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Yo tengo Orden de presentación

D

SOLICITUD DE

PATENTE DE INVENCION
PCT ENTRADA EN FASE NACIONAL

(71) SOLICITANTE

09-139683

21. EXPEDIENTE NO.

54. TITULO: MODULADORES DE RECEPTORES ACOPLADOS A PROTEINAS G Y USOS DE LOS MISMOS

51. CLASIFICACION INTERNACIONAL: A61K 31/455, A61P 27/00, C07D 487/00, C12N 5/06, G01N 33/53

71. SOLICITANTE: SENOMYX, INC.

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Poder No. ... no por Escr. N.
Fm 08-01-2010

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22. BOGOTA, D.C., 07 DIC. 2009

1/2

Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRÁMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION (X) MODELO DE UTILIDAD ( )	(X)	( )
- Indicación de que se solicita la concesión de una patente	(X)	( )
- Datos de identificación del solicitante o de la persona que presenta la solicitud	(X)	( )
- Descripción de la invención	(X)	( )
- Dibujos de ser estos pertinentes	(X)	( )
- Comprobante de pago de las tasas establecidas	(X)	( )

COMPLETA (X) INCOMPLETA ( )

DISEÑO INDUSTRIAL ( )

- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta la solicitud	( )	( )
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño	( )	( )
- Comprobante de pago de las tasas establecidas	( )	( )

COMPLETA ( ) INCOMPLETA ( )

EZQUEMA DE TRAZADO ( )

- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta la solicitud	( )	( )
- Representación gráfica del Esquema de Trazado	( )	( )
- Comprobante de pago de las tasas establecidas	( )	( )

COMPLETA ( ) INCOMPLETA ( )

Firma responsable: _____

Fecha: _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-139683- -00000-0000

Fecha: 2009-12-07 14:26:57 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1132

Industria y Comercio
SUPERINTENDENCIA

PETITO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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FORMULARIO UNICO DE SOLICITUD DE PATENTES
PCT
ENTRADA EN FASE NACIONAL

SOLICITUD DE:

(1)

[X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I [ ] Capítulo II

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Número Cual

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VER ANEXO No. 1

(5) PCT (86)

Solicitud Internacional No. **PCT/US2008/065650** Fecha **03/06/2008**

Publicación Internacional No. **WO 2008/154221 A2** Fecha **18/12/2008**

(6) Título (54) **MODULACION DE RECEPTORES QUIMIOSENSORIALES Y LIGANDOS RELACIONADOS CON LOS MISMOS**

(7) Clasificación Internacional (51) **A61K 31/495, A61P 27/00, C07D 487/00, C12N 5/06, G01N 33/53**

(8) Prioridad

SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	08/06/2007	11/760,592
US	08/08/2007	11/836,074
US	08/02/2008	61/027,410

(9) Comprobante de pago No. **09-91,513 y 09-91,515** Fecha **Diciembre 4 de 2009**

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

(10) Anexos

- [X] Comprobante de pago de la tasa de presentación de la solicitud.
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [ ] Poderes, si fuere el caso, junto con la sustitución del mismo a mi favor
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [X] Copia de la solicitud internacional (Resumen, descripción, reivindicaciones, dibujos).
- [X] Traducción de la solicitud internacional al castellano (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [X] Arte final 12x12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros: **Tarjeta Propietario, Extracto para la publicación**

(11) FIGURA CARACTERISTICA:

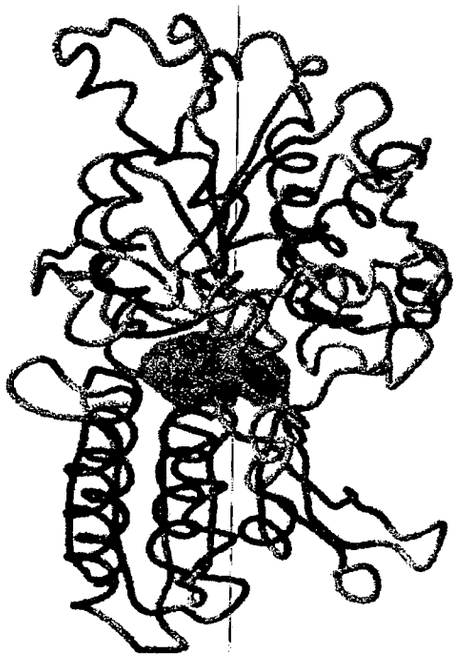


FIG. 5

(12) Solicito la concesión de la patente,

NOMBRE: **MARGARITA CASTELLANOS ABONDANO**

FIRMA:

C.C. No. 39'779.654 Usaquén - TPA 70.819 C.S.J.

07 DIC. 2009

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página. - MCA/gcb - P1855

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5

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-7

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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RECIBO OFICIAL DE CAJA : 09 - 91,513
FECHA : DICIEMBRE 4 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ALVARO CASTELLANOS	CONSIGNACION	BANCO DE BOGOTA	062754387	112277955	04/12/2009	14,245,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	TRAMITES DE SOL. DE PATENTE DE IN	540,000.00
		TOTAL : $	540,000.00

SON: QUINIENTOS CUARENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

6

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 09 - 91,515
FECHA : DICIEMBRE 4 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-139683- -00000-0000
Fecha: 2009-12-07 14:26:57 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1132

xxxxx C O N S I G N A C I O N xxxxx

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ALVARO CASTELLANOS	CONSIGNACION	BANCO DE BOGOTA	062754387	112277955	04/12/2009	14,245,000.00

xxxxx C O N C E P T O xxxxx

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVCIOS ADMINISTRATIVOS	1,225,000.00
		TOTAL : $	1,225,000.00

SON: UN MILLON DOSCIENTOS VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

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

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International Bureau

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A61P 27/00 (2006.01)

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11/836,074 8 August 2007 (08.08.2007) US
61/027,410 8 February 2008 (08.02.2008) US

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(72) Inventors; and

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[Continued on next page]

(54) **Title:** MODULATION OF CHEMOSENSORY RECEPTORS AND LIGANDS ASSOCIATED THEREWITH

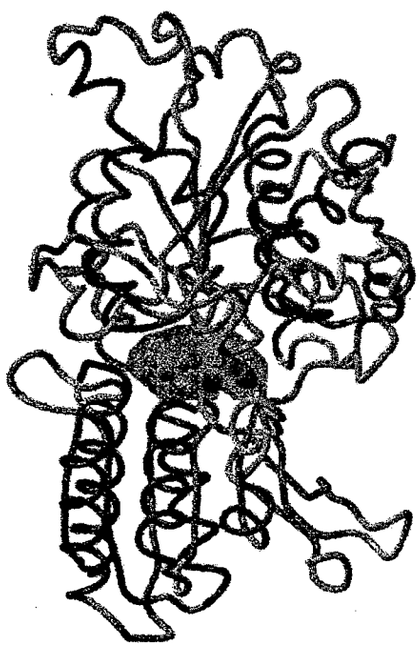


FIG. 5

(57) **Abstract:** The present invention includes methods for identifying modifiers of chemosensory receptors and their ligands, e.g., by determining whether a test entity is suitable to interact with one or more interacting sites within the Venus flytrap domains of the chemosensory receptors, and modifiers capable of modulating chemosensory receptors and their ligands. The present invention also includes modifiers of chemosensory receptors and their ligands having Formula (I), its subgenus, and specific compounds. Furthermore, the present invention includes ingestible compositions comprising the modifiers of chemosensory receptors and their ligands and methods of using the modifiers of chemosensory receptors and their ligands to enhance the sweet taste of an ingestible composition or treat a condition associated with a chemosensory receptor. In addition, the present invention include processes for preparing the modifiers of chemosensory receptors and their ligands.

WO 2008/154221 A2

WO 2008/154221 A2

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

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

MODULATION OF CHEMOSENSORY RECEPTORS AND LIGANDS ASSOCIATED THEREWITH

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Patent Application Serial No. 11/760,592, entitled "Modulation of Chemosensory Receptors and Ligands Associated Therewith", filed June 8, 2007; U.S. Patent Application Serial No. 11/836,074, entitled "Modulation of Chemosensory Receptors and Ligands Associated Therewith", filed August 8, 2007; and U.S. Patent Application Serial No. 61/027,410, entitled "Modulation of Chemosensory Receptors and Ligands Associated Therewith", filed February 8, 2008. The content of these applications are herein incorporated by reference in their entirety for all purposes.

BACKGROUND OF THE INVENTION

The taste system provides sensory information about the chemical composition of the external world. Taste transduction is one of the most sophisticated forms of chemical-triggered sensation in animals. Signaling of taste is found throughout the animal kingdom, from simple metazoans to the most complex of vertebrates. Sensations associated with taste are thought to involve distinct signaling pathways mediated by receptors, *i.e.*, metabotropic or ionotropic receptors. Cells which express taste receptors, when exposed to certain chemical stimuli, elicit taste sensation by depolarizing to generate an action potential, which is believed to trigger the sensation. This event is believed to trigger the release of neurotransmitters at gustatory afferent neuron synapses, thereby initiating signaling along neuronal pathways that mediate taste perception.

As such, taste receptors specifically recognize molecules that elicit specific taste sensation. These molecules are also referred to herein as "tastants." Many taste receptors belong to the 7-transmembrane receptor superfamily, which are also known as G protein-coupled receptors (GPCRs). Other tastes are believed to be mediated by channel proteins. G protein-coupled receptors control many physiological functions, such as endocrine function, exocrine function, heart rate, lipolysis, carbohydrate metabolism, and transmembrane signaling.

For example, family C of G-protein coupled receptors (GPCRs) from humans comprises eight metabotropic glutamate (mGlu(1-8)) receptors, two heterodimeric gamma-aminobutyric acid(B) (GABA(B)) receptors, a calcium-sensing receptor (CaR), three taste (T1R) receptors, a promiscuous L-alpha-amino acid receptor (GPRC6A), and five orphan receptors. The family C GPCRs are characterized by a large amino-terminal domain, which binds the endogenous orthosteric agonists. Additionally, allosteric modulators which bind to the seven transmembrane domains of the receptors have also been reported.

In general, upon ligand binding to a GPCR, the receptor presumably undergoes a conformational change leading to activation of a G protein. G proteins are comprised of three subunits: a guanyl nucleotide binding α-subunit, a β-subunit, and a γ-subunit. G proteins cycle between two forms, depending on whether GDP or GTP is bound to the α-subunit. When GDP is bound, the G protein exists as a heterotrimer: the $G_{\alpha\beta\gamma}$ complex. When GTP is bound, the α-subunit dissociates from the heterotrimer, leaving a $G_{\beta\gamma}$ complex. When a $G_{\alpha\beta\gamma}$ complex operatively associates with an activated G protein-coupled receptor in a cell membrane, the rate of exchange of GTP for bound GDP is increased and the rate of dissociation of the bound G_{α} subunit from the $G_{\alpha\beta\gamma}$ complex increases. The free G_{α} subunit and $G_{\beta\gamma}$ complex are thus capable of transmitting a signal to downstream elements of a variety of signal transduction pathways. These events form the basis for a multiplicity of different cell signaling phenomena, including for example the signaling phenomena that are identified as neurological sensory perceptions such as taste and/or smell.

Mammals are believed to have five basic taste modalities: sweet, bitter, sour, salty, and umami (the taste of monosodium glutamate). Numerous physiological studies in animals have shown that taste receptor cells may selectively respond to different chemical stimuli. In mammals, taste receptor cells are assembled into taste buds that are distributed into different papillae in the tongue epithelium. Circumvallate papillae, found at the very back of the tongue, contain hundreds to thousands of taste buds. By contrast, foliate papillae, localized to the posterior lateral edge of the tongue, contain dozens to hundreds of taste buds. Further, fungiform papillae, located at the front of the tongue, contain only a single or a few taste buds.

Each taste bud, depending on the species, contains 50-150 cells, including precursor cells, support cells, and taste receptor cells. Receptor cells are innervated at their base by afferent nerve endings that transmit information to the taste centers of the cortex through

synapses in the brain stem and thalamus. Elucidating the mechanisms of taste cell signaling and information processing is important to understanding the function, regulation, and perception of the sense of taste.

The gustatory system has been selected during evolution to detect nutritive and beneficial compounds as well as harmful or toxic substances. Outside the tongue, expression of $G\alpha_{gust}$ has also been localized to gastric and pancreatic cells, suggesting that a taste-sensing mechanism may also exist in the gastrointestinal (GI) tract. Expression of taste receptors has also been found in the lining of stomach and intestine, suggesting that taste receptors may play a role in molecular sensing of therapeutic entities and toxins.

Complete or partial sequences of numerous human and other eukaryotic chemosensory receptors are currently known. Within the last several years, a number of groups including the present assignee Senomyx, Inc. have reported the identification and cloning of genes from two GPCR families that are involved in taste modulation and have obtained experimental results related to the understanding of taste biology. These results indicate that bitter, sweet and amino acid taste, also referred as umami taste, are triggered by activation of two types of specific receptors located at the surface of taste receptor cells (TRCs) on the tongue *i.e.*, T2Rs and T1Rs. It is currently believed that at least 26 to 33 genes encode functional receptors (T2Rs) for bitter tasting substances in human and rodent respectively.

By contrast there are only 3 T1Rs, T1R1, T1R2 and T1R3, which are involved in umami and sweet taste. Structurally, the T1R and T2R receptors possess the hallmark of G protein-coupled receptors (GPCRs), *i.e.*, 7 transmembrane domains flanked by small extracellular and intracellular amino- and carboxyl-termini respectively.

T2Rs have been cloned from different mammals including rats, mice and humans. T2Rs comprise a novel family of human and rodent G protein-coupled receptors that are expressed in subsets of taste receptor cells of the tongue and palate epithelia. These taste receptors are organized in clusters in taste cells and are genetically linked to loci that influence bitter taste. The fact that T2Rs modulate bitter taste has been demonstrated in cell-based assays. For example, mT2R-5, hT2R-4 and mT2R-8 have been shown to be activated by bitter molecules in *in vitro* gustducin assays, providing experimental proof that T2Rs function as bitter taste receptors. See also T2Rs disclosed in U.S. Patent No. 7,105,650.

T1R family members in general include T1R1, T1R2, and T1R3, *e.g.*, rT1R3, mT1R3, hT1R3, rT1R2, mT1R2, hT1R2, and rT1R1, mT1R1 and hT1R1. It is known that the three T1R gene members T1R1, T1R2 and T1R3 form functional heterodimers that specifically recognize sweeteners and amino acids. It is generally believed that T1R2/T1R3 combination recognizes natural and artificial sweeteners while the T1R1/T1R3 combination recognizes several L-amino acids and monosodium glutamate (MSG), respectively. For example, co-expression of T1R1 and T1R3 in recombinant host cells results in a hetero-oligomeric taste receptor that responds to umami taste stimuli. Umami taste stimuli include by way of example monosodium glutamate and other molecules that elicit a "savory" taste sensation. By contrast, co-expression of T1R2 and T1R3 in recombinant host cells results in a hetero-oligomeric sweet taste receptor that responds to both naturally occurring and artificial sweeteners.

There is a need in the art to develop various ways of identifying compounds or other entities suitable for modifying receptors and their ligands associated with chemosensory or chemosensory related sensation or reaction. In addition, there is a need in the art for compounds or other entities with such characteristics.

BRIEF SUMMARY OF THE INVENTION

The present invention is based, at least in part, on the discovery that an extra-cellular domain, *e.g.*, the Venus flytrap domain of a chemosensory receptor, especially one or more interacting sites within the Venus flytrap domain, is a suitable target for compounds or other entities to modulate the chemosensory receptor and/or its ligands. Accordingly, the present invention provides screening methods for identifying modifiers of chemosensory receptors and their ligands as well as modifiers capable of modulating chemosensory receptors and their ligands.

In one embodiment, the present invention provides a method of screening for a candidate of a chemosensory receptor ligand modifier. The method comprises determining whether a test entity is suitable to interact with a chemosensory receptor *via* an interacting site within the Venus flytrap domain of the chemosensory receptor.

In another embodiment, the present invention provides a method of screening for a candidate of a chemosensory receptor ligand modifier. The method comprises determining whether a test entity is suitable to interact with a chemosensory receptor *via* a first interacting

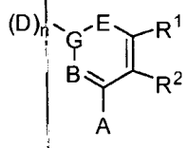
site within the Venus flytrap domain of the chemosensory receptor, wherein the first interacting site is identified in light of a second interacting site identified based on the interaction between a chemosensory receptor ligand and the chemosensory receptor.

In yet another embodiment, the present invention provides a method of screening for a candidate of a chemosensory receptor modifier. The method comprises determining whether a test entity is suitable to interact with a chemosensory receptor *via* an interacting site within the Venus flytrap domain of the chemosensory receptor, wherein the interacting site includes an interacting residue selected from the group consisting of N143, S144, I167, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, P185, T184, T326, E302, V384, A305, I325, I306, D307, E382, I279, I67, V66, V309, S303, T242, F103, Q328, and S168 of T1R2 and a combination thereof, wherein a test entity suitable to interact with the interacting site of the chemosensory receptor is indicative of a candidate of a chemosensory receptor modifier.

In yet another embodiment, the present invention provides a method of modulating the activity of a chemosensory receptor ligand. The method comprises contacting a chemosensory receptor ligand modifier with a cell containing T1R2 Venus flytrap domain in the presence of a chemosensory receptor ligand, wherein the chemosensory receptor ligand modifier interacts with an interacting site of the chemosensory receptor.

In still another embodiment, the present invention provides a chemosensory receptor ligand modifier, wherein in the presence of a chemosensory receptor ligand it interacts with T1R2 Venus flytrap domain *via* at least three interacting residues selected from the group consisting of N143, S144, I167, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, and S168 of T1R2.

In still another embodiment, the present invention provides a chemosensory receptor ligand modifier having a structure of Formula (I):



(I)

or a tautomer, salt, solvate, and/or ester thereof, wherein:

G forms a single bond with either D or E and a double bond with the other of D or E;

R^1 is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, $-NO_2$, $-OR^3$, $-S(O)_aR^3$, $-NR^3R^4$, $-CONR^3R^4$, $-CO_2R^3$, $-NR^3CO_2R^4$, $-NR^3CONR^4R^5$, $-NR^3CSNR^4R^5$, $-NR^3C(=NH)NR^4R^5$, $-SO_2NR^3R^4$, $-NR^4SO_2R^3$, $-NR^3SO_2NR^4R^5$, $-B(OR^3)(OR^4)$, $-P(O)(OR^3)(OR^4)$ or $-P(O)(R^3)(OR^4)$;

R^2 is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, $-NO_2$, $-OR^6$, $-S(O)_bR^6$, $-NR^6R^7$, $-CONR^6R^7$, $-CO_2R^6$, $-NR^6CO_2R^7$, $-NR^6CONR^7R^8$, $-NR^6CSNR^7R^8$, $-NR^6C(=NH)NR^7R^8$, $-SO_2NR^5R^6$, $-NR^5SO_2R^6$, $-NR^5SO_2NR^6R^7$, $-B(OR^5)(OR^6)$, $-P(O)(OR^5)(OR^6)$, or $-P(O)(R^5)(OR^6)$; or alternatively, R^1 and R^2, together with the atoms to which they are bonded, form an aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring wherein the ring is optionally fused to another aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring;

with the proviso that R^1 and R^2 are not both hydrogen;

A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, halo, -CN, $-NO_2$, $-OR^9$, $-S(O)_cR^9$, $-NR^9COR^{10}$, $-NHOR^9$, $-NR^9R^{10}$, $-NOR^9$, $-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$, $-NR^9C(=NH)NR^{10}R^{11}$, $-B(OR^{10})(OR^{11})$, $-P(O)(OR^{10})(OR^{11})$ or $-P(O)(R^{10})(OR^{11})$;

B is -N- or $-C(R^{12})-$;

R^{12} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, $-NR^{13}R^{14}$, -CN, $-OR^{13}$, $-S(O)_dR^{13}$, $-CO_2R^{13}$ or $-CONR^{13}R^{14}$;

G is -C- or $-S(O)_2-$;

provided that when G is $-S(O)_2-$, then G forms a single bond with E;

when the bond between D and G is a single bond, then D is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl,

halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, $-OR^{15}$, $-NH-OR^{15}$, $-S(O)_eR^{15}$, $-NR^{15}R^{16}$, $-NH-NHR^{15}$, $-CO_2R^{15}$, or $-CONR^{15}R^{16}$;

when G forms a double bond with D, then D is =O, =S , $=N-OR^{15}$, or $=N-NHR^{15}$;

n is 0 when G is $-S(O)_2-$, and n is 1 when G is -C-;

E is $-NR^{17}-$, -N- or $-C(R^{18})-$;

provided that E is $-NR^{17}-$ only when G forms a single bond with E;

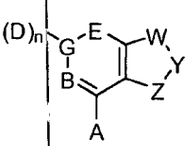
R^{17} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl or $-CO_2R^{19}$;

R^{18} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, $-NR^{20}R^{21}$, -CN, $-OR^{20}$, $-S(O)_fR^{20}$, $-CO_2R^{20}$ or $-CONR^{20}R^{21}$;

a, b, c, d, e and f are independently 0, 1 or 2; and

R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{13}, R^{14}, R^{15}, R^{16}, R^{18}, R^{20}, and R^{21} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl; or alternatively, R^3 and R^4, R^4 and R^5, R^6 and R^7, R^7 and R^8, R^9 and R^{10}, R^{10} and R^{11}, R^{13} and R^{14}, R^{15} and R^{16}, or R^{20} and R^{21}, together with the atoms to which they are bonded, form a cycloheteroalkyl or substituted cycloheteroalkyl ring.

In one embodiment of Formula (I), the compound of the present invention has structural Formula (II):



(II)

wherein:

Y forms a single bond with either W or Z and a double bond with the other of W or Z;

W is $-C(R^{24})-$, -S-, -N-, $-N(R^{25})-$, or -O-;

Y is $-C(R^{26})-$ or -N-;

Z is $-C(R^{27})-$, -S-, -N-, $-N(R^{28})-$, or -O-;

R^{24} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, $-NO_2$, $-OR^{29}$, $-S(O)_gR^{29}$, $-NR^{29}R^{30}$, $-CONR^{29}R^{30}$, $-CO_2R^{29}$, $-SO_2NR^{29}R^{30}$, $-NR^{29}SO_2R^{30}$, $-B(OR^{29})(OR^{30})$, $-P(O)(OR^{29})(OR^{30})$ or $-P(O)(R^{29})(OR^{30})$;

R^{26} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, halo, -CN, $-NO_2$, $-OR^{31}$, $-S(O)_hR^{31}$, $-OCOR^{31}$, $-NR^{31}R^{32}$, $-CONR^{31}R^{32}$, $-CO_2R^{31}$, $-SO_2NR^{31}R^{32}$, $-NR^{31}SO_2R^{32}$, $-B(OR^{31})(OR^{32})$, $-P(O)(OR^{31})(OR^{32})$ or $-P(O)(R^{31})(OR^{32})$;

R^{27} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, halo, -CN, $-NO_2$, $-OR^{33}$, $-S(O)_iR^{33}$, $-OCOR^{33}$, $-NR^{33}R^{34}$, $-CONR^{33}R^{34}$, $-COR^{33}$, $-CO_2R^{33}$, $-SO_2NR^{33}R^{34}$, $-NR^{33}SO_2R^{34}$, $-B(OR^{33})(OR^{34})$, $-P(O)(OR^{33})(OR^{34})$ or $-P(O)(R^{33})(OR^{34})$ or alternatively R^{24} and R^{26} or R^{26} and R^{27} together with the atoms to which they are bonded form a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring;

g, h and i are independently 0 or 1;

R^{25} and R^{28} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl; and

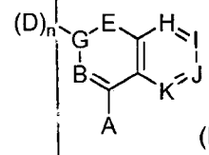
R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, and R^{34} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl; or alternatively R^{29} and R^{30}, R^{31} and R^{32} or R^{33} and R^{34} together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring; and

with the following provisos:

(a) when W is -O- or -S- or $-NR^{25}$, then Z is $-C(R^{27})$ or -N-; and

(b) when Z is -O- or -S- or $-NR^{28}$, then W is $-C(R^{24})$ or -N-.

In one embodiment of Formula (I), the compound of the present invention has structural Formula (III):



(III)

wherein:

H is -C(R^{35})- or -N-;

I is -C(R^{36}) or -N-;

J is -C(R^{37})- or -N-;

K is -C(R^{38})- or -N-;

R^{35} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, -NO_2, -OR^{39}, -$S(O)_jR^{39}$, -$OCOR^{39}$, -$NR^{39}R^{40}$, -$CONR^{39}R^{40}$, -CO_2R^{39}, -$SO_2NR^{39}R^{40}$, -$NR^{39}SO_2R^{40}$, -$B(OR^{39})(OR^{40})$, -$P(O)(OR^{39})(OR^{40})$ or -$P(O)(R^{39})(OR^{40})$;

R^{36} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, -NO_2, -OR^{41}, -$S(O)_kR^{41}$, -$OCOR^{41}$, -$NR^{41}R^{42}$, -$CONR^{41}R^{42}$, -CO_2R^{41}, -$SO_2NR^{41}R^{42}$, -$NR^{41}SO_2R^{42}$, -$B(OR^{41})(OR^{42})$, -$P(O)(OR^{41})(OR^{42})$ or -$P(O)(R^{41})(OR^{42})$;

R^{37} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl ,-CN, -NO_2, -OR^{43}, -$S(O)_lR^{43}$, -$OCOR^{43}$, -$NR^{43}R^{44}$, -$CONR^{43}R^{44}$, -CO_2R^{43}, -$SO_2NR^{43}R^{44}$, -$NR^{43}SO_2R^{44}$, -$B(OR^{43})(OR^{44})$, -$P(O)(OR^{43})(OR^{44})$ or -$P(O)(R^{43})(OR^{44})$;

R^{38} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, -NO_2, -OR^{45}, -$S(O)_mR^{45}$, -$OCOR^{45}$, -$NR^{45}R^{46}$, -$CONR^{45}R^{46}$, -COR^{45}, -CO_2R^{45}, -$SO_2NR^{45}R^{46}$, -$NR^{45}SO_2R^{46}$, -$B(OR^{45})(OR^{46})$, -$P(O)(OR^{45})(OR^{46})$ or -$P(O)(R^{45})(OR^{46})$; or alternatively R^{36} and R^{37} or R^{37} and R^{38} taken together with the atom to which they are bonded, form a cycloalkyl, substituted cycloalkyl,

cycloheteroalkyl, or substituted cycloheteroalkyl ring;

j, k, l and m are independently 0, 1 or 2; and

R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, and R^{46} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl or alternatively R^{39} and R^{40}, R^{41} and R^{42}, R^{43} and R^{44} or R^{45} and R^{46} together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

with the proviso that at most, two of H, I, J and K are -N-.

In one embodiment, the present invention provides an ingestible composition comprising a chemosensory receptor ligand modifier, wherein in the presence of a chemosensory receptor ligand it interacts with T1R2 Venus flytrap domain *via* at least three interacting residues selected from the group consisting of N143, S144, I167, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, and S168 of a human T1R2. In one embodiment, the chemosensory receptor ligand modifier is a compound having structural Formula (I), (II), or (III), or a tautomer, salt, solvate, and/or ester thereof. In another embodiment, the ingestible composition further comprises one or more sweeteners.

In one embodiment, the present invention provides a method of enhancing the sweet taste of an ingestible composition comprising contacting the ingestible composition or precursors thereof with a chemosensory receptor ligand modifier to form a modified ingestible composition. In one embodiment, the chemosensory receptor ligand modifier is a compound having structural Formula (I), (II), or (III), or a tautomer, salt, solvate, and/or ester thereof.

In one embodiment, the present invention provides a method of treating a condition associated with a chemosensory receptor comprising administering to a subject in need of such treatment an effective amount of an entity selected from the group consisting of a chemosensory receptor modifier, chemosensory receptor ligand modifier, and a combination thereof, wherein the entity interacts with an interacting site of the chemosensory receptor. In one embodiment, the chemosensory receptor ligand modifier is a compound having structural Formula (I), (II), or (III), or a tautomer, salt, solvate, and/or ester thereof.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 contains exemplary human T1R1 polymorphic variations.

Figure 2 contains exemplary human T1R2 polymorphic variations.

Figure 3 shows the dendograms for the sequence alignments of T1R1.

Figure 4 shows the dendograms for the sequence alignments of T1R2.

Figure 5 shows exemplary interacting spaces for sucralose and one of the compound of the present invention. Protein is represented as a ribbon diagram.

Figure 6 shows exemplary interacting spaces and residues for sucralose and one of the compounds of the present invention. Protein is represented as a ribbon diagram.

Figure 7 shows exemplary interacting spaces and residues associated with the hinge region for sucralose and one of the compounds of the present invention.

Figure 8 shows exemplary partial interacting surfaces and interacting residues proximal to the hinge region for sucrose and sucralose.

Figure 9 shows exemplary interacting spaces and residues associated with the lobes for sucralose and one of the compounds of the present invention.

Figure 10 shows exemplary interacting spaces and residues associated with an interacting site for sucralose and one of the compounds of the present invention.

Figure 11 shows exemplary results for mapping studies using human-rat chimeric receptors.

Figure 12 shows results for exemplary mutagenesis results.

DETAILED DESCRIPTION OF THE INVENTION

Prior to specifically describing the invention, the following definitions are provided.

The term "T1R" family includes polymorphic variants, alleles, mutants, and homologs that: (1) have about 30-40% amino acid sequence identity, more specifically about 40, 50, 60, 70, 75, 80, 85, 90, 95, 96, 97, 98, or 99% amino acid sequence identity to the T1Rs known or disclosed, *e.g.*, in patent application U.S. Serial No. 10/179,373 filed on June 26, 2002, Serial No. 09/799,629 filed on April 5, 2001 and U.S. Serial No. 10/035,045 filed on January 3, 2002, over a window of about 25 amino acids, optimally 50-100 amino acids; (2) specifically bind to antibodies raised against an immunogen comprising an amino acid sequence selected from the group consisting of the T1R sequences disclosed infra, and conservatively modified variants thereof; (3) specifically hybridize (with a size of at least about 100, optionally at least

about 500-1000 nucleotides) under stringent hybridization conditions to a sequence selected from the group consisting of the T1R DNA sequences disclosed infra, and conservatively modified variants thereof; (4) comprise a sequence at least about 40% identical to an amino acid sequence selected from the group consisting of the T1R amino acid sequences disclosed infra or (5) are amplified by primers that specifically hybridize under stringent hybridization conditions to the described T1R sequences.

In particular, these "T1Rs" include taste receptor GPCRs referred to as hT1R1, hT1R2, hT1R3, rT1R1, rT1R2, rT1R3, mT1R1, mT1R2, and mT1R3 having the nucleic acid sequences and amino acid sequences known or disclosed, *e.g.*, in U.S. Serial No. 10/179,373 filed on June 26, 2002, U.S. Serial No. 09/799,629 filed on April 5, 2001 and U.S. Serial No. 10/035,045 filed on January 3, 2002, and variants, alleles, mutants, orthologs and chimeras thereof which specifically bind and/or respond to sweet, umami, or any other chemosensory related ligands including activators, inhibitors and enhancers. Also T1Rs include taste receptor GPCRs expressed in humans or other mammals, *e.g.*, cells associated with taste and/or part of gastrointestinal system including without any limitation, esophagus, stomach, intestine (small and large), colon, liver, biliary tract, pancreas, gallbladder, *etc.* Also, T1R polypeptides include chimeric sequences derived from portions of a particular T1R polypeptide such as T1R1, T1R2 or T1R3 of different species or by combining portions of different T1Rs wherein such chimeric T1R sequences are combined to produce a functional sweet or umami taste receptor. For example chimeric T1Rs may comprise the extracellular region of one T1R, i.e., T1R1 or T1R2 and the transmembrane region of another T1R, either T1R1 or T1R2.

Topologically, certain chemosensory GPCRs have an "N-terminal domain;" "extracellular domains," a "transmembrane domain" comprising seven transmembrane regions, and corresponding cytoplasmic and extracellular loops, "cytoplasmic regions," and a "C-terminal region" (see, *e.g.*, Hoon *et al.*, *Cell* 96:541-51 (1999); Buck*et al.*, *Cell* 65:175-87 (1991)). These regions can be structurally identified using methods known to those of skill in the art, such as sequence analysis programs that identify hydrophobic and hydrophilic domains (*see, e.g.*, Stryer, Biochemistry, (3rd ed. 1988); see also any of a number of Internet based sequence analysis programs, such as those found at dot.imgen.bcm.tmc.edu). These regions are useful for making chimeric proteins and for *in vitro* assays of the invention, *e.g.*, ligand binding assays.

"Extracellular domains" therefore refers to the domains of chemosensory receptors, *e.g.*, T1R polypeptides that protrude from the cellular membrane and are exposed to the extracellular face of the cell. Such regions would include the "N-terminal domain" that is exposed to the extracellular face of the cell, as well as the extracellular loops of the transmembrane domain that are exposed to the extracellular face of the cell, *i.e.*, the extracellular loops between transmembrane regions 2 and 3, transmembrane regions 4 and 5, and transmembrane regions 6 and 7. The "N-terminal domain" starts at the N-terminus and extends to a region close to the start of the transmembrane region. These extracellular regions are useful for *in vitro* ligand binding assays, both soluble and solid phase. In addition, transmembrane regions, described below, can also be involved in ligand binding, either in combination with the extracellular region or alone, and are therefore also useful for *in vitro* ligand binding assays.

"Transmembrane domain," which comprises the seven transmembrane "regions," refers to the domains of chemosensory receptors, *e.g.*, T1R polypeptides that lie within the plasma membrane, and may also include the corresponding cytoplasmic (intracellular) and extracellular loops, also referred to as transmembrane "regions." The seven transmembrane regions and extracellular and cytoplasmic loops can be identified using standard methods, as described in Kyte *et al.*, *J. Mol. Biol.* 157:105-32 (1982)), or in Stryer, *supra*.

"Cytoplasmic domains" refers to the domains of chemosensory receptors, *e.g.*, T1R proteins that face the inside of the cell, *e.g.*, the "C-terminal domain" and the intracellular loops of the transmembrane domain, *e.g.*, the intracellular loops between transmembrane regions 1 and 2, transmembrane regions 3 and 4, and transmembrane regions 5 and 6. "C-terminal domain" refers to the region that spans from the end of the last transmembrane region to the C-terminus of the protein, and which is normally located within the cytoplasm.

The term "7-transmembrane receptor" means a polypeptide belonging to a superfamily of transmembrane proteins that have seven regions that span the plasma membrane seven times (thus, the seven regions are called "transmembrane" or "TM" domains TM I to TM VII).

The phrase "functional effects" or "activity" in the context of the disclosed assays for testing compounds that modulate a chemosensory receptor, *e.g.*, enhance T1R family member mediated signal transduction such as sweet or umami receptor functional effects or activity includes the determination of any parameter that is indirectly or directly under the influence of

the particular chemosensory receptor, *e.g.*, functional, physical and chemical effects. It includes, without any limitation, ligand binding, changes in ion flux, membrane potential, current flow, transcription, G protein binding, GPCR phosphorylation or dephosphorylation, signal transduction, receptor-ligand interactions, second messenger concentrations (*e.g.*, cAMP, cGMP, IP3, or intracellular Ca^{2+}), *in vitro*, *in vivo*, and *ex vivo* and also includes other physiologic effects such increases or decreases of neurotransmitter or hormone release.

The term "determining the functional effect" or receptor "activity" means assays for a compound that increases or decreases a parameter that is indirectly or directly under the influence of a chemosensory receptor, *e.g.*, functional, physical and chemical effects. Such functional effects can be measured by any means known to those skilled in the art, *e.g.*, changes in spectroscopic characteristics (*e.g.*, fluorescence, absorbance, refractive index), hydrodynamic (*e.g.*, shape), chromatographic, or solubility properties, patch clamping, voltage-sensitive dyes, whole cell currents, radioisotope efflux, inducible markers, oocyte chemosensory receptor, *e.g.*, T1R gene expression; tissue culture cell chemosensory receptor, *e.g.*, T1R expression; transcriptional activation of chemosensory receptor, *e.g.*, T1R genes; ligand binding assays; voltage, membrane potential and conductance changes; ion flux assays; changes in intracellular second messengers such as cAMP, cGMP, and inositol triphosphate (IP3); changes in intracellular calcium levels; neurotransmitter release, and the like.

"Inhibitors," "activators," and "modifiers" of chemosensory receptor, *e.g.*, T1R proteins are used interchangeably to refer to inhibitory, activating, or modulating molecules identified using *in vitro* and *in vivo* assays for chemosensory signal transduction, *e.g.*, ligands, agonists, antagonists, and their homologs and mimetics. Inhibitors are compounds that, *e.g.*, bind to, partially or totally block stimulation, decrease, prevent, delay activation, inactivate, desensitize, or down regulate taste transduction, *e.g.*, antagonists. Activators are compounds that, *e.g.*, bind to, stimulate, increase, open, activate, facilitate, enhance activation, sensitize, or up regulate chemosensory signal transduction, *e.g.*, agonists. Modifiers include compounds that, *e.g.*, alter, directly or indirectly, the activity of a receptor or the interaction of a receptor with its ligands, *e.g.*, receptor ligands and optionally bind to or interact with activators or inhibitors; G Proteins; kinases (*e.g.*, homologs of rhodopsin kinase and beta adrenergic receptor kinases that are involved in deactivation and desensitization of a receptor); and arrestins, which also deactivate and desensitize receptors. Modifiers include genetically modified versions of

chemosensory receptors, *e.g.*, T1R family members, *e.g.*, with altered activity, as well as naturally occurring and synthetic ligands, antagonists, agonists, small chemical molecules and the like. The term "chemosensory receptor ligand modifier" as used herein includes chemosensory receptor ligand enhancer. In the present invention this includes, without any limitation, sweet ligands (agonists or antagonists), umami ligands (agonists and antagonists), sweet enhancers and umami enhancers and sweet taste or umami taste inhibitors.

"Enhancer" herein refers to a compound that modulates (increases) the activation of a particular receptor, preferably the chemosensory, *e.g.*, T1R2/T1R3 receptor or T1R1/T1R3 receptor but which by itself does not result in substantial activation of the particular receptor. Herein such enhancers will enhance the activation of a chemosensory receptor by its ligand. Typically the "enhancer" will be specific to a particular ligand, *i.e.*, it will not enhance the activation of a chemosensory receptor by chemosensory ligands other than the particular chemosensory ligand or ligands closely related thereto.

"Putative enhancer" herein refers to a compound identified, *e.g.*, *in silico* or not, as a potential enhancer using assays which are described herein but which enhancer activity has not yet been confirmed *in vivo*, *e.g.*, in suitable taste tests.

The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer.

The "extra-cellular domain" and chemosensory receptor, *e.g.*, T1R receptor regions or compositions described herein also include "analogs," or "conservative variants" and "mimetics" ("peptidomimetics") with structures and activity that substantially correspond to the exemplary sequences. Thus, the terms "conservative variant" or "analog" or "mimetic" refer to a polypeptide which has a modified amino acid sequence, such that the change(s) do not substantially alter the polypeptide's (the conservative variant's) structure and/or activity, as defined herein. These include conservatively modified variations of an amino acid sequence, i.e., amino acid substitutions, additions or deletions of those residues that are not critical for protein activity, or substitution of amino acids with residues having similar properties (*e.g.*,

acidic, basic, positively or negatively charged, polar or non-polar, *etc.*) such that the substitutions of even critical amino acids does not substantially alter structure and/or activity.

More particularly, "conservatively modified variants" applies to both amino acid and nucleic acid sequences. With respect to particular nucleic acid sequences, conservatively modified variants refers to those nucleic acids which encode identical or essentially identical amino acid sequences, or where the nucleic acid does not encode an amino acid sequence, to essentially identical sequences. Because of the degeneracy of the genetic code, a large number of functionally identical nucleic acids encode any given protein.

For instance, the codons GCA, GCC, GCG and GCU all encode the amino acid alanine. Thus, at every position where an alanine is specified by a codon, the codon can be altered to any of the corresponding codons described without altering the encoded polypeptide.

Such nucleic acid variations are "silent variations," which are one species of conservatively modified variations. Every nucleic acid sequence herein which encodes a polypeptide also describes every possible silent variation of the nucleic acid. One of skill will recognize that each codon in a nucleic acid (except AUG, which is ordinarily the only codon for methionine, and TGG, which is ordinarily the only codon for tryptophan) can be modified to yield a functionally identical molecule. Accordingly, each silent variation of a nucleic acid which encodes a polypeptide is implicit in each described sequence.

Conservative substitution tables providing functionally similar amino acids are well known in the art. For example, one exemplary guideline to select conservative substitutions includes (original residue followed by exemplary substitution): ala/gly or ser; arg/lys; asn/gln or his; asp/glu; cys/ser; gln/asn; gly/asp; gly/ala or pro; his/asn or gln; ile/leu or val; leu/ile or val; lys/arg or gln or glu; met/leu or tyr or ile; phe/met or leu or tyr; ser/thr; thr/ser; trp/tyr; tyr/trp or phe; val/ile or leu. An alternative exemplary guideline uses the following six groups, each containing amino acids that are conservative substitutions for one another: 1) Alanine (A), Serine (S), Threonine (T); 2) Aspartic acid (D), Glutamic acid (E); 3) Asparagine (N), Glutamine (Q); 4) Arginine (R), Lysine (I); 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); and 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W); (see also, *e.g.*, Creighton, Proteins, W. H. Freeman and Company (1984); Schultz and Schimer, Principles of Protein Structure, Springer-Verlag (1979)). One of skill in the art will appreciate that the above-identified substitutions are not the only possible conservative substitutions. For example, for some

purposes, one may regard all charged amino acids as conservative substitutions for each other whether they are positive or negative. In addition, individual substitutions, deletions or additions that alter, add or delete a single amino acid or a small percentage of amino acids in an encoded sequence can also be considered "conservatively modified variations."

The terms "mimetic" and "peptidomimetic" refer to a synthetic chemical compound that has substantially the same structural and/or functional characteristics of the polypeptides, *e.g.*, extra-cellular domain or any region therewith of T1R2 or T1R1. The mimetic can be either entirely composed of synthetic, non-natural analogs of amino acids, or may be a chimeric molecule of partly natural peptide amino acids and partly non-natural analogs of amino acids. The mimetic can also incorporate any amount of natural amino acid conservative substitutions as long as such substitutions also do not substantially alter the mimetic's structure and/or activity.

As with polypeptides of the invention which are conservative variants, routine experimentation will determine whether a mimetic is within the scope of the invention, *i.e.*, that its structure and/or function is not substantially altered. Polypeptide mimetic compositions can contain any combination of non-natural structural components, which are typically from three structural groups: a) residue linkage groups other than the natural amide bond ("peptide bond") linkages; b) non-natural residues in place of naturally occurring amino acid residues; or c) residues which induce secondary structural mimicry, *i.e.*, to induce or stabilize a secondary structure, *e.g.*, a beta turn, gamma turn, beta sheet, alpha helix conformation, and the like. A polypeptide can be characterized as a mimetic when all or some of its residues are joined by chemical means other than natural peptide bonds. Individual peptidomimetic residues can be joined by peptide bonds, other chemical bonds or coupling means, such as *e.g.*, glutaraldehyde, N-hydroxysuccinimide esters, bifunctional maleimides, N,N'-dicyclohexylcarbodiimide (DCC) or N,N'-diisopropylcarbodiimide (DIC). Linking groups that can be an alternative to the traditional amide bond ("peptide bond") linkages include, *e.g.*, ketomethylene (*e.g.*, -C(O)-CH_2- for-C(O)-NH-), aminomethylene -CH_2(NH)-, ethylene, olefin -CH=CH-, ether -CH_2O-, thioether -CH_2S-, tetrazole (CN_4), thiazole, retroamide, thioamide or ester (see, *e.g.*, Spatola, Chemistry and Biochemistry of Amino Acids, Peptides and Proteins, Vol. 7, 267-357, Marcell Dekker, Peptide Backbone Modifications, NY (1983)). A polypeptide can also be characterized as a

mimetic by containing all or some non-natural residues in place of naturally occurring amino acid residues; non-natural residues are well described in the scientific and patent literature.

"Alkyl," by itself or as part of another substituent, refers to a saturated or unsaturated, branched, straight-chain or cyclic monovalent hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane, alkene or alkyne. The term "alkyl" includes "cycloalkyl" as defined hereinbelow. Typical alkyl groups include, but are not limited to, methyl; ethyls such as ethanyl, ethenyl, ethynyl; propyls such as propan-1-yl, propan-2-yl, cyclopropan-1-yl, prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl (allyl), cycloprop-1-en-1-yl; cycloprop-2-en-1-yl, prop-1-yn-1-yl, prop-2-yn-1-yl, *etc.*; butyls such as butan-1-yl, butan-2-yl, 2-methyl-propan-1-yl, 2-methyl-propan-2-yl, cyclobutan-1-yl, but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl, but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl, cyclobut-1-en-1-yl, cyclobut-1-en-3-yl, cyclobuta-1,3-dien-1-yl, but-1-yn-1-yl, but-1-yn-3-yl, but-3-yn-1-yl, *etc.*; and the like. The term "alkyl" is specifically intended to include groups having any degree or level of saturation, *i.e.*, groups having exclusively single carbon-carbon bonds, groups having one or more double carbon-carbon bonds, groups having one or more triple carbon-carbon bonds and groups having mixtures of single, double and triple carbon-carbon bonds. Where a specific level of saturation is intended, the expressions "alkanyl," "alkenyl," and "alkynyl" are used. In some embodiments, an alkyl group comprises from 1 to 20 carbon atoms (C_1-C_{20} alkyl). In other embodiments, an alkyl group comprises from 1 to 10 carbon atoms (C_1-C_{10} alkyl). In still other embodiments, an alkyl group comprises from 1 to 6 carbon atoms (C_1-C_6 alkyl). It is noted that when an alkyl group is further connected to another atom, it becomes an "alkylene" group. In other words, the term "alkylene" refers to a divalent alkyl. For example, $-CH_2CH_3$ is an ethyl, while $-CH_2CH_2-$ is an ethylene. That is, "Alkylene," by itself or as part of another substituent, refers to a saturated or unsaturated, branched, straight-chain or cyclic divalent hydrocarbon radical derived by the removal of two hydrogen atoms from a single carbon atom or two different carbon atoms of a parent alkane, alkene or alkyne. The term "alkylene" includes "cycloalkylene" as defined hereinbelow. The term "alkylene" is specifically intended to include groups having any degree or level of saturation, *i.e.*, groups having exclusively single carbon-carbon bonds, groups having one or more double carbon-carbon bonds, groups having one or more triple carbon-carbon bonds and groups having mixtures of single, double and triple carbon-carbon bonds. Where a specific

level of saturation is intended, the expressions "alkanylene," "alkenylene," and "alkynylene" are used. In some embodiments, an alkylene group comprises from 1 to 20 carbon atoms (C_1-C_{20} alkylene). In other embodiments, an alkylene group comprises from 1 to 10 carbon atoms (C_1-C_{10} alkylene). In still other embodiments, an alkylene group comprises from 1 to 6 carbon atoms (C_1-C_6 alkylene).

"Alkanyl," by itself or as part of another substituent, refers to a saturated branched, straight-chain or cyclic alkyl radical derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane. The term "alkanyl" includes "cycloakanyl" as defined hereinbelow. Typical alkanyl groups include, but are not limited to, methanyl; ethanyl; propanyls such as propan-1-yl, propan-2-yl (isopropyl), cyclopropan-1-yl, *etc.*; butanyls such as butan-1-yl, butan-2-yl (*sec*-butyl), 2-methyl-propan-1-yl (isobutyl), 2-methyl-propan-2-yl (*t*-butyl), cyclobutan-1-yl, *etc.*; and the like.

"Alkenyl," by itself or as part of another substituent, refers to an unsaturated branched, straight-chain or cyclic alkyl radical having at least one carbon-carbon double bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkene. The term "alkenyl" includes "cycloalkenyl" as defined hereinbelow. The group may be in either the *cis* or *trans* conformation about the double bond(s). Typical alkenyl groups include, but are not limited to, ethenyl; propenyls such as prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl (allyl), prop-2-en-2-yl, cycloprop-1-en-1-yl; cycloprop-2-en-1-yl; butenyls such as but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl , but-2-en-1-yl, but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl, cyclobut-1-en-1-yl, cyclobut-1-en-3-yl, cyclobuta-1,3-dien-1-yl, *etc.*; and the like.

"Alkynyl," by itself or as part of another substituent refers to an unsaturated branched, straight-chain or cyclic alkyl radical having at least one carbon-carbon triple bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkyne. Typical alkynyl groups include, but are not limited to, ethynyl; propynyls such as prop-1-yn-1-yl, prop-2-yn-1-yl, *etc.*; butynyls such as but-1-yn-1-yl, but-1-yn-3-yl, but-3-yn-1-yl, *etc.*; and the like.

"Alkoxy," by itself or as part of another substituent, refers to a radical of the formula -O-R^{199}, where R^{199} is alkyl or substituted alkyl as defined herein.

"Acyl" by itself or as part of another substituent refers to a radical $-C(O)R^{200}$, where R^{200} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroarylalkyl or substituted heteroarylalkyl as defined herein. Representative examples include, but are not limited to formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethylcarbonyl, benzoyl, benzylcarbonyl and the like.

"Aryl," by itself or as part of another substituent, refers to a monovalent aromatic hydrocarbon group derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system, as defined herein. Typical aryl groups include, but are not limited to, groups derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, trinaphthalene and the like. In some embodiments, an aryl group comprises from 6 to 20 carbon atoms (C_6-C_{20} aryl). In other embodiments, an aryl group comprises from 6 to 15 carbon atoms (C_6-C_{15} aryl). In still other embodiments, an aryl group comprises from 6 to 15 carbon atoms (C_6-C_{10} aryl).

"Arylalkyl," by itself or as part of another substituent, refers to an acyclic alkyl group in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with an aryl group as, as defined herein. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, 2-phenylethen-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, 2-naphthylethen-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. Where specific alkyl moieties are intended, the nomenclature arylalkanyl, arylalkenyl and/or arylalkynyl is used. In some embodiments, an arylalkyl group is (C_6-C_{30}) arylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety of the arylalkyl group is (C_1-C_{10}) alkyl and the aryl moiety is (C_6-C_{20}) aryl. In other embodiments, an arylalkyl group is (C_6-C_{20}) arylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety of the arylalkyl group is (C_1-C_8) alkyl and the aryl moiety is (C_6-C_{12}) aryl. In still other embodiments, an arylalkyl group is (C_6-C_{15}) arylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety of the arylalkyl group is (C_1-C_5) alkyl and the aryl moiety is (C_6-C_{10}) aryl.

"Cycloalkyl," by itself or as part of another substituent, refers to a saturated or unsaturated cyclic alkyl radical, as defined herein. Similarly, "Cycloalkylene," by itself or as

part of another substituent, refers to a saturated or unsaturated cyclic alkylene radical, as defined herein. Where a specific level of saturation is intended, the nomenclature "cycloalkanyl", "cycloalkenyl", or "cycloalkynyl" is used. Typical cycloalkyl groups include, but are not limited to, groups derived from cyclopropane, cyclobutane, cyclopentane, cyclohexane, and the like. In some embodiments, the cycloalkyl group comprises from 3 to 10 ring atoms (C_3-C_{10} cycloalkyl). In other embodiments, the cycloalkyl group comprises from 3 to 7 ring atoms (C_3-C_7 cycloalkyl). The cycloalkyl may be further substituted by one or more heteroatoms including, but not limited to, N, P, O, S, and Si, which attach to the carbon atoms of the cycloalkyl via monovalent or multivalent bond.

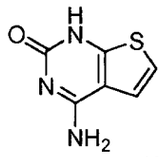
"Heteroalkyl," "Heteroalkanyl," "Heteroalkenyl" and "Heteroalkynyl," by themselves or as part of other substituents, refer to alkyl, alkanyl, alkenyl and alkynyl groups, respectively, in which one or more of the carbon atoms (and optionally any associated hydrogen atoms), are each, independently of one another, replaced with the same or different heteroatoms or heteroatomic groups. Similarly, "Heteroalkylene," "Heteroalkanylene," "Heteroalkenylene" and "Heteroalkynylene," by themselves or as part of other substituents, refer to alkylene, alkanylene, alkenylene and alkynyenel groups, respectively, in which one or more of the carbon atoms (and optionally any associated hydrogen atoms), are each, independently of one another, replaced with the same or different heteroatoms or heteroatomic groups. Typical heteroatoms or heteroatomic groups which can replace the carbon atoms include, but are not limited to, -O-, -S-, -N-, -Si-, -NH-, -S(O)-, $-S(O)_2-$, -S(O)NH-, $-S(O)_2NH-$ and the like and combinations thereof. The heteroatoms or heteroatomic groups may be placed at any interior position of the alkyl, alkenyl or alkynyl groups. Typical heteroatomic groups which can be included in these groups include, but are not limited to, -O-, -S-, -O-O-, -S-S-, -O-S-, $-NR^{201}R^{202}-$, =N-N=, -N=N-, $-N=N-NR^{203}R^{204}$, $-PR^{205}-$, $-P(O)_2-$, $-POR^{206}-$, $-O-P(O)_2-$, -SO-, $-SO_2-$, $-SnR^{207}R^{208}-$ and the like, where R^{201}, R^{202}, R^{203}, R^{204}, R^{205}, R^{206}, R^{207} and R^{208} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl.

