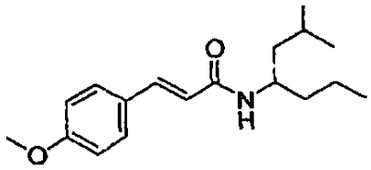


Preparado en una manera similar como se describe en el ejemplo 4 a partir del acido (E)-oct-2-enoico y el metiléster de D-leucina MS (M+H 270)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 92 µM

Ejemplo 79

3-(4-Metoxi-fenil)-N-(3-metil-1-propil-butil)-acrilamida



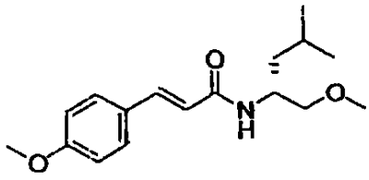
Preparado en una manera similar al ejemplo 4 utilizando el acido 3-(4-metoxi-fenil)-acrilico y la 3-metil-1-propil-butilamina

(ejemplo 2a) Rendimiento 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)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 1 84 µM

Ejemplo 80

N-(1-Metoximetil-3-metil-butil)-3-(4-metoxi-fenil)-acrilamida

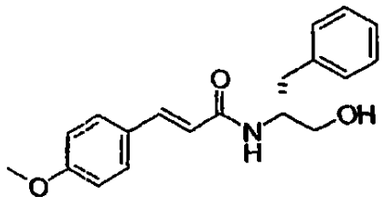


Preparado en una manera similar como se describe en el ejemplo 71 a partir del ácido 3-(4-metoxi-fenil)-acrilico y el D-leucinol Rendimiento 41% ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 93-0 96 (t 6H) 1 38-1 42 (m, 1H), 1 48-1 54 (m, 1H), 1 63-1 66 (m 1H) 3 36 (s 3H), 3 41-3 46 (m 2H), 3 82-3 83 (s, 3H), 4 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 tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 90 µM

Ejemplo 81

N-(1-Bencil-2-hidroxi-etil)-3-(4-metoxi-fenil)-acrilamida

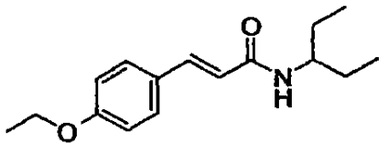


Preparado en una manera similar como se describe en el ejemplo 4 a partir del ácido 3-(4-metoxi-fenil)-acrílico y el D-fenilalaninol MS (M+H, 312 3)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 1 1 µM

Ejemplo 82

3-(4-Etoxi-fenil)-N-(1-etil-propil)-acrilamida

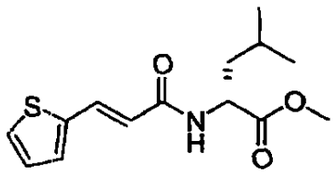


Preparado en una manera similar al ejemplo 4 utilizando el ácido 3-(4-etoxi-fenil)-acrilico y la 3-pentilamina MS (M+H, 262 2)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 1 35 µM

Ejemplo 83

Metiléster del ácido 4-metil-2-(3-tiofen-2-il-acriloilamino)-pentanoico

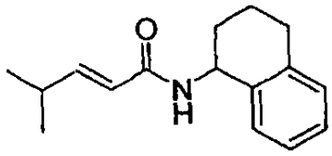


Preparado en una manera similar como se describe en el ejemplo 4 a partir del acido 3-tiofen-2-il-acrilico y el metiléster de D-leucina MS (M+H, 282 2)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 0 59 µM

Ejemplo 84

(1 2 3 4-tetrahidro-naftalen-1-il)-amida del acido 4-Metil-pent-2-enoico



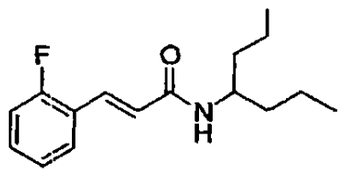
Preparado en una manera similar como se describe en el ejemplo 4 a partir del acido 4-metil-pent-2-enoico y la 1,2 3,4-tetrahidro-naftalen-1-ilamina MS (M+H, 244 2)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una línea celular

HEK293 de 1-5 µM

Ejemplo 85

3-(2-Fluoro-fenil)-N-(1-propil-butil)-acrilamida

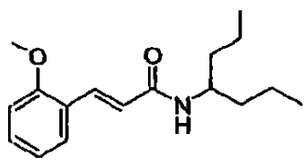


Preparado en una manera similar como se describe en el ejemplo 4 a partir del ácido 3-(2-fluoro-fenil)-acrílico y la 4-heptilamina MS (M+H, 264 2)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 16 µM

Ejemplo 86

3-(2-Metoxi-fenil)-N (1-propil-butil)-acrilamida



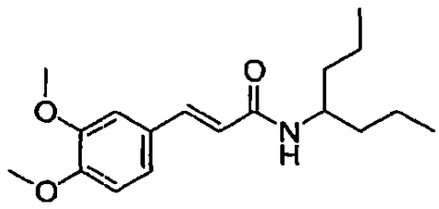
Preparado en una manera similar como se describe en el ejemplo 4 a partir del ácido 3-(2-metoxi-fenil)-acrílico y la 4-heptilamina MS (M+H, 276 2)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 90 µM

467.

Ejemplo 87

3-(3 4-Dimetoxi-fenil)-N-(1-propil-butil)-acrilamida

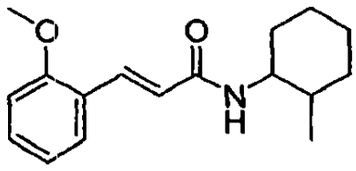


Preparado en una manera similar como se describe en el ejemplo 4 a partir del ácido 3-(3,4-dimetoxi-fenil)-acrilico y la 4-heptilamina MS (M+H, 306 2)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 97 µM y cuando se presenta en 0 3 µM mejora la efectividad del glutamato de monosodio con una relacion de EC_{50} de 2 4

Ejemplo 89

3-(2-Metoxi-fenil)-N-(2 metil-ciclohexil)-acrilamida



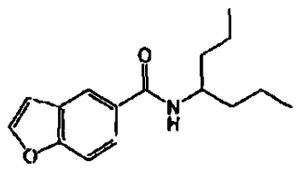
Preparado en una manera similar como se describe en el ejemplo 4 a partir del ácico 3-(2-metoxi-fenil)-acrilico y la 2-metil-ciclohexilamina MS (M+H 274 2)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular

HEK293 de 3 4 µM

Ejemplo 90

N-(heptan-4-il)benzofuran-4-carboxamida

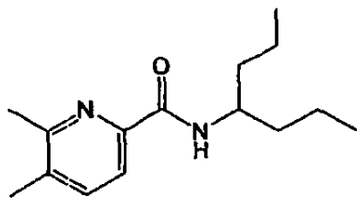


Preparado en una manera similar al ejemplo 4 utilizando el acido benzofuran-5-carboxilico y la heptan-4-amina Rendimiento 41% MS (M+H, 260 2)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 1 19 µM

Ejemplo 91

N-(heptan-4-il)-5 6-dimetilpicolinamida



Preparado en una manera similar al ejemplo 4, utilizando el ácido 5,6-dimetilpicolinico (Ejemplo 91a) y la 4-heptilamina Rendimiento 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)

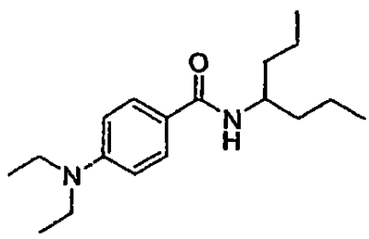
a ácido 5 6-Dimetilpicolinico Se llevó a reflujo 5 6-dimetilpicolinonitrilo (ejemplo 91b) en HCl concentrado (15 mL) durante la noche El solvente se evaporo y el residuo solido se co-evaporó varias veces con EtOH El secado proporciono 453 mg del ácido 5,6-Dimetilpicolinico (80%) como un solido blanco MS (M+H, 152 1)

b 5 6-dimetilpicolinonitrilo se llevó a reflujo la 2 3-lutidina (13 25 mmoles) durante la noche con 18 ml de AcOH glacial y 6 ml de peróxido de hidrógeno El solvente se evaporó y el residuo se co-evaporó dos veces con agua se basificó con Na_2CO_3 y se extrajo con cloroformo La capa orgánica se seco sobre Na_2SO_4 y se evaporó para dar 1 45 g de un producto cristalino El producto (615 mg, 5 mmoles) se hizo reaccionar con trimetilsilano carbonitrilo (5 5 mmoles) en diclorometano (10 mL) a temperatura ambiente durante 5 minutos seguido por la adicion de cloruro de dimetilcarbamoilo (5 mmoles) y la solucion se agito a temperatura ambiente durante 3 dias La mezcla de reaccion se trató con 10% de carbonato de potasio (10 mL), la capa orgánica se separo y la capa acuosa se extrajo 2 veces con diclorometano La fase orgánica se secó sobre Na_2SO_4 y se evaporó para dar 495 mg del 5 6-dimetilpicolinonitrilo (75%) ^1H 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)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 2 98 µM

Ejemplo 92

4-(dietilamino)-N-(heptan-4-il)benzamida



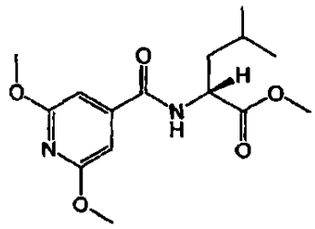
Preparado en una manera similar al ejemplo 4 utilizando el acido 4-dietilaminobenzoico y la 4-heptilamina (31%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 92 (t, 6H *J* = 7 17 Hz) 1 18 (t 6H *J*= 7 04 Hz) 1 41 (m, 4H), 1 55 (m, 4H), 3 39 (m, 4H), 4 15 (m, 1H) 5 62 (m 1H), 6 64 (d, 2H *J*= 10 26Hz), 7 64 (d 2H, *J*= 10 26 Hz) MS (M+H, 291)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 7 6 µM

471

Ejemplo 93

2-(2 6-dimetoxiisonicotinamido)-4-metilpentanoato de (R)-metilo

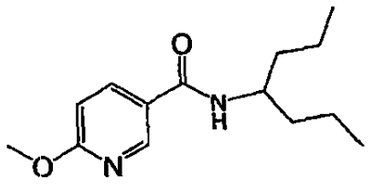


Preparado en una manera similar al ejemplo 4 utilizando el acido 2,6-Dimetoxi-isonicotínico y el metilester de D-leucina ^{1}H NMR (500 MHz $CDCl_3$) δ 0 92 (d, 3H, *J*=7 27 Hz), 0 93 (d, 3H *J*= 7 26 Hz), 1 41-1 58 (m, 8H), 3 95 (s, 3H), 4 08 (s, 3H) 4 15 (m 1H), 6 43 (d, 1H, *J*= 8 32 Hz) 7 47 (m amplio, 1H), 8 41 (d, 1H, *J*= 8 34 Hz) MS (M+H, 311)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 1 91 μM

Ejemplo 94

N-(heptan-4-il)-6-metoxinicotinamida



Preparado en una manera similar al ejemplo 4 utilizando 6-metoxinicotinato de sodio (ejemplo 94a) y 4-heptilamina

472.

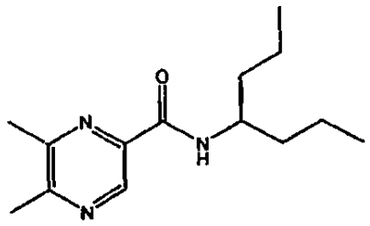
Rendimiento 44% MS (M+H 251)

a se disolvió el 6-metoxinicotinato de metilo (2 097 g, 12 56 mmoles) en dioxano (30 mL) Una solución acuosa de NaOH (1 0 N 25 mL) se agregó a la solucion y la mezcla se agitó a temperatura ambiente durante la noche El solvente se removió bajo presión reducida para proporcionar 2 2 g del 6-metoxinicotinato de sodio

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 2 66 µM

Ejemplo 95

(1-propilbutil)amida del ácido 5 6-dimetilpirazin-2-carboxilico



Preparado en una manera similar al ejemplo 4 utilizando el acido 5,6-dimetil-pirazin-2-carboxílico (ejemplo 95a) y la 4-heptilamina ^{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)

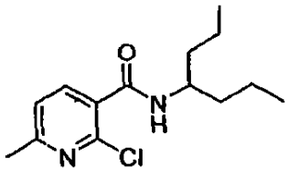
a Ácido 5,6-dimetil-pirazin-2-carboxilico A una solución del ácido 2 3-diaminopropiónico (1 0 g, 9 6 mmoles) en

metanol (20 mL) se agrego butan-2,3-diona (728 µL 11 5 mmoles) y NaOH (1 4 g, 56 6 mmoles) La mezcla se llevó a reflujo durante 2 horas y luego se enfrio a temperatura ambiente mientras que el aire se burbujeaba hasta el final durante 1 hora El precipitado blanco se filtró y el producto gelatinoso se concentró bajo vacio El producto sin purificar se removio en diclorometano, se lavó con 10% de ácido citrico se secó sobre $MgSO_4$ y se filtró El solvente se removio bajo presión reducida para dar el ácido 5,6-dimetil-pirazin-2-carboxilico como un sólido volatil El compuesto se utilizó como está en la siguiente etapa

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 1 01 µM

Ejemplo 96

2-cloro-N-(heptan-4-il)-6-metilnicotinamida

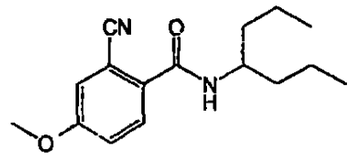


Preparado en una manera similar al ejemplo 4, utilizando el acido 2-cloro-6-metilnicotinico y la 4-heptilamina MS (M+H 269)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 3 9 µM

Ejemplo 97

2-ciano-N-(heptan-4-il)-4-metoxibenzamida

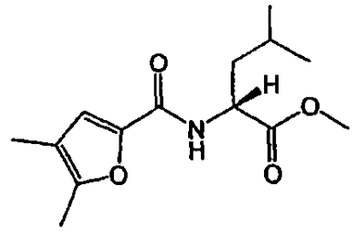


Preparado en una manera similar el ejemplo 4 utilizando el acido 2-ciano-4-metoxibenzoico y la 4-heptilamina Rendimiento 73% ^{1}H NMR (CD_3OD) δ 0 94 (t, 6H, *J*= 7 3 Hz) 1 38 (m, 4H), 1 53 (m, 4H), 4 02 (s, 3H), 4 12 (m, 1H), 7 27 (d 1H *J*= 9 40 Hz), 8 11 (d, 2H, *J* = 2 21 Hz) MS (M+H, 275)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 1 39 µM, y cuando se presenta en 1 µM mejora la efectividad del glutamato de monosodio con una relacion de EC_{50} de 4 52

Ejemplo 98

2-(2 3-dimetilfuran-5-carboxamido)-4-metilpentanoato de (R)-metilo



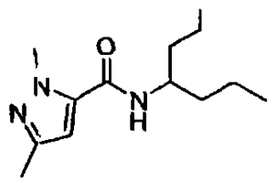
Preparado en una manera similar al ejemplo 4 utilizando el ácido 4 5-dimetil-furan-2-carboxílico y metiléster de D-leucina

Rendimiento 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)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 59 µM

Ejemplo 99

N-(heptan-4-il)-1 3-dimetil-1H-pirazol-5-carboxamida

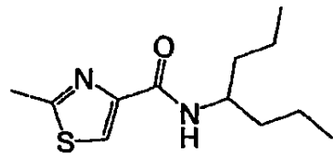


Preparado en una manera similar al ejemplo 4, utilizando el ácido 1 3-dimetil-1H-pirazol-5-carboxílico y 4-heptilamina ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 90 (t, 6H, *J*= 7 2 Hz) 1 41 (m 4H), 1 50 (m, 4H) 2 27 (s 3H), 3 77 (s, 3H) 4 09 (m 1H), 6 49 (d, 1H), 6 53 (s 1H) MS (M+H, 238)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 7 8 µM

Ejemplo 100

N-(heptan-4-il)-2-metiltiazol-4-carboxamida

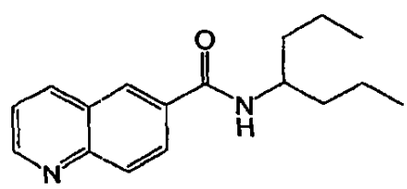


Preparado en una manera similar al ejemplo 4, utilizando el ácido 1,3-dimetil-1H-pirazol-5-carboxílico y la 4-heptilamina MS (M+H, 241)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 7 2 µM

Ejemplo 101

N-(heptan-4-il)quinolin-6-carboxamida

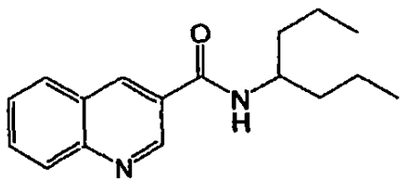


Preparado en una manera similar al ejemplo 4 utilizando el acido quinolin-6-carboxilico y la 4-heptilamina ^1H NMR (500 MHz $CDCl_3$) δ 0 96 (t, *J*= 7 2 Hz 6H), 1 42-1 58 (m, 6H) 1 62-1 70 (m 2H), 4 18-4 20 (m, 1H) 5 95 (d, *J*= 9 0 Hz 1H), 7 49 (br s 1H), 8 04 (dd, *J* = 8 5, 1 5 Hz 1H), 8 17 (d, *J*= 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)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 3 2 µM

Ejemplo 102

N-(heptan-4-il)quinolin-3-carboxamida

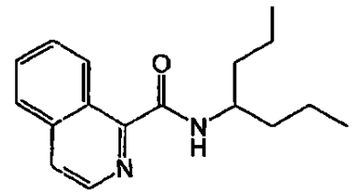


Preparado en una manera similar al ejemplo 4 utilizando el ácido quinolin-3-carboxílico y la heptilamina ^{1}H NMR (500 MHz $CDCl_3$) δ 0 96 (t *J*= 7 3 Hz 6H) 1 40-1 58 (m, 6H) 1 60-1 67 (m, 2H) 4 20-4 30 (m, 1H), 6 01 (d, *J*= 8 8 Hz, 1H), 7 61 (t *J*= 7 5,1H), 7 80 (t, *J*= 7 6 Hz 1H), 7 90 (d, *J*= 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)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 15 8 µM

Ejemplo 103

N-(heptan-4-il)isoquinolin-1-carboxamida

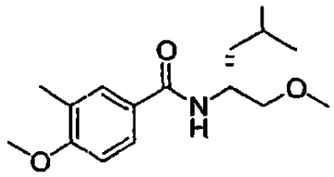


Preparado en una manera similar al ejemplo 4 utilizando el acido isoquinolin-1-carboxilico y heptamina ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 98 (t, *J*= 7 05 Hz, 6H), 1 42-1 56 (m, 6H), 1 58-1 66 (m, 2H), 4 20-4 32 (m, 1H), 5 83 (d, *J*= 9 1 Hz, 1H), 7 36 (d *J*= 4 2 1H) 7 60 (t, *J*= 7 7 Hz, 1H), 7 75 (t, *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

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 14 2 μM

Ejemplo 104

4-Metoxi-N-(1-metoximetil-3-metil-butil)-3-metil-benzamida



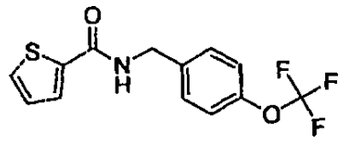
Preparado en una manera similar como se describe en el ejemplo 71 a partir del ácido 4-metoxi-3-metilbenzoico y D-leucinol Rendimiento 86% ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 94-

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)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 0 24 µM

Ejemplo 105

N-(4-(trifluorometoxi)bencil)tiofen-2-carboxamida

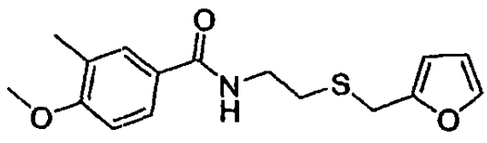


Preparado en una manera similar como se describe en el ejemplo 4 a partir del ácido tiofen-2-carboxílico y la (4-(trifluorometoxi)fenil)metanamina MS (M+H 303)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 2 4 µM

Ejemplo 106

N-(2-(furan-2-ilmetiltio)etil)-4-metoxi-3-metilbenzamida

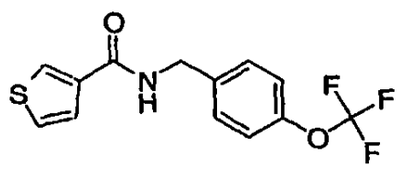


Preparado en una manera similar como se describe en el ejemplo 4 a partir del ácido 4-metoxi-3-metilbenzoico y la 2-(furan-2-ilmetiltio)etanamina Rendimiento 58% ^{1}H NMR (500 MHz, $CDCl_3$) 2 23 (s 3H), 2 76 (t 2H, *J*= 6 37 Hz), 3 59 (q, 2H, *J*= 12 2 Hz), 3 76 (s, 2H) 3 86 (s, 3H), 6 22 (dd, 1H, *J*= 3 49 Hz, *J*= 2 67 Hz), 6 30 (dd, 1H, *J*= 3 04 Hz, *J*= 1 78 Hz), 6 46 (m, 1H, 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 tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 5 6 µM

Ejemplo 107

4-trifluorometoxi-bencilamina del ácido tiofen-3-carboxilico



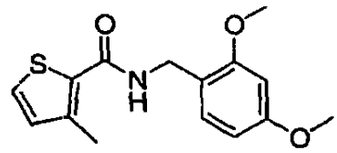
Preparado en una manera similar al ejemplo 4 utilizando el ácido tiofen-3-carboxílico y 4-trifluorometoxi-bencilamina MS (M+H, 302 0)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 2 2 µM, y cuando se presenta en 3 µM mejora la

efectividad del glutamato de monosodio con una relacion de EC_{50} de 8 5

Ejemplo 108

2 4-dimetoxi-bencilamina de 3-metil-tiofen-2-carboxilico

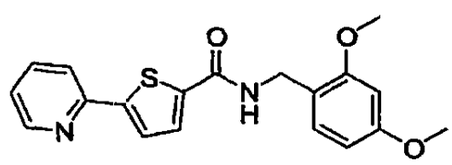


Preparado en una manera similar al ejemplo 4 utilizando ácido 3-metil-tiofen-2-carboxilico y 2,4-dimetoxi-bencilamina MS (M+H 292 2)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 5 6 µM y cuando se presenta en 3 µM mejora la efectividad del glutamato de monosodio con una relación de EC_{50} de 5 8

Ejemplo 109

2 4-Dimetoxi-bencilamida de 5-piridin-2-il-tiofen-2-carboxilico

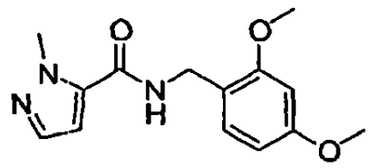


Preparado en una manera similar al ejemplo 4 utilizando el ácido 5-piridin-2-il-tiofen-2-carboxílico y 2 4-dimetoxi-bencilamina MS (M+H, 355 2)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 2 86 µM, y cuando se presenta en 3 µM mejora la efectividad del glutamato de monosodio con una relación de EC_{50} de 8

Ejemplo 110

2 4-dimetoxi-bencilamida del acido 2-Metil-2H-pirazol-3-carboxílico

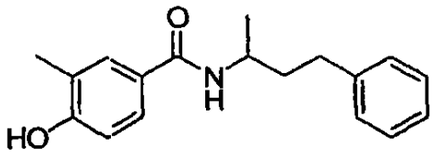


Preparado en una manera similar al ejemplo 4 utilizando ácido 2-metil-2H-pirazol-3-carboxílico y 2,4-dimetoxi-bencilamina MS (M+H, 276 2)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 6 µM y cuando se presenta en 3 µM mejora la efectividad del glutamato de monosodio con una relacion EC_{50} de 7 9

Ejemplo 111

4-Hidroxi-3-metil-N-(1-metil-3-fenil-propil)-benzamida

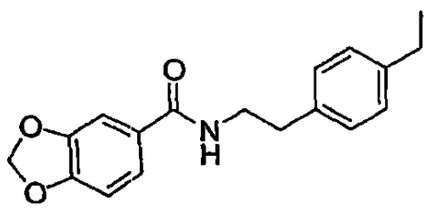


Preparado en una manera similar al ejemplo 4 utilizando el acido 4-hidroxi-3-metil-benzoico y 1-metil-3-fenil-propilamina MS (M+H, 284 2)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 2 7 µM, y cuando se presenta a 0 3 µM mejora la efectividad del glutamato de monosodio con una relación EC_{50} de 7

Ejemplo 112

[2-(4-etil-fenil)-etil]-amida del acido benzo[1,3]dioxol-5-carboxílico



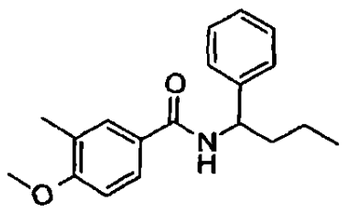
Preparado en una manera similar al ejemplo 4 utilizando el ácido benzo[1,3]dioxol-5-carboxílico y la 2-(4-etil-fenil)-etilamina MS (M+H, 298 2)

El compuesto tuvo una EC_{50} para la activación de un

receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 3 86 µM

Ejemplo 113

4-Metoxi-3-metil-N-(1-fenil-butil)-benzamida

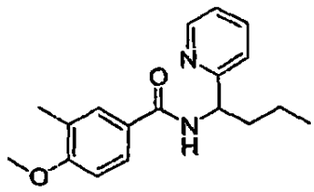


Preparado en una manera similar al ejemplo 4, utilizando el ácido 4-metoxi-3-metil-benzoico y la 1-fenil-butilamina MS (M+H, 298 2)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 2 5 µM

Ejemplo 114

4-Metoxi-3-metil-N-(1 piridin-2-il-butil)-benzamida



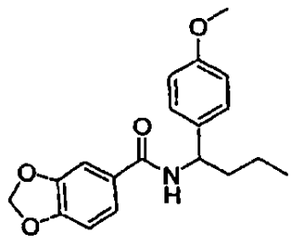
Preparado en una manera similar al ejemplo 4 utilizando el acido 4-metoxi-3-metil-benzoico y la 1-piridin-2-il-butilamina ^1H NMR (500 MHz, $CDCl_3$) δ 0 9 l-0 92 (t, 3H), 1 25-1 3 (m, 2H, 1 85-

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 tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 1 54 µM

Ejemplo 115

[1-(4-metoxi-fenil)-butil]-amida del acido Benzo[1,3]dioxol-5-carboxilico

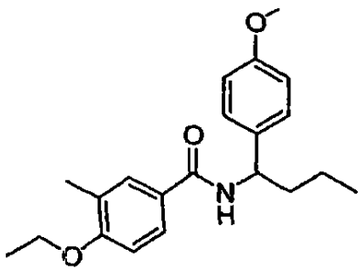


Preparado en una manera similar al ejemplo 4, utilizando el ácido benzo[1,3]dioxol-5-carboxilico y la 1-(4-metoxi-fenil)-butilamina ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 93-0 95 (t, 3H), 1 30-1 39 (m 2H) 1 80-1 90 (m 2H), 3 79 (s, 3H), 5 08-5 09 (dd 1H), 6 00 (s, 2H), 6 10-6 12 (d, 1H), 6 79-6 80 (d, 1H) 6 87 (s 1H), 6,88 (s 1H), 7 25-7 28 (m, 4H) MS (M+H, 328 1)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 4 12 µM

Ejemplo 116

4-Etoxi-N-[1-(4-metoxi-fenil)-butil]-3-metil-benzamida

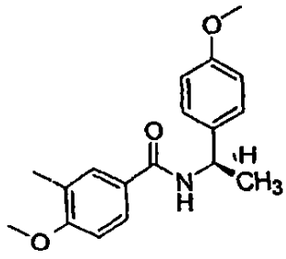


Preparado en una manera similar al ejemplo 4, utilizando el ácido 4-etoxi-3-metil-benzoico y la 1-(4-metoxi-fenil)-butilamina ^{1}H NMR (500 MHz $CDCl_3$) δ 0 93-0 96 (t, 3H), 1 31-1 41 (m, 2H), 1 41-1 45 (t, 3H), 1 82-1 92 (m 2H), 2 28 (s 3H) 3 79 (s, 3H), 4 04-4 08 (q 2H) 5 10-5 12 (d 1H), 6 12-6 14 (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)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 3 9 μM

Ejemplo 117

4-Metoxi-N-[1-(R)-(4-metoxi-fenil)-etil]-3-metil-benzamida

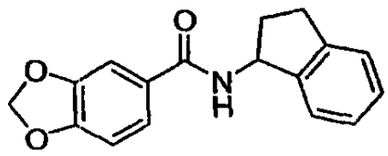


Preparado en una manera similar al ejemplo 4 utilizando el acido 4-metoxi-3-metil-benzoico y la 1-(R)-(4-metoxi-fenil)-etilamina MS (M+H 300 1)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 2 8 µM

Ejemplo 118

Indan-1-ilamida del acido Benzo[1,3]dioxol-5-carboxilico

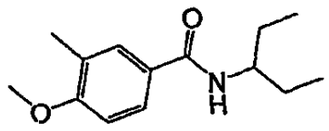


Preparado en una manera similar al ejemplo 4 utilizando el ácido benzo[1 3]dioxol-5-carboxilico e indan-1-ilamina MS (M+H, 282 2)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 1 2 µM, y cuando se presenta en 0 3 µM mejora la efectividad del glutamato de monosodio con una relación de EC_{50} de 5 33

Ejemplo 119

4-metoxi-3-metil-N-(pentan-3-il)benzamida

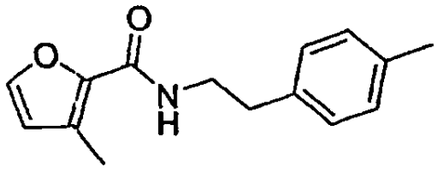


Preparado en una manera similar como se describe en el ejemplo 4, a partir del ácido 4-metoxi-3-metilbenzoico y la pentan-3-amina MS (M+H, 236)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 4 µM

Ejemplo 120

3-metil-N-(p-toliletil)furan-2-carboxamida

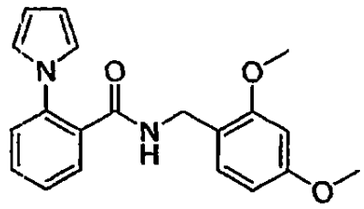


Preparado en una manera similar como se describe en el ejemplo 4 a partir del ácido 3-metilfuran-2-carboxilico y de la 2-p-toliletanamina MS (M+H, 244)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 6 µM, y cuando se presenta en 1 µM mejora la efectividad del glutamato de monosodio con una relación de EC_{50} de 3 3

Ejemplo 121

N-(2 4-dimetoxibencil)-2-(1H-pirrol-1-il)benzamida



Preparado en una manera 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 tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 1 66 µM y cuando se presenta en 1 µM mejora la efectividad del glutamato de monosodio con una relación de EC_{50} de 11

Los compuestos "amida adicionales que se sintetizaron y probaron experimentalmente y se encontro que tienen un nivel relativamente elevado de efectividad como un activador de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 Los resultados de esa prueba se muestran posteriormente en la Tabla A

Tabla A Amidas Acres

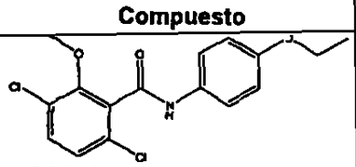
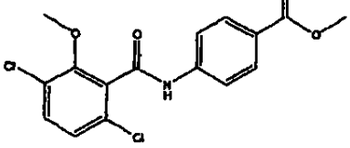
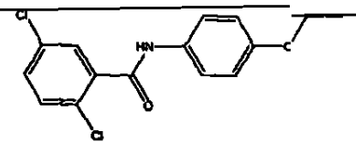
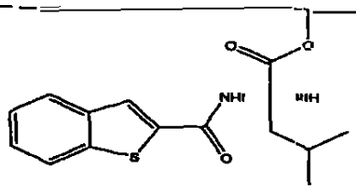
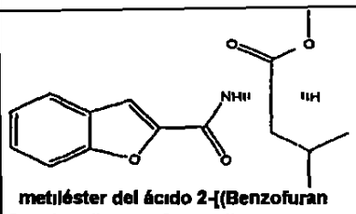
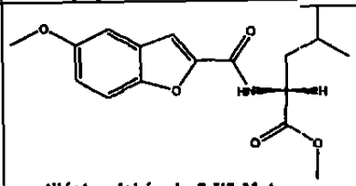
Compuesto No	Compuesto	EC_{50} Acre (uM)	relación EC_{50} (contra MSG)	@ (uM)
A1	 3 6-Dicloro-N (4-etoxi fenil)-2 metiloxi-benzamida	0 22	2 74	1
A2	 metiléster del ácido 4-(3 6-Dicloro-2 metoxi-benzoilamino)-benzoi o	0 93	6 98	0 01
A3	 2 5-dicloro N-(4-etoxifenil)benzamida	1 08	6 14	0 03
A4	 metilester del ácido 2-[(Benzo[b]tiofen-2 carbonil)-amino]-4-metil pentanoico	0 4		
A5	 metiléster del ácido 2-[(Benzofuran 2-carbonil)-amino]-4-metil pentanoico	0 31		
A6	 metiléster del ácido 2-[(5 Metoxi benzofuran-2-carbonil)-amino]-4-metil-pentanoico	0 32	2 86	1

Tabla A Amidas Acres

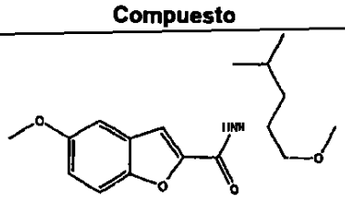
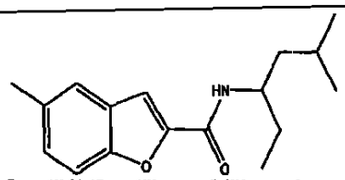
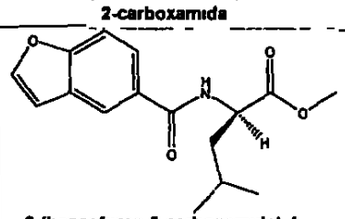
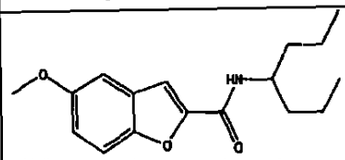
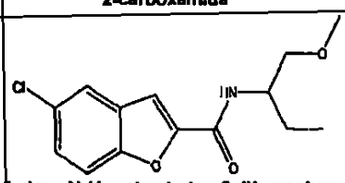
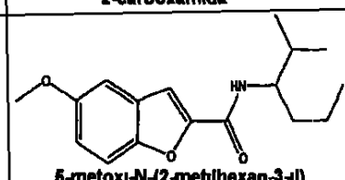
Compuesto No	Compuesto	EC_{50} Acre (uM)	relación EC_{50} (contra MSG)	@ (uM)
A7	 (R)-5-metoxi-N-(1-metoxi-4-metilpentan 2-il)benzofuran 2-carboxamida	0 46		
A8	 5-metil-N-(5-metilhexan-3-il)benzofuran 2-carboxamida	0 5		
A9	 2-(benzofuran-5-carboxamido)-4 metilpentanoato de metiléster(R)-metilo del ácido 2-[(Benzofuran-5-carbonil) amino]-4-metil-pentanoico	0 71		
A10	 N-(heptan-4-il)-5-metoxibenzofuran 2-carboxamida	0 91	4 5t	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		

Tabla A Amidas Acres

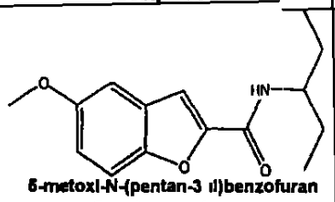
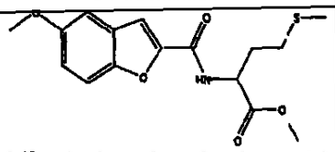
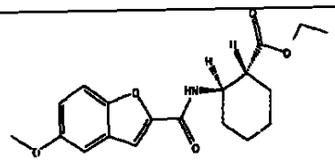
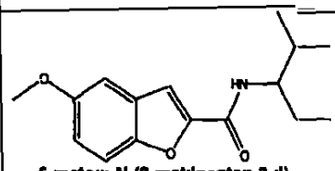
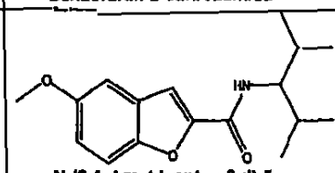
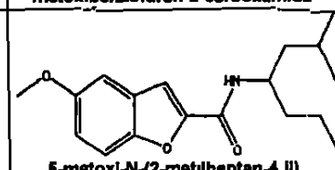
Compuesto No	Compuesto	EC_{50} Acre (uM)	relación EC_{50} (contra MSG)	@ (uM)
A13	 5-metoxi-N-(pentan-3-il)benzofuran 2-carboxamida	1 14	4 46	1
A14	 2-(6-metoxibenzofuran-2-carboxamido) 4-(metiltio)butanoato de metilo del metiléster del ácido 2-[(6 Metoxi benzofuran-2-carbonil)-amino]-4 metilsulfanil-butírico	1 14		
A15	 2-(6-metoxibenzofuran-2-carboxamido) ciclohexancarboxilato de (1R 2R)-etilo	1 14		
A16	 6-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 Acres

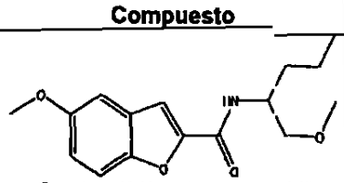
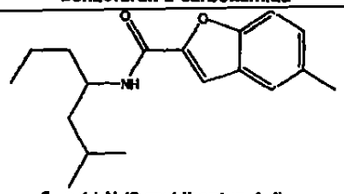
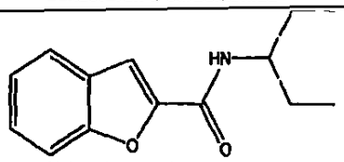
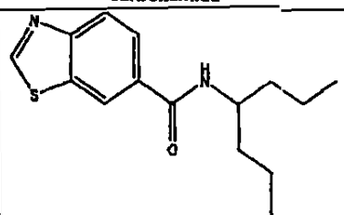
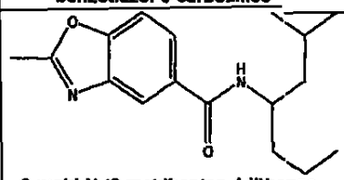
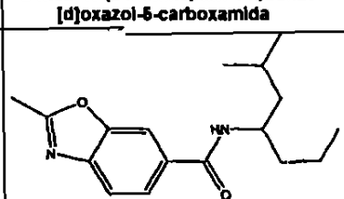
Compuesto No	Compuesto	EC_{50} Acre (uM)	relación EC_{50} (contra MSG)	@ (uM)
A19	 6-metoxi-N-(1-metoxipentan 2-il) benzofuran 2-carboxamida	1 3		
A20	 6-metil-N-(2-metilheptan-4 il) benzofuran 2-carboxamida	1 32		
A21	 N-(pentan-3-il)benzofuran-2 carboxamida	1 52	3 74	1
A22	 (1 propil-butil)-amida del ácido benzotiazol-6-carboxílico	1 58		
A23	 2-metil-N (2-metilheptan-4-il)benzo [d]oxazol-5-carboxamida	0 38		
A24	 2-metil-N-(2-metilheptan-4-il)benzo [d]oxazol-6-carboxamida	1 12		

Tabla A Amidas Acres

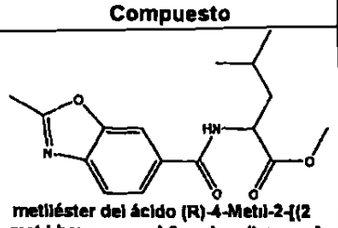
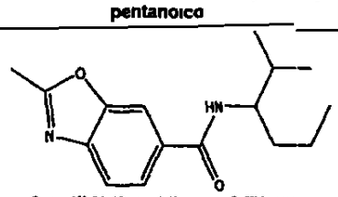
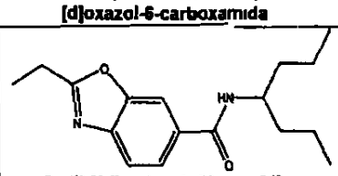
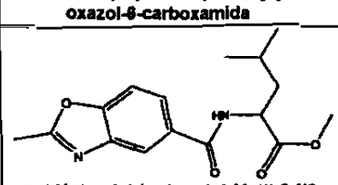
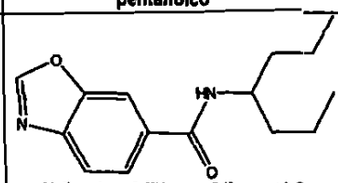
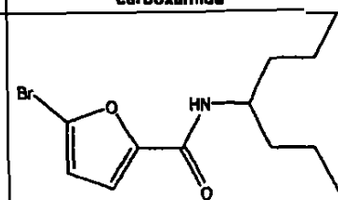
Compuesto No	Compuesto	EC_{50} Acre (uM)	relación EC_{50} (contra MSG)	@ (uM)
A25	 metiléster del ácido (R)-4-Metil-2-[(2 metil-benzooxazol-6-carbonil)-amino] pentanoico	1 48		
A26	 2-metil-N-(2-metilhexan-3-il)benzo [d]oxazol-6-carboxamida	1 6		
A27	 2-etil N-(heptan-4-il)benzo[d] oxazol-6-carboxamida	1 61		
A28	 metiléster del ácido (R)-4-Metil-2-[(2 metil-benzooxazol-6-carbonil)-amino] pentanoico	1 69		
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

Tabla A Amidas Acres

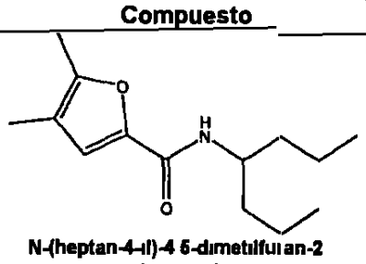
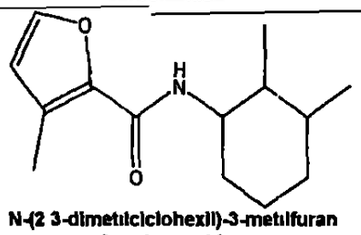
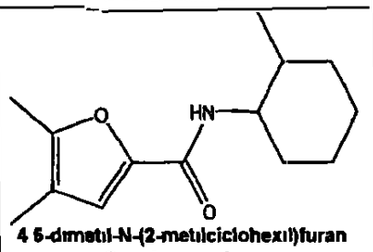
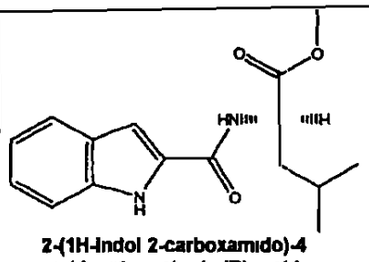
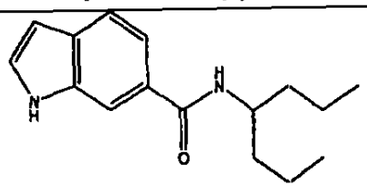
Compuesto No	Compuesto	EC_{50} Acre (uM)	relación EC_{50} (contra MSG)	@ (uM)
A31	 N-(heptan-4-il)-4 5-dimetilfuran-2 carboxamida	0 62	10 04	1
A32	 N-(2 3-dimetilciclohexil)-3-metilfuran 2-carboxamida	1 15		
A33	 4 5-dimetil-N-(2-metilciclohexil)furan 2-carboxamida	1 33		
A34	 2-(1H-Indol 2-carboxamido)-4 metilpentanoato de (R)-metilo	0 53		
A35	 N-(heptan-4 il) 1H-Indol-6-carboxamida	0 82	8 81	1

Tabla A Amidas Acres

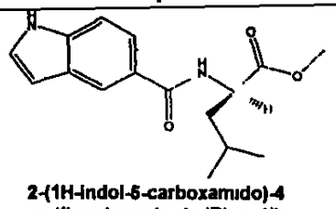
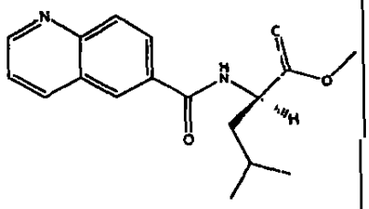
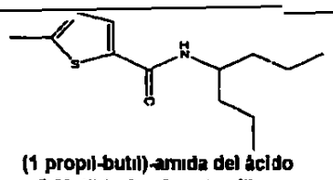
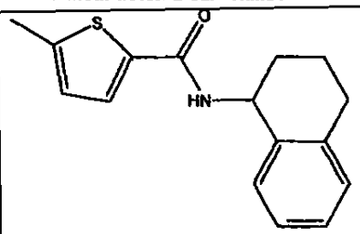
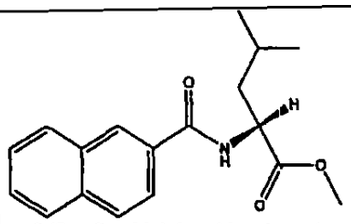
Compuesto No	Compuesto	EC_{50} Acre (uM)	relación EC_{50} (contra MSG)	@ (uM)
A36	 2-(1H-indol-5-carboxamido)-4 metilpentanoato de (R)-metilo	1 01		
A37	 4-metil-2-(quinolin-6-carboxamido) pentanoato de (R)-metilo	1 5		
A38	 (1 propil-butil)-amida del ácido 5 Metil-tiofen-2-carboxílicc	1 22	6 54	1
A39	 (1 2 3 4-tetrahidro-naftalen 1 il)-amida del ácido 5 Metil-tiofen 2-carboxílico	1 31	2 3	1
A40	 2-(2-naftamido)-4-metilpentanoato de (R)-metilo	0 37		