"Cycloheteroalkyl," or "Heterocyclyl,"by itself or as part of another substituent, refers to a saturated or unsaturated cyclic alkyl radical in which one or more carbon atoms (and optionally any associated hydrogen atoms) are independently replaced with the same or different

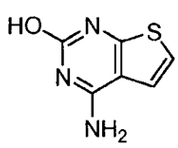
heteroatom. Similarly, "Cycloheteroalkylene," by itself or as part of another substituent, refers to a saturated or unsaturated cyclic alkylene radical in which one or more carbon atoms (and optionally any associated hydrogen atoms) are independently replaced with the same or different heteroatom. The cycloheteroalkyl may be further substituted by one or more heteroatoms including, but not limited to, N, P, O, S, and Si, which attach to the carbon atoms of the cycloheteroalkyl via monovalent or multivalent bond. Typical heteroatoms to replace the carbon atom(s) include, but are not limited to, N, P, O, S, Si, *etc.* Where a specific level of saturation is intended, the nomenclature "cycloheteroalkanyl" or "cycloheteroalkenyl" is used. Typical cycloheteroalkyl groups include, but are not limited to, groups derived from epoxides, azirines, thiiranes, imidazolidine, morpholine, piperazine, piperidine, pyrazolidine, pyrrolidone, quinuclidine, and the like. In some embodiments, the cycloheteroalkyl group comprises from 3 to 10 ring atoms (3-10 membered cycloheteroalkyl) In other embodiments, the cycloalkyl group comprise from 5 to 7 ring atoms (5-7 membered cycloheteroalkyl). A cycloheteroalkyl group may be substituted at a heteroatom, for example, a nitrogen atom, with a (C_1-C_6) alkyl group. As specific examples, N-methyl-imidazolidinyl, N-methyl-morpholinyl, N-methyl-piperazinyl, N-methyl-piperidinyl, N-methyl-pyrazolidinyl and N-methyl-pyrrolidinyl are included within the definition of "cycloheteroalkyl." A cycloheteroalkyl group may be attached to the remainder of the molecule *via* a ring carbon atom or a ring heteroatom.

"Compounds" refers to compounds encompassed by structural formulae disclosed herein and includes any specific compounds within these formulae whose structure is disclosed herein. Compounds may be identified either by their chemical structure and/or chemical name. When the chemical structure and chemical name conflict, the chemical structure is determinative of the identity of the compound. The compounds described herein may contain one or more chiral centers and/or double bonds and therefore, may exist as stereoisomers, such as double-bond isomers (*i.e.*, geometric isomers), enantiomers or diastereomers. Accordingly, the chemical structures depicted herein encompass all possible enantiomers and stereoisomers of the illustrated compounds including the stereoisomerically pure form (*e.g.*, geometrically pure, enantiomerically pure or diastereomerically pure) and enantiomeric and stereoisomeric mixtures. Enantiomeric and stereoisomeric mixtures can be resolved into their component enantiomers or stereoisomers using separation techniques or chiral synthesis techniques well known to the skilled artisan. The compounds may also exist in several tautomeric forms including the enol

form, the keto form and mixtures thereof. Accordingly, the chemical structures depicted herein encompass all possible tautomeric forms of the illustrated compounds. The compounds described also include isotopically labeled compounds where one or more atoms have an atomic mass different from the atomic mass conventionally found in nature. Examples of isotopes that may be incorporated into the compounds of the invention include, but are not limited to, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, *etc.* Compounds may exist in unsolvated forms as well as solvated forms, including hydrated forms and as N-oxides. In general, compounds may be hydrated, solvated or N-oxides. Certain compounds may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated herein and are intended to be within the scope of the present invention. Further, it should be understood, when partial structures of the compounds are illustrated, that brackets indicate the point of attachment of the partial structure to the rest of the molecule. The term "tautomer" as used herein refers to isomers that change into one another with great ease so that they can exist together in equilibrium. For example, the following compounds A and B are tautomers of each other:



(A)



(B)

"Halo," by itself or as part of another substituent refers to a radical -F, -Cl, -Br or -I.

"Heteroaryl," by itself or as part of another substituent, refers to a monovalent heteroaromatic radical derived by the removal of one hydrogen atom from a single atom of a parent heteroaromatic ring systems, as defined herein. Typical heteroaryl groups include, but are not limited to, groups derived from acridine, β-carboline, chromane, chromene, cinnoline, furan, imidazole, indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthroline, phenazine, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, xanthene, and the like. In some embodiments, the heteroaryl group comprises from 5 to 20 ring atoms (5-20 membered heteroaryl). In other embodiments, the heteroaryl group comprises from 5 to 10 ring

atoms (5-10 membered heteroaryl). Exemplary heteroaryl groups include those derived from furan, thiophene, pyrrole, benzothiophene, benzofuran, benzimidazole, indole, pyridine, pyrazole, quinoline, imidazole, oxazole, isoxazole and pyrazine.

"Heteroarylalkyl" by itself or as part of another substituent refers to an acyclic alkyl group in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with a heteroaryl group. Where specific alkyl moieties are intended, the nomenclature heteroarylalkanyl, heteroarylalkenyl and/or heteroarylalkynyl is used. In some embodiments, the heteroarylalkyl group is a 6-21 membered heteroarylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety of the heteroarylalkyl is (C_1-C_6) alkyl and the heteroaryl moiety is a 5-15-membered heteroaryl. In other embodiments, the heteroarylalkyl is a 6-13 membered heteroarylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety is (C_1-C_3) alkyl and the heteroaryl moiety is a 5-10 membered heteroaryl.

"Parent Aromatic Ring System" refers to an unsaturated cyclic or polycyclic ring system having a conjugated π electron system. Specifically included within the definition of "parent aromatic ring system" are fused ring systems in which one or more of the rings are aromatic and one or more of the rings are saturated or unsaturated, such as, for example, fluorene, indane, indene, phenalene, *etc.* Typical parent aromatic ring systems include, but are not limited to, aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, trinaphthalene and the like.

"Parent Heteroaromatic Ring System" refers to a parent aromatic ring system in which one or more carbon atoms (and optionally any associated hydrogen atoms) are each independently replaced with the same or different heteroatom. Typical heteroatoms to replace the carbon atoms include, but are not limited to, N, P, O, S, Si, *etc.* Specifically included within the definition of "parent heteroaromatic ring system" are fused ring systems in which one or more of the rings are aromatic and one or more of the rings are saturated or unsaturated, such as, for example, benzodioxan, benzofuran, chromane, chromene, indole, indoline, xanthene, *etc.* Typical parent heteroaromatic ring systems include, but are not limited to, arsindole, carbazole, β-carboline, chromane, chromene, cinnoline, furan, imidazole, indazole, indole, indoline,

indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthroline, phenazine, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, xanthene and the like.

"Patient" includes humans. The terms "human" and "patient" are used interchangeably herein.

"Pharmaceutically acceptable" refers to being suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use within the scope of sound medical judgment.

"Preventing" or "prevention" refers to a reduction in risk of acquiring a disease or disorder (*i.e.*, causing at least one of the clinical symptoms of the disease not to develop in a patient that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease).

"Protecting group" refers to a grouping of atoms that when attached to a reactive functional group in a molecule masks, reduces or prevents reactivity of the functional group. Examples of protecting groups can be found in Green *et al.*, "Protective Groups in Organic Chemistry", (Wiley, 2nd ed. 1991) and Harrison *et al.*, "Compendium of Synthetic Organic Methods", Vols. 1-8 (John Wiley and Sons, 1971-1996). Representative amino protecting groups include, but are not limited to, formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl ("CBZ"), *tert*-butoxycarbonyl ("Boc"), trimethylsilyl ("TMS"), 2-trimethylsilyl-ethanesulfonyl ("SES"), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl ("FMOC"), nitro-veratryloxycarbonyl ("NVOC") and the like. Representative hydroxy protecting groups include, but are not limited to, those where the hydroxy group is either acylated or alkylated such as benzyl, and trityl ethers as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers and allyl ethers.

"Saccharide ring" is also known as sugar ring and includes monosacchride, disaccharide, and polysaccharide ring. Preferably, the saccharide ring is a monosacharride ring. Examples of monosaccharides include glucose (dextrose), fructose, galactose, xylose and ribose. By "derivative of saccharide ring", it is meant the non-natural or artificial saccharide ring

wherein the stereochemistry centers are partially or completely different from those of the natural saccharide ring.

"Salt" refers to a salt of a compound, which possesses the desired pharmacological activity of the parent compound. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like.

"Solvate" means a compound formed by solvation (the combination of solvent molecules with molecules or ions of the solute), or an aggregate that consists of a solute ion or molecule, i.e., a compound of the present invention, with one or more solvent molecules. When water is the solvent, the corresponding solvate is "hydrate".

"N-oxide", also known as amine oxide or amine-N-oxide, means a compound that derives from a compound of the present invention via oxidation of an amine group of the compound of the present invention. An N-oxide typically contains the functional group R_3N^+-O^- (sometimes written as $R_3N{=}O$ or $R_3N{\rightarrow}O$).

"Substituted," when used to modify a specified group or radical, means that one or more hydrogen atoms of the specified group or radical are each, independently of one another, replaced with the same or different substituent(s). Substituent groups useful for substituting saturated carbon atoms in the specified group or radical include, but are not limited to $-R^a$, halo, $-O^-$, =O, $-OR^b$, $-SR^b$, $-S^-$, =S, $-NR^cR^c$, $=NR^b$, $=N-OR^b$, trihalomethyl, $-CF_3$, -CN, -OCN, -SCN,

-NO, $-NO_2$, $=N_2$, $-N_3$, $-S(O)_2R^b$, $-S(O)_2NR^b$, $-S(O)_2O^-$, $-S(O)_2OR^b$, $-OS(O)_2R^b$, $-OS(O)_2O^-$, $-OS(O)_2OR^b$, $-P(O)(O^-)_2$, $-P(O)(OR^b)(O^-)$, $-P(O)(OR^b)(OR^b)$, $-C(O)R^b$, $-C(S)R^b$, $-C(NR^b)R^b$, $-C(O)O^-$, $-C(O)OR^b$, $-C(S)OR^b$, $-C(O)NR^cR^c$, $-C(NR^b)NR^cR^c$, $-OC(O)R^b$, $-OC(S)R^b$, $-OC(O)O^-$, $-OC(O)OR^b$, $-OC(S)OR^b$, $-NR^bC(O)R^b$, $-NR^bC(S)R^b$, $-NR^bC(O)O^-$, $-NR^bC(O)OR^b$, $-NR^bC(S)OR^b$, $-NR^bC(O)NR^cR^c$, $-NR^bC(NR^b)R^b$ and $-NR^bC(NR^b)NR^cR^c$, where R^a is selected from the group consisting of alkyl, cycloalkyl, heteroalkyl, cycloheteroalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl; each R^b is independently hydrogen or R^a; and each R^c is independently R^b or alternatively, the two R^cs may be taken together with the nitrogen atom to which they are bonded form a 4-, 5-, 6- or 7-membered cycloheteroalkyl which may optionally include from 1 to 4 of the same or different additional heteroatoms selected from the group consisting of O, N and S. As specific examples, $-NR^cR^c$ is meant to include $-NH_2$, -NH-alkyl, N-pyrrolidinyl and N-morpholinyl. As another specific example, a substituted alkyl is meant to include –alkylene-O-alkyl, -alkylene-heteroaryl, -alkylene-cycloheteroalkyl, -alkylene-$C(O)OR^b$, -alkylene-$C(O)NR^bR^b$, and $-CH_2-CH_2-C(O)-CH_3$. The one or more substituent groups, taken together with the atoms to which they are bonded, may form a cyclic ring including cycloalkyl and cycloheteroalkyl.

Similarly, substituent groups useful for substituting unsaturated carbon atoms in the specified group or radical include, but are not limited to, $-R^a$, halo, $-O^-$, $-OR^b$, $-SR^b$, $-S^-$, $-NR^cR^c$, trihalomethyl, $-CF_3$, -CN, -OCN, -SCN, -NO, $-NO_2$, $-N_3$, $-S(O)_2R^b$, $-S(O)_2O^-$, $-S(O)_2OR^b$, $-OS(O)_2R^b$, $-OS(O)_2O^-$, $-OS(O)_2OR^b$, $-P(O)(O^-)_2$, $-P(O)(OR^b)(O^-)$, $-P(O)(OR^b)(OR^b)$, $-C(O)R^b$, $-C(S)R^b$, $-C(NR^b)R^b$, $-C(O)O^-$, $-C(O)OR^b$, $-C(S)OR^b$, $-C(O)NR^cR^c$, $-C(NR^b)NR^cR^c$, $-OC(O)R^b$, $-OC(S)R^b$, $-OC(O)O^-$, $-OC(O)OR^b$, $-OC(S)OR^b$, $-NR^bC(O)R^b$, $-NR^bC(S)R^b$, $-NR^bC(O)O^-$, $-NR^bC(O)OR^b$, $-NR^bC(S)OR^b$, $-NR^bC(O)NR^cR^c$, $-NR^bC(NR^b)R^b$ and $-NR^bC(NR^b)NR^cR^c$, where R^a, R^b and R^c are as previously defined.

Substituent groups useful for substituting nitrogen atoms in heteroalkyl and cycloheteroalkyl groups include, but are not limited to, $-R^a$, $-O^-$, $-OR^b$, $-SR^b$, $-S^-$, $-NR^cR^c$, trihalomethyl, $-CF_3$, -CN, -NO, $-NO_2$, $-S(O)_2R^b$, $-S(O)_2O^-$, $-S(O)_2OR^b$, $-OS(O)_2R^b$, $-OS(O)_2O^-$, $-OS(O)_2OR^b$, $-P(O)(O^-)_2$, $-P(O)(OR^b)(O^-)$, $-P(O)(OR^b)(OR^b)$, $-C(O)R^b$, $-C(S)R^b$, $-C(NR^b)R^b$, $-C(O)OR^b$, $-C(S)OR^b$, $-C(O)NR^cR^c$, $-C(NR^b)NR^cR^c$, $-OC(O)R^b$, $-OC(S)R^b$, $-OC(O)OR^b$, $-OC(S)OR^b$, $-NR^bC(O)R^b$, $-NR^bC(S)R^b$, $-NR^bC(O)OR^b$, $-NR^bC(S)OR^b$, $-NR^bC(O)NR^cR^c$, $-NR^bC(NR^b)R^b$ and $-NR^bC(NR^b)NR^cR^c$, where R^a, R^b and R^c are as previously defined.

Substituent groups from the above lists useful for substituting other specified groups or atoms will be apparent to those of skill in the art.

The substituents used to substitute a specified group can be further substituted, typically with one or more of the same or different groups selected from the various groups specified above.

"Treating" or "treatment" of any disease or disorder refers, in some embodiments, to ameliorating the disease or disorder (*i.e.*, arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In other embodiments "treating" or "treatment" refers to ameliorating at least one physical parameter, which may not be discernible by the patient. In yet other embodiments, "treating" or "treatment" refers to inhibiting the disease or disorder, either physically, (*e.*g., stabilization of a discernible symptom), physiologically, (*e.g.*, stabilization of a physical parameter) or both. In yet other embodiments, "treating" or "treatment" refers to delaying the onset of the disease or disorder.

"Therapeutically effective amount" means the amount of a compound that, when administered to a patient for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, *etc.*, of the patient to be treated.

"Vehicle" refers to a diluent, adjuvant, excipient or carrier with which a compound is administered.

The present invention is based, at least in part, on the discovery that an extra-cellular domain, *e.g.*, the Venus flytrap domain of a chemosensory receptor, especially one or more interacting sites within the Venus flytrap domain, is a suitable target for compounds or other entities to modulate the chemosensory receptor and/or its ligands. Accordingly, the present invention provides screening methods for identifying chemosensory receptor modifiers as well as chemosensory receptor ligand modifiers. In addition, the present invention provides compounds and compositions capable of modulating chemosensory receptors as well as chemosensory receptor ligands.

According to one aspect of the present invention, it provides methods of screening for chemosensory receptor modifiers by determining whether a test entity is suitable to interact with a chemosensory receptor *via* one or more interacting sites within the extra-cellular domain of the chemosensory receptor, *e.g.,* the Venus flytrap domain of the chemosensory receptor.

According to another aspect of the present invention, it provides methods of screening for chemosensory receptor ligand modifiers by determining whether a test entity is suitable to interact with a chemosensory receptor, and optionally its ligand *via* one or more interacting sites within the extra-cellular domain, *e.g.,* the Venus flytrap domain of the chemosensory receptor, optionally in the presence of a chemosensory receptor ligand.

In general, the extra-cellular domain of a chemosensory receptor refers to the extra-cellular amino-terminus of a chemosensory receptor and usually includes a ligand-binding domain and a cysteine-rich linker domain, which connects the ligand-binding domain and the rest of the protein. In Class C GPCRs, the ligand binding domain is generally referred to as a Venus flytrap domain, the structure of which has been elucidated, *e.g.*, using X-ray crystallography.

A Venus flytrap domain typically consists of two relatively rigid lobes connected by three strands forming a flexible "hinge" region. In the absence of a ligand, the Venus flytrap domain tends to adopt open conformations with well-separated lobes as well as closed conformations with lobes closer together. In one example, the Venus flytrap domain includes a region from amino acid 36 to amino acid 509 of human T1R1, amino acid 31 to amino acid 507 of human T1R2, and/or amino acid 35 to amino acid 511 of human T1R3.

The Venus flytrap domain of the present invention includes any ligand binding domain or ligand interacting domain within the extra-cellular domain of a chemosensory receptor. In one embodiment, the Venus flytrap domain of the present invention includes any ligand binding domain of a member of the T1R family. In another embodiment, the Venus flytrap domain of the present invention includes any extra-cellular domain of a chemosensory receptor with a structure comprising two lobes connected by a hinge region. In yet another embodiment, the Venus flytrap domain of the present invention includes any domain corresponding to the structure and/or function of a region including amino acid 36 to amino acid 509 of human T1R1, amino acid 31 to amino acid 507 of human T1R2, and/or amino acid 35 to amino acid 511 of human T1R3. In still another embodiment, the Venus flytrap domain of the present invention includes any ligand binding domain of T1R1, T1R2, and/or T1R3 as well as any polymorphic variation, allele, or mutation thereof. Exemplary illustrations of polymorphic variations for T1R1 and T1R2 are shown in Figures 1-4.

According to the present invention, a chemosensory receptor can be any receptor associated with chemosensory sensation or chemosensory ligand triggered signal transduction, *e.g., via* taste receptors or taste related receptors expressed in taste bud, gastrointestinal tract, *etc.* In one embodiment, a chemosensory receptor is a receptor that belongs to the 7-transmembrane receptor superfamily or G protein-coupled receptors (GPCRs). In another embodiment, a chemosensory receptor is a receptor carrying out signal transduction *via* one or more G proteins. In yet another embodiment, a chemosensory receptor is a receptor that belongs to family C or class C of GPCRs. In yet another embodiment, a chemosensory receptor is a receptor that belongs to the T1R family. In yet another embodiment, a chemosensory receptor is a receptor of T1R1, T1R2, T1R3, or their equivalences or variances or a combination thereof. In still another embodiment, a chemosensory receptor is a hetero-dimer of T1R2 and T1R3, or their equivalences or variances.

According to the present invention, an interacting site within the Venus flytrap domain of a chemosensory receptor can be one or more interacting residues or a three dimensional interacting space or a combination thereof. In one embodiment, the interacting site of the present invention is within the Venus flytrap domain of T1R2. In another embodiment, the interacting site of the present invention is within the Venus flytrap domain of T1R3. In yet another embodiment, the interacting site of the present invention is within the Venus flytrap domain of both T1R2 and T1R3.

Usually such an interacting site can be determined by any suitable means known or later discovered in the art. For example, such interacting site can be determined based on computer modeling, *e.g.*, using software such as Homology or Modeller (by Accelrys Corporation) to construct three dimensional homology models of a chemosensory receptor Venus flytrap domain, *e.g.*, the T1R2 and/or T1R3 Venus flytrap domains based on crystal structures of homologous Venus flytrap domains.

Such an interacting site can also be determined, *e.g.*, based on X-ray crystallography and the three dimensional structure of a chemosensory receptor determined therefrom, *e.g.*, the T1R2, T1R3, or T1R2/T1R3 heterodimer. Alternatively, for example, such an interacting site can be determined based on molecular mechanical techniques, *e.g.*, normal mode analysis, loop generation techniques, Monte Carlo and/or molecular dynamics simulations to explore motions and alternative conformations of the Venus flytrap domains, docking

simulations to dock candidate receptor ligands and candidate receptor ligand modifiers into these models or into experimentally determined structures of chemosensory receptors, *e.g.*, T1R1 and T1R2.

In addition, for example, such an interacting site can be determined based on mutagenesis, *e.g.*, site-directed mutagenesis or a combination of two or more suitable methods known or later discovered, *e.g.*, methods described herein.

In one example, such an interacting site is located in part of a chemosensory receptor, *e.g.*, T1R2 and can be determined in the presence or absence of the other part of the chemosensory receptor, *e.g.*, T1R3. In another example, such an interacting site can be determined in the presence or absence of a chemosensory receptor modifier and/or chemosensory receptor ligand modifier.

In one embodiment, the interacting site within the Venus flytrap domain of a chemosensory receptor includes one or more interacting residues of the Venus flytrap domain of a chemosensory receptor. According to the present invention, the interacting residue of the Venus flytrap domain of a chemosensory receptor is a residue associated with any direct or indirect interaction between a chemosensory receptor and a chemosensory receptor modifier or a chemosensory receptor ligand modifier or both.

In one example, the interacting residue of the present invention includes any residue of a chemosensory receptor associated with an interaction between a chemosensory receptor modifier and a chemosensory receptor. In another example, the interacting residue of the present invention includes any residue of a chemosensory receptor associated with an interaction between a chemosensory receptor ligand modifier and a chemosensory receptor. In yet another example, the interacting residue of the present invention includes any residue of a chemosensory receptor associated with an interaction between a chemosensory receptor, a chemosensory receptor modifier and a chemosensory receptor ligand modifier.

In still another example, the interacting residue of the present invention includes any residue of a chemosensory receptor associated with an interaction between a chemosensory receptor and a sweet flavor entity, *e.g.* any natural or synthesized sweet flavor compound including, without any limitation, non-caloric sweet flavor compounds, reduced caloric sweet flavor compounds, non-target caloric sweet flavor compounds, *etc.* Exemplary sweet flavor compounds include, without any limitation, cyclamic acid, mogroside, tagatose, maltose,

galactose, mannose, sucrose, fructose, lactose, aspartame, neotame and other aspartame derivatives, saccharin, sucralose, acesulfame K, glucose, erythritol, D-tryptophan, glycine, mannitol, sorbitol, maltitol, lactitol, isomalt, hydroganeted glucose syrup (HGS), hydrogenated starch hydrolyzate (HSH), stevioside, rebaudioside A and other sweet Ste*via*-based glycosides, alitame, carrelame and other guanidine-based sweeteners, tagatose, xylitol, high fructose corn syrup, *etc.*

In still another example, the interacting residue of the present invention includes any residue of a chemosensory receptor associated with an interaction between a chemosensory receptor and a sweet flavor entity enhancer. In still another example, the interacting residue of the present invention includes any residue of a chemosensory receptor associated with an interaction between a chemosensory receptor, a sweet flavor entity, and a sweet flavor entity enhancer.

In another instance, the interacting residue of the present invention is a residue within the Venus flytrap domain of a chemosensory receptor, wherein any mutation of which could result in a change of the activity of the chemosensory receptor or the impact of a chemosensory receptor ligand to the chemosensory receptor or both. For example, the interacting residue of the present invention can include any residue within the Venus flytrap domain of a chemosensory receptor, wherein the mutation of which results in a detectable change, *e.g.,* qualitative or quantitative change of the activity of the chemosensory receptor in response to a chemosensory receptor modifier and/or chemosensory receptor ligand modifier.

In yet another instance, the interacting residue of the present invention is a residue within the Venus flytrap domain of a chemosensory receptor that interacts or forms productive interaction(s), *e.g.*, van der Waals, burial of hydrophobic atoms or atomic groups, hydrogen bonds, ring stacking interactions, or salt-bridging electrostatic interactions with a chemosensory receptor modifier or chemosensory receptor ligand modifier, or both.

In still another instance, the interacting residue of the Venus flytrap domain of a chemosensory receptor can be any residue constituting one or more interacting structural components of the Venus flytrap domain, which are associated, directly or indirectly, with the interaction between a chemosensory receptor and a chemosensory receptor modifier or a chemosensory receptor ligand modifier or both. For example, the Venus flytrap domain structure of a chemosensory receptor generally includes two lobes joint by a hinge region.

Residues constituting an interacting structural component of the Venus flytrap domain can be, *e.g.,* residues constituting the hinge region, the inner side of each lobe, or residues on each lobe that are brought into close proximity during activation or conformational change of the Venus flytrap domain, including without any limitation, residues on the inner surfaces of the lobes pointing towards each other or on the tips of the lobes where the residues are partially exposed to solvent but still close to residues on the opposite lobe, *etc.*

Exemplary interacting residues of the Venus flytrap domain of a chemosensory receptor include any one or more residues of 1) N143, S144, and I167 of a human T1R2, 2) S40, S144, S165, Y103, D142, and P277 of a human T1R2, 3) K65, R383, D307, E302, and D278 of a human T1R2, 4) I167, P185, T184, T326, E302, V384, A305, I325, I306, R383, D307, E382, D278, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, and S168 of a human T1R2, 5) N143, S144, I167, K65, R383, D307, E302, D278, P185, T184, T326, E302, V384, A305, I325, I306, D307, E382, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, and S168 of a human T1R2, and 6) N143, I167, K65, R383, D307, E302, D278, P185, T184, T326, V384, A305, I325, I306, D307, E382, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, and S168 of a human T1R2.

Exemplary interacting residues of the Venus flytrap domain of a chemosensory receptor with respect to a chemosensory receptor modifier include one or more residues of 1) N143, S144, and I167 of a human T1R2, 2) S40, S144, S165, Y103, D142, and P277 of a human T1R2, 3) I167, P185, T184, T326, E302, V384, A305, I325, I306, R383, D307, E382, D278, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, and S168 of a human T1R2, 4) N143 and I167 of a human T1R2, 5) S40, S165, Y103, D142, and P277 of a human T1R2, and 6) I167, P185, T184, T326, V384, A305, I325, I306, R383, D307, E382, D278, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, and S168 of a human T1R2.

Exemplary interacting residues of the Venus flytrap domain of a chemosensory receptor with respect to a sweet flavor entity such as sucrose and sucralose include one or more residues of S40, S144, Y103, D142, P277 of a human T1R2. Exemplary interacting residues of the Venus flytrap domain of a chemosensory receptor with respect to a sweet flavor entity such as saccharin or acesulfame K include one or more residues of K65, R383, D307, E302, and D278 of a human T1R2.

Exemplary interacting residues of the Venus flytrap domain of a chemosensory receptor with respect to a chemosensory receptor ligand modifier, *e.g.*, chemosensory receptor ligand enhancer include one or more residues of 1) K65, R383, D307, E302, and D278 of a human T1R2, 2) S40, S144, S165, Y103, D142, and P277 of a human T1R2, and 3) I167, P185, T184, T326, E302, V384, A305, I325, I306, R383, D307, E382, D278, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, and S168 of a human T1R2.

In the context of the present invention, any reference to a particular interacting residue, *e.g.*, N143 of a human T1R2 receptor, includes all of its corresponding residues, *e.g.*, 1) any residue of a human or non-human T1R2 that corresponds to the same position in any method of sequence alignment, 2) any residue of a human or non-human T1R2 that corresponds to the same position in any method of computer modeling in the presence or absence of a ligand or ligand modifier, 3) any residue of a human or non-human T1R2 that corresponds to the structural or functional role of the particular interacting residue, 4) any residue of a human or non-human T1R2 that is a polymorphic variation, alleles, mutation, *etc.* of the particular residue, 5) any residue of a human or non-human T1R2 that is a conservative substitution or conservatively modified variant of the particular residue, and 6) any corresponding residue of a human or non-human T1R2 in its modified form, *e.g.*, artificial chemical mimetic of the particular interacting residue or un-modified form, *e.g.*, naturally occurring form.

In another embodiment, the interacting site within the Venus flytrap domain of a chemosensory receptor is a three dimensional interacting space within the Venus flytrap domain outlined or defined, partially or entirely, by interacting residues or one or more interfaces, *e.g.*, interacting points, lines or surfaces between a chemosensory receptor and one or more chemosensory receptor modifiers or chemosensory receptor ligand modifiers or a combination thereof. According to the present invention, a residue outlining or lining a space includes any residue having one or more backbones and/or side-chain atoms that are positioned so that they can potentially interact with atoms of a chemosensory receptor ligand or chemosensory receptor ligand modifier or both.

For example, the interacting space of the present invention can be any partial or whole space within the Venus flytrap domain that is usually occupied by one or more chemosensory receptor modifiers or chemosensory receptor ligand modifiers when they interact with a chemosensory receptor individually or together. In one example, the interacting space of

the present invention is a space within the Venus flytrap domain usually occupied by a chemosensory receptor modifier, *e.g.*, sweet flavor entity. In another example, the interacting space of the present invention is a space within the Venus flytrap domain usually occupied by a chemosensory receptor ligand modifier, *e.g.*, sweet flavor enhancer in the presence of a chemosensory receptor ligand. In yet another example, the interacting space of the present invention is a space within the Venus flytrap domain usually occupied by a chemosensory receptor modifier, *e.g.*, sweet flavor entity and a chemosensory receptor ligand modifier, *e.g.*, sweet flavor entity enhancer. In still another example, the interacting space of the present invention is a space within the Venus flytrap domain that is defined, shaped, or transformed into based on an interaction between a chemosensory receptor and its ligand or its ligand modifier occurred partially or entirely outside of the space.

According to the present invention, the Venus flytrap domain of a chemosensory receptor can be generally viewed as two lobes joined by a hinge region. Exemplary interacting space within the Venus flytrap domain of a chemosensory receptor includes any space associated with the hinge region, the inner side of one or two lobes, the tip of one or two lobes or a combination thereof of a chemosensory receptor.

Exemplary interacting space within the Venus flytrap domain of a chemosensory receptor with respect to a chemosensory receptor modifier includes any space within the Venus flytrap domain outlined or at least partially defined by the hinge region. According to the present invention, the hinge region usually comprises residues that are close to the three strands connecting the two lobes. In one example, the hinge region comprises residues that are homologous to residues observed coordinating agonists and antagonists in crystal structures of one or more Venus flytrap domains such as that of the mGluR receptor. In another example, the hinge region of T1R2 includes residues N143, S144, and I167 of T1R2.

Exemplary interacting sites within the Venus flytrap domain of a chemosensory receptor with respect to a chemosensory receptor ligand modifier include any space outlined or at least partially defined by the inner side of one or two lobes away from the hinge region, as well as residues on the tips of the lobes that are brought into close proximity to residues on the other lobe.

In yet another embodiment, the interacting site within the Venus flytrap domain of a chemosensory receptor is a combination of one or more interacting residues with an

interacting space of the chemosensory receptor. For example, the interacting site of a chemosensory receptor can be interacting residues associated with one interacting structural component of a chemosensory receptor in combination with a three dimensional space adjacent, *e.g.*, not less than 1 Angstrom and not more than 30 Angstroms, to that interacting structural component. Another example of the interacting site of a chemosensory receptor includes interacting residues associated with one interacting structural component of a chemosensory receptor in combination with a three dimensional space apart from the interacting structural component.

In general, the screening methods provided by the present invention can be carried out by any suitable means known or later discovered. In one embodiment, the screening methods provided by the present invention are carried out *in silico, e.g., via* "virtue screening" using any suitable computer modeling system or *via* specific or rational design of a compound using any suitable computer design system.

In another embodiment, the screening methods provided by the present invention are carried out *via* biological assays, *e.g.*, high throughput screening of interactions between compounds and a chemosensory receptor or its fragments, *e.g.*, genetically modified chemosensory receptors or fragments thereof such as mutated Venus flytrap domains of chemosensory receptors. In yet another embodiment, the screening methods provided by the present invention are carried out *via* a combination of biological assay(s) and computer modeling and/or design. For example, the screening methods provided by the present invention can be a combination of high-throughput screening of interactions between computer designed or pre-screened compounds and mutated Venus flytrap domains of chemosensory receptors.

In one example, the screening method provided by the present invention for chemosensory receptor modifiers includes determining an interacting site using a known chemosensory receptor modifier, *e.g.*, structurally similar to a chemosensory receptor modifier of interest and then determining whether a test entity is suitable to interact with the chemosensory receptor *via* the interacting site so determined.

In another example, the screening method provided by the present invention for chemosensory receptor modifiers includes determining whether a test entity is suitable to interact with a chemosensory receptor *via* a predetermined interacting site, *e.g.*, an interacting site selected or determined prior to screening, including without any limitation, selected or

determined based on known chemosensory receptor modifiers or desired characteristics of a chemosensory receptor modifiers.

In yet another example, the screening method provided by the present invention for chemosensory receptor ligand modifiers includes determining a docking site for a chemosensory receptor ligand and subsequently determining whether a test entity is suitable to interact with the chemosensory receptor ligand *via* an interacting site selected in light of the docking of the chemosensory receptor ligand. According to the present invention, docking process can include any known or later discovered methods. For instance, docking can be a process in which the center of mass, orientations, and internal degrees of freedom of a molecule are modified to fit them into a predetermined space in a structural model. In one example, docking can be a process which includes translating and rotating a chemosensory receptor ligand relative to the chemosensory receptor structural model, *e.g.*, the Venus flytrap domain of a chemosensory receptor model while simultaneously adjusting internal torsional angles of the chemosensory receptor ligand to fit it into the interacting site of the chemosensory receptor. An example of a widely used docking program is GLIDE from Schroedinger, Inc.

In yet another example, the screening method provided by the present invention for chemosensory receptor ligand modifiers includes determining a docking site for a chemosensory receptor ligand and subsequently determining an interacting site using a known modifier of the chemosensory receptor ligand and then determining whether a test entity is suitable to interact with the chemosensory receptor ligand *via* the interacting site so determined.

In yet another example, the screening method provided by the present invention for chemosensory receptor ligand modifiers includes determining whether a test entity is suitable to interact with a chemosensory receptor *via* a predetermined interacting site for chemosensory receptor ligand modifiers.

In still another example, the screening method provided by the present invention for chemosensory receptor ligand modifiers includes determining whether a test entity is suitable to interact with a chemosensory receptor by determining, *e.g.*, concurrently whether a chemosensory receptor ligand and the test entity are suitable to interact with the chemosensory receptor in a predetermined interacting site of the chemosensory receptor or an interacting site determined using known chemosensory receptor ligand and its modifier of interest.

In still another example, the screening method provided by the present invention for chemosensory receptor ligand modifiers includes determining whether a test entity is suitable to interact with a chemosensory receptor *via* an interacting site, either pre-determined or not, as well as whether a test entity is suitable to interact with a chemosensory receptor ligand.

In still another example, the screening method provided by the present invention for chemosensory receptor ligand modifiers includes determining whether a test entity is suitable to interact with a chemosensory receptor *via* an interacting site, either pre-determined or not, as well as whether such interaction can stabilize a conformation, *e.g.*, a semi-closed or closed conformation within the Venus flytrap domain formed by the interaction between a chemosensory receptor ligand and a chemosensory receptor, *e.g.*, by forming productive additional interactions within the hinge region, lobes of the Venus flytrap domain, or tips of the flytrap domain *via* van der Waals, burial of hydrophobic atoms or atomic groups, hydrogen bonds, ring stacking interactions, or salt-bridging electrostatic interactions, *etc.*

In general, any suitable means known or later discovered can be used to determine whether a test entity is suitable to interact with an interacting site of the present invention. For example, one could determine the suitability of a test entity based on whether part or all of a test entity fits into a particular space entailed by an interacting site, *e.g.*, whether a test entity fits into a particular space entailed by an interacting site substantially the same way a known chemosensory receptor modifier or chemosensory receptor ligand modifier does.

Alternatively one could determine the suitability of a test entity with respect to an interacting site based on whether it forms interactions with a chemosensory receptor similar to the interactions formed by a known chemosensory receptor modifier or chemosensory receptor ligand modifier when they interact with the interacting site.

In addition, one could determine the suitability of a test entity based on whether it forms productive interactions with an interacting site, *e.g.*, van der Waals, burial of hydrophobic atoms or atomic groups, hydrogen bonds, ring stacking interactions, or salt-bridging electrostatic interactions, *etc.* In one embodiment, one could determine the suitability of a test entity being a chemosensory receptor ligand modifier based on whether it forms productive interactions with an interacting site without forming van der Waals overlapping with one or more atoms of a chemosensory receptor or the chemosensory receptor ligand, *e.g.*, in the context of one or more

conformations of the Venus flytrap domain in light of the possible flexibility of the Venus flytrap domain.

According to the present invention, a test entity suitable to interact with one or more interacting sites within the Venus flytrap domain of a chemosensory receptor is indicative of a candidate for a chemosensory receptor modifier or chemosensory receptor ligand modifier. In one embodiment, a test entity suitable to interact with one or more interacting sites within the Venus flytrap domain of T1R2 is indicative of a candidate for a T1R2 receptor modifier or T1R2 receptor ligand modifier. In another embodiment, a test entity suitable to interact with one or more interacting sites within the Venus flytrap domain of T1R2 is indicative of a candidate for a T1R receptor modifier or T1R receptor ligand modifier. In yet another embodiment, a test entity suitable to interact with one or more interacting sites within the Venus flytrap domain of T1R2 is indicative of a candidate for a receptor modifier or receptor ligand modifier for a receptor of GPCR superfamily. In still another embodiment, a test entity suitable to interact with one or more interaction sites within the Venus flytrap domain of a chemosensory receptor is indicative of a candidate for a receptor modifier or receptor ligand modifier of a receptor that corresponds to the chemosensory receptor or belongs to the same family or class as of the chemosensory receptor.

According to the present invention, a test entity suitable to interact with one or more interacting sites within the Venus flytrap domain of a chemosensory receptor is indicative of a candidate for a chemosensory receptor modifier or chemosensory receptor ligand modifier. In one embodiment, a test entity suitable to interact with one or more interacting sites within the Venus flytrap domain of T1R2 is indicative of a candidate for a T1R2 receptor modifier or T1R2 receptor ligand modifier.

In one example, a test entity suitable to interact with one or more interacting sites containing one or more interacting residues of K65, D278, L279, D307, R383, and V384 of human T1R2 is indicative of a candidate for a T1R2 receptor ligand enhancer.

In another example, a test entity suitable to interact with one or more interacting sites containing one or more interacting residues of S40, S144, Y103, D142, and P277 of human T1R2 is indicative of a candidate for a T1R2 receptor ligand enhancer with respect to sucrose or sucralose or any ligand with a structure similar to sucrose or sucralose or any ligand interacting

with T1R2 in a way similar to that of sucrose or sucralose, *e.g., via* one or more interacting spaces and/or residues used by sucrose or sucralose.

In the context of the present application, any reference to a modifier, *e.g.* enhancer or inhibitor of a T1R2 receptor or T1R2 receptor ligand includes a modifier for any T1R receptor, any receptor of GPCR super-family, or any receptor corresponding to T1R2 receptor, *e.g.,* any receptor with a structure, function, or expression pattern overlapping or similar to that of T1R2. In the present invention, a test entity can be any compound or molecule, *e.g.*, any compound or entity that potentially could be a source for a desired chemosensory receptor modifier or chemosensory receptor ligand modifier. For example, a test entity can be a member of a combinatorial library, a member of a natural compound library, a "specifically designed" compound that is designed based on various desirable features or rationales, *etc.*

In general, a chemosensory receptor modifier or ligand includes any compound or entity capable of interacting with, *e.g.*, binding to a chemosensory receptor or modulating the structure or function of a chemosensory receptor, *e.g.*, activate, deactivate, increase, or decrease the signal transduction activity of a chemosensory receptor, especially *via* G-protein signal transduction pathway.

In one embodiment, a chemosensory receptor modifier or ligand is a compound or entity with sweet flavor including without any limitation any natural or synthesized sweet flavor compound, *e.g.,* non-caloric sweet flavor compounds, reduced caloric sweet flavor compounds, non-target caloric sweet flavor compounds, *etc.* Exemplary sweet flavor compounds include, without any limitation, cyclamic acid, mogroside, tagatose, maltose, galactose, mannose, sucrose, fructose, lactose, aspartame, neotame and other aspartame derivatives, saccharin, sucralose, acesulfame K, glucose, erythritol, D-tryptophan, glycine, mannitol, sorbitol, maltitol, lactitol, isomalt, hydroganeted glucose syrup (HGS), hydrogenated starch hydrolyzate (HSH), stevioside, rebaudioside A and other sweet *Stevia*-based glycosides, alitame, carrelame and other guanidine-based sweeteners, tagatose, xylitol, high fructose corn syrup, *etc.*

In another embodiment, a chemosensory receptor modifier or ligand (used interchangeably in the present invention) is a compound or entity capable of activating a chemosensory receptor, *e.g.*, activating the G-protein signal transduction pathway associated with the chemosensory receptor. In yet another embodiment, a chemosensory receptor modifier or ligand is a compound or entity capable of blocking or decreasing the activation of a

chemosensory receptor. In still another embodiment, a chemosensory receptor modifier or ligand is a compound or entity capable of modulating the activity of a chemosensory receptor and inducing a therapeutically desirable reaction or signal transduction. In still another embodiment, a chemosensory receptor modifier or ligand is a chemosensory receptor ligand modifier.

According to the present invention, a chemosensory receptor ligand modifier includes any compound or entity capable of interacting or modulating the activity of a chemosensory receptor modifier or the activity of a chemosensory receptor in the presence of a chemosensory receptor modifier. In one embodiment, a chemosensory receptor ligand modifier is an enhancer of a chemosensory receptor modifier. In another embodiment, a chemosensory receptor ligand modifier is an antagonist of a chemosensory receptor modifier. In yet another embodiment, a chemosensory receptor ligand modifier is an enhancer of a chemosensory receptor modifier without having substantial activity of the chemosensory receptor modifier. In still another embodiment, a chemosensory receptor ligand modifier is an enhancer of a sweet flavored compound without having substantial sweet flavor by itself, *e.g.*, as judged by animals or humans such as majority of a panel of at least eight human taste testers, *via* procedures commonly known in the field. In still yet another embodiment, a chemosensory receptor ligand modifier is an enhancer or inhibitor of a chemosensory receptor modifier and capable of inducing a desirable therapeutic reaction or signal transduction.

According to another aspect of the present invention, it provides chemosensory receptor ligand modifiers. In one embodiment, it provides chemosensory receptor ligand modifiers identified by the screen methods of the present invention. In another embodiment, it provides chemosensory receptor ligand modifiers capable of interacting with a chemosensory receptor *via* an interacting site of the present invention. In yet another embodiment, it provides chemosensory receptor ligand modifiers capable of interacting with a chemosensory receptor *via* one or more interacting residues of the chemosensory receptor. In still another embodiment, it provides chemosensory receptor ligand modifiers capable of interacting with a chemosensory receptor *via* an interacting space within the Venus flytrap domain that is outlined, defined, or shaped, partially or entirely, by interacting residues of the chemosensory receptor. In still yet another embodiment, it provides chemosensory receptor ligand modifiers excluding, *e.g.*, natural or synthesized sweet enhancers known prior to the present invention.

In the context of the present invention, "capable of interacting with" or "interacting with" means that a compound or molecule binds to or forms one or more molecular interactions, *e.g.*, productive interactions with another molecule, *e.g.*, a chemosensory receptor. Exemplary molecular interactions, *e.g.*, productive interactions include van der Waals, burial of hydrophobic atoms or atomic groups, hydrogen bonds, ring stacking interactions, salt-bridging electrostatic interactions, or a combination thereof.

In one embodiment, the present invention provides chemosensory receptor ligand modifiers capable of interacting with a chemosensory receptor *via* a group of interacting residues or a space within the Venus flytrap domain that is outlined, shaped, or defined, partially or entirely by the group or any subgroup of interacting residues, optionally in the presence of a chemosensory receptor ligand, *e.g.*, 1) S40, S144, S165, Y103, D142, P277 of a human T1R2, 2) K65, R383, D307, E302, and D278 of a human T1R2, 3) I167, P185, T184, T326, E302, V384, A305, I325, I306, R383, D307, E382, D278, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, and S168 of a human T1R2, 4) S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, and D278 of a human T1R2, 5) S40, S144, S165, Y103, D142, P277, I167, P185, T184, T326, E302, V384, A305, I325, I306, R383, D307, E382, D278, I279, I67, V66, V309, S303, T242, F103, Q328, and S168 of a human T1R2, 6) K65, R383, D307, E302, D278, I167, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, and S168 of a human T1R2, 7) S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, I167, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, and S168 of a human T1R2, 8) N143, S144, and I167 of a human T1R2, or 9) N143, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, I167, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, and S168 of a human T1R2.

In another embodiment, the present invention provides chemosensory receptor ligand enhancers capable of interacting with a chemosensory receptor in the presence of a chemosensory receptor ligand *via* one or more interacting residues of K65, D278, L279, D307, R383, V384 of a human T1R2.

In yet another embodiment, the present invention provides sucrose or sucralose enhancers capable of interacting with a chemosensory receptor in the presence of sucrose or

sucralose *via* one or more interacting residues of S40, S144, Y103, D142, P277 of a human T1R2.

In still another embodiment, the present invention provides chemosensory receptor ligand modifiers capable of interacting with a chemosensory receptor, optionally in the presence of a chemosensory receptor ligand *via* at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 interacting residues selected from the group of N143, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, I167, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, and S168 of a human T1R2.

In still another embodiment, the present invention provides chemosensory receptor ligand modifiers capable of interacting with a chemosensory receptor to stabilize a conformation, *e.g.*, semi-closed or closed conformation formed by the interaction between a chemosensory receptor and a chemosensory receptor ligand.

In still yet another embodiment, the present invention provides chemosensory receptor ligand modifiers, *e.g.,* saccharin, saccharin analogues, acesulfame K, acesulfame K analogues, or any compound capable of interacting with a chemosensory receptor *via* an interacting site that is similar to or overlaps with an interacting site used by saccharin or acesulfame K. In one example, the present invention provides chemosensory receptor ligand enhancers, *e.g.,* saccharin, saccharin analogues, acesulfame K, or acesulfame K analogues that interact with a chemosensory receptor via an interacting site including one or more interacting residues of K65, R383, D307, E302 and D278 of a human T1R2.

According to yet another aspect of the present invention, it provides chemosensory receptor modifiers. In one embodiment, it provides chemosensory receptor modifiers identified by the screen methods of the present invention. In another embodiment, it provides chemosensory receptor modifiers capable of interacting with a chemosensory receptor *via* an interacting site of the present invention. In yet another embodiment, it provides chemosensory receptor modifiers capable of interacting with a chemosensory receptor *via* one or more interacting residues of the chemosensory receptor. In still another embodiment, it provides chemosensory receptor modifiers capable of interacting with a chemosensory receptor *via* an interacting space within the Venus flytrap domain that is outlined, defined, or shaped, partially or entirely, by interacting residues of the chemosensory receptor. In still yet another embodiment,

it provides chemosensory receptor modifiers excluding, *e.g.*, natural or synthesized sweet flavor entities known prior to the present invention.

In one embodiment, the present invention provides chemosensory receptor modifiers capable of interacting with a chemosensory receptor *via* a group of interacting residues or a space within the Venus flytrap domain that is outlined, shaped, or defined, partially or entirely by the group or any subgroup of interacting residues, *e.g.*, 1) S40, S144, S165, Y103, D142, P277 of a human T1R2, 2) K65, R383, D307, E302, and D278 of a human T1R2, 3) I167, P185, T184, T326, E302, V384, A305, I325, I306, R383, D307, E382, D278, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, and S168 of a human T1R2, 4) S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, and D278 of a human T1R2, 5) S40, S144, S165, Y103, D142, P277, I167, P185, T184, T326, E302, V384, A305, I325, I306, R383, D307, E382, D278, I279, I67, V66, V309, S303, T242, F103, Q328, and S168 of a human T1R2, 6) K65, R383, D307, E302, D278, I167, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, and S168 of a human T1R2, 7) S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, I167, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, and S168 of a human T1R2, 8) N143, S144, and I167 of a human T1R2, or 9) N143, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, I167, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, and S168 of a human T1R2.

In still another embodiment, the present invention provides chemosensory receptor modifiers capable of interacting with a chemosensory receptor *via* at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 interacting residues selected from the group of N143, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, I167, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, and S168 of a human T1R2.

According to still another aspect of the present invention, it provides methods for modulating a chemosensory receptor and/or its ligand by modulating one or more interacting sites of the chemosensory receptor. For example, one can modulate a chemosensory receptor by contacting, *in vivo* or *in vitro*, a chemosensory receptor modifier or chemosensory receptor ligand modifier or both, (*e.g.*, optionally excluding natural sweet flavor entity or sweet enhancers known prior to the present invention) with cells containing the chemosensory receptor, wherein

the chemosensory receptor modifier or chemosensory receptor ligand is capable of interacting with or targeting one or more interacting sites of the chemosensory receptor.

In one embodiment, the method of modulating a chemosensory receptor and/or its ligand is by modulating one or more interacting residues or interacting spaces or a combination thereof. In another embodiment, the method of modulating a chemosensory receptor and/or its ligand is by interacting with one or more interacting residues in the presence of a chemosensory receptor ligand. In yet another embodiment, the method of modulating a chemosensory receptor or its ligand includes modulating the impact of a chemosensory receptor ligand on the chemosensory receptor by interacting with the chemosensory receptor *via* one or more interacting residues in the presence of the chemosensory receptor ligand.

In yet another embodiment, the method of modulating a chemosensory receptor and/or its ligand is by interacting with the chemosensory receptor *via* a group of interacting residues or a space outlined, shaped, or defined, partially or entirely, by the group or subgroup of interacting residues, optionally in the presence of a chemosensory receptor ligand, *e.g.*, 1) S40, S144, S165, Y103, D142, P277 of a human T1R2, 2) K65, R383, D307, E302, and D278 of a human T1R2, 3) I167, P185, T184, T326, E302, V384, A305, I325, I306, R383, D307, E382, D278, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, and S168 of a human T1R2, 4) S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, and D278 of a human T1R2, 5) S40, S144, S165, Y103, D142, P277, I167, P185, T184, T326, E302, V384, A305, I325, I306, R383, D307, E382, D278, I279, I67, V66, V309, S303, T242, F103, Q328, and S168 of a human T1R2, 6) K65, R383, D307, E302, D278, I167, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, and S168 of a human T1R2, 7) S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, I167, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, and S168 of a human T1R2, 8) N143, S144, and I167 of a human T1R2, or 9) N143, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, I167, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, and S168 of a human T1R2.

In yet another embodiment, the method of modulating a chemosensory receptor and/or its ligand is by interacting with the chemosensory receptor *via* one or more interacting residues of N143, S144, and I167 of a human T1R2.

In yet another embodiment, the method of modulating a chemosensory receptor and/or its ligand is by interacting with the chemosensory receptor, optionally in the presence of a chemosensory receptor ligand *via* one or more interacting residues of K65, D278, L279, D307, R383, V384 of a human T1R2.

In still another embodiment, the method of modulating a chemosensory receptor and/or its ligand is by interacting with the chemosensory receptor, optionally in the presence of sucrose or sucralose *via* one or more interacting residues of S40, S144, Y103, D142, P277 of a human T1R2.

In still another embodiment, the method of enhancing a chemosensory receptor and/or its ligand is by interacting with the chemosensory receptor, optionally in the presence of a chemosensory receptor ligand via one or more interacting residues of K65, D278, L279, D307, R383, V384, S40, S144, Y103, D142, P277 of a human T1R2.