Tabla A Amidas Acres

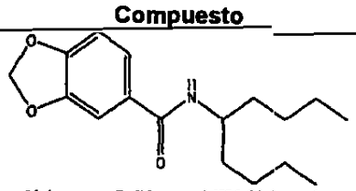
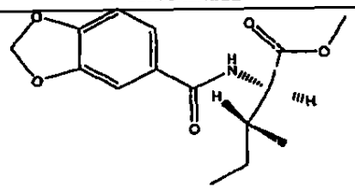
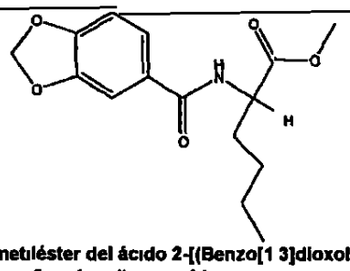
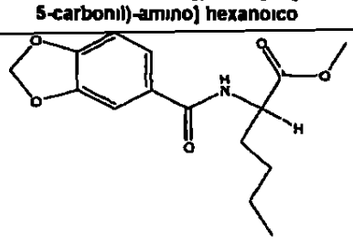
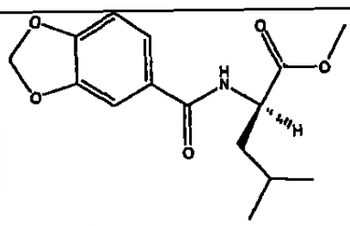
Compuesto No	Compuesto	EC_{50} Acre (uM)	relación EC_{50} (contra MSG)	@ (uM)
A41	 N (nonan-5-il)benzo[d][1,3]dioxol 5-carboxamida	0 7	2 14	3
A42	 2-(benzo[d][1 3]dioxol-5-carboxamido) 3-metilpentanoato de (2R 3R) metilo	0 35		
A43	 metiléster del ácido 2-[(Benzo[1 3]dioxol 5-carbonil)-amino] hexanoico	0 49		
A44	 metiléster del ácido (R)-2-[(Benzo[1 3] dioxol-5-carbonil) amino] hexanoico	0 61		
A45	 2-(benzo[d][1 3]dioxol-5-carboxamido) 4-metilpentanoato de (R)-etilo	0 88		

Tabla A Amidas Acres

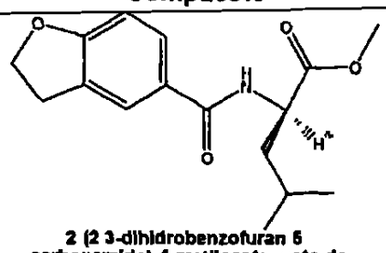
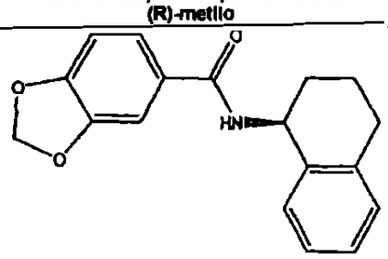
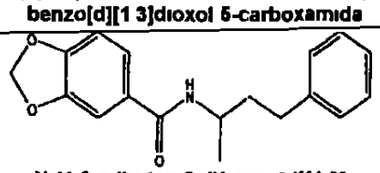
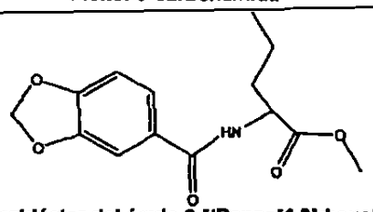
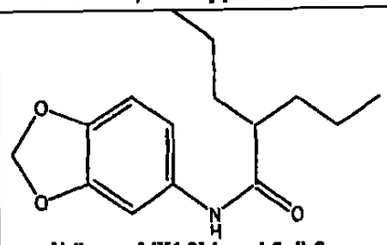
Compuesto No	Compuesto	EC_{50} Acre (uM)	relación EC_{50} (contra MSG)	@ (uM)
A46	 2 (2 3-dihidrobenzofuran 5 carboxamido)-4-metilpentanoato de (R)-metilo	1 32		
A47	 (S)-N (1,2,3 4 tetrahidronaftalen 1 il) benzo[d][1 3]dioxol 5-carboxamida	1 33	6 42	0 1
A48	 N-(4-fenilbutan 2-il)benzo[d][1 3] dioxol-5-carboxamida	1 51	9 27	1
A49	 metiléster del ácido 2-[(Benzo[1 3]dioxol 5-carbonil)-amino]-pentanoico	1 54	9 53	1
A50	 N-(benzo[d][1 3]dioxol-5 il) 2 propilpentanamida	1 57		

Tabla A Amidas Acres

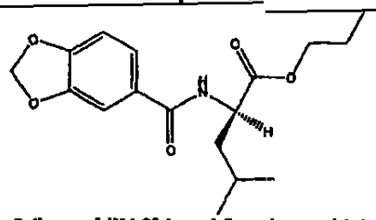
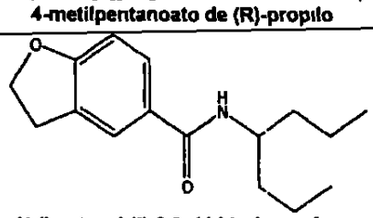
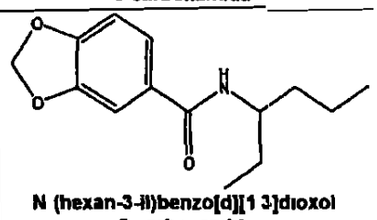
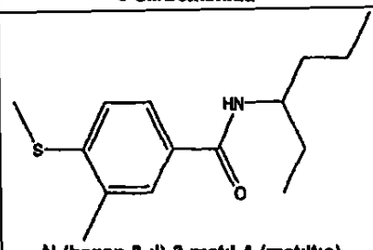
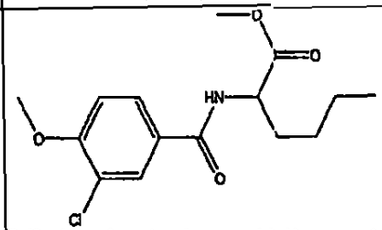
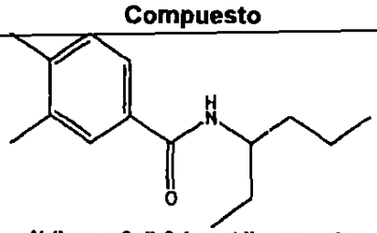
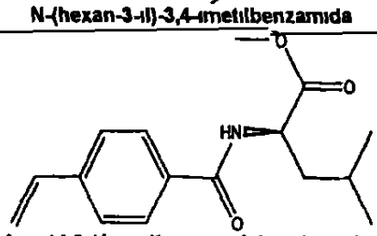
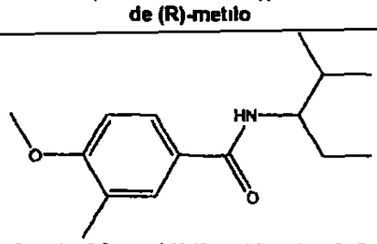
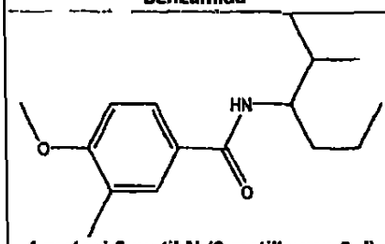
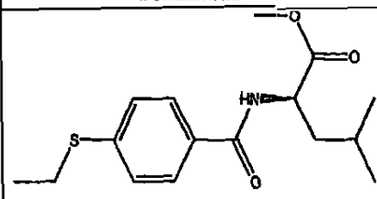
Compuesto No	Compuesto	EC_{50} Acre (uM)	relación EC_{50} (contra MSG)	@ (uM)
A51	 2-(benzo[d][1 3]dioxol-5-carboxamido) 4-metilpentanoato de (R)-propilo	1 58		
A52	 N-(heptan-4-il) 2 3-dihidrobenzofuran 5-carboxamida	1 65		
A53	 N (hexan-3-il)benzo[d][1 3]dioxol 5-carboxamida	1 83		
A54	 N-(hexan-3-il)-3-metil-4 (metiltio) benzamida	0 12		
A55	 2-(3-cloro-4-metoxibenzamido)hexanoato de metilo	0 12		

Tabla A Amidas Acres

Compuesto No	Compuesto	EC_{50} Acre (uM)	relación EC_{50} (contra MSG)	@ (uM)
A56	 N-(hexan-3-il)-3,4-metilbenzamida	0 14		
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 metilpentanoato de (R)-metilo	0 2		

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Tabla A Amidas Acres

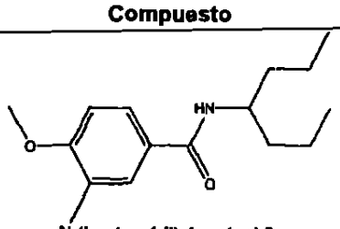
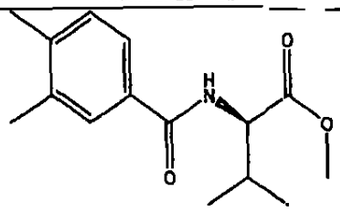
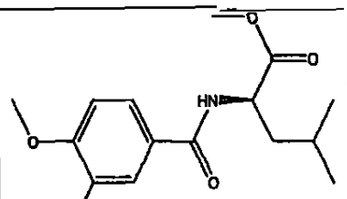
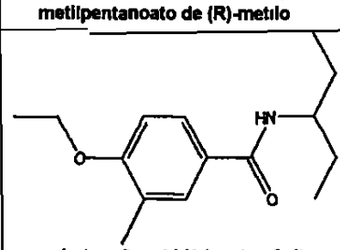
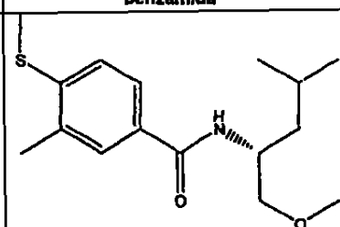
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A61	 N (heptan-4-il)-4-metoxi-3 metilbenzamida	0 22		
A62	 2-(3,4-dimetilbenzamido)-3 metilbutanoato de (R)-metilo	0 25		
A63	 2-(4-metoxi-3-metilbenzamido) 4-metilpentanoato de (R)-metilo	0 25		
A64	 4-etoxi-3-metil-N-(pentan-3-il) benzamida	0 26		
A65	 (R)-N-(1-metoxi-4-metilpentan 2-il) 3-metil-4-(metiltio)benzamida	0 29		

Tabla A Amidas Acres

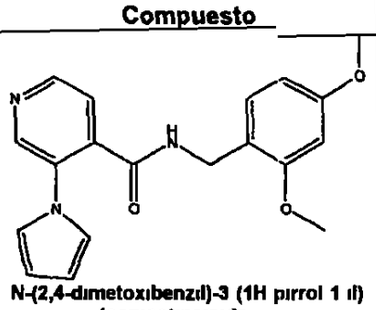
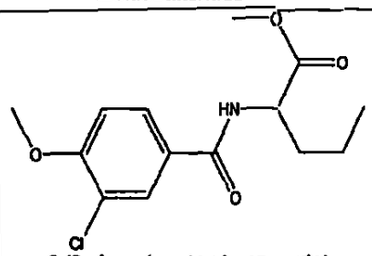
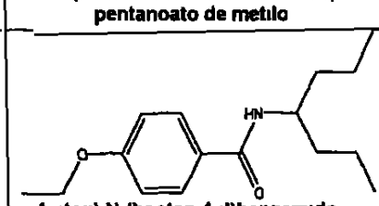
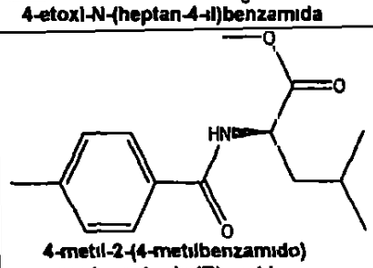
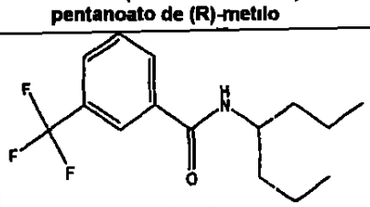
Compuesto No	Compuesto	EC_{50} Acre (uM)	relación EC_{50} (contra MSG)	@ (uM)
A66	 N-(2,4-dimetoxibenzil)-3 (1H pirrol 1 il) isonicotinamida	0 29		
A67	 2 (3-cloro-4-metoxibenzamido) pentanoato de metilo	0 29	10 75	1
A68	 4-etoxi-N-(heptan-4-il)benzamida	0 32	2 62	0 3
A69	 4-metil-2-(4-metilbenzamido) pentanoato de (R)-metilo	0 32		
A70	 N-(heptan-4-il)-3-N-(heptan-4 il)-3 (trifluorometil)benzamida	0 33		

Tabla A Amidas Acres

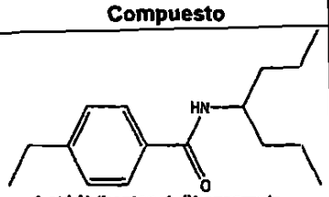
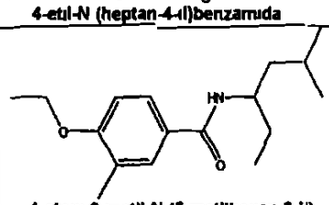
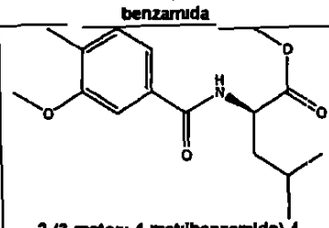
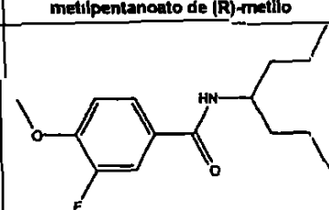
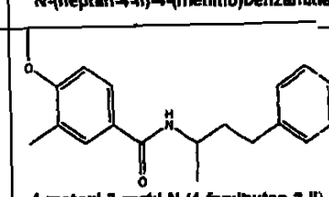
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A71	 4-etil-N (heptan-4-il)benzamida	0 34		
A72	 4-etoxi-3-metil-N-(6-metilhexan-3-il) benzamida	0.34		
A73	 2-(3-metoxi-4-metilbenzamido)-4 metilpentanoato de (R)-metilo	0 34		
A74	 3 fluoro-N-(heptan-4-il)-4 metoxibenzamida	0 35	4 98	0 3
A75	 N-(heptan-4-il)-4-(metiltio)benzamida	0 39		
A76	 4-metoxi-3-metil-N-(4 fenilbutan 2 il) benzamida	0 4		

Tabla A Amidas Acres

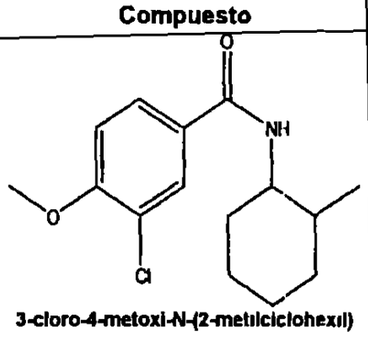
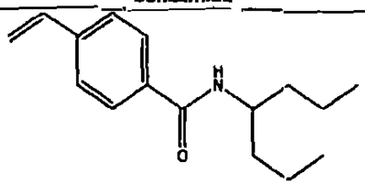
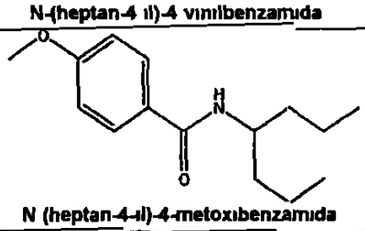
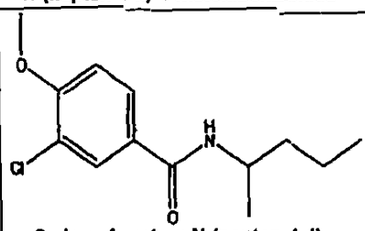
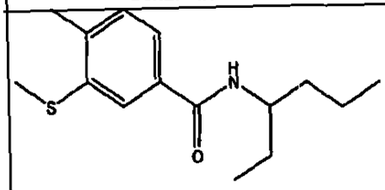
Compuesto No	Compuesto	EC_{50} Acre (uM)	relación EC_{50} (contra MSG)	@ (uM)
A77	 3-cloro-4-metoxi-N-(2-metilciclohexil) benzamida	0 44		
A78	 C N-(heptan-4 il)-4 vinilbenzamida	0 46	10 22	0 3
A79	 N (heptan-4-il)-4-metoxibenzamida	0 46		
A80	 3-cloro-4-metoxi N-(pentan 2 il) benzamida	0 47	5 12	0 1
A81	 N (hexan-3-il)-4-metil-3-(metiltio) benzamida	0 5		

Tabla A Amidas Acres

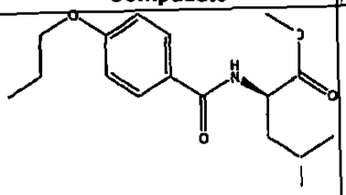
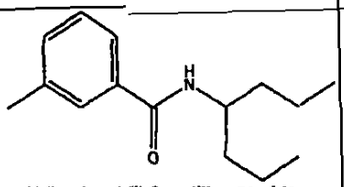
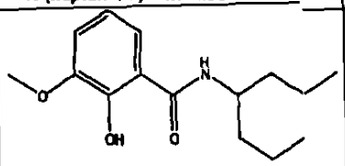
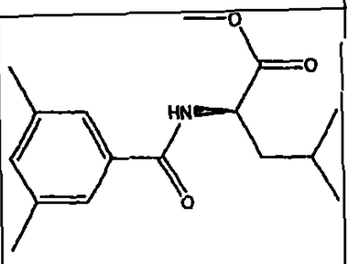
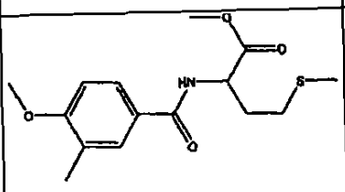
Compuesto No	Compuesto	EC_{50} Acre (uM)	relación EC_{50} (contra MSG)	@ (uM)
A82	 4-metil-2 (4-propoxibenzamido) pentanoato de (R)-metilo	0 51		
A83	 N-(heptan-4-il)-3-metilbenzamida	0 52		
A84	 N-(heptan-4-il)-2-hidroxi-3 metoxibenzamida	0 53		
A85	 2-(3 5-dimetilbenzamido)-4-metilpentanoato de (R)-metilo	0 53		
A86	 2-(4-metoxi-3-metilbenzamido)-4 (metiltio)butanoato de metilo	0 53		

Tabla A Amidas Acres

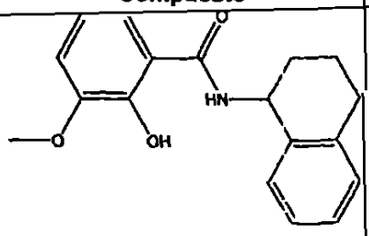
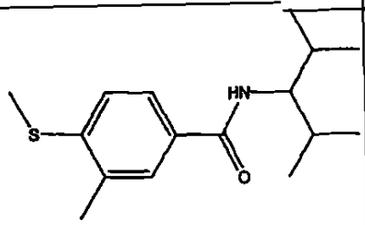
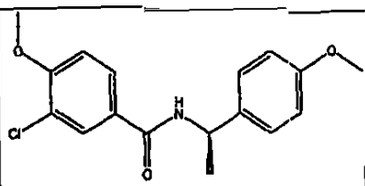
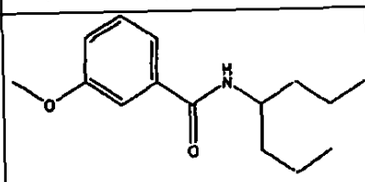
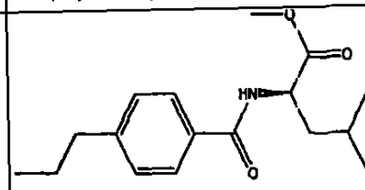
Compuesto No	Compuesto	EC_{50} Acre (uM)	relación EC_{50} (contra MSG)	@ (uM)
A87	 2-hidroxi-3-metoxi N-(1 2 3 4 tetrahidronaftalen 1-il)benzamida	0 54	3 8	1
A88	 N-(2,4-dimetilpentan-3-il)-3-metil 4 (metiltio)benzamida	0 55		
A89	 (R)-3-cloro-4-metoxi-N-(1 (4-metoxifenil)etil)benzamida	0 6	2 85	1
A90	 N (heptan-4-il)-3-metoxibenzamida	0 61		
A91	 4-metil-2-(4-propilbenzamido) pentanoato de (R)-metilo	0 62		

Tabla A Amidas Acres

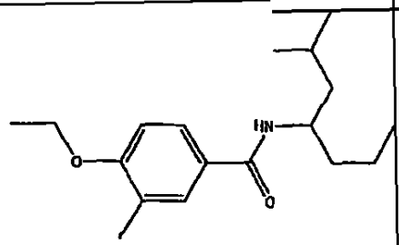
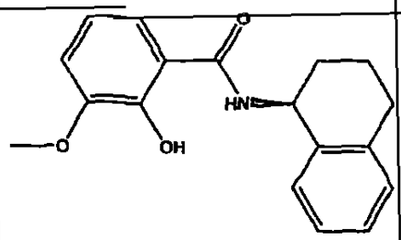
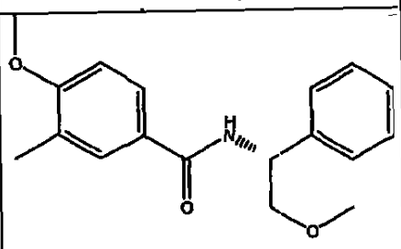
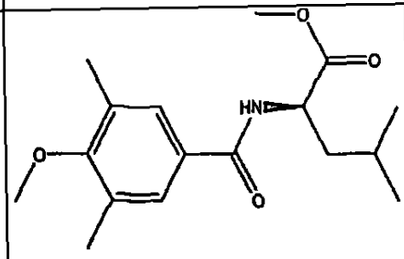
Compuesto No	Compuesto	EC_{50} Acre (uM)	relacion EC_{50} (contra MSG)	@ (uM)
A92	 4-etoxi-3-metil-N (2-metilhe ptan-4 il) benzamida	0 65		
A93	 (S) 2 hidroxi-3-metoxi-N-(1,2 3,4-tetrahidronaftalen 1 il)benzamida	0 7	5 7	1
A94	 (R)-4-metoxi-N-(2-metoxi 1 feniletil) 3-metilbenzamida	0 72		
A95	 2-(4-metoxi-3 5-dimetilbenzamido) 4-metilpentanoato de (R) metilo	0 74		

Tabla A Amidas Acres

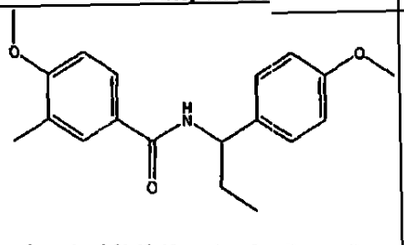
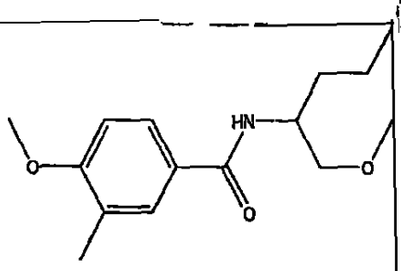
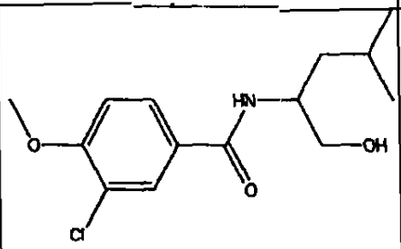
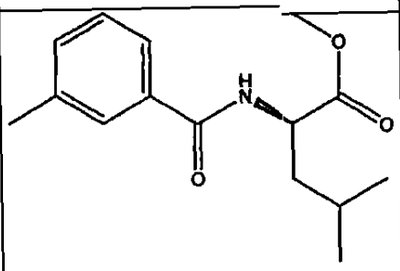
Compuesto No	Compuesto	EC_{50} Acre (uM)	relación EC_{50} (contra MSG)	@ (uM)
A96	 4-metoxi-N (1-(4-metoxifenil)propil) 3-metilbenzamida	0 76		
A97	 4-metoxi-N (1-metoxipentan-2-il) 3-metilbenzamida	0 85		
A98	 3-cloro N (1-hidroxi-4-metilpentan 2-il)-4-metoxibenzamida	0 88		
A99	 4-metil 2-(3-metilbenzamido) pentanoato de (R)-metilo	0 89		

Tabla A Amidas Acres

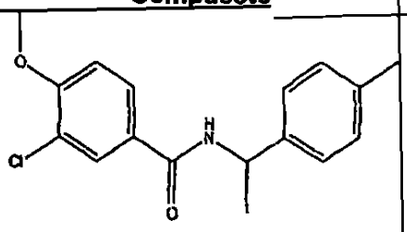
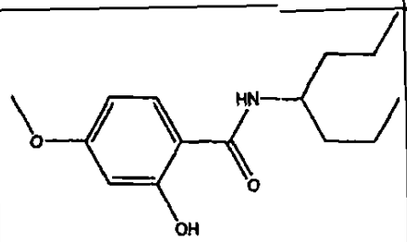
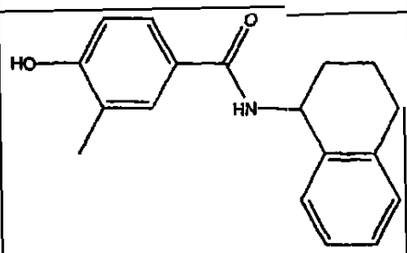
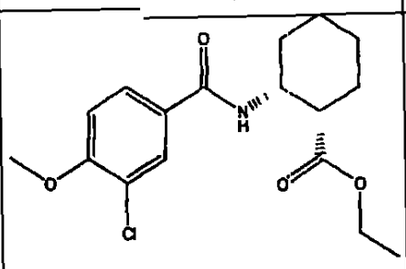
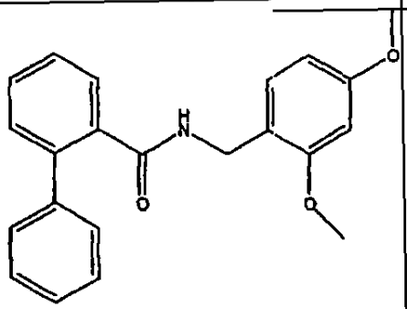
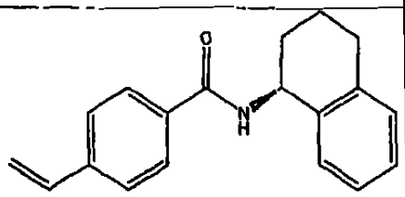
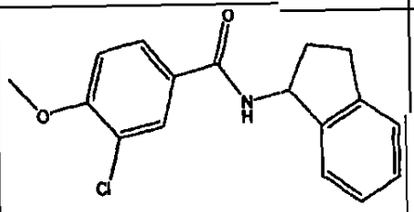
Compuesto No	Compuesto	EC_{50} Acre (uM)	relacion EC_{50} (contra MSG)	@ (uM)
A100	 3-cloro-4-metoxi N (1-p-toliletil) benzamida	1 1		
A101	 N (heptan-4-il) 2-hidroxi-4 metoxibenzamida	1 16	7 62	1
A102	 4 hidroxi-3-metil-N-(1 2,3,4 tetrahidronaftalen 1 il)benzamida	1 32	9 49	1
A103	 2-(3-cloro-4-metoxibenzamido) ciclohexancarboxilato de (1S 2R)-etilo	1 36		

Tabla A Amidas Acres

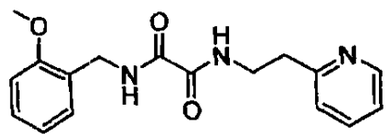
Compuesto No	Compuesto	EC_{50} Acre (uM)	relación EC_{50} (contra MSG)	@ (uM)
A104	 2,4-dimetoxi-benzilamida del acido Bifenil-2-carboxílico	1 37		
A105	 (S)-N-(1,2,3,4 tetrahidronaftalen 1-il)-4 vinilbenzamida	1 38	2 79	1
A106	 3-cloro-N-(2 3-dihidro 1H-inden 1 -il)-4-metoxibenzamida	1 39	4 01	0 3

Numerosos compuestos amida de la Fórmula (I) que caen dentro del subgénero de los compuestos oxalamida descritos en otro lado en la presente se sintetizan tambien y se prueban experimentalmente para efectividad como un activador de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293

Ejemplo 122

Procedimiento general A para la preparacion de una oxalamida

Sintesis de la N-(2-Metoxi-bencil)-N'-(2-piridil-2-il-etil)-oxalamida.



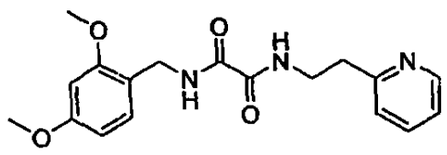
Se mezcló la 2-metoxibencilamina (5 mmoles) con trietilamina (2 equivalentes) en Dioxano anhidro Se agregó cloruro de etiloxalilo (1 equivalente) y la mezcla se agito a temperatura ambiente durante 0 5-2 horas Luego, se agregó la 2-(2-piridinil)etilamina (1 equivalente) y la suspensión se calento a 80°C durante la noche La solucion se concentro y el residuo se disolvió en acetato de etilo y se lavó con agua La capa organica se secó por sulfato de sodio y el solvente se evaporó para dar el producto sin purificar el cual se purificó por cromatografia de columna instantanea para producir el compuesto del titulo rendimiento 70%, p f 118-119°C, m/e = 314 [M+1] ^{1}H NMR ($CDCl_3$) δ 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 tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 34 µM, y cuando se presenta en 0 3 µM mejora la efectividad del glutamato de monosodio con una relación de EC_{50}

de 18 85

Ejemplo 123

N-(2 4-Dimetoxi-bencil)-N'-(2-piridin-2-il-etil)-oxalamida

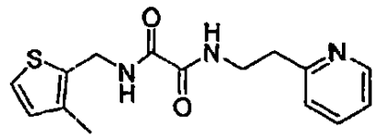


Preparado en una manera similar al ejemplo 122 utilizando el cloruro de etiloxalilo de la 2,4-dimetoxibencilamina y la 2-(2-piridinil)etilamina Rendimiento 72%, p f 123-124°C, m/e = 344 [M+1], ^{1}H NMR ($CDCl_3$) δ 3 02 (t 2H) 3 73 (dd 2H), 3 78 (s, 3H), 3 82 (s, 3H) 4 38 (d, 2H) 6 40 (dd, 1H), 6 44 (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

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 0 09 μM, y cuando se presenta en 0 3 μM mejora la efectividad del glutamato de monosodio con una relación EC_{50} de 6 51

Ejemplo 124

N-(3-Metil-tiofen-2-ilmetil)-N'-(2-piridin-2-il-etil)-oxalamida



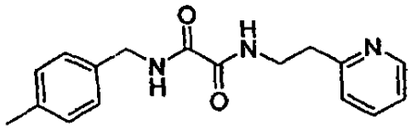
Preparado en una manera similar al ejemplo 122, utilizando la (3-metil-tiofen-2-il)-metilamina, cloruro de etiloxalilo y 2-(2-piridinil)etilamina Rendimiento 40%, p f 122-124°C m/e = 304 [M+1], ^{1}H NMR (*DMSO-d$_6$*) δ 2 19 (s, 3H), 2 92-2 95 (t, 2H) 3 48-3 52 (dd, 2H), 4 37-4 38 (d 2H) 6 79-6 80 (d 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)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 37 µM

Ejemplo 125

Procedimiento General B para la Síntesis de una Oxalamida

N-(4-metil-bencil)-N'-(2-piridin-2-il-etil)-oxalamida



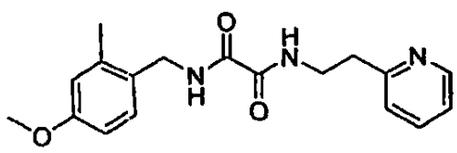
Se permitió hacer reaccionar la 4-metilbencilamina (1 mmol) con cloruro de etiloxalilo (1 equivalente) en la presencia de trietilamina (2 equivalentes) en acetonitrilo a temperatura

ambiente durante 0 5-1 hora Luego se agregó 2-(2-piridinil)etilamina (1 equivalente) y la suspensión se calentó a 160°C en un reactor de microondas durante 5 minutos La mezcla de reacción se sometió a HPLC preparativa para dar la oxalamida del título pura rendimiento 60% p f 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)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 41 µM

Ejemplo 126

N-(2-Metil-4-metoxibencil)-N'-(2-piridin-2-il-etil)-oxalamida



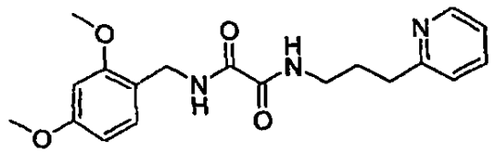
Preparado en una manera similar al ejemplo 122 utilizando 2-metil-4-metoxibencilamina cloruro de etiloxalilo y 2-(2-piridinil)etilamina Rendimiento 51%, p f 133-134°C m/e = 328 [M+1] ^{1}H NMR ($CDCl_3$) δ 2 29 (s, 3H), 3 04 (t 2H) 3 74-3 77 (m 2H), 3 7 (s, 3H), 4 40 (d, 2H) 6 69-6 73 (m, 2H), 7 13-7 18 (m, 3H) 7 51 (t 1H) 7 60-7 63 (m 1H) 8 17 (t, 1H), 8 58 (d, 1H)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular

HEK293 de 0 11 µM

Ejemplo 127

N-(2 4-Dimetoxi-bencil)-N'-(3-piridin-2-il-propil)-oxalamida

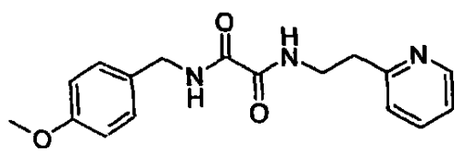


Preparado en una manera similar al ejemplo 125 utilizando el cloruro de etiloxalilo de la 2,4-dimetoxibencilamina y la 3-(2-piridinil)propilamina Rendimiento 60% m/e = 358 [M+1] ^{1}H NMR ($CDCl_3$) δ 1 99-2 04 (m 2H), 2 84 (t 2H) 3 36 (dd, 2H) 3 79 (s, 3H), 3 82 (s, 3H 4 60 (d, 2H), 6 41-6 45 (m, 2H) 7 10-7 17 (m, 3H) 7 57-7 60 (m, 1H), 7 81 (t, 1H), 7 89 (t, 1H), 8 54 (d, 1H)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 1 84 µM

Ejemplo 128

N-(4-Metoxibencil)-N'-(2-piridin-2-il-etil)-oxalamida



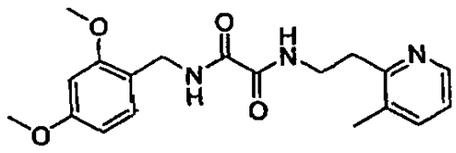
Preparado en una manera similar al ejemplo 125 utilizando la 4-metoxibencilamina, el cloruro de etiloxalilo y la 2-(2-piridinil)etilamina Rendimiento 50%, p f 156-158°C, ^{1}H NMR

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)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 75 µM

Ejemplo 129

N-(2 4-Dimetoxibencil)-N'-(2-(3-metilpiridin-2-il)etil)oxalamida



Preparado en una manera similar al ejemplo 125 utilizando la 2 4-dimetoxibencilamina, el cloruro de etiloxalilo y la 2-(3-metilpiridin-2-il)etilamina (ejemplo 129a) Rendimiento 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-Metilpiridin-2-il)etilamina A una solución del 2-(3-metilpiridin-2-il)acetonitrilo (ejemplo 129b) (95 mg, 0 72 mmoles) en THF (0 5 mL) se agregó 1M BH_3 THF (2 2 ml, 2 2 mmoles) en gotas a temperatura ambiente La temperatura resultante se calentó en un reactor de microondas a 130°C durante 7 minutos Luego, se agregó en gotas a temperatura ambiente 6 N

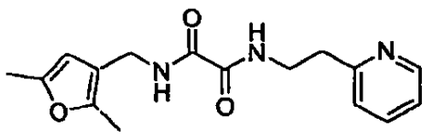
HCl acuoso (1 mL) La mezcla resultante se calento en un reactor de microondas a 120°C durante 4 minutos La mezcla de reaccion se lavó con Et_2O (3x3 mL), luego se enfrió a 0°C y NaOH 10 N acuoso (0 8 mL) se agrego La solucion acuosa se saturo con K_2CO_3 El producto se extrajo con $CHCl_3$ (6x5 mL) Los extractos orgánicos se secaron (1 1 de K_2CO_3/Na_2SO_4), se filtraron, se concentraron in vacuo para producir un aceite (8 mg, 85%) el cual se utilizó 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 mmoles) a -78°C bajo N_2 se agregó THF seco (75 mL) seguido inmediatamente por una solucion de MeCN seca (1 15 mL, 21 78 mmoles) en THF anhidro (30 mL) durante un periodo de 5 minutos La mezcla de reacción resultante se agitó continuamente a -78°C durante 1 hora Luego se agregó 2-bromo-3-metilpiridina (516 mg, 3 mmoles) La mezcla de reacción resultante se agitó a -78°C durante 1 hora, luego se calentó a temperatura ambiente y se extinguio con agua El solvente orgánico se evaporó al vacio, se disolvio en CH_2Cl_2 La capa orgánica se lavo con salmuera se secó ($MgSO_4$), se concentró, se purificó a través de una cromatografia en columna (20% de EtOAc en hexanos) para producir el producto cuantitativamente m/e = 133 [M+1]

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 1 64 µM

Ejemplo 130

N-(2 5-Dimetil-furan-3-ilmetil)-N'-(2-piridin-2-il-etil)-oxalamida

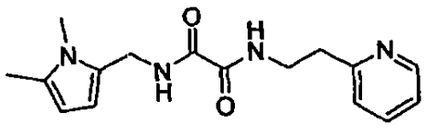


Preparado en una manera similar al ejemplo 122 utilizando la 2,5-dimetil-furan-3-ilmetilamina, el cloruro de etiloxalilo y la 2-(2-piridinil)etilamina Rendimiento 51%, p f 112-115°C, m/e = 302 [M+1], ^{1}H NMR (*DMSO-d$_6$*) δ 2 14 (s, 3H) 2 18 (s, 3H), 2 91-2 94 (t, 2H), 3 47-3 51 (dd, 2H) 3 98-3 99 (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)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado 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



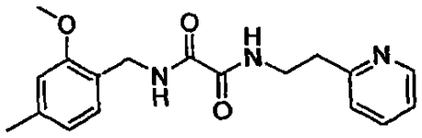
Preparado en una manera similar al ejemplo 122 utilizando 1,5-dimetil-1H-pirrol-2-ilmetilamina, cloruro de etiloxalilo y 2-(2-piridinil)etilamina Rendimiento 25% p f 147-

149°C, m/e = 301 [M+1], ^{1}H NMR (*DMFO-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 tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 2 3 μM

Ejemplo 132

N-(2-metoxi-4-metilbencil)-N'-(2-(piridin-2-il)etil)oxalamida



Preparado en una manera similar al ejemplo 125 utilizando (2-metoxi-4-metilfenil)metanamina (ejemplo 132a) cloruro de etiloxalilo y 2-(2-piridinil)etilamina, rendimiento 20% p f 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-metoxi-4-metilfenil)metanamina A una solución de la 2-metoxi-4-metilbenzamida (ejemplo 132b) (200 mg, 1 21 mmoles) en THF (0 5 mL) se agrego 1 M BH_3•THF (2 4 ml 2 42 mmoles) lentamente a temperatura ambiente La mezcla resultante se calento en un reactor de microondas a 130°C durante 7 minutos Luego se agregó en gotas a temperatura ambiente 6 N

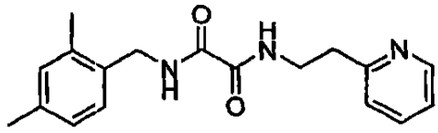
HCl acuoso (1 mL) La mezcla resultante se calentó en un reactor de microondas a 120°C durante 4 minutos La mezcla de reacción se calentó a Et_2O (3x3 mL) luego se enfrio a 0°C y se agregó 10 N NaOH acuoso (0 8 mL) La solución acuosa se saturó con K_2CO_3 El producto se extrajo con $CHCl_3$ (6x5 mL) Los extractos organicos se secaron (1 1 de K_2CO_3/Na_2SO_4), se filtraron, se concentración al vacio para producir 180 mg de (2-metoxi-4-metilfenil)metanamina la cual se utilizo directamente en el Ejemplo 11

b 2-metoxi-4-metilbenzamida se mezcló el 2-metoxi-4-metilbenzoico (500 mg, 3 01 mmoles) con clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (577 mg, 3 01 mmoles) y 1-hidroxibenzotriazol (407 mg 3 01 mmoles) en 25 ml de diclorometano a temperatura ambiente y se agita durante 5 minutos Se agregó una solucion de amoniaco 2M en metanol (4 5 ml, 9 03 mmoles), la mezcla de reacción se agitó a temperatura ambiente durante aproximadamente 5 horas, luego se diluyó con diclorometano, se lavo con 1N HCl, $NaHCO_3$ saturado, agua y salmuera, se secó sobre $MgSO_4$, se filtró y se evaporo para dar 440 mg de 2-metoxi-4-metilbenzamida, rendimiento 88%

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 04 uM

Ejemplo 133

N-(2 4-dimetilbencil)-N'-(2-(piridin-2-il)etil)oxalamida



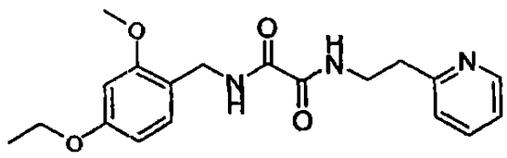
Preparado en una manera similar al ejemplo 125 utilizando (2,4-dimetilfenil)metanamina (ejemplo 133a) cloruro de etiloxalilo y 2-(2-piridinil)etilamina, rendimiento 60%, p f 148-149°C, m/e= 312 [M+1], ^{1}H NMR ($CDCl_3$) 2 28 (s, 3H) 2 30 (s 3H), 3 05 (t, 2H), 3 76 (dd 2H), 4 43 (d 2H) 6 99 (m 2H), 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-Dimetilfenil)metanamina Se coloco hidruro a una solución de hidruro de litio-aluminio 1M en THF (15 2 ml 15 2 mmoles) en un matraz pre-secado bajo argón a 0°C una solución de 2,4-dimetilbenzonitrilo (1 0 g 7 6 mmoles) en 15 ml de eter anhidro se agregó en gotas Después de la adición, la mezcla de reacción se calento lentamente a temperatura ambiente y se agitó durante 3 horas luego se enfrió a 0°C, se agregó sulfato de sodio anhidro y se agregó 1 ml de agua en gotas La mezcla se diluyó con acetato de etilo, la materia insoluble se extrajo por filtrado, el filtrado se lavó con agua y salmuera, se seco sobre $MgSO_4$, se filtró y se evaporó para dar 1 03 g de la (2 4-dimetilfenil)metanamina pura en rendimiento cuantitativo sin purificación

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 07 uM

Ejemplo 134

N-(4-etoxi-2-metoxibencil)-N'-(2-(piridin-2-il)etil)oxalamida



Preparado en una manera similar al ejemplo 125 utilizando (4-etoxi-2-metoxifenil)metanamina (ejemplo 134a), cloruro de etiloxalilo y 2-(2 piridinil)etilamina, rendimiento 10% p f 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-etoxi-2-metoxifenil)metanamina A una solución de 4-etoxi-2-metoxibenzaldehido (ejemplo 134b) (880 mg 4 88 mmoles) en 50 ml de metanol anhidro, se agregaron acetato de amonio (7 5 g, 97 60 mmoles) y cianoborohidruro de sodio (613 mg, 9 76 mmoles) La mezcla de reacción se agitó a temperatura ambiente durante aproximadamente 4 horas, luego se concentró en un evaporador giratorio, el residuo se diluyó con agua y se basifico con 15% de NaOH acuoso se extrajo con acetato de etilo, se lavó con agua y salmuera, se secó sobre

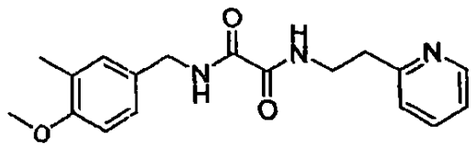
$MgSO_4$, se filtró y el solvente se evaporó, el residuo se llevó a cromatografía en columna en gel de sílice (DCM/MeOH 9 1) para producir 150 mg del producto, rendimiento 17% (el método no se optimizó)

b 4-Etoxi-2-metoxibenzaldehido A una solución de 4-hidroxi-2-metoxibenzaldehído (1 0 g, 6 57 mmoles) en 10 ml de acetona, se agregó carbonato de potasio (0 91 g, 6 57 mmoles) e yodometano (1 6 ml, 19 71 mmoles) la mezcla de reaccion se agitó a temperatura ambiente durante la noche La acetona se removio en un evaporador giratorio, el residuo se diluyó con agua y acetato de etilo, se extrajo con acetato de etilo, se lavo con salmuera, se seco sobre $MgSO_4$ se filtró y se evaporó para dar el producto sin purificar, el cual se llevó a cromatografía en columna en gel de sílice (acetato de etilo/hexano = 1 4) para dar 943 mg del producto, rendimiento 80%

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 1 uM

Ejemplo 135

N-(4-Metoxi-3-metilbencil)-N'-(2-(piridin-2-il)etil)oxalamida



Preparado en una manera similar al ejemplo 125

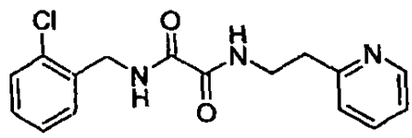
utilizando la (4-metoxi-3-metilfenil)-metanamina (Ejemplo 135a), cloruro de etiloxalilo y 2-(2-piridinil)etilamina, rendimiento 12% p f 145-147°C m/e= 328 [M+1], ^{1}H NMR ($CDCl_3$) 2 19 (s, 3H), 3 04 (t 2H) 3 76 (dd 2H), 3 81 (s 3H), 4 37 (d, 2H) 6 76 (d, 1H) 7 06 (m, 2H), 7 16 (m, 2H), 7 61 (m, 1H), 7 66 (s, 1H) 8 18 (s, 1H) 8 58 (d, 1H)

a 4-Metoxi-3-metilfenil)metanamina Preparada en una manera similar al ejemplo 134a utilizando 4-metoxi-3-metilbenzaldehido, acetato de amonio, y cianoborohidruro de sodio en MeOH rendimiento 22% (110 mg)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 1 04 uM

Ejemplo 136

N-(2-clorobencil)-N'-(2-(piridin-2-il)etil)oxalamida.

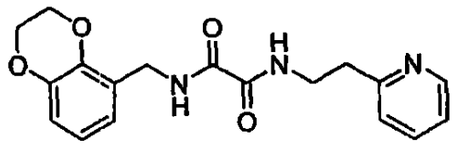


Preparado en una manera similar al ejemplo 125 utilizando (2-clorofenil)metanamina, cloruro de etiloxalilo y 2-(2-piridinil)etilamina rendimiento 45%, *m/e* = 318 [M+1]

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 01 uM

Ejemplo 137

N-((2 3-dihidrobenzo[b][1 4]dioxin-5-il)metil)-N'-(2-piridin-2-il)etil)oxalamida

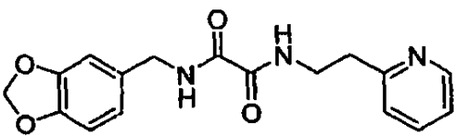


Preparado en una manera similar al ejemplo 122 utilizando (2,3-dihidrobenzo[b][1,4]dioxin-5-il)metanamina cloruro de etiloxalilo, y 2-(2-piridinil)etilamina, rendimiento 50%, *m/e* = 342 [M+1]

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 3 uM

Ejemplo 138

N-(benzo[d][1 3]dioxol-5-ilmetil)-N'-(2-(piridin-2-il)etil)oxalamida



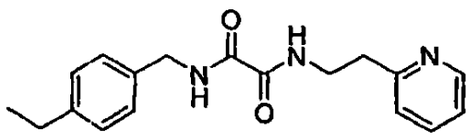
Preparado en una manera similar al ejemplo 125 utilizando benzo[d][1,3]dioxol-5-ilmetanamina, cloruro de etiloxalilo y 2-(2-piridinil)etilamina, rendimiento 35%, *m/e* = 328 [M+1]

El compuesto tuvo una EC_{50} para la activación de un

receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 5 uM

Ejemplo 139

N-(4-Etilbencil)-N'-(2-(piridin-2-il)etil)oxalamida

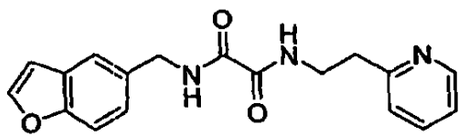


Preparado en una manera similar al ejemplo 125 utilizando 4-etilbencilamina, cloruro de etiloxalilo y 2-(2-piridinil)etilamina rendimiento 38%, *m/e* = 312 [M+1]

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 79 uM

Ejemplo 140

N-(Benzofuran-5-ilmetil)-N'-(2-(piridin-2-il)etil)oxalamida



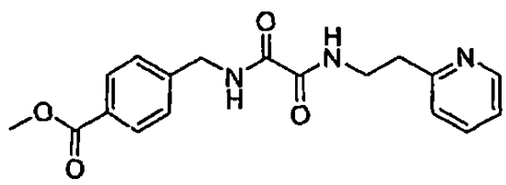
Preparado en una manera similar al ejemplo 125 utilizando benzofuran-5-ilmetilamina, cloruro de etiloxalilo y 2-(2-piridinil)etilamina, rendimiento 64% *m/e* = 324 [M+1]

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular

HEK293 de 1 78 uM

Ejemplo 141

N-((4-Metoxicarbonilfenil)metil)-N'-(2-(piridin-2-il)etil)oxalamida

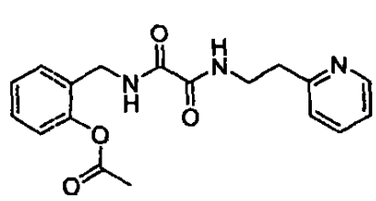


Preparado en una manera similar al ejemplo 122 utilizando 4-metilcarbonilfenilmetilamina, cloruro de etiloxalilo y 2-(2-piridinil)etilamina, rendimiento 52%, *m/e* = 34 [M+1]

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 3 63 uM

Ejemplo 142

N-((2-Carbamoilfenil)metil)-N'-(2-(piridin-2-il)etil)oxalamida

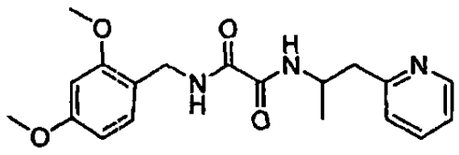


Preparado en una manera similar al ejemplo 122 utilizando 2-carbamoilfenilmetilamina, cloruro de etiloxalilo, y 2-(2-piridinil)etilamina rendimiento 48% *m/e* = 34 [M+1]

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 8 5 uM

Ejemplo 143

N-(2 4-Dimetoxibencil)-N'-(1-(piridin-2-il)propan-2-il)oxalamida



Preparado en una manera similar al ejemplo 125 utilizando 2,4-dimetoxibencilamina, cloruro de etiloxalilo, y 1-(piridin-2-il)propan-2-ilamina (ejemplo 143a), rendimiento 34% *m/e* = 357 [M+1]

a 1-(Piridin-2-il)propan-2-ilamina Preparada en una manera similar al ejemplo 129a utilizando 2-(piridin-2-il)propan-nitrilo (ejemplo 143b), el producto sin purificar se utilizó directamente en el ejemplo 143 rendimiento 53%, *m/e* = 137 [M+1]

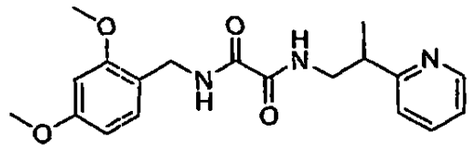
b 2-(piridin-2-il)propan-nitrilo se disolvio 5 mmoles de 2-(piridin-2-il)acetonitrilo en 8 ml de THF anhidro y se colocó en un baño con hielo Se agregó t-butóxido de potasio (1 equivalente) y la reacción se agitó durante 30 minutos Se disolvio yoduro de metilo (1 equivalente) en 5 ml de THF anhidro y se agregó lentamente durante 30 minutos Se agito la reacción durante la noche a temperatura ambiente El solvente se evaporó y la mezcla

sin purificar se disolvio en acetato de etilo y se lavó con agua Se evaporó la capa de acetato de etilo y el producto se purificó por TLC preparativa (30% de acetato de etilo/Hexano) rendimiento 71% *m/e* = 133 [M+1]

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 4 uM

Ejemplo 144

N-(2 4-Dimetoxibencil)-N'-(2-(piridin-2-il)propil)oxalamida



Preparado en una manera similar al ejemplo 125 utilizando 2,4-dimetoxibencilamina, cloruro de etiloxalilo y 2-(piridin-2-il)propilamina (ejemplo 144a), rendimiento 35%, *m/e* = 357 [M+1]

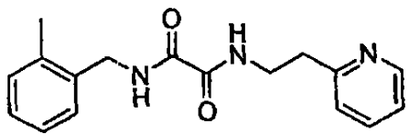
a 2-(piridin-2-il)propilamina 10 mmoles de 2-metilpiridina se disolvió en THF anhidro y se mantuvo bajo condicion inerte a 0°C Se agregó butil-litio (1 2 equivalentes) en gotas y se agitó durante 15 minutos adicionales a 0°C mientras que se permitió a la temperatura volver a la temperatura ambiente Después de agitar a temperatura ambiente durante 1 hora, la mezcla de reacción se enfrió de nuevo a 0°C y se agregó en gotas acetonitrilo (2 equivalentes) La reacción se agitó durante la noche

a temperatura ambiente Después del enfriamiento la reaccion a 0°C 30 ml de metanol se agrego en la mezcla de reacción Se agrego borohidruro de sodio (3 equivalentes) en una porcion lentamente a 0°C La reaccion se agitó durante otra hora permitiendo a la temperatura elevarse a la temperatura ambiente La mezcla de reacción se diluyó con agua y se extrajo exhaustivamente con acetato de etilo Los extractos combinados se lavaron con agua, con salmuera y se secaron sobre sulfato de sodio La solución se concentró y se disolvio en éter El producto se extrajo con HCl 3 N acuoso, y el extracto acidico se lavó con eter y se hizo básico con NaOH El producto se extrajo exhaustivamente con eter Los extractos de éter combinados se lavaron con agua y se secaron sobre sulfato de sodio El solvente se evaporo para producir suficiente producto puro, rendimiento 47%, *m/e* = 137 [M+1]

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 1 07 uM

Ejemplo 145

N-(2-Metoxibencil)-N'-(2-(piridin-2-il)etil)oxalamida



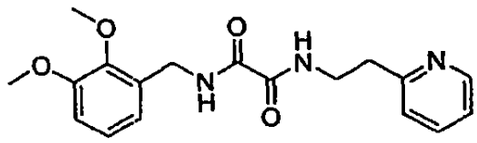
Preparado en una manera similar al ejemplo 125

utilizando 2-metilbencilamina, cloruro de etiloxalilo y 2-(piridin-2-il)etilamina *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)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 0 59 uM

Ejemplo 146

N-(2 3-Dimetoxibencil)-N'-(2-(piridin-2-il)etil)oxalamida

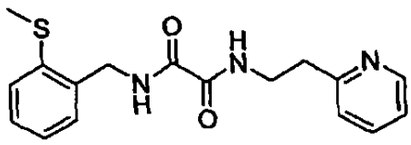


Preparado en una manera similar al ejemplo 125 utilizando 2,3-dimetoxibencilamina, cloruro de etiloxalilo y 2-(piridin-2-il)etilamina, *m/e* = 343 [M+1]

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 69 uM

Ejemplo 147

N-(2-(Metiltio)bencil)-N -(2-(piridin-2-il)etil)oxalamida

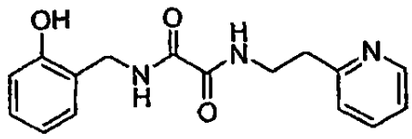


Preparado en una manera similar al ejemplo 125 utilizando 2-metiltiobencilamina cloruro de etiloxalilo, y 2-(piridin-2-il)etilamina, *m/e* = 330 [M+1], ^{1}H NMR ($CDCl_3$) δ 2 49 (s, 3H), 3 08 (t, 2H), 3 77 (dt, 2H), 4 55 (d, 2H), 7 11-7 14 (m 1H), 7 15-7 20 (m 2H), 7 22-7 27 (m 3H), 7 62 (t, 1H), 7 78-7 83 (m, 1H) 8 08-8 11 (m, 1H) 8 56 (d, 1H)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 0 96 uM

Ejemplo 148

N-(2-Hidroxibencil)-N'-(2-(piridin-2-il)etil)oxalamida

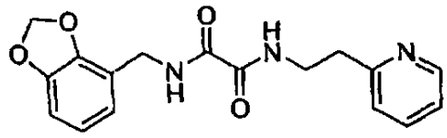


Preparado en una manera similar al ejemplo 125 utilizando 2-hidroxibencilamina cloruro de etiloxalilo y 2-(piridin-2-il)etilamina, *m/e* = 300 [M+1]

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 3 11 uM

Ejemplo 149

N-(Benzo[d][1 3]dioxol-4-ilmetil)-N'-(2-piridin-2-il)etil)oxalamida



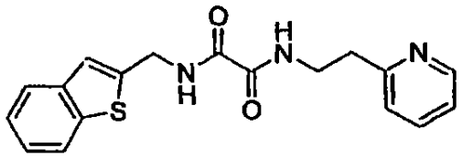
Preparado en una manera similar al ejemplo 125 utilizando benzo[d][1,3]dioxol-4-ilmetilamina (ejemplo 149a) cloruro de etiloxalilo y 2-(piridin-2-il)etilamina rendimiento 12% *m/e* = 328 [M+1] ^{1}H NMR ($CDCl_3$) δ 3 12 (m 2H), 3 77-3 80 (m 2H), 4 46-4 47 (d 2H) 5 98 (s, 2H), 6 74-6 79 (m, 3H), 7 24 (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-ilmetilamina Preparada en una manera similar al ejemplo 134a a partir del benzo[d][1,3]dioxol-4-carbaldehído y el acetato de amonio El material sin purificar contuvo aproximadamente 20% del producto (*m/e* = 152 2 [M+1]) y se utilizo directamente en el ejemplo 149

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 17 uM

Ejemplo 150

N-(Benzo[b]tiofen-2-ilmetil)-N'-(2-(piridin-2-il)etil)oxalamida

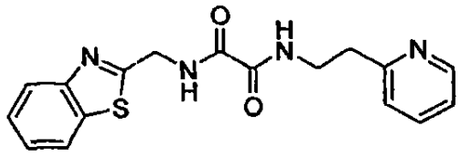


Preparado en una manera similar al ejemplo 125 utilizando benzo[b]tiofen-2-ilmetanamina, cloruro de etiloxalilo y 2-(piridin-2-il)etilamina, rendimiento 32%, *m/e* = 240 [M+1] ^{1}H NMR (DMSO-d_6) δ 2 92-2 95 (t, 2H), 3 48-3 53 (m, 2H), 4 55-4 56 (d 2H), 7 20-7 25 (m, 2H) 7 38-7 41 (m 2H), 7 50 (s, 1H), 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)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 74 uM

Ejemplo 151

N-(Benzo[d]tiazol-2-ilmetil)-N'-(2-(piridin-2-il)etil)oxalamida



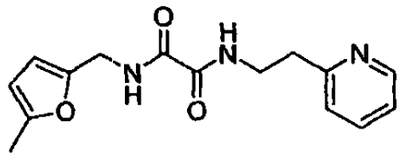
Preparado en una manera similar al ejemplo 125 utilizando benzo[d]tiazol-2-ilmetanamina, cloruro de etiloxalilo y 2-(piridin-2-il)etilamina rendimiento 33% *m/e* = 341 [M+1], ^{1}H NMR (DMSO-d_6) δ 2 95-2 98 (t, 2H) 3 52-3 57 (m, 2H), 4 72-4 73 (d

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 7 (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 tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 4 4 uM

Ejemplo 152

N-((5-Metilfuran-2-il)metil)-N2-(2-(piridin-2-il)etiloxalamida

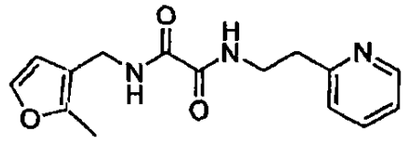


Preparado en una manera similar al ejemplo 125 utilizando (5-metilfuran-2-il)metanamina, cloruro de etiloxalilo y 2-(piridin-2-il)etilamina rendimiento 38% *m/e* = 288 [M+1] ^{1}H NMR (DMSO-d_6) δ 2 20 (s, 3H), 2 92-2 95 (t 2H), 3 48-3 52 (m, 2H) 4 23-4 24 (d, 2H), 5 96-5 97 (d, 1H), 6 06-6 07 (d, 1H), 7 20-7 25 (m, 2H), 7 68-7 71 (1 1H), 8 48-8 49 (d 1H) 8 85-8 87 (t 1H) 9 04-9 07 (t, 1H)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 4 9 uM

Ejemplo 153

N-((2-Metilfuran-3-il)metil)-N'-(2-(piridin-2-il)etil)oxalamida



Preparado en una manera similar al ejemplo 125 utilizando (2-metilfuran-3-il)metanamina (ejemplo 153a) cloruro de etiloxalilo y 2-(piridin-2-il)etilamina, rendimiento 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)

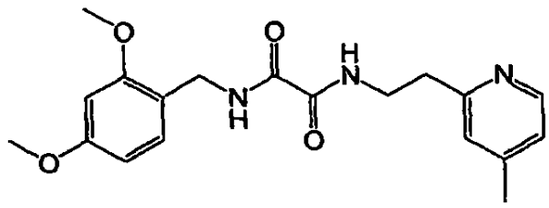
a (2-Metilfuran-3-il)metanamina Una solucion de 10 mmoles (1 256 mmoles) de 2-metilfuran-3-carboxilato de metilo y 38 9 mmoles (2 1 g) de NaOMe en 20 ml de formamida se agitó a 100°C durante 30 minutos La mezcla de reacción se vertio en agua helada (20 mL) y se extrajo con acetato de etilo (3x) El extracto se seco sobre MgSO4 y se concentró para dar 1 05 g (83%) de la 2-metilfuran-3-carboxamida como un aceite (*m/e* = 126 2 [M+1]) La amida se disolvió en THF seco (10 mL) y se agregó en gotas a 15 ml de 1M $LiAlH_4$ con 15 ml de THF a 0°C bajo argon Luego, la mezcla se agitó durante 5 horas a 60°C Despues del enfriamiento, se agregó 50% de THF acuoso (30 mL) a la mezcla a 5-10°C El precipitado resultante se removió por filtración y la solución filtrada se secó y se concentró para dar un

producto oleoso (0 93 g, 84%)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 1 82 uM

Ejemplo 154

N-(2 4-Dimetoxibencil)-N'-(2-(4-metilpiridin-2-il)etil)oxalamida



Preparado en una manera similar al Ejemplo 122 utilizando 2 4-dimetoxibencilamina, cloruro de etiloxalilo y 2-(4-metilpiridin-2-il)etilamina (ejemplo 154a) rendimiento 11% *m/e* = 358 [M+1] p f 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-Metilpiridin-2-il)etilamina Preparado en una manera similar al ejemplo 129 utilizando 2-(4-metilpiridin-2-il)acetonitrilo (ejemplo 154b), rendimiento 83%, *m/e* = 137 [M+1]

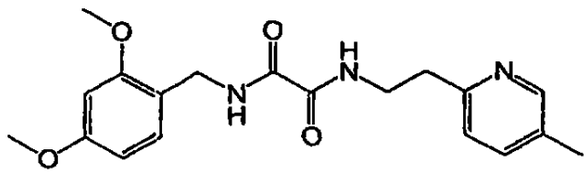
b 2-(4-Metilpiridin 2-il)acetonitrilo Preparado en una manera similar al ejemplo 129b utilizando 2-bromo-4-metilpiridina, acetonitrilo y n-BuLi rendimiento 88%, *m/e* = 133 [M+1]

El compuesto tuvo una EC_{50} para la activación de un

receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 de 1 64 uM

Ejemplo 155

N-(2 4-Dimetoxibencil)-N'-(2-(5-metilpiridin-2-il)etil)oxalamida



Preparado en una manera similar al Ejemplo 122 utilizando 2,4-dimetoxibencilamina, cloruro de etiloxalilo y 2-(5-metilpiridin-2-il)etilamina (ejemplo 155a) rendimiento 9% *m/e* = 358 [M+1], p f 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)

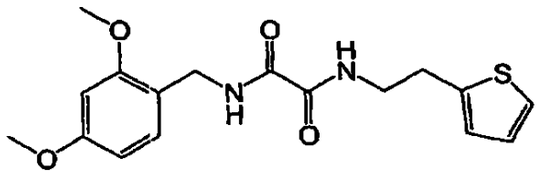
a 2-(5-Metilpiridin-2-il)etilamina Preparada en una manera similar a 129a utilizando 2-(5-metilpiridin-2-il)acetonitrilo (155b) rendimiento 40% *m/e* = 137 [M+1]

b 2-(5-Metilpiridin-2-il)acetonitrilo preparado en una manera similar al 129b utilizando 2-bromo-5-metilpiridina acetonitrilo y n-BuLi, rendimiento 68% *m/e* = 133 [M+1]

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 07 uM

Ejemplo 156

N-(2 4-Dimetoxibencil)-N'-(2-(tiofen-2-il)etil)oxalamida

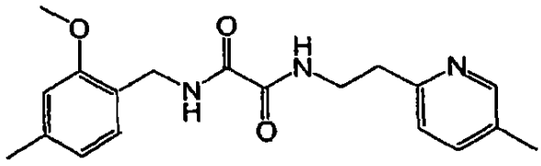


Preparado en una manera similar al Ejemplo 122, utilizando 2,4-dimetoxibencilamina, cloruro de etiloxalilo y 2-(tiofen-2-il)etilamina, rendimiento 72%, *m/e* = 349 [M+1], p f 146-147°C, ^{1}H NMR ($CDCl_3$) δ 3 06 (t, 2H), 3 58 (q, 2H), 3 80 (s, 3H) 3 83 (s, 3H), 4 40 (d, 2H) 6 41 (dd, 1H), 6 45 (d, 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)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 4 87 uM

Ejemplo 157

N^1-(2-metoxi-4-metilbencil)-N^2-(2-(5-metilpiridin-2-il)etil)oxalamida



Preparado en una manera similar al Ejemplo 125, utilizando 2-metoxi-4-metilbencilamina (ejemplo 132a), cloruro de

etiloxalilo y 2-(4-metilpiridin-2-il)etilamina (ejemplo 155a) Rendimiento 20% p f 116-117°C, ^{1}H NMR ($CDCl_3$) δ 2 31 (s 3H), 2 34 (s, 3H), 3 00 (t, 2H), 3 71 (q, 2H), 3 84 (s, 3H), 4 42 (d 2H), 6 69 (s, 1H), 6 71 (d, 1H) 7 05 (d 1H) 7 11 (d 1H) 7 43 (d 1H), 7 84 (br s, 1H), 8 04 (br s, 1H), 8 39 (s, 1H) MS (M+H, 342)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 03 uM

Los compuestos 'oxalamida" adicionales se sintetizaron y se probaron experimentalmente y se encontró que tienen un nivel relativamente elevado de efectividad como un activador de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 Los resultados de la prueba se muestran posteriormente en la Tabla B

Tabla B Oxalamidas Acres

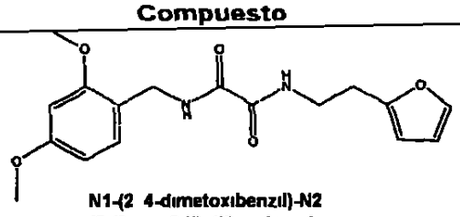
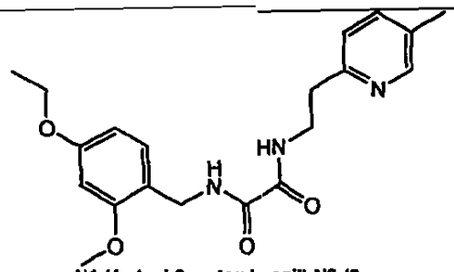
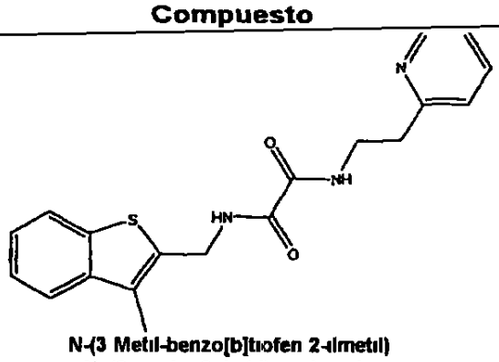
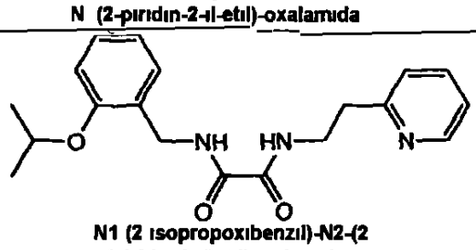
Compuesto No	Compuesto	EC_{50} Acre (uM)	relación EC_{50} (contra MSG)
B1	 N1-(2 4-dimetoxibenzil)-N2 (2-(furan-2-il)etil)oxalamida	0 18	
B2	 N1-(4-etoxi 2-metoxibenzil)-N2-(2 (6-metilpiridin 2 il)etil)oxalamida	0 19	

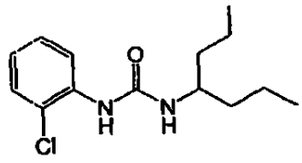
Tabla B - Oxalamidas Acres

Compuesto No	Compuesto	EC_{50} Acre (uM)	relación EC_{50} (contra MSG)
B3	 N-(3 Metil-benzo[b]tiofen 2-ilmetil) N (2-piridin-2-il-etil)-oxalamida	0 81	
B4	 N1 (2 isopropoxibenzil)-N2-(2 (piridin-2-il)etil)oxalamida	I 22	

Numerosos compuestos amida de la Formula (I) que caen dentro del subgenero de los compuestos "urea" descritos en algun otro lado en la presente se sintetizaron y se probaron experimentalmente para efectividad como un activador de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293

Ejemplo 158

1-(4-clorofenil)-3-(heptan-4-il)urea

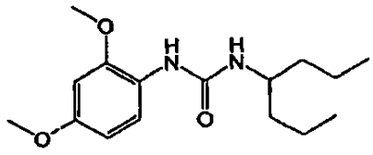


A una solucion de la heptan-4-amina (0 18 mL, 1 mmol) en CH_2Cl_2 (5 mL) se agrego 1-cloro-2-isocianatobenceno (0 12 mL, 1 mmol) a temperatura ambiente La mezcla de reacción se agito durante 2 horas Se precipitó un sólido blanco La mezcla de reacción se filtró El solido se lavo con CH_2Cl_2 para producir 1-(4-clorofenil)-3-(heptan-4-il)urea (180 mg, 67%) como un solido blanco p f 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)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 37 μM, y cuando se presenta en 1 μM mejora la efectividad del glutamato de monosodio con una relación de EC_{50} de 4 95

Ejemplo 159

1-(2 4-dimetoxifenil)-3-(heptan-4-il)urea



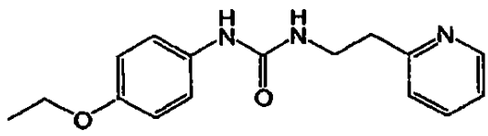
Preparado en una manera similar al ejemplo 158 utilizando heptan-4-amina y 1-isocianato-2,4-dimetoxibenceno Rendimiento 88% p f 172-173°C ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 93 (t 6H) 1 45 (m 8H) 3 82 (s 3H), 3 83 (m 1H) 3 84 (s 1H)

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)

El compuesto tuvo una EC_{50} para la activacion de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 98 µM, y cuando se presenta en 0 3 µM mejora la efectividad del glutamato de monosodio con una relación de EC_{50} de 7 61

Ejemplo 160

1-(4-etoxifenil)-3-(2-(piridin-2-il)etil)urea

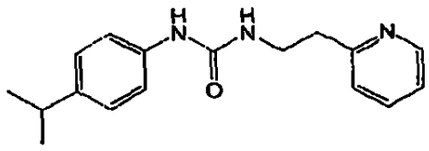


Preparado en una manera similar al ejemplo 158 utilizando 2-(piridin-2-il)etanamina y 1-etoxi-4-isocianatobenceno Rendimiento 95% p f 163-164°C ^{1}H NMR (500 MHz, $CDCl_3$) δ 1 43 (t, 3H), 3 03 (t, 2H), 3 68 (t, 2H), 4 03 (q, 2H), 5 69 (br s, 1H), 6 45 (br s, 1H) 6 84 (m 2H), 7 14 (m, 3H), 7 20 (d, 1H), 7 64 (dt, 1H) 8 43 (dd, 1H) MS (M+H, 286)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 4 1 µM y cuando se presenta en 1 µM mejora la efectividad del glutamato de monosodio con una relación de EC_{50} de 4 2

Ejemplo 161

1-(4-isopropilfenil)-3-(2-(piridin-2-il)etil)urea



Preparado en una manera similar al ejemplo 158 utilizando 2-(piridin-2-il)etilamina y 1-isocianato-4-isopropilbenceno Se purifica a través de cromatografía en columna (1% de MeOH en CH_2Cl_2 a 3% de MeOH en CH_2Cl_2) para producir 1-(4-isopropilfenil)-3-(2-(piridin-2-il)etil)urea (130 mg 50%) como un solido blanco p f 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)

El compuesto tuvo una EC_{50} para la activación de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 de 0 98 μM

Los compuestos 'urea adicionales se sintetizaron y se probaron experimentalmente y se encontro que tienen un nivel relativamente elevado de efectividad como un indicador de un receptor acre hT1R1/hT1R3 expresado en una linea celular HEK293 Los resultados de esa prueba se muestran posteriormente en la Tabla C

Tabla C - Ureas Acres

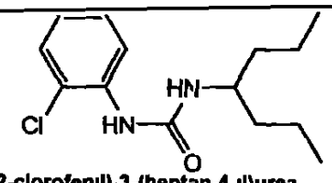
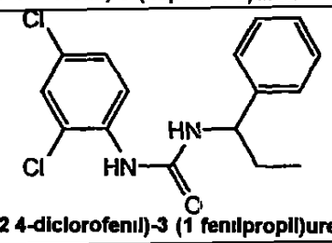
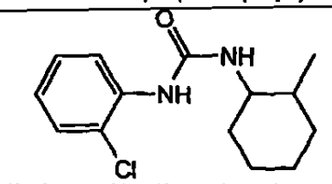
Compuesto No	Nombre IUPAC	EC_{50} Acre (uM)	relación Ec50 (contra MSG)	Con (uM)
C1	 1 (2-clorofenil)-3-(heptan-4 il)urea	0 37	4 95	1
C2	 1-(2 4-diclorofenil)-3 (1 fenilpropil)urea	0 49	4 52	1
C3	 1-(2-clorofenil)-3-(2-metilciclohexil)urea	0 52	3 24	3

Tabla C Ureas Acres

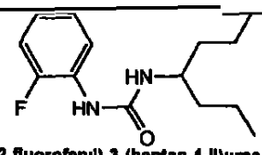
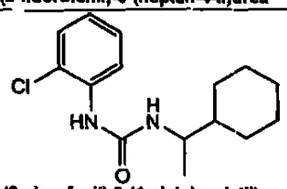
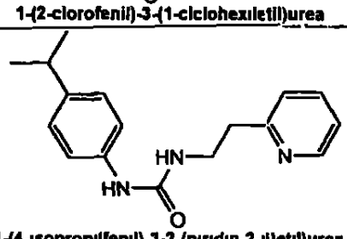
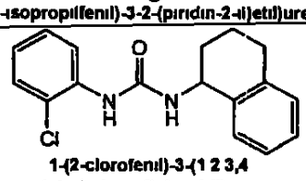
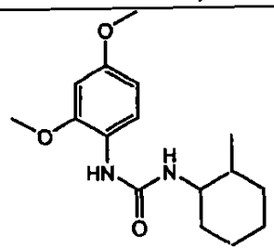
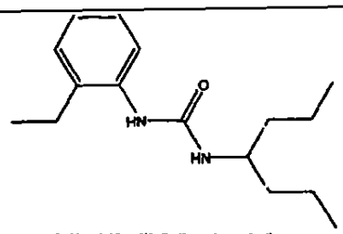
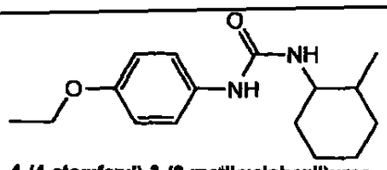
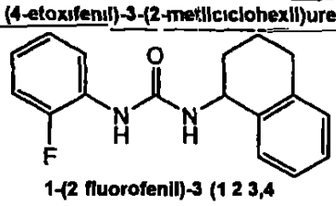
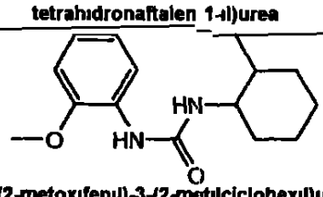
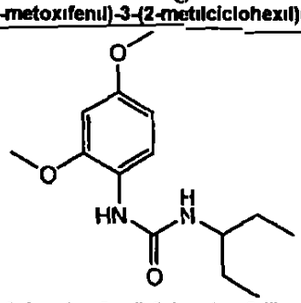
Compuesto No	Nombre IUPAC	EC_{50} Acre (uM)	relación Ec50 (contra MSG)	Con (uM)
C4	 1-(2 fluorofenil)-3 (heptan-4-il)urea	0 79	12 15	3
C5	 1-(2-clorofenil)-3-(1-ciclohexiletil)urea	0 84	9 08	1
C6	 1-(4-isopropilfenil)-3-2-(piridin-2-il)etil)urea	0 98		
C7	 1-(2-clorofenil)-3-(1 2 3,4 tetrahidronaftalen 1-il)urea	0 99	3 68	1
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		

Tabla C Ureas Acres

Compuesto No	Nombre IUPAC	EC_{50} Acre (uM)	relación Ec_{50} (contra MSG)	Con (uM)
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		
C13	 1 (2 4-dimetoxifenil)-3-(pentan-3 il)urea	1 72	11 87	1

Numerosos compuestos amida de la Fórmula (I) que caen dentro del subgénero de los compuestos acrilamida descritos en alguna otra parte en la presente se sintetizaron también y se probaron experimentalmente para efectividad con un activador de un receptor acre hT1R1/hT1R3 expresado en una línea celular HEK293 Los resultados de esa prueba se muestran posteriormente en la Tabla D

Tabla D Acrilamidas Acres

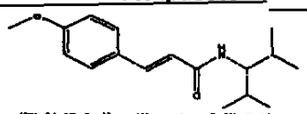
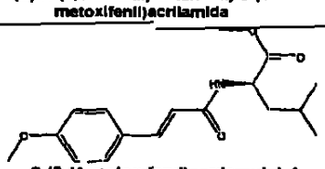
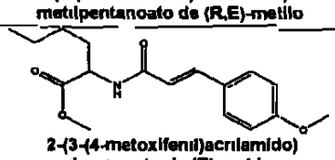
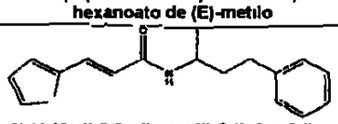
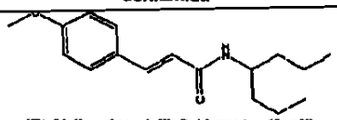
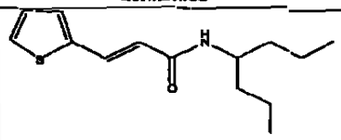
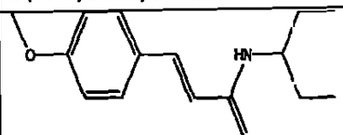
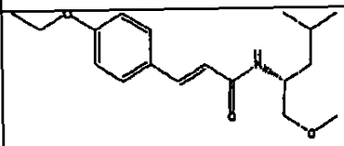
Compuesto No	Compuesto	EC_{50} Acre (uM)	relación Ec_{50} (contra MSG)	@ (uM)
D1	 (E)-N-(2,4-dimetilpentan-3-il)-3 (4-metoxifenil)acrilamida	0 29	3 46	1
D2	 2 (3-(4-metoxifenil)acrilamido)-4 metilpentanoato de (R,E)-metilo	0 32		
D3	 2-(3-(4-metoxifenil)acrilamido) hexanoato de (E)-metilo	0 63		
D4	 N-(1 Metil-3 fenil-propil)-3-tiofen 2-il acrilamida	0 69	9 73	1
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-il) acrilamida	0 82	9 62	1
D8	 (R E)-3-(4-etoxifenil)-N-(1-metoxi-4 metilpentan-2-il)acrilamida	0 94		

Tabla D Acrilamidas Acres

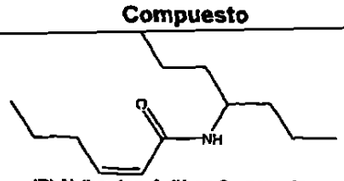
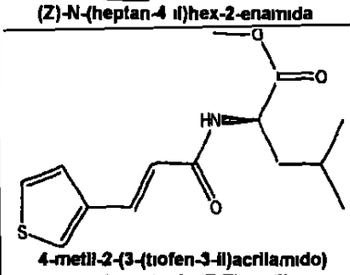
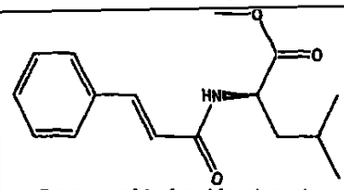
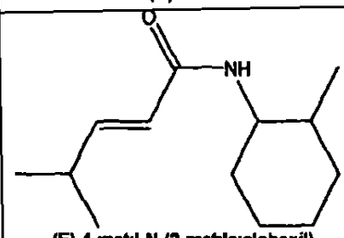
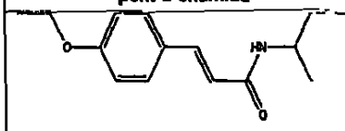
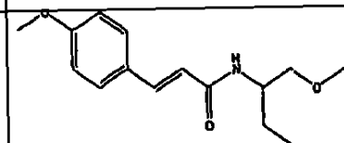
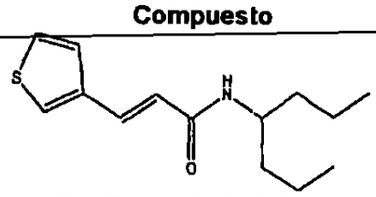
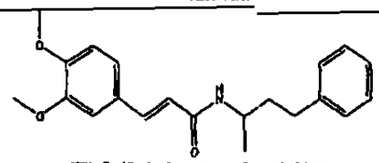
Compuesto No	Compuesto	EC_{50} Acre (uM)	relación Ec_{50} (contra MSG)	@ (uM)
D9	 (Z)-N-(heptan-4-il)hex-2-enamida	0 98		
D10	 4-metil-2-(3-(tiofen-3-il)acrilamido) pentanoato de (R,E)-metilo	1 09		
D11	 2-cinamamido-4-metilpentanoato de (R)-metilo	1 17		
D12	 (E)-4-metil N (2-metilciclohexil) pent-2-enamida	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

Tabla D Acrilamidas Acres

Compuesto No	Compuesto	EC_{50} Acre (uM)	relación Ec_{50} (contra MSG)	@ (uM)
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 Acre/Sabroso Utilizando Panelistas.