In still another embodiment, the method of modulating a chemosensory receptor and/or its ligand is by interacting with the chemosensory receptor, optionally in the presence of a chemosensory receptor ligand *via* at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 interacting residues selected from the group of N143, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, I167, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, and S168 of a human T1R2.

In still another embodiment, the method of modulating a chemosensory receptor and/or its ligand is by interacting with the chemosensory receptor, optionally in the presence of a chemosensory receptor ligand *via* at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 interacting residues selected from the group of N143, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, I167, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, and S168 of a human T1R2.

According to the present invention, a method of modulating a chemosensory receptor and/or its ligand includes modulating the activity, structure, function, expression, and/or modification of a chemosensory receptor as well as modulating, treating, or taking prophylactic measure of a condition, *e.g.*, physiological or pathological condition, associated with a chemosensory receptor.

In general, a physiological or pathological condition associated with a chemosensory receptor includes a condition associated with a taste, *e.g.*, sweet, umami, bitter,

sour, salty, or a combination thereof or a condition associated with, *e.g.*, gastrointestinal system, metabolic disorders, functional gastrointestinal disorders, *etc.*

In one embodiment, the method of the present invention, *e.g.*, modulating a chemosensory receptor and/or its ligand includes modulating, increasing or decreasing a sweet or umami taste or a subject's reaction, physiological or otherwise, to a sweet or umami taste. In another embodiment, the method of the present invention, *e.g.*, modulating a chemosensory receptor and/or its ligand includes enhancing a sweet or umami taste or a subject's reaction, physiological or otherwise, to a sweet or umami taste.

In yet another embodiment, the method of the present invention, *e.g.*, modulating a chemosensory receptor and/or its ligand includes modulation, treatment, and/or prophylactic measure of a condition associated with gastrointestinal system including without any limitation conditions associated with esophageal motility (*e.g.*, cricopharyngeal achalasia, globus hystericus, achalasia, diffuse esophageal spasm and related motor disorders, scleroderma involving the esophagus, *etc.*), inflammatory disorders (*e.g.*, gastroesophageal reflux and esophagitis, infectious esophagitis, *etc.*), peptic ulcer, duodenal ulcer, gastric ulcer, gastrinoma, stress ulcers and erosions, drug-associated ulcers and erosions, gastritis, esophageal cancer, tumors of the stomach, disorders of absorption (*e.g.*, absorption of specific nutrients such as carbohydrate, protein, amino acid, fat, cholesterol and fat-soluble vitamins, water and sodium, calcium, iron, water-soluble vitamins, *etc.*), disorders of malabsorption, defects in mucosal function (*e.g.*, inflammatory or infiltrative disorders, biochemical or genetic abnormalities, endocrine and metabolic disorders, protein-losing enteropathy, *etc.*), autoimmune diseases of the digestive tract (*e.g.*, celiac disease, Crohn's disease, ulcerative colitis, *etc.*), irritable bowel syndrome, inflammatory bowel disease, complications of inflammatory bowel disease, extraintestinal manifestations of inflammatory bowel disease, disorders of intestinal motility, vascular disorders of the intestine, anorectial disorders (*e.g.*, hemorrhoids, anal inflammation, *etc.*), colorectal cancer, tumors of the small intestine, cancers of the anus, derangements of hepatic metabolism, hyperbilirubinemia, hepatitis, alcoholic liver disease and cirrhosis, biliary cirrhosis, neoplasms of the liver, infiltrative and metabolic diseases affecting the liver (*e.g.*, fatty liver, reye's syndrome, diabetic glycogenosis, glycogen storage disease, Wilson's disease, hemochromatosis), diseases of the gallbladder and bile ducts, disorders of the pancreas (*e.g.*,

pancreatitis, pancreatic exocrine insufficiency, pancreatic cancer, *etc.*), endocrine tumors of the gastrointestinal tract and pancreas, *etc.*

In still another embodiment, the method of the present invention, *e.g.,* modulating a chemosensory receptor and/or its ligand includes modulation, treatment, and/or prophylactic measure of a condition associated with metabolic disorders, *e.g.*, appetite, body weight, food or liquid intake or a subject's reaction to food or liquid intake, or state of satiety or a subject's perception of a state of satiety, nutrition intake and regulation, (*e.g.*, protein-energy malnutrition, physiologic impariements associated with protein-energy malnutrition, *etc.*), obesity, secondary obsesity (*e.g.*, hypothyroidism, Cushing's disease, insullinoma, hypothalamic disorders, *etc.*), eating disorders (*e.g.*, anorexia nervosa, bulimia, *etc.*), vitamin deficiency and excess, insulin metabolism, diabetes (type I and type II) and complications thereof (*e.g.*, circulatory abnormalities, retinopathy, diabetic nephropathy, diabetic neuropathy, diabetic foot ulcers, *etc.*), glucose metabolism, fat metabolism, hypoglycemia, hyperglycermia, hyperlipoproteinemias, *etc.*

In still yet another embodiment, the method of the present invention, *e.g.*, modulating a chemosensory receptor and/or its ligand includes modulation, treatment, and/or prophylactic measure of a condition associated with functional gastrointestinal disorders, *e.g.*, in the absence of any particular pathological condition such as peptic ulcer and cancer, a subject has abdominal dyspepsia, *e.g.*, feeling of abdominal distention, nausea, vomiting, abdominal pain, anorexia, reflux of gastric acid, or abnormal bowel movement (constipation, diarrhea and the like), optionally based on the retention of contents in gastrointestinal tract, especially in stomach. In one example, functional gastrointestinal disorders include a condition without any organic disease of the gastrointestinal tract, but with one or more reproducible gastrointestinal symptoms that affect the quality of life of a subject, *e.g.*, human.

Exemplary functional gastrointestinal disorders include, without any limitation, functional dyspepsia, gastroesophageal reflux condition, diabetic gastroparesis, reflux esophagitis, postoperative gastrointestinal dysfunction and the like, nausea, vomiting, sickly feeling, heartburn, feeling of abdominal distention, heavy stomach, belching, chest writhing, chest pain, gastric discomfort, anorexia, dysphagia, reflux of gastric acid, abdominal pain, constipation, diarrhea, breathlessness, feeling of smothering, low incentive or energy level, pharyngeal obstruction, feeling of foreign substance, easy fatigability, stiff neck, myotonia, mouth dryness (dry mouth, thirst, *etc.*) tachypnea, burning sensation in the gastricintestinal tract,

cold sensation of extremities, difficulty in concentration, impatience, sleep disorder, headache, general malaise, palpitation, night sweat, anxiety, dizziness, vertigo, hot flash, excess sweating, depression, *etc.*

In still yet another embodiment, the method of the present invention, *e.g.*, modulating a chemosensory receptor and/or its ligand includes increasing or promoting digestion, absorption, blood nutrient level, and/or motility of gastrointestinal tract in a subject, *e.g.*, promotion of gastric emptying (*e.g.*, clearance of stomach contents), reduction of abdominal distention in the early postprandial period, improvement of anorexia, *etc.* In general, such promotion can be achieved either directly or *via* increasing the secretion of a regulatory entity, *e.g.*, hormones, *etc.*

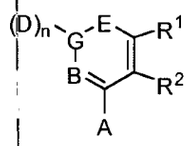
In still yet another embodiment, the method of the present invention, *e.g.*, modulating a chemosensory receptor and/or its ligand includes increasing one or more gastrointestinal functions of a subject, *e.g.*, to improve the quality of life or healthy state of a subject.

In still yet another embodiment, the method of the present invention, *e.g.*, modulating a chemosensory receptor and/or its ligand includes modulating the activity of T1R (*e.g.*, T1R1, T1R2, or T1R3) expressing cells, *e.g.*, liver cells (*e.g.*, hepatocytes, endothelial cells, Kupffer cells, Stellate cells, epithelial cells of bile duct, *etc.*), heart cells (*e.g.*, endothelial, cardiac, and smooth muscle cells, *etc.*), pancreatic cells (*e.g.*, alpha cell, beta cell, delta cell, neurosecretory PP cell, D1 cell, *etc.*), cells in the nipple (*e.g.*, ductal epithelial cells, *etc.*), stomach cells (*e.g.*, mucous cells, parietal cells, chief cells, G cells, P/D1 cells), intestinal cells (*e.g.*, enteroendocrine cells, brush cells, *etc.*), salivary gland cells (*e.g.*, Seromucous cells, mucous cells, myoepithelial cells, intercalated duct cell, striated duct cell, *etc.*), L cells (*e.g.*, expressing GLP-1, *etc.*), enterochromaffin cells (*e.g.*, expressing serotonin), enterochromaffin-like cells, G cells (*e.g.*, expressing gastrin), D cells (delta cells, *e.g.*, expressing somatostatin), I cells (*e.g.*, expressing cholescystokinin (CCK), K cells (*e.g.*, expressing gastric inhibitory polypeptide), P/D1 cells (*e.g.*, expressing ghrelin), chief cells (*e.g.*, expressing pepsin), and S cells (*e.g.*, expressing secretin). In one example, the method of the present invention includes increasing the expression level of T1R in T1R expressing cells. In another example, the method of the present invention includes increasing the secretion level of T1R expressing cells.

In still yet another embodiment, the method of the present invention, *e.g.*, modulating a chemosensory receptor and/or its ligand includes modulating the expression, secretion, and/or functional level of T1R expressing cells associated with hormone, peptide, enzyme producing. In one example, the method of the present invention includes modulating the level of glucose, *e.g.*, inhibitors of a chemosensory receptor such as T1R2 can be used to decrease glucose level (*e.g.*, glucose absorption) in a subject. In another example, the method of the present invention includes modulating the level of incretins, *e.g.*, agonist of a chemosensory receptor such as T1R2 can be used to increase glucagons-like peotide 1 (GLP-1) and thus increase the production of insulin. In yet another example, the method of the present invention includes modulating the expression, secretion, and/or activity level of hormones or peptides produced by T1R expressing cells or gastrointestinal hormone producing cells, *e.g.*, ligands for 5HT receptors (*e.g.*, serotonin), incretins (*e.g.*, GLP-1 and glucose-dependent insulinotropic polypeptide (GIP)), gastrin, secretin, pepsin, cholecystokinin, amylase, ghrelin, leptin, somatostatin, *etc.* In still another example, the method of the present invention includes modulating the pathways associated with hormones, peptides, and/or enzymes secreted by T1R expressing cells.

Exemplary chemosensory receptor ligand modifiers provided by the present invention and/or suitable to be used for methods of the present invention include compounds of the following formulae.

In one embodiment of the present invention, the chemosensory receptor ligand modifier is a compound having a structural Formula (I):



(I)

or a tautomer, salt, solvate, and/or ester thereof, wherein:

G forms a single bond with either D or E and a double bond with the other of D or E;

R^1 is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, $-NO_2$, $-OR^3$, $-S(O)_aR^3$, $-NR^3R^4$, $-CONR^3R^4$, $-CO_2R^3$, $-NR^3CO_2R^4$, $-NR^3CONR^4R^5$, $-NR^3CSNR^4R^5$, $-NR^3C(=NH)NR^4R^5$,

$-SO_2NR^3R^4$, $-NR^4SO_2R^3$, $-NR^3SO_2NR^4R^5$, $-B(OR^3)(OR^4)$, $-P(O)(OR^3)(OR^4)$ or $-P(O)(R^3)(OR^4)$;

R^2 is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, $-NO_2$, $-OR^6$, $-S(O)_bR^6$, $-NR^6R^7$, $-CONR^6R^7$, $-CO_2R^6$, $-NR^6CO_2R^7$, $-NR^6CONR^7R^8$, $-NR^6CSNR^7R^8$, $-NR^6C(=NH)NR^7R^8$, $-SO_2NR^5R^6$, $-NR^5SO_2R^6$, $-NR^5SO_2NR^6R^7$, $-B(OR^5)(OR^6)$, $-P(O)(OR^5)(OR^6)$, or $-P(O)(R^5)(OR^6)$; or alternatively, R^1 and R^2, together with the atoms to which they are bonded, form an aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring wherein the ring is optionally fused to another aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring;

with the proviso that R^1 and R^2 are not both hydrogen;

A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, halo, -CN, $-NO_2$, $-OR^9$, $-S(O)_cR^9$, $-NR^9COR^{10}$, $-NHOR^9$, $-NR^9R^{10}$, $-NOR^9$, $-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$, $-NR^9C(=NH)NR^{10}R^{11}$, $-B(OR^{10})(OR^{11})$, $-P(O)(OR^{10})(OR^{11})$ or $-P(O)(R^{10})(OR^{11})$;

B is -N- or $-C(R^{12})-$;

R^{12} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, $-NR^{13}R^{14}$, -CN, $-OR^{13}$, $-S(O)_dR^{13}$, $-CO_2R^{13}$ or $-CONR^{13}R^{14}$;

G is -C- or $-S(O)_2-$;

provided that when G is $-S(O)_2-$, then G forms a single bond with E;

when the bond between D and G is a single bond, then D is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, $-OR^{15}$, -NH-OR^{15}, $-S(O)_eR^{15}$, $-NR^{15}R^{16}$, -NH-NHR^{15}, $-CO_2R^{15}$, or $-CONR^{15}R^{16}$;

when G forms a double bond with D, then D is =O, =S , =N-OR^{15}, or =N-NHR^{15};

n is 0 when G is $-S(O)_2-$, and n is 1 when G is -C-;

E is $-NR^{17}-$, -N- or $-C(R^{18})-$;

provided that E is $-NR^{17}-$ only when G forms a single bond with E;

R^{17} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl or $-CO_2R^{19}$;

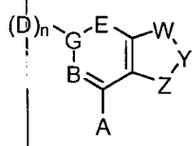
R^{18} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, $-NR^{20}R^{21}$, -CN, $-OR^{20}$, $-S(O)_fR^{20}$, $-CO_2R^{20}$ or $-CONR^{20}R^{21}$;

a, b, c, d, e and f are independently 0, 1 or 2; and

R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{13}, R^{14}, R^{15}, R^{16}, R^{18}, R^{20}, and R^{21} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl; or alternatively, R^3 and R^4, R^4 and R^5, R^6 and R^7, R^7 and R^8, R^9 and R^{10}, R^{10} and R^{11}, R^{13} and R^{14}, R^{15} and R^{16}, or R^{20} and R^{21}, together with the atoms to which they are bonded, form a cycloheteroalkyl or substituted cycloheteroalkyl ring.

In one embodimentof Formula (I), R^1 and R^2, together with the atoms to which they are bonded, form an aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring where the ring is optionally fused to another aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring.

In one embodimentof Formula (I), the chemosensory receptor ligand modifier is a compound having a structural Formula (II),



(II)

wherein:

Y forms a single bond with either W or Z and a double bond with the other of W or Z;

W is $-C(R^{24})-$, -S-, -N-, $-N(R^{25})-$, or -O-;

Y is -C(R^{26})- or -N-;

Z is -C(R^{27})-, -S-, -N-, -N(R^{28})-, or -O-;

R^{24} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl -CN, -NO_2, -OR^{29}, -$S(O)_gR^{29}$, -$NR^{29}R^{30}$, -$CONR^{29}R^{30}$, -CO_2R^{29}, -$SO_2NR^{29}R^{30}$, -$NR^{29}SO_2R^{30}$, -$B(OR^{29})(OR^{30})$, -$P(O)(OR^{29})(OR^{30})$ or -$P(O)(R^{29})(OR^{30})$;

R^{26} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl -CN, -NO_2, -OR^{31}, -$S(O)_hR^{31}$, -$NR^{31}R^{32}$, -$CONR^{31}R^{32}$, -CO_2R^{31}, -$OCOR^{31}$, -$SO_2NR^{31}R^{32}$, -$NR^{31}SO_2R^{32}$, -$B(OR^{31})(OR^{32})$, -$P(O)(OR^{31})(OR^{32})$ or -$P(O)(R^{31})(OR^{32})$;

R^{27} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl -CN, -NO_2, -OR^{33}, -$S(O)_iR^{33}$, -$NR^{33}R^{34}$, -$CONR^{33}R^{34}$, -COR^{33}, -CO_2R^{33}, -$OCOR^{33}$, -$SO_2NR^{33}R^{34}$, -$NR^{33}SO_2R^{34}$, -$B(OR^{33})(OR^{34})$, -$P(O)(OR^{33})(OR^{34})$ or -$P(O)(R^{33})(OR^{34})$; or alternatively R^{24} and R^{26} or R^{26} and R^{27} together with the atoms to which they are bonded form a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring;

g, h and i are independently 0 or 1;

R^{25} and R^{28} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl; and

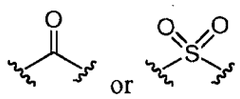
R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, and R^{34} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl; or alternatively R^{29} and R^{30}, R^{31} and R^{32}, or R^{33} and R^{34} together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring; and

with the following provisos:

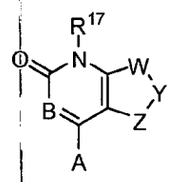
(a) when W is -O- or -S- or -NR^{25}, then Z is –C(R^{27}) or -N-; and

(b) when Z is -O- or -S- or -NR^{28}, then W is -C(R^{24}) or -N-.

In one embodiment of Formula (II), $(D)_n$-G is

 or .

In one embodiment of Formula (II), the compound of the present invention has structural Formula (IIa):



(IIa)

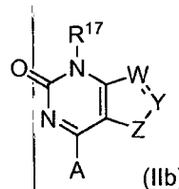
with the following provisos:

(a) when W is -O- or -S- or $-NR^{25}$, then Z is $-C(R^{27})$ or -N-;

(b) when Z is -O- or -S- or $-NR^{28}$, then W is $-C(R^{24})$ or -N-; and

(c) when B is -N-, then A is not halo.

In one embodiment of Formula (IIa), the compound of the present invention has structural Formula (IIb):



(IIb)

wherein, W is $-C(R^{24})$- or -N-; Y is $-C(R^{26})$- or -N-; and Z is -S-, $-N(R^{28})$- or -O-.

In one embodiment of Formula (IIb), W is -C(R24)-, and Y is -C(R26)-.

In one embodiment of Formula (IIb), W is $-C(R^{24})$-; Y is $-C(R^{26})$-; R^{24} is hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, -CN, $-NO_2$, $-OR^{29}$, $-S(O)_gR^{29}$, $-OCOR^{29}$, $-NR^{29}R^{30}$, $-CONR^{29}R^{30}$ or $-CO_2R^{29}$; and R^{26} is hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, -CN, $-NO_2$, $-OR^{31}$, $-OCOR^{31}$, $-S(O)_hR^{31}$, $-NR^{31}R^{32}$, $-CONR^{31}R^{32}$or $-CO_2R^{31}$. In a preferred embodiment, R^{24} is hydrogen, $-CF_3$, alkyl or substituted alkyl; and R^{26} is hydrogen, $-CF_3$, alkyl or substituted alkyl.

In one embodiment of Formula (IIb), W is $-C(R^{24})$-; and Y is $-C(R^{26})$-; A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, -CN, $-NO_2$, $-S(O)_cR^9$, $-NR^9R^{10}$,

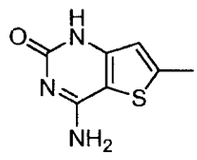
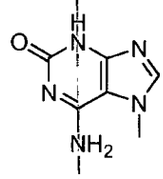
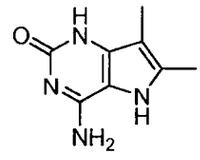
$-CONR^9R^{10}$, $-CO_2R^9$ or $-NR^9CO_2R^{10}$; R^{17} is hydrogen, alkyl, substituted alkyl, arylalkyl, or substituted arylalkyl; R^{24} is hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, -CN, $-NO_2$, $-OR^{29}$, $-S(O)_gR^{29}$, $-OCOR^{29}$, $-NR^{29}R^{30}$, $-CONR^{29}R^{30}$ or $-CO_2R^{29}$; and R^{26} is hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, -CN, $-NO_2$, $-OR^{31}$, $-S(O)_hR^{31}$, $-OCOR^{31}$, $-NR^{31}R^{32}$, $-CONR^{31}R^{32}$or $-CO_2R^{31}$.

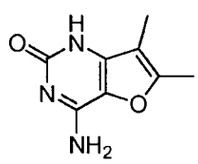
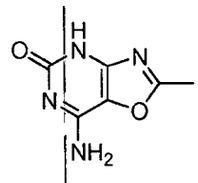
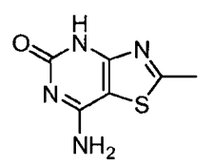
In one embodiment of Formula (IIb), W is $-C(R^{24})-$; and Y is $-C(R^{26})-$; A is $-NR^9COR^{10}$, $-NHOR^9$, $-NR^9R^{10}$, $-NOR^9$, $-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-OR^9$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$ or $-NR^9C(=NH)NR^{10}R^{11}$; R^{17} is hydrogen, alkyl, substituted alkyl, arylalkyl, or substituted arylalkyl; R^{24} is hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, -CN, $-NO_2$, $-OR^{29}$, $-S(O)_gR^{29}$, $-OCOR^{29}$, $-NR^{29}R^{30}$, $-CONR^{29}R^{30}$ or $-CO_2R^{29}$; and R^{26} is hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, -CN, $-NO_2$, $-OR^{31}$, $-S(O)_hR^{31}$, $-OCOR^{31}$, $-NR^{31}R^{32}$, $-CONR^{31}R^{32}$or $-CO_2R^{31}$. In a preferred embodiment, A is -OH, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHOCH_3$, $-NOCH_3$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$ or $-CH_2NHC(O)CH_3$; R^{17} is hydrogen, methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *t*-butyl, phenyl or benzyl; and R^{24} is hydrogen, $-CF_3$, methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl or *t*-butyl; and R^{26} is hydrogen, $-CF_3$, methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl or *t*-butyl. In a more preferred embodiment, A is $-NH_2$, R^{17} is hydrogen or methyl, R^{24} is hydrogen, $-CF_3$, methyl or ethyl, and R^{26} is hydrogen, $-CF_3$, methyl or ethyl.

In some embodiments of Formula (IIb), R^{28} is hydrogen, alkyl or arylalkyl.

In some embodiments of Formula (IIb), R^{28} is hydrogen, methyl or benzyl.

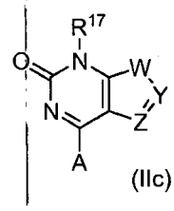
In some specific embodiments of Formula (IIb), the compounds have structural formula selected from the group consisting of:


, 
, 
,



, and

;

or a tautomer, salt, solvate, and/or ester thereof. In some preferred embodiments, the salt of these compounds is hydrochloride or trifluoroacetate salt.

In one embodiment of Formula (IIa), the compound of the present invention has structural Formula (IIc):


(IIc)

wherein, W is -S-, -N(R^{25})-, or -O-; Y is -C(R^{26})- or -N-; and Z is -C(R^{27})- or -N-. In a preferred embodiment, Y is -C(R^{26})-, and Z is -C(R^{27})-.

In one embodiment of Formula (IIa), W is -S-, -N(R^{25})-, or -O-; Y is -C(R^{26})- or -N-; Z is -C(R^{27})- or -N-; R^{27} is hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, -CN, -NO_2, -OR^{33}, -$S(O)_iR^{33}$, -$OCOR^{33}$, -$NR^{33}R^{34}$, -$CONR^{33}R^{34}$ or -CO_2R^{33}; and R^{26} is hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, -CN, -NO_2, -$OR^{31,}$ -$S(O)_hR^{31,}$ -$OCOR^{31,}$ -$NR^{31}R^{32}$, -$CONR^{31}R^{32}$ or -CO_2R^{31}.

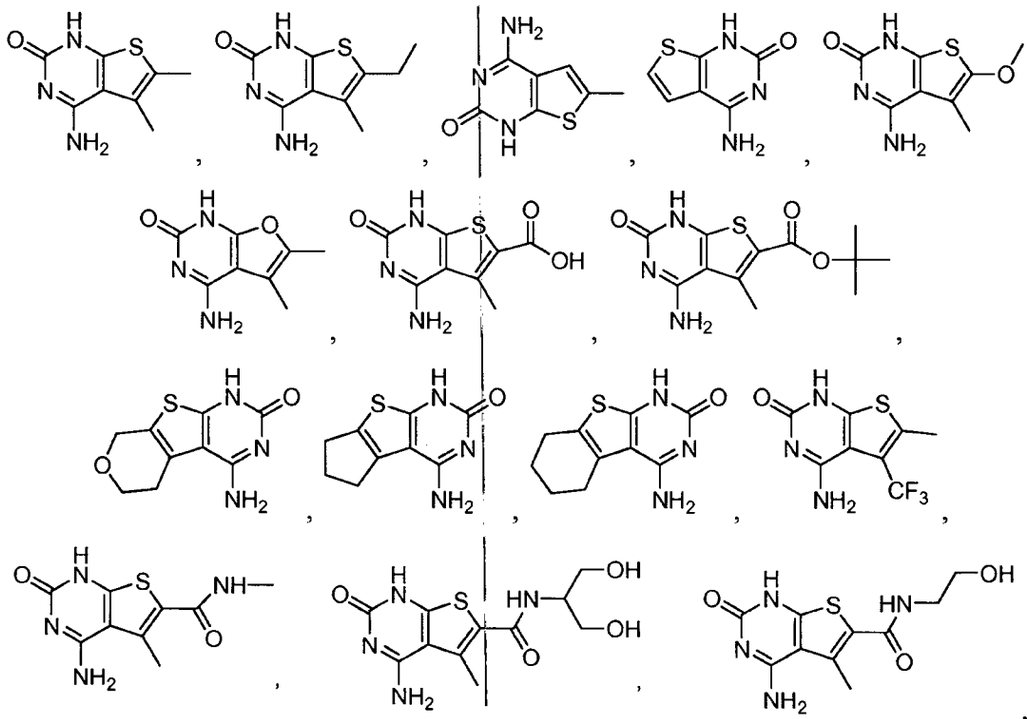
In one embodiment of Formula (IIa), W is -S-, -N(R^{25})-, or -O-; Y is -C(R^{26})- or -N-; Z is -C(R^{27})- or -N-; R^{26} and R^{27} together with the atom to which they are bonded form a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring.

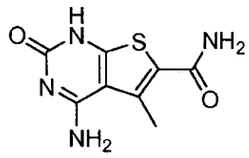
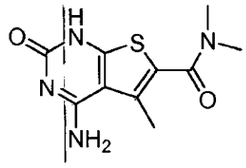
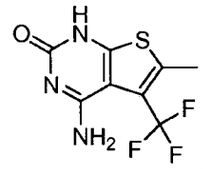
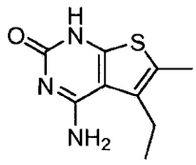
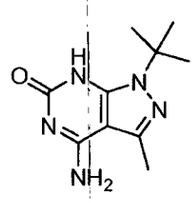
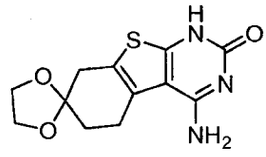
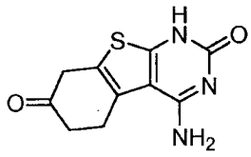
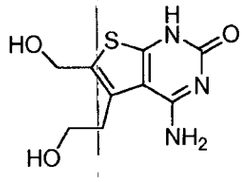
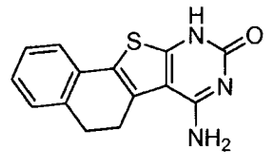
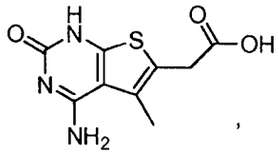
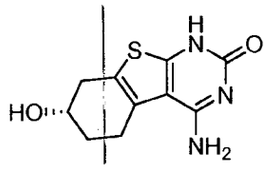
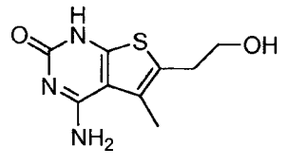
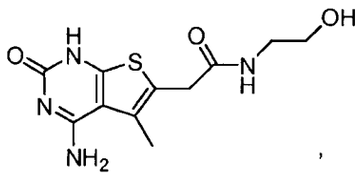
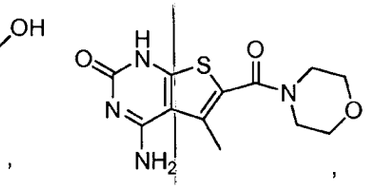
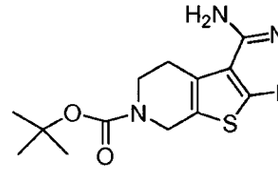
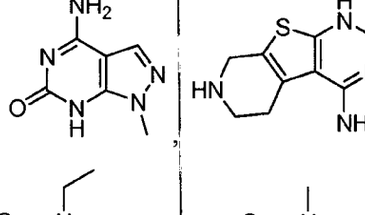
In one embodiment of Formula (IIa), W is -S-, -N(R^{25})-, or -O-; Y is -C(R^{26})- or -N-; Z is -C(R^{27})- or -N-; A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, -NR^9COR^{10}, -$NHOR^9$, -NOR^9, -OR^9, -$NR^9CONR^{10}R^{11}$, -$NR^9CSNR^{10}R^{11}$ or -$NR^9C(=NH)NR^{10}R^{11}$, -CN, -NO_2, -$S(O)_cR^9$, -NR^9R^{10}, -$C(O)NR^9R^{10}$, -CO_2R^9 or -$NR^9CO_2R^{10}$; and R^{17} is hydrogen, alkyl, substituted alkyl, arylalkyl, or substituted arylalkyl.

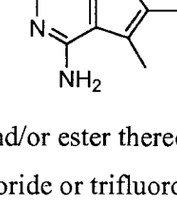
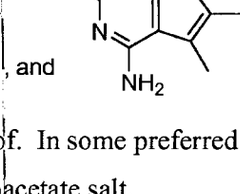
In one embodiment of Formula (IIa), W is -S-, -N(R^{25})-, or -O-; Y is -C(R^{26})- or -N-; Z is -C(R^{27})- or -N-; A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, -NR^9COR^{10}, -$NHOR^9$, -NOR^9, -OR^9, -$NR^9CONR^{10}R^{11}$, -$NR^9CSNR^{10}R^{11}$ or

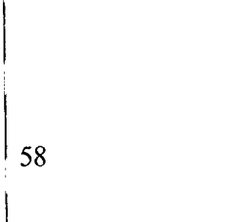
$-NR^9C(=NH)NR^{10}R^{11}$, -CN, $-NO_2$, $-S(O)_cR^9$, $-NR^9R^{10}$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-CO_2R^9$ or $-NR^9CO_2R^{10}$; R^{17} is hydrogen, alkyl, substituted alkyl, arylalkyl, or substituted arylalkyl; R^{27} is hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, -CN, $-NO_2$, $-OR^{33}$, $-S(O)_iR^{33}$, $-OCOR^{33}$, $-NR^{33}R^{34}$, $-C(O)NR^{33}R^{34}$ or $-CO_2R^{33}$; and R^{26} is hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, -CN, $-NO_2$, $-OR^{31}$, $-S(O)_hR^{31}$, $-OC(O)R^{31}$, $-NR^{31}R^{32}$, $-C(O)NR^{31}R^{32}$or $-CO_2R^{31}$, or alternatively R^{26} and R^{27} together with the atom(s) to which they are bonded form a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring. In a more preferred embodiment, A is $-NH_2$; R^{17} is hydrogen, methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *t*-butyl, phenyl or benzyl; R^{26} and R^{27} are independently hydrogen, alkanyl, substituted alkanyl, alkoxy, carboxylic acid, carboxylic acid amide, or carboxylic acid ester; or alternatively, R^{26} and R^{27} together with the atom(s) to which they are bonded form a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring.

In some specific embodiments of Formula (IIa), the compounds have structural formula selected from the group consisting of:




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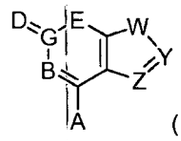
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or a tautomer, salt, solvate, and/or ester thereof. In some preferred embodiments, the salt of these compounds is hydrochloride or trifluoroacetate salt.

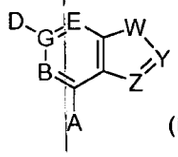
In one embodiment of Formula (II), the compound of the present invention has structural Formula (IIe):



(IIe)

wherein, G forms a single bond with E and a double bond with D; B is -N-; E is -NR^{17}-; D is =S , =N-OR^{15}, or =N-NHR^{15}; W is -S-, -N(R^{25})- or -O-; Y is -C(R^{26})-; and Z is -C(R^{27})-.

In one embodiment of Formula (II), the compound of the present invention has structural Formula (IIf):



(IIf)

wherein,

G forms a double bond with E and a single bond with D;

B is -N-;

E is -N-;

D is -OR^{15}, -NH-OR^{15}, -NH-NHR^{15}, -$S(O)_eR^{15}$, or -$NR^{15}R^{16}$;

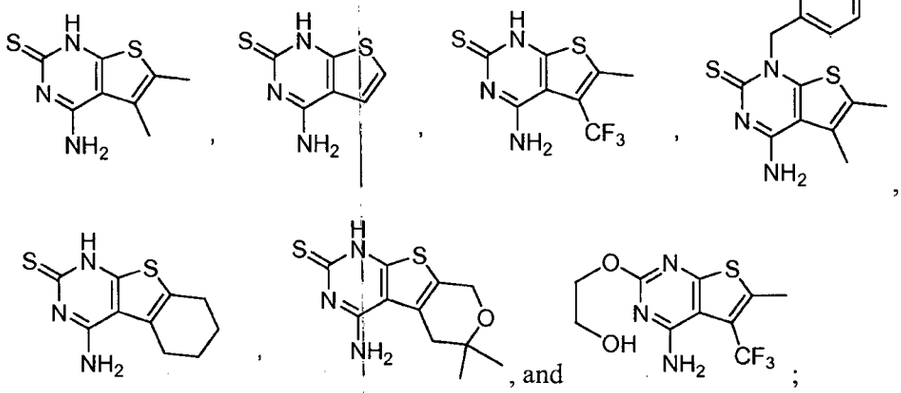
W is -S-, -N(R^{25})- or -O-;

Y is -C(R^{26})-; and

Z is -C(R^{27})-.

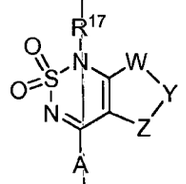
In one embodiment of Formula (IIe) or (IIf), A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, -OR^9, -SR^9, -CN, -NR^9R^{10}, -$CONR^9R^{10}$, -CO_2R^9, -$NR^9CO_2R^{10}$, -$NR^9CONR^{10}R^{11}$, -$NR^9CSNR^{10}R^{11}$ or –$NR^9C(=NH)NR^{10}R^{11}$. More preferably, R^{17} is hydrogen, alkyl, substituted alkyl, arylalkyl, or substituted arylalkyl; R^{26} and R^{27} are independently hydrogen, alkanyl, substituted alkanyl, alkoxy; or alternatively, R^{26} and R^{27} together with the atom(s) to which they are bonded form a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring.

In some specific embodiments of Formula (IIe) or (IIf), the compound of the present invention has structural formula selected from the group consisting of



or a tautomer, salt, solvate, and/or ester thereof. In some preferred embodiments, the salt of these compounds is hydrochloride or trifluoroacetate salt.

In a embodiment of Formula (II), the compound of the present invention has structural Formula (IId):



(IId)

with the following provisos:

(a) when W is -O- or -S- or -NR^{25}, then Z is –$C(R^{27})$ or -N-; and

(b) when Z is -O- or -S- or -NR^{28}, then W is -$C(R^{24})$ or -N-.

In a embodiment of Formula (IId), W is -S-, NR^{25}, -O-; Y is -CR^{26}-; Z is -$C(R^{27})$-; and W and Y forms a single bond and Y and Z forms a double bond.

In a embodiment of Formula (IId), W is -$C(R^{24})$-; Y is -CR^{26}-; Z is -S-, -NR^{28}-, -O-; and W and Y forms a double bond and Y and Z forms a single bond.

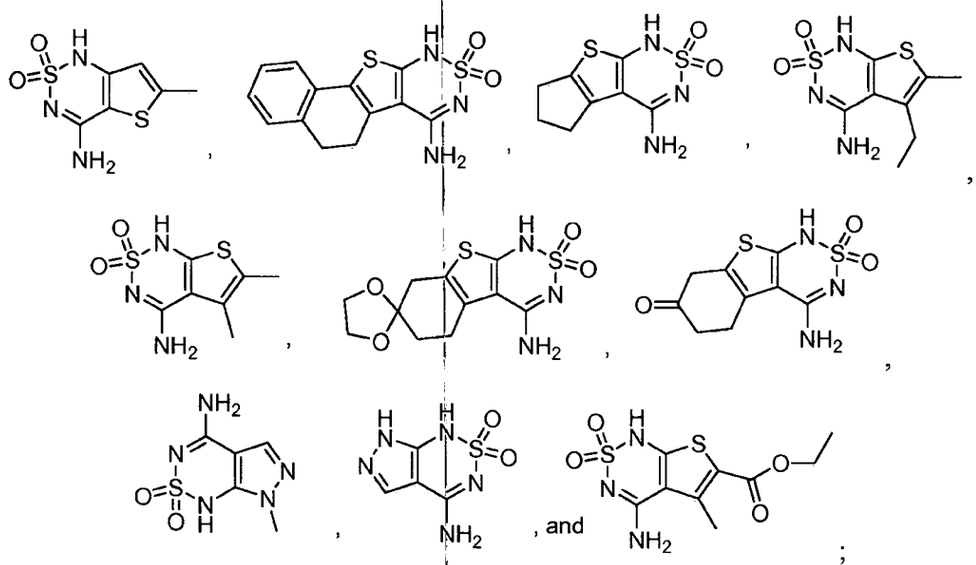
In a embodiment of Formula (IId), W is -S-, NR^{25}, -O-; Y is -N-; Z is -$C(R^{27})$-; and W and Y forms a single bond and Y and Z forms a double bond.

In a embodiment of Formula (IId), W is - NR^{25}; Y is -N-; and Z is -$C(R^{27})$-; and Y forms a single bond with each of W and a double bond with Z.

In some embodiments of Formula (IId), A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, -OR^9, -SR^9, -CN, -NR^9R^{10}, -$CONR^9R^{10}$, -CO_2R^9, -$NR^9CO_2R^{10}$, -$NR^9CONR^{10}R^{11}$, -$NR^9CSNR^{10}R^{11}$ or -$NR^9C(=NH)NR^{10}R^{11}$. Preferably, R^{17} is hydrogen. More

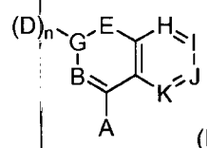
preferably, R^{26} and R^{27} are independently hydrogen, alkanyl, substituted alkanyl, alkoxy, carboxylic acid, carboxylic acid ester; or alternatively, R^{26} and R^{27} together with the atom(s) to which they are bonded form a cycloalkyl or substituted cycloalkyl ring.

In some specific embodiments of Formula (IId), the compound of the present invention has structural formula selected from the group consisting of:



or a tautomer, salt, solvate, and/or ester thereof. In some preferred embodiments, the salt of these compounds is hydrochloride salt or trifluoroacetate salt.

In one embodimentof Formula (I), the chemosensory receptor ligand modifier is a compound having a structural Formula (III):



(III)

wherein:

H is -C(R^{35})- or -N-;

I is -C(R^{36}) or -N-;

J is -C(R^{37})- or -N-;

K is -C(R^{38})- or -N-;

R^{35} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted

heteroaryl, heteroarylalkyl or substituted heteroarylalkyl, -CN, -NO_2, -OR^{39}, -$S(O)_jR^{39}$, -$NR^{39}R^{40}$, -$CONR^{39}R^{40}$, -CO_2R^{39}, -$SO_2NR^{39}R^{40}$, -$NR^{39}SO_2R^{40}$, -$B(OR^{39})(OR^{40})$, -$P(O)(OR^{39})(OR^{40})$ or -$P(O)(R^{39})(OR^{40})$;

R^{36} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl, -CN, -NO_2, -OR^{41}, -$S(O)_kR^{41}$, -$NR^{41}R^{42}$, -$CONR^{41}R^{42}$, -CO_2R^{41}, -$OCOR^{41}$, -$SO_2NR^{41}R^{42}$, -$NR^{41}SO_2R^{42}$, -$B(OR^{41})(OR^{42})$, -$P(O)(OR^{41})(OR^{42})$ or -$P(O)(R^{41})(OR^{42})$;

R^{37} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl ,-CN, -NO_2, -OR^{43}, -$S(O)_lR^{43}$, -$NR^{43}R^{44}$, -$CONR^{43}R^{44}$, -CO_2R^{43}, -$OCOR^{43}$, -$SO_2NR^{43}R^{44}$, -$NR^{43}SO_2R^{44}$, -$B(OR^{43})(OR^{44})$, -$P(O)(OR^{43})(OR^{44})$ or -$P(O)(R^{43})(OR^{44})$; or alternatively R36 and R37, taken togerther with the atom to which they are bonded, form a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, or substituted cycloheteroalkyl ring;

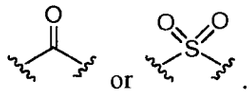
R^{38} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl, -CN, -NO_2, -OR^{45}, -$S(O)_mR^{45}$, -$NR^{45}R^{46}$, -$CONR^{45}R^{46}$, -COR^{45}, -CO_2R^{45}, -$OCOR^{45}$, -$SO_2NR^{45}R^{46}$, -$NR^{45}SO_2R^{46}$, -$B(OR^{45})(OR^{46})$, -$P(O)(OR^{45})(OR^{46})$ or -$P(O)(R^{45})(OR^{46})$;

j, k, l and m are independently 0, 1 or 2; and

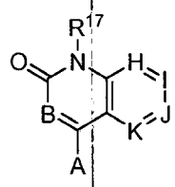
R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, and R^{46} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl or alternatively R^{39} and R^{40}, R^{41} and R^{42}, R^{43} and R^{44}, or R^{45} and R^{46} together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

with the proviso that at most, two of H, I, J and K are -N-. By "at most two of H, I, J and K are –N-", it is meant that there are zero nitrogen atom, one nitrogen atom, or two nitrogn atoms among H, I, J and K.

In one embodiment of Formula (III), $(D)_n$-G is



In one embodiment of Formula (III), the compound of the present invention has structural Formula (IIIa):



(IIIa)

In one embodiment of Formula (IIIa), A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, $-OR^9$, $-NO_2$, $-S(O)_cR^9$, $-NHOR^9$, $-NR^9COR^{10}$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$, or $-NR^9C(=NH)NR^{10}R^{11}$. Preferably, A is -OH, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHOCH_3$, $-NOCH_3$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$ or $-CH_2NHC(O)CH_3$.

In one embodiment of Formula (IIIa), R^{17} is hydrogen, alkyl, substituted alkyl, arylalkyl, or substituted arylalkyl. Preferably, R^{17} is hydrogen, methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *t*-butyl, phenyl or benzyl.

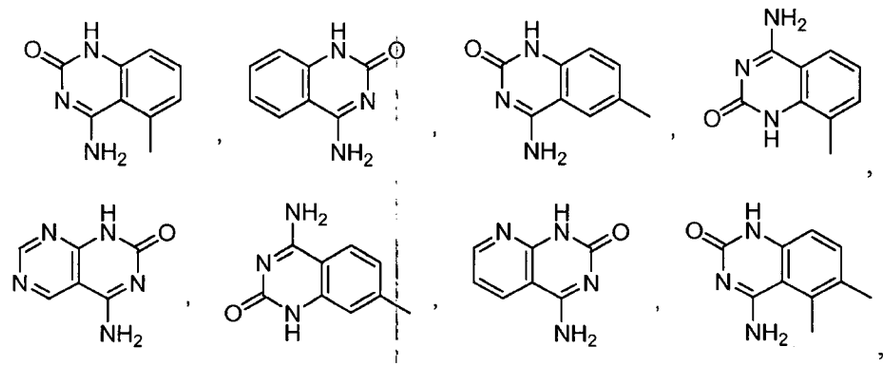
In one embodiment of Formula (IIIa), H is $-C(R^{35})-$; I is $-C(R^{36})$; J is $-C(R^{37})-$; and K is $-C(R^{38})-$.

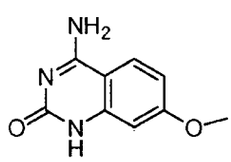
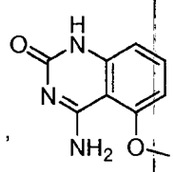
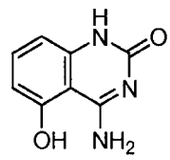
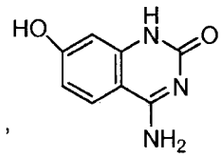
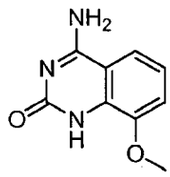
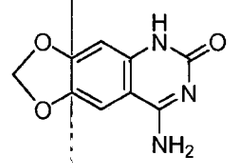
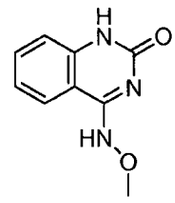
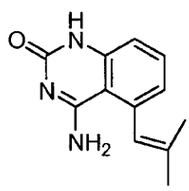
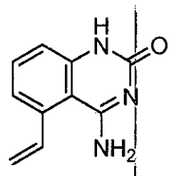
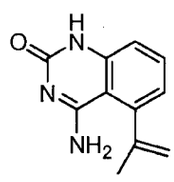
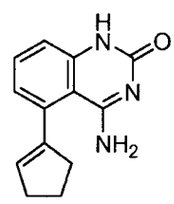
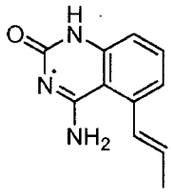
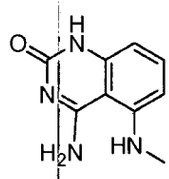
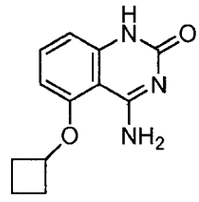
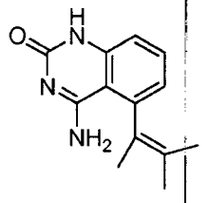
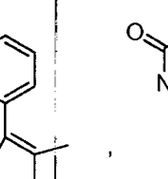
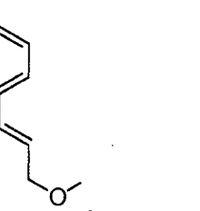
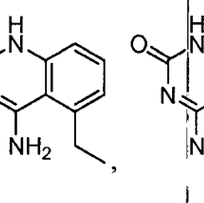
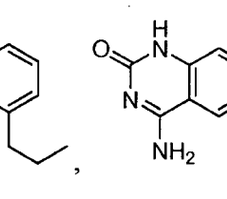
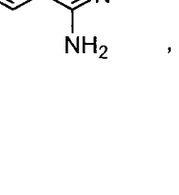
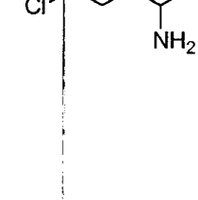
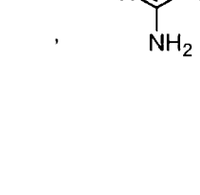
In one embodiment of Formula (IIIa), A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, -CN, $-OR^9$, $-NO_2$, $-S(O)_cR^9$, $-NHOR^9$, $-NR^9COR^{10}$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$ or $-NR^9CO_2R^{10}$; and R^{17} is hydrogen, alkyl, substituted alkyl, arylalkyl, or substituted arylalkyl.

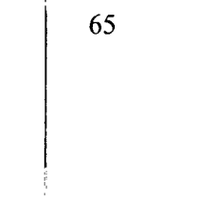
In one embodiment of Formula (IIIa), A is -OH, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHOCH_3$, $-NOCH_3$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$ or $-CH_2NHC(O)CH_3$; and R^{17} is hydrogen, methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *t*-butyl, phenyl or benzyl.

In one embodiment of Formula (IIIa), R^{35} is hydrogen, alkyl, substituted alkyl, halo, heteroalkyl, substituted heteroalkyl, -CN, $-NO_2$, $-OR^{39}$, $-S(O)_jR^{39}$, $-OCOR^{39}$, $-NR^{39}COR^{40}$, $-CONR^{39}R^{40}$, $-CO_2R^{39}$, $NR^{39}R^{40}$, $-SO_2NR^{39}R^{40}$, or-$NR^{39}SO_2R^{40}$; R^{36} is hydrogen, alkyl, substituted alkyl, halo, heteroalkyl, substituted heteroalkyl, -CN, $-NO_2$, $-OR^{41}$, $-S(O)_jR^{41}$, $-OCOR^{41}$, $NR^{41}R^{42}$, $-NR^{41}COR^{42}$, $-CONR^{41}R^{42}$, $-CO_2R^{41}$, $-SO_2NR^{41}R^{42}$, or-$NR^{41}SO_2R^{42}$; R^{37} is hydrogen, alkyl, substituted alkyl, halo, heteroalkyl, substituted heteroalkyl, -CN, $-NO_2$, $-OR^{43}$, $-S(O)_jR^{43}$, $-OCOR^{43}$, $NR^{43}R^{44}$, $-NR^{43}COR^{44}$, $-CONR^{43}R^{44}$, $-CO_2R^{43}$, $-SO_2NR^{43}R^{44}$, or $-NR^{43}SO_2R^{44}$; or alternatively R^{36} and R^{37}, together with the atoms to which they are bonded, form a cycloheteroalkyl or substituted cycloheteroalkyl ring; and R^{38} is hydrogen, alkyl, substituted alkyl, halo, heteroalkyl, substituted heteroalkyl, -CN, $-NO_2$, $-OR^{45}$, $-S(O)_jR^{45}$, $-OCOR^{45}$, $NR^{45}R^{46}$, $-NR^{45}COR^{46}$, $-CONR^{45}R^{46}$, $-CO_2R^{45}$, $-SO_2NR^{45}R^{46}$, $-NR^{45}SO_2R^{46}$. It is preferable that R^{38} is hydrogen, alkanyl, substituted alkanyl, alkenyl, substituted alkenyl, cycloalkanyl, substituted cycloalkanyl, cycloalkenyl, substituted cyclcoalkenyl, halo, heteroalkyl, substituted heteroalkyl, -CN, $-NO_2$, $-OR^{45}$, $-S(O)_jR^{45}$, $-OCOR^{45}$, $NR^{45}R^{46}$, $-NR^{45}COR^{46}$, $-CONR^{45}R^{46}$, $-CO_2R^{45}$, $-SO_2NR^{45}R^{46}$, $-NR^{45}SO_2R^{46}$. It is also preferable that A is $-NH_2$, R^{17} is hydrogen, methyl, ethyl or benzyl; and R^{35}, R^{36}, R^{37} and R^{38} are independently hydrogen, fluoro, chloro, bromo, methyl, trifluromethyl, ethyl, isopropyl, cyclopropyl, propenyl, methylpropenyl, butenyl, methylbutenyl, substituted propenyl, substituted methylpropenyl, substituted butenyl, substituted methylbutenyl, -NH-alkanyl, -NH-(substituted alkanyl), -OH, $-OCH_3$, -O-cycloalkanyl, –O-benzyl, $-CO_2H$.