Selección General de Panelistas La selección basica de los catadores de sabor sensible Los panelistas potenciales probaron sus capacidades para clasificar las intensidades de las soluciones que representan los cinco sabores básicos Los panelistas clasificaron y evaluaron la intensidad de cinco diferentes concentraciones de cada uno de los siguientes compuestos sacarosa (dulce), cloruro de sodio (salado), ácido cítrico (agrio), cafeina (amargo) y glutamato de monosodio (sabroso) Con el fin de seleccionar la participacion en la prueba, los panelistas necesitan clasificar y evaluar correctamente las muestras para intensidad con un numero razonable de errores

Pruebas Preeliminares de Sabor Los panelistas seleccionados en el procedimiento anterior fueron considerados calificados para realizar los procedimientos de Prueba

Preeliminares de Sabor Las pruebas preeliminares de sabor se utilizan para evaluar nuevos compuestos para intensidad de sabores basicos y desagradables Un grupo pequeño de panelistas (n=5) probaron aproximadamente 5 concentraciones del compuesto (rango normalmente entre 1-100 µM, en ciclos de medio logaritmo por ejemplo, 1, 3 10 30 y 100 µM) en agua y en una solución de 12 mM de MSG para evaluar el mejoramiento Los panelistas evaluan los cincos sabores basicos (dulce, salado agrio, amargo y sabroso) asi como desagradables (tales como químicos metálicos, azufre) en la escala de magnitud etiquetada Las muestras se sirven en 10 mL de porciones a temperatura ambiente El propósito de la prueba es determinar la concentracion más elevada en la cual no exista objecion de sabor desagradable, y determinar si el sabor sabroso obvio o la mejora de sabor sabroso existen en cualquiera de las concentraciones probadas

Si el compuesto es efectivo y no tiene sabor desagradable objecionable éste se prueba con un (panel experto) entrenado en un estudio más grande

Seleccion del Panelista Entrenado Se utilizo un panel experto entrenado para evaluar ademas compuestos que han sido probados con la prueba de sabor preeliminar

Se seleccionaron panelistas para el panel entrenado a partir de un grupo mas grande de panelistas de sabor calificados Se entrenaron ademas a panelistas en el sabor sabroso clasificando y evaluando experimentos utilizando combinaciones

MSG e IMP Los panelistas completaron una serie de clasificaciones y evaluaciones y la diferencia a partir de pruebas de referencia con soluciones sabrosas En los experimentos de clasificación y evaluacion los panelistas evaluaron concentraciones de MSG faciles (0, 6, 18, 36 mM) y concentraciones de MSG mas difíciles (3, 6, 12, 18 mM de MSG) en agua

Prueba del Compuesto con Panel Entrenado Los compuestos probados por el panel entrenado se evaluaron en experimentos de diferencia a partir de la referencia Se les dio a los panelistas una muestra de referencia (12 mM de MSG + 100 µM de IMP) y se les pidió evaluar muestras en una escala de -5 a +5 en términos de diferencia en sabor sabroso a partir de la referencia (puntuación - 5 = sabor mucho menos sabroso que la referencia 0 = el mismo sabor sabroso como el de referencia, +5 = sabor mucho más sabroso que el de referencia) Las muestras de sabor fueron soluciones con cantidades variables de MSG IMP y el compuesto Normalmente, cada sesion compara la muestra de referencia a numerosas muestras de prueba Las pruebas incluyen normalmente muestras con concentraciones variables de MSG e IMP, asi como una muestra ciega de la referencia misma, para evaluar la exactitud del panel Los resultados de las pruebas de sabor se describen en la tabla 3 y muestran que los compuestos de la invencion han sido encontrados para proporcionar sabor sabroso o mejorar el sabor sabroso en 3 µM + MSG cuando se

compara a 100 µM de IMP + MSG Los compuestos se probaron contra la referencia en muestras con y sin 12 mM MSG Todas las muestras se presentaron en volumenes de 10 ml a temperatura ambiente Dos sesiones se completaron para cada compuesto probado para evaluar la reproductibilidad del panel

Prueba de Sabor en Prototipo del Producto Podria hacerse de manera similar como se describe anteriormente

Tabla 3 Resultados de Prueba de Sabor Sabroso

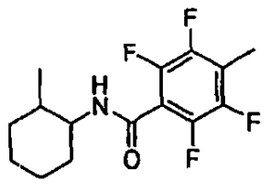
Compuesto No	Nombre Quimico	Datos de Sabor
Ejemplo 1	N-(heptan 4 il)benzo[d][1 3]dioxol 5-carboxamida	12 mM MSG + 3 µM cpd tan concentrado como 12mM MSG+ 100 µM IMP
Ejemplo 6	(R)-metil 2-(benzo[d][1 3]dioxol 6-carboxamido)-4-metilpentanoato	12 mM MSG + 10 µM cpd tan concentrado como 12mM MSG+ 100 µM IMP
Ejemplo 71	(R)-N-(1-metoxi 4 metilpentan-2 il) 3 4-dimetilbenzamida	12 mM MSG + 3 µM cpd tan concentrado 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 concentrado como 12 mM MSG+ 100 µM IMP
Ejemplo104	4-Metoxi-N-(1-metoximetil-3-metil butil)-3-metil-benzamida	12 mM MSG + 3 µM cpd tan concentrado 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 concentrado como 12mM MSG+ 100 µM IMP
Ejemplo157	N^1 (2-metoxi-4-metilbencil) N^2-(2-(5 metilpiridin-2 il)etil)oxalamida	12 mM MSG + 0 3 µM cpd tan concentrado como 12mM MSG+ 100 µM IMP

Ejemplos de Amidas Dulces

Numerosos compuestos amida de la Formula (I) se sintetizaron y probaron experimentalmente para efectividad como un activador de un receptor 'dulce' hT1R2/hT1R3 expresado en una línea celular HEK293 Ejemplos de la síntesis y la prueba de efectividad biológica en términos de mediciones EC_{50} Dulces de tales compuestos dulces se listan posteriormente Además, muchas de las amidas 'dulces" de la Fórmula (I) se clasificaron tambien para la actividad en ensayos de EC_{50} acre y EC_{50}, y como se ilustra posteriormente algunos de los compuestos amida de la Formula (I) tienen actividad significativa y potencial para servir simultáneamente como mejoradores de sabor dulce y sabroso para uso en productos y composiciones comestibles y medicinales

Ejemplo 162

2 3 5 6-tetrafluoro-4-metil-N-(2-metilciclohexil)benzamida



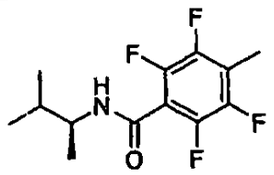
Se mezclaron en 200 ml de DCM anhidro y 30 ml de DMF anhidro acido 2,3 5,6-tetrafluoro-*p*-toluico (4 00 g 19 22 mmoles), HOBt (5 19 g, 38 44 mmoles) y EDCI (4 41 g 23 06 mmoles) La mezcla se enfrió a 0°C y se permitió agitar bajo Ar durante 15 minutos A la mezcla se agregó 2-

metilciclohexanamina (3 05 mL 23 06 mmoles) y la mezcla de reacción se permitio calentar lentamente a temperatura ambiente y se agito durante la noche La mezcla de reaccion se diluyó con DCM, se lavó con 1N HCl, agua $NaHCO_3$ acuoso, agua y salmuera, secando sobre $MgSO_4$ la filtración y la remoción del solvente *in vacuo,* produjo el producto sin purificar como un sólido amarillo pálido La recristalización ($EtOH/H_2O$) y el secado *in vacuo* dio 5 23 g del compuesto del titulo como un solido blanco (mezcla de 2 diasteromeros, 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) p f 202-204°C

El compuesto tuvo una EC_{50} para la activación de un receptor dulce hT1R2/hT1R3 expresado en una linea celular HEK293 de 0 39 μM

Ejemplo 163

(S)-2 3 5 6-tetrafluoro-4-metil-N-(3-metilbutan-2-il)benzamida

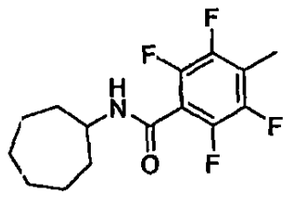


Preparado en una manera similar al Ejemplo 162 utilizando (S)-3-metilbutan-2-amina y ácido 2,3,5,6-tetrafluoro-*p*-toluico (93%) ^1H NMR ($CDCl_3$) δ 0 98 (d J= 6 9 Hz 6H) 1 18 (d, J= 6 8 Hz, 3H), 2 29 (m 3H) 4 09 (m 1H), 5 72 (bs, 1H) MS (304 1, M+H) p f 146-147°C

El compuesto tuvo una EC_{50} para la activación de un receptor dulce hT1R2/hT1R3 expresado en una línea celular HEK293 de 0 6 µM

Ejemplo 164

N-cicloheptil-2 3 5 6 tetrafluoro-4-metilbenzamida

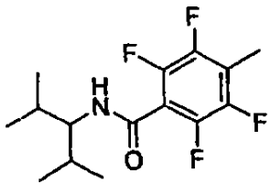


Preparado en una manera similar al Ejemplo 162 utilizando cicloheptilamina y acido 2,3,5,6-tetrafluoro-*p*-toluico (94%) ^{1}H NMR ($CDCl_3$) δ 1 53 (m 6H), 1 57 (m, 4H), 2 03 (m 2H) 2 28 (m 3H), 4 17 (m 1H) 5 85 (bs, 1H) MS (304 1 M+H) p f 164-165°C

El compuesto tuvo una EC_{50} para la activación de un receptor dulce hT1R2/hT1R3 expresado en una línea celular HEK293 de 1 85 µM

Ejemplo 165

N-(2 4-dimetilpentan-3-il)-2,3 5 6-tetrafluoro-4-metilbenzamida

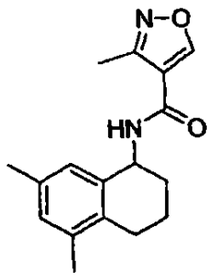


Preparado en una manera similar al Ejemplo 162 utilizando 2,4-dimetilpentan 3-amina y ácido 2,3,5,6-tetrafluoro-*p*-toluico (90%) ^{1}H NMR ($CDCl_3$) δ 0 91 (d J = 6 7 Hz, 6H), 1 00 (d, J = 6 8 Hz, 6H), 1 85 (m 2H), 2 29 (m 3H) 3 82 (m 1H) 5 52 (bd 1H) MS (306 1 M+H) p f 184-187°C

El compuesto tuvo una EC_{50} para la activación de un receptor dulce hT1R2/hT1R3 expresado en una linea 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 solucion del ácido 3-metilisoxazol-4-carboxilico (83 mg 0 067 mmoles), HOBt (100 mg 0 74 mmoles) y EDCI HCl (142 mg, 0 74 mmoles) en DMF (4 mL) se agregó 5,7-dimetil-1 2,3 4-tetrahidronaftil-1-amina (ejemplo 166a) (130 mg, 0 74 mmoles) La mezcla de reacción se agitó durante 24 horas a temperatura ambiente en cuyo tiempo el solvente se removió bajo presion reducida y el residuo se purificó por cromatografía en columna instantánea (10 1 Hex EtOAc) para producir 134 mg de *N*-

(5,7-dimetil-1,2,3,4-tetrahidronaftalen-1-il)-3-metilisoxazol-4-carboxamida (70%) como un solido espumoso blanco ^{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) P f 57-58°C

a 5,7-dimetil-1,2 3 4-tetrahidronaftalen-1-amina Una cantidad catalítica del niquel Raney (suspensión en agua) se lavo con MeOH seco bajo argón en un matraz de fondo redondo A una solución del Ni Raney lavado en amoniaco metanólico (25 mL 7N), se agregó 5,7-dimetil-3 4-dihidronaftalen-1(2H)-ona oxima (ejemplo 166b) (420 mg 2 22 mmoles) y la mezcla se agitó bajo un balón de H_2 durante 20 horas Una vez completada la reaccion se filtró a través de celite, el filtrado se concentró *in vacuo*, se diluyo con EtOAc, se lavo con agua y salmuera, se secó sobre $MgSO_4$, se filtró y el solvente se removio bajo presión reducida para producir 360 mg de 5,7-dimetil-1 2 3 4 tetrahidronaftalen-1-amina (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)

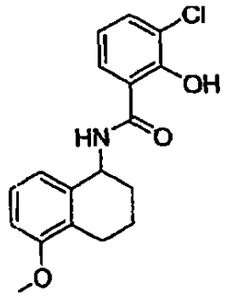
b Preparación de la 5,7-dimetil-3,4-dihidronaftalen-1(2H)-ona oxima A una mezcla de la 5,7-dimetil-3,4-dihidronaftalen-1(2H)-ona (2 0 g, 11 48 mmoles) y clorhidrato de

hidroxilamina (1 6 g, 19 73 mmoles) en 10 ml de agua a 70°C, se agregaron MeOH (14 mL), THF (3 mL) y una solución de acetato de sodio (2 53 g, 30 83 mmoles, en 7 mL de H_2O) La agitación se continuó durante 85 minutos a 70°C, en cuyo tiempo un precipitado se formó y 10 ml de agua se agregaron La mezcla resultante se agitó a temperatura ambiente durante 2 horas En la terminacion, el producto se recolecto por filtracion para producir 2 12 g de 5,7-dimetil-3,4-dihidronaftalen-1(2H)-ona oxima (98%) MS (M+H, 190)

El compuesto tuvo una EC_{50} para la activacion de un receptor dulce hT1R2/hT1R3 expresado en una linea celular HEK293 de 0 76 µM

Ejemplo 167

3-cloro-2-hidroxi-*N*-(5-metoxi-1,2,3,4-tetrahidronaftalen-1-il)benzamida



Preparado en una manera similar al Ejemplo 166 utilizando 5-metoxi-1 2,3,4-tetrahidronaftalen-1-amina (Ejemplo 167a) Rendimiento 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) p f 175-176°C

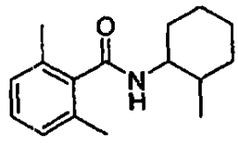
a 5-Metoxı-1,2,3,4-tetrahıdronaftalen-1-amına

Preparada en una manera sımılar al ejemplo 166a utılizando 5-metoxı-3,4-dıhıdronaftalen-1(2H)-ona Rendımiento 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)

El compuesto tuvo una EC_{50} para la activación de un receptor dulce hT1R2/hT1R3 expresado en una linea celular HEK293 de 0 21 μM

Ejemplo 168

2 6-dımetıl-N-(2-metılcıclohexıl)benzamıda



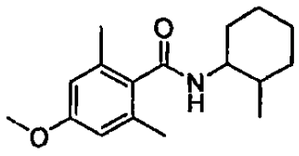
Preparado en una manera sımılar al Ejemplo 162 utılizando ácıdo 2 6-dımetılbenzoıco y 2-metılcıclohexılamına Rendımiento 59% ^{1}H NMR (500 MHz, $CDCl_3$) δ 0 88-0 94 (3H, dd) 1 14-1 89 (9H m), 2 21-2 22 (6H, d), 3 39-3 45 (1H m) 7 02-

7 03 (2H, d), 7 12-7 15 (1H, t), 8 11-8 13 (1H, d) MS (M+H 246 2)

El compuesto tuvo una EC_{50} para la activación de un receptor dulce hT1R2/hT1R3 expresado en una línea celular HEK293 de 1 88 µM

Ejemplo 169

4-metoxi-2 6-dimetil-N-(2-metilciclohexil)benzamida



Preparado en una manera similar al Ejemplo 166, utilizando ácido 4-metoxi-2,6 dimetilbenzoico (ejemplo 169a) y 2-metilciclohexilamina ^{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 acido 4-metoxi-2,6-dimetilbenzoico Se disolvió sin purificación adicional el 2-bromo-5-metoxi-1 3-dimetilbenceno (Ejemplo 169b) (3 38 g 15 79 mmoles) en 100 ml de THF seco La mezcla se enfrió a -78°C y bajo n-butil-litio de argón (solucion de 1 6 M en hexanos, 9 9 ml, 15 8 mmoles) se agrego en gotas durante 15 minutos y la mezcla se agitó durante 15 minutos más a -78°C Entonces piezas pequeñas de hielo seco se agregaron y la mezcla se agito 20 minutos a -78°C Entonces el enfriamiento se removió y la mezcla se agitó siempre y cuando la evolución del

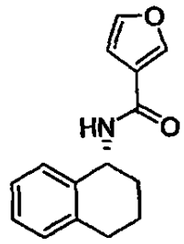
dióxido de carbono continuo Luego, la mezcla se vertio sobre hielo (100 mL) y se acidificó utilizando 6N HCl La capa orgánica se separó y la fase acuosa se extrajo con EtOAc Los extractos organicos se combinaron, se lavaron con salmuera agua se secaron sobre $MgSO_4$ y se concentraron bajo vacio El producto del ácido 4-metoxi-2,6-dimetilbenzoico se obtuvo como un solido blanco (2 7 g 95%) (M+H 181)

b 2-Bromo-5-metoxi-1,3-dimetilbenceno 20 mmoles de 1-metoxi-3,5-dimetilbenceno (2 82 mL) se disolvió en 100 ml de acetonitrilo seco seguido por 22 mmoles (3 56 g) de N-bromosuccinimida La mezcla se agitó a temperatura ambiente durante la noche Luego, el solvente se evaporo bajo presion reducida y se extrajo por filtración un solido y se lavó con hexanos proporcionando 2-bromo-5-metoxi-1,3-dimetilbenceno (3 9 g 92%) como un sólido blanco ^1H NMR (500 MHz $CDCl_3$) δ 2 41 (6H, s), 3 78 (3H s), 6 67 (2H, s)

El compuesto tuvo una EC_{50} para la activación de un receptor dulce hT1R2/hT1R3 expresado en una linea celular HEK293 de 2 1 μM

Ejemplo 170

(R)-N-(1 2 3 4-tetrahidronaftalen-1-il)furan-3-carboxamida

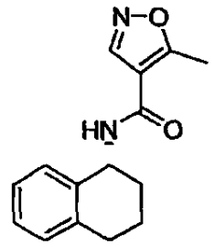


A una solución del ácido furan-3-carboxílico (100 mg, 0 68 mmoles), HOBt (240 mg 1 78 mmoles) y EDCI HCl (196 mg, 1 03 mmoles) en CH_2Cl_2 (8 mL) y DMF (1 5 mL) a 0°C, se agregó (*R*)-1 2 3,4-tetrahidronaftalen 1-amina (160 µL 1 06 mmoles) La reaccion se agito a temperatura ambiente durante 24 horas despues de lo cual se agregó CH_2Cl_2 La solución resultante se lavó con $NaHCO_3$ saturado H_2O, salmuera, se secó sobre $MgSO_4$ y se concentró *in vacuo* La recristalizacion a partir de $EtOH/H_2O$ produjo (*R*)-*N*-(1 2 3 4-tetrahidronaftalen-1-il)-2,5-dihidrofuran-3-carboxamida ^1H 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)

El compuesto tuvo una EC_{50} para la activación de un receptor dulce hT1R2/hT1R3 expresado en una linea celular HEK293 de 6 6 µM

Ejemplo 171

(*R*)-5-metil-*N*-(1 2 3 4-tetrahidronaftalen-1-il)isoxazol-4-carboxamida

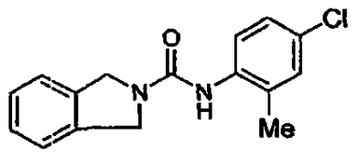


Preparado en una manera similar al Ejemplo 170 utilizando el ácido 5-metilisoxazol-4-carboxílico Purificado por TLC preparativa (5 1 Hex EtOAc) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1 80 (m, 3H), 2 12 (m, 1H), 2 74 (s, 3H) 2 85 (m, 2H), 5 35 (m, 1H), 5 89 (br d, 1H *J*= 7 75 Hz) 7 10 (m, 1H) 7 18 (m, 2H), 7 32 (m, 1H) 8 26 (s, 1H) MS (M+H 257)

El compuesto tuvo una EC_{50} para la activación de un receptor dulce hT1R2/hT1R3 expresado en una línea celular HEK293 de 8 1 μM

Ejemplo 172

N-(4-cloro-2-metilfenil)isoindolin-2-carboxamida



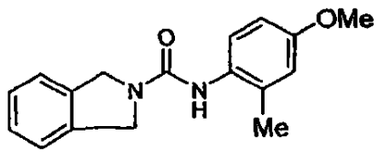
A una solución de isoindolina (238 mg 2 0 mmoles) en 1,4-dioxano seco (10 mL) se agregó isocianato de 4-cloro-2-

metilfenilo (335 mg, 2 0 mmoles) bajo argón a temperatura ambiente La mezcla de reaccion se agitó entonces a temperatura ambiente durante la noche El solvente se evaporo bajo presion reducida y el residuo se purifico por recristalización a partir de etanol para dar el compuesto del título (540 mg, 94%) como un solido blanco ^{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 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 tuvo una EC_{50} para la activación de un receptor dulce hT1R2/hT1R3 expresado en una linea celular HEK293 de 0 89 μM

Ejemplo 173

N-(4-metoxi-2-metilfenil)isoindolin-2-carboxamida



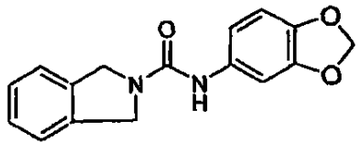
A una solucion de la isoindolina (576 mg, 4 0 mmoles) en 1,4-dioxano seco (20 mL) se agregó isocianato de 4-metoxi-2-metilfenilo (815 mg, 5 0 mmoles) bajo argón a temperatura ambiente La mezcla de reacción se agito entonces a temperatura

ambiente durante la noche El solvente se evaporó bajo presion reducida, y el residuo se purificó por cromatografia en gel de sílice (EtOAc/hexanos 1 1) para dar el compuesto del titulo (1 18 g, 84%) como un sólido blanco ^{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 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 tuvo una EC_{50} para la activación de un receptor dulce hT1R2/hT1R3 expresado en una linea celular HEK293 de 4 5 μM

Ejemplo 174

N-(3 4-metilendioxifenil)isoindolin-2-carboxamida



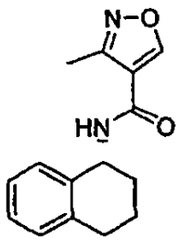
A una solucion de la 3 4-(metilendioxi)anilina (150 mg, 1 09 mmoles) en DCM seco (4 mL) se agrego en gotas cloroformiato de fenilo (0 138 ml, 1 09 mmoles) y trietilamina (0 153 ml, 1 09 mmoles) Después que la mezcla de reacción se agito a temperatura ambiente durante 8 horas, se agregaron

isoindolina (0 123 ml, 1 09 mmoles) y trietilamina (0 153 ml, 1 09 mmoles), y la mezcla de reacción se agitó durante la noche El solvente se removio entonces bajo presion reducida y el residuo se purifico por cromatografía en gel de sílice (EtOAc/Hexano 1 3) para dar el compuesto del titulo (185 mg, 60%) como un solido blanco p f 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)

El compuesto tuvo una EC_{50} para la activación de un receptor dulce hT1R2/hT1R3 expresado en una linea celular HEK293 de 1 05 µM

Ejemplo 175

(1,2 3 4-tetrahidro-naftalen-1-il)-amida del ácido 3-Metil-isoxazol-4-carboxílico



A una solucion del acido 3-Metil-isoxazol-4-carboxilico (0 52 g 4 06 mmoles) en DCM (15 mL) y DMF (2 mL) se agrego HBOt (1 1 g, 8 14 mmoles) y EDCI (0 896 g, 4 67 mmoles) La solución amarilla transparente se enfrió a 0°C y se permitió agitar bajo Ar durante 15 minutos A la solución se le agregó (R)-1-

Amino-1,2,3 4-tetrahidronaftaleno (0 73 ml, 5 04 mmoles) y la mezcla de reacción se permitió calentar lentamente a temperatura ambiente y se agitó durante la noche La dilucion con DCM (50 mL) se siguio por la extraccion acuosa ($NaHCO_3$), agua, salmuera (50 mL), se seco sobre $MgSO_4$, la filtración y la remocion del solvente *in vacuo* La cromatografía de gel de silice (0–25% de Hexano EtOAC) produjo el compuesto del titulo (650 mg 62 5%) como un sólido pegajoso ^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 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 tuvo una EC_{50} para la activacion de un receptor dulce hT1R2/hT1R3 expresado en una línea celular HEK293 de 5 8 μM

Numerosos compuestos amida de la Formula (I) se sintetizaron y se probaron experimentalmente tambien para efectividad como un activador de un receptor "dulce" hT1R2/hT1R3 expresado en una línea celular HEK293

Los resultados de esa prueba se muestran posteriormente en la Tabla E

Tabla E Amidas Mejoradoras Endulzantes

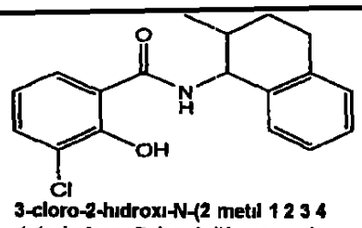
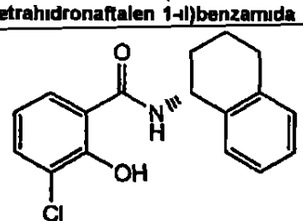
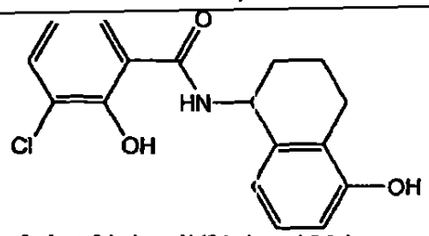
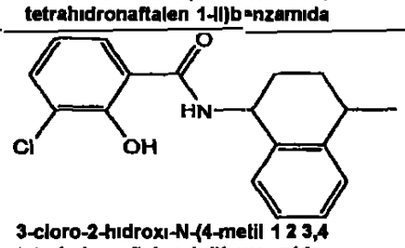
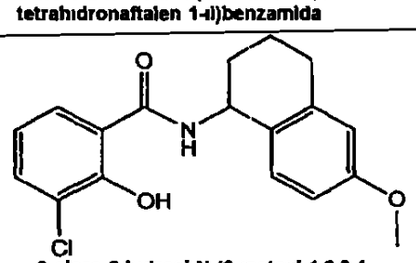
Compuesto No	Compuesto	EC_{50} Dulce (uM)	EC_{50} Acre (uM)	relación EC_{50} Acre
E1	 3-cloro-2-hidroxi-N-(2 metil 1 2 3 4 tetrahidronaftalen 1-il)benzamida	0 19		
E2	 (R)-3-cloro 2-hidroxi-N-(1 2 3 4-tetrahidronaftalen 1-il)benzamida	0 65		
E3	 3-cloro 2 hidroxi-N-(6 hidroxi 1 2 3,4 tetrahidronaftalen 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 Endulzantes

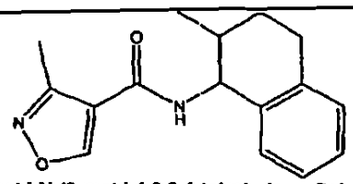
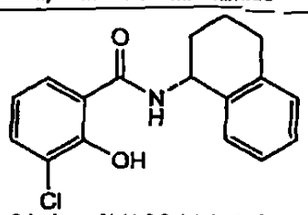
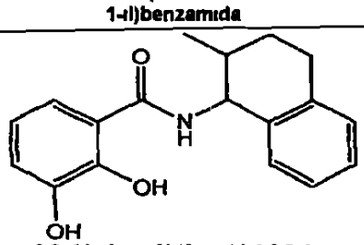
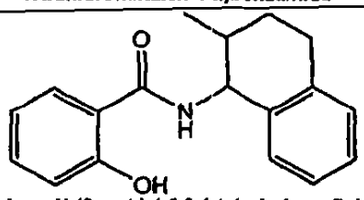
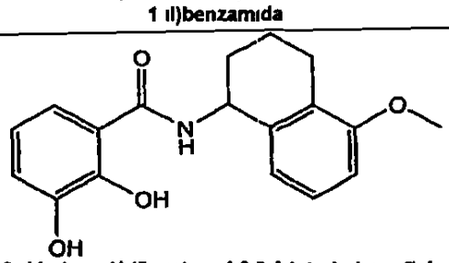
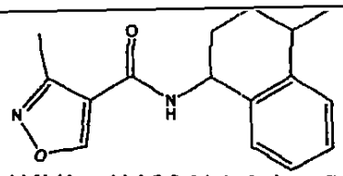
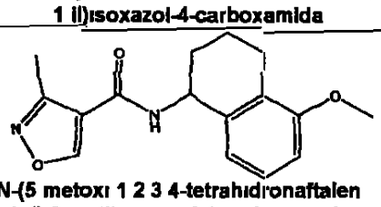
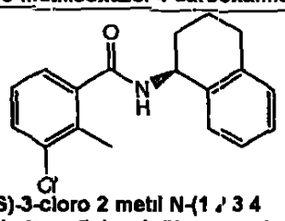
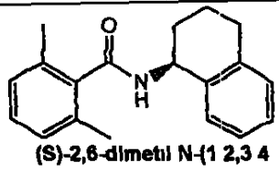
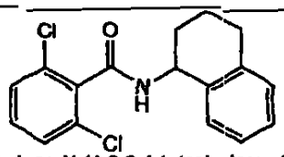
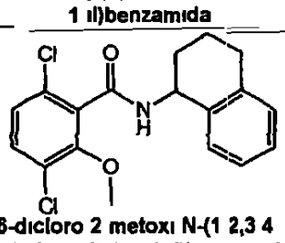
Compuesto No	Compuesto	EC_{50} Dulce (uM)	EC_{50} Acre (uM)	relación EC_{50} Acre
E6	 3-metil-N-(2-metil 1 2 3,4 tetrahidronaftalen 1-il)isoxazol-4-carboxamida	1 48		
E7	 3-cloro-2-hidroxi N (1 2 3 4 tetrahidronaftalen 1-il)benzamida	1 81		4 04
E8	 2 3-dihidroxi-N-(2-metil 1 2 3 4 tetrahidronaftalen 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 Endulzantes

Compuesto No	Compuesto	EC_{50} Dulce (uM)	EC_{50} Acre (uM)	relación EC_{50} Acre
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	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		

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Tabla E Amidas Mejoradoras Endulzantes

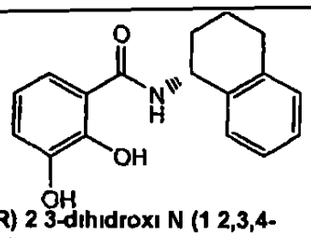
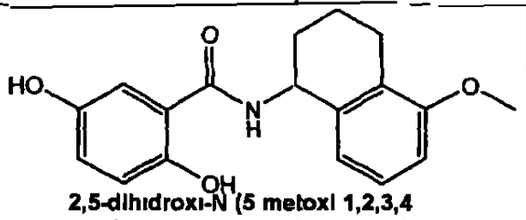
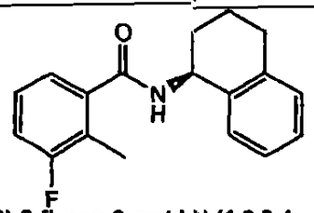
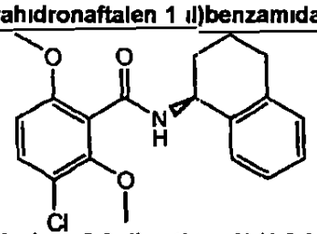
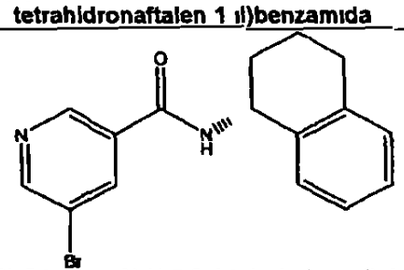
Compuesto No	Compuesto	EC_{50} Dulce (uM)	EC_{50} Acre (uM)	relación EC_{50} Acre
E17	 (R) 2 3-dihidroxi N (1 2,3,4-tetrahidronaftalen 1-il)benzamida	3 17		
E18	 2,5-dihidroxi-N (5 metoxi 1,2,3,4 tetrahidronaftalen 1-il)benzamida	3 38		
E19	 (S)-3 fluoro 2-metil N (1 2,3,4 tetrahidronaftalen 1 il)benzamida	3 57		
E20	 (S)-3-cloro 2 6-dimetilioxi-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 Endulzantes

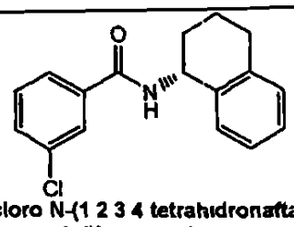
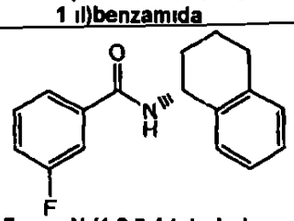
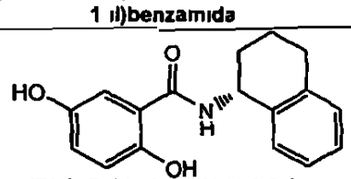
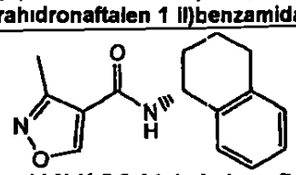
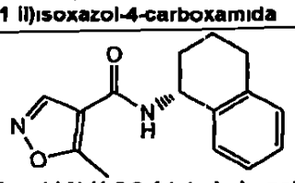
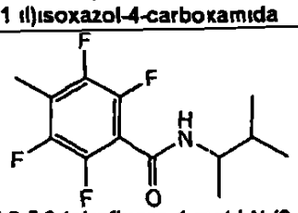
Compuesto No	Compuesto	EC_{50} Dulce (uM)	EC_{50} Acre (uM)	relación EC_{50} Acre
E22	 (R)-3-cloro N-(1 2 3 4 tetrahidronaftalen 1 il)benzamida	4 52		
E23	 (R)-3 fluoro N-(1 2 3 4 tetrahidronaftalen 1 il)benzamida	4 86		
E24	 (R) 2 5-dihidroxi N-(1 2 3,4 tetrahidronaftalen 1 il)benzamida	6 04		
E25	 (R)-3 metil N-(1 2 3 4 tetrahidronaftalen 1 il)isoxazol-4-carboxamida	7 79		
E26	 (R) 5-metil N (1 2 3 4 tetrahidronaftalen 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 Endulzantes

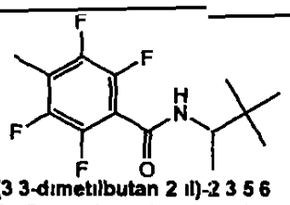
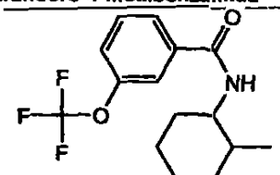
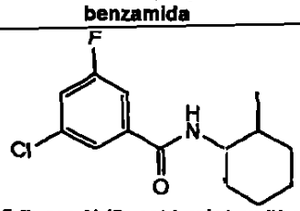
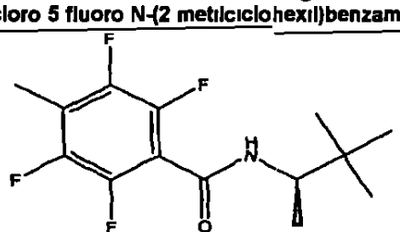
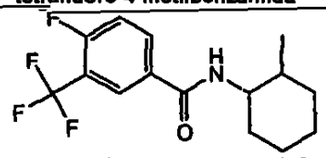
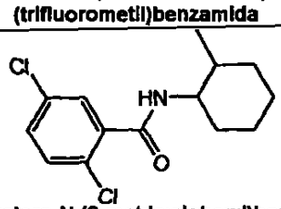
Compuesto No	Compuesto	EC_{50} Dulce (uM)	EC_{50} Acre (uM)	relación EC_{50} Acre
E28	 N-(3 3-dimetilbutan 2 il)-2 3 5 6 tetrafluoro-4 metilbenzamida	0 21		
E29	 N-(2-metilciclohexil)-3-(trifluorometoxi) benzamida	0 42		
E30	 3-cloro 5 fluoro N-(2 metilciclohexil)benzamida	0 45		
E31	 (R) N (3 3-dimetilbutan 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		

Tabla E Amidas Mejoradoras Endulzantes

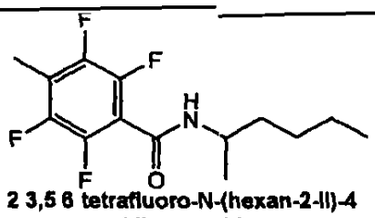
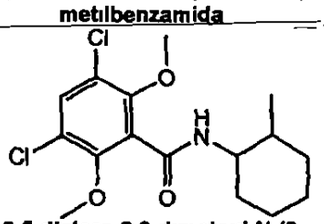
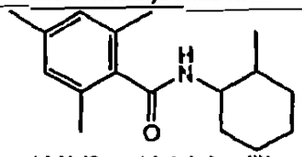
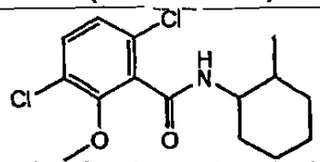
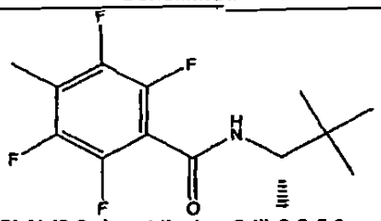
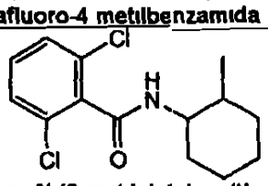
Compuesto No	Compuesto	EC_{50} Dulce (uM)	EC_{50} Acre (uM)	relación EC_{50} Acre
F34	 2 3,5 6 tetrafluoro-N-(hexan-2-il)-4 metilbenzamida	0 71		
F35	 3 5-dicloro 2,6-dimetoxi N (2-metilciclohexil)benzamida	0 71		
E36	 2,4 6 trimetil N-(2 metilciclohexil)benzamida	0 72		
E37	 3,6-dicloro 2 metoxi N (2 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 Endulzantes

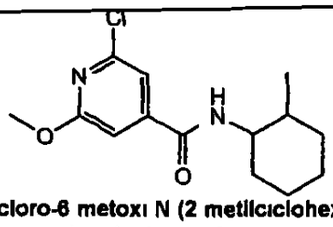
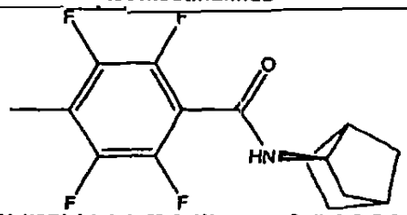
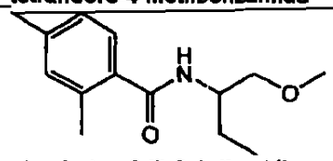
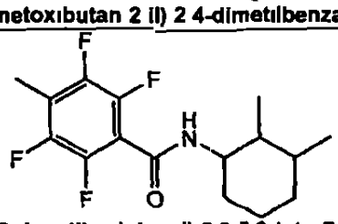
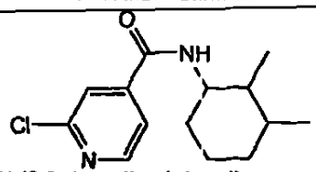
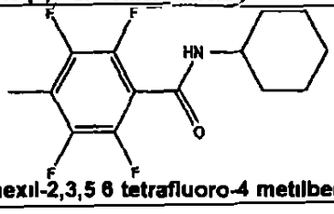
Compuesto No	Compuesto	EC_{50} Dulce (uM)	EC_{50} Acre (uM)	relacion EC_{50} Acre
E40	 2-cloro-6 metoxi N (2 metilciclohexil) isonicotinamida	0 95		9 77
F41	 N-((2R) biciclo[2 2 1]heptan-2 il)-2,3 5 6 tetrafluoro-4 metilbenzamida	1 02		
E42	 N-(1 metoxibutan 2 il) 2 4-dimetilbenzamida	1 06		
E43	 N-(2,3-dimetilciclohexil) 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 Endulzantes

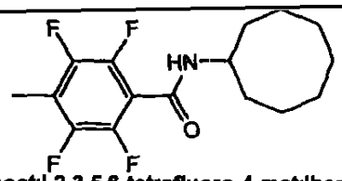
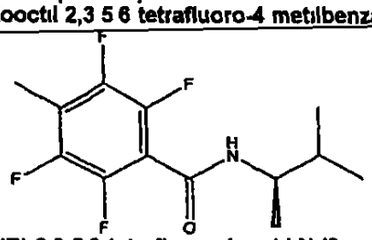
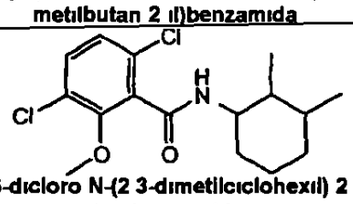
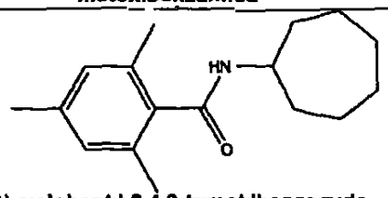
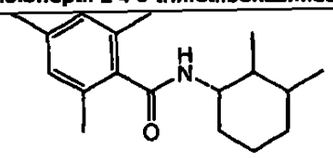
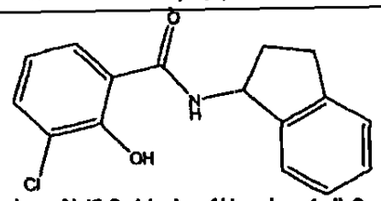
Compuesto No	Compuesto	EC_{50} Dulce (uM)	EC_{50} Acre (uM)	relación EC_{50} Acre
E46	 N-ciclooctil 2,3 5 6 tetrafluoro-4 metilbenzamida	1 25		
E47	 (R)-2,3 5 6 tetrafluoro-4 metil N (3 metilbutan 2 il)benzamida	1 25		
E48	 3,6-dicloro N-(2 3-dimetilciclohexil) 2 metoxibenzamida	1 29		
E49	 N-cicloheptil 2 4 6 trimetilbenzamida	1 39		
E50	 N-(2,3-dimetilciclohexil) 2,4,6-trimetilbenzamida	1 41		
E51	 3-cloro N (2,3-dihidro 1H inden 1 il) 2 hidroxibenzamida	1 49		

Tabla E Amidas Mejoradoras Endulzantes

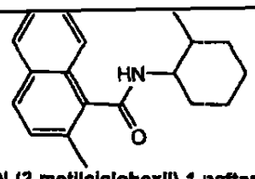
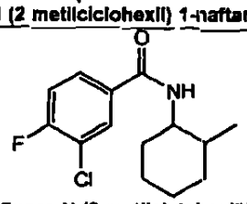
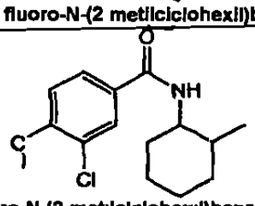
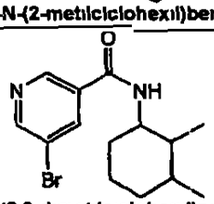
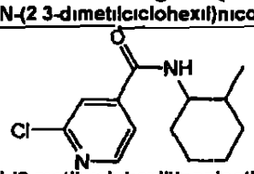
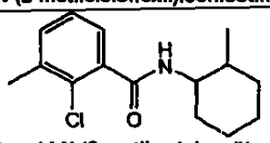
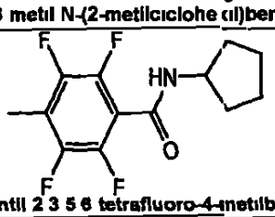
Compuesto No.	Compuesto	EC_{50} Dulce (uM)	EC_{50} Acre (uM)	relación EC_{50} Acre
E52	 2 metil N (2 metilciclohexil) 1-naftamida	1 52		
F53	 3-cloro-4 fluoro-N-(2 metilciclohexil)benzamida	1 7		
E54	 3 4-dicloro-N-(2-metilciclohexil)benzamida	1 83		10 66
E55	 5 bromo N-(2 3-dimetilciclohexil)nicotinamida	1 89		
E56	 2-cloro-N (2 metilciclohexil)isonicotinamida	1 92		2 08
E57	 2-cloro-3 metil N-(2-metilciclohexil)benzamida	1 95		
E58	 N-ciclopentil 2 3 5 6 tetrafluoro-4-metilbenzamida	2 23		

Tabla E Amidas Mejoradoras Endulzantes

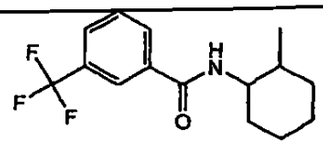
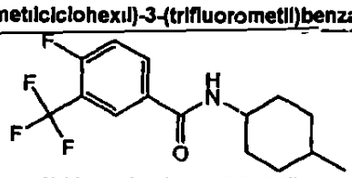
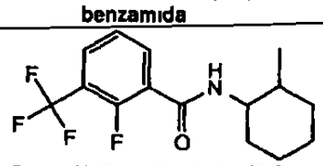
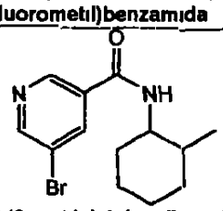
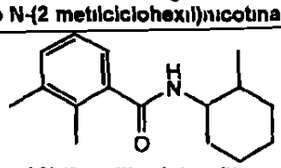
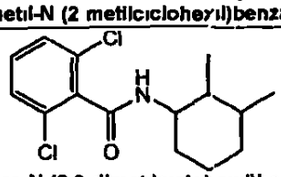
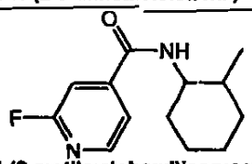
Compuesto No	Compuesto	EC_{50} Dulce (uM)	EC_{50} Acre (uM)	relación EC_{50} Acre
E59	 N-(2-metilciclohexil)-3-(trifluorometil)benzamida	2 34		2 07
E60	 4 fluoro N-(4 metilciclohexil) 3-(trifluorometil) benzamida	2 37		
E61	 2 fluoro N-(2 metilciclohexil)-3 (trifluorometil)benzamida	2 4		
E62	 5-bromo N-(2 metilciclohexil)nicotinamida	2 42		
E63	 2 3-dimetil-N (2 metilciclohexil)benzamida	2 6		
E64	 2 6-dicloro N-(2 3-dimetilciclohexil)benzamida	2 77		
E65	 2 fluoro-N-(2 metilciclohexil)isonicotinamida	2 83		

Tabla E Amidas Mejoradoras Endulzantes

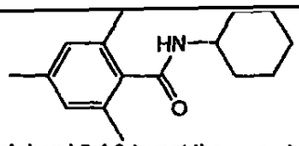
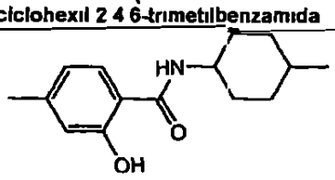
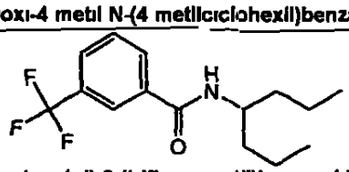
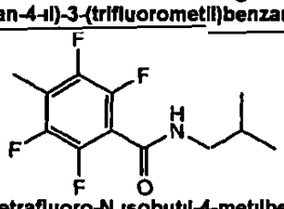
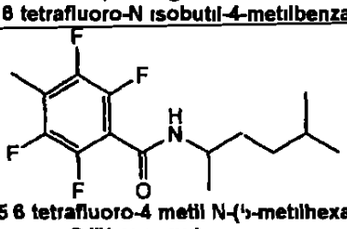
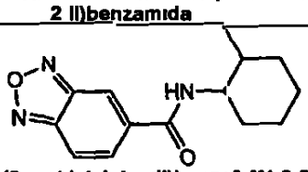
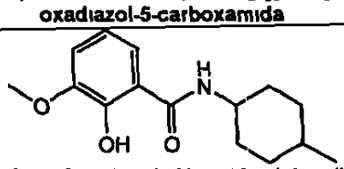
Compuesto No	Compuesto	EC_{50} Dulce (uM)	EC_{50} Acre (uM)	relación EC_{50} Acre
E66	 N-ciclohexil 2 4 6-trimetilbenzamida	2 86		
E67	 2 hidroxi-4 metil N-(4 metilciclohexil)benzamida	2 98		
E68	 N-(heptan-4-il)-3-(trifluorometil)benzamida	3 03	0 33	
E69	 2 3 5 6 tetrafluoro-N isobutil-4-metilbenzamida	3 19		
E70	 2 3 5 6 tetrafluoro-4 metil N-(5-metilhexan 2 il)benzamida	3 2		
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		

Tabla E Amidas Mejoradoras Endulzantes

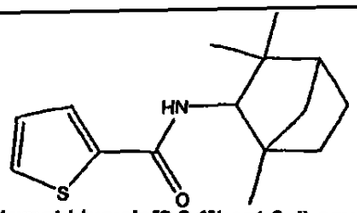
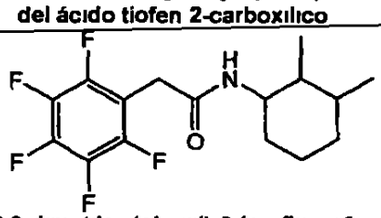
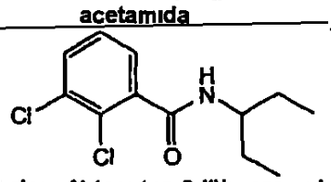
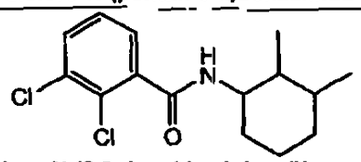
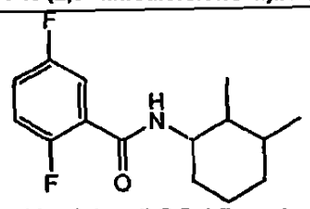
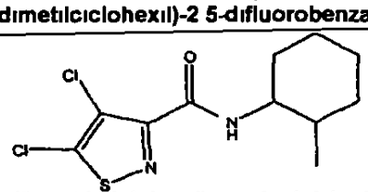
Compuesto No	Compuesto	EC_{50} Dulce (uM)	EC_{50} Acre (uM)	relación EC_{50} Acre
E73	 (1,3 3-trimetil biciclo[2 2 1]hept 2 il)-amida del ácido tiofen 2-carboxílico	3 36		
E74	 N-(2,3-dimetilciclohexil) 2 (perfluorofenil) acetamida	3 62		
E75	 2,3-dicloro-N-(pentan-3-il)benzamida	3 78		
E76	 2,3-dicloro N (2,3-dimetilciclohexil)benzamida	3 99		
F77	 N-(2 3-dimetilciclohexil)-2 5-difluorobenzamida	4 11		
E78	 (2 metil-ciclohexil)-amida del ácido 4,5-dicloro isotiazol-3-carboxílico	4 24	8 51	