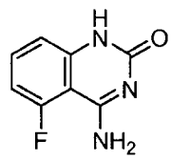
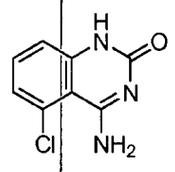
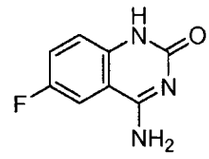
In some specific embodiments of Formula (IIIa), the compound has structural formula selected from the group consisting of

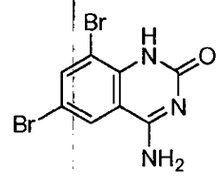
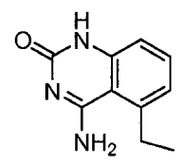
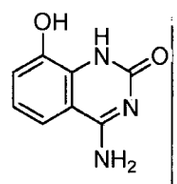



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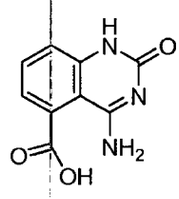
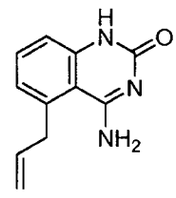
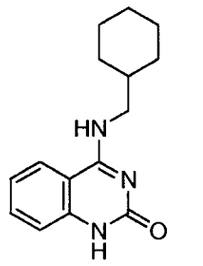
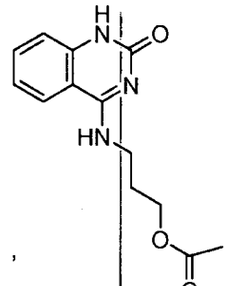
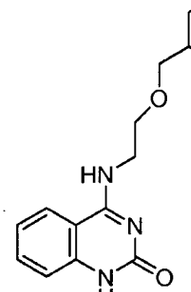
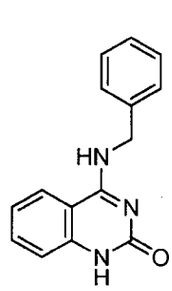
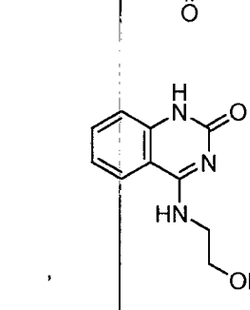
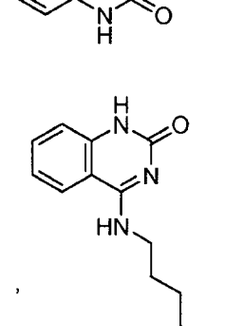
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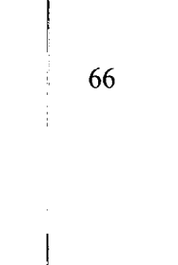
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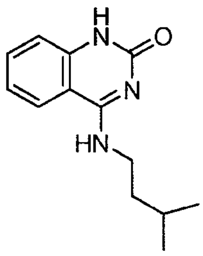
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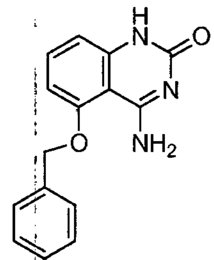
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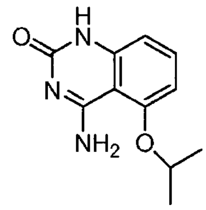
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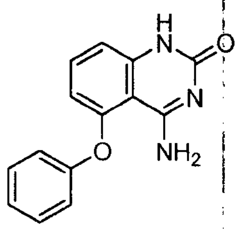
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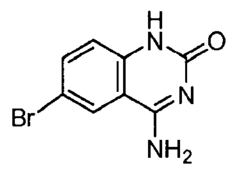
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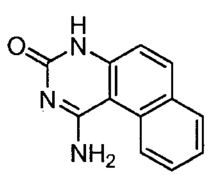
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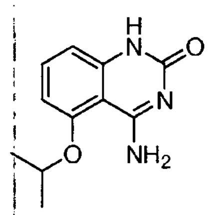
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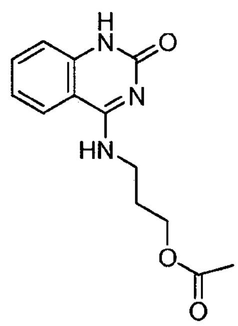
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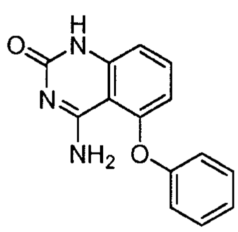
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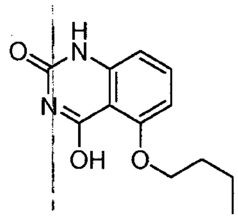
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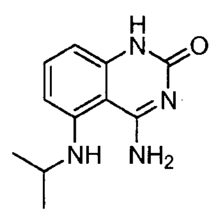
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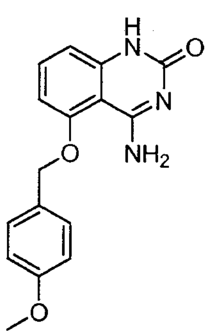
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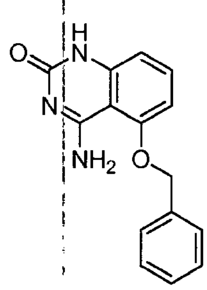
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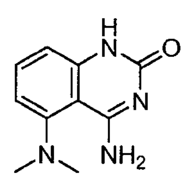
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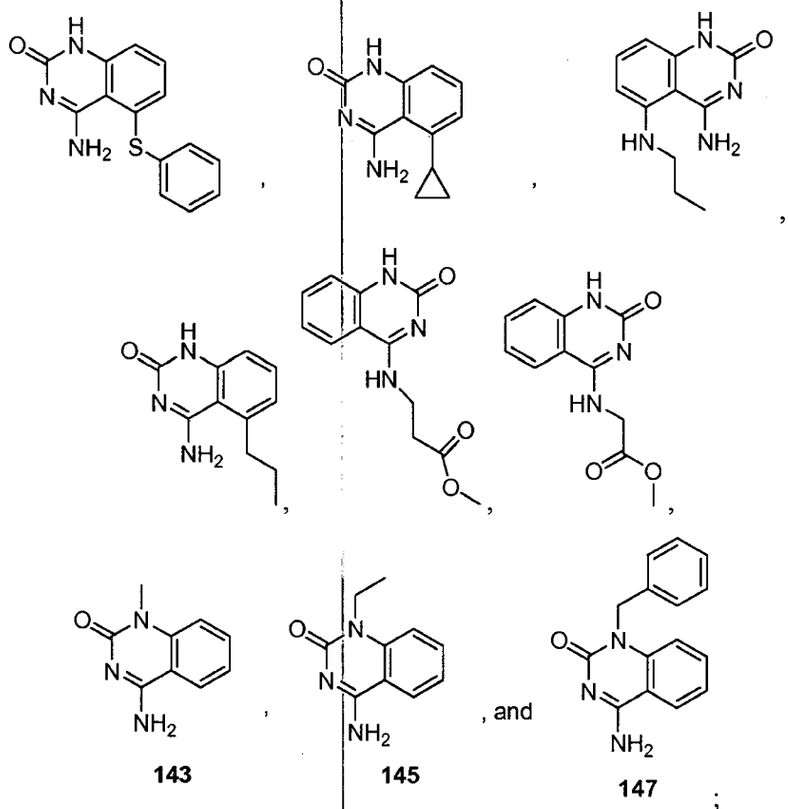
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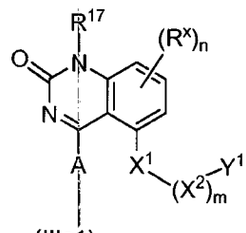
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143 145 147 ;

or a tautomer, salt, solvate, and/or ester thereof. In some preferred embodiments, the salt of these compounds is hydrochloride or trifluoroacetate salt.

In one embodiment of Formula (IIIa), the compound of the present invention has structural Formula (IIIa1):



(IIIa1)

wherein,

A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, $-OR^9$, $-NO_2$, $-S(O)_cR^9$, $-NOR^9$, $-NHOR^9$, $-NR^9COR^{10}$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$ or $-NR^9CO_2R^{10}$;

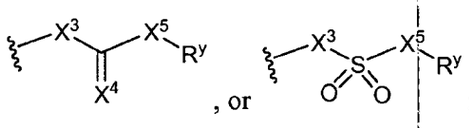
R^{17} is hydrogen, alkyl, substituted alkyl, arylalkyl, or substituted arylalkyl;

X^1 is $-CH_2-$, $-O-$, $-NR^9-$, $-S-$, $-S(O)-$, or $-S(O)_2-$;

X^2 is alkylene, substituted alkylene, heteroalkylene, or substituted heteroalkylene;

m is 0 or 1;

Y^1 is cycloheteroalkyl, substituted cycloheteroalkyl, or



;

X^3 and X^5 are independently a covalent bond, $-O-$ or $-NR^9-$;

X^4 is O, NR^9, N-OR^9, or S;

R^x is halo, $-NO_2$, -CN, -OH, $-NH_2$, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl;

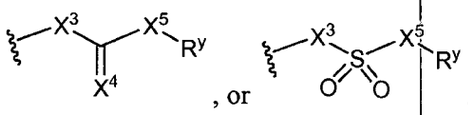
n is 0, 1, 2, or 3;

R^y is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl, $-NR^9R^{10}$; and

each R^9 and R^{10} is independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl;

with the proviso that when X^1 is $-O-$ or $-S-$, and m is zero; then X^3 is not $-O-$.

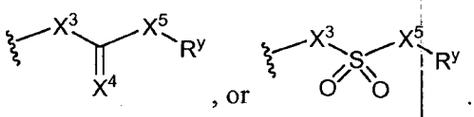
In one embodiment of Formula (IIIa1), X^1 is $-CH_2-$; and Y^1 is



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In one embodiment of Formula (IIIa1), X^1 is $-O-$, $-NR^9-$, or $-S-$; m is 0 or 1, and Y^1 is cycloheteroalkyl or substituted cycloheteroalkyl.

In one embodiment of Formula (IIIa1), X^1 is $-O-$, $-NR^9-$, or $-S-$; m is 1, and Y^1 is



.

In some embodiments of Formula (IIIa1), X^2 is methylene, ethylene, propylene, dimethylethylene, methylcyclopropylene, or cyclopropylmethylene.

In some embodiments of Formula (IIIa1), A is hydrogen, alkyl, substituted alkyl, -CN, -OR^9, -NO_2, -$S(O)_cR^9$, -NOR^9, -$NHOR^9$, -NR^9COR^{10}, -NR^9R^{10}, -$CONR^9R^{10}$, -CO_2R^9 or -$NR^9CO_2R^{10}$.

In some embodiments of Formula (IIIa1), R^{17} is hydrogen, alkyl, substituted alkyl.

In some embodiments of Formula (IIIa1), Y^1 is cycloheteroalkyl or substituted cycloheteroalkyl. It is preferable that Y^1 is piperidinyl, substituted piperidinyl, tetrahydrofuranyl, subsitituted tetrahydrofuranyl, tetrahydropyranyl, subsitituted tetrahydropyranyl, dihydrofuranyl, substituted dihydrofuranyl, pyrrolidinyl, substituted pyrrolidinyl, oxetanyl, or substituted oxetanyl. It is also preferable that the substituted cycloheteroalkyl comprises one or more substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, -OR^9, -NO_2, -$S(O)_cR^9$, -NOR^9, -$NHOR^9$, -NR^9COR^{10}, -NR^9R^{10}, -$CONR^9R^{10}$, -CO_2R^9, and -$NR^9CO_2R^{10}$.

In some embodiments of Formula (IIIa1), X^4 is O.

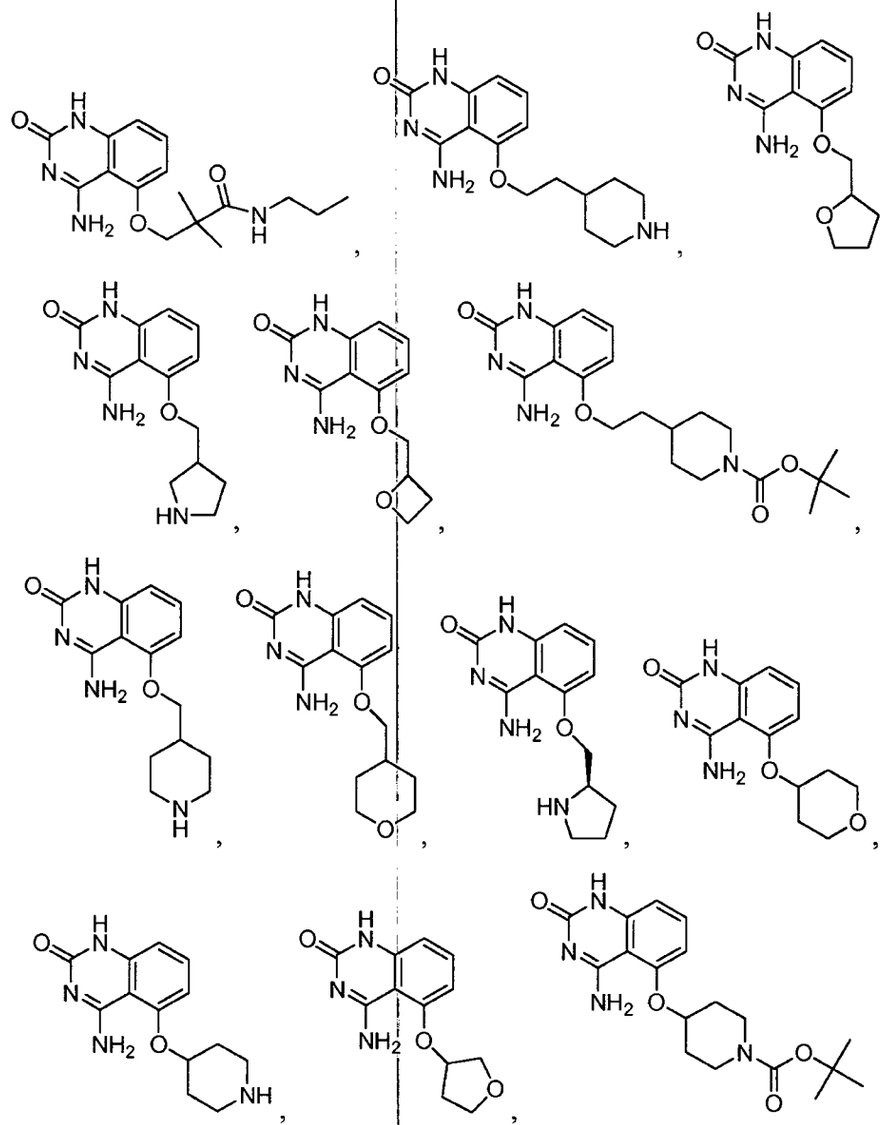
In some embodiments of Formula (IIIa1), -X^3-$C(X^4)$-X^5- is –C(O)-, -C(O)-NH-, -NH-C(O)-, -NH-C(O)-NH-, -C(O)-O-, -O-C(O)-, -O-C(O)-O-, -NH-C(O)-O-, -O-C(O)-NH-, –C(NH)-, -C(NH)-NH-, -NH-C(NH)-, -NH-C(NH)-NH-, -C(NH)-O-, -O-C(NH)-, -O-C(NH)-O-, -NH-C(NH)-O-, -O-C(NH)-NH-, -C(N-OH)-, or -C(S)-.

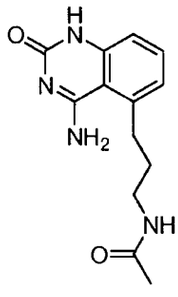
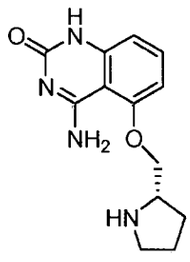
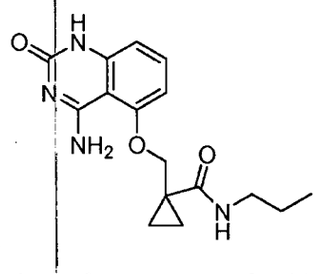
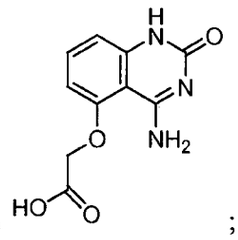
In some embodiments of Formula (IIIa1), A is hydrogen, alkyl, substituted alkyl, or -NR^9R^{10}; R^{17} is hydrogen; and Y^1 is piperidinyl, substituted piperidinyl, tetrahydrofuranyl, subsitituted tetrahydrofuranyl, tetrahydropyranyl, subsitituted tetrahydropyranyl, dihydrofuranyl, substituted dihydrofuranyl, pyrrolidinyl, substituted pyrrolidinyl, oxetanyl, or substituted oxetanyl.

In some embodiments of Formula (IIIa1), A is hydrogen, alkyl, substituted alkyl, or -NR^9R^{10}; R^{17} is hydrogen; Y^1 is -X^3-$C(X^4)$-X^5-; and -X^3-$C(X^4)$-X^5- is –C(O)-, -C(O)-NH-, -NH-C(O)-, -NH-C(O)-NH-, -C(O)-O-, -O-C(O)-, -O-C(O)-O-, -NH-C(O)-O-, -O-C(O)-NH-, –

C(NH)-, -C(NH)-NH-, -NH-C(NH)-, -NH-C(NH)-NH-, -C(NH)-O-, -O-C(NH)-, -O-C(NH)-O-, -NH-C(NH)-O-, -O-C(NH)-NH-, -C(N-OH)-, or -C(S)-.

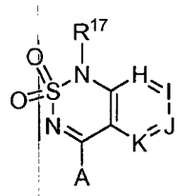
In some specific embodiments of Formula (IIIa1), the compound has structural formula selected from the group consisting of




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or a tautomer, salt, solvate, and/or ester thereof. In some preferable embodiments, the salt of these compounds is hydrochloride or trifluoroacetate salt.

In one embodiment of Formula (III), the compound of the present invention has structural Formula (IIIb):


(IIIb).

In one embodiment of Formula (IIIb), A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, -CN, $-NO_2$, $-OR^9$, $-S(O)_cR^9$, $-NR^9COR^{10}$, $-NHOR^9$, $-NR^9R^{10}$, $-NOR^9$, $-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$, or $-NR^9C(=NH)NR^{10}R^{11}$.

In one embodiment of Formula (IIIb), R^{17} is hydrogen, alkyl, or substituted alkyl.

In one embodiment of Formula (IIIb), A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, $-OR^1$, $-SR^1$, -CN, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$ or $-NR^9C(=NH)NR^{10}R^{11}$; and R^{17} is hydrogen, alkyl, or substituted alkyl.

In one embodiment of Formula (IIIb), H is $-C(R^{35})-$ or -N-; I is $-C(R^{36})-$; J is $-C(R^{37})-$; and K is $-C(R^{38})-$ or -N-.

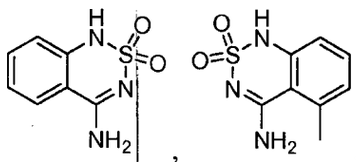
In one embodiment of Formula (IIIb), H is $-C(R^{35})-$; I is $-C(R^{36})-$; J is $-C(R^{37})-$; and K is $-C(R^{38})-$.

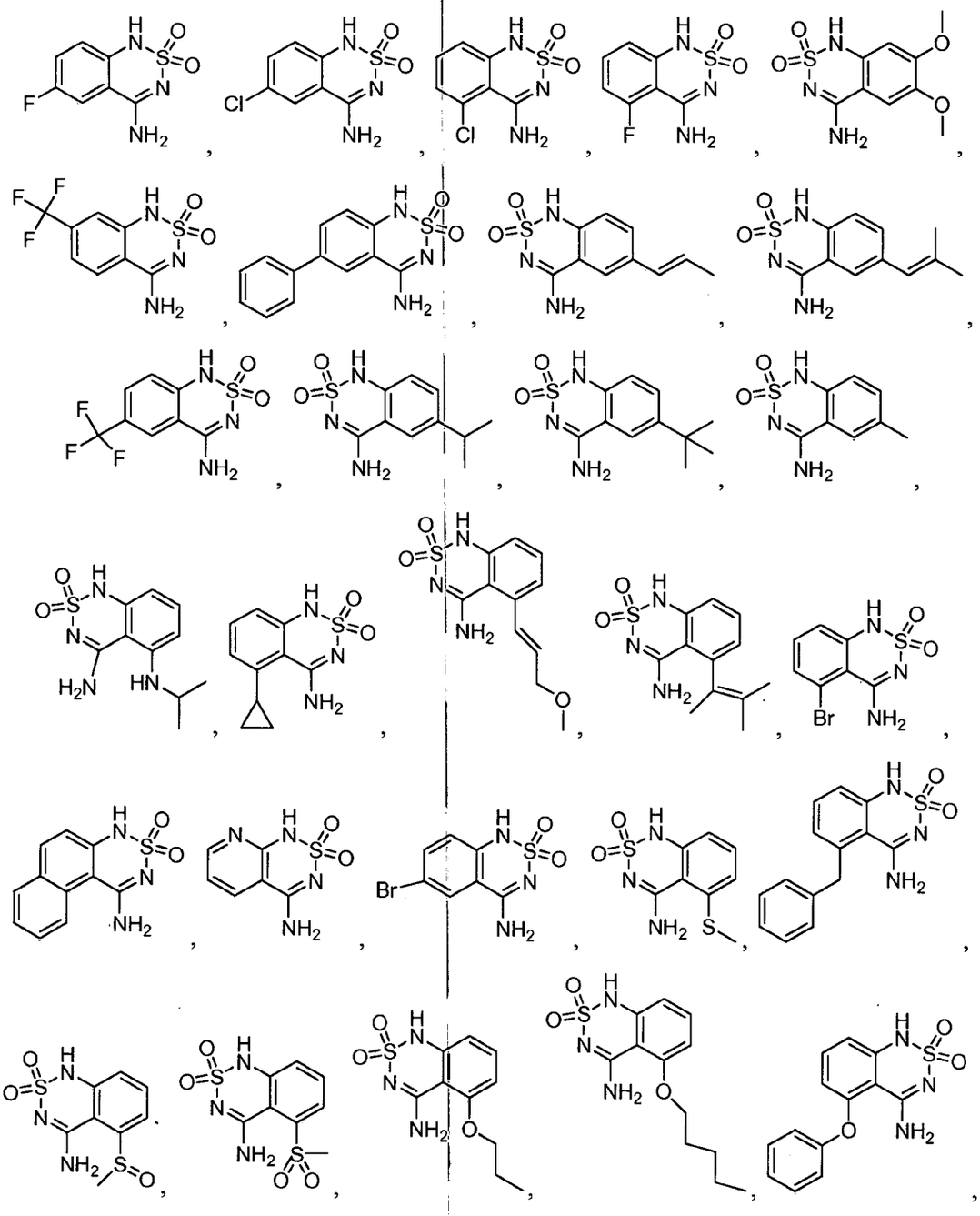
In one embodiment of Formula (IIIb), R^{35} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, halo, heteroalkyl,

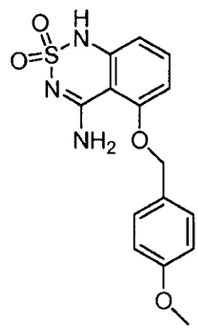
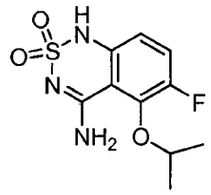
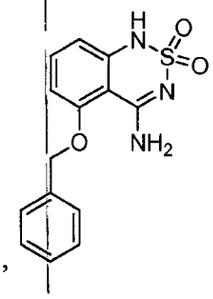
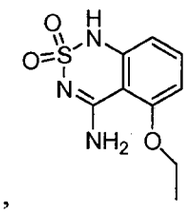
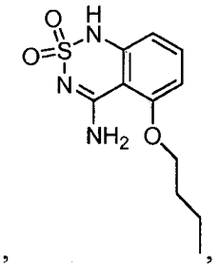
substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl, -CN, $-NO_2$, $-OR^{39}$, $-S(O)_jR^{39}$, $-OCOR^{39}$, $-NR^{39}R^{40}$, $-CONR^{39}R^{40}$, $-CO_2R^{39}$, $-SO_2NR^{39}R^{40}$, $-NR^{39}SO_2R^{40}$; R^{36} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl, -CN, $-NO_2$, $-OR^{41}$, $-S(O)_kR^{41}$, $-OCOR^{41}$, $-NR^{41}R^{42}$, $-CONR^{41}R^{42}$, $-CO_2R^{41}$, $-SO_2NR^{41}R^{42}$, $-NR^{41}SO_2R^{42}$; R^{37} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl ,-CN, $-NO_2$, $-OR^{43}$, $-S(O)_lR^{43}$, $-OCOR^{43}$, $-NR^{43}R^{44}$, $-CONR^{43}R^{44}$, $-CO_2R^{43}$, $-SO_2NR^{43}R^{44}$, $-NR^{43}SO_2R^{44}$; R^{38} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl, -CN, $-NO_2$, $-OR^{45}$, $-S(O)_mR^{45}$, $-OCOR^{45}$, $-NR^{45}R^{46}$, $-CONR^{45}R^{46}$, $-COR^{45}$, $-CO_2R^{45}$, $-SO_2NR^{45}R^{46}$, $-NR^{45}SO_2R^{46}$.

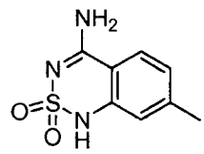
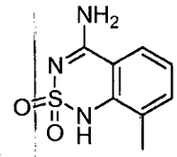
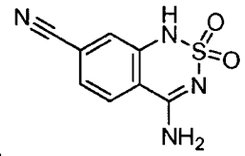
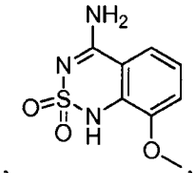
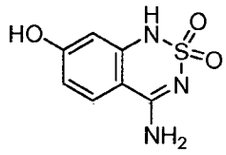
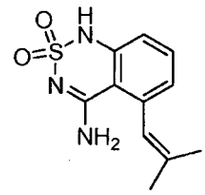
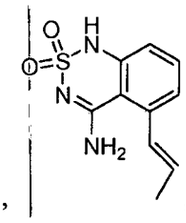
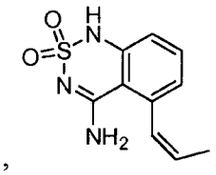
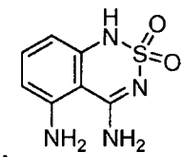
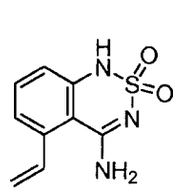
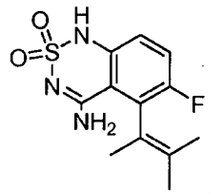
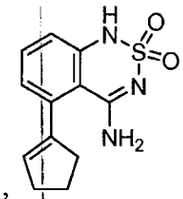
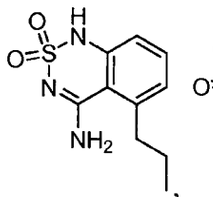
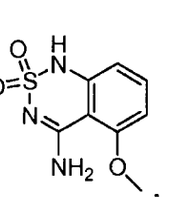
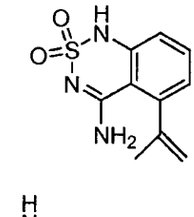
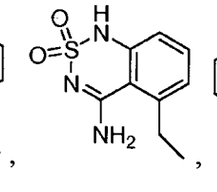
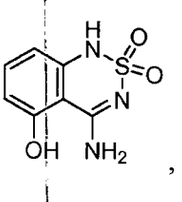
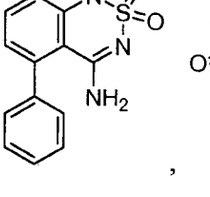
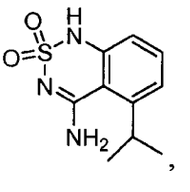
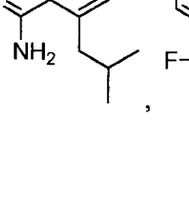
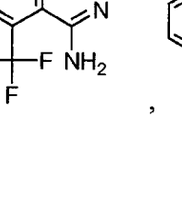
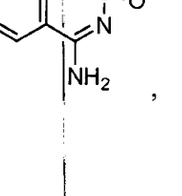
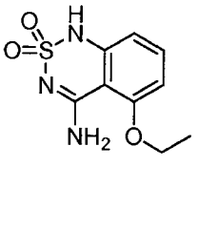
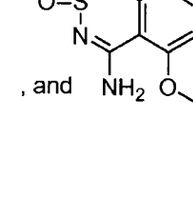
In one embodiment of Formula (IIIb), A is $-NH_2$, R^{17} is hydrogen, methyl, ethyl or benzyl; and R^{35}, R^{36}, R^{37} and R^{38} are independently hydrogen, fluoro, chloro, bromo, -CN, alkanyl, substituted alkanyl, alkenyl, substitued alkenyl, alkynyl, substituted alkynyl, cycloalkanyl, substituted cycloalkanyl, cycloalkenyl, substitued cycloalkenyl, heteroalkanyl, substituted heteroalkanyl, cycloheteroalkyl, substituted cycloheteroalkyl, -O-alkanyl, -O-(substituted alkanyl), -O-alkenyl, -O-(substituted alkenyl), -NH-alkanyl, -NH-(substituted alkanyl), -NH-alkenyl, -NH-(substituted alkenyl), -S-alkanyl, -S-(substituted alkanyl), -S-alkenyl, or -S-(substituted alkenyl).

In some specific embodiments of Formula (IIIb), the compound has structural formula selected from the group consisting of:

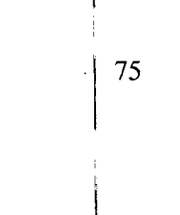





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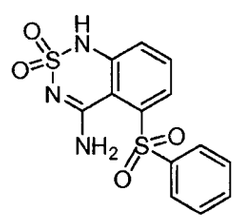
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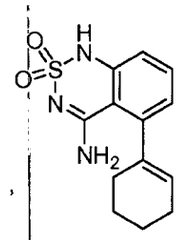
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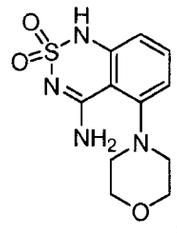
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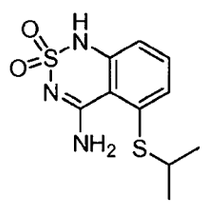
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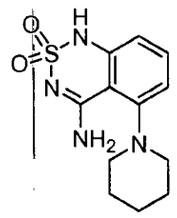
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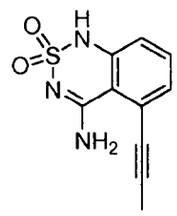


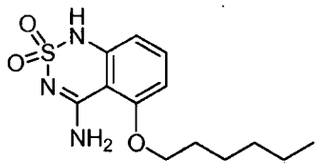


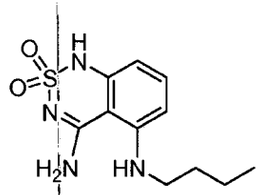


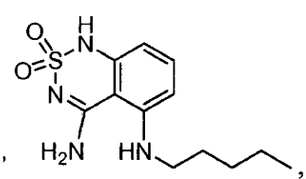


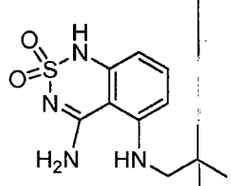


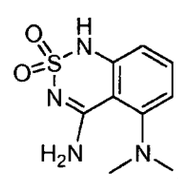


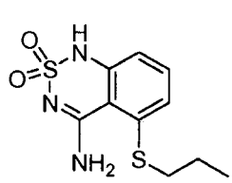


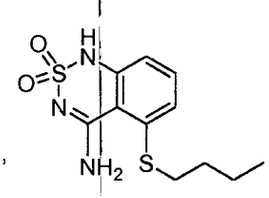


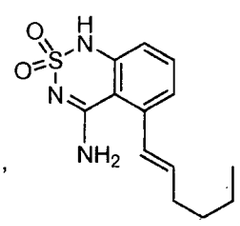


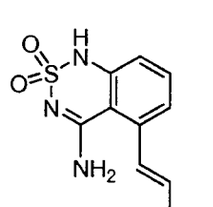


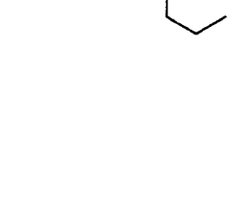


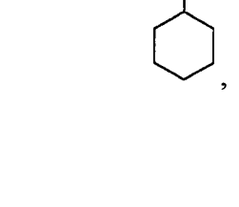


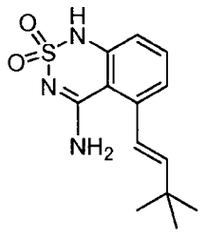
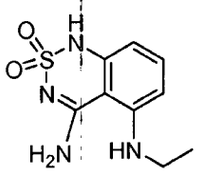
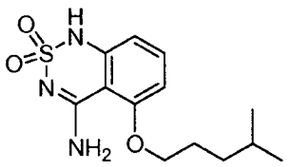
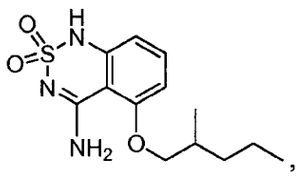
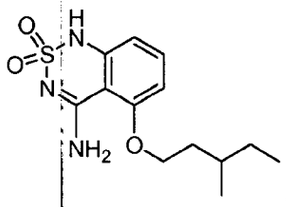
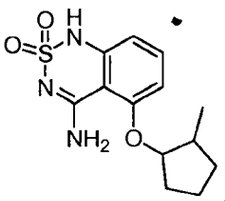
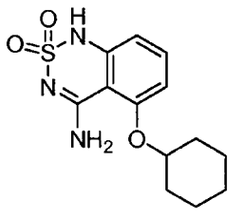
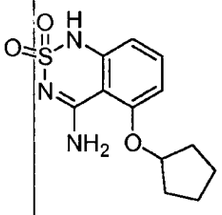
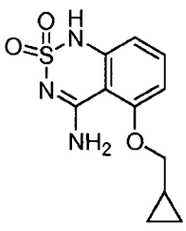
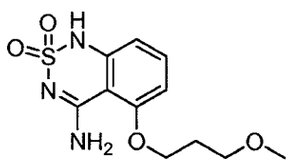
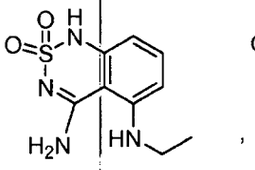
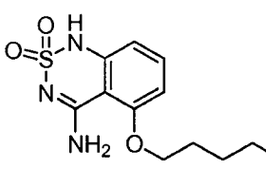
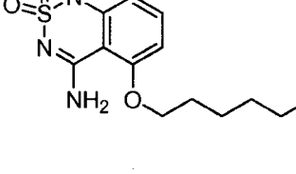
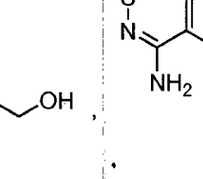
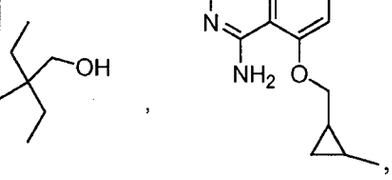
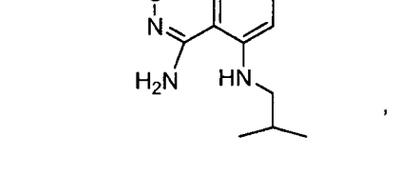
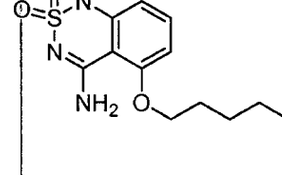
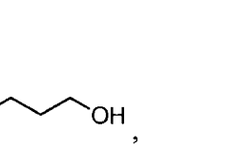






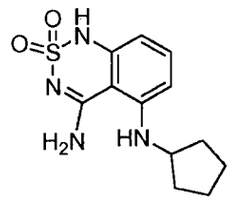
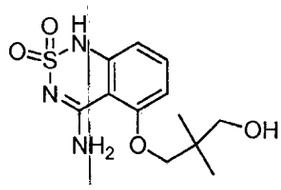
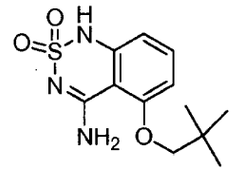
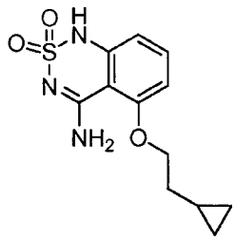
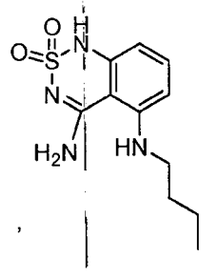


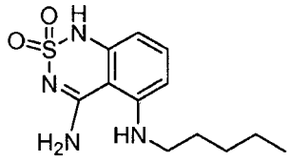
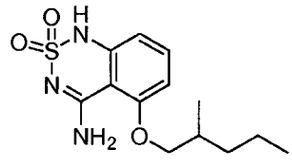
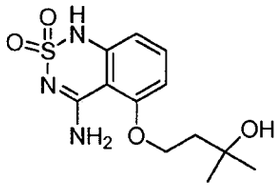
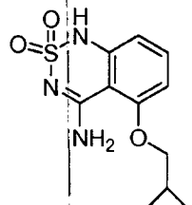
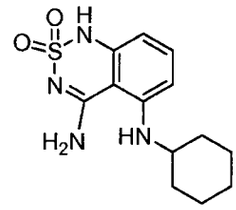
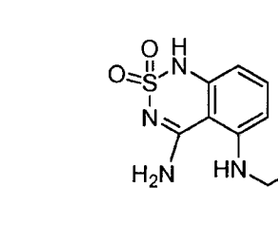
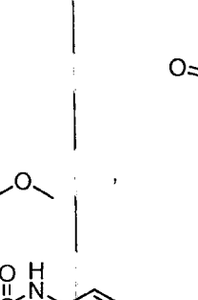
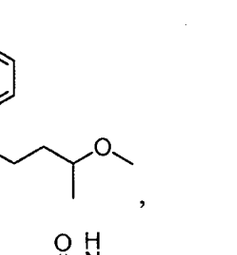
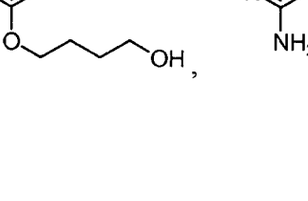
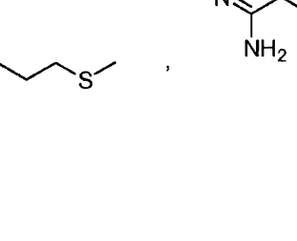


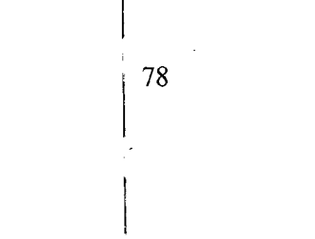

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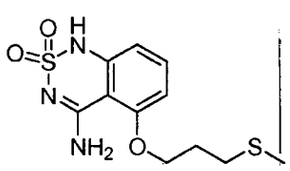
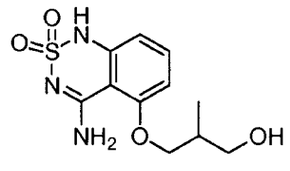
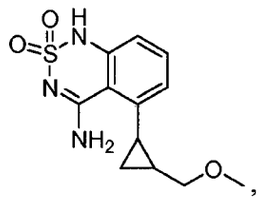
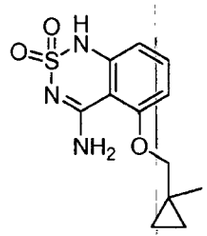
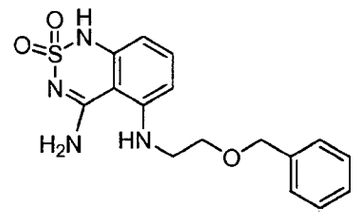
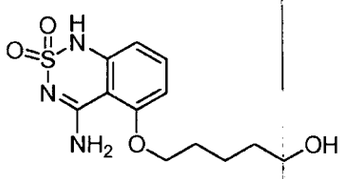
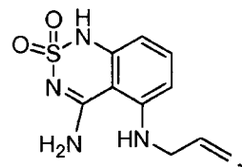
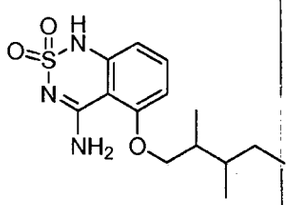
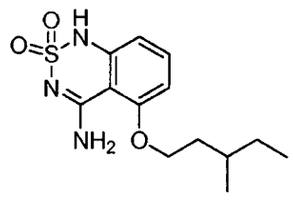
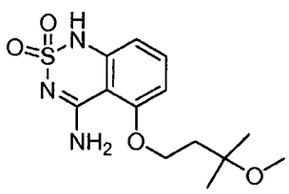
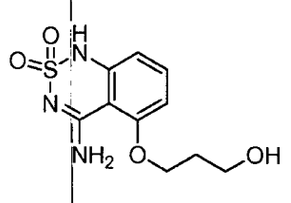
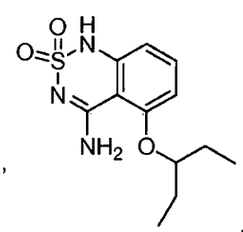
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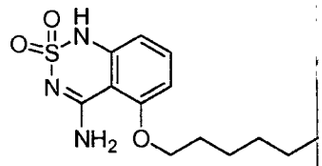
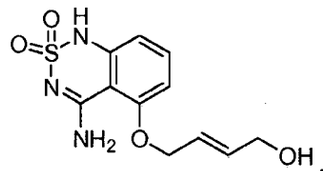
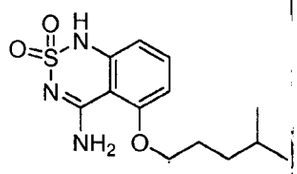
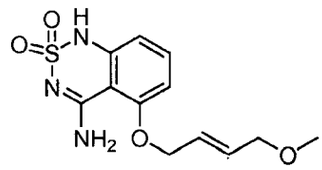
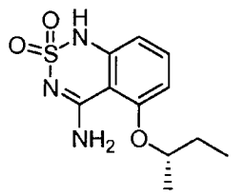
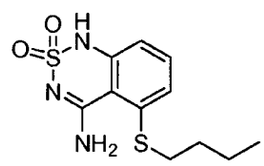
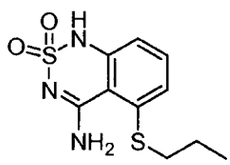

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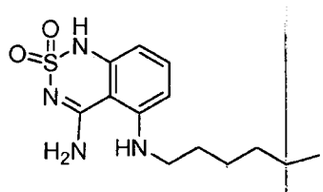
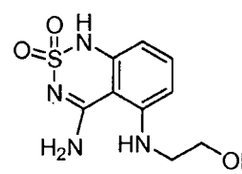
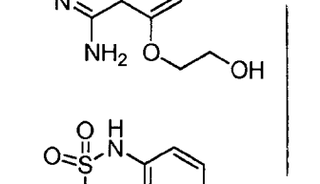
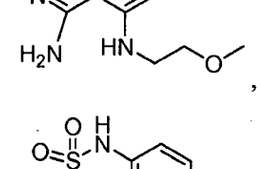
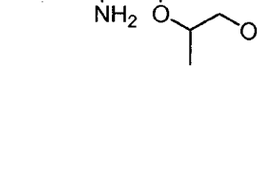
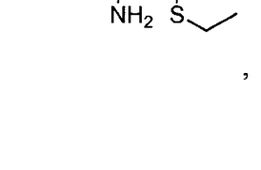
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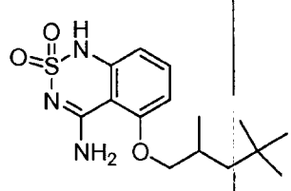
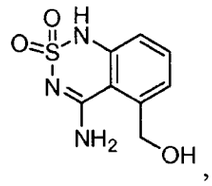
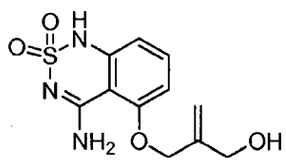
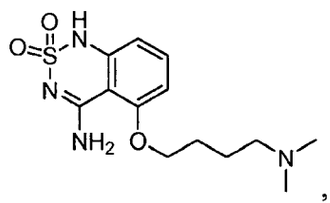
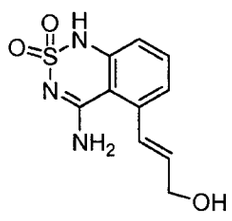
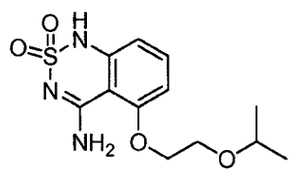
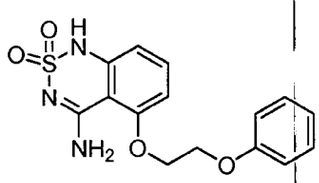
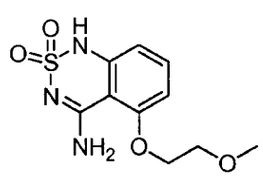
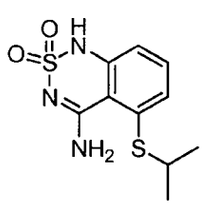
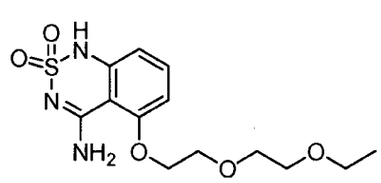
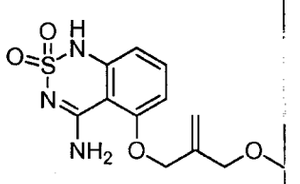
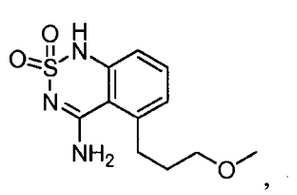
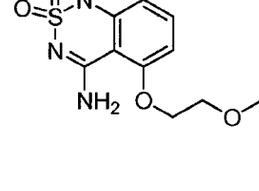
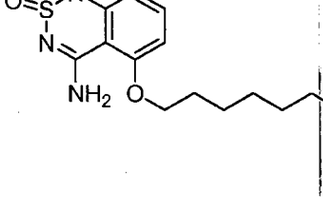














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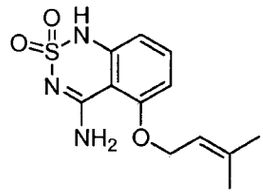
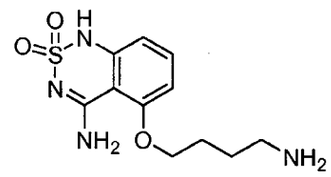
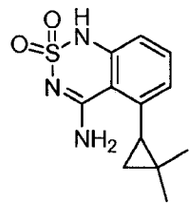
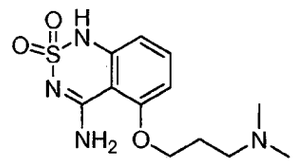
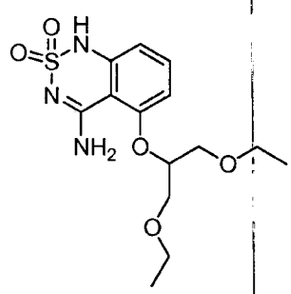
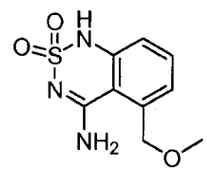
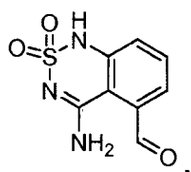
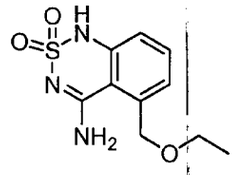
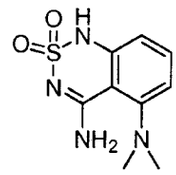
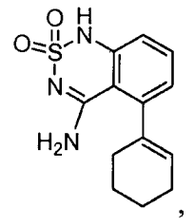
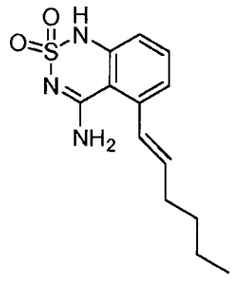
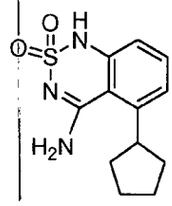
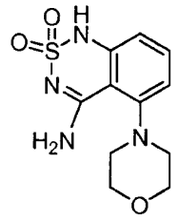
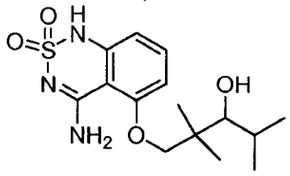
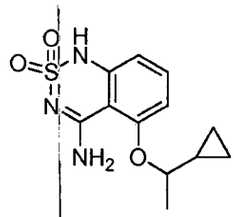
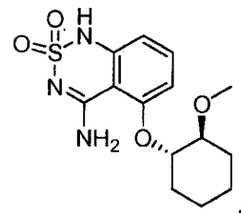

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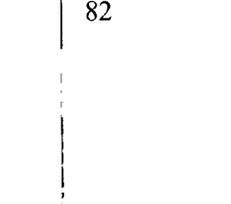
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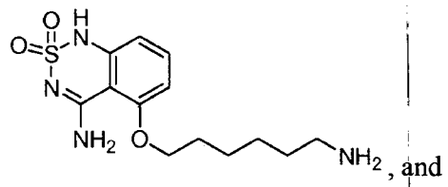
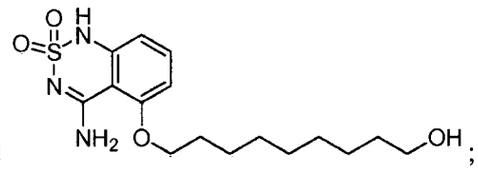
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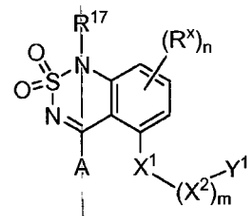
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or a tautomer, salt, solvate, and/or ester thereof. In some preferred embodiments, the salt of these compounds is hydrochloride or trifluoroacetate salt.

In one embodiment of Formula (IIIb), the compound of the present invention has structural Formula (IIIb1):



(IIIb1)

wherein,

A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, $-OR^9$, $-NO_2$, $-S(O)_cR^9$, $-NOR^9$, $-NHOR^9$, $-NR^9COR^{10}$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$ or $-NR^9CO_2R^{10}$;

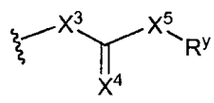
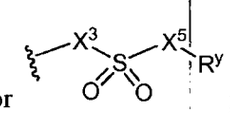
R^{17} is hydrogen, alkyl, substituted alkyl, arylalkyl, or substituted arylalkyl;

X^1 is $-CH_2-$, $-O-$, $-NR^9-$, $-S-$, $-S(O)-$, or $-S(O)_2-$;

X^2 is alkylene, substituted alkylene, heteroalkylene, or substituted heteroalkylene;

m is 0 or 1;

Y^1 is heteroaryl, substituted heteroaryl, cycloheteroalkyl, substituted cycloheteroalkyl, or


, or

;

X^3 and X^5 are independently a covalent bond, $-O-$ or $-NR^9-$;

X^4 is O, NR^9, N-OR^9, or S;

R^x is halo, $-NO_2$, -CN, -OH, $-NH_2$, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl;

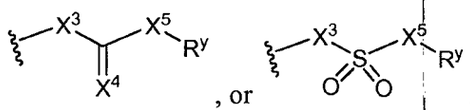
n is 0, 1, 2, or 3;

R^y is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl, $-NR^9R^{10}$; and

each R^9 and R^{10} is independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl;

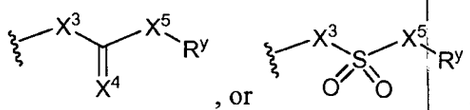
with the proviso that when X^1 is –O– or –S–, and m is zero; then X^3 is not –O–.

In one embodiment of Formula (IIIb1), X^1 is $-CH_2-$; and Y^1 is



In one embodiment of Formula (IIIb1), X^1 is –O–, $-NR^9-$, or –S–; m is 0 or 1, and Y^1 is cycloheteroalkyl or substituted cycloheteroalkyl.

In one embodiment of Formula (IIIb1), X^1 is –O–, $-NR^9-$, or –S–; m is 1, and Y^1 is



In some embodiments of Formula (IIIb1), X^2 is alkanylene, substituted alkanylene, heteroalkanylene, substituted heteroalkanylene, alkenylene, substituted alkenylene, heteroalkenylene, or substituted heteroalkenylene.

In some embodiments of Formula (IIIb1), X^2 is methylene, ethylene, propylene, *iso*-propylene, butylene, *iso*-butylene, *sec*-butylene, pentylene, hexylene, heptylene, dimethylethylene, methylcyclopropylene, cyclopropylmethylene, ethenylene, propenylene, or butenylene.

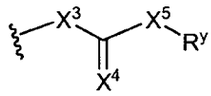
In one embodiment of Formula (IIIb1), A is hydrogen, alkyl, substituted alkyl, -CN, $-NO_2$, $-OR^9$, $-S(O)_cR^9$, $-NR^9COR^{10}$, $-NHOR^9$, $-NR^9R^{10}$, $-NOR^9$, $-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$, $-NR^9C(=NH)NR^{10}R^{11}$.

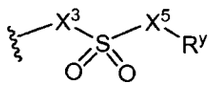
In one embodiment of Formula (IIIb1), R^{17} is hydrogen, alkyl, or substituted alkyl.

In one embodiment of Formula (IIIb1), Y^1 is cycloheteroalkanyl, substituted cycloheteroalkanyl, cycloheteroalkenyl, or substituted cycloheteroalkenyl. It is preferable that Y^1 is piperidinyl, substituted piperidinyl, tetrahydrofuranyl, subsitituted tetrahydrofuranyl, tetrahydropyranyl, subsitituted tetrahydropyranyl, dihydrofuranyl, substituted dihydrofuranyl, pyrrolidinyl, substituted pyrrolidinyl, oxetanyl, substituted oxetanyl, saccharide ring or its derivative, substituted saccharide ring or its derivative.