Tabla E Amidas Mejoradoras Endulzantes

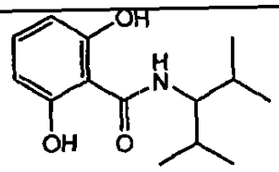
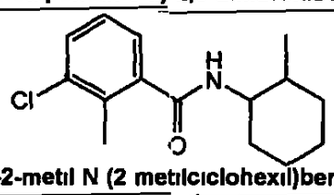
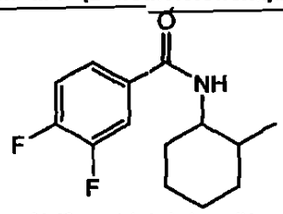
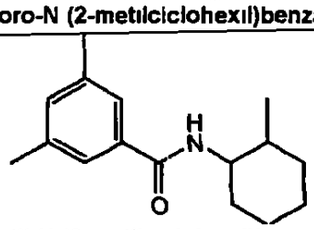
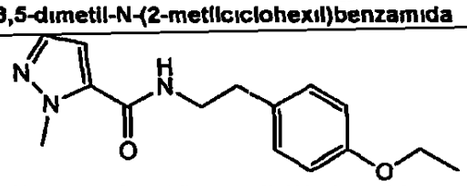
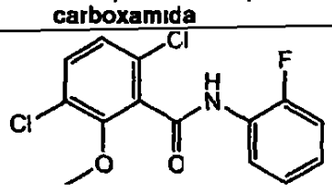
Compuesto No	Compuesto	EC_{50} Dulce (uM)	EC_{50} Acre (uM)	relación EC_{50} Acre
E79	 N-(2,4-dimetilpentan-3-il)-2,6-dihidroxibenzamida	4 26		
E80	 3-cloro-2-metil N (2 metilciclohexil)benzamida	4 29		
E81	 3 4-difluoro-N (2-metilciclohexil)benzamida	4 37		6 98
E82	 3,5-dimetil-N-(2-metilciclohexil)benzamida	4 48		
E83	 N-(4-etoxifenetil) 1-metil 1H-pirazol-5 carboxamida	4 68		
E84	 3,6-dicloro N (2 fluorofenil) 2 metoxibenzamida	0 83		16 51

Tabla E Amidas Mejoradoras Endulzantes

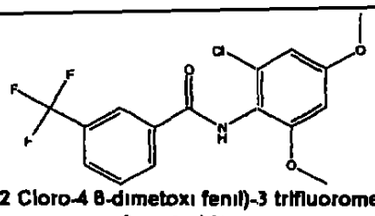
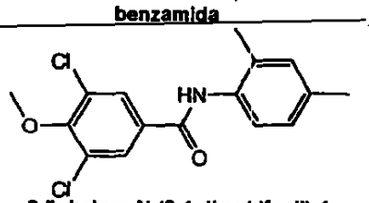
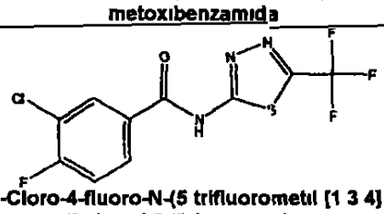
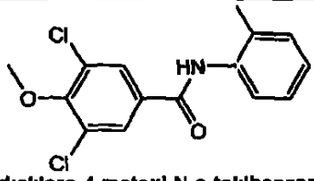
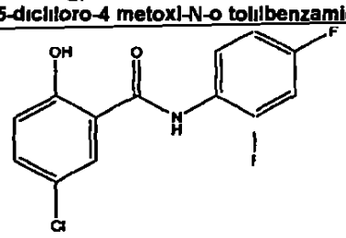
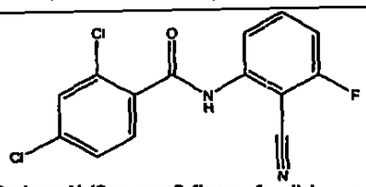
Compuesto No	Compuesto	EC_{50} Dulce (uM)	EC_{50} Acre (uM)	relación EC_{50} Acre
E85	 N-(2 Cloro-4 6-dimetoxi fenil)-3 trifluorometil benzamida	1 42		
E86	 3 5-dicloro N (2 4-dimetilfenil)-4-metoxibenzamida	1 48		
E87	 3-Cloro-4-fluoro-N-(5 trifluorometil [1 3 4] tiadiazol 2-il) benzamida	1 55		
E88	 3 5-diclloro-4 metoxi-N-o tolilbenzamida	1 84		
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		

Tabla E Amidas Mejoradoras Endulzantes

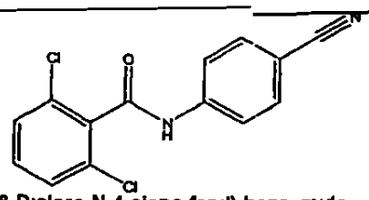
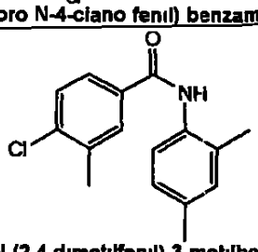
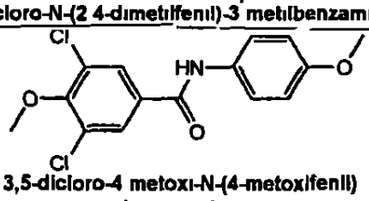
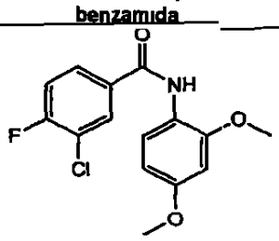
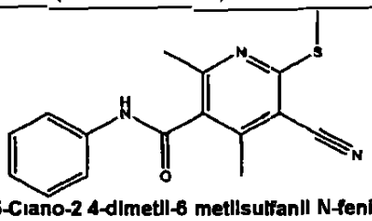
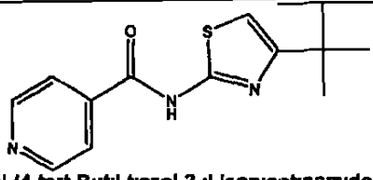
Compuesto No	Compuesto	EC_{50} Dulce (uM)	EC_{50} Acre (uM)	relación EC_{50} Acre
F91	 2 6 Dicloro N-4-ciano fenil) benzamida	2 74		
E92	 4-cloro-N-(2 4-dimetilfenil)-3 metilbenzamida	2 74		
E93	 3,5-dicloro-4 metoxi-N-(4-metoxifenil) benzamida	3 24		
E94	 3-cloro N-(2 4-dimetoxifenil)-4-fluorobenzamida	3 56		
E95	 5-Ciano-2 4-dimetil-6 metilsulfanil N-fenil nicotinamida	3 58		
E96	 N-(4 tert Butil tiazol-2 il isonicotinamida	3 73		

Tabla E Amidas Mejoradoras Endulzantes

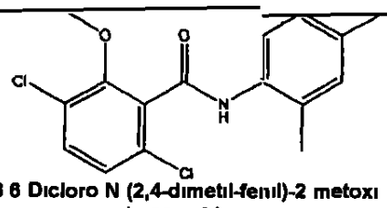
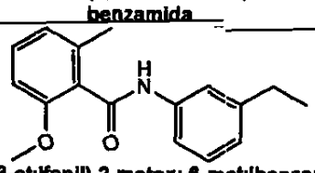
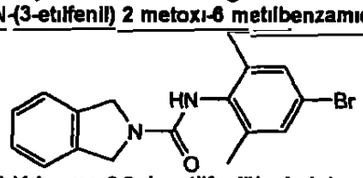
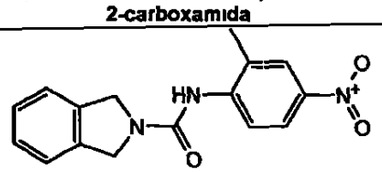
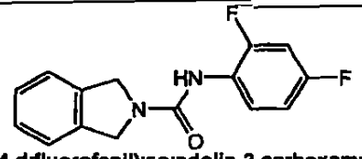
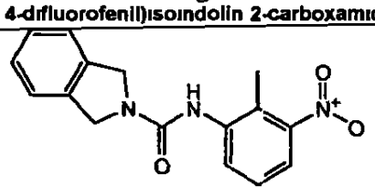
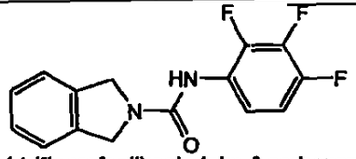
Compuesto No	Compuesto	EC_{50} Dulce (uM)	EC_{50} Acre (uM)	relación EC_{50} Acre
E97	 3 6 Dicloro N (2,4-dimetil-fenil)-2 metoxi benzamida	4 25		
E98	 N-(3-etilfenil) 2 metoxi-6 metilbenzamida	4 63		
E99	 N-(4 bromo 2 6-dimetilfenil)isoindolin 2-carboxamida	0 93		
E100	 N-(2 metil-4 nitrofenil)isoindolin-2-carboxamida	1 3		
E101	 N-2 4-difluorofenil)isoindolin 2-carboxamida	1 37		
E102	 N-(2-metil-3-nitrofenil)isoindolin 2-carboxamida	2 01		
E103	 N 2,3 4 trifluorofenil)isoindolin 2-carboxamida	2 58		

Tabla E Amidas Mejoradoras Endulzantes

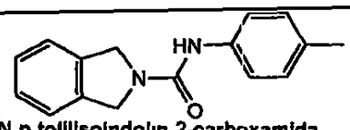
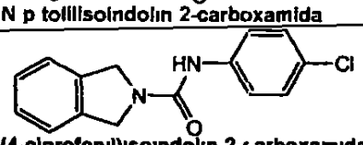
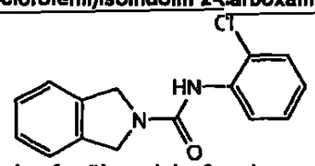
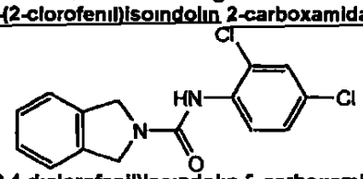
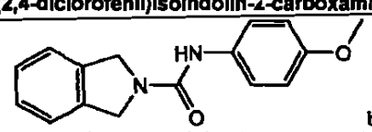
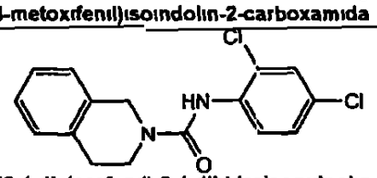
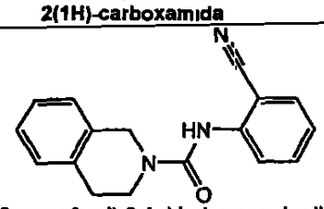
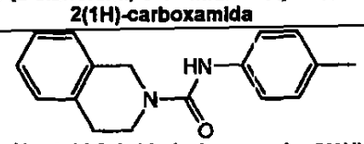
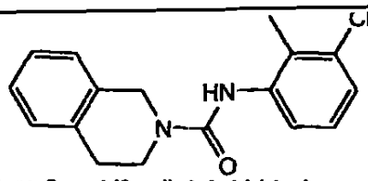
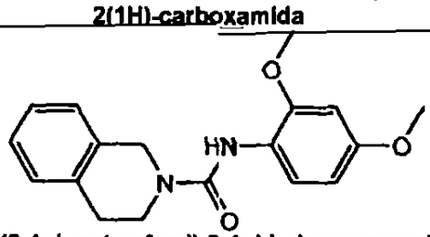
Compuesto No	Compuesto	EC_{50} Dulce (uM)	EC_{50} Acre (uM)	relación EC_{50} Acre
F104	 N p tolilisoindolin 2-carboxamida	3 05		
E105	 N-(4-clorofenil)isoindolin 2-carboxamida	3 4		
F106	 N-(2-clorofenil)isoindolin 2-carboxamida	3 85		
E107	 N-(2,4-diclorofenil)isoindolin-2-carboxamida	4 15		
E108	 N-(4-metoxifenil)isoindolin-2-carboxamida b	4 99		
E109	 N-(2 4-diclorofenil)-3 4-dihidroisoquinolin 2(1H)-carboxamida	2 34		
F110	 N-(2-cianofenil)-3 4-dihidroisoquinolin 2(1H)-carboxamida	2 5		
E111	 N p tolil-3,4-dihidroisoquinolin 2(1H) carboxamida	4 27		

Tabla E Amidas Mejoradoras Endulzantes

Compuesto No	Compuesto	EC_{50} Dulce (uM)	EC_{50} Acre (uM)	relación EC_{50} Acre
F112	 N-(3-cloro-2 metilfenil)-3,4-dihidroisoquinolin 2(1H)-carboxamida	4 33		
E113	 N (2,4-dimetoxifenil)-3,4-dihidroisoquinolin 2(1H)-carboxamida	4 44		

Medicion de Mejoramiento de Sabor Dulce y sabor Dulce Utilizando Panelistas Humanos

Propósito Para investigar la intensidad de varios sabores y sabores desagradables de un compuesto experimental Para determinar la concentración máxima del compuesto experimental que no produce una caracteristica indeseable a sabor desagradable

Vista general Varias concentraciones del compuesto experimental (normalmente soluciones acuosas que contienen concentraciones de 1, 3, 10 y 30 uM del compuesto experimental, y opcionalmente concentraciones de 50 uM y/o 100 uM) se prueban individualmente por sujetos entrenados y se clasifican por la intensidad de varios atributos de sabor El compuesto

experimental puede probarse también cuando se disuelve en una solución degustante clave

Procedimiento Una cantidad apropiada del compuesto experimental se disuelve en agua normalmente conteniendo tambien 0 1% de etanol, que se utiliza para ayudar a la dispersión inicial del compuesto en la solucion almacenada acuosa Cuando es apropiado, el compuesto experimental puede disolverse tambien en soluciones acuosas de un degustante clave" (por ejemplo, 4% de sacarosa, 6% de sacarosa, 6% de fructosa/glucosa, o 7% de fructosa/glucosa, un pH 7 1 ó 2 8)

Cinco Sujetos humanos se utilizan para pruebas de sabor preeliminar Los sujetos tienen una capacidad demostrada para probar los atributos de sabor deseados y se les entrena para utilizar una Escala de Magnitud Etiquetada (LMS) de 0 (Dulzor Apenas Detectable) Los sujetos se abstienen de comer o beber (excepto agua) por al menos 1 hora antes de la prueba Los sujetos comen una galleta y se enjuagan con agua cuatro veces para limpiar la boca antes de las pruebas de sabor

Las soluciones acuosas se distribuyen en volumenes de 10 ml dentro de vasos de muestra de 1 onza y se sirven a los sujetos a temperatura ambiente Las muestras del compuesto experimental disueltas en un degustante clave apropiado (por ejemplo, 4% de sacarosa, 6% de fructosa o 6% de fructosa/glucosa, normalmente en pH 7 1) en varias concentraciones del compuesto experimental pueden servir

también a los sujetos Los sujetos reciben tambien una muestra de referencia del degustante clave (por ejemplo sacarosa, fructosa o fructosa/glucosa, normalmente a un pH de 7 1) en diferentes concentraciones para comparacion

Los sujetos prueban las soluciones, iniciando con la concentración más baja y la intensidad de relación entre los siguientes atributos en la Escala de Magnitud Etiquetada (LMS) para el dulzor, la salinidad acidez, amargura, sabrosura (acre) y otros (sabor desagradable) Los sujetos se enjuagan tres veces con agua entre las degustaciones Si una concentracion particular produce una caracteristica indeseable de sabor desagradable, las degustaciones subsecuentes de concentraciones más elevadas se eliminan Después de un descanso, los Sujetos prueban una solución del degustante clave (por ejemplo, 4% de sacarosa, 6% de fructosa o 6% de fructosa/glucosa normalmente en un pH 7 1) sin el compuesto experimental Luego, las soluciones del degustante clave mas el compuesto experimental se prueba incrementando el orden de concentración La solucion degustante clave puede emplazarse para comparacion con soluciones de degustante clave + el compuesto experimental si es necesario Se permite la discusión entre los panelistas

La concentracion máxima de un compuesto experimental que no produce una caracteristica objetable de sabor desagradable es la concentracion mas elevada en donde un compuesto particular será probado en experimentos sensoriales

subsecuentes Para confirmar los resultados de prueba preeliminares, la prueba puede repetirse con otro grupo pequeño de panelistas

La prueba de perfil preeliminar es siempre la primera prueba realizada en un nuevo compuesto experimental Dependiendo de los resultados de la prueba de perfil preeliminar, pueden realizarse pruebas cuantitativas adicionales para caracterizar ademas el compuesto experimental

Procedimientos de Prueba de Sabor Humano de "Diferencia a partir de la Referencia"

Propósito Para determinar cómo la intensidad de una muestra de prueba de un compuesto experimental difiere de aquella de una muestra de referencia en terminos de dulzor Este tipo de estudio requiere un panel mas grande (normalmente 15-20 sujetos) con el fin de obtener datos estadísticamente significativos

Vista general Un grupo de 10 o mas panelistas pruebas pares de soluciones en donde una muestra es la "Referencia" (que normalmente no incluye un compuesto experimental y es una sustancia aprobada o una sustancia Generalmente Reconocida como Segura (GRAS) es decir un edulcorante) y una muestra es la 'Prueba" (que puede o no incluir un compuesto) Los sujetos evaluan la diferencia en la intensidad de la muestra de prueba comparada a la muestra de referencia para el atributo clave en

una escala de -5 (mucho menos dulce que la referencia) a +5 (mucho mas dulce que la referencia) Una puntuación de 0 indica que la muestra de prueba es igualmente tan dulce como la de referencia

Procedimiento

Diez o mas Sujetos se utilizan para las pruebas de Diferencia a partir de la Referencia Los sujetos han sido previamente familizarizados con el sabor del atributo clave y se les entrena para el uso de la escala -5 a +5 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 cuatro veces para limpiar la boca

Diez soluciones pueden incluir el compuesto experimental en agua el compuesto experimental más un degustante clave (por ejemplo, 4% de sacarosa, 6% de sacarosa 6% de fructosa, 6% de fructosa/glucosa o 7% de fructosa/glucosa, a un pH 7 1 ó 2 8), y un rango del degustante clave de solamente soluciones como referencias

Las muestras del degustante clave sin el compuesto experimental se utilizan para determinar si el panel se clasifica exactamente, es decir, la referencia se prueba de nuevo a si misma (ciega) para determinar que tan exacto se clasifica el panel en un día de prueba dada Las soluciones se distribuyen en volumenes de 10 ml dentro de vasos de muestra de 1 onza y se sirven a los Sujetos a temperatura ambiente

Los sujetos prueban primero la muestra de referencia, luego prueban inmediatamente la muestra de prueba y evaluan la diferencia en intensidad del atributo clave en la escala de Diferencia a partir de la Referencia (-5 a +5) Todas las muestras se escupen Los sujetos pueden volver a probar las muestras pero pueden sólo utilizar el volumen de la muestra dada Los sujetos pueden enjugarse al menos dos veces con agua entre lo pares de muestras Se puede requerir comer una galleta entre los pares de muestra dependiendo de las muestras probadas

Las puntuaciones para cada prueba se promedian a traves de Sujetos y se calcula el error estándar La exactitud del panel puede determinarse utilizando la puntuacion a partir de la prueba de referencia ciega Las pruebas ANOVA y de comparación multiple (tal como prueba de Diferencia Honestamente Significativa de Tukey) pueden utilizarse para determinar diferencias entre los pares siempre que la muestra de referencia sea la misma entre todas las pruebas Si el par de prueba idéntico se prueba en otra sesión, una prueba t del Student (acoplada de dos extremos, alfa = 0 05) puede utilizarse para determinar si existe alguna diferencia en las evaluaciones entre las sesiones

Un numero de edulcorantes de referencia diferentes se han utilizado para la medición del mejorador de sabor dulce Por ejemplo, para la (R)-3-metil-N-(1,2,3 4-tetrahidronaftalen-1-il)isoxazol-4-carboxamida de prueba, una muestra de referencia que consiste de 4% de sacarosa se utiliza, la cual tiene un mayor

dulzor que el nivel de umbral (es decir 2% de sacarosa) y un dulzor en la region de la percepcion de sabor dulce en donde los sujetos humanos son mas sensibles a cambios pequeños en la percepción del sabor dulce Para la prueba de la 2,3,5 6-tetrafluoro-4-metil-N-(2-metilciclohexil)benzamida, una mezcla de 50 50 de fructosa glucosa se utilizó para modelar mejor las soluciones de jarabe de maíz de fructosa elevada comunmente utilizadas en la industria de bebidas Se demostró una mezcla de 6% de fructosa/glucosa que es aproximadamente igual en percepción de sabor dulce como del 6% de sacarosa, que esta dentro del rango en donde los panelistas son sensibles a cambios pequeños en la percepcion del sabor dulce Despues de los estudios iniciales en 6% de fructosa/glucosa en pH 7 1, los estudios cambian para evaluar el rendimiento del compuesto en un fenotipo del producto mas similar a una bebida de cola, es decir concentraciones mas elevadas de edulcorante y un pH inferior

Los resultados de algunas pruebas de sabor humano de los compuestos amida dulces de la invención en las composiciones acuosas pretendidas para modelar la composición de una bebida carbonatada se muestran posteriormente en la Tabla F

Tabla F Resultados de Prueba de Sabor Dulce

Compuesto No	Contenido de solucion	pH	Solución Dulce Equivalente Percibida
174	50 uM Compuesto 174 + 4% de sacarosa	*	6% de sacarosa
171	30 uM Compuesto 171 + 6% de fructosa/ glucosa	*	Mayor que 6% pero menos que 8% de fructosa/glucosa
170	30 uM Compuesto 170 + 6% de fructosa/ glucosa	pH 7 1	Mayor que 6% pero menos que 8% de fructosa/glucosa
162	10 uM Compuestc 162 + 6% de fructosa/ glucosa	pH 7 1	Mayor que o igual a 8% de fructosa/glucosa
162	10 uM Compuestc 162 + 7% de fructosa/ glucosa	pH 2 8	Mayor que o igual a 9% de fructosa/glucosa
168	30 uM Compuestc 168 + 6% de fructosa/ glucosa	pH 7 1	Igual a 8% de fructosa/ glucosa
163	10 uM Compuesto 163 + 6% de fructosa/ glucosa	pH 7 1	Mayor que 6% pero menos que 8% de fructosa/glucosa

* El pH de estas soluciones acuosas no se midió o controló

Ejemplo 176

Preparación de Sopa Utilizando una Solucion de Caldo en Etanol

Un compuesto de la invencion se diluye utilizando 200 proof de etanol a 1000x de la concentracion deseada en la sopa El compuesto puede someterse a sonicación y calentarse (si está estable) para asegurar la solubilidad completa en etanol La sopa a partir de la base de caldillo se hace agregando 6 g de base de caldillo vegetal en 500 ml de agua caliente en una vasija de vidrio o de barro El agua se calienta a 80°C La concentracion del MSG en el caldillo disuelto es 2 2 g/L y no existe IMP agregado Después que se disuelve la base de caldillo, la solucion de caldo de etanol se agrega a la base de la sopa Para 500 mL de sopa,

0 5 mL del caldo en etanol 1000x se agrega para una concentracion de etanol final de 0 1% Si el etanol interfiere con el sabor de la sopa, una concentracion mas elevada de solucion de caldo de etanol puede prepararse siempre que el compuesto sea soluble

Ejemplo 177

Preparacion de Papas Fritas

Una mezcla de sal de un compuesto de la invencion se hace mezclando con sal de manera que 1 4% de la mezcla de sal agregada p/p a las papas fritas resultaria en la concentracion deseada del compuesto Para 1 ppm final del compuesto en las papas fritas, 7 mg del compuesto se mezcla con 10 g de sal El compuesto se muele utilizando un mortero y una mano de mortero con la sal y el compuesto y la sal se mezclan bien Las papas fritas se fraccionan en pequeñas piezas uniformes utilizando un mezclador Para cada 98 6 g de papas fritas, 1 4 g de la mezcla de sal se pesa Las piezas de papas fritas se calientan primero en un microondas durante 50 segundos o hasta que estén calientes Las piezas se separan en una pieza grande de lámina de aluminio La mezcla de sal se esparce uniformemente sobre las papas fritas Las papas fritas se colocan entonces en una bolsa de plástico asegurando que toda la sal se coloque en la bolsa también La mezcla de sal y las papas fritas se agitan para asegurar que la sal se esparza uniformemente sobre las papas fritas

Ejemplo 178

Preparación de Galletas

Un compuesto de la invencion se diluye utilizando 200 proof de etanol a 1000x de la concentración deseada en el producto final El compuesto puede someterse a sonicacion y calentarse (si es estable) para asegurar la solubilidad completa en etanol La solución que contiene el compuesto de la invención se mezcla entonces con otros ingredientes liquidos (es decir agua, huevos liquidos y saborizantes) hasta que se mezcla bien La mezcla se mezcla con un emulsificador seco tal como lecitina y se mezcla además con una materia grasa La materia grasa se mezcla con los componentes secos (es decir, harina azucar, sal, cacao) que han sido mezclados bien La pasta se reparte en una hoja para hornear, y se hornea a una temperatura deseada hasta el final

Ejemplo 179

Preparacion de Jugo

Un compuesto de la invencion se diluye utilizando 200 proof de etanol a 1000x de la concentracion deseada en jugo El compuesto se mezcla entonces con el componente de alcohol de sabores naturales y/o artificiales para hacer una "clave" La clave de sabor se mezcla con una porcion de jugo concentrado para asegurar homogeneidad El resto del concentrado de jugo se diluye con agua y se mezcla Los edulcorantes, tales como HFCS

(Jarabe de Maiz Alto en Fructosa), aspartame o sucralosa, se mezclan y se combinan Se agrega la porcion de sabor/compuesto como una etapa final, y se mezcla

Ejemplo 180

Jugo de Tomate Sazonado o Mezcla de Jugo de Tomate

Un compuesto de la invención se agrega como un ingrediente seco a la mezcla sazonada y se mezcla completamente La mezcla sazonada se dispersa dentro de una porción de la pasta de tomate se mezcla y esa pasta mezclada se mezcla además dentro de la pasta restante La pasta se diluye entonces con agua Ésta puede procesarse a temperatura elevada durante un tiempo corto

Será evidente para aquellos con experiencia en la tecnica que varias modificaciones y variaciones pueden hacerse en la presente invención sin apartarse del alcance o espiritu de la invención Otras modalidades de la invencion seran evidentes para aquellos con experiencia en la tecnica a partir de la consideracion de la especificación y la práctica de la invención descrita en la presente Se pretende que la especificación y los ejemplos se consideren como ejemplares solamente, con un alcance y espiritu verdaderos de la invención que se indican por las siguientes reivindicaciones

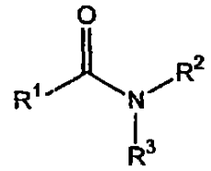
REIVINDICACIONES

1 Un método para modular el sabor de un producto comestible o medicinal, caracterizado porque comprende

a) proporcionar al menos un producto comestible o medicinal o un precursor del mismo, y

b) combinar el producto comestible o medicinal o precursor del mismo con al menos una cantidad que modula el sabor sabroso de al menos un compuesto amida de origen no natural o una sal comestiblemente aceptable del mismo de manera que forma un producto comestible o medicinal modificado

en donde el compuesto amida tiene la fórmula



en donde R^1 comprende un residuo hidrocarburo que tiene al menos tres atomos de carbono y opcionalmente uno o diez heteroátomos seleccionados independientemente de oxigeno nitrógeno azufre halógenos o fósforo, y

en donde uno de R^2 y R^3 es H los otros R^2 y R^3 comprenden un residuo hidrocarburo que tiene al menos tres atomos de carbono y opcionalmente uno o diez heteroatomos independientemente seleccionados de oxigeno, nitrógeno azufre halógenos o fosforo y en donde el compuesto amida tiene un peso molecular de 500 gramos por mol o menos

2 El método de conformidad con la reivindicacion 1

caracterizado porque el compuesto amida tiene un peso molecular de 175 a 500 gramos por mol

3 El metodo de conformidad con la reivindicacion 1 caracterizado porque el compuesto amida tiene un peso molecular de 200 a 450 gramos por mol

4 El metodo de conformidad con la reivindicacion 1 caracterizado porque el compuesto amina tiene un peso molecular de 225 a 400 gramos por mol

5 El método de conformidad con la reivindicación 1 caracterizado porque el compuesto amina tiene un peso molecular de 225 a 400 gramos por mol

6 El metodo de conformidad con la reivindicación 1 caracterizado porque R^1 y uno de R^2 y R^3 tienen entre 3 y 14 átomos de carbono

7 El método de conformidad con la reivindicación 1 caracterizado porque R^1 y uno de R^2 y R^3 tienen entre 4 y 12 atomos de carbono

8 El método de conformidad con la reivindicación 1 caracterizado porque R^1 y uno de R^2 y R^3 tienen entre 4 y 10 átomos de carbono

9 El método de conformidad con la reivindicacion 1, caracterizado porque R^1 tiene entre 3 y 16 atomos de carbono y 0 1 2, 3 4 ó 5 heteroátomos seleccionados de oxígeno, nitrógeno, azufre, fluor, o cloro

10 El metodo de conformidad con la reivindicacion 1

caracterizado porque uno de R^2 o R^3 tiene entre 3 y 16 átomos de carbono y 0 1, 2 3, 4 o 5 heteroátomos seleccionados independientemente de oxigeno, nitrogeno azufre fluor o cloro

11 El metodo de conformidad con la reivindicación 1 caracterizado porque uno de R^2 o R^3 tiene entre 4 y 14 atomos de carbono y 0, 1, 2 3, 4 ó 5 heteroátomos seleccionados independientemente de oxigeno nitrógeno, azufre

12 El método de conformidad con la reivindicación 1 caracterizado porque uno de R^2 o R^3 tiene entre 5 y 12 atomos de carbono y 0, 1 2, o 3 heteroátomos seleccionados independientemente de oxigeno nitrogeno, y azufre

13 El metodo de conformidad con la reivindicacion 1, caracterizado porque R^1 tiene entre 3 y 16 atomos de carbono y 0 1 2, 3, 4 o 5 heteroatomos seleccionados de oxígeno nitrógeno, azufre fluor o cloro y uno de R^2 o R^3 tiene entre 5 y 12 átomos de carbono y 0, 1, 2 o 3 heteroatomos seleccionados independientemente de oxigeno nitrógeno y azufre

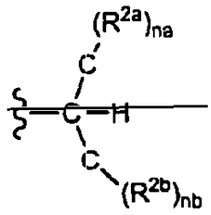
14 El metodo de conformidad con la reivindicacion 1 caracterizado porque R^1 y uno de R^2 y R^3 se seleccionan independientemente del grupo que consiste de arilalquenilo heteroarilalquenilo arilalquilo heteroarilalquilo, alquilo, alcoxi-alquilo, alquenilo cicloalquilo, cicloalquenilo, arilo heteroarilo $-R^4OH$ $-R^4O R^5$ $-R^4CN$ $-R^4CO_2H$, $-R^4CO_2R^5$, $-R^4COR^5$, $-R^4SR^5$, y $-R^4SO_2R^5$ y un derivado opcionalmente sustituido del mismo que comprende 1 2, 3 ó 4 grupos carbonilo amino grupos hidroxilo o

halógeno, y en donde R^4 y R^5 son residuos hidrocarburo de C_1-C_6

15 El metodo de conformidad con la reivindicación 7 caracterizado porque R^1 y uno de R^2 y R^3 se seleccionan independientemente del grupo que consiste de arilalquenilo, heteroarilalquenilo, arilalquilo, heteroarilalquilo alquilo, alcoxi-alquilo alquenilo cicloalquilo cicloalquenilo heterociclo, arilo y grupos heteroarilo y derivados opcionalmente sustituidos de los mismos que comprende 1 2 3 ó 4 grupos sustituyentes seleccionados independientemente de grupos hidrógeno 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

16 El método de conformidad con la reivindicacion 1 caracterizado porque uno de R^2 y R^3 es un residuo orgánico ramificado o ciclico que tiene un átomo de carbono directamente unido a (a) el atomo de nitrogeno de amida y (b) dos átomos de carbono adicionales y en donde el residuo orgánico ramificado o cíclico comprende átomos de hidrogeno, hasta 10 átomos de carbono adicionales opcionales y a partir de cero a cinco heteroatomos seleccionados independientemente de oxigeno nitrógeno, azufre fluor, y cloro

17 El método de conformidad con la reivindicación 1 caracterizado porque uno de R^2 y R^3 tiene la formula

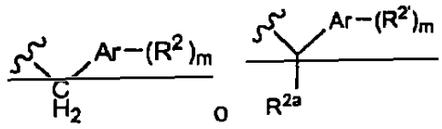


en donde na y nb se seleccionan independientemente de 1 2 y 3 y cada R^{2a} o R^{2b} residuo sustituyente se selecciona independientemente de hidrógeno un halógeno, un hidroxi, o un residuo que contiene carbono opcionalmente teniendo de cero a cinco heteroátomos seleccionados independientemente de oxigeno, nitrógeno azufre un halogeno

18 El metodo de conformidad con la reivindicación 1 caracterizado porque R^2 y R^3 es un radical alquilo ramificado que tiene cinco a 12 atomos de carbono

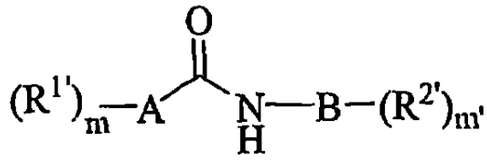
19 El metodo de conformidad con la reivindicación 1 caracterizado porque uno de R^2 y R^3 es un anillo cicloalquilo o cicloalquenilo que comprende de 5 a 12 atomos de carbono en el anillo que pueden opcionalmente sustituirse con 1, 2 3 ó 4 seleccionados independientemente de grupos hidrógeno, hidroxi 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

20 El método de conformidad con la reivindicación 1 caracterizado porque uno de R^2 y R^3 tienen la estructura



en donde Ar es un anillo fenilo, piridilo furanilo tiofuranilo o pirrol, m es 0 1, 2 ó 3 cada R^2 se selecciona independientemente de hidrógeno 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 R^{2a} se selecciona 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 comprende 1 a 12 atomos de carbono

21 El método de conformidad con la reivindicacion 1 caracterizado porque el compuesto amida tiene la fórmula



en donde A comprende un anillo arilo o heteroarilo de 5 o 6 miembros

m es 0 1, 2 3 ó 4,

cada R^1 se selecciona independientemente de alquilo alcoxilo, 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 de C_1 C_6

22 El metodo de conformidad con la reivindicación 21 caracterizado porque A es un anillo fenilo o anillo piridilo

23 El método de conformidad con la reivindicación 22,

caracterizado porque m es 1, 2 o 3

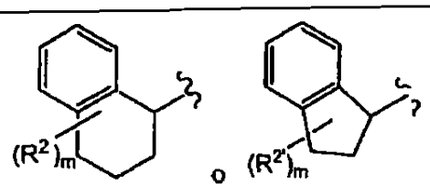
24 El método de conformidad con la reivindicacion 23, caracterizado porque cada R^1 se selecciona independientemente de hidrogeno hidroxi, fluoro cloro NH_2 $NHCH_3$ $N(CH_3)_2$ $COOCH_3$, SCH_3, SEt metilo etilo isopropilo, vinilo trifluorometilo, metoxi, etoxi isopropoxi y trifluorometoxi, o un grupo arilo o heteroarilo monociclico

25 El método de conformidad con la reivindicacion 21 caracterizado porque A es un anillo fenilo y cada R^1 se selecciona independientemente de grupos hidrógeno hidroxi fluoro cloro NH_2 $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo etilo isopropilo, vinilo, trifluorometilo metoxi etoxi isopropoxi y trifluorometoxi

26 El metodo de conformidad con la reivindicación 24 caracterizado porque R^2 es un alquilo ramificado de C_3-C_{10}

27 El metodo de conformidad con la reivindicacion 21 caracterizado porque R^2 es un alquilo ramificado de C_3-C_{10} sustituido con uno o dos sustituyentes independientemente seleccionados de hidrógeno hidroxi fluor, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, O_2CCH_3 CO_2CH_3, SCH_3 SEt metilo etilo, isopropilo vinilo, trifluorometilo metoxi, etoxi, isopropoxi y trifluorometoxi

28 El método de conformidad con la reivindicacion 9 caracterizado porque R^2 es un anillo de 1-(1,2 3 4) tetrahidronaftaleno o un anillo 2,3-dihidro-1H-indeno que tiene la fórmula



en donde m es 0, 1, 2 ó 3, y cada R^2 puede unirse ya sea a un anillo aromatico o no aromatico y se selecciona independientemente de hidroxi fluoro, 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

29 El método de conformidad con la reivindicacion 25, caracterizado porque R^2 es opcionalmente un anillo fenilo opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente de grupos hidroxi, fluoro, 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

30 El metodo de conformidad con la reivindicación 21 caracterizado porque R^2 es un alquilester inferior del acido carboxílico α-sustituido o un acido carboxilico α-sustituido

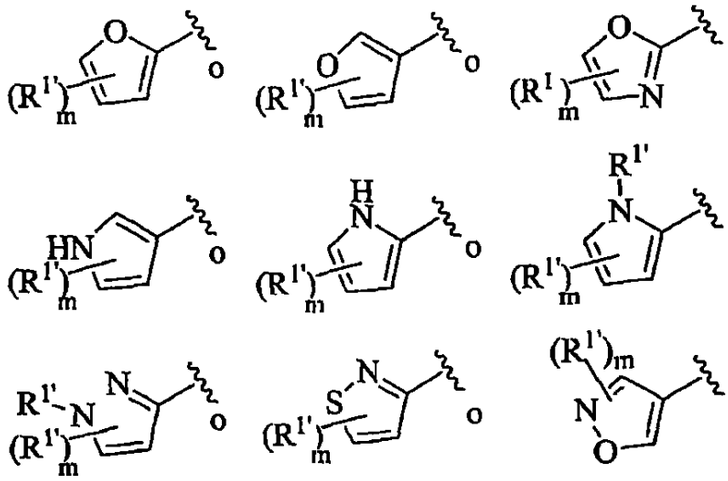
31 El metodo de conformidad con la reivindicación 25 caracterizado porque R^2 es un metiléster del ácido carboxilico α-sustituido

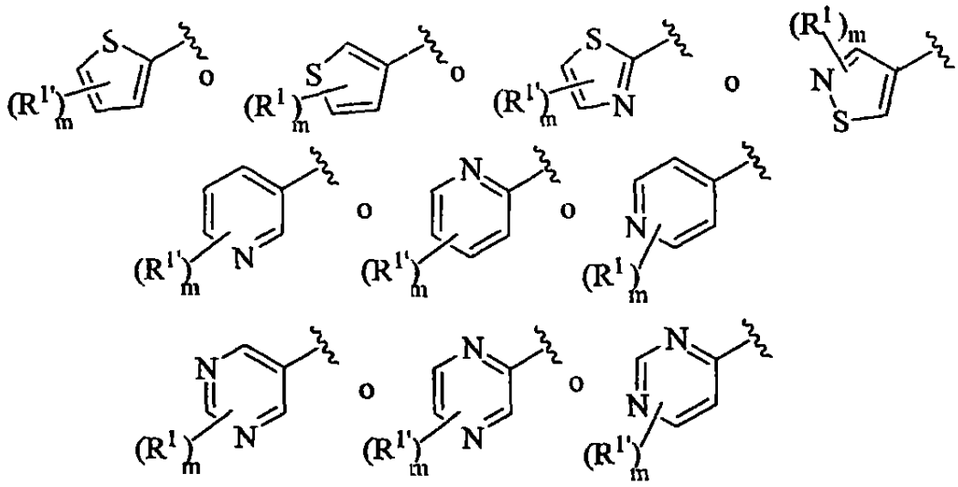
32 El metodo de conformidad con la reivindicación 31 caracterizado porque el ácido carboxilico α-sustituido o residuo de éster de ácido carboxilico α-sustituido corresponden a aquel de un ácido α-amino que ocurre naturalmente o un ester del mismo o su

enantiomero opuesto

33 El metodo de conformidad con la reivindicacion 21 caracterizado porque A es un heteroarilo monociclico en donde cada R^1 se selecciona independientemente de grupos hidrogeno hidroxi fluoro cloro NH_2 $NHCH_3$, $N(CH_3)_2$ $COOCH_3$ SCH_3 SEt metilo, etilo, isopropilo vinilo trifluorometilo, metoxi, etoxi, isopropoxi y trifluorometoxi

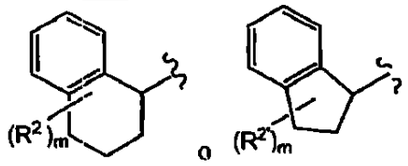
34 El método de conformidad con la reivindicacion 21 caracterizado porque A tiene una de las siguientes formulas





en donde m es 0, 1, 2 o 3 y cada R^1 se selecciona independientemente de hidroxi fluoro, 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 o un grupo arilo o heteroarilo monociclico

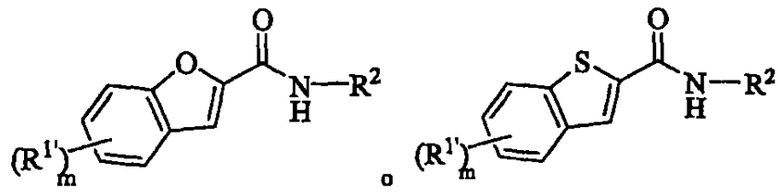
35 El metodo de conformidad con la reivindicación 34 caracterizado porque R^2 tiene la fórmula



en donde m es 0 1 2 o 3, y cada R^1 puede unirse a cualquier anillo aromático o no aromático y se selecciona independientemente de grupos hidroxi fluoro, 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

36 El método de conformidad con la reivindicación 21 caracterizado porque A es un monociclico biciclico enlazado o heteroarilo biciclico fundido aromático, opcionalmente sustituido con 0 1, 2 3 o 4 sustituyentes seleccionados independientemente de grupos hidroxi, fluoro, 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

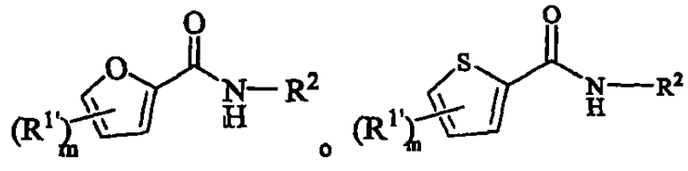
37 El metodo de conformidad con la reivindicacion 1, caracterizado porque el compuesto amida tiene la formula



en donde m es 0, 1, 2 ó 3 y cada R^1 puede unirse junto con los anillos fenilo o heteroarilo y cada R^1 se selecciona independientemente de hidroxi fluoro cloro NH_2 $NHCH_3$ $N(CH_3)_2$, $CO2CH_3$, SCH_3, SEt, metilo etilo isopropilo vinilo trifluorometilo metoxi, etoxi, isopropoxi, y trifluorometoxi

38 El método de conformidad con la reivindicacion 37, caracterizado porque m es 1 ó 2

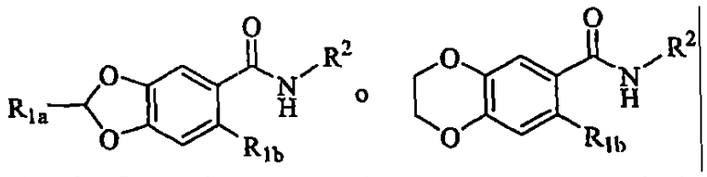
39 El método de conformidad con la reivindicación 1, caracterizado porque el compuesto amida tiene la fórmula



en donde m es 0, 1 2 o 3 y cada R^1 se selecciona independientemente de hidroxi fluoro 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

40 El método de conformidad con la reivindicacion 39, caracterizado porque m es 1 ó 2

41 El método de conformidad con la reivindicacion 1 caracterizado porque el compuesto amida tiene la formula

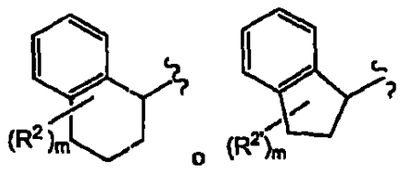


en donde R_{1a} o R_{1b} son independientemente hidrogeno o un alquilo inferior

42 El método de conformidad con la reivindicacion 41, caracterizado porque R_{1a} o R_{1b} son independientemente hidrógeno o metilo

43 El método de conformidad con la reivindicacion 41, caracterizado porque R^2 es un alquilo ramificado de C_3-C_{10}

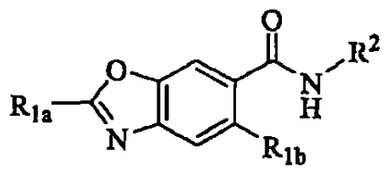
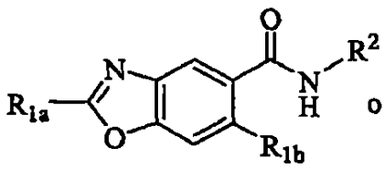
44 El método de conformidad con la reivindicacion 41 caracterizado porque R^2 tiene la fórmula



en donde m es 0, 1, 2 o 3, y cada R^2 puede unirse junto al anillo aromatico o no aromatico y cada R^2 se selecciona

independientemente de grupo hidroxi fluoro, 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

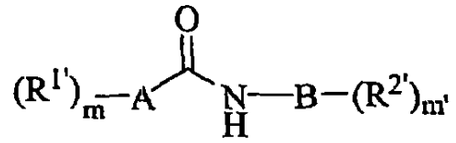
45 El método de conformidad con la reivindicación 1, caracterizado porque el compuesto amida tiene la fórmula


o

o

en donde R_{1a} o R_{1b} es independientemente hidrogeno o un alquilo inferior

46 El método de conformidad con la reivindicacion 45 caracterizado porque R_{1a} es un alquilo inferior y R^2 es un alquilo de C_3-C_{10} ramificado