In one embodiment of Formula (IIIb1), Y^1 is heteroaryl or substituted heteroaryl. It is preferable that Y^1 is pyridinyl, substituted pyridinyl, pyrrolyl, substituted pyrrolyl, furanyl, substituted furanyl, pyrazolyl, substituted pyrazolyl, isoxazolyl, substituted isoxazolyl, oxazolyl, and substituted oxazolyl. It is also preferable that the substituted cycloheteroalkanyl or the substituted cycloheteroalkenyl comprises one or more substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, $-OR^9$, $-NO_2$, $-S(O)_cR^9$, $-NOR^9$, $-NHOR^9$, $-NR^9COR^{10}$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$, and $-NR^9CO_2R^{10}$.

In one embodiment of Formula (IIIb1), Y is



or


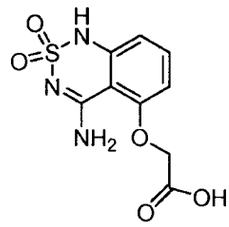
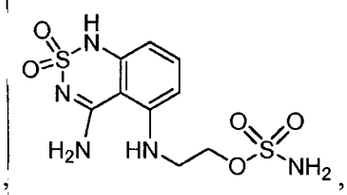
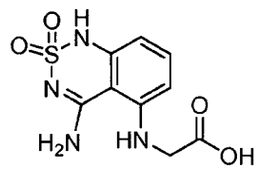
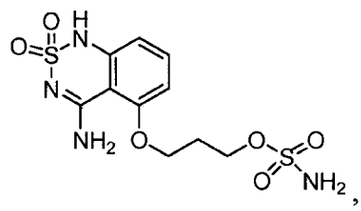
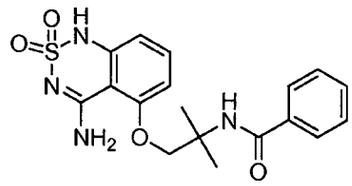
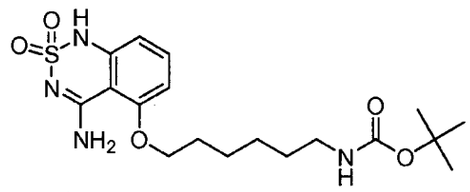
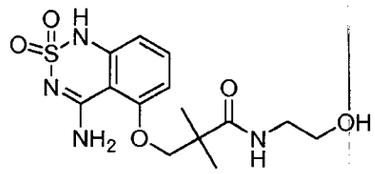
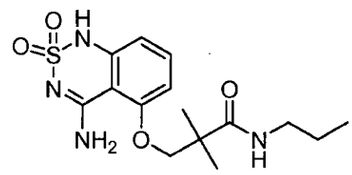
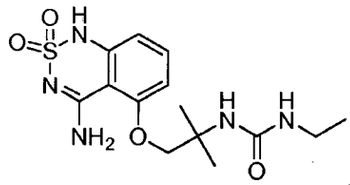
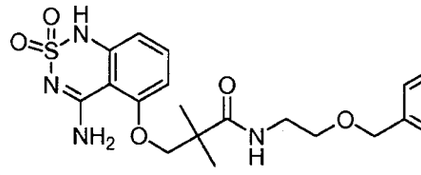
. It is preferable that X^4 is O.

In one embodiment of Formula (IIIb1), $-X^3-C(X^4)-X^5-$ is –C(O)-, -C(O)-NH-, -NH-C(O)-, -NH-C(O)-NH-, -C(O)-O-, -O-C(O)-, -O-C(O)-O-, -NH-C(O)-O-, -O-C(O)-NH-, –C(NH)-, -C(NH)-NH-, -NH-C(NH)-, -NH-C(NH)-NH-, -C(NH)-O-, -O-C(NH)-, -O-C(NH)-O-, -NH-C(NH)-O-, -O-C(NH)-NH-, -C(N-OH)-, or -C(S)-.

In one embodiment of Formula (IIIb1), A is hydrogen, alkyl, substituted alkyl, or $-NR^9R^{10}$; R^{17} is hydrogen; and Y^1 is piperidinyl, substituted piperidinyl, tetrahydrofuranyl, subsitituted tetrahydrofuranyl, tetrahydropyranyl, subsitituted tetrahydropyranyl, dihydrofuranyl, substituted dihydrofuranyl, pyrrolidinyl, substituted pyrrolidinyl, oxetanyl, substituted oxetanyl, monosaccharide ring, substituted monosaccharide ring, pyridinyl, substituted pyridinyl, pyrrolyl, substituted pyrrolyl, furanyl, substituted furanyl, pyrazolyl, substituted pyrazolyl, isoxazolyl, substituted isoxazolyl, oxazolyl, or substituted oxazolyl.

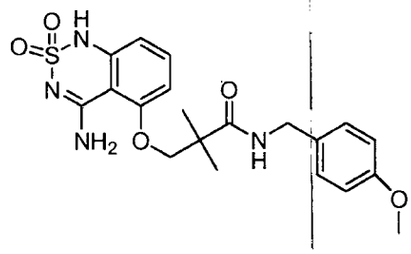
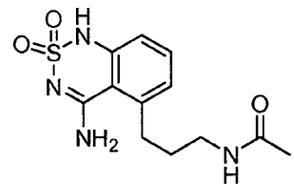
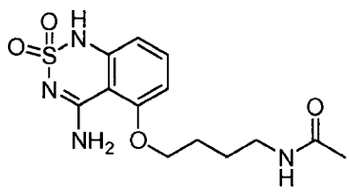
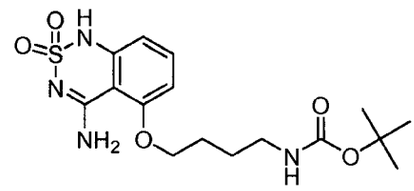
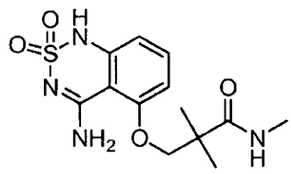
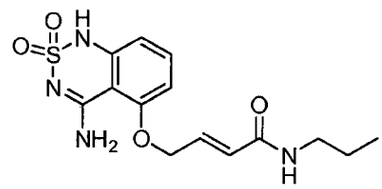
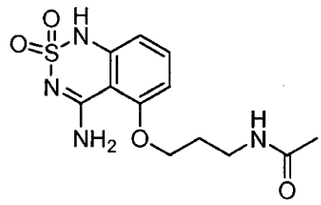
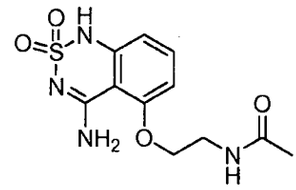
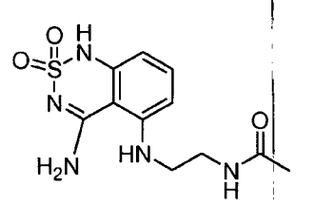
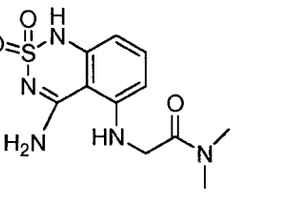
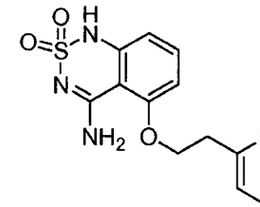
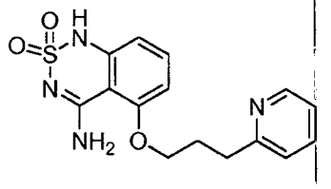
In one embodiment of Formula (IIIb1), A is hydrogen, alkyl, substituted alkyl, or $-NR^9R^{10}$; R^{17} is hydrogen; Y^1 is $-X^3-C(X^4)-X^5-$; and $-X^3-C(X^4)-X^5-$ is –C(O)-, -C(O)-NH-, -NH-C(O)-, -NH-C(O)-NH-, -C(O)-O-, -O-C(O)-, -O-C(O)-O-, -NH-C(O)-O-, -O-C(O)-NH-, –C(NH)-, -C(NH)-NH-, -NH-C(NH)-, -NH-C(NH)-NH-, -C(NH)-O-, -O-C(NH)-, -O-C(NH)-O-, -NH-C(NH)-O-, -O-C(NH)-NH-, $-S(O)_2-$, $-NH-S(O)_2-$, $-S(O)_2-NH-$, $-O-S(O)_2-$, $-S(O)_2-O-$, -C(N-OH)-, or -C(S)-.

In some specific embodiments of Formula (IIIb1), the compound has structural formula selected from the group consisting of


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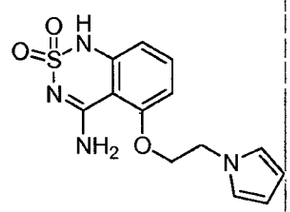
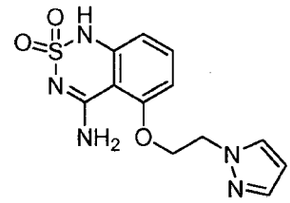
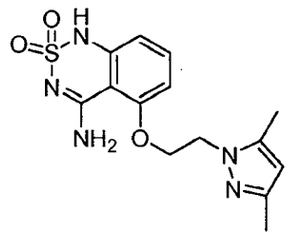
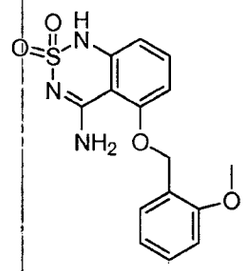
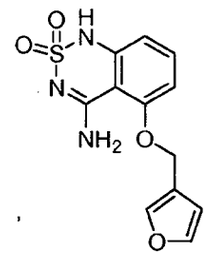
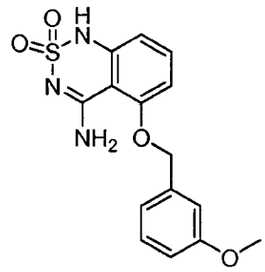
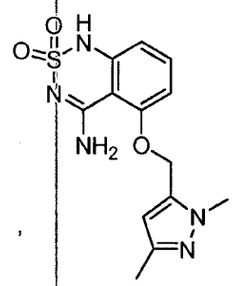
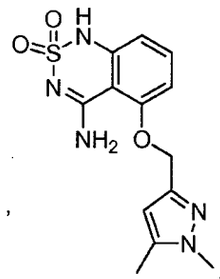
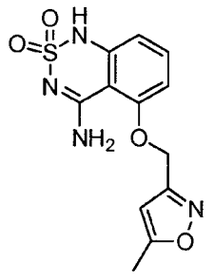
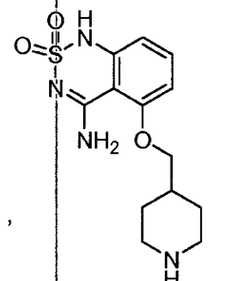
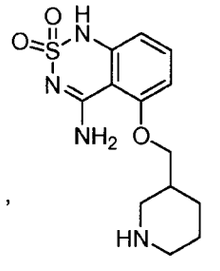
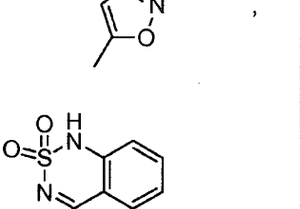
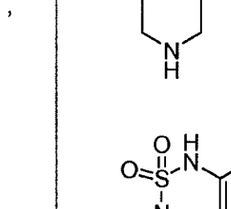
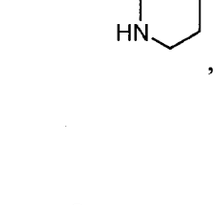
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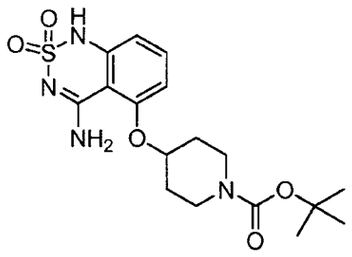
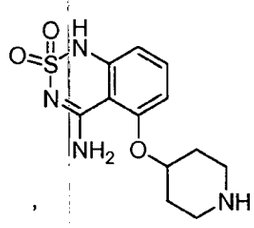
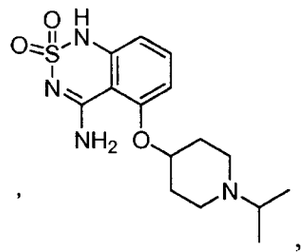
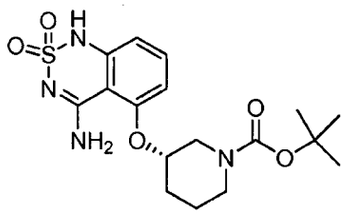
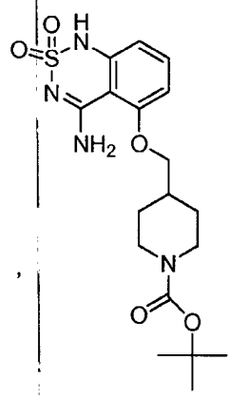
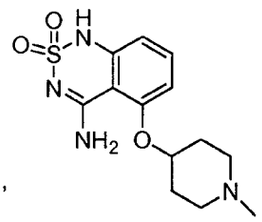
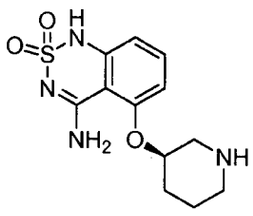
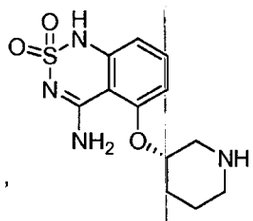
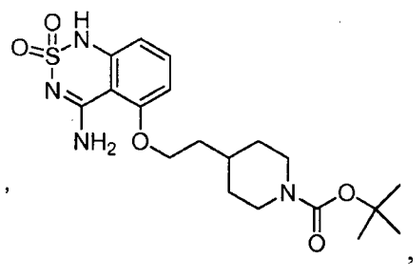
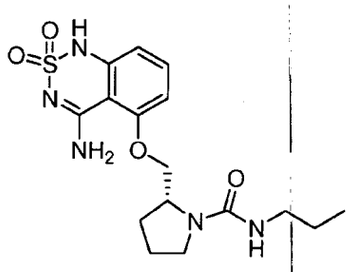
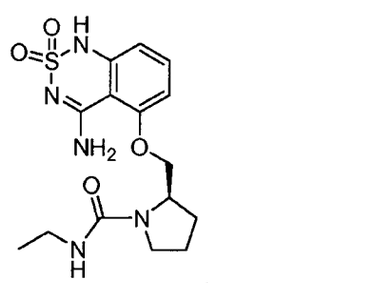
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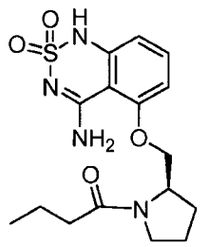
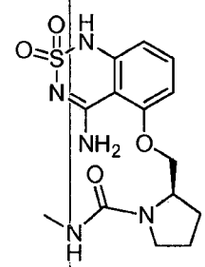
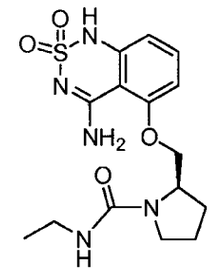
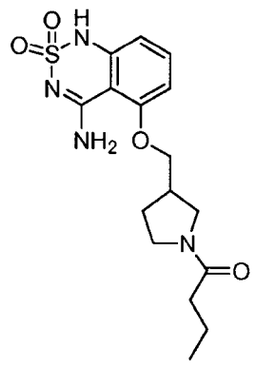
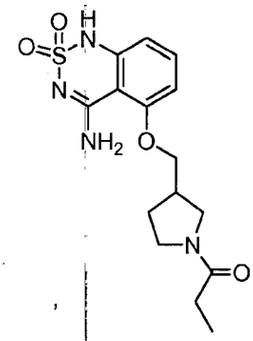
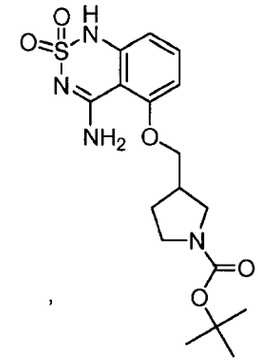
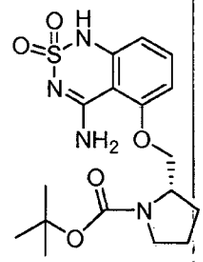
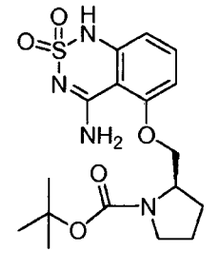
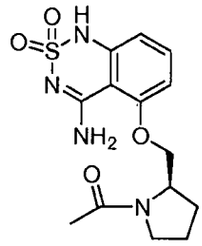
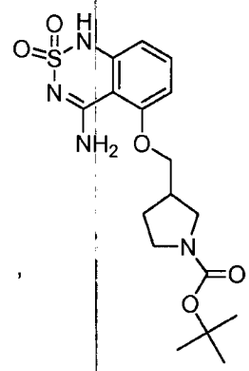
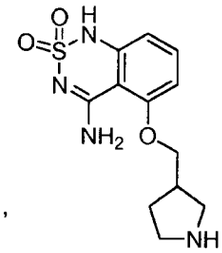
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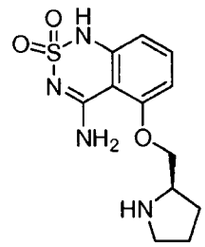
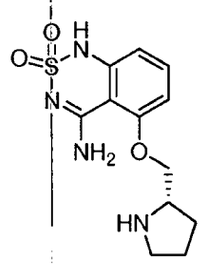
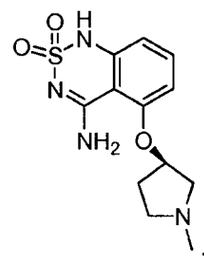
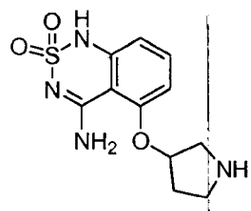
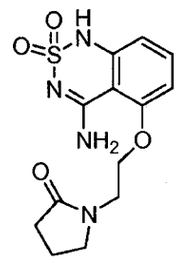
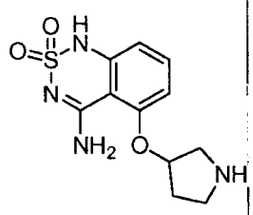
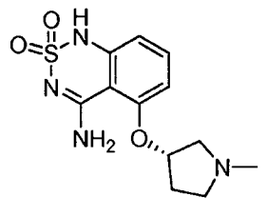
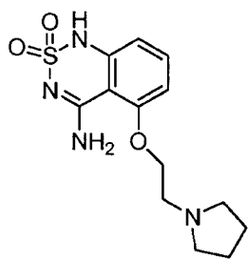
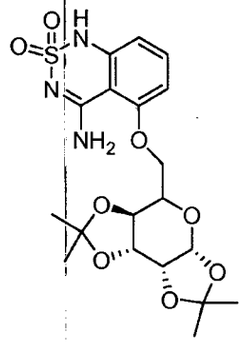
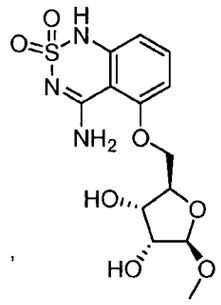
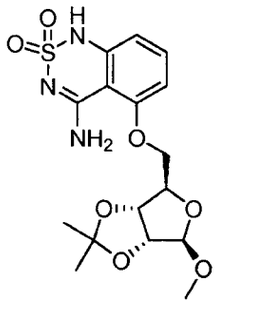
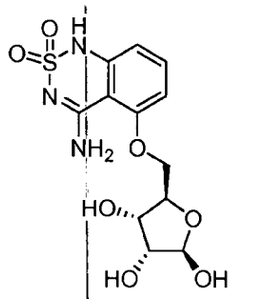
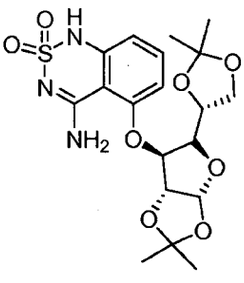

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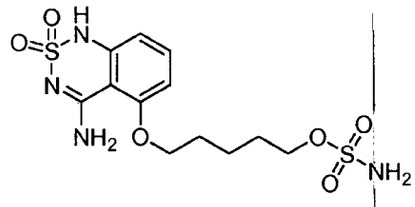
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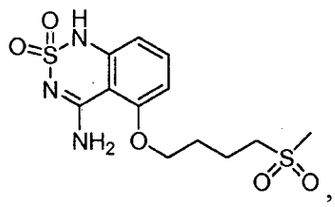
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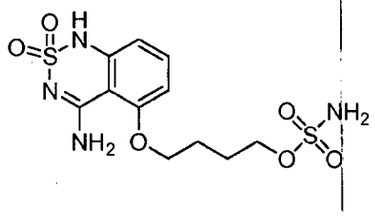

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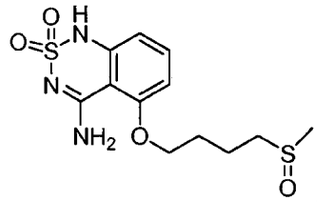

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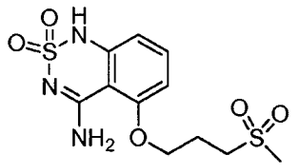

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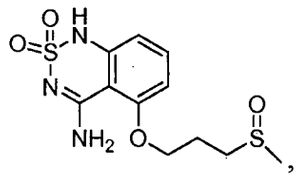


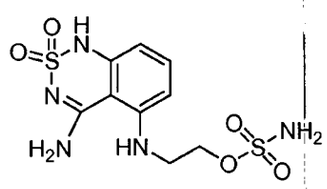


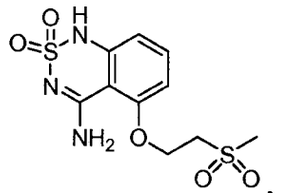


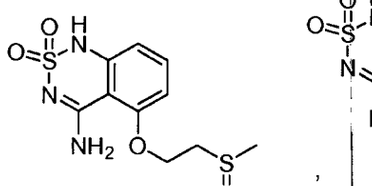


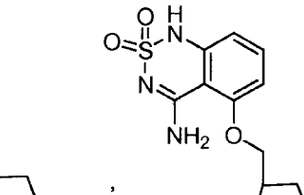


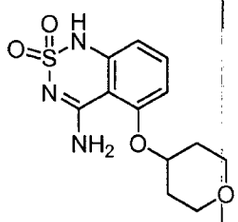


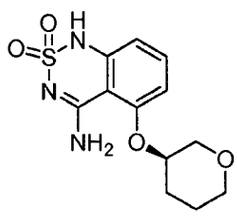


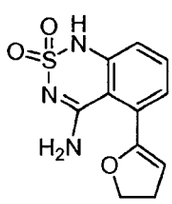


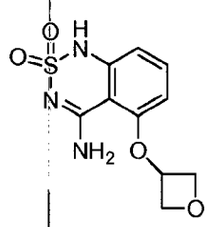


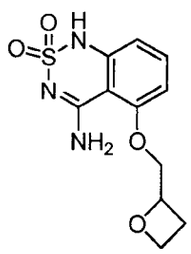


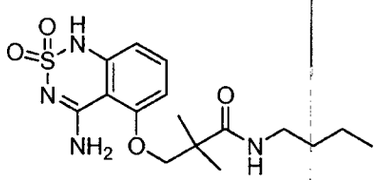


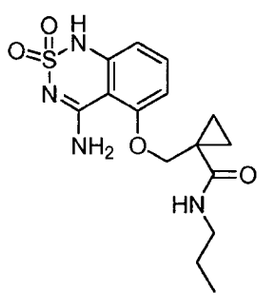


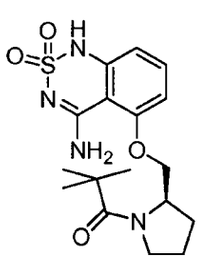


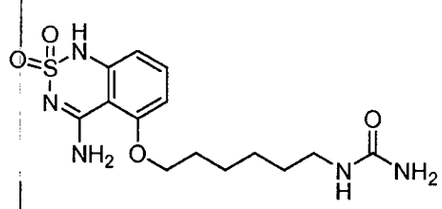


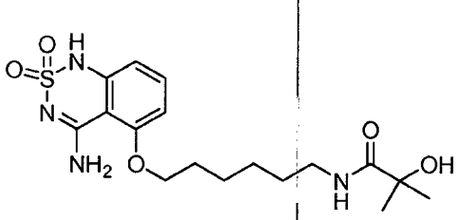


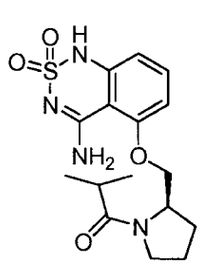


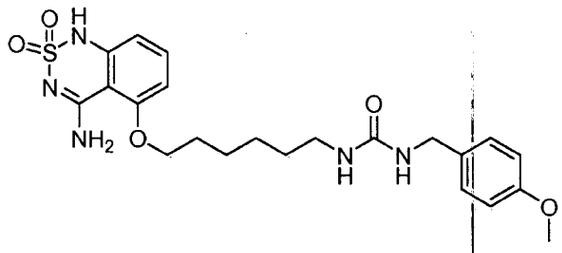


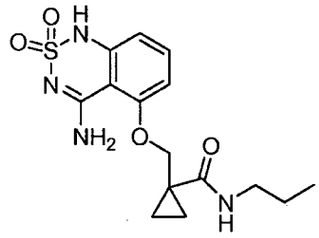


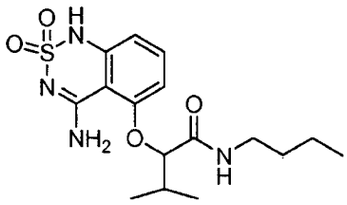


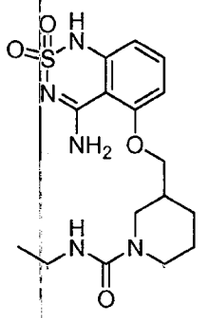


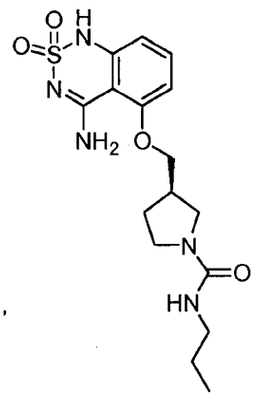


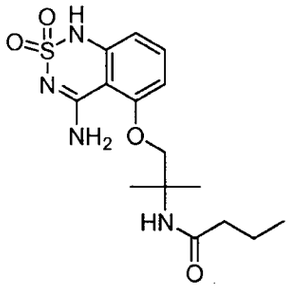


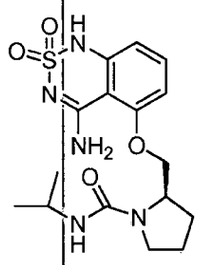


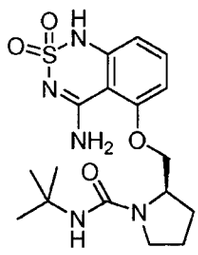


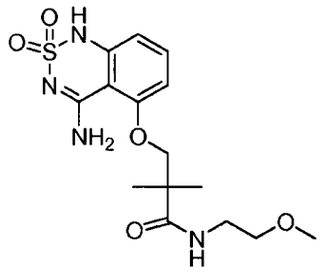


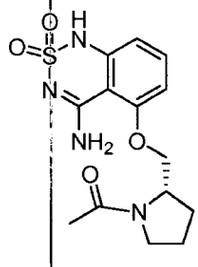


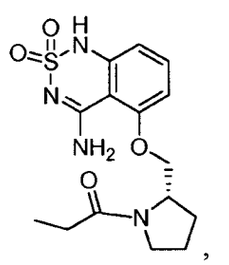


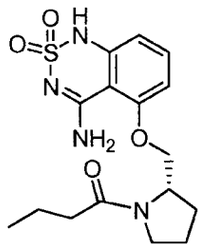
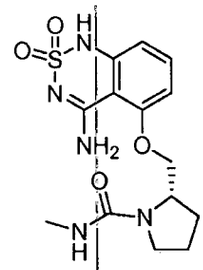
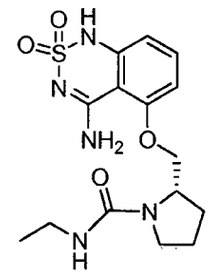
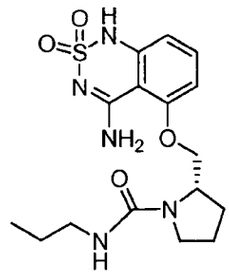
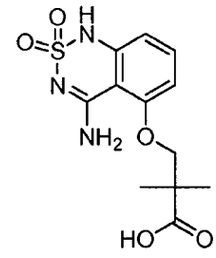
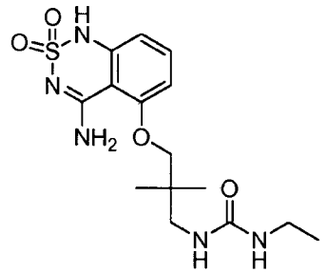
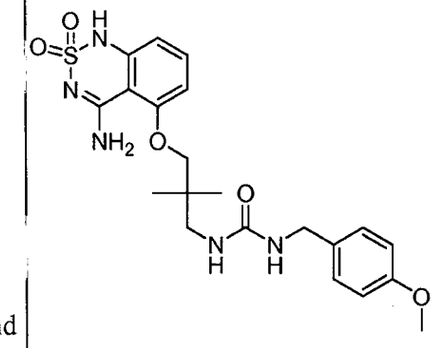






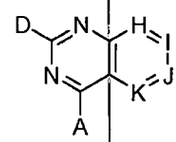





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or a tautomer, salt, solvate, and/or ester thereof. In some preferred embodiments, the salt of these compounds is a hydrochloride or trifluoroacetate salt.

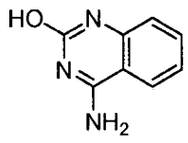
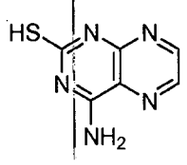
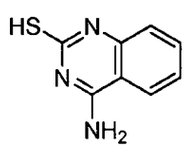
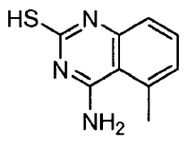
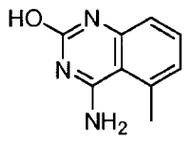
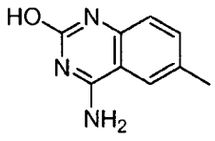
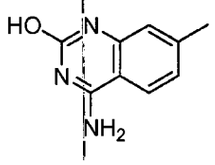
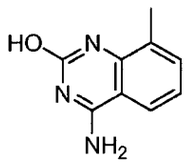
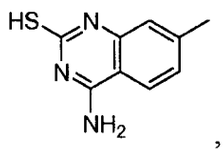
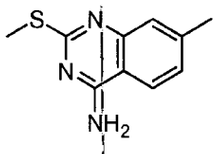
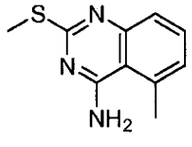
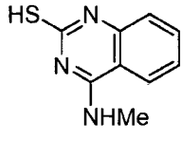
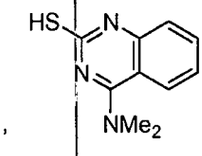
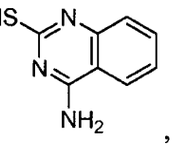
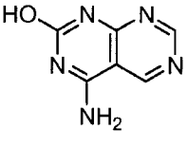
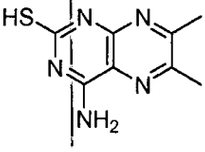
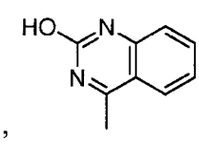
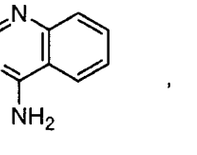
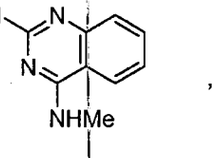
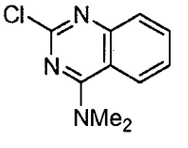
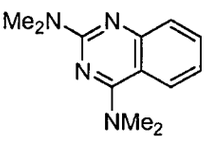
In one embodiment of Formula (III), the compound of the present invention has structural formula (IIIc)

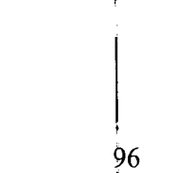

(IIIc)

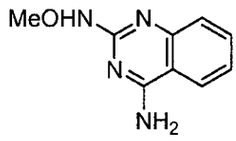
wherein D is halo, $-OR^{15}$, $-NH-OR^{15}$, $-NH-NHR^{15}$, $-S(O)_eR^{15}$, or $-NR^{15}R^{16}$.

In one embodiment of Formula (IIIc), R^{35}, R^{36}, R^{37}, and R^{38} are independently hydrogen, alkyl, or substituted alkyl. It is preferable that H is $-C(R^{35})-$; I is $-C(R^{36})$; J is $-C(R^{37})-$; and K is $-C(R^{38})-$.

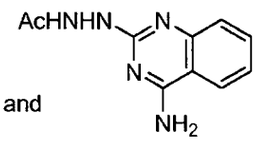
In some specific embodiments of Formula (IIIc), the compound has strucutural formula selected from the group consisting of





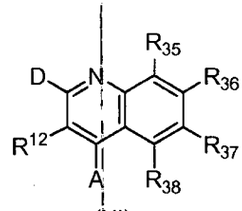
, and



;

or a tautomer, salt, solvate, and/or ester thereof. In some preferred embodiments, the salt of these compounds is hydrochloride or trifluoroacetate salt.

In one embodiment of Formula (III), the compound of the present invention has structural Formula (XI):



(XI)

wherein,

R^{12} is hydrogen, -OH, -SH, -CN, $-CH_2OH$ or $-CO_2H$;

D is -OH or -SH; and

A is -OH, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, or $-CH_2NHC(O)CH_3$;

provided that when R^{12} is hydrogen, then R^{35}, R^{36}, R^{37}, and R^{38} are not hydrogen.

In one embodiment of Formula (XI), R^{12} is -OH, -SH, -CN, $-CH_2OH$ or $-CO_2H$; and A is $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, or $-CH_2NHC(O)CH_3$.

In some embodiments of Formula (XI),

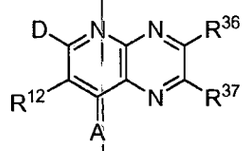
when R^{36}, R^{37}, R^{38} and R^{35} are hydrogen, D is –OH, and A is $-CO_2H$; then R^{12} is not $-CO_2H$ or -OH;

when R^{36}, R^{37}, R^{38} and R^{35} are hydrogen, D is –OH, and A is $–NH_2$; then R^{12} is not $-CO_2H$ or CN;

when R^{36}, R^{38} and R^{35} are hydrogen, R^{37} is -OMe, D is –OH, and A is $-CH_2OH$; then R^{12} is not $-CH_2OH$; and

when R^{36}, R^{38} and R^{35} are hydrogen, R^{37} is hydrogen or methyl, D is –OH, and A is –CO_2H; then R^{12} is not -SH.

In one embodiment of Formula (III), the compound of the present invention has structural Formula (XII):



(XII)

,

wherein

R^{12} is hydrogen, -OH, -SH, -CN, -CH_2OH or -CO_2H;

D is -SH or –OH;

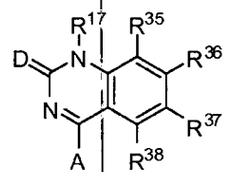
A is -OH, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -$NHC(O)CH_3$, -$NHC(O)OCH_3$, -$NHC(O)NH_2$, -$NHC(S)NH_2$, -$NHC(NH)NH_2$, -CN, -CH_2OH, -CH_2NH_2, -CH_2NHCH_3, -$CH_2N(CH_3)_2$, -CO_2H, -$CONH_2$, -$CONHCH_3$, or -$CH_2NHC(O)CH_3$;

R^{36} is hydrogen, -OCH_3, -OC_2H_5, -OC_3H_7, -CH_3, -C_2H_5, -$CH(CH_3)_2$, -CH_2OH, -CH_2OCH_3, -CN, -$C(O)NR^{41}R^{42}$, -CO_2R^{41}, -$SO_2NR^{39}R^{40}$, -$NR^{39}SO_2R^{40}$, -$B(OR^{39})(OR^{40})$, -$P(O)(OR^{39})(OR^{40})$ or -$P(O)(R^{39})(OR^{40})$; and

R^{37} is hydrogen, -OCH_3, -OC_2H_5, -OC_3H_7, -CH_3, -C_2H_5, -$CH(CH_3)_2$, -CH_2OH, -CH_2OCH_3, -CN, -$C(O)NR^{43}R^{44}$, -CO_2R^{43}, -$SO_2NR^{43}R^{44}$, -$NR^{43}SO_2R^{44}$, -$B(OR^{43})(OR^{44})$, -$P(O)(OR^{43})(OR^{44})$ or -$P(O)(R^{43})(OR^{44})$.

In one embodiment of Formula (XII), R^{12} is -OH, -SH, -CN, -CH_2OH or -CO_2H.

In one embodiment of Formula (III), the compound of the present invention has structural Formula (XIII):



(XIII)

,

wherein:

D is =O or =S;

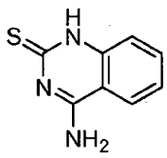
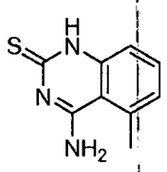
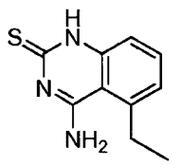
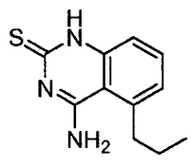
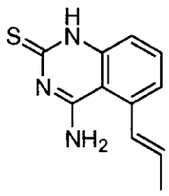
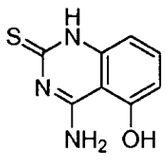
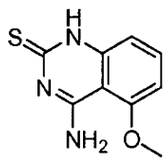
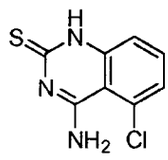
A is -OH, NH_2, -$NHCH_3$, -$N(CH_3)_2$, -$NHC(O)CH_3$, -$NHC(O)OCH_3$, -$NHC(O)NH_2$,

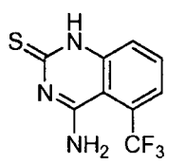
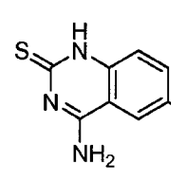
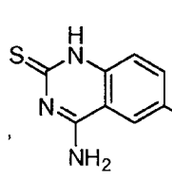
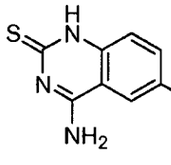
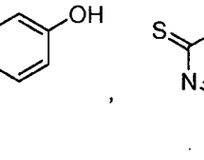
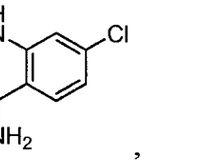
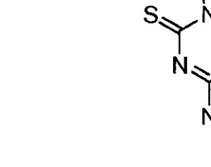
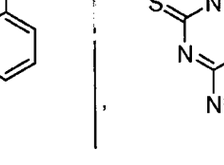
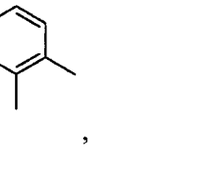
$-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, or $-CH_2NHC(O)CH_3$;

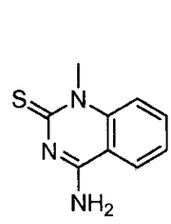
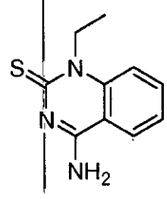
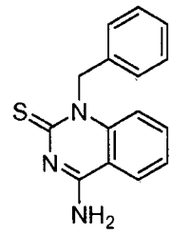
R^{17} is hydrogen, alkyl, aryl, arylalkyl.

In one embodiment of Formula (XIII), when A is $-NH_2$, and R^{35}, R^{36}, R^{37} and R^{38} are hydrogen; then R^{17} is not methyl, ethyl or phenyl.

In some specific embodiments of Formula (XIII), the compound has structural formula selected from the group consisting of

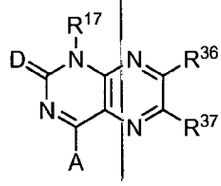









or a tautomer, salt, solvate, and/or ester thereof. In some preferred embodiments, the salt of these compounds is hydrochloride or trifluoroacetate salt.

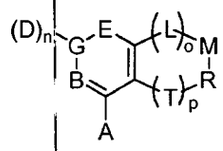
In one embodiment of Formula (III), the compound of the present invention has structural Formula (XIV):



(XIV),

wherein A is -OH, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, or $-CH_2NHC(O)CH_3$; and R^{17} is alkyl, aryl, or arylalkyl.

In one embodiment of Formula (I), the chemosensory receptor ligand modifier is a compound having a structural Formula (IV):



(IV),

wherein:

L is $-CHR^{60}-$, $-NR^{47}$, -O- or -S-;

M is $-CHR^{61}-$, $-NR^{48}$, -O- or -S-;

R is $-CHR^{62}-$, $-NR^{49}$, -O- or -S-;

T is $-CHR^{63}-$, $-NR^{50}$, -O- or -S-;

o and p are independently 0, 1, or 2;

R^{60} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted

arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl ,-CN, $-NO_2$, $-OR^{64}$, $-S(O)_tR^{64}$, $-OCOR^{64}$, $-NR^{64}COR^{65}$, $-NR^{64}R^{65}$, $-CONR^{64}R^{65}$, $-CO_2R^{64}$, $-SO_2NR^{64}R^{65}$, $-NR^{64}SO_2R^{65}$, $-B(OR^{64})(OR^{65})$, $-P(O)(OR^{64})(OR^{65})$ or $-P(O)(R^{64})(OR^{65})$;

R^{61} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl ,-CN, $-NO_2$, $-OR^{66}$, $-S(O)_uR^{66}$, $-OCOR^{66}$, $-NR^{66}COR^{67}$, $-NR^{66}R^{67}$, $-CONR^{66}R^{67}$, $-CO_2R^{66}$, $-SO_2NR^{66}R^{67}$, $-NR^{66}SO_2R^{67}$, $-B(OR^{66})(OR^{67})$, $-P(O)(OR^{66})(OR^{67})$ or $-P(O)(R^{66})(OR^{67})$;

R^{62} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl ,-CN, $-NO_2$, $-OR^{68}$, $-S(O)_vR^{68}$, $-OCOR^{68}$, $-NR^{68}COR^{69}$, $-NR^{68}R^{69}$, $-CONR^{68}R^{69}$, $-CO_2R^{68}$, $-SO_2NR^{68}R^{69}$, $-NR^{68}SO_2R^{69}$, $-B(OR^{68})(OR^{69})$, $-P(O)(OR^{68})(OR^{69})$ or $-P(O)(R^{68})(OR^{69})$;

R^{63} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl ,-CN, $-NO_2$, $-OR^{70}$, $-S(O)_xR^{70}$, $-OCOR^{70}$, $-NR^{70}COR^{71}$, $-NR^{70}R^{71}$, $-CONR^{70}R^{71}$, $-CO_2R^{70}$, $-SO_2NR^{70}R^{71}$, $-NR^{70}SO_2R^{71}$, $-B(OR^{70})(OR^{71})$, $-P(O)(OR^{70})(OR^{71})$ or $-P(O)(R^{70})(OR^{71})$; or alternatively R^{60} and R^{61}, R^{61} and R^{62}, or R^{62} and R^{63} together with the atoms to which they are bonded form an aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring;

t, u, v and x are independently 0, 1 or 2;

R^{64} to R^{71} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl or alternatively R^{64} and R^{65}, R^{66} and R^{67}, R^{68} and R^{69}, or R^{70} and R^{71} together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring; and

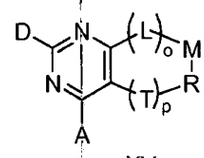
R^{47} to R^{50} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl,

heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl;

with the proviso that at most only one of L, M, R and T is a heteroatom.

In one embodiment of Formula (IV), B is -N-, and E is $-NR^{17}-$ or -N-. It is preferable that G is -C-.

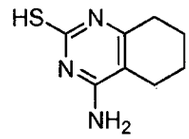
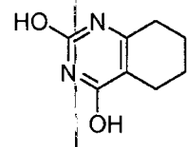
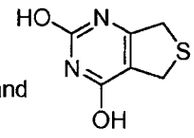
In one embodiment of Formula (IV), the compound of the present invention has structural Formula (XV):



XV

wherein D is -SH or –OH; and A is -OH, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, or $-CH_2NHC(O)CH_3$.

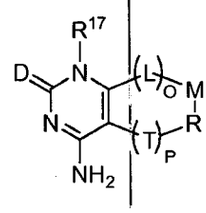
In some specific embodiments of Formula (XV), the compound has structural formula selected from the group consisting of


, 
, and 
;

or a tautomer, salt, solvate, and/or ester thereof. In some preferred embodiments, the salt of these compounds is hydrochloride or trifluoroacetate salt.

In one embodiment of Formula (IV), B is -N-; E is $-NR^{17}-$ or -N-; A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, $-OR^9$, $-SR^9$, -CN, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$ or $-NR^9C(=NH)NR^{10}R^{11}$; and D is =O, =S , $=N-OR^{15}$.

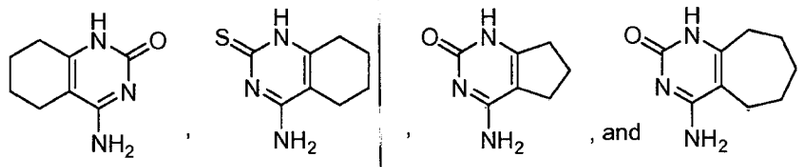
In one embodiment of Formula (IV), the compound of the present invention has structural Formula (IVb):



(IVb),

wherein L is $-CHR^{60}-$; M is $-CHR^{61}-$; R is $-CHR^{62}-$; T is $-CHR^{63}-$.

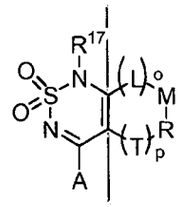
In some specific embodiments of Formula (IV), the compound has structural formula selected from the group consisting of:



;

or a tautomer, salt, solvate, and/or ester thereof. In some preferred embodiments, the salt of these compounds is hydrochloride or trifluoroacetate salt.

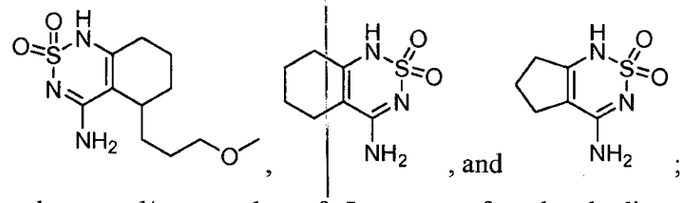
In one embodiment of Formula (IV), the compound of the present invention has structural Formula (IVa):



(IVa).

In one embodiment of Formula (IVa), L is $-CHR^{60}-$; M is $-CHR^{61}-$; R is $-CHR^{62}-$; and T is $-CHR^{63}-$. It is preferable that A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, $-OR^9$, $-SR^9$, -CN, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$ or $-NR^9C(=NH)NR^{10}R^{11}$.

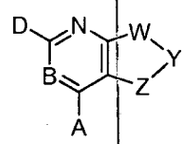
In some specific embodiments of Formula (IVa), the compound has structural formula selected from the group consisting of:



;

or a tautomer, salt, solvate, and/or ester thereof. In some preferred embodiments, the salt of these compounds is hydrochloride or trifluoroacetate salt.

In one embodiment of Formula (II), the compound of the present invention has structural Formula (Va):



(Va)

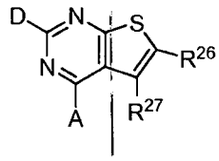
wherein D is hydrogen, alkyl, aryl, halo, -OH, $-NH_2$, $-SR^{15}$, $-CH_3$, $-CO_2H$ or $-CONH_2$; A is $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, or $-CH_2NHC(O)CH_3$; and R^{15} is hydrogen, alkyl, substituted alkyl, arylalkyl.

In one embodiment of Formula (Va), Y forms a single bond with W and a double bond with Z; W is $-C(R^{24})-$ or –N-; Y is $–C(R^{26})-$ or –N-; and Z is –S-, $-N(R^{28})$, or –O-.

In one embodiment of Formula (Va), Y forms a double bond with W and a single bond with Z; W is –S-, $-N(R^{25})$, or –O-; Y is $–C(R^{26})-$ or –N-; and Z is $-C(R^{27})-$ or –N-.

In some embodiments of Formula (Va), wherein B is $–C(R^{12})-$.

In one embodiment of Formula (Va), the compound of the present invention has structural Formula (V):



(V)

wherein:

R^{26} is hydrogen, alkyl, halo, $-CO_2R^{54}$, $-CONR^{54}R^{55}$, $-SO_2NR^{54}R^{55}$, $-NR^{54}SO_2R^{55}$, $-B(OR^{54})(OR^{55})$, $-P(O)(OR^{54})(OR^{55})$ or $-P(O)(R^{54})(OR^{55})$;

R^{27} is hydrogen, alkoxy, alkyl, substituted alkyl, halo, -CN, $-C(O)NR^{56}R^{57}$, $-CO_2R^{56}$, $-SO_2NR^{56}R^{57}$, $-NR^{56}SO_2R^{57}$, $-B(OR^{56})(OR^{57})$, $-P(O)(OR^{56})(OR^{57})$ or $-P(O)(R^{56})(OR^{57})$; or alternatively R^{52} and R^{53} together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring and

R^{54}, R^{55}, R^{56}, and R^{57} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl; or alternatively R^{54} and R^{55} or R^{56} and R^{57} together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

provided that when R^{26} and R^{27} are hydrogen, and D is –SH; then A is $-NH_2$.

In one embodiment of Formula (V),

when D is methyl, A is dimethylamino, and R^{53} is hydrogen; then R^{52} is not methyl, ethyl or carboxyl;

when D is methyl, A is dimethylamino, and R^{53} is methyl; then R^{52} is not methyl;

when D is -SCH_3, A is dimethylamino, and R^{53} is hydrogen; then R^{52} is not carboethoxy;

when D is hydrogen, A is dimethylamino, and R^{53} is hydrogen; then R^{52} is not carboxyl or carboethoxy;

when D is hydrogen, A is dimethylamino and R^{53} is methyl; then R^{52} is not methyl;

when D is hydrogen, A is methylamino and R^{53} is hydrogen; then R^{52} is not methyl, ethyl or carboethoxy;

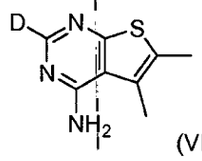
when D is hydrogen, A is methylamino and R^{53} is methyl; then R^{52} is not methyl or carboethoxy;

when D is hydrogen, A is methylamino and R^{53} is -CH_2NMe; then R^{52} is not methyl or carboethoxy;

when D is phenyl, A is methylamino and R^{53} is hydrogen then R^{52} is not methyl; and

when D is phenyl, A is -$NH(CO)CH_3$ and R^{53} is methyl then R^{52} is not carbomethoxy.

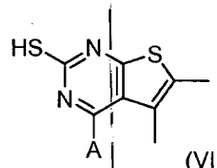
In one embodiment of Formula (V), the compound of the present invention has structural formula (VI):



(VI),

wherein D is hydrogen, -CH_3, -C_2H_5, phenyl or benzyl.

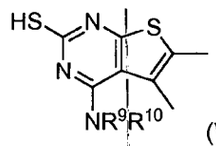
In one embodiment of Formula (V), the compound of the present invention has structural formula (VII):



(VII),

wherein A is hydrogen, -CH_3, -C_2H_5, phenyl or benzyl.

In one embodiment of Formula (V), the compound of the present invention has structural formula (VIII):



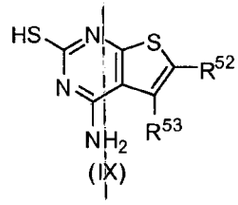
(VIII)

wherein

R^9 and R^{10} are independently hydrogen, $-CH_3$, $-C_2H_5$, phenyl or benzyl; and

provided that both R^9 and R^{10} are not hydrogen.

In one embodiment of Formula (V), the compound of the present invention has structural formula (IX):



(IX)

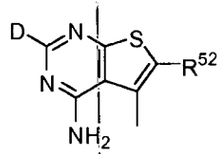
wherein

R^{52} is alkyl, substituted alkyl, -CN, $-C(O)NR^{54}R^{55}$, $-CO_2R^{54}$, $-SO_2NR^{54}R^{55}$, $-NR^{54}SO_2R^{55}$, $-B(OR^{54})(OR^{55})$, $-P(O)(OR^{54})(OR^{55})$, or $-P(O)(R^{54})(OR^{55})$;

R^{53} is alkyl, CO_2R^{56} or $-CONR^{56}R^{57}$, $-SO_2NR^{56}R^{57}$, $-NR^{56}SO_2R^{57}$, $-B(OR^{56})(OR^{57})$, $-P(O)(OR^{56})(OR^{57})$ or $-P(O)(R^{56})(OR^{57})$; and

R^{54} to R^{57} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl; or alternatively R^{52} and R^{53} together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring.