47 El método de conformidad con la reivindicación 1, caracterizado porque el compuesto amida tiene la fórmula



en donde A comprende 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 alcoxilo, alcoxi-alquilo, hidroxialquilo OH CN CO_2H CHO, COR^6 CO_2R^6 SH SR^6 halogeno, alquenilo cicloalquilo cicloalquenilo arilo y heteroarilo y R^6 es alquilo de C_1-C_6

B es un anillo arilo o heteroarilo de 5 ó 6 miembros

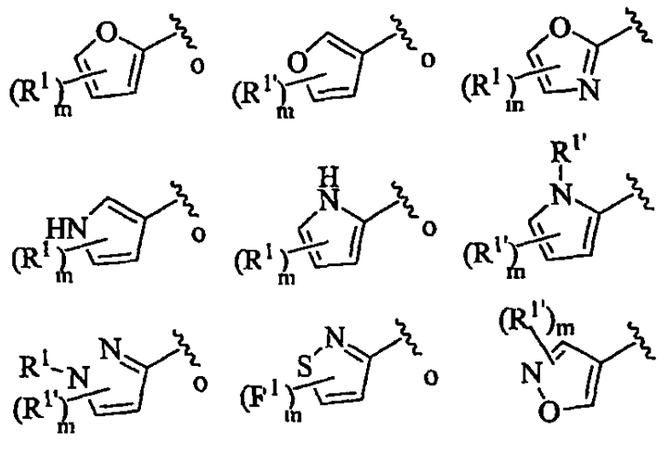
m es 0, 1 2 3 o 4,

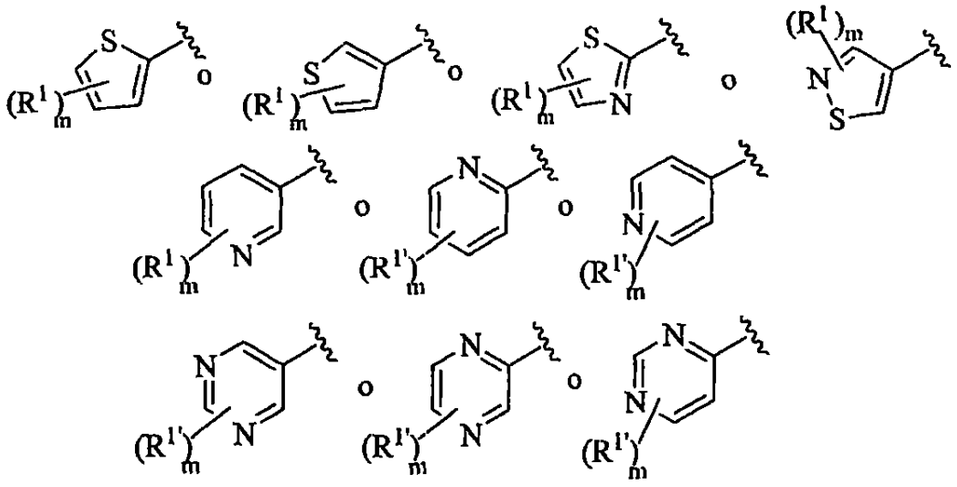
R^2 se selecciona a partir del grupo que consiste de alquilo alcoxilo alcoxi-alquilo OH CN, CO_2H, CHO COR^6 CO_2R^6 SR^6 halogeno alquenilo, cicloalquilo cicloalquenilo, arilo y heteroarilo y R^6 es alquilo de C_1-C_6

48 El método de conformidad con la reivindicacion 47 caracterizado porque A es un anillo heteroarilo monociclico o biciclico fusionado en donde cada R^1 y cada R^2 se seleccionan independientemente de grupos hidrógeno hidroxi, fluoro cloro NH_2 $NHCH_3$ $N(CH_3)_2$, $COOCH_3$ SCH_3 SEt metilo etilo isopropilo vinilo, trifluorometilo, metoxi, etoxi isopropoxi, y grupos trifluorometoxi

49 El método de conformidad con la reivindicación 47 caracterizado porque A es un anillo heteroarilo monociclico

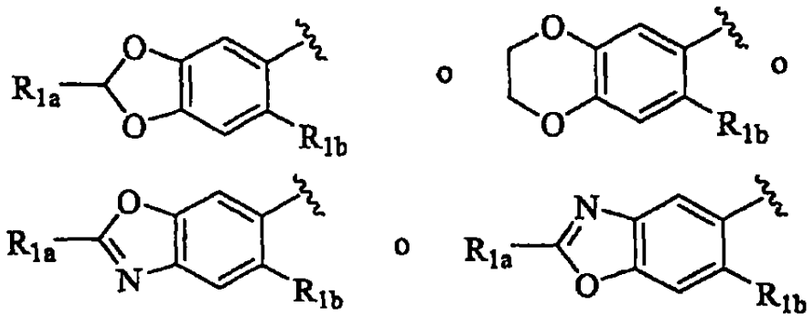
50 El método de conformidad con la reivindicacion 47 caracterizado porque A tiene una de las formulas





en donde m es 0 1 2 o 3, y cada R^1 puede unirse junto al anillo aromático o no aromatico y cada R^2 se selecciona independientemente de grupos hidrogeno, 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 grupos del trifluorometoxi

51 El metodo de conformidad con la reivindicacion 47, caracterizado porque radical $(R^1)_m$-A tiene la fórmula

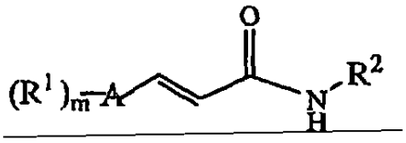


en donde R_{1a} y R_{1b} son independientemente hidrógeno o un alquilo inferior

52 El método de conformidad con la reivindicación 48 caracterizado porque B es un anillo fenilo y cada R^2 se selecciona independientemente de grupos hidrógeno, 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

53 El método de conformidad con la reivindicacion 47 caracterizado porque A es un anillo fenilo sustituido y B es un anillo ciclohexilo sustituido

54 El método de conformidad con la reivindicacion 1 caracterizado porque el compuesto amida tiene la formula



en donde A es un anillo arilo o heteroarilo de 5 ó 6 miembros

m es 0 1 2, 3 ó 4,

cada R^1 se selecciona independientemente de alquilo, alcoxilo, alcoxi-alquilo OH CN CO_2H, CO_2R^6, CHO COR^6 SR^6 halogeno alquenilo cicloalquilo, cicloalquenilo arilo y heteroarilo

55 El método de conformidad con la reivindicacion 54 caracterizado porque A es un anillo fenilo piridilo furanilo, o tiofuranilo y cada R^1 se selecciona independientemente grupos hidrógeno 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 trifluorometoxi

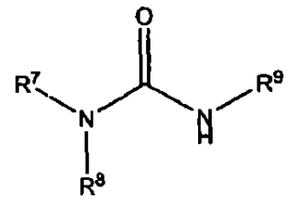
56 El método de conformidad con la reivindicación 55, caracterizado porque A es un anillo fenilo y m tiene 1, 2 3 ó 4

57 El método de conformidad con la reivindicacion 56 caracterizado porque m es 1 ó 2

58 El metodo de conformidad con la reivindicacion 55, caracterizado porque R^2 es un alquilo ramificado de C_3 C_{10}

59 El método de conformidad con la reivindicación 55, caracterizado porque R^2 es un éster de alquilo inferior de acido carboxilico α-sustituido

60 El metodo de conformidad con la reivindicación 1, caracterizado porque el compuesto amida es un compuesto urea que tiene la fórmula

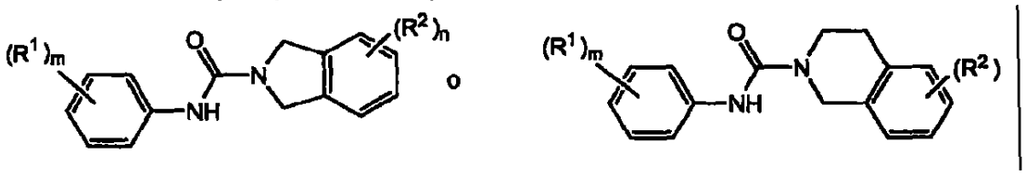


en donde R^9 y uno o dos de R^7 y R^8 comprenden un residuo hidrocarburo que tiene al menos tres átomos de carbono y opcionalmente uno a diez heteroatomos seleccionados a partir de oxigeno nitrogeno azufre halógenos o fósforo y en donde opcionalmente uno de R^7 y R^8 es hidrogeno

61 El método de conformidad con la reivindicación 60, caracterizado porque R^7 y R^8 juntos forman un anillo heterociclico

o heteroarilo que tiene 5 6 o 7 átomos en el anillo que pueden sustituirse opcionalmente con 1, 2 ó 3 sustituyentes independientemente seleccionados a partir de hidroxi fluoro cloro NH_2 $NHCH_3$ $N(CH_3)_2$, $COOCH_3$ SCH_3, SEt, metilo, etilo, isopropilo vinilo trifluorometilo, metoxi, etoxi isopropoxi y trifluorometoxi

62 El método de conformidad con la reivindicacion 61, caracterizado porque el compuesto urea tiene la estructura



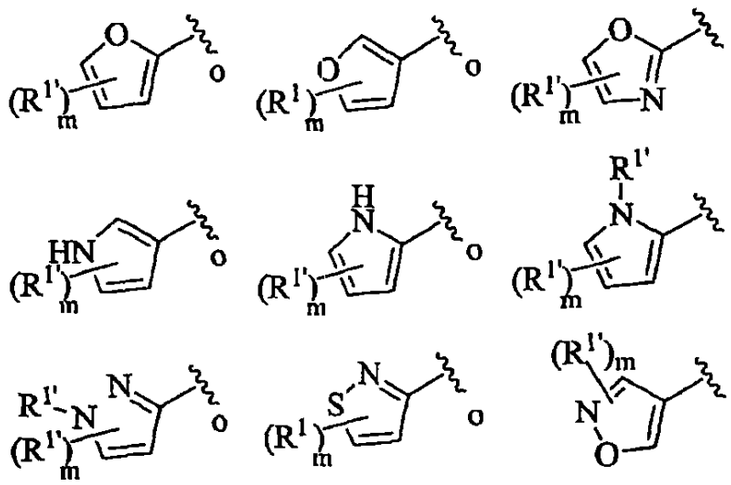
63 El metodo de conformidad con la reivindicacion 60, caracterizado porque uno de R^7 y R^8 es hidrógeno

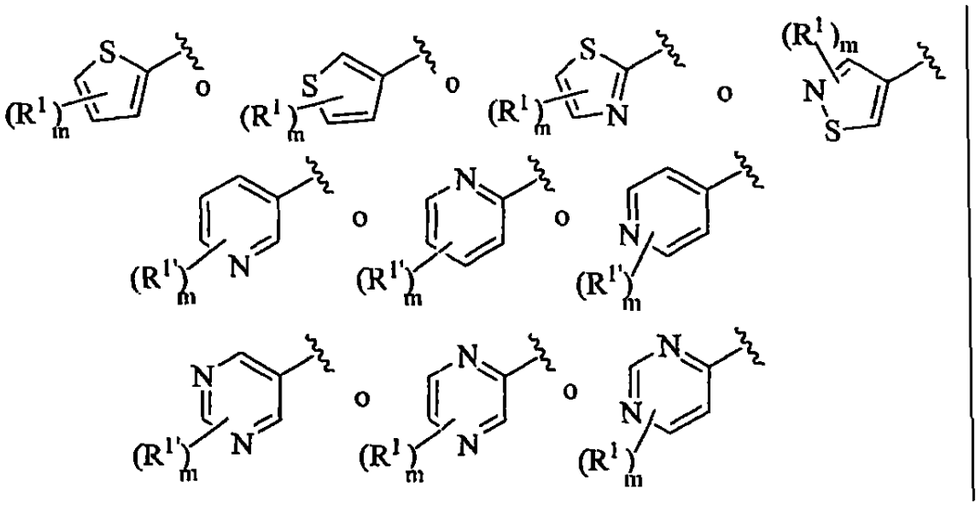
64 El metodo de conformidad con la reivindicacion 63 caracterizado porque R^9 y uno de R^7 y R^8 se seleccionan independientemente a partir ce arilalquenilos heteroarilalquenilos arilalquilos heteroarilalquilos, alquilos, alcoxi-alquilos alquenilos cicloalquilos, cicloalquenilos arilos y heteroarilos cada uno de cuyos grupos que contienen carbono pueden sustituirse opcionalmente con 1 2, o 3 sustituyentes seleccionados independientemente de grupos hidrógeno hidroxi, fluoro cloro NH_2 $NHCH_3$, $N(CH_3)_2$ $COOCH_3$ SCH_3 SEt metilo, etilo isopropilo, vinilo, trifluorometilo metoxi etoxi, isopropoxi y trifluorometoxi

65 El metodo de conformidad con la reivindicacion 63,

caracterizado porque $^{1}R^{9}$ y uno de R^{7} y R^{8} se selecciona independientemente de alquilo fenilo ciclohexilo o piridilo cada uno de los cuales pueden opcionalmente comprender uno a cuatro sustituyentes independientemente seleccionados de hidroxi fluoro cloro, MH_2, $NHCH_3$, $N(CH_3)_2$ CO_2CH_3, SEt, SCH_3 metilo, etilo, isopropilo vinilo trifluorometilo, metoxi etoxi, isopropoxi y trifluorometoxi

66 El método de conformidad con la reivindicación 63 caracterizado porque uno de R^{7} y R^{8} tiene una de las fórmulas



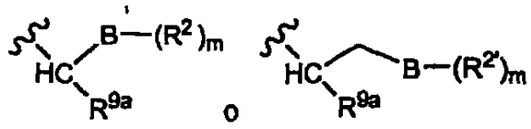


en donde m es 0 1, 2 o 3 y cada R^1 seleccionado independientemente de hidrógeno, hidroxi, fluoro cloro NH_2 $NHCH_3$ $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo, etilo isopropilo, vinilo trifluorometilo metoxi, etoxi isopropoxi, y trifluorometoxi

67 El metodo de conformidad con la reivindicacion 63 caracterizado porque uno de R^7 y R^8 es un anillo fenilo opcionalmente sustituido con 1 2 ó 3 sustituyentes independientemente seleccionados de hidrógeno, hidroxi, fluoro, cloro NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$ SCH_3, SEt metilo etilo isopropilo vinilo, trifluorometilo, metoxi, etoxi, isopropoxi y trifluorometoxi

68 El metodo de conformidad con la reivindicación 63, caracterizado porque R^9 es un alquilo ramificado de C_3 C_{10}

69 El método de conformidad con la reivindicacion 63 caracterizado porque R^9 tiene la estructura



en donde B es un anillo fenilo, piridilo, furanilo tiofuranilo pirrol, ciclopentilc ciclohexilo, o piperidilo m es 0 1 2 o 3, y cada R^2 se selecciona independientemente de hidrógeno, hidroxi, fluoro, 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 un 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 comprende 1 a 12 atomos de carbono

70 El metodo de conformidad con la reivindicacion 63, caracterizado porque el compuesto urea tiene la formula

1-(2-clorofenil)-3-(heptan-4-il)urea,

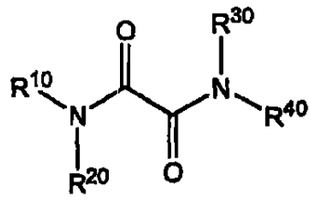
1-(2,4-diclorofenil)-3-(1-fenilpropil)urea

1-(2 4-dimetoxifenil)-3-(heptan-4-il)urea,

1-(2-fluorofenil)-3-(heptan-4-il)urea o

1-(4-isopropilfenil)-3-(2-(piridin-2-il)etil)urea

71 El metodo de conformidad con la reivindicación 1, caracterizado porque el compuesto amida es un compuesto oxalamida que tiene la formula



en donde R^{10} y R^{30} se seleccionan independientemente de residuos hidrocarburo que tienen al menos tres átomos de carbono y opcionalmente uno a diez heteroátomos seleccionados independientemente de oxigeno, nitrógeno, azufre halogenos o fósforos, y

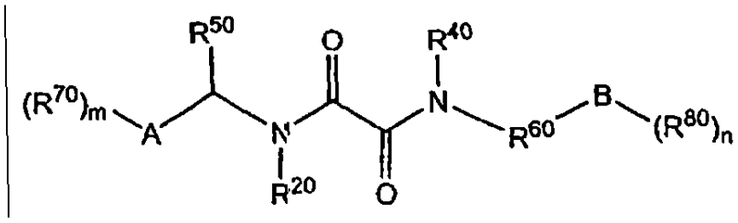
en donde R^{20} y R^{40} se seleccionan independientemente de hidrógeno y un residuo hidrocarburo que tiene al menos tres atomos de carbono y opcionalmente uno a diez heteroátomos seleccionados independientemente de oxigeno, nitrógeno, azufre halogenos o fosforos

72 El metodo de conformidad con la reivindicación 71 caracterizado porque R^{20} y R^{40} son hidrógeno

73 El método de conformidad con la reivindicación 71 caracterizado porque R^{10} y R^{30} se selecciona independientemente del grupo que consiste de arilalquilos heteroariloalquilos cicloalquilo-alquilos, y heterociclo-alquilos que comprende cinco a 15 atomos de carbono y en donde cada uno de R^{10} y R^{30} pueden comprender opcionalmente uno a uno a cuatro sustituyentes independientemente seleccionados de hidrógeno, 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

74 El método de conformidad con la reivindicación 1 caracterizado porque el compuesto amida es un compuesto oxalamida que tiene la fórmula



en donde A y B son independientemente arilo heteroarilo cicloalquilo o un heterociclo que comprende de 5 a 12 atomos en el anillo,

m y n son independientemente 0 1, 2, 3 ó 4-8, R^{20} y R^{40} son hidrógeno

R^{50} es hidrogeno o un alquilo o residuo alquilo sustituido que comprende uno a cuatro atomos de carbono

R^{60} esta ausente o un alquileno de C_1-C_5 o un alquileno de C_1-C_5 sustituido,

R^{70} y R^{80} se seleccionan independientemente a partir del grupo que consiste de hidrogeno 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 de C_1-C_8, cicloalquilo de C_3-C_6 y alquenilo de C_1-C_6

75 El método de conformidad con la reivindicacion 74, caracterizado porque A y B son independientemente un anillo fenilo piridilo, furanilo, benzofuranilo, pirrol, benzotiofeno, piperidilo ciclopentilo, ciclohexilo o cicloheptilo

m y n son independientemente 0 1, 2 ó 3

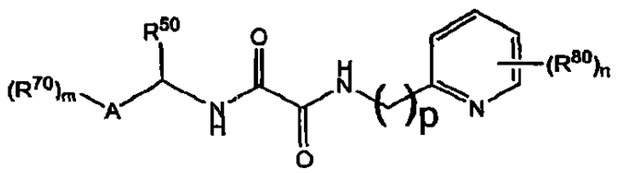
R^{20} y R^{40} es hidrogeno

R^{50} es hidrógeno o metilo

R^{60} es un alquileno de C_2,

R^{70} y R^{80} se seleccionan independientemente de hidrógeno 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

76 El metodo de conformidad con la reivindicacion 1 caracterizado porque el compuesto amida es un compuesto oxalamida que tiene la fórmula



en donde A es un anillo fenilo, piridilo furanilo pirrol, piperidilo, ciclopentilo ciclohexilo o cicloheptilo,

m y n son independientemente 0 1 2 o 3

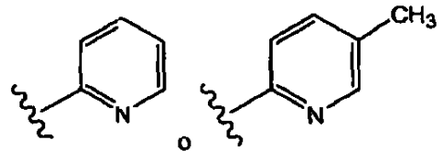
R^{50} es hidrogeno o metilo

P es 1 ó 2 y

R^{70} y R^{80} se seleccionan independientemente del grupo

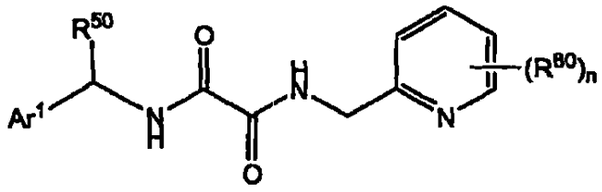
que consiste de hidrógeno, hidroxi fluoro cloro, NH_2 $NHCH_3$ $N(CH_3)_2$ $COOCH_3$, SCH_3, SEt, metilo etilo, isopropilo vinilo trifluorometilo metoxi etoxi isopropoxi y trifluorometoxi, o dos de R^{70} juntos forman un anillo de metilendioxi

77 El metodo de conformidad con la reivindicacion 76, caracterizado porque el radical piridil-R^{80} tiene la estructura



o

78 El metodo de conformidad con la reivindicacion 1 caracterizado porque el compuesto amida es un compuesto oxalamida que tiene la fórmula



en donde AR^1 es un anillo arilo o heteroarilo sustituido que comprende cinco a 12 átomos de carbono,

R^{50} es hidrogeno o metilo,

n es 0 1 2 3

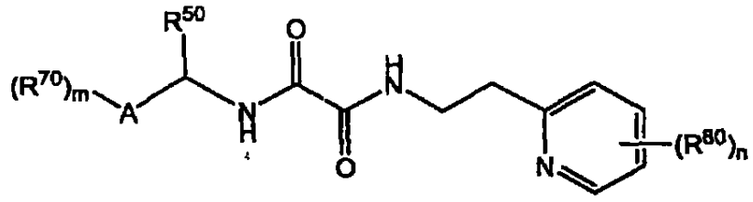
cada R^{80} se selecciona independientemente del grupo que consiste de hidroxi fluoro, cloro, NH_2 $NHCH_3$ $N(CH_3)_2$, CO_2CH_3, SEt SCH_3 metilo etilo isopropilo vinilo trifluorometilo metoxi, etoxi isopropoxi, y trifluorometoxi

79 El metodo de conformidad con la reivindicación 78

caracterizado porque AR^1 es un fenilo de 2- 3-, o 4- mono sustituido 2 4- 2 3- 2,5 2 6 3 5- o 3,6- fenilo disustituido, 3-alquil-4-fenilo sustituido un fenilo tri-sustituido en donde los grupos sustituyentes se seleccionan independientemente del grupo que consiste 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 o dos de los sustituyentes juntos forman un anillo metilendioxi en el anillo fenilo

80 El metodo de conformidad con la reivindicación 78 caracterizado porque AR^1 es un anillo heteroarilo sustituido que comprende 5 a 12 átomos de carbono y en donde los grupos sustituyentes se seleccionan independientemente del grupo que consiste de hidrogeno 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

81 El metodo de conformidad con la reivindicaçion 1 caracterizado porque el compuesto amida es un compuesto oxalamida que tiene la fórmula



en donde A es un anillo arilo o heteroarilo sustituido

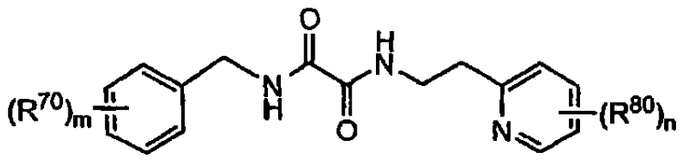
que comprende cinco a 12 átomos de carbono

R^{50} es hidrogeno o metilo,

m y n son independientemente 0, 1, 2 ó 3,

cada R^{70} o R^{80} se selecciona independientemente del grupo que consiste de hidrógeno, hidroxi, fluoro, cloro NH_2 $NHCH_3$, $N(CH_3)_2$, $COOCH_3$ SCH_3 SEt, metilo, etilo, isopropilo vinilo trifluorometilo, metoxi, etoxi, isopropoxi, y trifluorometoxi

82 El metodo de conformidad con la reivindicación 1 caracterizado porque el compuesto amida es un compuesto oxalamida que tiene la fórmula



en donde m y n son independientemente 0 1 2 ó 3 y

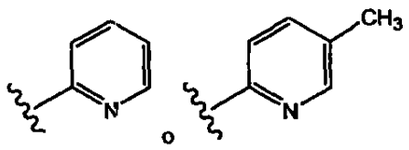
R^{70} y R^{80} se seleccionan independientemente del grupo que consiste de hidrógeno, alquilo, alcoxilo, alcoxi-alquilo OH SR^9 halogeno CN NO_2 CO_2R^9 COR^9 $CONR^9R^{10}$, NR^9R^{10} NR^9COR^{10}, SOR^9, SO_2R^9 $SO_2NR^9R^{10}$, $NR^9SO_2R^{10}$, alquenilo cicloalquilo, cicloalquenilo arilo heteroarilo y heterociclo

R^9 y R^{10} se seleccionan independientemente de H alquilo de C_1-C_6, cicloalquilo de C_3-C_6 y alquenilo de C_1-C_6

83 El metodo de conformidad con la reivindicacion 82, caracterizado porque R^{70} y R^{80} se seleccionan independientemente de grupos que consiste de hidrógeno hidroxi, fluoro, cloro NH_2, $NHCH_3$ $N(CH_3)_2$ O_2CCH_3, SH, SCH_3 metilo, etilo isopropilo

vinilo, trifluorometilo metoxi, etoxi isopropoxi y trifluorometoxi

84 El método de conformidad con la reivindicacion 82 caracterizado porque el radical piridil-R^{80} tiene la estructura



85 El metodo de conformidad con cualquiera de las reivindicaciones 1-84, caracterizado porque el log^{10} del coeficiente de particion del compuesto amida entre n-octanol y agua es menor que 5 5

86 El metodo de conformidad con la reivindicacion 1 caracterizado porque el producto comestible o medicinal modificado es un articulo para el consumo animal

87 El metodo de conformidad con la reivindicación 1-84, caracterizado porque el producto comestible o medicinal modificado es un articulo para el consumo humano

88 El método de conformidad con cualquiera de las reivindicaciones 1-84 caracterizado porque el producto comestible o medicinal modificado se selecciona del grupo que consiste de confiterias productos para panaderia helados productos cremosos, bocadillos dulces y sabrosos, barras de bocadillos, productos de reemplazo de comidas comidas preparadas sopas pastas, fideos alimentos enlatados, alimentos congelados alimentos secos alimentos refrigerados aceites y grasas alimentos para bebés o alimentos para untar

89 El metodo de conformidad con cualquiera de las reivindicaciones 1-84 caracterizado porque el producto comestible o medicinal modificado comprende uno o más de carne pollo pescado, vegetales granos o frutas

90 El método de conformidad con la reivindicacion 1, caracterizado porque el producto comestible o medicinal modificado es un alimento congelado un alimento crudo, o un alimento cocido completa o parcialmente

91 El método de conformidad con la reivindicacion 1 caracterizado porque el producto comestible o medicinal modificado es una sopa una sopa deshidratada o instantánea, o una sopa seca

92 El metodo de conformidad con la reivindicación 1 caracterizado porque el producto comestible o medicinal modificado es un bocadillo

93 El metodo de conformidad con la reivindicacion 1 caracterizado porque el producto comestible o medicinal modificado es un producto auxiliar para cocinar producto de solución de comida un producto para aderezar comidas, un condimento o un marinado

94 El método de conformidad con la reivindicación 1 caracterizado porque el producto comestible o medicinal modificado es una torta, galleta, pastel, caramelo, goma masticable, gelatina, helado, sorbete budin, mermelada jalea, aderezo para ensaladas condimentos, cereal frutas en conserva

o compota

95 El método de conformidad con cualquiera de las reivindicaciones 1-84 caracterizado porque el producto comestible o medicinal modificado es una bebida una mezcla de bebida o un concentrado de bebida

96 El metodo de conformidad con la reivindicacion 1, caracterizado porque el producto comestible o medicinal modificado es una soda o jugo

97 El método de conformidad con la reivindicación 1 caracterizado porque el producto comestible o medicinal modificado es una bebida alcohólica

98 El método de conformidad con la reivindicacion 1-84 caracterizado porque el producto comestible o medicinal modificado es una composicion farmaceutica para administracion oral

99 El método de conformidad con la reivindicación 1, caracterizado porque el producto comestible o medicinal modificado es un producto de higiene oral

100 El método de conformidad con la reivindicacion 1-84 caracterizado porque el compuesto amida está presente en el producto comestible o medicinal modificado en una concentracion de aproximadamente 0 01 ppm a aproximadamente 30 ppm

101 El metodo de conformidad con la reivindicacion 1 caracterizado porque el compuesto amida está presente en el producto comestible o medicinal modificado en una concentración

de aproximadamente 0 05 ppm a aproximadamente 15 ppm

102 El metodo de conformidad con la reivindicación 1, caracterizado porque el compuesto amida está presente en el producto comestible o medicinal modificado en una concentracion de aproximadamente 0 1 ppm a aproximadamente 5 ppm

103 El método de conformidad con la reivindicación 1 caracterizado porque el compuesto amida está presente en el producto comestible o medicinal modificado en una concentracion de aproximadamente 0 1 ppm a aproximadamente 3 ppm

104 El metodo de conformidad con la reivindicación 1-84, caracterizado porque una solución acuosa que comprende la cantidad de modificacion de sabor sabroso del compuesto amida tiene un sabor sabroso cuando se determina por la mayoria de un grupo de expertos de al menos ocho catadores de sabor humanos

105 El método de conformidad con la reivindicación 1-84 caracterizado porque una solucion acuosa que comprende la cantidad de modificación de sabor sabroso del compuesto amida y 12 mM de glutamato de monosodio tendrá un sabor sabroso incrementado cuando se compara a una solucion acuosa control que comprende 12 mM de glutamato de monosodio, cuando se determina por la mayoria de un grupo de expertos de al menos ocho catadores de sabor humanos

106 El metodo de conformidad con la reivindicación 1, caracterizado porque una solución acuosa que comprende una cantidad de modificación de sabor sabroso del compuesto amida y

12 mM de glutamato de monosodio tendra un sabor sabroso incrementado cuando se compara a una solucion acuosa control que comprende 12 mM de glutamato de monosodio y 100 µM de monofosfato de inosina cuando se determina por la mayoria de un grupo de expertos de al menos ocho catadores de sabor humanos

107 El método de conformidad con la reivindicacion 1, caracterizado porque una solucion acuosa que comprende aproximadamente 10 ppm del compuesto amida y aproximadamente 12 mM de glutamato de monosodio tendrá un sabor sabroso incrementado cuando se compara a una solucion acuosa control que comprende unicamente el glutamato de monosodio cuando se determina por la mayoria de un grupo de expertos de al menos ocho catadores de sabor humanos

108 El método de conformidad con cualquiera de las reivindicaciones 1 caracterizado porque el compuesto amida es un agonista sabroso para un receptor hT1R1/hT1R3

109 El método de conformidad con cualquiera de las reivindicaciones 1-84, caracterizado porque el compuesto amida tiene un EC_{50} para el receptor hT1R1/hT1R3 menor que aproximadamente 2 µM

110 El metodo de conformidad con la reivindicacion 1 caracterizado porque el compuesto amida, cuando se disolvió en una solucion acuosa que comprende aproximadamente *1* μM del compuesto amida disminuye el EC_{50} observado de glutamato de monosodio para un receptor hT1R1/hT1R3 expresado en una linea

celular HEK293-Gα15 por al menos 50%

111 El método de conformidad con la reivindicación 1 caracterizado porque el producto comestible o medicinal modificado tiene un sabor sabroso incrementado cuando se compara con el producto comestible o medicinal preparado sin el compuesto amida, cuando se determina por la mayoria de un grupo de expertos de al menos ocho catadores de sabor humanos

112 El método de conformidad con la reivindicacion 1 caracterizado porque el compuesto amida es comestiblemente aceptable

113 El método de conformidad con la reivindicación 1 caracterizado porque el compuesto amida es o puede mostrarse generalmente para ser reconocido como seguro

114 El metodo de conformidad con la reivindicación 1, caracterizado porque el compuesto amida cuando se combina con el alimento para ratas y se alimenta a ratas Crl CD(SD)IGS BR en una concentración de aproximadamente 100 miligramos/Kilogramo-Cuerpo-Peso/dia para 90 no causa efectos toxicos adversos en las ratas

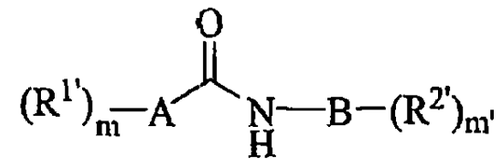
115 El producto comestible o medicinal modificado producido por cualquiera de las reivindicaciones 1-84

116 Un metodo para incrementar el sabor dulce de un producto comestible o medicinal, caracterizado porque comprende

a) proporcionar al menos un producto comestible o medicinal o un precursor del mismo y

b) combinar el producto o precursor comestible o medicinal del mismo con al menos una cantidad que modula el sabor sabroso o una cantidad que modula el sabor dulce de al menos un compuesto amida de origen no natural o una sal comestiblemente aceptable del mismo, de manera que se forma 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 ó 12 atomos en el anillo

m es 0 1, 2 3 ó 4

cada R^1 se selecciona independientemente del grupo que consiste de alquilo de C_1-C_4 haloalquilo de C_1-C_4 haloalcoxi de C_1-C_4 alcoxilo de C_1-C_4, alcoxialquilo de C_1-C_4, hidroxialquilo de C_1-C_4 OH NH_2 NHR^6, $NR^6{}_2$, CN CO_2H, CHO, CO_2R^6, SH, SR^6, y halógeno, en donde R^6 es alquilo de C_1-C_4

R^2 comprende un alquilo o cicloalquilo opcionalmente ramificado con uno a cuatro sustituyentes seleccionados independientemente de alquilo, alcoxilo alcoxi-alquilo, hidroxialquilo OH, NH_2 NHR^b $NR^6{}_2$ CN CO_2H CHO, COR^6 SH SR^6, halógeno alquenilo cicloalquilo, cicloalquenilo, arilo y heteroarilo y R^6 es alquilo de C_1-C_6 y

y en donde el compuesto amida tiene un peso molecular

de 500 gramos por mol o menos

117 El metodo de conformidad con la reivindicacion 56 caracterizado porque cada R^1 y cada sustituyente opcional para R^2 se seleccionan independientemente a partir del grupo que consiste de hidrógeno hidroxi, fluoro cloro, NH_2 $NHCH_3$ $N(CH_3)_2$, $COOCH_3$ SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo metoxi, etoxi isopropoxi y trifluorometoxi

118 El método de conformidad con la reivindicacion 117, caracterizado porque A es un anillo arilo que comprende 6 a 12 carbonos en el anillo

119 El método de conformidad con la reivindicacion 117 caracterizado porque A es un anillo naftilo

120 El metodo de conformidad con la reivindicacion 117 caracterizado porque A es un anillo fenilo

121 El metodo de conformidad con la reivindicación 120 caracterizado porque m es 1, 2 3 ó 4

122 El método de conformidad con la reivindicacion 121 caracterizado porque R^2 es un alquilo ramificado de C_3 C_{10}

123 El metodo de conformidad con la reivindicacion 121 caracterizado porque R^2 es un alquilo ramificado de C_3 C_{10} sustituido con 1 2 o 3 grupos sustituyentes seleccionados 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 trifluorometoxi fenilo y piridilo

124 El método de conformidad con la reivindicacion 121 caracterizado porque R^2 es un anillo cicloalquilo o cicloalquenilo que tienen 3 a 10 átomos de carbono en el anillo opcionalmente sustituido con 1, 2 o 3 sustituyentes independientemente seleccionados del grupo que consiste 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

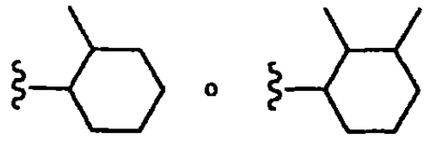
125 El metodo de conformidad con la reivindicacion 121 caracterizado porque R^2 es un anillo cicloalquilo o cicloalquenilo que tienen 5 a 8 átomos de carbono en el anillo, opcionalmente sustituido con 1 2 ó 3 sustituyentes independientemente seleccionados del grupo que consiste de hidroxi fluoro cloro NH_2, $NHCH_3$, $N(CH_3)_2$ CO_2CH_3, SEt SCH_3, metilo, etilo, isopropilo vinilo trifluorometilo, metoxi etoxi isopropoxi, y grupos del trifluorometoxi

126 El metodo de conformidad con la reivindicación 121, caracterizado porque R^2 es un anillo ciclopentilo, ciclohexilo cicloheptilo o ciclooctilo opcionalmente sustituido con 1 2 ó 3 sustituyentes seleccionados independientemente del grupo que consiste 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

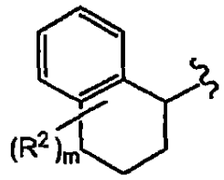
127 El método de conformidad con la reivindicación 121 caracterizado porque R^2 es un ciclohexilo, opcionalmente

sustituidos con 1, 2 o 3 grupos metilo

128 El metodo de conformidad con la reivindicación 121, caracterizado porque R^2 tiene la fórmula

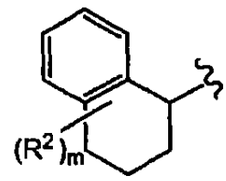


129 El método de conformidad con la reivindicación 121, caracterizado porque R^2 es un 1-indano que tiene la formula



en donde m es 0 1, 2 ó 3 y cada R^2 puede unirse ya sea a un anillo aromático o no aromatico y 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

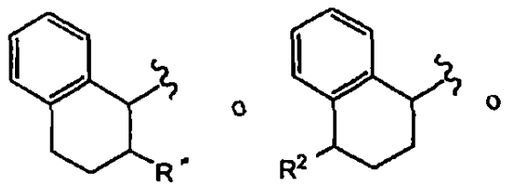
130 El método de conformidad con la reivindicacion 121 caracterizado porque R^2 es un 1-(1,2 3 4) tetrahidronaftaleno que tiene la formula

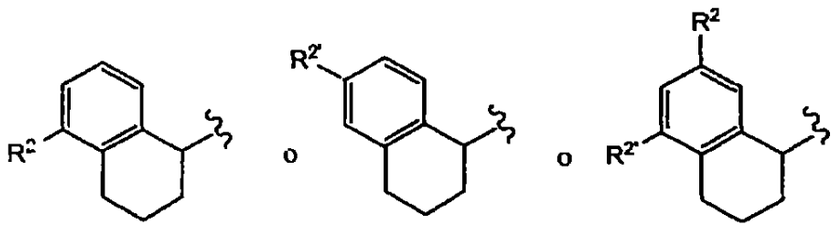


en donde m es 0, 1 2 o 3 y cada R^2 puede unirse ya

sea a un anillo aromático o no aromático y se selecciona independientemente de hidroxi fluoro, cloro NH_2 $NHCH_3$, $N(CH_3)_2$ $COOCH_3$ SCH_3, SEt metilo, etilo, isopropilo vinilo trifluorometilo metoxi etoxi, isopropoxi y trifluorometoxi

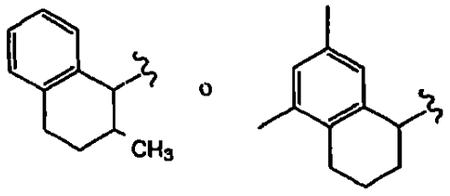
131 El metodo de conformidad con la reivindicacion 121 caracterizado porque R^2 tiene la formula





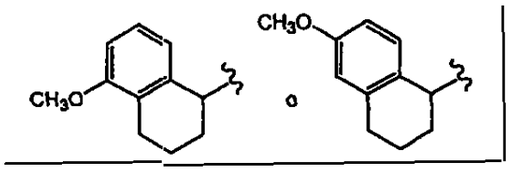
en donde R^2 se selecciona independientemente del grupo que consiste de hidrogeno hidroxi, fluoro, cloro NH_2 $NHCH_3$, $N(CH_3)_2$ $COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo metoxi etoxi, isopropoxi y trifluorometoxi

132 El método de conformidad con la reivindicación 121, caracterizado porque R^2 tiene la fórmula

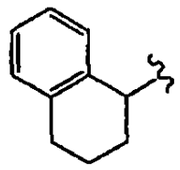


133 El metodo de conformidad con la reivindicación

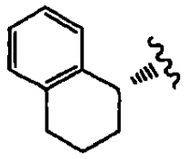
121, caracterizado porque R^2 tiene la fórmula



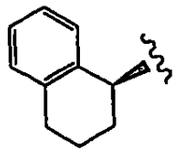
134 El método de conformidad con la reivindicacion 121, caracterizado porque R^2 es un anillo de 1-(1,2 3,4) tetrahidroftaleno que tiene la formula



135 El metodo de conformidad con la reivindicación 121 caracterizado porque R^2 es un anillo de 1-(1,2,3,4) tetrahidroftaleno que tiene la formula



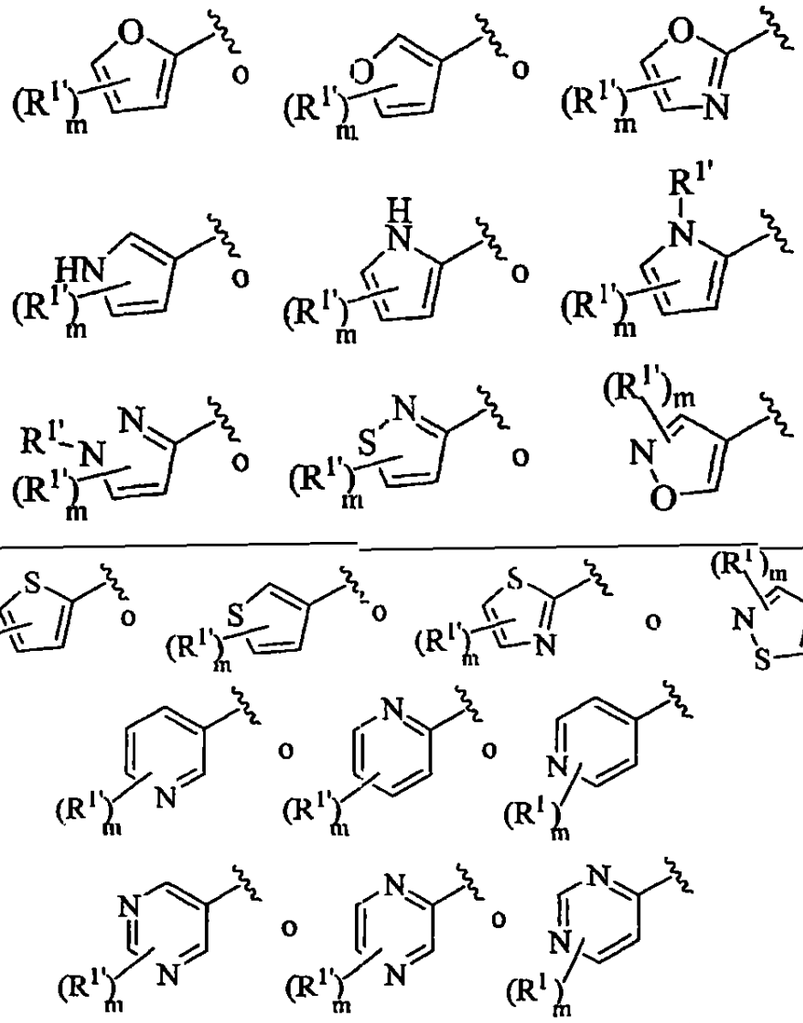
136 El método de conformidad con la reivindicacion 121 caracterizado porque R^2 es un anillo de 1-(1 2 3,4) tetrahidroftaleno que tiene la formula



137 El metodo de conformidad con la reivindicacion 117 caracterizado porque A es un heteroarilo monociclico

138 El metodo de conformidad con la reivindicación

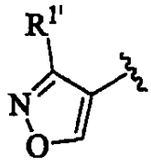
117, caracterizado porque A tiene una de las fórmulas



en donde m, es 0 1 2 o 3 y cada R^1 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 o trifluorometoxi

139 El metodo de conformidad con la reivindicacion

117, caracterizado porque A tiene la formula



en donde R^1 es hidrogeno hidroxi fluoro cloro NH_2 $NHCH_3$, $N(CH_3)_2$ O_2CCH_3, SH SCH_3 metilo etilo isopropilo, vinilo, trifluorometilo, metoxi etoxi isopropoxi o trifluorometoxi

140 El metodo de conformidad con la reivindicacion 138 caracterizado porque R^2 es un alquilo ramificado de C_3 C_{10}

141 El método de conformidad con la reivindicación 138, caracterizado porque R^2 es un alquilo ramificado de C_3 C_{10}, sustituido con grupos de 1 2 ó 3 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, trifluorometoxi, fenilo y piridilo

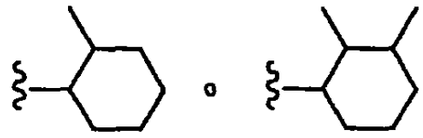
142 El metodo de conformidad con la reivindicación 138 caracterizado porque R^2 es un cicloalquilo que tiene 3 a 10 atomos de carbono en el anillo opcionalmente sustituido con 1, 2 ó 3 sustituyentes independientemente seleccionados del grupo que consiste de hidroxi fluoro cloro NH_2, $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt, SCH_3, grupos metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi etoxi isopropoxi, trifluorometoxi

143 El método de conformidad con la reivindicación 138 caracterizado porque R^2 es un ciclopentilo, ciclohexilo,

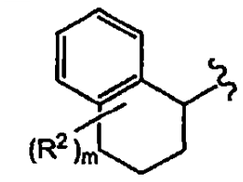
cicloheptilo o ciclooctilo opcionalmente sustituido con 1 2 ó 3 sustituyentes seleccionados independientemente del grupo que consiste de los grupos hidroxi, fluoro cloro NH_2 $NHCH_3$, $N(CH_3)_2$, CO_2CH_3, SEt SCH_3, metilo etilo isopropilo vinilo trifluorometilo metoxi, etoxi isopropoxi y trifluorometoxi

144 El método de conformidad con la reivindicacion 138, caracterizado porque R^2 es un ciclohexilo, grupos metilo opcionalmente sustituido con 1, 2 ó 3

145 El método de conformidad con la reivindicacion 138 caracterizado porque R^2 tiene la fórmula



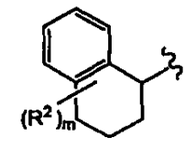
146 El metodo de conformidad con la reivindicación 138 caracterizado porque R^2 es un 1-indano que tiene la formula



en donde m es 0, 1 2 o 3 y cada R^2 puede unirse ya sea al anillo aromático o no aromático y 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

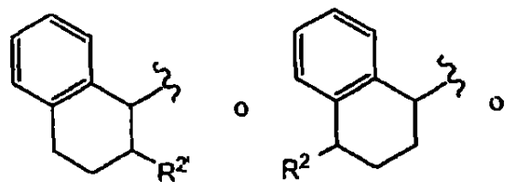
147 El metodo de conformidad con la reivindicacion

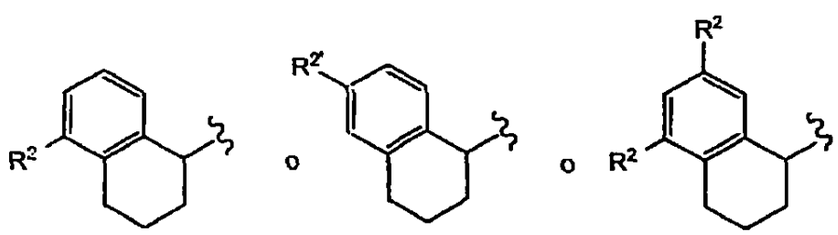
138, caracterizado porque R' es un 1-(1 2 3,4)tetrahidronaftaleno que tiene la fórmula



en donde m es 0, 1, 2 o 3 y cada R^2 puede unirse ya sea al anillo aromatico o no aromatico y 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

148 El metodo de conformidad con la reivindicación 138 caracterizado porque R^2 tiene la fórmula

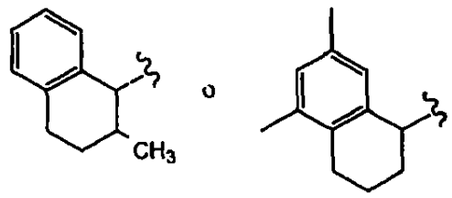




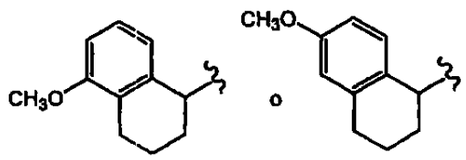
en donde cada R^2 se selecciona independientemente del grupo que consiste de hidrogeno hidroxi fluoro cloro NH_2, $NHCH_3$, $N(CH_3)_2$ O_2CCH_3, SH, SCH_3, metilo etilo, isopropilo vinilo trifluorometilo metoxi, etoxi isopropoxi o trifluorometoxi

149 El método de conformidad con la reivindicacion

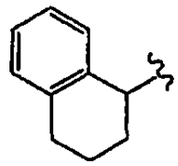
138 caracterizado porque R^2 tiene la fórmula



150 El método de conformidad con la reivindicacion 138 caracterizado porque R^2 tiene la formula



151 El metodo de conformidad con la reivindicacion 138 caracterizado porque R^2 es un anillo de 1-(1,2,3,4) tetrahidroftaleno que tiene la fórmula



152 El metodo de conformidad con la reivindicacion 116, caracterizado porque el producto comestible o medicinal modificado es un articulo para el consumo animal

153 El método de conformidad con la reivindicación 116 caracterizado porque el producto comestible o medicinal modificado es un articulo para el consumo humano

154 El método de conformidad con cualquiera de las reivindicaciones 116-151, caracterizado porque el producto comestible o medicinal modificado se selecciona del grupo que

consiste de confiterias, productos para panaderia helados, productos cremosos bocadillos dulces y sabrosos barras de bocadillos, productos de reemplazo de comidas comidas preparadas, sopas pastas fideos, alimentos enlatados, alimentos congelados alimentos secos alimentos refrigerados aceites y grasas, alimentos para bebés y alimentos para untar

155 El método de conformidad con cualquiera de las reivindicaciones 116-151, caracterizado porque el producto comestible o medicinal modificado comprende una o más carnes pollo, pescado, vegetales granos o frutas

156 El metodo de conformidad con la reivindicación 116, caracterizado porque el producto comestible o medicinal modificado es un alimento congelado, un alimento crudo o un alimento cocido completo o parcialmente

157 El método de conformidad con la reivindicacion 116 caracterizado porque el producto comestible o medicinal modificado es una sopa, una sopa deshidratada o instantanea o una sopa seca

158 El metodo de conformidad con la reivindicacion 116 caracterizado porque el producto comestible o medicinal modificado es un bocadillo

159 El método de conformidad con la reivindicación 116 caracterizado porque el producto comestible o medicinal modificado es un producto auxiliar para cocinar, producto de solucion de comida un producto para aderezar comidas un

condimento o un marinado

160 El metodo de conformidad con la reivindicacion 116, caracterizado porque el producto comestible o medicinal modificado es una torta galleta pastel, caramelo goma masticable, gelatina helado sorbete, budin mermelada, jalea, aderezo para ensaladas condimentos cereal, frutas en conserva, o compota

161 El metodo de conformidad con cualquiera de las reivindicaciones 116-151 caracterizado porque el producto comestible o medicinal modificado es una bebida una mezcla de bebida, o un concentrado de bebida

162 El metodo de conformidad con la reivindicación 116-151, caracterizado porque el producto comestible o medicinal modificado es una soda o jugo

163 El metodo de conformidad con la reivindicación 116-151 caracterizado porque el producto comestible o medicinal modificado es una bebida alcohólica

164 El método de conformidad con la reivindicación 116-151, caracterizado porque el producto comestible o medicinal modificado es una composición farmaceutica para administración oral

165 El método de conformidad con la reivindicación 116, caracterizado porque el producto comestible o medicinal modificado es un producto de higiene oral

166 El método de conformidad con la reivindicacion

116-151 caracterizado porque el compuesto amida está presente en el producto comestible o medicinal modificado en una concentracion de aproximadamente 0 001 ppm a aproximadamente 100 ppm

167 El método de conformidad con la reivindicacion 117 caracterizado porque el compuesto amida está presente en el producto comestible o medicinal modificado en una concentración de aproximadamente 0 1 ppm a aproximadamente 30 ppm

168 El método de conformidad con la reivindicacion 116, caracterizado porque el compuesto amida está presente en el producto comestible o medicinal modificado en una concentración de aproximadamente 0 05 ppm a aproximadamente 15 ppm

169 El metodo de conformidad con la reivindicación 116-151, caracterizado porque el compuesto amida esta presente en el producto comestible o medicinal modificado en una concentración de aproximadamente 0 1 ppm a aproximadamente 5 ppm

170 El método de conformidad con la reivindicacion 116 caracterizado porque el compuesto amida está presente en el producto comestible o medicinal modificado en una concentracion de aproximadamente 0 1 ppm a aproximadamente 3 ppm

171 El método de conformidad con la reivindicacion 116-151, caracterizado porque el producto comestible o medicinal modificado tiene un sabor sabroso incrementado cuando se compara al producto comestible o medicinal preparado sin el

compuesto amida, cuando se determina por la mayoría de un grupo de expertos de al menos ocho catadores de sabor humanos

172 El metodo de conformidad con la reivindicación 116, caracterizado porque una solucion acuosa comprende una cantidad de sabor dulce de un edulcorante seleccionado del grupo que consiste de sacarosa, fructuosa, glucosa, eritritol, isomalto, lactitol manitol, sorbitol, xilitol un terpenoide natural conocido, flavonoides, o edulcorante de proteina, aspartame, sacarina acelsufame-K ciclamato sucralosa y alitame o mezclas de los mismos y una cantidad que modula el sabor sabroso de al menos un compuesto amida tiene un sabor más dulce que una solución acuosa control que comprende la cantidad del sabor dulce del edulcorante conocido cuando se determina por la mayoria de un grupo de expertos de al menos ocho catadores de sabor humanos

173 El método de conformidad con la reivindicación 116 caracterizado porque una solución acuosa que comprende la cantidad que modifica el sabor dulce del compuesto amida y aproximadamente 6 gramos/100 mililitros de sacarosa tiene un sabor mas dulce que una solución acuosa control que comprende 6% gramos/100 mililitros de sacarosa, cuando se determina por la mayoria de un grupo de expertos de al menos ocho catadores de sabor humanos

174 El método de conformidad con la reivindicación 116, caracterizado porque una solución acuosa que comprende la cantidad que modifica el sabor dulce del compuesto amida y 6%

gramos/100 mililitros de una mezcla de 50 50 de sacarosa y fructuosa tendrá un sabor mas dulce que una solución acuosa control que comprende 6% gramos/100 mililitros de una mezcla de 50 50 de sacarosa y fructuosa, cuando se determina por la mayoría de un grupo de expertos de al menos ocho catadores de sabor humanos

175 El método de conformidad con la reivindicacion 116, caracterizado porque una solucion acuosa que comprende la cantidad que modifica el sabor dulce del compuesto amida y aproximadamente 1 6 mM de aspartame tiene un sabor más dulce que una solución acuosa control que comprende aproximadamente 1 6 mM de aspartame cuando se determina por la mayoria de un grupo de expertos de al menos ocho catadores de sabor humanos

176 El método de conformidad con la reivindicacion 116, caracterizado porque una solucion acuosa que comprende la cantidad que modifica el sabor dulce del compuesto amida y aproximadamente 1 5 mM de acesulfame-K tiene un sabor más dulce que una solución acuosa control que comprende aproximadamente 1 5 mM de acesulfame-K cuando se determina por la mayoria de un grupo de expertos de al menos ocho catadores de sabor humanos

177 El metodo de conformidad con la reivindicación 116 caracterizado porque una solucion acuosa que comprende la cantidad que modifica el sabor dulce del compuesto amida y aproximadamente 10 mM de ciclamato tiene un sabor mas dulce

que una solucion acuosa control que comprende aproximadamente 10 mM de ciclamato, cuando se determina por la mayoria de un grupo de expertos de al menos ocho catadores de sabor humanos

178 El método de conformidad con la reivindicacion 116 caracterizado porque una solución acuosa que comprende la cantidad que modifica el sabor dulce del compuesto amida y aproximadamente 0 4 mM de sucralosa tiene un sabor más dulce que una solucion acuosa control que comprende aproximadamente 0 4 mM de sucralosa, cuando se determina por la mayoria de un grupo de expertos de al menos ocho catadores de sabor humanos

179 El metodo de conformidad con la reivindicacion 116 caracterizado porque una solucion acuosa que comprende la cantidad que modifica el sabor dulce del compuesto amida y aproximadamente 0 2 mM de alitame tiene un sabor mas dulce que una solución acuosa control que comprende aproximadamente 0 2 mM de alitame cuando se determina por la mayoria de un grupo de expertos de al menos ocho catadores de sabor humanos

180 El metodo de conformidad con la reivindicacion 116, caracterizado porque el producto comestible o medicinal modificado tiene un sabor más dulce cuando se compara con el producto comestible o medicinal preparado sin el compuesto amida cuando se determina por la mayoria de un grupo de expertos de al menos ocho catadores de sabor humanos

181 El método de conformidad con la reivindicación 116 caracterizado porque el compuesto amida que modula la

unión de un dulcificante seleccionado del grupo que consiste de sacarosa, fructuosa, glucosa, eritritol isomalto lactitol manitol, sorbitol xilitol ciertos terpenoides naturales conocidos flavonoides, o edulcorantes de proteinas, aspartame, sacarina acesufame-K ciclamato, sucralosa y alitame o eritritol para un receptor hT1R2/hT1R^3 expresado en una linea celular HEK293-Gα15

182 El metodo de conformidad con la reivindicacion 116, caracterizado porque el compuesto amida tiene un EC_{50} para unir un receptor hT1R2/hT1R3 expresado en una línea celular HEK293-Gα15 de menos de aproximadamente 10 μM

183 El método de conformidad con cualquiera de las reivindicaciones 116-151, caracterizado porque el compuesto amida tiene un EC_{50} para unir un receptor hT1R2/hT1R3 expresado en una linea celular HEK293-Gα15 de menos de aproximadamente 5 μM

184 El método de conformidad con la reivindicacion 116, caracterizado porque el compuesto amida tiene un EC_{50} para unir un receptor hT1R2/hT1R3 expresado en una linea celular HEK293-Gα15 de menos de aproximadamente 2 μM

185 El metodo de conformidad con la reivindicacion 116 caracterizado porque el compuesto amida tiene un EC_{50} para unir un receptor hT1R2/hT1R3 expresado en una linea celular HEK293-Gα15 de menos de aproximadamente 1 μM

186 El método de conformidad con la reivindicación

116-151 caracterizado porque el compuesto amida no es un compuesto peptido

187 El metodo de conformidad con la reivindicación 116 caracterizado porque el compuesto amida es comestiblemente aceptable

188 El método de conformidad con la reivindicacion 116, caracterizado porque el compuesto amida es o puede determinarse generalmente para ser reconocido como seguro para el uso en los productos alimenticios en una concentración especificada en el producto terminado

189 El metodo de conformidad con la reivindicacion 116, caracterizado porque el compuesto amida cuando se combina con el alimento para ratas y se alimenta a ratas Crl CD(SD)IGS BR en una concentracion de aproximadamente 100 miligramos/Kilogramo-Cuerpo Peso/dia para 90 dias no causa efectos tóxicos adversos en las ratas

190 El producto comestible o medicinal modificado producido por cualquiera de las reivindicaciones 116-189

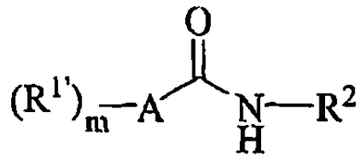
191 Un método para incrementar el sabor dulce de un producto comestible o medicinal caracterizado porque comprende

a) proporcionar al menos un producto comestible o medicinal, o un precursor del mismo, y

b) combinar el producto o precursor comestible o medicinal del mismo con aproximadamente 0 001 ppm a aproximadamente 100 ppm de al menos un compuesto amida que

ocurre no naturalmente o un sal comestiblemente aceptable del mismo de manera que forman 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 ó 12 átomos en el anillo,

m es 0 1 2 3 o 4

cada R^1 se selecciona independientemente del grupo que consiste 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

R^2 es un anillo fenilo opcionalmente sustituido con 1 2 ó 3 sustituyentes independientemente seleccionados del grupo que consiste 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

en donde el compuesto amida tiene un peso molecular de 500 gramos por mol o menos

192 El método de conformidad con la reivindicación 191 caracterizado porque el producto comestible o medicinal modificado se selecciona del grupo que consiste de confiterias, productos para panadería, helados productos cremosos,

bocadillos dulces y sabrosos barras de bocadillos productos de reemplazo de comidas comidas preparadas, sopas, pastas, fideos alimentos enlatados, alimentos congelados, alimentos secos alimentos refrigerados, aceites y grasas, alimentos para bebes o alimentos para untar

193 El método de conformidad con la reivindicación 191, caracterizado porque el producto comestible o medicinal modificado es una torta, galleta, pastel caramelo goma masticable, gelatina helado sorbete budin, mermelada jalea aderezo para ensaladas, condimentos, cereal frutas en conserva o compota

194 El metodo de conformidad con la reivindicación 191, caracterizado porque el producto comestible o medicinal modificado es una bebida, una mezcla de bebida o un concentrado de bebida

195 El metodo de conformidad con la reivindicación 191, caracterizado porque el producto comestible o medicinal modificado es una soda o jugo

196 El método de conformidad con la reivindicación 191 caracterizado porque el producto comestible o medicinal modificado es una bebida alcohólica

197 El metodo de conformidad con la reivindicacion 191 caracterizado porque el producto comestible o medicinal modificado es una composicion farmacéutica para administracion oral

198 El metodo de conformidad con la reivindicacion 191, caracterizado porque el producto comestible o medicinal modificado es un producto de higiene oral

199 El método de conformidad con la reivindicacion 191 caracterizado porque el compuesto amida está presente en el producto comestible o medicinal modificado en una concentracion de aproximadamente 0 001 ppm a aproximadamente 100 ppm

200 El método de conformidad con la reivindicación 191 caracterizado porque el compuesto amida está presente en el producto comestible o medicinal modificado en una concentración de aproximadamente 0 1 ppm a aproximadamente 10 ppm

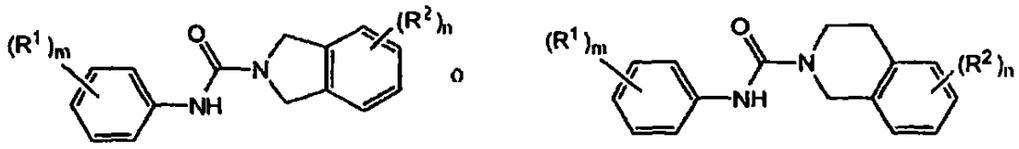
201 El producto comestible o medicinal modificado producido por el método de conformidad con las reivindicaciones 191-200

202 Un método para modular el sabor dulce de un comestible o producto medicinal caracterizado porque comprenden

a) proporcionar al menos un producto comestible o medicinal o un precursor del mismo y

b) combinar el producto o precursor comestible o medicinal del mismo con aproximadamente 0 001 ppm a aproximadamente 100 ppm de al menos un compuesto urea que ocurre no naturalmente, o un sal comestiblemente aceptable del mismo de manera que forman un producto comestible o medicinal modificado,

en donde el compuesto urea tiene la estructura

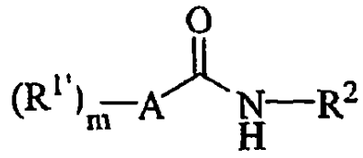


en donde m y n estan independientemente 0, 1, 2 ó 3 y cada R^1 y R^2 se selecciona independientemente de fluoro, cloro, NH_2 $NHCH_3$ $N(CH_3)_2$ CO_2CH_3 SEt, SCH_3, metilo etilo isopropilo vinilo trifluorometilo metoxi, etoxi, isopropoxi, y trifluorometoxi

203 El metodo de conformidad con la reivindicacion 202 caracterizado porque n es 0

204 Un producto comestible o medicinal producido por el metodo de conformidad con la reivindicación 202

205 Un producto comestible o medicinal, o un precursor del mismo que comprende aproximadamente 0 001 ppm a aproximadamente 100 ppm de al menos un compuesto amida que ocurre no naturalmente, o una sal comestiblemente aceptable del mismo en donde el compuesto amida tiene la fórmula



en donde A comprende un anillo arilo o heteroarilo de 5 ó 6 miembros,

m tiene 0 1, 2 3 ó 4,

cada R^1 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

R^2 comprende entre 4 y 14 atomos de carbono y 0, 1, 2, 3 4 ó 5 heteroatomos seleccionados independientemente de oxigeno, nitrogeno, azufre

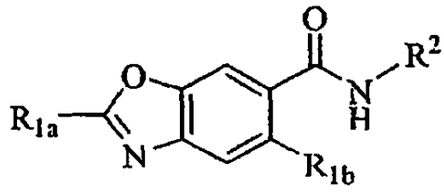
206 El producto comestible o medicinal o un precursor del mismo de conformidad con la reivindicación 205, caracterizado porque A es un anillo fenilo

207 El producto comestible o medicinal, o un precursor del mismo de conformidad con la reivindicacion 206 caracterizado porque m es 1, 2 ó 3

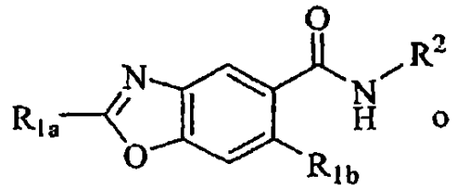
208 El producto comestible o medicinal o un precursor del mismo de conformidad con la reivindicación 206, caracterizado porque R^2 un alquilo ramificado de C_3 C_{10}

209 El producto comestible o medicinal o un precursor del mismo de conformidad con la reivindicación 206, caracterizado porque R^2 es un ácido carboxilico α-sustituido o metilester de ácido carboxilico α-sustituido

210 El producto comestible o medicinal, o un precursor del mismo de conformidad con la reivindicación 205 caracterizado porque el compuesto amida tiene la formula



o



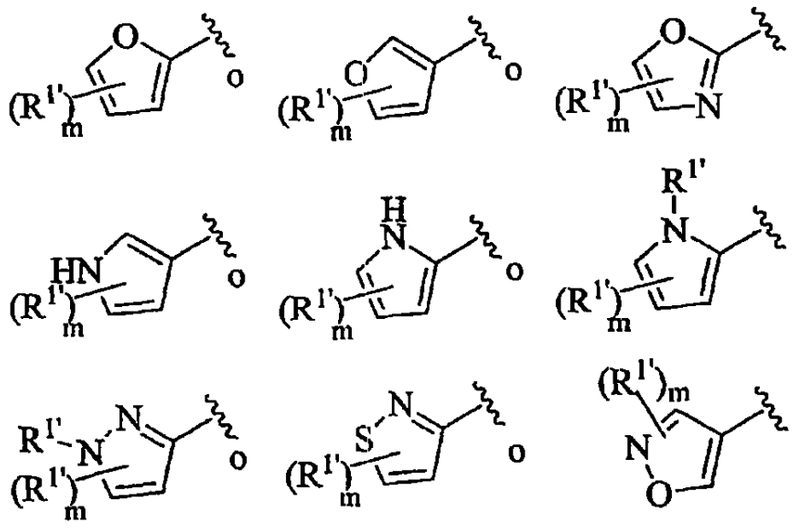
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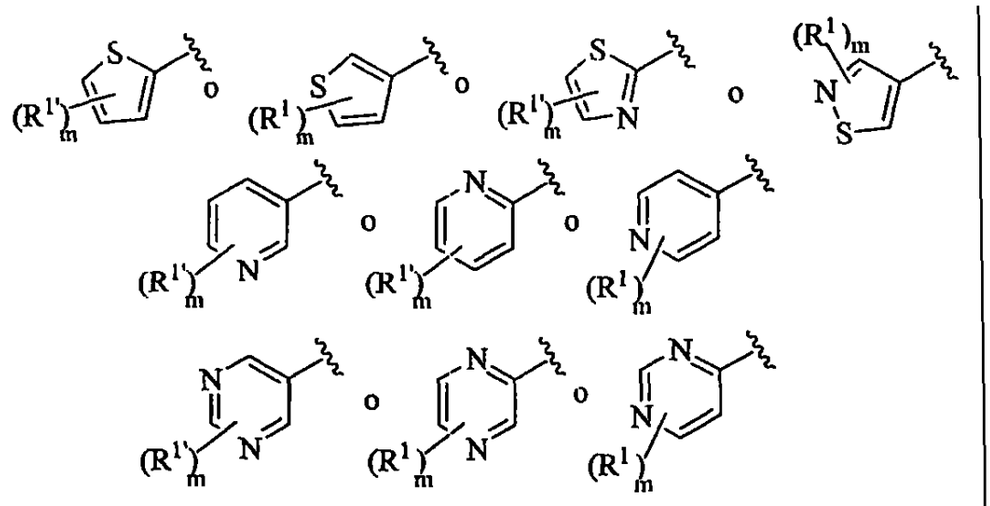
en donde R_{1a} y R_{1b} es independientemente hidrógeno o metilo

211 El producto comestible o medicinal o un precursor del mismo de conformidad con la reivindicación 210 caracterizado porque R^2 es un alquilo ramificado de C_3 C_{10}

212 El producto comestible o medicinal o un precursor del mismo de conformidad con la reivindicación 210 caracterizado porque R^2 un ácido carboxílico α-sustituido o metiléster de ácido carboxílico α-sustituido

213 El producto comestible o medicinal, o un precursor del mismo de conformidad con la reivindicacion 205, caracterizado porque A es un heteroarilo monociclico que tiene una de las fórmulas





en donde m es 0, 1, 2 ó 3, y cada R^1 se selecciona independientemente de hidrógeno 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

214 El producto comestible o medicinal, o un precursor del mismo de conformidad con la reivindicación 213, caracterizado porque R^2 es un alquilo de C_3 C_{10}

215 El producto comestible o medicinal, o un precursor del mismo de conformidad con la reivindicación 213 caracterizado porque R^2 un ácido carboxilico α-sustituido o metiléster de acido carboxilico α-sustituido

216 El producto comestible o medicinal, o un precursor del mismo de conformidad con la reivindicación 205, caracterizado porque el producto comestible o medicinal modificado es un articulo para el consumo humano

217 El producto comestible o medicinal, o un precursor del mismo de conformidad con cualquiera de las reivindicaciones 205-215, caracterizado porque el producto comestible o medicinal modificado se selecciona del grupo que consiste de confiterías, productos para panaderia, helados productos cremosos, bocadillos dulces y sabrosos barras de bocadillos, productos de reemplazo de comidas, comidas preparadas sopas, pastas, fideos alimentos enlatados, alimentos congelados, alimentos secos, alimentos refrigerados, aceites y grasas alimentos para bebes o alimentos para untar

218 Un producto comestible o un precursor del mismo de conformidad con la reivindicacion 205 caracterizado porque comprende uno o más de carne, pollo, pescado vegetales granos o frutas

219 Un producto comestible o un precursor del mismo de conformidad con la reivindicación 205, caracterizado porque es un alimento congelado, un alimento crudo, o un alimento cocido completa o parcialmente

220 Un producto comestible o un precursor del mismo de conformidad con la reivindicación 205, caracterizado porque es una sopa una sopa deshidratada o concentrada o una sopa seca

221 Un producto comestible o un precursor del mismo de conformidad con la reivindicación 205, caracterizado porque el producto comestible o medicinal modificado es un bocadillo

222 Un producto comestible o un precursor del mismo

de conformidad con cualquiera de las reivindicaciones 205-215 caracterizado porque el producto comestible o medicinal modificado es un producto auxiliar para cocinar producto de solución de comida, un producto para aderezar comidas un condimento o un marinado

223 Un producto comestible o un precursor del mismo de conformidad con la reivindicacion 205 caracterizado porque el producto comestible o medicinal modificado es una torta galleta pastel, caramelo goma masticable gelatina, helado, sorbete budin mermelada, jalea, aderezo para ensaladas condimentos cereal, frutas en conserva o compota

224 Un producto comestible o un precursor del mismo de conformidad con cualquiera de las reivindicaciones 205-215 caracterizado porque el producto comestible o medicinal modificado es una bebida una mezcla de bebida, o un concentrado de bebida

225 Un producto comestible o un precursor del mismo de conformidad con la reivindicación 205 caracterizado porque el producto comestible o medicinal modificado es una soda, o jugo

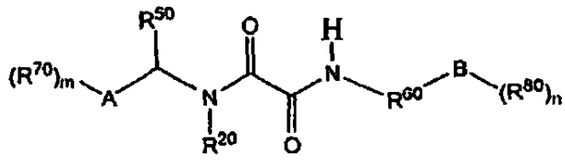
226 Un producto comestible o un precursor del mismo de conformidad con la reivindicacion 205 caracterizado porque el producto comestible o medicinal modificado es una bebida alcohólica

227 Un producto comestible o un precursor del mismo de conformidad con cualquiera de las reivindicaciones 205-215,

caracterizado porque el producto comestible o medicinal modificado es una composición farmacéutica para administración oral

228 Un producto comestible o un precursor del mismo de conformidad con la reivindicacion 205 caracterizado porque el producto comestible o medicinal modificado es un producto de higiene oral

229 Un producto comestible o medicinal o un precursor del mismo que comprende al menos una cantidad que modula el sabor sabroso de al menos un compuesto oxalamida o una sal comestiblemente aceptable del mismo, en donde el compuesto oxalamida tiene la formula



en donde A y B son independientemente un arilo heteroarilo, cicloalquilo o un heterociclo que comprende 5 a 12 átomos en el anillo

m y n tienen independientemente 0, 1, 2, 3 ó 4-8

R^{50} es hidrógeno c un alquilo que comprenden uno a cuatro átomos de carbono

R^{60} esta ausente o un alquileno de C_1-C_5,

R^{70} y R^{80} se seleccionan independientemente del grupo que consiste de hidrogeno, 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, o dos de R^{70} juntos forman un anillo metilendioxi

230 Un producto comestible o un precursor del mismo de conformidad con la reivindicacion 229 caracterizado porque A y B son independientemente un anillo fenilo, piridilo furanilo benzofuranilo pirrol benzotiofeno, piperidilo, ciclopentilo ciclohexilo, o cicloheptilo,

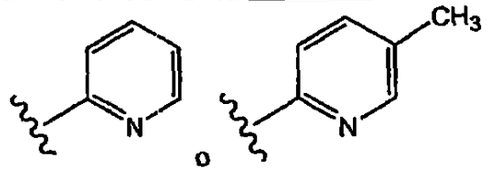
m y n son independientemente 0 1 2 ó 3,

R^{50} es hidrógeno o metilo,

R^{60} es $-CH_2-$ o $-CH_2CH_2-$

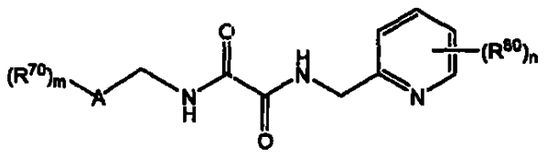
231 Un producto comestible o un precursor del mismo de conformidad con la reivindicación 230 caracterizado porque B es un anillo de piridina opcionalmente sustituido

232 Un producto comestible o un precursor del mismo de conformidad con la reivindicacion 231 caracterizado porque el radical piridilo-R^{60} tiene la estructura



o

233 Un producto comestible o un precursor del mismo de conformidad con la reivindicación 229 caracterizado porque el compuesto amida es un compuesto oxalamida que tiene la fórmula



en donde A es un anillo arilo o heteroarilo sustituido comprendiendo cinco a 12 atomos de carbono,

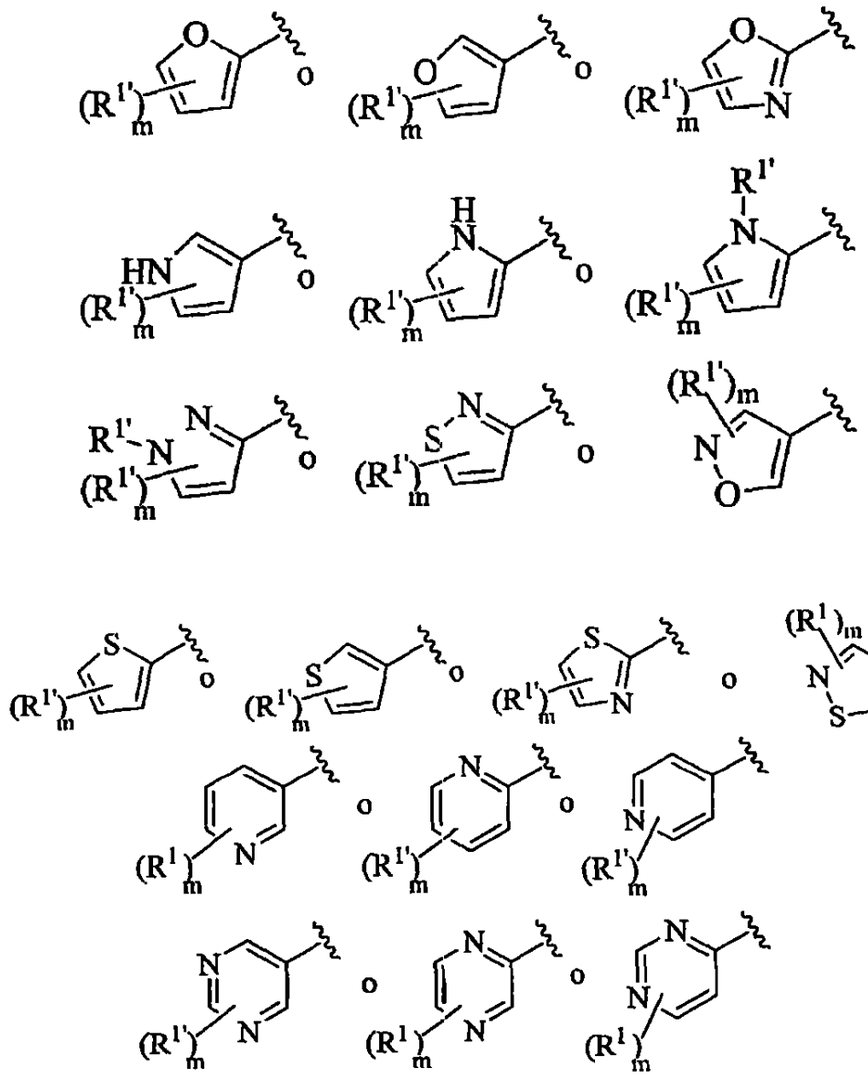
m y n son 0 1, 2 ó 3

cada R^{70} y R^{80} se selecciona independientemente del grupo que consiste de hidrógeno 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 o dos de R^{70} juntos forman un anillo metilendioxi

234 Un producto comestible, o un precursor del mismo de conformidad con la reivindicación 233 caracterizado porque A es un fenilo de 2-, 3-, o 4-mono sustituido 2,4, 2,3, 2,5 2 6, 3 5-, o 3,6-fenilo disustituido 3-alquil-4-fenilo sustituido, un fenilo tri-sustituido en donde los grupos R^{70} se seleccionan independientemente del grupo que consiste 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 o dos de R^{70} juntos forman un anillo metilendioxi

235 Un producto comestible, o un precursor del mismo de conformidad con la reivindicación 233, caracterizado porque A es un anillo heteroarilo sustituido que comprende 5 a 12 atomos de carbono y en donde los grupos sustituyentes se seleccionan independientemente del grupo que consiste del grupo hidrogeno, 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

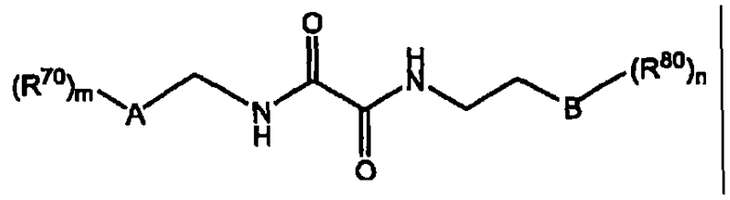
236 Un producto comestible o un precursor del mismo de conformidad con la reivindicación 233, caracterizado porque A tiene una de las fórmulas



en donde m es 0, 1 2 ó 3, y cada R^1 se selecciona independientemente de hidroxi fluoro cloro, NH_2, $NHCH_3$,

$N(CH_3)_2$, $COOCH_3$, SCH_3 SEt metilo etilo isopropilo, vinilo trifluorometilo, metoxi, etoxi isopropoxi y trifluorometoxi

237 Un compuesto oxalamida que tiene la fórmula



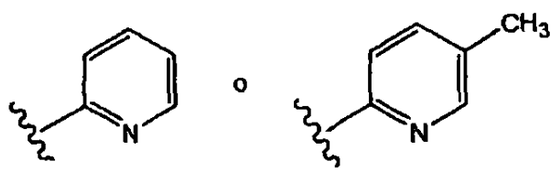
en donde A y B son un anillo arilo o heteroarilo sustituido que comprende tres a doce átomos de carbono en el anillo

m y n son independientemente 0, 1 2 o 3

cada R^{70} y R^{80} se selecciona independientemente del grupo que consiste de hidroxi fluoro 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 metilendioxi o una sal comestiblemente aceptable del mismo

238 El compuesto oxalamida de conformidad con la reivindicación 237, caracterizado porque B es un anillo piridilo

239 El compuesto oxalamida de conformidad con la reivindicación 237 caracterizado porque el radical piridilo-R^{80} tiene la estructura

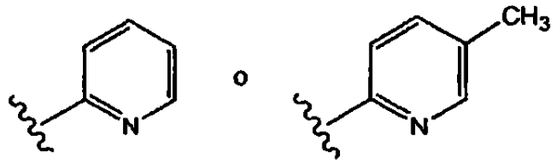


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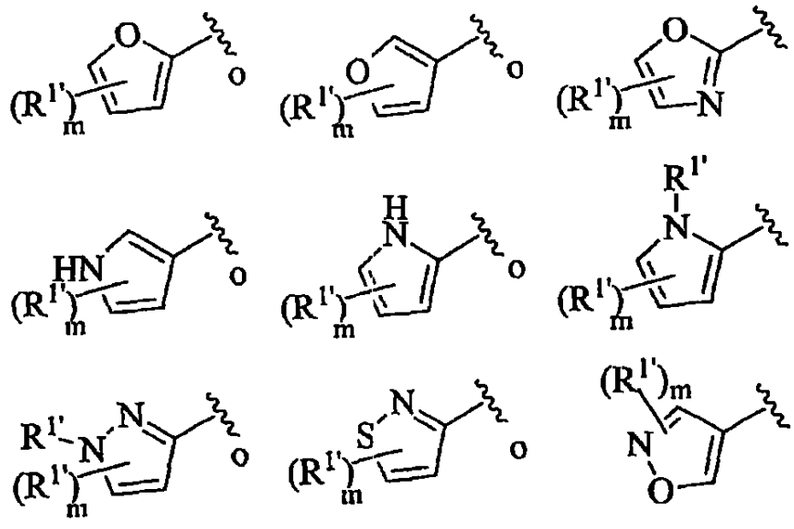
240 El compuesto oxalamida de conformidad con la reivindicación 238, caracterizado porque A es un anillo fenilo

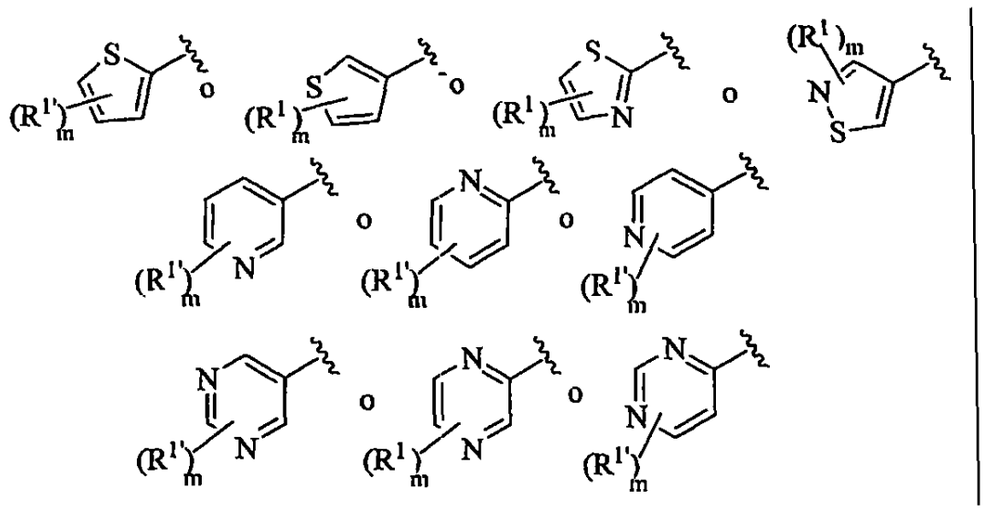
241 El compuesto oxalamida de conformidad con la reivindicación 240 caracterizado porque B es un anillo piridilo

242 El compuesto oxalamida de conformidad con la reivindicación 240 caracterizado porque el radical piridilo-R^{80} tiene la estructura



243 El compuesto oxalamida de conformidad con la reivindicación 237, caracterizado porque A tiene una de las fórmulas





en donde m es 0 1, 2 ó 3, y cada R^1 se selecciona independientemente de hidroxi fluoro, cloro NH_2 $NHCH_3$ $N(CH_3)_2$, $COOCH_3$, SCH_3 SEt, metilo etilo isopropilo, vinilo trifluorometilo, metoxi, etoxi isopropoxi, y trifluorometoxi

244 El compuesto oxalamida de conformidad con la reivindicación 243 caracterizado porque B es un anillo piridilo

245 El compuesto oxalamida de conformidad con la reivindicación 244 caracterizado porque el radical piridilo-R^{80} tiene la estructura



246 Un compuesto oxalamida de conformidad con la reivindicación 237 que tiene la fórmula

N1-(2-metoxi-4-metilbencil)-N2-(2-(5-metilpiridin-2-il)

etil)oxalamida

N1-(2-metoxi-4-metilbencil)-N2-(2-(piridin-2-il)etil) oxalamida,

N1-(2 4-dimetoxibencil)-N2-(2-(5-metilpiridin-2-il)etil) oxalamida

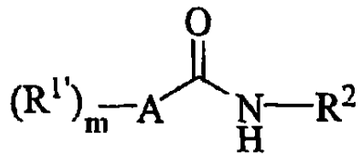
N1-(2 4-dimetilbencil)-N2-(2-(piridin-2-il)etil)oxalamida,

N1-(2 4-dimetoxibencil)-N2-(2-(piridin-2-il)etil) oxalamida,

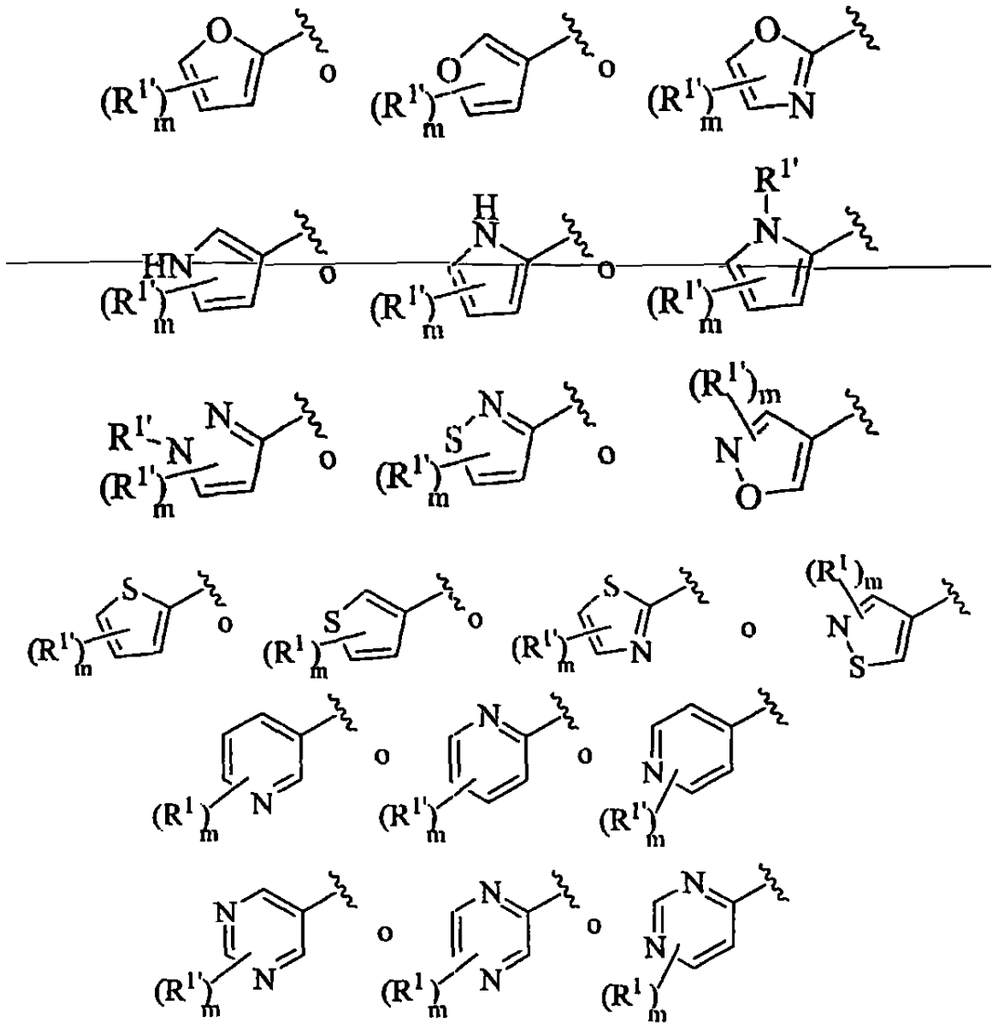
N-(2 4-Dimetoxi-bencil)-N'-(2-piridin-2-il-etil)-oxalamida

o una sal comestiblemente aceptable del mismo

247 Un producto comestible o medicinal o un precursor del mismo que comprende al menos un cantidad que modula el sabor dulce de al menos un compuesto amida que ocurre no naturalmente o una sal comestiblemente aceptable del mismo en donde el compuesto amida tiene la formula



en donde A es un anillo fenilo opcionalmente sustituido o es un anillo heteroarilo que tiene una de las formulas



en donde m es 0 1 2 o 3 y cada R^1 se selecciona independientemente de hidroxi fluoro, 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

en donde R^2 es un alquilo ramificado de C_3 C_{10}, o un

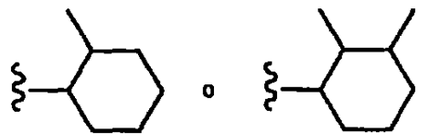
grupo ciclohexilo tetrahidronaftaleno, o indanilo opcionalmente sustituido con 1 2 o 3 sustituyentes independientemente seleccionados del grupo que consiste de hidroxi fluoro, cloro, NH_2 $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3 SEt, metilo, etilo, isopropilo, vinilo trifluorometilo metoxi, etoxi isopropoxi y trifluorometoxi