In one embodiment of Formula (V), the compound of the present invention has structural formula (X):



(X)

wherein,

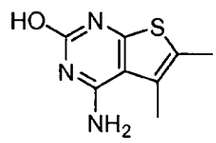
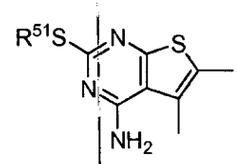
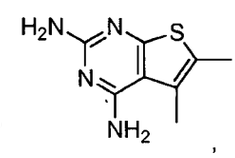
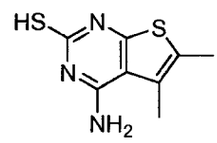
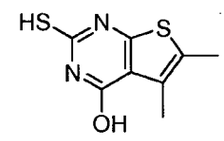
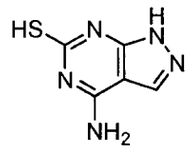
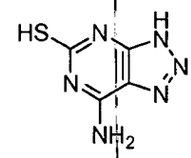
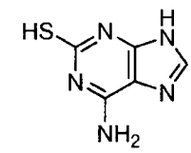
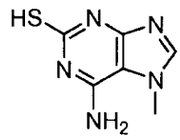
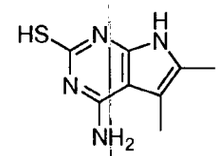
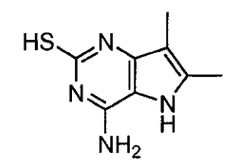
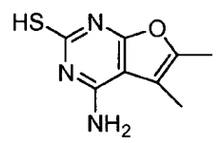
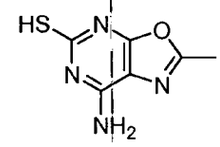
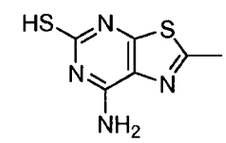
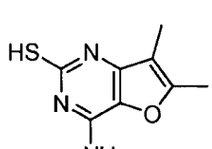
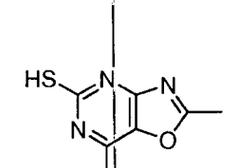
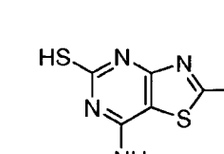
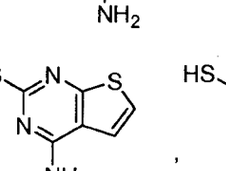
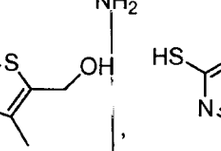
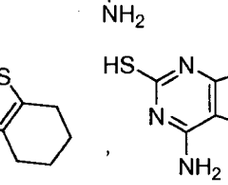
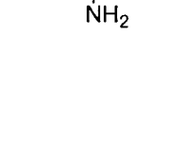
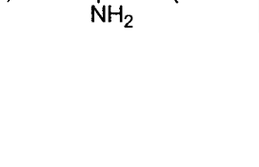
D is -OH, -SH or $-NH_2$,

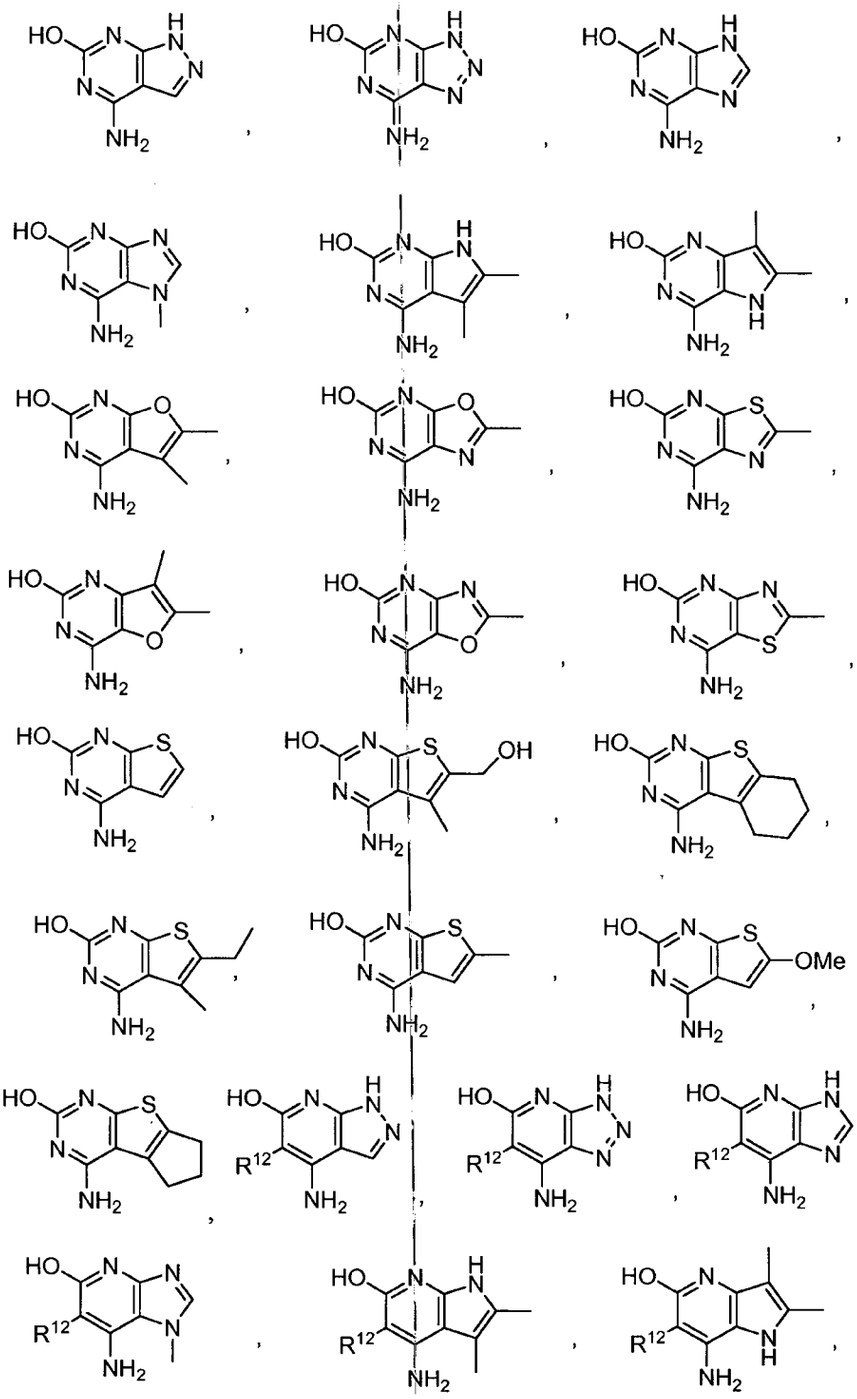
R^{52} is alkyl, substituted alkyl, alkoxy, -CN, $-C(O)NR^{54}R^{55}$, $-CO_2R^{54}$, $-SO_2NR^{54}R^{55}$, $-NR^{54}SO_2R^{55}$, $-B(OR^{54})(OR^{55})$, $-P(O)(OR^{54})(OR^{55})$, $-P(O)(R^{54})(OR^{55})$,

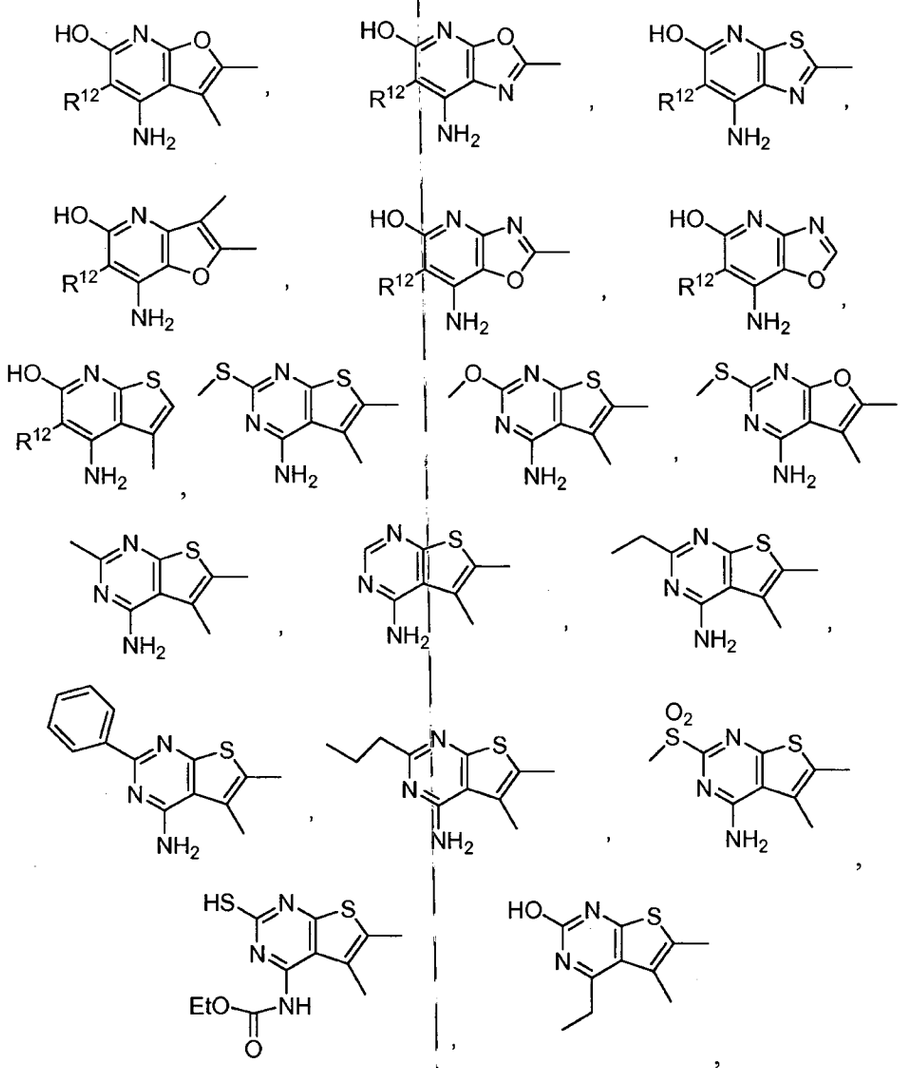
R^{54} and R^{55} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl; or alternatively

R^{54} and R^{55} together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring.

In some specific embodiments of Formula (Va), the compound has structural formula selected from the group consisting of:





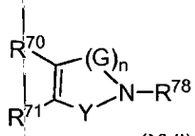
wherein,

R^{12} is –OH, -SH, -CN, $-CH_2OH$, or $–CO_2H$; and

R^{51} is $–CH_3$, $-CH_2CH_3$, benzyl, or $–CH_2CO_2CH_2CH_3$;

or a tautomer, salt, solvate, and/or ester thereof. In some preferred embodiments, the salt of these compounds is hydrochloride or trifluoroacetate salt.

In another embodiment of the present invention, the chemosensory receptor ligand modifier is a compound having a structure Formula (XVI):



(XVI)

or a tautomer, salt, solvate, and/or ester thereof wherein:

n is 1, 2 or 3;

each G is independently $-C(R^{77})(R^{79})-$, -C(O)-, $-NR^{77}-$ or $-S(O)_2-$;

provided that when n is greater than one then only one G is -C(O)-, -C(S), $-S(O)_2-$ or $-NR^{77}-$;

Y is -C(O)-, -C(S) or $-S(O)_2-$;

R^{70} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, $-NO_2$, $-OR^{72}$, $-S(O)_aR^{72}$, $-NR^{72}R^{73}$, $-CONR^{72}R^{73}$, $-CO_2R^{72}$, $-NR^{72}CO_2R^{73}$, $-NR^{72}CONR^{73}R^{74}$, $-NR^{72}CSNR^{73}R^{74}$ or $-NR^{72}C(=NH)NR^{73}R^{74}$, $-SO_2NR^{72}R^{73}$, $-NR^{72}SO_2R^{73}$, $-NR^{72}SO_2NR^{73}R^{74}$, $-B(OR^{72})(OR^{73})$, $-P(O)(OR^{72})(OR^{73})$ or $-P(O)(R^{72})(OR^{73})$;

a and b are independently 0, 1 or 2;

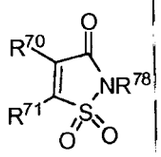
R^{71} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, $-NO_2$, $-OR^{74}$, $-S(O)_bR^{74}$, $-NR^{74}R^{75}$, $-CONR^{74}R^{75}$, $-CO_2R^{74}$, $-NR^{74}CO_2R^{75}$, $-NR^{74}CONR^{75}R^{76}$, $-NR^{74}CSNR^{75}R^{76}$ or $-NR^{74}C(=NH)NR^{75}R^{76}$, $-SO_2NR^{74}R^{75}$, $-NR^{74}SO_2R^{75}$, $-NR^{74}SO_2NR^{75}R^{76}$, $-B(OR^{74})(OR^{75})$, $-P(O)(OR^{74})(OR^{75})$, $-P(O)(R^{74})(OR^{75})$ or alternatively, R^{71} and R^{72} together with the atoms to which they are bonded form an aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring where the ring is optionally fused to another aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring;

R^{72} to R^{76} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl or alternatively, R^{72} and R^{73}, R^{73} and R^{74}, R^{74} and R^{75} and R^{75} and R^{76} together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring; and

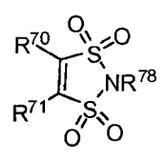
R^{77} to R^{79} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl or alternatively, R^{77} and R^{79}, together with the atoms to which they are bonded form a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring.

In some embodiments of Formula (XVI), when G is -C(O)- and R^{78} is hydrogen, R^{71} and R^{72} do not form a phenyl ring. In other embodiments, R^{70} and R^{71} together with the atoms to which they are bonded form an aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring where the ring is optionally fused to another aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring.

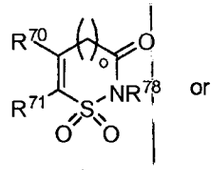
In still other embodiments of Formula (XVI), a compound of structural formula (XVII), (XVIII), (XIX) or (XX) is provided:



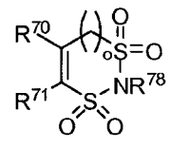
(XVII)



(XVIII)



(XIX)

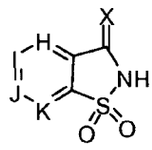


(XX)

where o is 1 or 2.

In some embodiments, R^{70} and R^{71} together with the atoms to which they are bonded form an aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring where the ring is optionally fused to another aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring.

In another embodiment of Formula (XVI), the chemosensory receptor ligand modifier is a compound having a structure Formula (XXI):



(XXI)

wherein:

X is O or S;

H is -N- or -CR^{81}-;

I is -N- or -CR^{82}-;

J is -N- or -CR^{83}-;

K is -N- or -CR^{84}-;

with the proviso that no more than 2 of H, I ,J or K are -N-;

R^{81} is hydrogen, alkoxy, -OCH_3, -OC_2H_5, -OC_3H_7, alkyl, -CH_3, -C_2H_5, -$CH(CH_3)_2$, -CH_2OH, halo, chloro, fluoro, -CH_2OCH_3, -CN, -$C(O)NR^{85}R^{86}$, -CO_2R^{85}, -$SO_2NR^{85}R^{86}$, -$NR^{85}SO_2R^{86}$, -$B(OR^{85})(OR^{86})$, -$P(O)(OR^{85})(OR^{86})$ or -$P(O)(R^{85})(OR^{86})$;

R^{82} is hydrogen, alkoxy, -OCH_3, -OC_2H_5, -OC_3H_7, alkyl, -CH_3, -C_2H_5, -$CH(CH_3)_2$, -CH_2OH, halo, chloro, fluoro, -CH_2OCH_3, -CN, -$C(O)NR^{88}R^{87}$, -CO_2R^{88}, -$SO_2NR^{88}R^{87}$, -$NR^{88}SO_2R^{87}$, -$B(OR^{88})(OR^{87})$, -$P(O)(OR^{88})(OR^{87})$ or -$P(O)(R^{88})(OR^{87})$;

R^{83} is hydrogen, alkoxy, -OCH_3, -OC_2H_5, -OC_3H_7, alkyl, -CH_3, -C_2H_5, -$CH(CH_3)_2$, -CH_2OH, halo, chloro, fluoro, -CH_2OCH_3, -CN, -$C(O)NR^{90}R^{89}$, -CO_2R^{90}, -$SO_2NR^{90}R^{89}$, -$NR^{90}SO_2R^{89}$, -$B(OR^{90})(OR^{89})$, -$P(O)(OR^{90})(OR^{89})$ or -$P(O)(R^{90})(OR^{89})$;

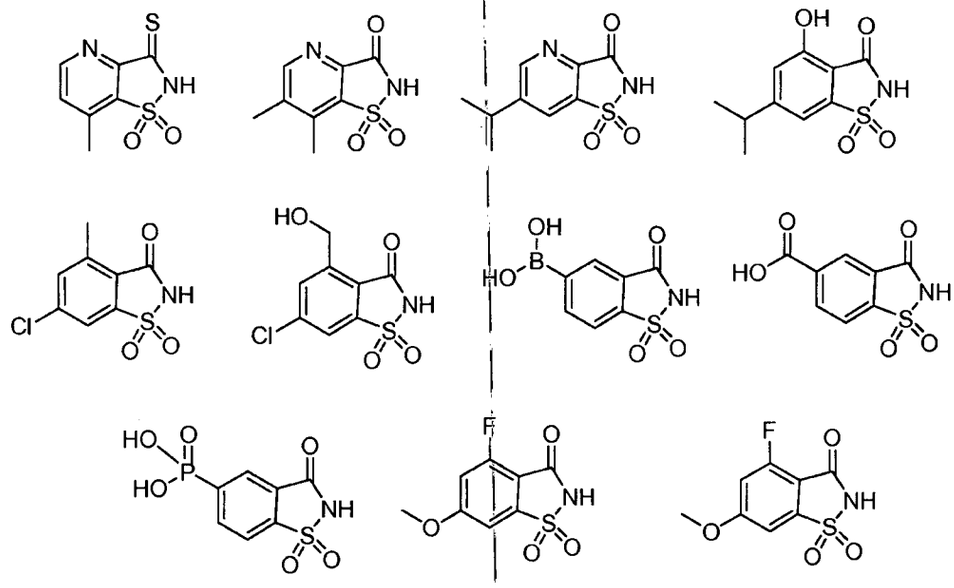
R^{84} is hydrogen, alkoxy, -OCH_3, -OC_2H_5, -OC_3H_7, alkyl, -CH_3, -C_2H_5, -$CH(CH_3)_2$, -CH_2OH, halo, chloro, fluoro, -CH_2OCH_3, -CN, -$C(O)NR^{92}R^{91}$, -CO_2R^{90}, -$SO_2NR^{92}R^{91}$, -$NR^{92}SO_2R^{91}$, -$B(OR^{92})(OR^{91})$, -$P(O)(OR^{92})(OR^{91})$ or -$P(O)(R^{92})(OR^{91})$; and

R^{85} to R^{91} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl or alternatively R^{85} and R^{86}, R^{87} and R^{88}, R^{89} and R^{90}, or R^{91} and R^{92} together with the atoms to which they are bonded form a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring;

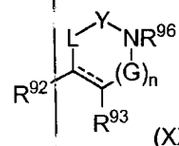
provided that R^{81}, R^{82}, R^{83} and R^{84} are not all hydrogen.

In some embodiments of Formula (XXII), R^{81}, R^{82}, R^{83} and R^{84} are independently hydrogen, alkoxy, $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, alkyl, $-CH_3$, $-C_2H_5$, $-CH(CH_3)_2$, $-CH_2OH$, halo, chloro, fluoro, $-CH_2OCH_3$, -CN, -C(O)NHMe, $-CO_2H$, $-CO_2CH_3$, $-SO_2N(CH_3)_2$, $-NHSO_2CH_3$, $-B(OH)_2$ or $-P(O)(OH)_2$.

In still other embodiments of Formula (XXII), compounds having the structures below are provided:



In another embodiment of the present invention, the chemosensory receptor ligand modifier is a compound having a structure Formula (XXII):



(XXII)

or a tautomer, salt, solvate, and/or ester thereof, wherein:

each G is independently $-C(R^{94})(R^{95})-$, -C(O)-, $-NR^{94}-$ or $-S(O)_2-$;

n is 1, 2 or 3;

provided that when n is greater than one then only one G is -C(O)-, $-S(O)_2-$ or $-NR^{94}-$;

Y is -C(O)-, -C(S)- or $-S(O)_2-$;

L is $-C(R^{104})(R^{105})-$, -O-, or $-NR^{104}-$;

R^{92} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted

heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, -NO_2, -OR^{98}, -$S(O)_yR^{98}$, -$NR^{98}R^{99}$, -$CONR^{98}R^{99}$, -CO_2R^{98}, -$NR^{98}CO_2R^{99}$, -$NR^{98}CONR^{99}R^{100}$, -$NR^{98}CSNR^{99}R^{100}$ or –$NR^{98}C(=NH)NR^{99}R^{100}$, -$SO_2NR^{98}R^{99}$, -$NR^{98}SO_2R^{99}$, -$NR^{98}SO_2NR^{99}R^{100}$, -$B(OR^{98})(OR^{99})$, -$P(O)(OR^{98})(OR^{99})$ or -$P(O)(R^{98})(OR^{99})$;

R^{93} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, -NO_2, -OR^{100}, -$S(O)_zR^{101}$, -$NR^{101}R^{102}$, -$CONR^{101}R^{102}$, -CO_2R^{101}, -$NR^{101}CO_2R^{102}$, -$NR^{101}CONR^{102}R^{103}$, -$NR^{101}CSNR^{102}R^{103}$ or –$NR^{101}C(=NH)NR^{102}R^{103}$, -$SO_2NR^{101}R^{102}$, -$NR^{101}SO_2R^{102}$, -$NR^{101}SO_2NR^{102}R^{103}$, -$B(OR^{101})(OR^{102})$, -$P(O)(OR^{101})(OR^{102})$, -$P(O)(R^{101})(OR^{102})$ or alternatively, R^{92} and R^{93} together with the atoms to which they are bonded form an aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring where the ring is optionally fused to another aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring;

y and z are independently 0, 1 or 2;

R^{98} to R^{103} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl or alternatively, R^{98} and R^{99}, R^{99} and R^{100}, R^{101} and R^{102}, or R^{102} and R^{103} together with the atoms to which they are bonded form a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring;

R^{94} to R^{95} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl or alternatively, R^{94} and R^{95}, together with the atoms to which they are bonded form a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring;

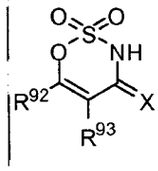
R^{96} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl; and

R^{104} to R^{105} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl,

arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl or alternatively, R^{104} and R^{105}, together with the atoms to which they are bonded form a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring.

In some embodiments, when L is O, R^{95} is hydrogen, R^{92} is methyl and the bond connecting the carbon atoms bonded to R^{92} and R^{93} is a double bond then R^{93} is not hydrogen.

In some embodiments of Formula (XXII), a compound of structural formula (XXIII) is provided:

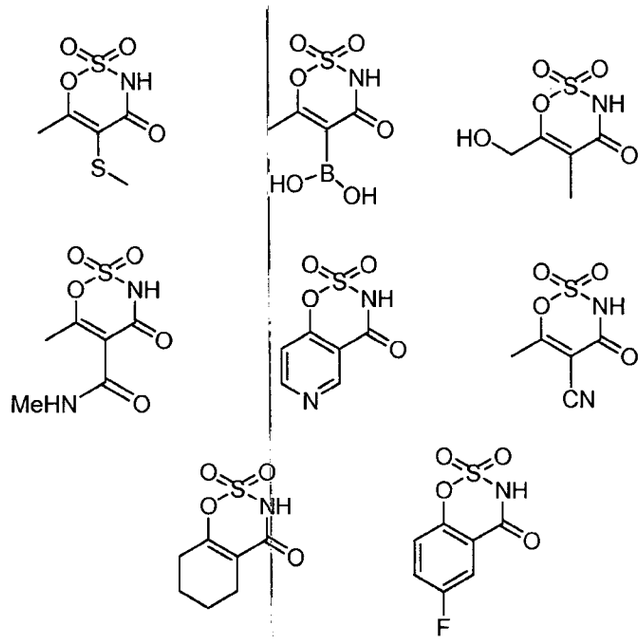


(XXIII)

where when R^{92} is $-CH_3$ then R^{93} is not hydrogen and that both R^{92} and R^{93} are not hydrogen.

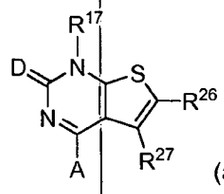
In some embodiments of Formula (XXII), R^{92} and R^{93} are independently are independently hydrogen, $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, alkyl, $-CH_3$, $-C_2H_5$, $-CH(CH_3)_2$, $-CH_2OH$, halo, chloro, fluoro, $-CH_2OCH_3$, -CN, $-SCH_3$, -C(O)NHMe, $-CO_2H$, $-CO_2CH_3$, $-SO_2N(CH_3)_2$, $-NHSO_2CH_3$, $-B(OH)_2$ or $-P(O)(OH)_2$. In other embodiments, R^{92} and R^{93} together with the atoms to which they are attached form a cycloalkyl, cycloheteroalkyl, aryl or heteroaryl ring.

In other embodiments of Formula (XXII), compounds having the structures below are provided:

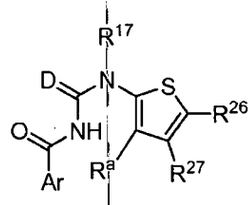


The definitions and substituents for various genus and subgenus of the present compounds have been described above in detail. It should be understood by one skilled in the art that any combination of the definitions and subsituents described above should not result in a inoperable species or compound. By "inoperable species or compound", it is meant a compound structure that violates the relevant scientific principle (such as, for example, a carbon atom connecting to more than four covalent bonds) or is so unstable that separation of the compound from a reaction is impossible (such as, for example, more than three carbonyl groups connecting to each other continuously).

In one embodiment, the present invention provides a process of preparing a compound having structural Formula (a):


(a),

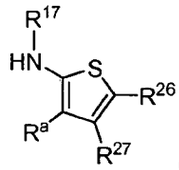
comprising reacting a compound having structural Formula (b)



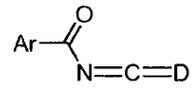
(b)

with a base, wherein D is oxygen or sulfur; A is $-NH_2$ or $-OR^b$; R^{17} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, or substituted arylalkyl; R^{26} and R^{27} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, $-NO_2$, $-OR^{31}$, $-S(O)_hR^{31}$, $-NR^{31}R^{32}$, $-CONR^{31}R^{32}$, $-CO_2R^{31}$, $-SO_2NR^{31}R^{32}$, or $-NR^{31}SO_2R^{32}$; or alternatively R^{26} and R^{27}, together with the atoms to which they are bonded, form a cycloalkyl, substituted cycloalkyl, heterocycloalkyl, or substituted heterocycloalkyl ring; Ar is aryl or substituted aryl; and R^a is -CN, $-C(O)R^b$, $-C(O)OR^b$, $-C(O)N(R^b)_2$; each R^b is independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, or substituted heteroarylalkyl; h is 0, 1 or 2; and R^{31} and R^{32} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl; or alternatively R^{31} and R^{32}, together with the atoms to which they are bonded, form a cycloheteroalkyl or substituted cycloheteroalkyl ring. It is preferable that the base is an inorganic base, such as NaOH.

In one embodiment, the compound having structural Formula (b) is prepared by reacting a compound having structural Formula (c):



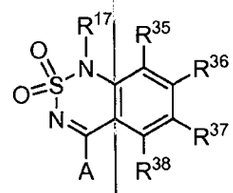
(c), with a compound having structural Formula (d):



(d).

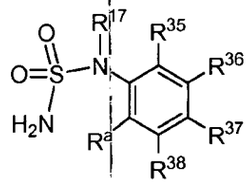
Preferably, the above Ar group is phenyl or substituted phenyl.

In another embodiment, the present invention provides a process of preparing a compound having structural Formula (e):



(e),

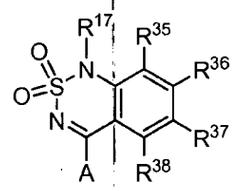
comprising reacting a compound having structural Formula (f)



(f),

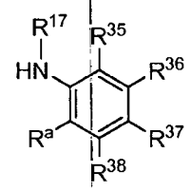
with a base, wherein A is $-NH_2$ or $-OR^b$; R^{17} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, or substituted arylalkyl; R^{35}, R^{36}, R^{37}, and R^{38} are each independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl, -CN, $-NO_2$, $-OR^{41}$, $-S(O)_kR^{41}$, $-NR^{41}R^{42}$, $-CONR^{41}R^{42}$, $-CO_2R^{41}$, $-SO_2NR^{41}R^{42}$, and $-NR^{41}SO_2R^{42}$; or alternatively, R^{35} and R^{36}, R^{36} and R^{37}, or R^{37} and R^{38}, together with the atoms to which they are bonded, form a cycloalkyl, substituted cycloalkyl, heterocycloalkyl, or substituted heterocycloalkyl ring; R^a is is -CN, $-C(O)R^b$, $-C(O)OR^b$, $-C(O)N(R^b)_2$; each R^b is independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, or substituted heteroarylalkyl; and R^{41} and R^{42} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl; or alternatively R^{41} and R^{42}, together with the atoms to which they are bonded, form a cycloheteroalkyl or substituted cycloheteroalkyl ring. It is preferable that the base is an inorganic base, such as NaOH.

In another embodiment, the present invention provides a process of preparing a compound having structural Formula (e):



(e),

comprising reacting a compound having structural Formula (g)



(g)

with $NH_2S(O)_2NH_2$ or Cl-$S(O)_2$-NH_2 in the presence of a base to provide directly a compound having structural Formula (e); or alternatively to provide the compound having structural formula (f) of claim 221 which is further reacted with a base to provide a compound having structural Formula (e). It is preferable that the base is an organic base, such as DBU.

In general, the compounds of the present invention, *e.g.*, compounds with the formulae described herein can be synthesized according to the processes described above and the following exemplary procedures and/or schemes.

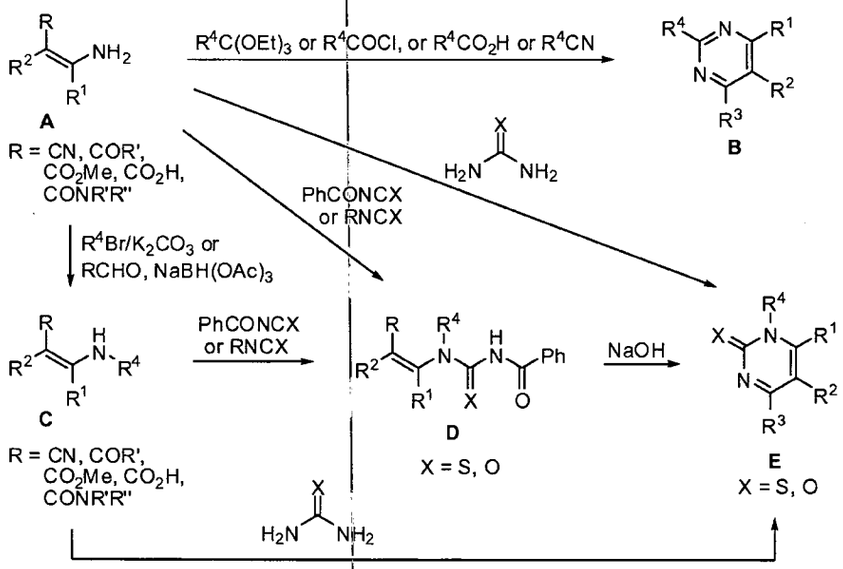
As discussed hereinabove, a salt of the compound of the present invention generally can be formed by reacting the compound with an acid or base. In one embodiment, the present invention further provides a synthetic method for preparing a salt of the compound having any of the above-mentioned structural formula at a large scale. The synthetic method enables preparation of a large quantitiy of a salt of the present compound quickly and economically. The synthetic method can be applied in either a laboratory setting or an industrial setting. One example of the synthetic method is described in details as Example 165 hereinbelow.

In general, the compounds of the present invention, *e.g.*, compounds with the formulae described herein can be synthesized according to the following exemplary procedures and/or schemes.

Pyrimidines **B** including fused pyrimidine derivatives such as quinazolines and pyrido[2,3-d]pyrimidines are synthesized from 2-amino nitriles, 2-amino ketones, or 2-amino carboxyl derivatives **A** by reaction with the corresponding carboxyl derivatives as illustrated in Scheme 1 (Rad-Moghadam *et al.*, *J. of Heterocyclic Chem.* **2006**, *43*, 913; Roy *et al.*, *J. Org.*

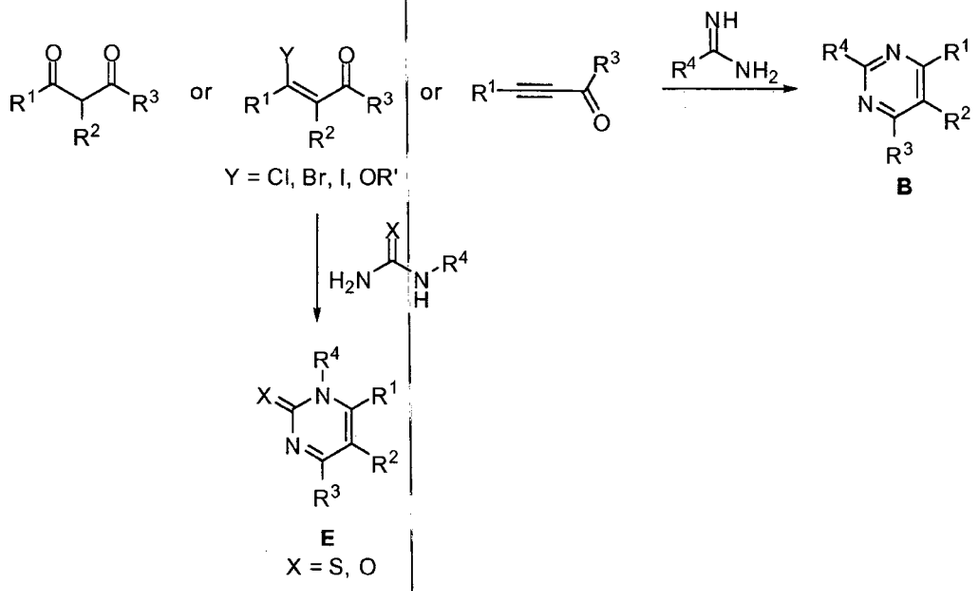
Chem. **2006**, *71*, 382; Jung *et al.*, *J. Med. Chem.* **2006**, *49*, 955; Khabnadideh *et al.*, *Bioorg. Med. Chem.* **2005**, *13*, 2637). The amino group in the starting material **A** can be further functionalized by alkylation (Brown *et al.*, *J. Med. Chem.* **1990**, *33*, 1771) or reductive amination (Uehling *et al.*, *J. Med. Chem.* **2006**, *49*, 2758, *etc.*) to provide the corresponding *N*-monosubstituted 2-amino nitriles, 2-amino ketones or 2-amino carboxyl derivatives **C**. The coupling reaction of **A** or **C** with iso(thio)cyanates such as, for example, benzoyliso(thio)cyanates and subsequent cyclization by treatment with NaOH provides the pyrimidin-2(1H)-(thi)one derivatives **E** including, but not limited to, fused pyrimidin-2(1H)-(thi)ones such as quinazolin-2(1H)-(thi)one and pyrido[2,3-d]pyrimidin-2(1H)-(thi)one derivatives (El-Sherbeny *et al.*, *Med. Chem. Rev.* **2000**, *10*, 122 and references cited therein; Reddy *et al.*, *Synthetic Commun.* **1988**, *18*, 525; Wilson, *Org. Lett.* **2001**, *3*, 585, and references cited therein). Direct cyclization of **A** or **C** with (thio)ureas in the presence of NaOH also results in the formation of pyrimidin-2(1H)-(thi)one derivatives **E** (Scheme 1) (Naganawa *et al.*, *Bioorg. Med. Chem.* **2006**, *14*, 7121 and references cited therein).

Scheme 1



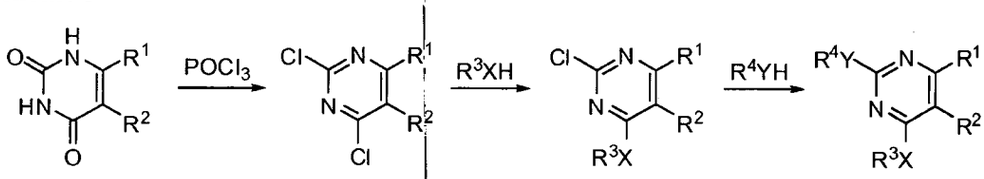
Pyrimidines **B** and pyrimidin-2(1H)-(thi)ones **E** can also be prepared from corresponding 1,3-dicarbonyl derivatives and α,β-unsaturated carbonyl derivatives by condensation with guanidines, amidines, or (thio)urea derivatives as shown in Scheme 2 (Sharma *et al.*, *Eur. J. Med. Chem.* **2006**, *41*, 83, and references cited therein; Bellur *et al.*, *Tetrahedron* **2006**, *62*, 5426 and references cited therein; Hauser *et al.*, *J. Org. Chem.* **1953**, *18*, 588).

Scheme 2



Various pyrimidines and pyrimidin-2(1H)-(thi)ones as well as their fused pyrimidine and pyrimidin-2(1H)-(thi)one derivatives such as quinazolines and quinazolin-2(1H)-ones can be synthesized from pyrimidine-2,4(1H,3H)-dione derivatives as well as the fused pyrimidine-2,4(1H,3H)-diones such as quinazoline-2,4(1H,3H)-dione and pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione derivatives (Scheme 3). Reaction of pyrimidine-2,4(1H,3H)-dione derivatives with phosgene or $POCl_3$ provides the corresponding 2,4-dichloropyrimidines (Lee *et al.*, *Synlett.* **2006**, 65 and references cited therein). Subsequent displacements of the two chlorides with various nucleophiles resulted in the formation of pyrimidines and pyrimidin-2(1H)-(thi)ones as well as fused pyrimidine and pyrimidin-2(1H)-(thi)one derivatives (Kanuma *et al.*, *Bioorg. & Med. Chem. Lett.* **2005**, *15*, 3853 and references cited therein; Liu *et al.*, *Bioorg. & Med. Chem. Lett.* **2007**, *17*, 668; Wilson *et al.*, *Bioorg. & Med. Chem.* **2007**, *15*, 77; Boarland *et al.*, *J. Chem. Soc.* **1951**, 1218).

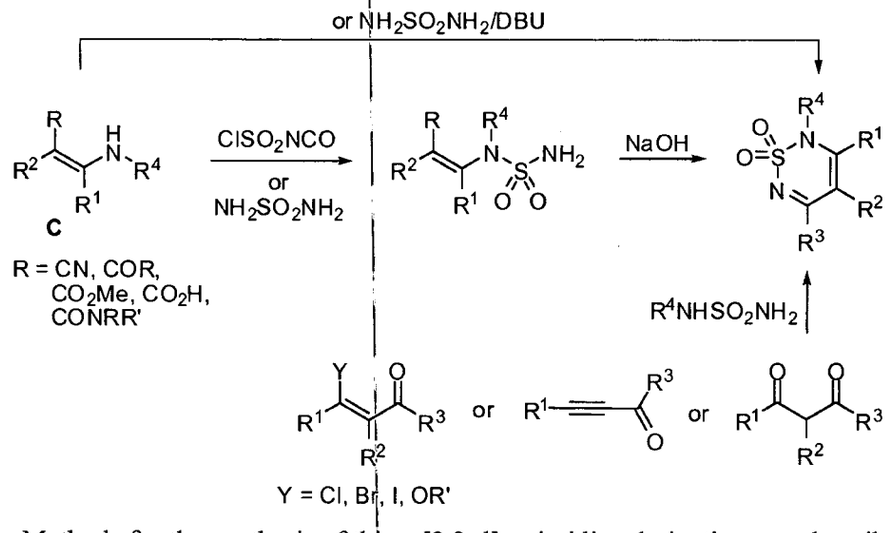
Scheme 3



Similarly, [1,2,6]thiadiazine-2,2-dioxides and fused [1,2,6]thiadiazine-2,2-dioxide derivatives such as, for example, 1H-benzo[c][1,2,6]thiadiazine-2,2-dioxides are also

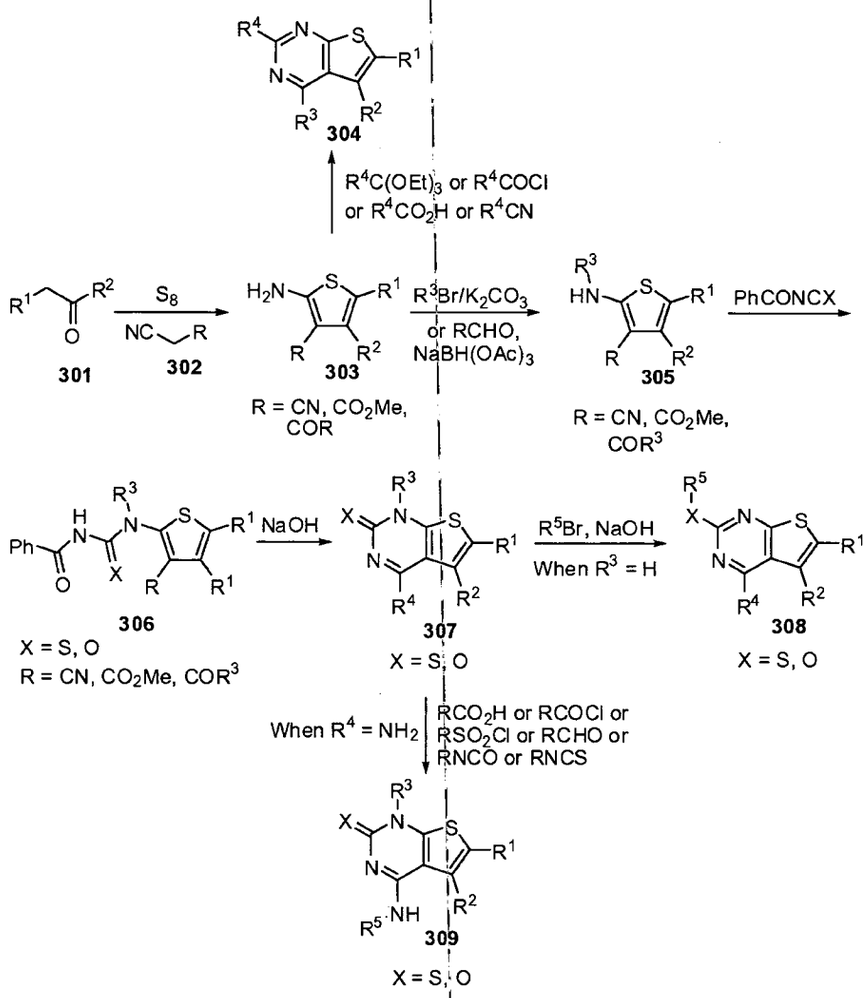
synthesized from 2-amino nitriles, 2-amino ketones, or 2-amino carboxyl derivatives **A** or **C** (Scheme 4), by reaction with NH_2SO_2Cl (Hirayama *et al.*, *Bioorg. & Med. Chem.* **2002**, *10*, 1509; Kanbe *et al.*, *Bioorg. & Med. Chem. Lett.* **2006**, *16*, 4090 and references cited therein) or $NH_2SO_2NH_2$ (Maryanoff *et al.*, *J. Med. Chem.* **2006**, *49*, 3496, and references cited therein) and followed by cyclization in the presence of NaOH (Goya *et al.*, *Heterocycles*, **1986**, *24*, 3451; Albrecht *et al.*, *J. Org. Chem.* **1979**, *44*, 4191; Goya *et al.*, *Arch. Pharm. (Weinheim)* **1984**, *317*, 777). The condensation of the corresponding 1,3-dicarbonyl derivatives, α,β-unsaturated carbonyl derivatives with sulfamide derivatives (Scheme 4) also results in the formation of [1,2,6]thiadiazine-2,2-dioxide derivatives (Wright, *J. Org. Chem.* **1964**, *29*, 1905).

Scheme 4



Methods for the synthesis of thieno[2,3-d]pyrimidine derivatives are described in Scheme 5. 2-Amino thiophene derivatives **303** are synthesized *via* the Gewald reaction (Chen *et al.*, *Synthetic Communication* **2004**, *34*, 3801 and references cited therein; Elmegeed *et al.*, *Eur. J. Med. Chem.* **2005**, *40*, 1283 and references cited therein). Compound **303** can be cyclized with the corresponding carboxyl derivatives to give the thieno[2,3-d]pyrimidine derivatives **304** (Rad-Moghadam, *J. Heterocyclic Chem.* **2006**, *43*, 913; Seijas *et al.*, *Tetrahedron Lett.* **2000**, *41*, 2215, and references cited therein; Jung *et al.*, *J. Med. Chem.* **2006**, *49*, 955.).

Scheme 5

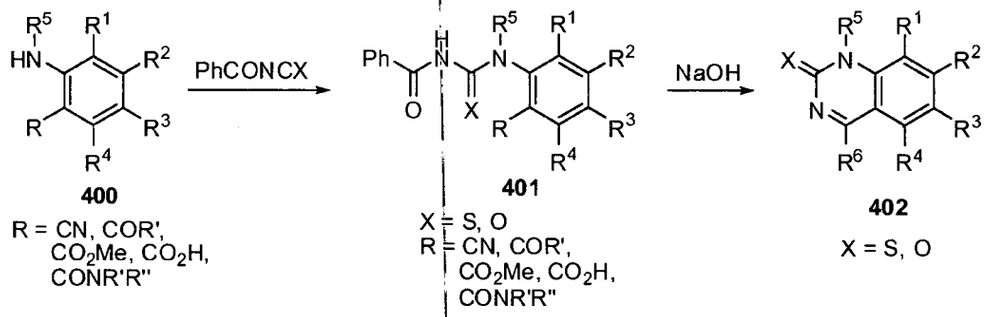


2-Amino thiophene derivatives **303** can be further alkylated by either treatment with R_3Br/K_2CO_3 or with $RCHO/NaBH(OAc)_3$ to give the *N*-alkylated 2-amino thiophene derivatives **305** (Brown *et al.*, *J. Med. Chem.* **1990**, *33*, 1771; Uehling *et al.*, *J. Med. Chem.* **2006**, *49*, 2758 and references cited therein), which are then reacted, for example, with benzoyliso(thio)cyanate to give the corresponding benzoyl (thio)urea derivatives **306**. Compounds **306** may be cyclized by treatment with NaOH to provide thieno[2,3-d]pyrimidine derivatives **7** (El-Sherbeny *et al.*, *Med. Chem. Rev.* **2000**, *10*, 122, and references cited therein; Reddy *et al.*, *Synthetic Commun.* **1988**, *18*, 525; Wilson, *Org. Lett.* **2001**, *3*, 585 and references cited therein). When R^3 = H, compounds **307** may be reacted with $R_5Br/NaOH$ to give the

alkylated products **8** (Hirota *et al.*, *Bioorg. Med. Chem.* **2003**, *11*, 2715.). When $R^4 = NH_2$, the amino group can be further functionalized to give the products **309**.

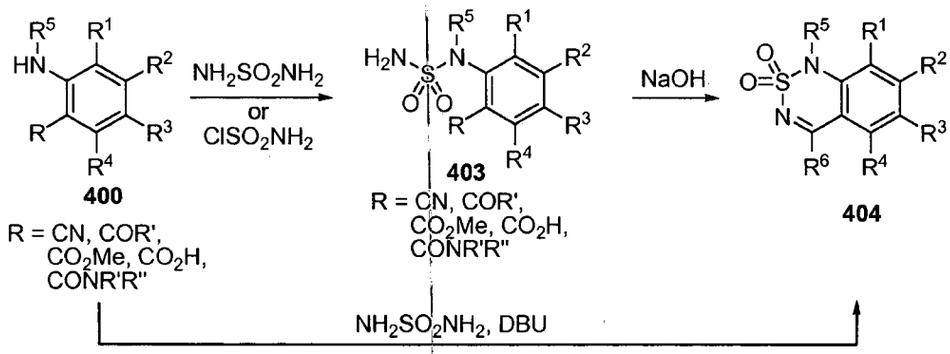
Similarly, quinazolin-2(1H)-one and quinazolin-2(1H)-thione derivatives **402** were synthesized from various 2-aminobenzoic acid derivatives, 2-aminobenzonitrile derivatives, 2-aminoacetophenone derivatives and 2-aminobenzamide derivatives **400** as shown in Scheme 6. Coupling reaction of compounds **400** with benzoyl iso(thio)cyanates lead to the formation of corresponding benzoyl (thio)urea derivatives **401**. Their cyclization in the presence of NaOH provides the quinazolin-2(1H)-(thi)one derivatives **402** (El-Sherbeny, *Med. Chem. Rev.* **2000**, *10*, 122 and references cited therein; Reddy *et al.*, *Synthetic Commun.* **1988**, *18*, 525; Wilson, *Org. Lett.* **2001**, *3*, 585 and references cited therein).

Scheme 6



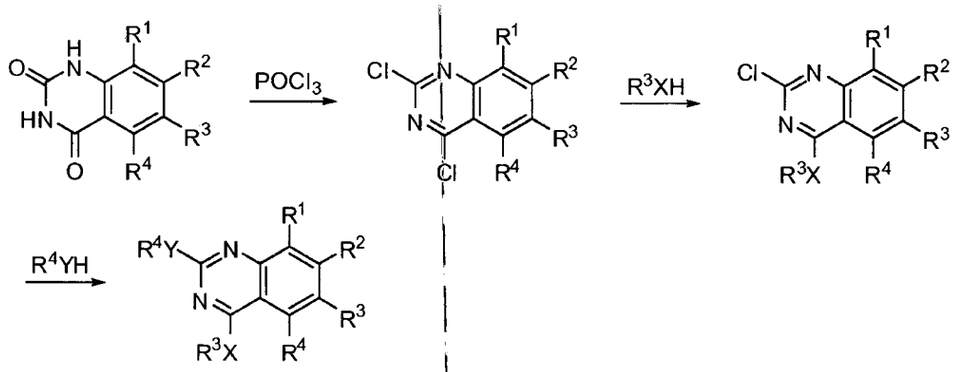
1H-benzo[c][1,2,6]thiadiazine-2,2-dioxide derivatives **404** are synthesized from the same starting materials **400** (Scheme 7) *via* their reactions with sulfamide or sulfamoyl chloride, followed by cyclization with NaOH. Direct reaction of compounds **400** with sulfamide in the presence of DBU at the elevated temperature also resulted in the formation of 1H-benzo[c][1,2,6]thiadiazine-2,2-dioxide derivatives **404** (Maryanoff *et al.*, *J. Med. Chem.* **2006**, *49*, 3496, and references cited therein).

Scheme 7



Quinazoline derivatives are also synthesized from quinazoline-2,4(1H,3H)-diones (Scheme 8). Reaction of quinazoline-2,4(1H,3H)-diones with $POCl_3$ provided the corresponding dichloroquinazolines (Zunszain *et al.*, *Bioorg. & Med. Chem.* **2005**, *13*, 3681 and references cited therein). Subsequent displacements of the two chlorides with various nucleophiles resulted in formation of quinazoline derivatives (Scheme 8) (Kanuma *et al.*, *Bioorg. & Med. Chem. Lett.* **2005**, *15*, 3853 and references cited therein; Blackburn, *Bioorg. & Med. Chem. Lett.* **2006**, *16*, 2621).

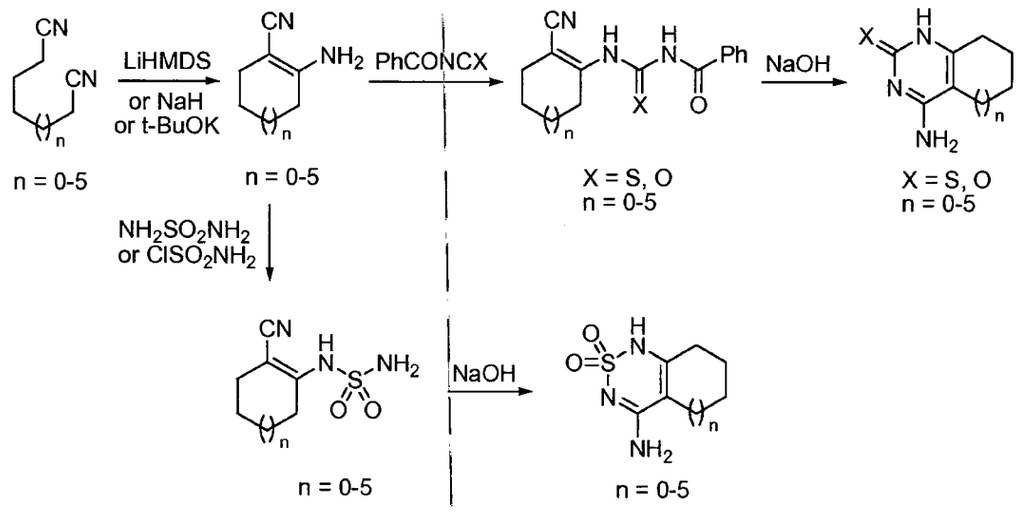
Scheme 8



4-Amino-5,6,7,8-tetrahydroquinazolin-2(1H)-(thi)one derivatives and 4-amino-5,6,7,8-tetrahydro-1H-benzo[c][1,2,6]thiadiazine-2,2-dioxide derivatives, as well as structural analogs with different ring sizes, as shown in Scheme 9, are generally synthesized according to the methods described therein. Thorpe-Ziegler cyclization of dinitriles in the presence of base provides β-amino-α,β-unsaturated nitrile derivatives (Winkler *et al.*, *Tetrahedron* **2005**, *61*, 4249; Yoshizawa *et al.*, *Green Chem.* **2002**, *4*, 68, and references cited therein; Rodriguez-Hahn *et al.*, *Synthetic Commun.* **1984**, *14*, 967, and references cited therein;

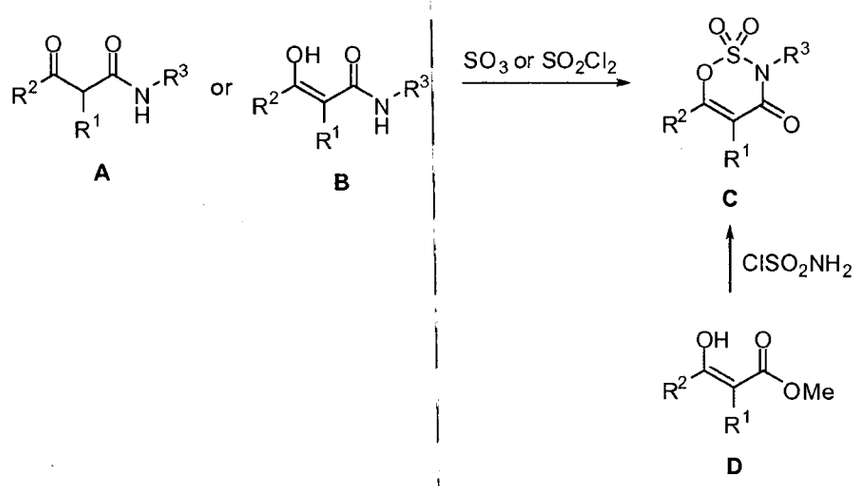
Francis *et al.*, *J. Med. Chem.* **1991**, *34*, 2899). The β-amino-α,β-unsaturated nitriles may be reacted, for example, with benzoyliso(thio)cyanate and subsequently cyclized by treatment with NaOH to provide 4-amino-5,6,7,8-tetrahydroquinazolin-2(1H)-(thi)one derivatives (El-Sherbeny *et al.*, *Med. Chem. Rev.* **2000**, *10*, 122, and references cited therein; Reddy *et al.*, *Synthetic Commun.* **1988**, *18*, 525) as well as their structural analogs with different ring sizes (Scheme 9). Similarly reaction of β-amino-α,β-unsaturated nitrile derivatives with sulfamoyl chloride, followed by treatment with NaOH provides 4-amino-5,6,7,8-tetrahydro-1H-benzo[c][1,2,6]thiadiazine-2,2-dioxide derivatives, as well as structural analogs with different ring size (Scheme 9) (Hirayama *et al.*, *Bioorg. & Med. Chem.* **2002**, *10*, 1509; Kanbe *et al.*, *Bioorg. & Med. Chem. Lett.* **2006**, *16*, 4090 and references cited therein).

Scheme 9



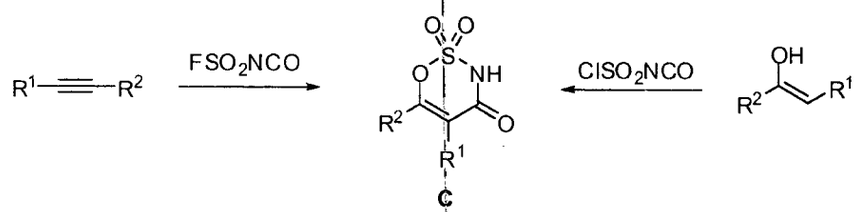
Acesulfame and fused acesulfame derivatives **C** such as benzo[e][1,2,3]oxathiazin-4(3H)-one-2,2-dioxides can be synthesized *via* the reaction of 1,3-dicarbonyl derivatives **A** or 2-hydroxy carboxyl derivatives **B** and **D** with SO_3 or $ClSO_2NH_2$, as described in Scheme 10 (Linkies *et al*, *Synthesis* **1990**, 405 and references cited therein; Ahmed *et al.*, *J. Org. Chem.* **1988**, *53*, 4112; Ahmed *et al.*, *Heterocycles* **1989**, *29*, 1391).

Scheme 10



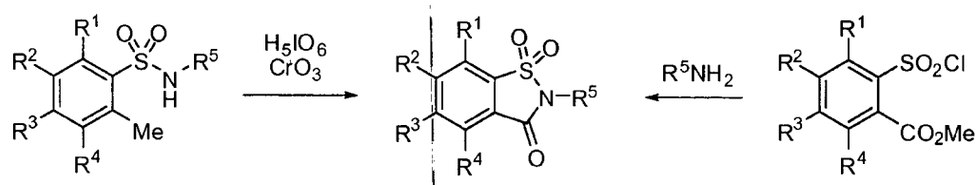
Acesulfame derivatives **C** can also be synthesized *via* cyclization of alkynes or enols with FSO_2NCO (Clauss *et al.*, *Tetrahedron Lett.* **1970**, *2*, 119) or $ClSO_2NCO$ (Rasmussen *et al.*, *J. Org. Chem.* **1973**, *38*, 2114; Etter *et al.*, *J. Org. Chem.* **1986**, *51*, 5405; Tripathi *et al.*, *Indian J. Chem. Sect. B* **1987**, *26B*, 1082.) as shown in Scheme 11.

Scheme 11



Saccharin derivatives may be synthesized by direct oxidative cyclization of N-alkyl-o-methyl-arenesulfonamides as shown in Scheme 12 (Xu *et al.*, *Tetrahedron* **2006**, *62*, 7902 and references cited therein; Pal *et al.*, *Letters in Drug Design & Discovery* **2005**, *2*, 329). Cyclization of o-carboxyl-arenesulfonyl chloride derivatives with primary amines can also provide saccharin derivatives (Robinson *et al.*, *Eur. J. Org. Chem.* **2006**, *19*, 4483 and references cited therein; Yamada *et al.*, *J. Med. Chem.* **2005**, *48*, 7457 and references cited therein; Da Settimo *et al.*, *J. Med. Chem.* **2005**, *48*, 6897). Other heteroaromatic fused isothiazol-3(2H)-one-1,1-dioxide derivatives may be synthesized similarly.

Scheme 12



According to the present invention, chemosensory receptor modifiers or chemosensory receptor ligand modifiers of the present invention can be used for one or more methods of the present invention, *e.g.*, modulating a chemosensory receptor and/or its ligands. In general, chemosensory receptor modifiers and chemosensory receptor ligand modifiers of the present invention are provided in a composition, such as, *e.g.*, an ingestible composition. As used herein, an "ingestible composition" includes any substance intended for oral consumption either alone or together with another substance. The ingestible composition includes both "food or beverage products" and "non-edible products". By "Food or beverage products", it is meant any edible product intended for consumption by humans or animals, including solids, semi-solids, or liquids (e.g., beverages). The term "non-edible products" or "noncomestible composition" includes supplements, nutraceuticals, functional food products (e.g., any fresh or processed food claimed to have a health-promoting and/or disease-preventing properties beyond the basic nutritional function of supplying nutrients), pharmaceutical and over the counter medications, oral care products such as dentifrices and mouthwashes, cosmetic products such as sweetened lip balms and other personal care products that use sucralose and or other sweeteners.

The ingestible composition also includes pharmaceutical, medicinal or comestible composition, or alternatively in a formulation, *e.g.*, a pharmaceutical or medicinal formulation or a food or beverage product or formulation.

In one embodiment, the chemosensory receptor modifiers or chemosensory receptor ligand modifiers provided by the present invention can be used at very low concentrations on the order of a few parts per million, in combination with one or more known sweeteners, natural or artificial, so as to reduce the concentration of the known sweetener required to prepare an ingestible composition having the desired degree of sweetness.

Commonly used known or artificial sweeteners for use in such combinations of sweeteners include but are not limited to the common saccharide sweeteners, *e.g.*, sucrose,

fructose, glucose, and sweetener compositions comprising natural sugars, such as corn syrup (including high fructose corm syrup) or other syrups or sweetener concentrates derived from natural fruit and vegetable sources, semi-synthetic "sugar alcohol" sweeteners such as erythritol, isomalt, lactitol, mannitol, sorbitol, xylitol, maltodextrin, and the like, and artificial sweeteners such as aspartame, saccharin, acesulfame-K, cyclamate, sucralose, and alitame. Sweeteners also include cyclamic acid, mogroside, tagatose, maltose, galactose, mannose, sucrose, fructose, lactose, neotame and other aspartame derivatives, glucose, D-tryptophan, glycine, maltitol, lactitol, isomalt, hydrogenated glucose syrup (HGS), hydrogenated starch hydrolyzate (HSH), stevioside, rebaudioside A and other sweet *Stevia*-based glycosides, carrelame and other guanidine-based sweeteners, etc. The term "sweeteners" also includes combinations of sweeteners as disclosed herein.

Chemosensory receptor modifiers and chemosensory receptor ligand modifiers of the present invention can also be provided, individually or in combination, with any ingestible composition known or later discovered. For example, the ingestible composition can be a comestible compostion or noncomestible composition. By "comestible composition", it is meant any composition that can be consumed as food by humans or animals, including solids, gel, paste, foamy material, semi-solids, liquids,or mixtures thereof. By "noncomestible composition", it is meant any composition that is intended to be consumed or used by humans or animals not as food, including solids, gel, paste, foamy material, semi-solids, liquids,or mixtures thereof. The noncomestible composition includs, but is not limited to medical composition, which refers to a noncomestible composition intended to be used by humans or animals for therapeutic purposes. By "animal", it includes any non-human animal, such as, for example, farm animals and pets.

In one embodiment, the chemosensory receptor modifiers and chemosensory receptor ligand modifiers are added to a noncomestible composition or non-edible product, such as supplements, nutraceuticals, functional food products (e.g., any fresh or processed food claimed to have a health-promoting and/or disease-preventing properties beyond the basic nutritional function of supplying nutrients), pharmaceutical and over the counter medications, oral care products such as dentifrices and mouthwashes, cosmetic products such as sweetened lip balms and other personal care products that use sucralose and or other sweeteners.

In general, over the counter (OTC) product and oral hygiene product generally refer to product for household and/or personal use which may be sold without a prescription and/or without a visit to a medical professional. Examples of the OTC products include, but are not limited to Vitamins and dietary supplements; Topical analgesics and/or anaesthetic; Cough, cold and allergy remedies; Antihistamines and/or allergy remedies; and combinations thereof. Vitamins and dietary supplements include, but are not limited to vitamins, dietary supplements, tonics/bottled nutritive drinks, child-specific vitamins, dietary supplements, any other products of or relating to or providing nutrition, and combinations thereof. Topical analgesics and/or anaesthetic include any topical creams/ointments/gels used to alleviate superficial or deep-seated aches and pains, e.g. muscle pain; teething gel; patches with analgesic ingredient; and combinations thereof. Cough, cold and allergy remedies include, but are not limited to decongestants, cough remedies, pharyngeal preparations, medicated confectionery, antihistamines and child-specific cough, cold and allergy remedies; and combination products. Antihistamines and/or allergy remedies include, but are not limited to any systemic treatments for hay fever, nasal allergies, insect bites and stings. Examples of oral hygiene product include, but are not limited to mouth cleaning strips, toothpaste, toothbrushes, mouthwashes/dental rinses, denture care, mouth fresheners at-home teeth whiteners and dental floss.

In another embodiment, the chemosensory receptor modifiers and chemosensory receptor ligand modifiers are added to food or beverage products or formulations. Examples of food and beverage products or formulations include, but are not limited to sweet coatings, frostings, or glazes for comestible products or any entity included in the Soup category, the Dried Processed Food category, the Beverage category, the Ready Meal category, the Canned or Preserved Food category, the Frozen Processed Food category, the Chilled Processed Food category, the Snack Food category, the Baked Goods category, the Confectionary category, the Dairy Product category, the Ice Cream category, the Meal Replacement category, the Pasta and Noodle category, and the Sauces, Dressings, Condiments category, the Baby Food category, and/or the Spreads category.

In general, the Soup category refers to canned/preserved, dehydrated, instant, chilled, UHT and frozen soup. 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" usually means: (i) Cooking aid products such as: powders, granules, pastes, concentrated liquid products, including concentrated bouillon, bouillon and bouillon like products in pressed cubes, tablets or powder or granulated form, which are sold separately as a finished product or as an ingredient within a product, sauces and recipe mixes (regardless of technology); (ii) Meal solutions products such as: dehydrated and freeze dried soups, including dehydrated soup mixes, dehydrated instant soups, dehydrated ready-to-cook soups, dehydrated or ambient preparations of ready-made dishes, meals and single serve 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.

The Beverage category usually means beverages, beverage mixes and concentrates, including but not limited to, carbonated and non-carbonated beverages, alcoholic and non-alcoholic beverages, ready to drink beverages, liquid concentrate formulations for preparing beverages such as sodas, and dry powdered beverage precursor mixes. The Beverage category also include the alcoholic drinks, the soft drinks, sports drinks, isotonic beverages, and hot drinks. The alcoholic drinks include, but are not limited to beer, cider/perry, FABs, wine, and spirits. The soft drinks include, but are not limited to carbonates, sucha as colas and non-cola carbonates; fruit juice, such as juice, nectars, juice drinks and fruit flavoured drinks; bottled water, which includes sparkling water, spring water and purified/table water; functional drinks, which can be carbonated or still and include sport, energy or elixir drinks; concentrates, such as liquid and powder concentrates in ready to drink measure. The hot drinks include, but are not limited to coffee, such as fresh, instant, and combined coffee; tea, such as black, green, white, oolong, and flavored tea; and other hot drinks including flavour-, malt- or plant-based powders, granules, blocks or tablets mixed with milk or water.

The Snack Food category generally refers to any food that can be a light informal meal including, but not limited to Sweet and savoury snacks and snack bars. Examples of snacke food include, but are not limited to fruit snacks, chips/crisps, extruded snacks, tortilla/corn chips, popcorn, pretzels, nuts and other sweet and savoury snacks. Examples of snack bars include, but are not limited to granola/muesli bars, breakfast bars, energy bars, fruit bars and other snack bars.

The Baked Goods category generally refers to any edible product the process of preparing which involves exposure to heat or excessive sunlight. Examples of baked goods include, but are not limited to bread, buns, cookies, muffins, cereal, toaster pastries, pastries, waffles, tortillas, biscuits, pies, bagels, tarts, quiches, cake, any baked foods, and any combination thereof.

The Ice Cream category generally refers to frozen dessert containing cream and sugar and flavoring. Examples of ice cream include, but are not limited to: impulse ice cream; take-home ice cream; frozen yoghurt and artisanal ice cream; soy, oat, bean (e.g., red bean and mung bean), and rice-based ice creams.

The Confectionary category generally refers to edible product that is sweet to the taste. Examples of confectionary include, but are not limited to candies, gelatins, chocolate confectionery, sugar confectionery, gum, and the likes and any combination products.

The Meal Replacement categroy generally refers to any food intended to replace the normal meals, particularly for people having health or fitness concerns. Examples of meal replacment include, but are not limited to slimming products and convalescence products.

The Ready Meal category generally refers to any food that can be served as meal without extensive preparation or processing. The read meal include products that have had recipe "skills" added to them by the manufacturer, resulting in a high degree of readiness, completion and convenience. Examples of ready meal include, but are not limited to canned/preserved, frozen, dried, chilled ready meals; dinner mixes; frozen pizza; chilled pizza; and prepared salads.

The Pasta and Noodle categroy includes any pastas and/or noodles including, but not limited to canned, dried and chilled/fresh pasta; and plain, instant, chilled, frozen and snack noodles.

The Canned/Preserved Food category includes, but is not limited to canned/preserved meat and meat products, fish/seafood, vegetables, tomatoes, beans, fruit, ready meals, soup, pasta, and other canned/preserved foods.

The Frozen Processed Food category includes, but is not limited to frozen processed red meat, processed poultry, processed fish/seafood, processed vegetables, meat substitutes, processed potatoes, bakery products, desserts, ready meals, pizza, soup, noodles, and other frozen food.

The Dried Processed Food category includes, but is not limited to rice, dessert mixes, dried ready meals, dehydrated soup, instant soup, dried pasta, plain noodles, and instant noodles.

The Chill Processed Food categroy includes, but is not limited to chilled processed meats, processed fish/seafood products, lunch kits, fresh cut fruits, ready meals, pizza, prepared salads, soup, fresh pasta and noodles.

The Sauces, Dressings and Condiments category includes, but is not limited to tomato pastes and purees, bouillon/stock cubes, herbs and spices, monosodium glutamate (MSG), table sauces, soy based sauces, pasta sauces, wet/cooking sauces, dry sauces/powder mixes, ketchup, mayonnaise, mustard, salad dressings, vinaigrettes, dips, pickled products, and other sauces, dressings and condiments.

The Baby Food categroy includes, but is note limted to milk- or soybean-based formula; and prepared, dried and other baby food.

The Spreads category includes, but is not limited to jams and preserves, honey, chocolate spreads, nut based spreads, and yeast based spreads.

The Dairy Product category generally refers to edible product produced from mammal's milk. Examples of dariy product include, but are not limited to drinking milk products, cheese, yoghurt and sour milk drinks, and other dairy products.

Additional examples for comestible composition, particularly food and beverage products or formulations, are provided as follows. Exemplary comestible compositions include one or more confectioneries, chocolate confectionery, tablets, countlines, bagged selflines/softlines, boxed assortments, standard boxed assortments, twist wrapped miniatures, seasonal chocolate, chocolate with toys, alfajores, other chocolate confectionery, mints, standard mints, power mints, boiled sweets, pastilles, gums, jellies and chews, toffees, caramels and

nougat, medicated confectionery, lollipops, liquorice, other sugar confectionery, gum, chewing gum, sugarized gum, sugar-free gum, functional gum, bubble gum, bread, packaged/industrial bread, unpackaged/artisanal bread, pastries, cakes, packaged/industrial cakes, unpackaged/artisanal cakes, cookies, chocolate coated biscuits, sandwich biscuits, filled biscuits, savory biscuits and crackers, bread substitutes, breakfast cereals, rte cereals, family breakfast cereals, flakes, muesli, other cereals, children's breakfast cereals, hot cereals, ice cream, impulse ice cream, single portion dairy ice cream, single portion water ice cream, multi-pack dairy ice cream, multi-pack water ice cream, take-home ice cream, take-home dairy ice cream, ice cream desserts, bulk ice cream, take-home water ice cream, frozen yoghurt, artisanal ice cream, dairy products, milk, fresh/pasteurized milk, full fat fresh/pasteurized milk, semi skimmed fresh/pasteurized milk, long-life/uht milk, full fat long life/uht milk, semi skimmed long life/uht milk, fat-free long life/uht milk, goat milk, condensed/evaporated milk, plain condensed/evaporated milk, flavored, functional and other condensed milk, flavored milk drinks, dairy only flavored milk drinks, flavored milk drinks with fruit juice, soy milk, sour milk drinks, fermented dairy drinks, coffee whiteners, powder milk, flavored powder milk drinks, cream, cheese, processed cheese, spreadable processed cheese, unspreadable processed cheese, unprocessed cheese, spreadable unprocessed cheese, hard cheese, packaged hard cheese, unpackaged hard cheese, yoghurt, plain/natural yoghurt, flavored yoghurt, fruited yoghurt, probiotic yoghurt, drinking yoghurt, regular drinking yoghurt, probiotic drinking yoghurt, chilled and shelf-stable desserts, dairy-based desserts, soy-based desserts, chilled snacks, fromage frais and quark, plain fromage frais and quark, flavored fromage frais and quark, savory fromage frais and quark, sweet and savory snacks, fruit snacks, chips/crisps, extruded snacks, tortilla/corn chips, popcorn, pretzels, nuts, other sweet and savory snacks, snack bars, granola bars, breakfast bars, energy bars, fruit bars, other snack bars, meal replacement products, slimming products, convalescence drinks, ready meals, canned ready meals, frozen ready meals, dried ready meals, chilled ready meals, dinner mixes, frozen pizza, chilled pizza, soup, canned soup, dehydrated soup, instant soup, chilled soup, hot 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 purees, 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. Exemplary comestible compositions also include 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. Exemplary comestible compositions also include breakfast cereals, sweet beverages or solid or liquid concentrate compositions for preparing beverages, ideally so as to enable the reduction in concentration of previously known saccharide sweeteners, or artificial sweeteners.

Typically at least a chemosensory receptor modulating amount, a chemosensory receptor ligand modulating amount, a sweet flavor modulating amount, a sweet flavoring agent amount, or a sweet flavor enhancing amount of one or more of the chemosensory receptor modifiers or chemosensory receptor ligand modifiers of the present invention will be added to the comestible or medicinal product, optionally in the presence of known sweeteners, *e.g.*, so that the sweet flavor modified comestible or medicinal product has an increased sweet taste as compared to the comestible or medicinal product prepared without the modifiers of the present

invention, 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 commonly known in the field.

The concentration of sweet flavoring agent needed to modulate or improve the flavor of the comestible or medicinal product or composition will of course depend on many variables, including the specific type of comestible composition and its various other ingredients, especially the presence of other known sweet flavoring agents and the concentrations thereof, the natural genetic variability and individual preferences and health conditions of various human beings tasting the compositions, and the subjective effect of the particular compound on the taste of such chemosensory compounds.

One application of the chemosensory receptor modifiers and/or chemosensory receptor ligand modifiers is for modulating (inducing, enhancing or inhibiting) the sweet taste or other taste properties of other natural or synthetic sweet tastants, and comestible compositions made therefrom. A broad but also low range of concentrations of the compounds or entities of the present invention 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 10 ppm, from about 0.01 ppm to about 5 ppm, or from about 0.02 ppm to about 2 ppm, or from about 0.01 ppm to about 1 ppm.

In yet another embodiment, the chemosensory receptor modifier and chemosensory receptor ligand modifier of the present invention can be provided in pharmaceutical compositions containing a therapeutically effective amount of one or more compounds of the present invention, preferably in purified form, together with a suitable amount of a pharmaceutically acceptable vehicle, so as to provide the form for proper administration to a patient.

When administered to a patient, the compounds of the present invention and pharmaceutically acceptable vehicles are preferably sterile. Water is a preferred vehicle when a compound of the present invention is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid vehicles, particularly for injectable solutions. Suitable pharmaceutical vehicles also include excipients such as starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol

and the like. The present pharmaceutical compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. In addition, auxiliary, stabilizing, thickening, lubricating and coloring agents may be used.

Pharmaceutical compositions comprising a compound of the present invention may be manufactured by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes. Pharmaceutical compositions may be formulated in conventional manner using one or more physiologically acceptable carriers, diluents, excipients or auxiliaries, which facilitate processing of compounds of the present invention into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

The present pharmaceutical compositions can take the form of solutions, suspensions, emulsion, tablets, pills, pellets, capsules, capsules containing liquids, powders, sustained-release formulations, suppositories, emulsions, aerosols, sprays, suspensions, or any other form suitable for use. In some embodiments, the pharmaceutically acceptable vehicle is a capsule (see *e.g.*, Grosswald *et al.*, United States Patent No. 5,698,155). Other examples of suitable pharmaceutical vehicles have been described in the art (see Remington: The Science and Practice of Pharmacy, Philadelphia College of Pharmacy and Science, 20th Edition, 2000).

For topical administration a compound of the present invention may be formulated as solutions, gels, ointments, creams, suspensions, *etc.* as is well-known in the art.

Systemic formulations include those designed for administration by injection, *e.g.*, subcutaneous, intravenous, intramuscular, intrathecal or intraperitoneal injection, as well as those designed for transdermal, transmucosal, oral or pulmonary administration. Systemic formulations may be made in combination with a further active agent that improves mucociliary clearance of airway mucus or reduces mucous viscosity. These active agents include, but are not limited to, sodium channel blockers, antibiotics, N-acetyl cysteine, homocysteine and phospholipids.

In some embodiments, the compounds of the present invention are formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compounds of the present invention for intravenous administration are solutions in sterile isotonic aqueous buffer. For injection, a compound of the present invention may be formulated in aqueous solutions, preferably in physiologically

compatible buffers such as Hanks' solution, Ringer's solution, or physiological saline buffer. The solution may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. When necessary, the pharmaceutical compositions may also include a solubilizing agent.

Pharmaceutical compositions for intravenous administration may optionally include a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. When the compound of the present invention is administered by infusion, it can be dispensed, for example, with an infusion bottle containing sterile pharmaceutical grade water or saline. When the compound of the present invention is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

Pharmaceutical compositions for oral delivery may be in the form of tablets, lozenges, aqueous or oily suspensions, granules, powders, emulsions, capsules, syrups, or elixirs, for example. Orally administered pharmaceutical compositions may contain one or more optionally agents, for example, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry coloring agents and preserving agents, to provide a pharmaceutically palatable preparation.

Moreover, where in tablet or pill form, the pharmaceutical compositions may be coated to delay disintegration and absorption in the gastrointestinal tract, thereby providing a sustained action over an extended period of time. Selectively permeable membranes surrounding an osmotically active driving compound are also suitable for orally administered compounds of the present invention. In these later platforms, fluid from the environment surrounding the capsule is imbibed by the driving compound, which swells to displace the agent or agent composition through an aperture. These delivery platforms can provide an essentially zero order delivery profile as opposed to the spiked profiles of immediate release formulations. A time delay material such as glycerol monostearate or glycerol stearate may also be used. Oral compositions can include standard vehicles such as mannitol, lactose, starch, magnesium

stearate, sodium saccharine, cellulose, magnesium carbonate, *etc.* Such vehicles are preferably of pharmaceutical grade.

For oral liquid preparations such as, for example, suspensions, elixirs and solutions, suitable carriers, excipients or diluents include water, saline, alkyleneglycols (*e.g.*, propylene glycol), polyalkylene glycols (*e.g.*, polyethylene glycol) oils, alcohols, slightly acidic buffers between pH 4 and pH 6 (*e.g.*, acetate, citrate, ascorbate at between about 5.0 mM to about 50.0 mM) *etc.* Additionally, flavoring agents, preservatives, coloring agents, bile salts, acylcarnitines and the like may be added.

For buccal administration, the pharmaceutical compositions may take the form of tablets, lozenges, *etc.* formulated in conventional manner.

Liquid drug formulations suitable for use with nebulizers and liquid spray devices and EHD aerosol devices will typically include a compound of the present invention with a pharmaceutically acceptable vehicle. Preferably, the pharmaceutically acceptable vehicle is a liquid such as alcohol, water, polyethylene glycol or a perfluorocarbon. Optionally, another material may be added to alter the aerosol properties of the solution or suspension of compounds of the invention. Preferably, this material is liquid such as an alcohol, glycol, polyglycol or a fatty acid. Other methods of formulating liquid drug solutions or suspension suitable for use in aerosol devices are known to those of skill in the art (see, *e.g.*, Biesalski, United States Patent No. 5,112,598; Biesalski, United States Patent No. 5,556,611).

A compound of the present invention may also be formulated in rectal or vaginal pharmaceutical compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, a compound of the present invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, a compound of the present invention may be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

When a compound of the present invention is acidic, it may be included in any of the above-described formulations as the free acid, a pharmaceutically acceptable salt, a solvate or

hydrate. Pharmaceutically acceptable salts substantially retain the activity of the free acid, may be prepared by reaction with bases and tend to be more soluble in aqueous and other protic solvents than the corresponding free acid form.

A compound of the present invention, and/or pharmaceutical composition thereof, will generally be used in an amount effective to achieve the intended purpose. For use to treat or prevent diseases or disorders the compounds of the present invention and/or pharmaceutical compositions thereof, are administered or applied in a therapeutically effective amount.

The amount of a compound of the present invention that will be effective in the treatment of a particular disorder or condition disclosed herein will depend on the nature of the disorder or condition and can be determined by standard clinical techniques known in the art. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. The amount of a compound of the present invention administered will, of course, be dependent on, among other factors, the subject being treated, the weight of the subject, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

For example, the dosage may be delivered in a pharmaceutical composition by a single administration, by multiple applications or controlled release. In some embodiment, the compounds of the present invention are delivered by oral sustained release administration. Dosing may be repeated intermittently, may be provided alone or in combination with other drugs and may continue as long as required for effective treatment of the disease state or disorder.

Suitable dosage ranges for oral administration depend on potency, but are generally between about 0.001 mg to about 200 mg of a compound of the present invention per kilogram body weight. Dosage ranges may be readily determined by methods known to the artisan of ordinary skill the art.

Suitable dosage ranges for intravenous (i.v.) administration are about 0.01 mg to about 100 mg per kilogram body weight. Suitable dosage ranges for intranasal administration are generally about 0.01 mg/kg body weight to about 1 mg/kg body weight. Suppositories generally contain about 0.01 milligram to about 50 milligrams of a compound of the present invention per kilogram body weight and comprise active ingredient in the range of about 0.5% to about 10% by weight. Recommended dosages for intradermal, intramuscular, intraperitoneal,

subcutaneous, epidural, sublingual or intracerebral administration are in the range of about 0.001 mg to about 200 mg per kilogram of body weight. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems. Such animal models and systems are well-known in the art.

Preferably, a therapeutically effective dose of a compound of the present invention described herein will provide therapeutic benefit without causing substantial toxicity. Toxicity of compounds of the present invention may be determined using standard pharmaceutical procedures and may be readily ascertained by the skilled artisan. The dose ratio between toxic and therapeutic effect is the therapeutic index. A compound of the present invention will preferably exhibit particularly high therapeutic indices in treating disease and disorders. The dosage of a compound of the present invention described herein will preferably be within a range of circulating concentrations that include an effective dose with little or no toxicity.

In certain embodiments of the present invention, the compounds of the present invention and/or pharmaceutical compositions thereof can be used in combination therapy with at least one other agent. The compound of the present invention and/or pharmaceutical composition thereof and the other agent can act additively or, more preferably, synergistically. In some embodiments, a compound of the present invention and/or pharmaceutical composition thereof is administered concurrently with the administration of another agent, which may be part of the same pharmaceutical composition as the compound of the present invention or a different pharmaceutical composition. In other embodiments, a pharmaceutical composition of the present invention is administered prior or subsequent to administration of another agent.

In still another embodiment, the chemosensory receptor modifiers and chemosensory receptor ligand modifiers of the present invention and/or pharmaceutical compositions thereof may be advantageously used in human medicine.

When used to treat and/or prevent diseases or disorders, the compounds described herein and/or pharmaceutical compositions may be administered or applied singly, or in combination with other agents. The compounds and/or pharmaceutical compositions thereof may also be administered or applied singly, in combination with other active agents.

Methods of treatment and prophylaxis by administration to a patient of a therapeutically effective amount of a compound described herein and/or pharmaceutical

composition thereof are provided herein. The patient may be an animal, more preferably, a mammal and most preferably, a human.

In one example, the compounds described herein and/or pharmaceutical compositions thereof, are administered orally. The compounds of the present invention and/or pharmaceutical compositions thereof may also be administered by any other convenient route, for example, by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, rectal and intestinal mucosa, *etc.*). Administration can be systemic or local. Various delivery systems are known, (*e.g.*, encapsulation in liposomes, microparticles, microcapsules, capsules, *etc.*) that can be used to administer a compound described herein and/or pharmaceutical composition thereof. Methods of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, intranasal, intracerebral, intravaginal, transdermal, rectally, by inhalation, or topically, particularly to the ears, nose, eyes, or skin. The preferred mode of administration is left to the discretion of the practitioner and will depend in-part upon the site of the medical condition. In most instances, administration will result in the release of the compounds and/or pharmaceutical compositions thereof into the bloodstream.

In another example, it may be desirable to administer one or more compounds of the present invention and/or pharmaceutical composition thereof locally to the area in need of treatment. This may be achieved, for example, and not by way of limitation, by local infusion during surgery, topical application, *e.g.*, in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. In one embodiment, administration can be by direct injection at the site (or former site) of the condition.

In yet another example, it may be desirable to introduce one or more compounds of the present invention and/or pharmaceutical compositions thereof into the central nervous system by any suitable route, including intraventricular, intrathecal and epidural injection. Intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir.

A compound of the present invention and/or pharmaceutical composition thereof may also be administered directly to the lung by inhalation. For administration by inhalation, a

compound of the present invention and/or pharmaceutical composition thereof may be conveniently delivered to the lung by a number of different devices. For example, a Metered Dose Inhaler ("MDI"), which utilizes canisters that contain a suitable low boiling propellant, (*e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or any other suitable gas) may be used to deliver compounds of the present invention and/or pharmaceutical compositions thereof directly to the lung.

Alternatively, a Dry Powder Inhaler ("DPI") device may be used to administer a compound of the invention and/or pharmaceutical composition thereof to the lung. DPI devices typically use a mechanism such as a burst of gas to create a cloud of dry powder inside a container, which may then be inhaled by the patient. DPI devices are also well known in the art. A popular variation is the multiple dose DPI ("MDDPI") system, which allows for the delivery of more than one therapeutic dose. For example, capsules and cartridges of gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the present invention and a suitable powder base such as lactose or starch for these systems.

Another type of device that may be used to deliver a compound of the present invention and/or pharmaceutical composition thereof to the lung is a liquid spray device supplied, for example, by Aradigm Corporation, Hayward, CA. Liquid spray systems use extremely small nozzle holes to aerosolize liquid drug formulations that may then be directly inhaled into the lung.

In yet another example, a nebulizer is used to deliver a compound of the present invention and/or pharmaceutical composition thereof to the lung. Nebulizers create aerosols from liquid drug formulations by using, for example, ultrasonic energy to form fine particles that may be readily inhaled (see *e.g.*, Verschoyle *et al.*, *British J. Cancer*, **1999**, 80, Suppl. 2, 96). Examples of nebulizers include devices supplied by Sheffield Pharmaceuticals, Inc (See, Armer *et al.*, United States Patent No. 5,954,047; van der Linden *et al.*, United States Patent No. 5,950,619; van der Linden *et al.*, United States Patent No. 5,970,974), and Batelle Pulmonary Therapeutics, Columbus, OH.

In yet another example, an electrohydrodynamic ("EHD") aerosol device is used to deliver a compound of the present invention and/or pharmaceutical composition thereof to the lung. EHD aerosol devices use electrical energy to aerosolize liquid drug solutions or suspensions (see *e.g.*, Noakes *et al.*, United States Patent No. 4,765,539). The electrochemical

properties of the formulation may be important parameters to optimize when delivering a compound of the present invention and/or pharmaceutical composition thereof to the lung with an EHD aerosol device and such optimization is routinely performed by one of skill in the art. EHD aerosol devices may more efficiently deliver compounds to the lung than other pulmonary delivery technologies.

In yet another example, the compounds of the present invention and/or pharmaceutical compositions thereof can be delivered in a vesicle, in particular a liposome (Langer, **1990**, *Science* 249:1527-1533; Treat *et al.*, in "Liposomes in the Therapy of Infectious Disease and Cancer," Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353-365 (1989); *see* generally "Liposomes in the Therapy of Infectious Disease and Cancer," Lopez-Berestein and Fidler (eds.), Liss, New York, pp.353-365 (1989)).

In yet another example, the compounds of the present invention and/or pharmaceutical compositions thereof can be delivered *via* sustained release systems, preferably oral sustained release systems. In one embodiment, a pump may be used (See, Langer, *supra*, Sefton, **1987**, *CRC Crit. Ref. Biomed Eng.* 14:201; Saudek *et al.*, **1989**, *N. Engl. J Med.* 321:574).

In yet another example, polymeric materials can be used (*see* "Medical Applications of Controlled Release," Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); "Controlled Drug Bioavailability," Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Langer *et al.*, **1983**, *J Macromol. Sci. Rev. Macromol Chem.* 23:61; *see also* Levy *et al.*, **1985**, *Science* 228: 190; During *et al.*, **1989**, *Ann. Neurol.* 25:351; Howard *et al.*, **1989**, *J. Neurosurg.* 71:105).

In still other embodiments, polymeric materials are used for oral sustained release delivery. Preferred polymers include sodium carboxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose and hydroxyethylcellulose (most preferred, hydroxypropyl methylcellulose). Other preferred cellulose ethers have been described (Alderman, *Int. J. Pharm. Tech. & Prod. Mfr.*, **1984**, 5(3) 1-9). Factors affecting drug release are well known to the skilled artisan and have been described in the art (Bamba *et al.*, *Int. J. Pharm.*, **1979**, 2, 307).

In yet another example, enteric-coated preparations can be used for oral sustained release administration. Preferred coating materials include polymers with a pH-dependent solubility (*i.e.*, pH-controlled release), polymers with a slow or pH-dependent rate of swelling,

dissolution or erosion (*i.e.*, time-controlled release), polymers that are degraded by enzymes (*i.e.*, enzyme-controlled release) and polymers that form firm layers that are destroyed by an increase in pressure (*i.e.*, pressure-controlled release).

In still another example, osmotic delivery systems are used for oral sustained release administration (Verma *et al.*, *Drug Dev. Ind. Pharm.*, **2000**, 26:695-708). In yet other embodiments, OROS™ osmotic devices are used for oral sustained release delivery devices (Theeuwes *et al.*, United States Patent No. 3,845,770; Theeuwes *et al.*, United States Patent No. 3,916,899).

In still another example, a controlled-release system can be placed in proximity of the target of the compounds and/or pharmaceutical composition of the invention, thus requiring only a fraction of the systemic dose (See, *e.g.*, Goodson, in "Medical Applications of Controlled Release," *supra,* vol. 2, pp. 115-138 (1984). Other controlled-release systems discussed in Langer, **1990**, *Science* 249:1527-1533 may also be used.

Having now generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting. It is understood that various modifications and changes can be made to the herein disclosed exemplary embodiments without departing from the spirit and scope of the invention.

EXAMPLES

EXPERIMENT 1: Modeling and Identification of Potential Chemosensory Receptor Ligand Enhancer

General procedure

The general procedures for identifying a potential chemosensory receptor ligand enhancer is summarized as the following.

1. Constructing a model of the structure of the Venus flytrap T1R2 domain

2. Docking a chemosensory receptor ligand, *e.g.*, a sweetener into the active site of the structure of the Venus flytrap domain of T1R2, with or without T1R3 present

3. Docking a chemosensory receptor ligand enhancer, *e.g.*, a sweet enhancer into the active site in the presence of the chemosensory receptor ligand, *e.g.*, the sweetener

4. Selecting a chemosensory receptor ligand enhancer, *e.g.*, sweet enhancer candidate based on two criteria: a) it fits the active site in the model, and b) it forms productive

interactions with the Venus flytrap domain of T1R2 and with the chemosensory receptor ligand, *e.g.*, the sweetener. Interactions can be van der Waals, burial of hydrophobic atoms or atomic groups, hydrogen bonds, ring stacking interactions, or salt-bridging electrostatic interactions. Key residues for such interactions include the hinge residues, the near active site, the pincer residues, *e.g.*, interacting residues described in the present invention. Candidates are not restricted to fitting completely within the active site, as it is open and chemosensory receptor ligand enhancer candidates may extend beyond the active site as long as they partially extend into it.

Model of the structure

A model of the structure of the Venus Flytrap T1R2 domain may come from crystal structures of T1R2 or of T1R2 complexed with T1R3. The domains may be in open or in closed form, and may or may not be APO or contain a ligand. Alternatively a model of the structure of the Venus Flytrap T1R2 domain may be built using standard homology modeling methods using crystal structures of available Venus flytrap domains such as the mGluR receptor Venus flytrap domains as templates to construct the model.

An example of a procedure for building such a model is to use the commercial software Homology or Modeller from the Accelrys Corporation that is well documented in the literature and available commercially. Alternative conformations of the model may further be explored using additional molecular mechanical techniques that may include but are not limited to normal mode analysis to explore relative movement of the lobes of the model, loop generation techniques to generate alternative conformations of loops in the model, or Monte Carlo and/or molecular dynamics simulations.

Docking

A chemosensory receptor ligand, *e.g.*, *sweetener* was first *docked* into the active site of T1R2. Its modeled pose in the active site was selected by its ability to form productive van der Waals, ring stacking, hydrogen bonding, and/or salt bridging interactions with interacting residues within the active site of the Venus flytrap domain of T1R2.

A candidate for a chemosensory receptor ligand modifier, *e.g.*, sweet enhancer was then *docked* into the active site in the presence of the ligand, *e.g.*, the sweetener described in the previous paragraph. Its active pose and its candidacy as a potential chemosensory receptor ligand modifier, *e.g.*, sweet enhancer was based on its ability to form productive interactions in

the form of van der Waals, ring stacking, hydrogen bonding, and/or salt bridging interactions with interacting residues described in the present invention, with additional residues of the T1R2 domain, and optionally with the chemosensory receptor ligand, *e.g.*, the sweetener placed in the active site as described above.

Candidate for Chemosensory Receptor Ligand Modifiers

A molecule was considered a candidate if it can be docked into the active site in the presence of a chemosensory receptor ligand, *e.g.*, sweetener, forming productive interactions with interacting residues described in the present invention. We defined two spaces within the active site: a first space occupied by a chemosensory receptor ligand, *e.g.*, sweetener, and a second space occupied by a chemosensory receptor ligand modifier, *e.g.*, enhancer. Modeling and mutagenesis results established key residues that were considered to be likely to line these spaces for the chemosensory receptor ligand, *e.g.*, sweeteners and chemosensory receptor ligand modifier, *e.g.*, sweet enhancers. In the context of our study, "residue lining the space" meant that the residue had backbone and/or side-chain atoms that were positioned so that they can potentially interact with atoms of the chemosensory receptor ligand, *e.g.*, sweetener (space #1) and/or chemosensory receptor ligand modifier, *e.g.*, sweet enhancer (space #2). While the chemosensory receptor ligand, *e.g.*, sweetener and chemosensory receptor ligand modifier, *e.g.*, sweet enhancer themselves cannot occupy the same space, their corresponding spaces may overlap due to the ability of residues to contact both the chemosensory receptor ligand, *e.g.*, sweetener and the chemosensory receptor ligand modifier, *e.g.*, sweet enhancer, due to protein flexibility, due to ligand flexibility, and due to the potential for multiple binding modes for a chemosensory receptor ligand, *e.g.*, sweetener or chemosensory receptor ligand modifier, *e.g.*, sweet enhancer. Information on important residues lining space #1 and space #2 came from modeling and docking and from site directed mutagenesis.

The hinge residues are considered to be associated with the first space (space #1). We have discovered that one of the spaces occupied by a chemosensory receptor ligand, *e.g.*, sweetener is partially lined by residues herein called hinge residues. Many Venus flytrap domains have been crystallized with agonists including mGluR1, mGluR2, and mGluR3 that show agonists forming interactions with homologous residues to those identified herein for T1R2. Many chemosensory receptor ligands, *e.g.*, sweeteners docked to the model of T1R2 can be docked to this region. Our site directed mutagenesis also provides strong evidence to support

the finding that *hinge residues* or residues spatially adjacent to it are key residues to the activation of a chemosensory receptor, *e.g.*, T1R2 related receptor. Since chemosensory receptor ligands, *e.g.*, sweeteners vary in size, there are additional residues lining this first space for larger residues where the list of these additional residues is dependent, partially on the size of the chemosensory receptor ligand, *e.g.*, sweetener.

Pincer residues are considered to be associated with the second space (space #2). Venus flytrap domains are known to transition from an "open" state to a "closed" state on agonist binding. The flytrap domain is comprised of two lobes commonly referred to in the literature as the upper lobe and lower lobe. In the "open" state the lobes are further apart, while in the closed state the lobes undergo a relative motion that brings the upper and lower lobe closer together. In addition to direct stabilization of the closed state of T1R2 by the agonist, our modeling study has demonstrated that there is additional stabilization of the closed state through interactions of residues on the upper lobe with corresponding residues on the lower lobe that are herein called the "pincer residues". We have discovered that an interacting site, *e.g.*, interacting space for a chemosensory receptor ligand modifier, *e.g.*, sweet enhancer is the space that is partially lined by these pincer residues, since additional interactions in this region can further stabilize the closed, agonized form of the Venus flytrap domain. Our site directed mutagenesis study also provides evidence to support the finding that pincer residues and residues spatially adjacent to them are key residues associated with modulation of chemosensory receptor ligand, *e.g.*, enhancement activity of the ligand.

The first space and second space can be swapped. In the above discussion the chemosensory receptor modifier, *e.g.*, sweetener binds to the hinge while the chemosensory receptor ligand modifier, *e.g.*, sweet enhancer binds to the pincer region. This is just one example and should not be construed restrictively. For example, our modeling and docking study has also demonstrated that a likely binding mode for saccharine as an agonist (sweetener) involves binding to the pincer region. Such result was further supported by our site-directed mutagenesis. With a chemosensory receptor modifier, *e.g.*, sweetener bound to the pincer region there is opportunity for further stabilization of the closed form of the Venus flytrap domain through binding of a chemosensory receptor ligand modifier, *e.g.*, sweet enhancer to the hinge region.

Procedural Definitions.

1. Docking.

Docking is generally considered as the process of translating and rotating the candidate molecule relative to a chemosensory receptor, *e.g.*, T1R2 structural model while simultaneously adjusting internal torsional angles of the candidate molecule to fit the candidate molecule into the active site of the chemosensory receptor, *e.g.*, T1R2 structural model. Poses of the candidate molecule (positions, relative orientations, and internal torsions) are selected based on whether the molecule fits the active site, and whether the molecule can form productive van der Waals interactions, hydrogen bonds, ring stacking interactions, and salt bridge interactions with residues of the active site and with the chemosensory receptor ligand, *e.g.*, sweetener. Key residues can be identified. A candidate is considered more likely if it interacts with sets of residues in the active site as the hinge region, the near active site, the pincer residues, and the totality of the active site. It is also considered more likely if it forms direct interactions with a chemosensory receptor ligand, *e.g.*, a sweetener.

2. Homology Modeling

Homology modeling is generally considered as the process of constructing a model of the Venus flytrap domain of a chemosensory receptor, *e.g.*, T1R2 from its amino acid sequence and from the three dimensional coordinates of one or more homologous Venus flytrap domain proteins. Homology modeling may be performed using standard methods well-described in the literature and available in commercial software such as the Homology program or Modeler from the Accelrys Corporation. Models based on experimentally determined structures of open and closed forms, as well as animation of models using normal mode analysis, were used to define the pincer residues discussed above.

Exemplary Illustrations of Modeling Studies

Figures 5 to 10 illustrate interacting spaces and residues associated with one of our molecular modeling studies.

EXPERIMENT 2: Mutagenesis Study for Identification of Chemosensory Receptor Ligand Modifier: Enhancer

In our previous patent applications (International Publication No. WO07047988 and International Publication No. WO070104709), we described a method using human-rat chimeric sweet-umami chimeric receptors to map the binding sites of sweet and umami tastants.

Our data demonstrated that a number of sweeteners, including sucrose, fructose, arspartame, neotame, D-tryptophan (D-Trp), Acesulfame K, saccharin and dulcin, all interact with the T1R2 Venus flytrap domain (VFT), while the umami tastants, including L-glutamate, inosine-5'-monophosphate (IMP), and guanosine-5'-monophosphate (GMP), all interact with the T1R1 Venus flytrap domain.

Under the guidance of molecular modeling, we performed site-directed mutagenesis on human T1R2 VFT. The mutagenesis was done using the routine PCR-based method. Human T1R2 mutants were transiently transfected into HEK293 cell together with the human T1R3 wild type cDNA, and the transfected cells were characterized using an automated FLIPR machine or a calcium imaging system as described in our previous patent applications. In order to control for plasma membrane expression, protein folding and other factors that might contribute to changes in receptor activity, we used 2 sweeteners which interact with other domains of the human sweet receptor as positive controls. The 2 control sweeteners were cyclamate and compound X (Senomyx). It is known from our previous data that cyclamate interacts with the human T1R3 transmembrane domain, while compound X interacts with the human T1R2 transmembrane domain.

The mutagenesis data for a number of sweeteners are summarized in the following tables. Based on the data, we concluded that 6 residues (S40, S144, S165, Y103, D142, P277) are critical for interaction with those sweeteners.

Mutagenesis data on FLIPR

	Aspartame (15 Mm)	D-Trp (20 mM)	Fructose (200 mM)	Sucrose (200 mM)	Sucralose (3.2 mM)	Cyclamate (80 mM)	S3819 (25 μM)
WT	+++	+++	+++	+++	+++	+++	+++
V384F	++	++	++	++	++	+++	+++
V384A	++	++	++	++	++	+++	+++
E382A	+	++	+	+	++	++	++
S165I	-	-	+	+	++	++	++
D278A	++	++	++	+	-	+++	+++
K65A	++	++	+	+	+	++	++
S165A	+++	++	++	++	++	++	+++
I67A	+++	+++	+++	+++	+++	+++	+++
N143A	+++	++	++	++	+++	+++	+++
S303A	+++	+++	++	++	++	+++	+++
Q328A	+++	+++	+++	+++	+++	+++	+++
T184A	+++	++	+++	+++	+++	+++	+++
T242A	+++	++	++	++	++	+++	+++
L279A	+++	+++	++	++	++	++	+++
T326A	++	++	++	++	++	++	++

Mutagenesis data on calcium imaging

	Aspartame (15 mM)	D-Trp (20 mM)	Fructose (200 mM)	Sucrose (200 mM)	Sucralose (3.2 mM)	Cyclamate (80 mM)	S3819 (25 μM)
WT	++	++	++	++	++	++	++
I167A	+	+	+	+	+	+	+
Y103A	-	+	+	+	-	+	+
D278A	+	+	+	+	-	++	++
D307A	+	+	-	-	+	+	+
E302A	-	+	+	+	+	+	+
S165I	-	-	+	+	+	+	+
S40A	-	-	-	-	-	+	+
D142A	-	-	-	-	-	+	+
R383A	-	-	-	-	-	-	+
A305F	-	-	-	-	-	-	+

Y215A	-	-	-	-	-	-	-
D142I	-	-	-	-	-	-	-

Additional mutations on R383

	Aspartame (15 mM)	Neotame (80 μM)	Sucrose (200 mM)	Sucralose (3.2 mM)	D-Trp (20 mM)	Cyclamate (80 mM)	S3819 (25 μM)
WT	++	+++	++	+++	+++	+++	+++
R383H	+	++	+	++	++	++	++
R383Q	-	+	-	+	+	+	+
R383I	-	-	-	-	-	-	-
R383F	-	++	-	-	+	+	+
R383K	-	+	-	+	+	+	+
R383N	-	+	-	+	+	+	+
R383S	-	+	-	+	+	+	+
R383A	-	-	-	-	-	-	+

The sweet enhancer, compound A, is selective for the human sweet receptor, and inactive on the rat sweet receptor. Using the previously described human-rat chimeric receptors, we mapped the binding site of compound A to hT1R2 VFT. As shown in Figure 11, compound A enhanced the sucralose activity on human sweet receptor (h2/h3) but not rat sweet receptor (r2/r3). When we replaced the rat receptor T1R2 VFT with its human counterpart (h2-r2/r3), the receptor can be enhanced by compound A. On the other hand, when we replaced the human receptor T1R2 VFT with its rat counterpart (r2-h2/h3), the receptor can no longer be enhanced by compound A. We conclude that compound A interacts with human T1R2 VFT. Due to the different sensitivity of human and rat receptors to sucralose, different sucralose concentrations were used to achieve ~EC20 of the different receptors.