248 El producto comestible o producto medicinal, o un precursor del mismo de conformidad con la reivindicación 247 caracterizado porque R^2 es un alquilo ramificado de C_3 C_{10}

249 El producto comestible o producto medicinal, o un precursor del mismo de conformidad con la reivindicación 247, caracterizado porque R^2 es un anillo ciclohexilo opcionalmente sustituido

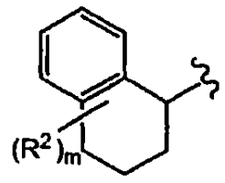
250 El producto comestible o producto medicinal o un precursor del mismo de conformidad con la reivindicación 247 caracterizado porque R^2 es un ciclohexilo, opcionalmente sustituido con 1, 2 ó 3 grupos metilo

251 El producto comestible o producto medicinal o un precursor del mismo de conformidad con la reivindicacion 247 caracterizado porque R^2 tiene la fórmula



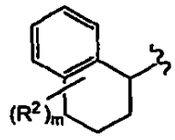
252 El producto comestible o producto medicinal, o un precursor del mismo de conformidad con la reivindicación 247,

caracterizado porque R^2 es un 1-indanilo que tiene la formula



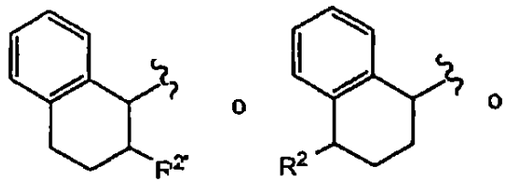
en donde m es 0, 1, 2 ó 3, y cada R^2 se selecciona independientemente de hidrógeno, hidroxi fluoro, cloro NH_2 $NHCH_3$, $N(CH_3)_2$ $COOCH_3$, SCH_3 SEt metilo, etilo, isopropilo vinilo, trifluorometilo, metoxi, etoxi, isopropoxi y trifluorometoxi

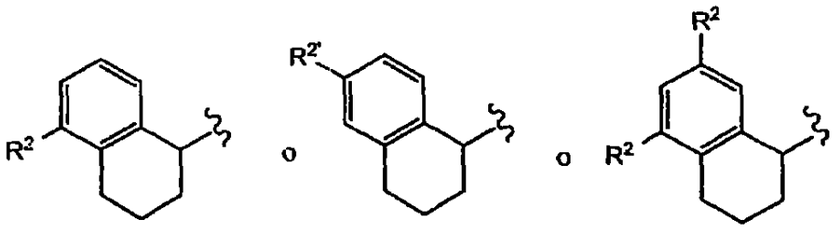
253 El producto comestible o producto medicinal, o un precursor del mismo de conformidad con la reivindicacion 247 caracterizado porque R^2 es un 1-(1,2 3,4)tetrahidronaftaleno que tiene la fórmula



en donde m es 0, 1, 2 o 3, y cada R^2 puede unirse a cualquiera del anillo aromático o no aromático y se selecciona independientemente de hidroxi, fluoro, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$ SCH_3, SEt metilo etilo isopropilo vinilo, trifluorometilo metoxi etoxi isopropoxi y trifluorometoxi

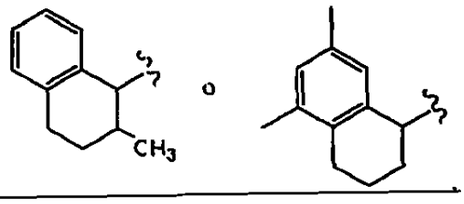
254 El producto comestible o producto medicinal, o un precursor del mismo de conformidad con la reivindicación 247 caracterizado porque R^2 tiene la fórmula



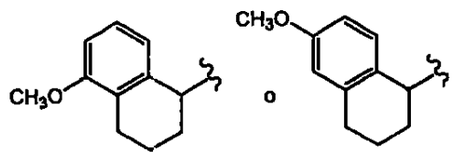


en donde R^2 es hidrógeno hidroxi fluoro cloro, NH_2 $NHCH_3$ $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt metilo, etilo isopropilo, vinilo trifluorometilo metoxi etoxi isopropoxi y trifluorometoxi

255 El producto comestible o producto medicinal o un precursor del mismo de conformidad con la reivindicacion 247 caracterizado porque R^2 tiene la formula

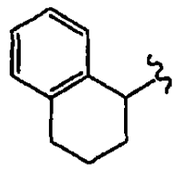


256 El producto comestible o producto medicinal o un precursor del mismo de conformidad con la reivindicacion 247 caracterizado porque R^2 tiene la formula

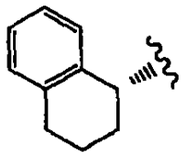


257 El producto comestible o producto medicinal o un

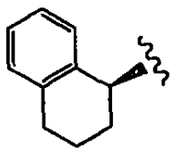
precursor del mismo de conformidad con la reivindicación 247 caracterizado porque R^2 es un anillo 1-(1,2 3,4)tetrahidronaftaleno que tiene la fórmula



258 El producto comestible o producto medicinal o un precursor del mismo de conformidad con la reivindicación 247, caracterizado porque R^2 es un anillo (R)-1-(1,2,3 4)tetrahidronaftaleno que tiene la formula



259 El producto comestible o producto medicinal, o un precursor del mismo de conformidad con la reivindicacion 247 caracterizado porque R^2 es un anillo (R)-1-(1,2 3 4)tetrahidronaftaleno que tiene la formula



260 El producto comestible o medicinal, o un precursor del mismo de conformidad con la reivindicación 247 caracterizado porque el producto comestible o producto medicinal modificado es una comida para el consumo humano

261 El producto comestible o medicinal, o un precursor del mismo de conformidad con la reivindicacion 247 caracterizado porque el producto comestible o medicinal modificado se selecciona del grupo que consiste de confiterías, productos de panaderia, helados, productos cremosos, bocadillos dulces y sabrosos barras de bocadillos, productos de reemplazo de comidas comidas preparadas, sopas, pastas, fideos, alimentos enlatados alimentos congelados alimentos secos alimentos refrigerados, aceites y grasas, alimentos para bebés o alimentos para untar

262 Un producto comestible o un precursor del mismo de conformidad con la reivindicacion 247 caracterizado porque comprende uno o más de carne, pollo pescado, vegetales, granos, o frutas

263 Un producto comestible, o un precursor del mismo de conformidad con la reivindicación 247 caracterizado porque el producto comestible o medicinal modificado es un alimento congelado, un alimento crudo o un alimento cocido completa o parcialmente

264 Un producto comestible o un precursor del mismo de conformidad con la reivindicación 247, caracterizado porque es una sopa una sopa deshidratada o concentrada o una sopa seca

265 Un producto comestible, o un precursor del mismo de conformidad con la reivindicacion 247 caracterizado porque el producto comestible o medicinal modificado es un bocadillo

266 Un producto comestible, o un precursor del mismo de conformidad con la reivindicacion 247, caracterizado porque el producto comestible o medicinal modificado es un producto auxiliar para cocinar producto de solucion de comida un producto para aderezar comidas, un condimento o un marinado

267 Un producto comestible, o un precursor del mismo de conformidad con la reivindicación 247, caracterizado porque el producto comestible o medicinal modificado es una torta, galleta, pastel caramelo, goma masticable gelatina helado sorbete budin mermelada jalea, aderezo para ensaladas, condimentos, cereal, frutas en conserva o compota

268 Un producto comestible o un precursor del mismo de conformidad con la reivindicación 247 caracterizado porque el producto comestible o medicinal modificado es una bebida, una mezcla de bebida o un concentrado de bebida

269 Un producto comestible o un precursor del mismo de conformidad con la reivindicación 247, caracterizado porque el producto comestible o medicinal modificado es una soda o jugo

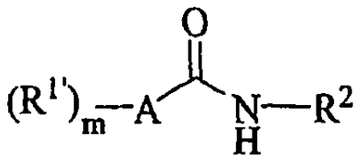
270 Un producto comestible o un precursor del mismo de conformidad con la reivindicación 247 caracterizado porque el producto comestible o medicinal modificado es una bebida alcohólica

271 Un producto comestible o un precursor del mismo de conformidad con la reivindicación 247 caracterizado porque el producto comestible o medicinal modificado es una composicion

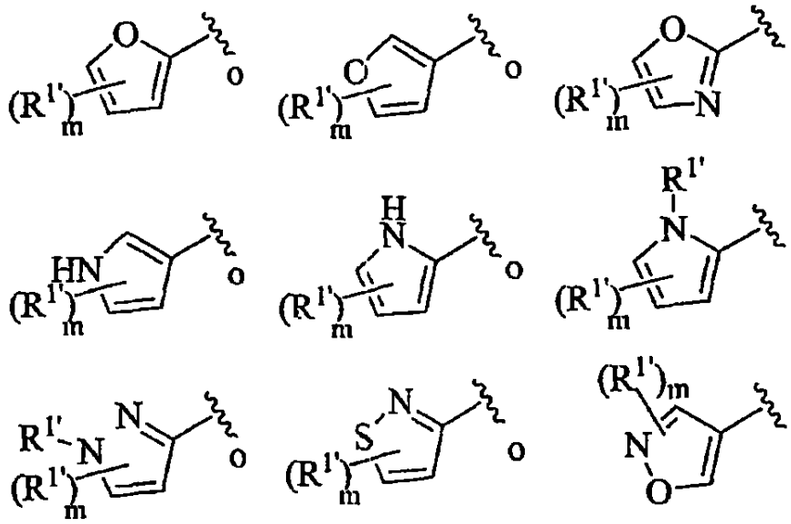
farmacéutica para administración oral

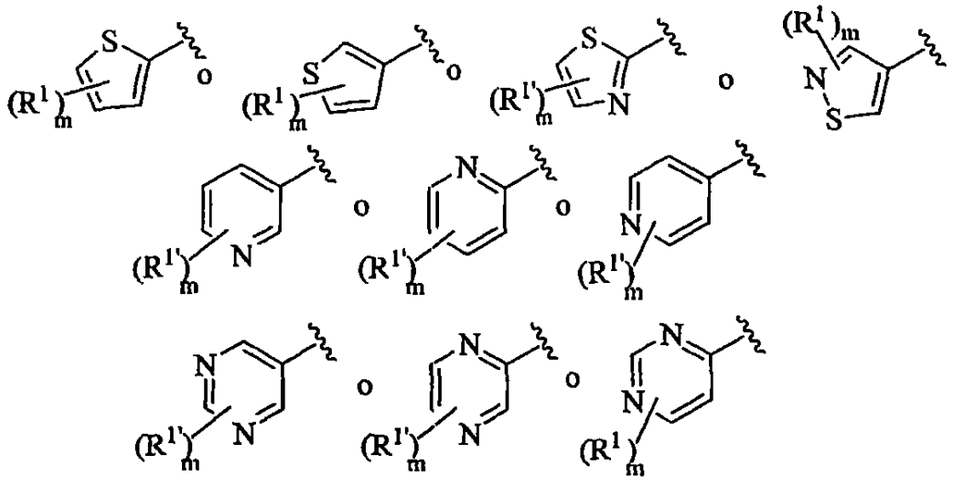
272 Un producto comestible, o un precursor del mismo de conformidad con la reivindicación 247 caracterizado porque el producto comestible o medicinal modificado es un producto de higiene oral

273 Un compuesto amida que tiene la formula



en donde A es un anillo fenilo o es un anillo del heteroarilo que tiene una de las fórmulas





en donde m es 0 1 2 o 3, y cada R^1 se selecciona independientemente de hidroxi fluoro, 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

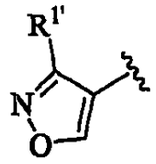
en donde R^2 es (a) un alquilo ramificado de C_3-C_{10} o (b) un grupo ciclohexilo tetrahidronaftaleno, o indanilo opcionalmente sustituido con 1 2 ó 3 sustituyentes independientemente seleccionados del grupo que consiste de hidroxi fluoro cloro NH_2 $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3 SEt, metilo etilo isopropilo vinilo trifluorometilo, metoxi, etoxi, isopropoxi y trifluorometoxi, o una sal comestiblemente aceptable del mismo

274 El compuesto amida de conformidad con la reivindicación 273, caracterizado porque R^2 es un alquilo ramificado de C_3-C_{10}

275 El compuesto amida de conformidad con la reivindicación 274 caracterizado porque A es un anillo fenilo opcionalmente sustituido

276 El compuesto amida de conformidad con la reivindicación 274 caracterizado porque A es un anillo piridilo opcionalmente sustituido

277 El compuesto amida de conformidad con la reivindicacion 274, caracterizado porque A es un anillo heteroarilo que tiene la fórmula

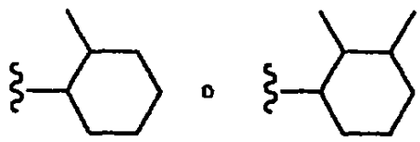


en donde R^1 es hidrógeno hidroxi fluoro cloro, NH_2 $NHCH_3$ $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo vinilo trifluorometilo metoxi, etoxi isopropoxi y trifluorometoxi

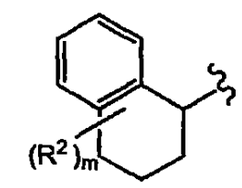
278 El compuesto amida de conformidad con la reivindicación 275 caracterizado porque R^2 es un anillo ciclohexilo opcionalmente sustituido

279 El compuesto amida de conformidad con la reivindicacion 275, caracterizado porque el anillo ciclohexilo se sustituye con 1, 2 o 3 grupos metilo

280 El compuesto amida de conformidad con la reivindicación 275 caracterizado porque R^2 tiene la fórmula

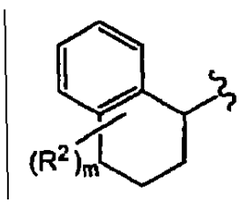


281 El compuesto amida de conformidad con la reivindicación 275 caracterizado porque R^2 es 1-indanilo que tiene la fórmula



en donde m es 0 1 2 o 3 y cada R^2 se selecciona independientemente de hidroxi fluoro, cloro, NH_2 $NHCH_3$, $N(CH_3)_2$, $COOCH_3$ SCH_3, SEt metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi etoxi isopropoxi, y trifluorometoxi

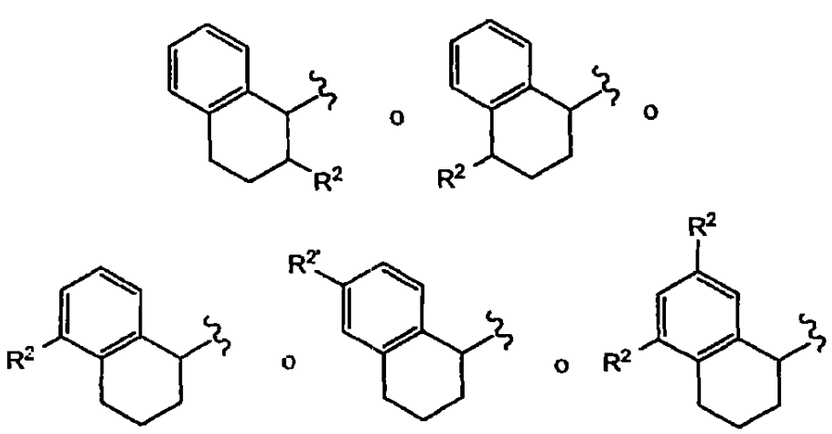
282 El compuesto amida de conformidad con la reivindicación 275 caracterizado porque R^2 es un 1-(1 2 3 4)tetrahidronaftaleno que tiene la fórmula



en donde m es 0 1, 2 ó 3, y cada R^2 puede unirse a cualquiera del anillo aromatico o no aromático y se selecciona independientemente de hidroxi, fluoro, cloro, NH_2, $NHCH_3$ $N(CH_3)_2$ $COOCH_3$ SCH_3 SEt, metilo, etilo isopropilo, vinilo

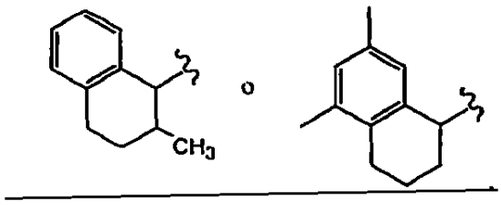
trifluorometilo, metoxi etoxi isopropoxi, y trifluorometoxi

283 El compuesto amida de conformidad con la reivindicación 275 caracterizado porque R^2 tiene la fórmula

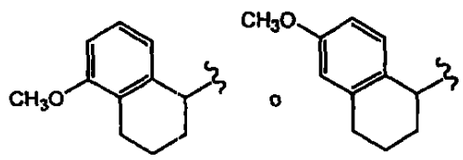


en donde cada R^2 se selecciona independientemente del grupo que consiste de hidrogeno hidroxi, fluoro, cloro, NH_2, $NHCH_3$, $N(CH_3)_2$, $COOCH_3$ SCH_3 SEt metilo etilo isopropilo, vinilo trifluorometilo metoxi etoxi isopropoxi, y trifluorometoxi

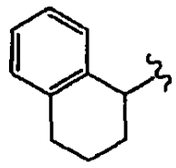
284 El compuesto amida de conformidad con la reivindicación 275 caracterizado porque R^2 tiene la fórmula



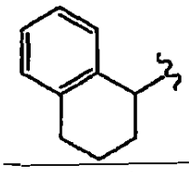
285 El compuesto amida de conformidad con la reivindicacion 275 caracterizado porque R^2 tiene la formula



286 El compuesto amida de conformidad con la reivindicación 275 caracterizado porque R^2 es un anillo 1-(1 2 3 4)tetrahidronaftaleno que tiene la fórmula



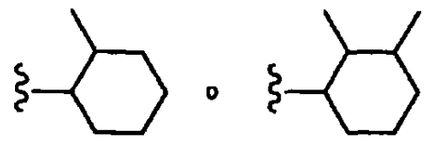
287 El compuesto amida de conformidad con la reivindicación 275 caracterizado porque R^2 es un anillo (R)-1-(1 2 3,4)tetrahidronaftaleno que tiene la fórmula



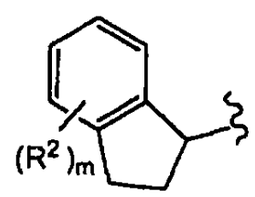
288 El compuesto amida de conformidad con la reivindicación 277 caracterizado porque R^2 es un anillo ciclohexilo opcionalmente sustituido

289 El compuesto amida de conformidad con la reivindicacion 277, caracterizado porque el anillo ciclohexilo se sustituye con 1, 2 ó 3 grupos metilo

290 El compuesto amida de conformidad con la reivindicación 277 caracterizado porque R^2 tiene la fórmula

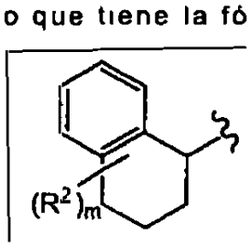


291 El compuesto amida de conformidad con la reivindicación 277 caracterizado porque R^2 es 1-indanilo que tiene la formula



en donde m es 0, 1 2 o 3 y cada R^2 puede unirse a cualquier anillo aromatico o no aromático y se selecciona independientemente de hidrógeno hidroxi fluoro cloro NH_2 $NHCH_3$, $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo, etilo, isopropilo, vinilo, trifluorometilo, metoxi, etoxi isopropoxi y trifluorometoxi

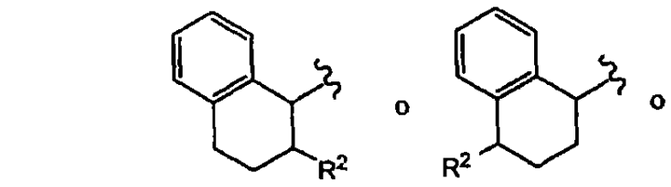
292 El compuesto amida de conformidad con la reivindicación 277, caracterizado porque R^2 es 1-(1,2 3,4)tetrahidronaftaleno que tiene la fórmula

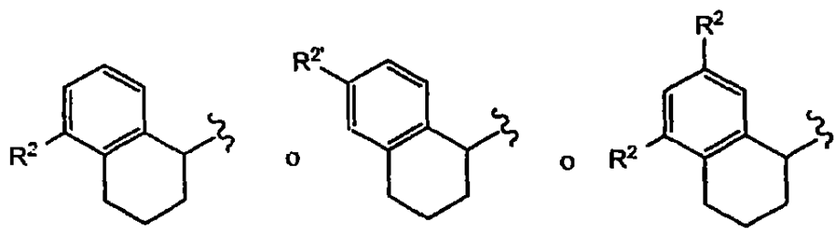


en donde m es 0, 1 2 o 3, y cada R^2 puede unirse a cualquiera del anillo aromático o no aromatico y se selecciona independientemente de hidroxi fluoro cloro NH_2 $NHCH_3$

$N(CH_3)_2$ $COOCH_3$ SCH_3 SEt metilo, etilo isopropilo vinilo trifluorometilo, metoxi etoxi isopropoxi y trifluorometoxi

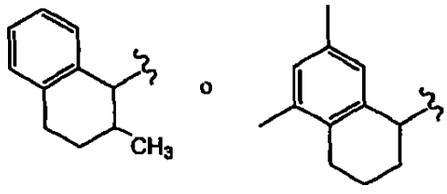
293 El compuesto amida de conformidad con la reivindicacion 277, caracterizado porque R^2 tiene la fórmula



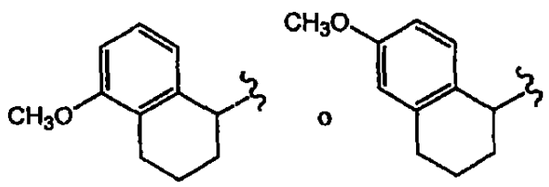


en donde cada R^2 se selecciona independientemente del grupo que consiste de hidrogeno hidroxi fluoro, cloro NH_2, $NHCH_3$, $N(CH_3)_2$ $COOCH_3$ SCH_3 SEt metilo etilo isopropilo, vinilo trifluorometilo, metoxi, etoxi isopropoxi y trifluorometoxi

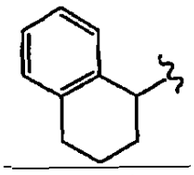
294 El compuesto amida de conformidad con la reivindicación 277, caracterizado porque R^2 tiene la fórmula



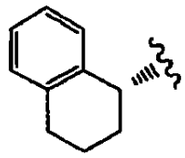
295 El compuesto amida de conformidad con la reivindicación 277 caracterizado porque R^2 tiene la fórmula



296 El compuesto amida de conformidad con la reivindicacion 277 caracterizado porque R^2 es un anillo 1-(1 2 3,4)tetrahidronaftaleno que tiene la fórmula



297 El compuesto amida de conformidad con la reivindicacion 277 caracterizado porque R^2 es un anillo (R)-1-(1 2,3 4)tetrahidronaftaleno que tiene la fórmula



298 Un compuesto amida caracterizado porque tiene la formula

3-cloro-2-hidroxi-N-(2-metil-1 2 3 4-tetrahidronaftalen-1-il)benzamida,

3-cloro-2-hidroxi-N-(5-metoxi-1 2,3,4-tetrahidronaftalen-1-il)benzamida,

(R)-3-cloro-2-hidroxi-N-(1,2,3,4-tetrahidronaftalen-1-il)benzamida

3-cloro-2-hidroxi-N-(5-hidroxi-1 2 3,4-tetrahidronaftalen-

1-il)benzamida

3-cloro-2-hidroxi-N-(4-metil-1,2,3 4-tetrahidronaftalen-1-il)benzamida,

3-cloro-2-hidroxi-N-(6-metoxi-1 2 3,4-tetrahidronaftalen-1-il)benzamida

3-cloro-2-hidroxi-N-(1,2,3,4-tetrahidronaftalen-1-il)benzamida,

2 3-dihidroxi-N-(2-metil-1 2,3,4-tetrahidronaftalen-1-il)benzamida,

2-hidroxi-N-(2-metil-1,2 3,4-tetrahidronaftalen-1-il)benzamida,

2,3-dihidroxi-N-(5-metoxi-1 2 3 4-tetrahidronaftalen-1-il)benzamida,

(S)-2 6-dimetil-N-(1,2 3,4-tetrahidronaftalen-1-il)benzamida,

N-(5 7-dimetil-1 2,3 4-tetrahidronaftalen-1-il)-3-metilisoxazol-4-carboxamida

3-metil-N-(2-metil-1 2,3 4-tetrahidronaftalen-1-il) isoxazol-4-carboxamida

3-metil-N-(4-metil-1,2 3 4-tetrahidronaftalen-1-il) isoxazol-4-carboxamida

N-(5-metoxi-1 2 3 4 tetrahidronaftalen-1-il)-3-metilisoxazol-4-carboxamida,

(R)-5-bromo-N-(1 2 3,4-tetrahidronaftalen-1-il) nicotinamida,

(R)-3-metil-N-(1,2 3,4-tetrahidronaftalen-1-il)isoxazol-4-carboxamida,

(S)-5-bromo-N-(1 2,3 4-tetrahidronaftalen-1-il) nicotinamida,

(R)-N-(1 2 3 4-tetrahidronaftalen-1-il)furan-3-carboxamida

(R)-5-metil-N-(1 2 3 4-tetrahidronaftalen-1-il)isoxazol-4-carboxamida

(R)-N-(1 2 3 4-tetrahidronaftalen-1-il)furan-3-carboxamida

3-metil-N-(1 2,3,4-tetrahidronaftalen-1-il)isoxazol-4-carboxamida

N-(3,3-dimetilbutan 2-il)-2,3 5,6-tetrafluoro-4-metilbenzamida,

2 3 5 6-tetrafluoro-4-metil-N-(3-metilbutan-2-il)benzamida,

2 3 5 6-tetrafluoro-4-metil-N-(2-metilciclohexil)benzamida,

N-(2-metilciclohexilo)-3-(trifluorometoxi)benzamida

3-cloro-5-fluoro-N-(2-metilciclohexil)benzamida

(R)-N-(3,3-dimetilbutan-2-il)-2,3,5 6-tetrafluoro-4-metilbenzamida,

4-fluoro-N-(2-metilciclohexil)-3-(trifluorometil)benzamida

(S)-2 3 5 6-tetrafluoro-4-metil-N-(3-metilbutan-2-

il)benzamida

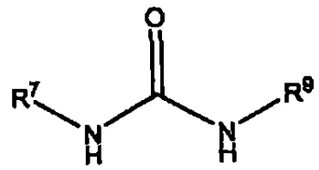
2,5-dicloro-N-(2-metilciclohexil)benzamida,

3 5-dicloro-2 6-dimetoxi-N-(2-metilciclohexilo)benzamida, o

2 6-dimetil-N-(2-metilciclohexilo)benzamida

o una sal comestiblemente aceptable del mismo

299 Un compuesto de urea que tiene la fórmula



en donde R^7 es un arilo o heteroarilo que comprenden tres a diez atomos de carbono en el anillo que se sustituyen opcionalmente con 1, 2 o 3 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, y

R^9 es un grupo alquilo ramificado de C_3 C_{10}, o un ciclohexilo, tetrahidronaftaleno o indanilo opcionalmente sustituido con 1, 2 ó 3 sustituyentes independientemente seleccionados del grupo que consiste de hidroxi fluoro 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 una sal comestiblemente aceptable del mismo

300 El compuesto de conformidad con la reivindicacion

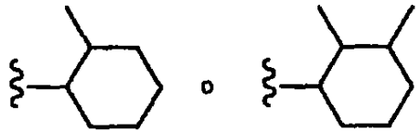
299, caracterizado porque R^7 es un anillo fenilo opcionalmente sustituido

301 El compuesto de conformidad con la reivindicacion 300, caracterizado porque R^9 es un alquilo ramificado de C_3 C_{10}

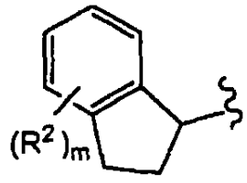
302 El compuesto de conformidad con la reivindicacion 300, caracterizado porque R^9 es un anillo ciclohexilo opcionalmente sustituido

303 El compuesto de conformidad con la reivindicación 302 caracterizado porque el anillo ciclohexilo se sustituye con 1 2 o 3 grupos metilo

304 El compuesto de conformidad con la reivindicación 302, caracterizado porque R^9 tiene la formula

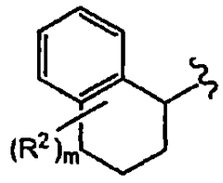


305 El compuesto de conformidad con la reivindicación 299 caracterizado porque R^9 es un 1-indanilo que tiene la fórmula



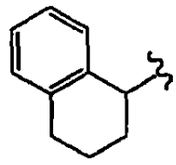
en donde m es 0, 1, 2 o 3, y cada R^9 se selecciona independientemente de hidrogeno hidroxi fluoro, cloro NH_2, $NHCH_3$, $N(CH_3)_2$ $COOCH_3$, SCH_3 SEt, metilo etilo, isopropilo vinilo trifluorometilo, metoxi, etoxi isopropoxi y trifluorometoxi

306 El compuesto amida de conformidad con la reivindicación 299 caracterizado porque R^9 es 1-(1 2,3 4)tetrahidronaftaleno que tiene la fórmula

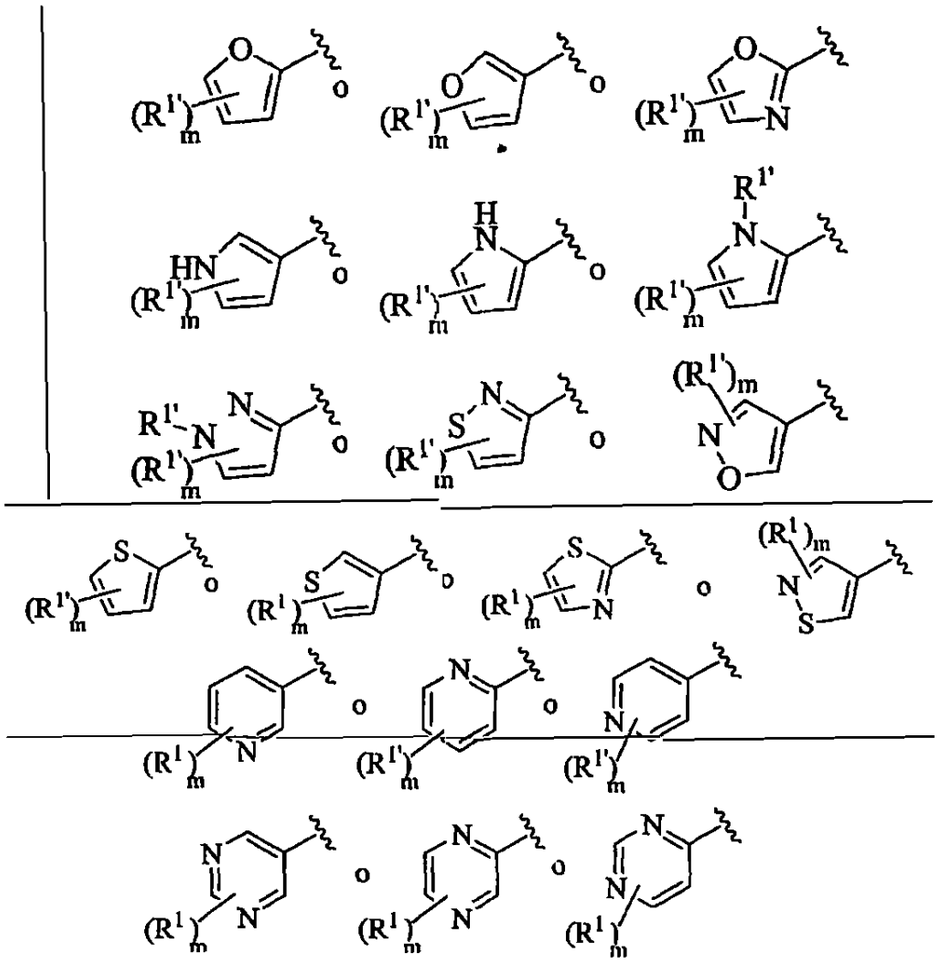


en donde m es 0, 1 2 ó 3, y cada R^9 puede unirse a cualquier anillo aromatico o no aromático y se selecciona independientemente de hidroxi fluoro cloro, NH_2 $NHCH_3$ $N(CH_3)_2$, $COOCH_3$ SCH_3 SEt metilo, etilo isopropilo, vinilo, trifluorometilo metoxi etoxi isopropoxi, y trifluorometoxi

307 El compuesto amida de conformidad con la reivindicacion 299 caracterizado porque R^9 es un anillo 1-(1 2,3 4)tetrahidronaftaleno que tiene la formula



308 El compuesto amida de conformidad con la reivindicacion 299, caracterizado porque R^7 es un anillo heteroarilo que tiene una de las fórmulas



en donde m es 0 1 2 o 3, y cada R^1 se selecciona independientemente de hidrógeno, hidroxi fluoro cloro NH_2, $NHCH_3$ $N(CH_3)_2$, $COOCH_3$, SCH_3, SEt, metilo etilo isopropilo vinilo, trifluorometilo metoxi etoxi isopropoxi y trifluorometoxi

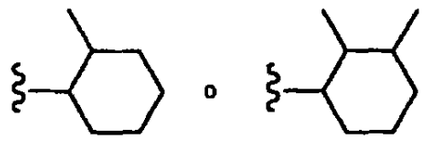
309 El compuesto de conformidad con la reivindicacion 308, caracterizado porque R^9 es un alquilo ramificado de C_3-C_{10}

310 El compuesto de conformidad con la reivindicación

308, caracterizado porque R_9 es un anillo ciclohexilo opcionalmente sustituido

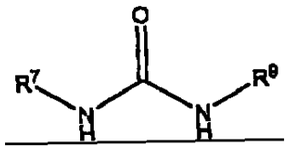
311 El compuesto de conformidad con la reivindicacion 308 caracterizado porque el anillo ciclohexilo se sustituye con 1 2 ó 3 grupos metilo

312 El compuesto de conformidad con la reivindicación 308 caracterizado porque R^9 tiene la fórmula

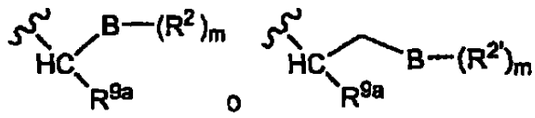


313 Un producto comestible o medicinal, o un precursor del mismo caracterizado porque comprende al menos una cantidad modular de sabor sabroso de al menos un compuesto de conformidad con las reivindicaciones 299-312

314 Un compuesto de urea que tiene la formula



en donde R^7 es un anillo arilo o heteroarilo que comprenden tres a diez atomos de carbono en el anillo que se sustituyen opcionalmente con 1, 2 o 3 sustituyentes independientemente seleccionados de hidroxi fluoro 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^9 tiene la estructura



en donde R^9 es hidrogeno un alquilo de C_1-C_{10} B es un anillo fenilo piridilo, furanilo tiofuranilo, pirrol, ciclopentilo ciclohexilo o piperidilo, m es 0 1 2 o 3 y cada R^2 se selecciona independientemente de hidrogeno hidroxi, fluoro 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 una sal comestiblemente aceptable del mismo

315 El compuesto de conformidad con la reivindicacion 314 caracterizado porque R^7 es un anillo fenilo opcionalmente sustituido y B es fenilo o piridilo

316 El compuesto de conformidad con la reivindicacion 314 caracterizado porque R^7 es un anillo fenilo opcionalmente sustituido y B es ciclohexilo opcionalmente sustituido

317 Un producto comestible o medicinal, o un precursor del mismo caracterizado porque comprende al menos una cantidad modulada de sabor sabroso de al menos un compuesto de conformidad con la reivindicacion 314

318 Un compuesto amida que tiene la fórmula

(R)-metilo 2-(3-cloro-4-metoxibenzamido)-4-metilpentanoato,

4-metoxi-3-metil-N-(5-metilhexan-3-il)benzamida

N-(heptan-4-il)-2-metilbenzo[d][1 3]dioxol-5-

carboxamida,

4-metil-2-(4-metil-3-(metiltio)benzamido)pentanoato de (S)-metilo,

4-metoxi-3-metil-N (2-metilheptan-4-il)benzamida,

N-(heptan-4-il)-6-metilbenzo[d][1,3]dioxol-5-carboxamida

3 4-dimetil-N-(2-metilhexan-3-il)benzamida,

4-metil-2-(5-metilbenzofuran-2-carboxamido)pentanoato de (R)-metilo,

N-(hexan-3-il)-4-metoxi-3-metilbenzamida

N-(heptan-4-il)-3-metil-4-(metiltio)benzamida,

N-(hexan-3-il)-3-metil-4-(metiltio)benzamida,

2-(3-cloro-4-metoxibenzamido)hexanoato de metilo,

3 4-dimetilo-N-(2-metilheptan-4-il)benzamida,

N-(hexan-3-il)-3,4-dimetilbenzamida

N-(heptan-4-il)-3,4-dimetilbenzamida

4-metil-2-(4-(metiltio)benzamido)pentanoato de (R)-metilo

4-etoxi-N-(heptan-4-il)-3-metilbenzamida,

3 4-dimetil-N-(5-metilhexan-3-il)benzamida,

4-metil-2-(4-vinilbenzamido)pentanoato de (R)-metilo

4-metoxi-3-metil-N-(2-metilhexan-3-il)benzamida

N-(heptan-4-il)benzo[d][1,3]dioxol-5-carboxamida,

2-(benzo[d][1 3]dioxol-6-carboxamido)-4-metilpentanoato de (R)-metilo

690
692

(R)-N-(1-metoxi-4-metilpentan 2-il)-3,4-dimetilbenzamida

(R)-metil-2-(2 3-dimetilfuran-5-carboxamido)-4-metilpentanoato o

4-Metoxi-N-(1-metoximetil-3-metil-butil)-3-metil-benzamida

o una sal comestiblemente aceptable del mismo

319 Un compuesto amida que tiene la fórmula

N-(heptan-4-il)benzo [d] [1 3]dioxol-5-carboxamida o

N-(2,4-Dimetoxi-bencil)-N -(2-piridin-2-il-etil)-oxalamida o una sal comestiblemente aceptable del mismo

320 Un producto comestible o medicinal que comprenden los compuestos de conformidad con la reivindicación 319 a una concentración entre aproximadamente 0 01 a aproximadamente 10 ppm

321 El producto comestible o medicinal de conformidad con la reivindicacion 320, caracterizado porque el producto comestible o medicinal es una comida para el consumo humano

322 Un compuesto urea que tiene la fórmula

1-(2-clorofenil)-3-(heptan-4-il)urea,

1-(2,4-diclorofenil) 3-(1-fenilpropil)urea,

1-(2 4-dimetoxifenil)-3-(heptan-4-il)urea

1-(2-fluorofenil)-3-(heptan-4-il)urea,

1-(4-isopropilfenil)-3-(2-(piridin-2-il)etil)urea

o una sal comestiblemente aceptable del mismo

694
693

RESUMEN

La presente invención se relaciona al descubrimiento de que ciertos compuestos amida no peptidos que no ocurren naturalmente y los derivados amida tal como oxalamidas ureas y acrilamidas, son modificadores de sabor y apreciacion utiles tal como un saborizante o agentes de sabor y el sabor o mejorador de apreciacion mas particularmente sabor (la apreciacion "acre o glutamato de monosodio) o modificadores de sabor dulce, - agentes saborizantes de sabor o dulce o mejoradotes de sabor dulce para comida bebida, y otros comestibles o productos o composiciones comestibles o medicinales oralmente administradas

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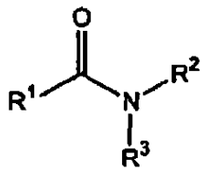
Reivindicación(es)

1 Un método para modular el sabor de un producto comestible o medicinal caracterizado porque comprende

a) proporcionar al menos un producto comestible o medicinal o un precursor del mismo y

b) combinar el producto comestible o medicinal o precursor del mismo con al menos una cantidad que modula el sabor sabroso de al menos un compuesto amida de origen no natural o una sal comestiblemente aceptable del mismo de manera que forma un producto comestible o medicinal modificado

en donde el compuesto amida tiene la fórmula



en donde R^1 comprende un residuo hidrocarburo que tiene al menos tres atomos de carbono y opcionalmente uno o diez heteroátomos seleccionados independientemente de oxígeno nitrogeno azufre halógenos o fósforo y

en donde uno de R^2 y R^3 es H los otros R^2 y R^3 comprenden un residuo hidrocarburo que tiene al menos tres átomos de carbono y opcionalmente uno o diez heteroátomos independientemente seleccionados de oxigeno nitrógeno azufre halógenos o fósforo y en donde el compuesto amida tiene un peso molecular de 500 gramos por mol o menos

2 El metodo de conformidad con la reivindicación 1 caractenzado porque el compuesto amida tiene un peso molecular de 175 a 500 gramos por mol

3 El método de conformidad con la reivindicación 1 caracterizado porque el compuesto amida tiene un peso molecular de 200 a 450 gramos por mol

4 El método de conformidad con la reivindicación 1 caractenzado porque el compuesto amina tiene un peso molecular de 225 a 400 gramos por mol

5 El método de conformidad con la reivindicación 1 caractenzado porque el compuesto amina tiene un peso molecular de 225 a 400 gramos por mol

6 El método de conformidad con la reivindicación 1 caractenzado porque R^1 y uno de R^2 y R^3 tienen entre 3 y 14 átomos de carbono

7 El método de conformidad con la reivindicación 1 caractenzado porque R^1 y uno de R^2 y R^3 tienen entre 4 y 12 átomos de carbono

8 El método de conformidad con la reivindicación 1 caractenzado porque R^1 y uno de R^2 y R^3 tienen entre 4 y 10 átomos de carbono

9 El método de conformidad con la reivindicación 1 caractenzado porque R^1 tiene entre 3 y 16 átomos de carbono y 0 1 2 3 4 ó 5 heteroátomos seleccionados de oxigeno nitrógeno azufre fluor o cloro

10 El método de conformidad con la reivindicación 1 caractenzado porque uno de R^2 o R^3 tiene entre 3 y 16 átomos de carbono y 0 1 2 3 4 ó 5 heteroátomos seleccionados independientemente de oxígeno nitrógeno azufre fluor o cloro

11 El método de conformidad con la reivindicación 1 caractenzado porque uno de R^2 o R^3 tiene entre 4 y 14 átomos de carbono y 0 1 2 3 4 ó 5 heteroátomos seleccionados independientemente de oxígeno nitrógeno azufre

12 El método de conformidad con la reivindicación 1 caracterizado porque uno de R^2 o R^3 tiene entre 5 y 12 átomos de carbono y 0 1 2 o 3 heteroátomos seleccionados independientemente de oxígeno nitrógeno y azufre

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT . 800176089-2

RECIBO OFICIAL DE CAJA 06 - 15,743
FECHA FEBRERO 27 DE 2006

SUPERINDUSTRIA Y COMERCIO
Radicacion 06822161
Fecha (AMD) 20060303 16 58 41 Folios 693
Tramite 811 PCT-PATENT 378 FASE NULI 411 PRESENTAC
Dependencia 0659 DIVISION DE NUEVAS SOLICITUDES

***** 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	49935719	27/02/2006	41,987,000 00

***** C O N C E P T O *****

CANT	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL	DE PATENTE DE IN	463,000 00
			TOTAL $	463,000 00

SON CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No _____

Cdo 15159- 891-001-8

SUPERINDUSTRIA Y COMERCIO
Radicacion 06822161 00000000 Folios 696
Fecha (AMD): 2006-03-06 16 58 41
Tramite 611 PCT-PATENT 37F FASE NAL 411 PRESENTAL
Dependencia 2430 DIVI ION DE NUEVAS CREACIONES

Industria y Comercio
SUPERINTENDENCIA

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Delegatura de Propiedad Industrial
División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION ( ) MODELO DE UTILIDAD ( )	( )	( )
Indicación de que se solicita la concesión de una patente	( )	( )
Datos de identificación del solicitante o de la persona que se presenta la solicitud	( )	( )
Descripción de la invención	( )	( )
Dibujos de ser estos pertinentes	( )	( )
Comprobante de Pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )
DISEÑO INDUSTRIAL ( )		
Indicación de que se solicita el registro de Diseño Industrial	( )	( )
Datos de identificación del solicitante o de la persona que se presenta la solicitud	( )	( )
Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseno	( )	( )
Comprobante de Pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )
ESQUEMA DE TRAZADO ( )		
Indicacion de que se solicita el registro de Diseño Industrial	( )	( )
Datos de identificación del solicitante o de la persona que se presenta la solicitud	( )	( )
Representacion gráfica del Esquema Trazado	( )	( )
Comprobante de Pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )

Firma Responsable _____

Fecha _____

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

697

Bogotá,
2020

Doctor(a)
FERRERO EMILIO

REFERENCIA	Radicación No	6 22161
	Solicitud internacional	US2004/025419
	Fecha inicio fase nacional	06/03/2006
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No	3998

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que

1 La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante (Art 26-k) Decisión 486

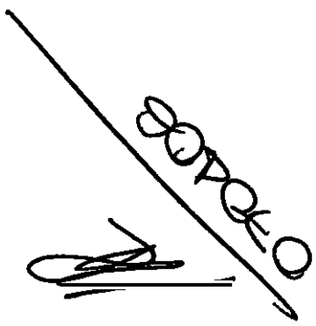
2 La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5 2, literal e), del capítulo quinto del título primero de la Circular Unica No 10 de 2001

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha
adpa11 07 ABR. 2006


APOLLO