Following compound A, 8 more analogues have been identified to enhance the sucralose activity of human sweet receptor. The same mapping experiments were carried out on these 8 analogues, and we observed the same activity pattern as compound A as summarized in the following table. We conclude that all 8 compound A analogues interact with human T1R2 VFT.

After mapping the enhancers to human T1R2 VFT, we performed mutagenesis analysis to further define the interaction site. As summarized in the following table, six residues (K65, D278, L279, D307, R383, V384) were identified as critical for the activities of compound A and analogous. These compounds, namely, compounds A and A1 to A8, are representative compounds of the present invention including compounds of structural Formula (I) and its subgeneric formulas. Interestingly, V384 is also important for the activities of 2 structurally related sweeteners (as shown in Figure 12), saccharin and acesulfame K (AceK), indicating that these sweeteners might occupy similar space in the human T1R2 VFT. The concentrations for the sweeteners are Aspartame (15 mM), D-Trp (20 mM), Sucrose (200 mM), Sucralose (3.2 mM), AceK (8 mM), Saccharin (3.2 mM), Cyclamate (80 mM), S3819 (25 μM).

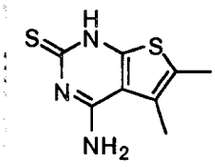
	h2/h3	r2/r3	h2-r2/r3	r2-h2/h3
Compound A (25 μM)	+	-	+	-
Compound A1 (25 μM)	+	-	+	-
Compound A2 (25 μM)	+	-	+	-
Compound A3 (25 μM)	+	-	+	-
Compound A4 (25 μM)	+	-	+	-
Compound A5 (25 μM)	+	-	+	-
Compound A6 (25 μM)	+	-	+	-
Compound A7 (25 μM)	+	-	+	-
Compound A8 (100 μM)	+	-	+	-

		Enhancement Activity (at 25 μM) for Compound A and its analogs								
hT1R2	Sucralose	A	A4	A1	A5	A2	A6	A3	A8	A7
WT	++	++	++	+++	++	+++	++	+	++	+++
V384A	++	++	++	+++	++	+++	++	+	++	+++
E382A	++	++	++	+++	++	+++	++	+	++	+++
Y103A	-	+	+	++	+	++	+	+	++	++
P277A	+	++	+	+++	+	+++	+	+	++	+++
D278A*	-	++	+	+++	+	+++	+	+	+	++
K65A	+	-	-	-	-	-	-	-	-	-
L279A	++	-	-	-	-	-	-	-	-	-
V384F	++	+	+	+	+	+	+	-	-	+
S165I	++	++	++	+++	++	+++	++	+	++	+++
I67A	++	++	++	+++	++	+++	++	+	++	+++
S165A	++	+	++	+++	++	+++	++	+	++	+++
N143A	++	++	++	+++	++	+++	++	+	++	+++
T326A	++	++	++	+++	++	+++	++	+	++	+++
T242A	++	++	++	+++	++	+++	++	+	++	+++
S303A	++	++	++	+++	++	+++	++	+	++	+++
Q328A	++	++	++	+++	++	+++	++	+	++	+++
T184V	++	++	++	+++	++	+++	++	+	++	+++
T184A	++	++	++	+++	++	+++	++	+	++	+++
V64M	++	++	++	+++	++	+++	++	+	++	+++
S168T	++	++	++	+++	++	+++	++	+	++	+++
R383H	++	++	++	+++	++	+++	++	+	++	+++
S40T	+	++	++	+++	++	+++	++	+	++	+++
I167A	+	+	+	++	+	++	+	+	+	++
E302A	+	+	+	++	+	++	+	+	+	++
R383F	+	-	-	-	-	-	-	-	-	-
D307A	+	-	-	-	-	-	-	-	-	-
D142A	-	+	+	++	+	++	+	+	+	++
S40A	-	+	+	++	+	++	+	+	+	++
R383A	-	+	+	++	+	++	+	+	+	++
A305F	-	-	-	-	-	-	-	-	-	-

* D278 is a critical residue for the enhancers, because all enhancers in the above table show agonist activity on D278A mutant, i.e., they activate the mutant receptor in the absence of sucralose.

EXPERIMENT 3: Chemical Synthesis of the Compounds of the Present Invention

Example 1: 4-Amino-5,6-dimethylthieno[2,3-d]pyrimidine-2(1H)-thione



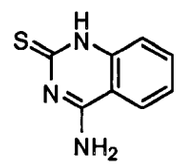
7

A solution of N-(3-cyano-4,5-dimethylthiophen-2-ylcarbamothioyl)benzamide (example 1a) (1.90 g, 6.03 mmol) and NaOH (2 N, 8.3 mL) in EtOH (25 mL) was stirred at 100°C under nitrogen for half an hour. After cooling to room temperature, the clear reaction solution was filtered and the filtrate was carefully neutralized with 10 % AcOH with vigorous stirring at 0 °C. The resultant precipitate was collected by filtration, washed with warm water and then 20 % EtOH in water to give the final product 4-amino-5,6-dimethylthieno[2,3-d]pyrimidine-2(1H)-thione (1.11 g, 87 %) as an off-white solid. M.p.: > 260 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.25 (s, 3H), 2.26 (s, 3H). MS 212 (MH^+).

Example 1a: N-(3-Cyano-4,5-dimethylthiophen-2-ylcarbamothioyl)benzamide

To a solution of 2-amino-4,5-dimethylthiophene-3-carbonitrile (1.52 g, 10.0 mmol) in 1.4-dioxane (20 mL) was added benzoylisothiocyanate (1.63 g, 10.0 mmol). The reaction mixture was then stirred at room temperature under nitrogen overnight. The precipitation was collected by filtration, washed with EtOAc/Hexanes (1:4), and dried under vacuum overnight to give N-(3-Cyano-4,5-dimethylthiophen-2-ylcarbamothioyl)benzamide as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3H), 2.31 (s, 3H), 7.58-7.54 (m, 2H), 7.68-7.66 (m, 1H), 7.94 (d, J = 7.2 Hz, 2H), 9.13 (bs, 1H). MS 316 (MH^+).

Example 2: 4-Aminoquinazoline-2(1H)-thione



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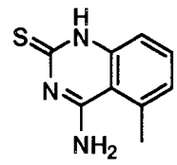
Prepared as in example 1 from N-(2-cyanophenylcarbamothioyl)benzamide (Example 2a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.25 (dt, J = 1.0, 8.2 Hz, 1H), 7.35 (d, J = 8.2

Hz, 1H), 7.65 (dt, J = 1.0, 8.2 Hz, 1H), 8.05 (dd, J = 1.0, 8.1 Hz, 1H), 8.30 (s, 1H), 8.35 (s, 1H), 12.34 (s, 1H). MS 178 (MH^+).

Example 2a: N-(2-Cyanophenylcarbamothioyl)benzamide:

Prepared as in Example 1a from 2-aminobenzonitrile and benzoyl isothiocyanate as a pale-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.35-7.56 (m, 3H), 7.67 (t, 1H), 7.75-7.76 (d, J = 5.2 Hz, 2H), 7.89-7.91 (d, J = 7.2 Hz, 2H), 7.98-8.01 (dd, $J1$ = 1.6 Hz, $J2$ = 8.2 Hz, 2H), 11.90 (s, 1H), 12.54 (s, 1H). MS 282 (MH^+).

Example 3: 4-Amino-5-methylquinazoline-2(1H)-thione



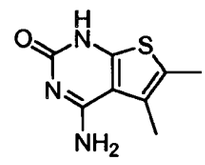
155

Prepared as in example 1 from N-(2-cyano-3-methylphenylcarbamothioyl)benzamide (Example 3a) as an off-white solid. M.p.: > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.68 (s, 3H), 7.03 (d, J = 6.8 Hz, 1H), 7.13 (b, 1H), 7.22 (d, J = 6.8 Hz, 1H), 7.48 (t, J = 6.8 Hz, 1H), 8.50 (b, 1H), 12.26 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 23.26, 109.86, 114.37, 127.16, 134.31, 136.97, 143.57, 160.58, 179.67. MS 192 (MH^+).

Example 3a: N-(2-Cyanophenylcarbamothioyl)benzamide

Prepared as in example 1a from 2-amino-6-methylbenzonitrile and benzoyl isothiocyanate as a pale-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.40 (m, 1H), 7.52-7.69 (m, 5H), 7.98-8.01 (m, 2H), 11.99 (s, 1H), 12.54 (s, 1H). MS 296 (MH^+).

Example 4 : 4-amino-5,6-dimethylthieno[2,3-d]pyrimidin-2(1H)-one



1

A solution of N-(3-cyano-4,5-dimethylthiophen-2-ylcarbamoyl)benzamide (example 4a) (44.35 g, 148.1 mmol) and NaOH (2 N, 204 mL) in EtOH (400 mL) was stirred at 100 °C under nitrogen for four hours. The clear reaction solution was filtered and the filtrate was

cooling to room temperature, and then was carefully neutralized with 10 % AcOH (~ 120 mL) with vigorous stirring at 0 °C. After stirring overnight from 0 °C to room temperature, the resultant precipitate was collected by filtration, washed with warm water (60-70 °C, 150 mL x 4) and 20 % EtOH in water (200mL x 2), and then dried at 50 °C under vacuum overnight to give the final product 4-amino-5,6-dimethylthieno[2,3-d]pyrimidin-2(1H)-one (27.7 g, 96 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (brs, 1H), 2.24 (s, 3H), 2.19 (s, 3H). MS 196 (MH^+).

Example 4a: N-(3-cyano-4,5-dimethylthiophen-2-ylcarbamoyl)benzamide

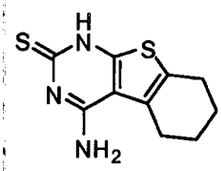
To a solution of 2-amino-4,5-dimethylthiophene-3-carbonitrile (example 4b) (25 g, 164.5 mmol) in 1.4-dioxane (600 mL) was added benzoyl isocyanate (24.2 g, 164.5 mmol). The reaction mixture was then stirred at room temperature under nitrogen overnight. The precipitate was collected by filtration, washed with 1.4-dioxane (20 mL x 3), and dried under vacuum at 40 °C for 3 hours to give N-(3-cyano-4,5-dimethylthiophen-2-ylcarbamoyl)benzamide (44.35 g, 90%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.10 (s, 3H), 2.24 (s, 3H), 7.52-7.56 (m, 2H), 7.64-7.69 (m, 1H), 8.01-8.03 (m, 2H), 11.57 (brs, 1H), 12.05 (brs, 1H). MS 300 (MH^+).

Example 4b: 2-amino-4,5-dimethylthiophene-3-carbonitrile

To a solution of butanone (162.0 mL, 1.8 mol), sulfur (57.99 g, 1.8 mol), and malononitrile (119.49 g, 1.8 mol) in anhydrous Ethanol (1.2 L) was added at 0°C triethylamine (251.4 mL, 1.8 mol). The reaction was stirred at 0°C for 15 minutes then heated at 80°C for 70 minutes. After cooling to room temperature, ethanol (920 mL) was removed reduced pressure and aqueous NaCl (30%, 750 mL) was added. The resulting mixture was stirred for 10 minutes and extracted with diethyl ether (1L). The aqueous layer was further extracted with diethyl ether (500 mL) and the insoluble solids were removed by filtration after which the organic layer was separated and combined with the first diethyl ether extract. The combined organic extract was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was stirred for 2 hours in dichloromethane (300 mL) and a solid was collected. More solid was isolated from the dichloromethane solution cooled to -78°C. The combined solid product was refluxed in dichloromethane (600 mL) for 10 minutes then stirred at room temperature for 30 minutes and cooled to -78°C. The resultant precipitate was collected by filtration to give the crude product (115 g). The filtrate was concentrated and the residue was chromatographed on silica gel

(eluent: dichloromethane) to provide a solid that was combined with the previous crude product. The resulting residue was purified by flash chromatography on silica gel (dichloromethane) to yield 2-amino-4,5-dimethylthiophene-3-carbonitrile (105 g, 38%) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.93 (d, J = 1.2 Hz, 3H), 2.07 (d, J = 1.2 Hz, 3H), 3.33 (s, 2H). MS 153 (MH^+).

Example 5: 4-Amino-5,6-butylenethieno[2,3-d]pyrimidine-2(1H)-thione



39

Prepared as in Example 1 from N-(3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-ylcarbamothioyl)benzamide (Example 5a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.75 (m, 4H), 2.62 (m, 2H), 2.74 (m, 2H). MS 238 (MH^+).

Example 5a:

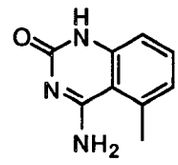
N-(3-Cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-ylcarbamothioyl)-benzamide.

Prepared as in example 1a from 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (example 5b) and benzoylisothiocyanate as a pale-yellow solid. MS 342 (MH^+).

Example 5b: 2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile

A solution of cyclohexanone (1.96 g, 20.0 mmol), malononitrile (1.32 g, 20.0 mmol), sulfur (640 mg, 20.0 mmol), and triethylamine (2.03 g, 20 mmol) in EtOH (50 mL) was refluxed for 6 h under nitrogen. The solvent was removed under reduced pressure and the residue partitioned between EtOAc and water. The organic layer was separated, washed with brine, and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by chromatography on silica gel eluting with EtOAc/Hexanes (2:3) to give the title product as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79 (m, 4H), 2.50 (m, 4H), 4.59 (s, 2H). MS 179 (MH^+).

Example 6: 4-Amino-5-methylquinazolin-2(1H)-one



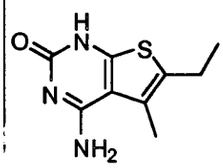
157

Prepared as in example 1 from N-(2-cyano-3-methylphenylcarbamoyl)benzamide (example 6a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.04 (s, 3H), 7.43 (d, J = 7.2 Hz, 1H), 7.51 (d, J = 7.2 Hz, 1H), 7.97 (t, J = 7.2 Hz, 1H). MS 176 (MH^+).

Example 6a: N-(2-Cyano-3-methylphenylcarbamoyl)benzamide

Prepared as in example 1a from 2-amino-6-methylbenzonitrile and benzoyl isocyanate as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.19 (d, J = 7.6 Hz, 1H), 7.52-7.68 (m, 5H), 8.02-8.08 (m, 2H), 11.32 (s, 1H), 11.46 (s, 1H). MS 280 (MH^+).

Example 7: 4-Amino-6-ethyl-5-methylthieno[2,3-d]pyrimidin-2(1H)-one



75

Prepared as in Example 1 from N-(3-cyano-5-ethyl-4-methylthiophen-2-ylcarbamoyl)benzamide (Example 7a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.11 (t, J = 7.6 Hz, 3H), 2.26 (s, 3H), 2.60-2.67 (q, J = 7.6 Hz, 2H). MS 210 (MH^+).

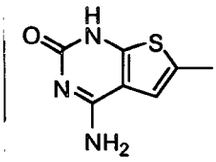
Example 7a: N-(3-Cyano-5-ethyl-4-methylthiophen-2-ylcarbamoyl)benzamide

Prepared as in example 1a from 2-amino-5-ethyl-4-methylthiophene-3-carbonitrile (example 7b) and benzoyl isocyanate as a pale-yellow solid. MS 314 (MH^+).

Example 7b: 2-Amino-5-ethyl-4-methylthiophene-3-carbonitrile

Prepared as in example 5b from 2-pentanone, malononitrile, and sulfur as a yellow solid. MS 167 (MH^+).

Example 8: 4-Amino-6-methylthieno[2,3-d]pyrimidin-2(1H)-one



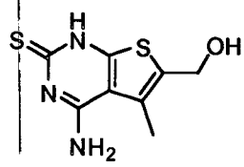
77

Prepared as in Example 1 from N-(3-cyano-5-methylthiophen-2-ylcarbamoyl)benzamide (Example 8a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.34 (s, 3H), 6.97 (s, 1H), 7.50 (s, 1H). MS 182 (MH^+).

Example 8a: N-(3-Cyano-5-methylthiophen-2-ylcarbamoyl)benzamide

Prepared as in Example 1a from 2-amino-5-methylthiophene-3-carbonitrile and benzoyl isocyanate as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.36 (d, J = 1.2 Hz, 3H), 6.89 (d, J = 1.2 Hz, 1H), 7.55 (t, J = 8.0 Hz, 2H), 7.66 (d, J = 7.2 Hz, 1H), 8.03-8.01 (m, 2H), 11.60 (brs, 1H), 12.08 (bs, 1H). MS 286 (MH^+).

Example 9: 4-Amino-6-(hydroxymethyl)-5-methylthieno[2,3-d]pyrimidine-2(1H)-thione



37

Prepared as in Example 1 from N-(3-cyano-5-(hydroxymethyl)-4-methylthiophen-2-ylcarbamothioyl)benzamide (Example 9a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.30 (s, 3H), 4.54-4.55 (d, J = 5.2 Hz, 2H), 5.54 (t, 1H). MS 228 (MH^+).

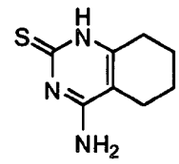
Example 9a: N-(3-Cyano-5-(hydroxymethyl)-4-methylthiophen-2-ylcarbamothioyl)-benzamide

Prepared as in example 1a from 2-amino-5-(hydroxymethyl)-4-methylthiophene-3-carbonitrile (Example 9b) and benzoyl isothiocyanate as a yellow solid. MS 332 (MH^+).

Example 9b: 2-Amino-5-(hydroxymethyl)-4-methylthiophene-3-carbonitrile

Prepared as in example 5b from 4-hydroxybutan-2-one, malononitrile, and sulfur as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.97 (s, 3H), 4.30-4.31 (d, J = 5.6 Hz, 2H), 5.10 (t, 1H), 7.00 (s, 2H).

Example 10: 4-Amino-5,6,7,8-tetrahydroquinazoline-2(1H)-thione



201

Prepared as in Example 1 from N-(2-cyanocyclohex-1-enylcarbamothioyl)benzamide (Example 10a) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.60-1.65 (m, 4H), 2.13 (m, 2H), 2.38 (m, 2H), 6.93 (s, 1H), 7.56 (s, 1H), 11.84 (s, 1H). MS 182 (MH^+).

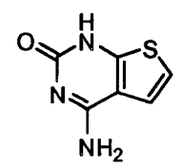
Example 10a: N-(2-Cyanocyclohex-1-enylcarbamothioyl)benzamide

Prepared as in Example 1a from 2-aminocyclohex-1-enecarbonitrile (Example 10b) and benzoyl isothiocyanate as a white solid. MS 286 (MH^+).

Example 10b: 2-Aminocyclohex-1-enecarbonitrile

A stirred mixture of 1,7-heptanedinitrile (24.44 g, 0.2 mol) and *t*-BuOK (22.44 g, 0.2 mol) was heated at 80 °C for 3 h under nitrogen. The mixture was then cooled down to room temperature and stored at that temperature overnight. The residue was treated with water, and extracted with ether (2X). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by recrystallization from MeOH to give the title compound as a white solid (18.2 g, 75 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58-1.71 (m, 4H), 2.12-2.20 (m, 4H), 4.23 (bs, 2H). MS 123 (MH^+).

Example 11: 4-Amino-6-methylthieno[2,3-d]pyrimidin-2(1H)-one



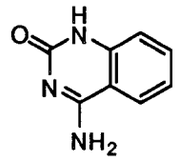
69

Prepared as in Example 1 from N-(3-cyanothiophen-2-ylcarbamoyl)benzamide (Example 11a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.97 (s, J = 5.2 Hz, 1H), 7.31 (d, J = 6.0 Hz, 1H), 7.60 (s, 2H), 11.38 (bs, 1H). MS 168 (MH^+).

Example 11a: N-(3-Cyanothiophen-2-ylcarbamoyl)benzamide

Prepared as in Example 1a from 2-aminothiophene-3-carbonitrile and benzoyl isocyanate as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.23-7.19 (m, 2H), 7.55 (t, J = 8.0 Hz, 2H), 7.70-7.66 (m, 1H), 8.04-8.02 (m, 2H), 11.62 (bs, 1H), 12.18 (bs, 1H). MS 272 (MH^+).

Example 12: 4-Aminoquinazolin-2(1H)-one



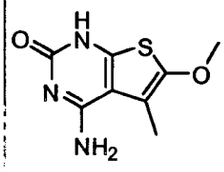
149

Prepared as in Example 1 from N-(2-cyanophenylcarbamoyl)benzamide (Example 12a) as a white solid (156 mg, 41%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.12-7.20 (m, 2H), 7.59-7.63 (m, 1H), 8.08-8.10 (d, 1H), 8.60 (b, 2H), 11.2 (b, 1H). ^{13}C NMR (DMSO-d_6) δ 108.72, 115.98, 122.32, 125.51, 135.38, 142.96, 154.96, 163.51. MS 162 (MH^+).

Example 12a: N-(2-Cyanophenylcarbamoyl)benzamide

Prepared as in Example 1a from 2-aminobenzonitrile and benzoyl isocyanate as a white powder (661 mg, 59 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.27-7.29 (t, 1H), 7.52-7.56 (t, 1H), 7.64-7.74 (m, 2H), 7.82-7.85 (dd, 1H), 8.02-8.04 (m, 2H), 8.22-8.24 (d, 1H). MS 266 (MH^+).

Example 13: 4-Amino-6-methoxy-5-methylthieno[2,3-d]pyrimidin-2(1H)-one



79

Prepared as in Example 1 from N-(3-cyano-5-methoxy-4-methylthiophen-2-ylcarbamoyl)benzamide (Example 13a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.19 (s, 3H), 3.78 (s, 3H), 2.74 (s, 2H). MS 212 (MH^+).

Example 13a: N-(3-Cyano-5-methoxy-4-methylthiophen-2-ylcarbamoyl)benzamide.

Prepared as in Example 1a from 2-amino-5-methoxy-4-methylthiophene-3-carbonitrile (example 13b) and benzoyl isocyanate as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.03 (s, 3H), 3.86 (s, 3H), 7.54 (t, J = 7.2

Hz, 2H), 7.67 (t, J = 7.6 Hz, 1H), 8.01-8.03 (d, J = 8.4 Hz, 2H), 11.60 (s, 1H), 12.03 (s, 1H). MS 316 (MH^+).

Example 13b: 2-Amino-5-methoxy-4-methylthiophene-3-carbonitrile

Prepared as in Example 5b from 1-methoxypropan-2-one, malononitrile, and sulfur as a brown solid. MS 169 (MH^+).

Example 14: 4-Amino-6-methylquinazolin-2(1H)-one



161

Prepared as in Example 1 from N-(2-cyano-4-methylphenylcarbamoyl)benzamide (Example 14a) as a white solid (259 mg, 57 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.29 (s, 3H), 6.99-7.05 (m, 1H), 7.35-7.37 (d, 1H), 7.72 (b, 2H), 7.79 (s, 1H) 10.55 (bs, 1H). MS 176 (MH^+).

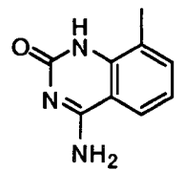
Example 14a: N-(2-Cyano-4-methylphenylcarbamoyl)benzamide

Prepared as in Example 1a from 2-amino-5-methylbenzonitrile (Example 14b) as a white powder (724 mg, 46 %). MS 280 (MH^+).

Example 14b: 2-Amino-5-methylbenzonitrile

5-Methyl-2-nitrobenzonitrile (1.92 g, 11.84 mmol) was added in portions to a stirred solution of $SnCl_2$ (11.22 g, 59.2 mmol) in conc. HCl (12 mL) and EtOH (12 mL). The reaction temperature was maintained at 20-30 °C using an ice bath. The reaction mixture was then stirred at room temperature for 1 h and poured into an ice cold aqueous solution of NaOH (6N, app. 30 mL) to neutralize to pH7. The product was extracted into EtOAc, washed with brine, dried over $MgSO_4$ and concentrated to provide the title product (1.56 g, 99 %) as a yellow-brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.21 (s, 3H), 5.79 (bs, 2H), 6.68-6.71 (d, 1H), 7.10-7.13 (dd, 1H), 7.15 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 20.13, 93.99, 116.12, 118.94, 125.38, 132.32, 135.76, 150.21. MS 133 (MH^+).

Example 15: 4-Amino-8-methylquinazolin-2(1H)-one



165

Prepared as in Example 1 from N-(2-cyano-6-methylphenylcarbamoyl)benzamide (Example 15a) as a white solid (60 mg, 56 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.29 (s, 3H), 6.96-7.00 (t, 1H), 7.37-7.38 (d, 1H), 7.70-7.72 (b, 2H), 7.80-7.82 (d, 1H), 9.87 (bs, 1H). MS 176 (MH^+).

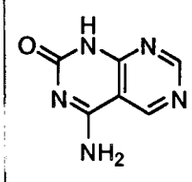
Example15a: N-(2-Cyano-6-methylphenylcarbamoyl)benzamide

Prepared as in Example 1a from 2-amino-3-methylbenzonitrile (Example 15b) and benzoyl isocyanate as a white powder (186 mg, 67 %). MS 280 (MH^+).

Example 15b: 2-Amino-3-methylbenzonitrile

To a solution of 2-bromo-6-methylaniline (126 µL, 1 mmol) in dry NMP (3 mL) was added CuCN (197 mg, 2.2 mmol). The mixture was irradiated in a microwave at 220 °C for 40 minutes, cooled to room temperature and poured into a mixture of ammonia (50 % w/v, 10 mL) and ice. The mixture was stirred for 30 min and the product was extracted with dichloromethane (3 x 20 mL). The organic layers were combined, washed with water and brine, dried over $MgSO_4$ and concentrated. The crude material was purified on silica gel (50 % EtOAc/hexanes) to yield a brown oil that crystallized on standing (128 mg, 96 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.08 (s, 3H), 5.68 (bs, 2H), 6.51-6.55 (t, 1H), 7.17-7.19 (d, 1H), 7.22-7.24 (dd, 1H). MS 133 (MH^+).

Example 16: 4-Aminopyrimido[4,5-d]pyrimidin-2(1H)-one



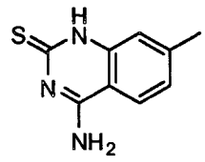
181

Prepared as in Example 1 from N-(2-cyano-4,5-dimethylfuran-3-ylcarbamoyl)benzamide (Example 16a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (s, 1H), 8.92 (s, 1H), 9.24 (s, 2H), 11.50 (b, 1H). MS 164 (MH^+).

Example 16a: N-(2-Cyano-4,5-dimethylfuran-3-ylcarbamoyl)benzamide

Prepared as in Example 1a from 4-aminopyrimidine-5-carbonitrile and benzoyl isocyanate as an off-white powder. MS 268 (MH^+).

Example 17: 4-Amino-7-methylquinazoline-2(1H)-thione



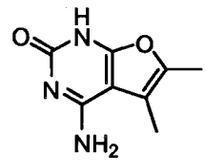
167

Prepared as in Example 1 from N-(2-cyano-5-methylphenylcarbamothioyl)benzamide (Example 17a). ^1H NMR (400 MHz, DMSO-d_6) δ 2.35 (s, 3H), 7.08 (d, J = 8.0 Hz, 1H), 7.13 (s, 1H), 7.93 (d, J = 8.0 Hz, 1H), 8.21 (s, 1H), 8.24 (s, 1H), 12.26 (s, 1H). MS 192 (MH^+).

Example 17a: N-(2-Cyano-5-methylphenylcarbamothioyl)benzamide

Prepared as in Example 1a from 2-amino-4-methylbenzonitrile and benzoyl isothiocyanate as a pale-yellow powder. ^1H NMR (400 MHz, DMSO-d_6) δ 7.32 (d, J = 8.0 Hz, 1H), 7.51-7.58 (m, 3H), 7.67 (t, J = 7.8 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.98-8.01 (m, 2H), 11.88 (s, 1H), 12.49 (s, 1H). MS 296 (MH^+).

Example 18: 4-Amino-5,6-dimethylfuro[2,3-d]pyrimidin-2(1H)-one



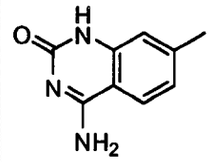
23

Prepared as in Example 1 from N-(2-cyano-4,5-dimethylfuran-3-ylcarbamoyl)benzamide (Example 18a). ^1H NMR (400 MHz, DMSO-d_6) δ 2.11 (s, 3H), 2.20 (s, 3H). MS 180 (MH^+).

Example 18a: N-(2-Cyano-4,5-dimethylfuran-3-ylcarbamoyl)benzamide

Prepared in a similar manner to Example 1a from 2-amino-4,5-dimethylfuran-3-carbonitrile and benzoyl isocyanate as an off-white solid. MS 284 (MH^+).

Example 19: 4-Amino-7-methylquinazolin-2(1H)-one



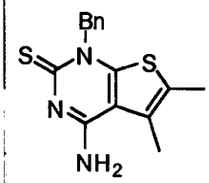
163

Prepared as in Example 1 from N-(2-cyano-5-methylphenylcarbamoyl)benzamide (Example 19a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.59 (s, 3H), 7.37 (s, 1H), 7.49 (d, J = 7.2 Hz, 1H), 8.21 (d, J = 7.2 Hz, 1H). MS 176 (MH^+).

Example 19a: N-(2-Cyano-5-methylphenylcarbamoyl)benzamide

Prepared as in Example 1a from 2-amino-4-methylbenzonitrile and benzoyl isocyanate as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.10-7.13 (m, 1H), 7.54 (t, J = 7.8 Hz, 2H), 7.66 (t, J = 7.8 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 8.02-8.04 (m, 2H), 8.07 (s, 1H), 11.32 (s, 1H), 11.44 (s, 1H). MS 280 (MH^+).

Example 20: 4-Amino-1-benzyl-5,6-dimethylthieno[2,3-d]pyrimidine-2(1H)-thione



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Prepared as in Example 1 from N-(benzyl(3-cyano-4,5-dimethylthiophen-2-yl)carbamothioyl)benzamide (Example 20a). MS 302 (MH^+).

Example 20a: N-(Benzyl(3-cyano-4,5-dimethylthiophen-2-yl)carbamothioyl)-benzamide.

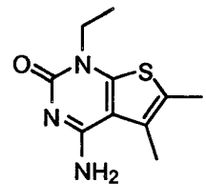
Prepared as in Example 1a from 2-(benzylamino)-4,5-dimethylthiophene-3-carbonitrile (Example 20b) and benzoyl isothiocyanate. MS 406 (MH^+).

Example 20b: 2-(Benzylamino)-4,5-dimethylthiophene-3-carbonitrile

To a solution of 2-amino-4,5-dimethylthiophene-3-carbonitrile (151 mg, 1.0 mmol) and benzaldehyde (106 mg, 1mmol) in 15 mL of 4 % acetic acid in dichloroethane was added silica supported cyanoborohydride (2.0 g. 2.0 mmol). The reaction was placed in a microwave reactor for 5 minutes at 135 °C. Silica supported cyanoborohydride was removed by

filtration, and the product was purified by prep HPLC using acetonitrile/water as solvent. MS 243 (MH^+).

Example 21: 4-Amino-1-ethyl-5,6-dimethylthieno[2,3-d]pyrimidin-2(1H)-one



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Prepared as in Example 1 from N-((3-cyano-4,5-dimethylthiophen-2-yl)(ethyl)carbamoyl)benzamide (Example 21a). MS 224 (MH^+).

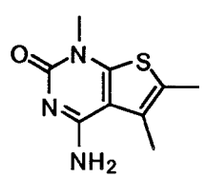
Example 21a: N-((3-Cyano-4,5-dimethylthiophen-2-yl)(ethyl)carbamoyl)benzamide.

Prepared in a similar manner to Example 1a from 2-(ethylamino)-4,5-dimethylthiophene-3-carbonitrile (Example 21b) and benzoyl isocyanate. MS 328 (MH^+).

Example 21b: 2-(Ethylamino)-4,5-dimethylthiophene-3-carbonitrile

To a mixture of 2-(benzylamino)-4,5-dimethylthiophene-3-carbonitrile (302 mg, 2.0 mmol), potassium carbonate (276 mg, 2.0 mmol), and a catalytic amount of potassium iodide in acetonitrile (1 mL) in a 20 mL microwave vial was added ethyl iodide (310 mg, 2.0 mmol). The reaction vial was placed in a microwave reactor for 15 minutes at 165 °C. The reaction mixture was dissolved in ethyl acetate and washed with water and brine. The ethyl acetate portion was dried over sodium sulfate and solvent was evaporated under reduced pressure, and the product was purified by prep HPLC using acetonitrile/water as solvent. MS 181 (MH^+).

Example 22: 4-Amino-1,5,6-trimethylthieno[2,3-d]pyrimidin-2(1H)-one



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Prepared as in Example 1 from N-((3-cyano-4,5-dimethylthiophen-2-yl)(methyl)carbamoyl)benzamide (Example 22a). MS 210 (MH^+).

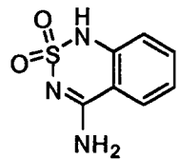
Example 22a: N-((3-Cyano-4,5-dimethylthiophen-2-yl)(methyl)carbamoyl)-benzamide.

Prepared as in Example 1a from 4,5-dimethyl-2-(methylamino)thiophene-3-carbonitrile (Example 22b) and benzoyl isocyanate. MS 314 (MH^+).

Example 22b: 4,5-Dimethyl-2-(methylamino)thiophene-3-carbonitrile

Prepared as in Example 21b from 2-amino-4,5-dimethylthiophene-3-carbonitrile and methyl iodide.

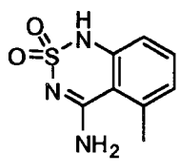
Example 23: 1H-Benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



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A stirred mixture of 2-cyanoaniline (236 mg, 2.0 mmol), sulfamide (192 mg, 2.0 mmol) and DBU (304 mg, 2.0 mmol) was heated at 160 °C under nitrogen for 3 days. After cooling to room temperature, the reaction mixture was diluted with water and extracted three times with EtOAc. The aqueous layer was removed under vacuum and the residue was purified by chromatography on silica gel eluting with 10% MeOH in dichloromethane to give the title compound as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.03 (dd, J = 0.8, 8.0 Hz, 1H), 7.12 (dt, J = 0.8, 8.0 Hz, 1H), 7.56 (dt, J = 0.8, 8.0 Hz, 1H), 7.85 (dd, J = 0.8, 8.0 Hz, 1H). MS 198 (MH^+).

Example 24: 5-Methyl-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



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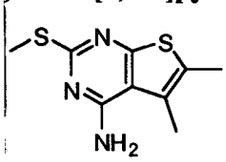
A solution of N-(2-cyano-3-methylphenyl)sulfamide (Example 24a) (211 mg, 1.0 mmol) in EtOH was treated with NaOH (2.0 N, 1.0 mL, 2.0 mmol) and the resultant solution was

heated to 100 °C and stirred at that temperature for 0.5 h. After cooling to room temperature, the clear reaction solution was filtered and the filtration was carefully neutralized with 10 % AcOH while with vigorous stirring at 0 °C. The resultant precipitate was collected by filtration, washed with warm water and 20 % EtOH in water to give the title product 5-Methyl-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.59 (s, 3H), 6.85-6.87 (d, J = 8.4 Hz, 1H), 6.92-6.94 (d, J = 7.2 Hz, 1H), 7.24 (s, 1H), 7.37 (t, J = 7.6 Hz, 1H), 8.24 (s, 1H), 10.76 (s, 1H). MS 212 (MH^+).

Example 24a: N-(2-Cyano-3-methylphenyl)sulfamide

A solution of 2-amino-6-methylbenzonitrile (1.32 g, 10 mmol) and sulfamide (4.81 g, 50 mmol) in dry 1,4-dioxane (50 mL) was refluxed under nitrogen for 3 days. After the reaction mixture was cooled down to room temperature, the precipitate was filtered and washed with dioxane. The filtrate was concentrated under reduced pressure, and the residue was purified by chromatography on silica gel eluting with EtOAc/hexanes (3:7) to give the title compound as a pale-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.44 (s, 3H), 7.19-7.21 (m, 3H), 7.39-7.41 (d, J = 8.4 Hz, 1H), 7.53 (t, J = 8.0 Hz, 1H), 9.41 (s, 1H).

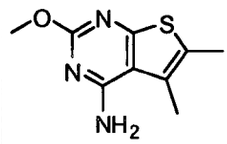
Example 25: 5,6-Dimethyl-2-(methylthio)thieno[2,3-d]pyrimidin-4-amine



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To a suspension of N-(3-cyano-4,5-dimethylthiophen-2-ylcarbamothioyl)-benzamide (Example 1a) (1.33 g, 4.22 mmol) in ethanol (25 mL) was added NaOH (2.0 N, 5.8 mL) at room temperature under nitrogen. After stirring at 100 °C under nitrogen for 0.5 h, the reaction mixture was cooled in an ice bath and MeI (0.8 mL) was added dropwise. After stirring for another 0.5 h, the resulting precipitate was collected by filtration, rinsed with water, 20 % EtOH/H_2O, and dried under vacuum to give the title compound (840 mg, 89 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.32 (s, 3H), 2.34 (s, 3H), 2.42 (s, 3H), 6.93 (bs, 2H). MS 226 (MH^+).

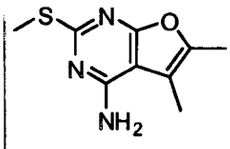
Example 26: 2-Methoxy-5,6-dimethylthieno[2,3-d]pyrimidin-4-amine



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Prepared in a similar manner to Example 25 from N-(3-cyano-4,5-dimethylthiophen-2-ylcarbamoyl)benzamide (Example 4a) and methyl iodide in 86 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.36 (s, 3H), 3.53 (s, 3H), 6.0 (bs, 2H). MS 210 (MH^+).

Example 27: 5,6-Dimethyl-2-(methylthio)furo[2,3-d]pyrimidin-4-amine



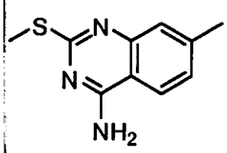
113

Prepared as in Example 25 from N-(2-cyano-4,5-dimethylfuran-3-ylcarbamothioyl)benzamide (Example 27a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.16 (s, 3H), 2.23 (s, 3H), 2.41 (s, 3H), 6.92 (s, 2H). MS 210 (MH^+).

Example 27a: N-(2-Cyano-4,5-dimethylfuran-3-ylcarbamothioyl)benzamide

Prepared as in Example 1a from 2-amino-4,5-dimethylfuran-3-carbonitrile and benzoyl isothiocyanate. MS 300 (MH^+).

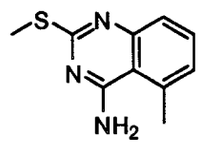
Example 28: 7-Methyl-2-(methylthio)quinazolin-4-amine



171

Prepared as in Example 25 from N-(2-cyano-5-methylphenylcarbamothioyl)benzamide (Example 17a) . ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.40 (s, 3H), 2.45 (s, 3H), 7.17 (dd, J = 2.0, 8.8 Hz, 1H), 7.32 (s, 1H), 7.71 (b, 2H), 8.01 (d, J = 8.4 Hz, 1H). MS 206 (MH^+).

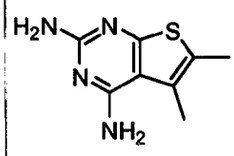
Example 29: 5-Methyl-2-(methylthio)quinazolin-4-amine



173

Prepared as in Example 25 from N-(2-cyano-3-methylphenylcarbamothioyl)benzamide (Example 3a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.46 (s, 3H), 2.75 (s, 3H), 7.11 (d, J = 7.2 Hz, 1H), 7.33 (d, J = 7.2 Hz, 1H), 7.51 (dd, J = 0.8, 7.2 Hz, 1H). MS 206 (MH^+).

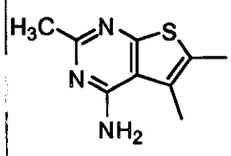
Example 30: 5,6-Dimethylthieno[2,3-d]pyrimidine-2,4-diamine



5

A mixture of 2-amino-4,5-dimethylthiophene-3-carbonitrile (500 mg, 3.29 mmol), cyanoguanidine (276.6mg, 3.29 mmol) and HCl (2 N, 1.5 mL) in water (10 mL) was refluxed under nitrogen for 2 h. The reaction mixture was cooled to room temperature, and basified with diluted NaOH aqueous solution to PH 7~8. After evaporation of water, the residue was purified by preparative HPLC eluting with acetonitrile and water to give the title compound (33 mg, 5 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.22 (s, 3H), 2.27 (s, 3H), 5.85 (bs, 2H), 6.29 (bs, 2H). MS 195 (MH^+).

Example 31: 2,5,6-Trimethylthieno[2,3-d]pyrimidin-4-amine

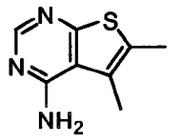


115

A mixture of 2-amino-4,5-dimethylthiophene-3-carbonitrile (200 mg, 1.32 mmol), ammonia acetate (204 mg, 2.64 mmol), and triethyl orthoacetate (2.0 mL) was stirred in a sealed tube at 120 °C overnight. After the reaction mixture was cooling down to room temperature, the precipitate was collected by filtration, rinsed with EtOAc and dried in the air to give title

compound (52 mg, 60 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.45 (s, 3H), 2.56 (s, 3H), 5.28 (bs, 2H). MS 194 (MH^+).

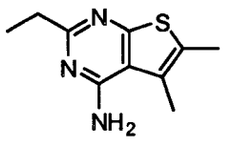
Example 32: 5,6-Dimethylthieno[2,3-d]pyrimidin-4-amine



117

Prepared as in Example 31 from 2-amino-4,5-dimethylthiophene-3-carbonitrile and triethyl orthoformate. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.36 (s, 3H), 2.39 (s, 3H), 6.85 (bs, 2H), 8.14 (s, 1H). MS 180 (MH^+).

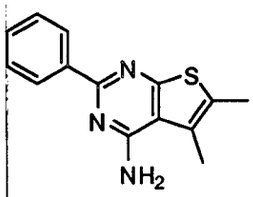
Example 33: 2-Ethyl-5,6-dimethylthieno[2,3-d]pyrimidin-4-amine



119

Prepared as in Example 31 from 2-amino-4,5-dimethylthiophene-3-carbonitrile and triethyl orthopropanate. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.19 (t, J = 7.6 Hz, 3H), 2.33(s,3H), 2.36 (s, 3H), 2.61 (q, J = 7.6 Hz, 2H), 6.74 (bs, 2H). MS 208 (MH^+).

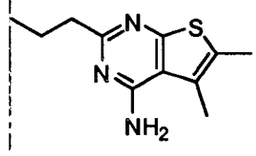
Example 34: 5,6-Dimethyl-2-phenylthieno[2,3-d]pyrimidin-4-amine



121

A mixture of 2-amino-4,5-dimethylthiophene-3-carbonitrile (152 mg, 1.0 mmol), ammonia acetate (308.3 mg, 4.0 mmol) and triethyl orthobenzoate (2.0 mL) in a sealed tube was put in a microwave at 200 °C for 20 min. After the reaction mixture was cooled to room temperature, it was diluted with EtOAc, washed with saturated $NaHCO_3$ and H_2O. The solvent was removed by vacuum and the residue was purified by preparative HPLC eluting with acetonitrile and water to give the title compound (80 mg, 31 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 2.48 (s, 3H), 5.34 (bs, 2H), 7.46-7.43 (m, 3H), 8.4-8.38 (m, 2H). MS 256 (MH^+).

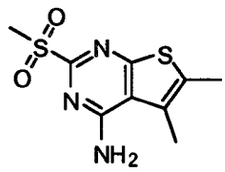
Example 35: 5,6-Dimethyl-2-propylthieno[2,3-d]pyrimidin-4-amine



123

Prepared as in Example 34 from 2-amino-4,5-dimethylthiophene-3-carbonitrile and triethyl orthobutanate. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.87 (t, J = 7.6 Hz, 3H), 1.72-1.67 (m, 2H), 2.33(s, 3H), 2.36 (s, 3H), 2.57 (t, J = 7.2 Hz, 2H), 6.73 (bs, 2H). MS 222 (MH^+).

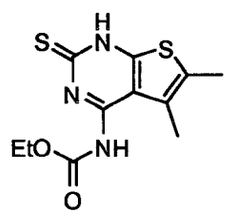
Example 36: 5,6-Dimethyl-2-(methylsulfonyl)thieno[2,3-d]pyrimidin-4-amine



125

To a suspension of 5,6-dimethyl-2-(methylthio)thieno[2,3-d]pyrimidin-4-amine (Example 1) (200 mg, 0.89 mmol) in DCM (25 mL) was added *m*-chloroperoxybenzoic acid (767 mg, 4.44 mmol). After stirring at room temperature overnight, the reaction mixture was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by preparative HPLC eluting with acetonitrile and water to give the title compound (45 mg, 20 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.42 (s, 6H), 3.27 (s, 3H). MS 258 (MH^+).

Example 37: Ethyl 5,6-dimethyl-2-thioxo-1,2-dihydrothieno[2,3-d]pyrimidin-4-ylcarbamate

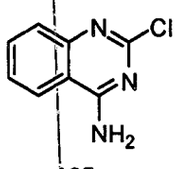


133

To a suspension of 4-amino-5,6-dimethylthieno[2,3-d]pyrimidine-2(1H)-thione (211 mg, 1 mmol) in DMF (5 mL) was added Et_3N (0.21 mL, 1.5 mmol) and ethyl chloroformate (0.143 mL, 1.5 mmol). The reaction mixture was stirred at room temperature overnight, then diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, filtered and evaporated.

The residue was purified on Biotage SP-1 eluting with EtOAc/hexane to give the title compound (154 mg, 54 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.22 (t, J = 7.2 Hz, 3H), 2.38 (s, 3H), 2.39 (s, 3H), 4.25 (q, J = 7.2 Hz, 2H), 7.25-7.21 (m, 2H). MS 284 (MH^+)

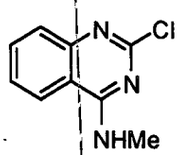
Example 38: 2-Chloroquinazolin-4-amine



185

To a solution of 2,4-dichloroquinazoline (2.0 g, 10 mmol) in THF (10 mL), was added ammonia (28-30 % in water, 18 mL). The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc, washed with saturated $NaHCO_3$, water and brine, dried over Na_2SO_4, filtered and evaporated. The resulting solid was washed with EtOAc to give the title compound (1.3 g, 72 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.52-7.48 (m, 1H), 7.6-7.58 (m, 1H), 7.8-7.76 (m, 1H), 8.22-8.20 (m, 1H), 8.32 (bs, 2H).

Example 39: 2-Chloro-N-methylquinazolin-4-amine



187

Prepared as in Example 38 from 2,4-dichloroquinazoline and methylamine. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.98 (d, J = 4.4 Hz, 3H), 7.53-7.49 (m, 1H), 7.61-7.58 (m, 1H), 7.79-7.75 (m, 1H), 88.19-8.17 (m, 1H),.78 (bs, 1H).

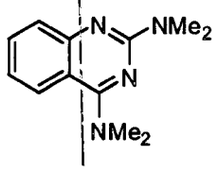
Example 40: 2-Chloro-N,N-dimethylquinazolin-4-amine



189

Prepared as in Example 38 from 2,4-dichloroquinazoline and dimethylamine. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.42 (s, 6H), 7.42-7.39 (m, 1H), 7.72-7.70 (m, 1H), 7.79-7.77 (m, 1H), 8.03-8.01 (m, 1H). MS 208 (MH^+).

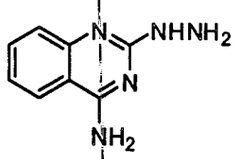
Example 41: N2,N2,N4,N4-Tetramethylquinazoline-2,4-diamine



191

Prepared as in Example 38 from 2,4-dichloroquinazoline and dimethylamine. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.27-3.23 (m, 12H), 7.01-6.97 (m, 1H), 7.51-7.47 (m, 2H), 7.80-7.78 (m,1H). MS 217 (MH^+).

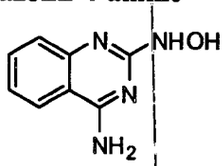
Example 42: 2-Hydrazinylquinazolin-4-amine



193

A mixture of 2-chloroquinazolin-4-amine (Example 38) (100 mg, 0.56 mmol) and hydrazine (0.09 mL, 2.79 mmol) in ethanol (5 mL) was heated in a sealed tube at 80 °C overnight. After the reaction mixture was cooled down, the resulting precipitate was collected by filtration, rinsed with ethanol and dried in the air to give the title compound (84 mg, 86 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.2 (bs, 2H), 4.6 (bs, 2H), 7.0 (t, J = 7.2 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.43 (s, 1H), 7.61 (s, 1H), 7.87 (d, J = 7.6 Hz, 1H).

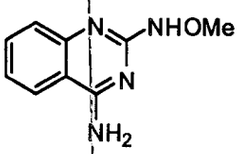
Example 43: 2-(Hydroxyamino)quinazolin-4-amine



195

Prepared as in Example 42 from 2-chloroquinazolin-4-amine (Example 38) and hydroxylamine. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.44-7.35 (m, 2H), 7.78-7.74 (m, 2H), 8.24-8.22 (m, 1H), 8.95-8.76 (m, 2H). MS 177 (MH^+).

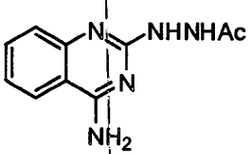
Example 44: 2-(Methoxyamino)quinazolin-4-amine



197

Prepared as in Example 42 from 2-chloroquinazolin-4-amine (Example 38) and methoxylamine. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.79 (s, 3H), 7.48-7.44 (m, 1H), 7.86-7.80 (m, 2H), 8.27 (d, J = 8.0 Hz, 1H), 8.99 (s, 1H), 9.16 (s, 1H), 12.39-12.08 (m, 1H). MS 191 (MH^+).

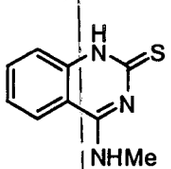
Example 45: N'-(4-Aminoquinazolin-2-yl)acetohydrazide



199

Prepared as in Example 42 from 2-chloroquinazolin-4-amine (Example 38) and methoxylamine. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.86 (s, 3H), 7.09 (t, J = 7.2 Hz,1H), 7.27 (d, J = 8.4 Hz,1H), 7.54-7.44 (m, 3H), 8.04-7.99 (m, 2H), 9.63 (s, 1H). MS 218 (MH^+).

Example 46: 4-(Methylamino)quinazoline-2(1H)-thione



175

A mixture of 2-chloro-N-methylquinazolin-4-amine (Example 39) (100 mg, 0.52 mmol), thiourea (47.5 mg, 0.62 mmol) and formic acid (0.02 mL, 0.52 mmol) in ethanol (5 mL) was refluxed for 1.5 h. After cooling to room temperature, the reaction mixture was neutralized with diluted NaOH aqueous solution. The solvent was removed under vacuum and the residue was purified by preparative HPLC eluting with acetonitrile and water to give the title compound (18 mg, 18 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.99 (d, J = 4.8 Hz, 3H), 7.25 (t, J = 7.6 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.65-7.61 (m, 1H), 8.0 (d, J = 8.0 Hz, 1H), 8.70 (d, J = 4.4 Hz, 1H), 12.32 (s, 1H). MS 192 (MH^+).

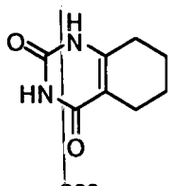
Example 47: 4-(Dimethylamino)quinazoline-2(1H)-thione



177

Prepared as in Example 46 from 2-chloro-N,N-dimethylquinazolin-4-amine (Example 40) and thiourea. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.31 (s, 6H), 7.24-7.19 (m, 1H), 7.40-7.38 (m, 1H), 7.65-7.61 (m, 1H), 8.00 (d, J = 8.0 Hz, 1H), 12.35(s, 1H). MS 206 (MH^+).

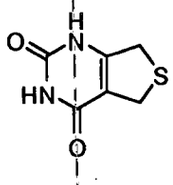
Example 48: 5,6,7,8-Tetrahydroquinazoline-2,4(1H,3H)-dione



203

A solution of 2-oxocyclohexanecarbonitrile (615 mg, 5.0 mmol) and urea (600 mg, 10.0 mmol) in 1.25 N HCl in EtOH (20 mL) was refluxed over night. After it was cooled down to 0 °C, the precipitation was collected by filtration, washed with EtOH/H_2O, and dried under vacuum overnight to give the product as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 1.67-1.80 (m, 4H), 2.25-2.29 (m, 2H), 2.38-2.42 (m, 2H). MS 167 (MH^+).

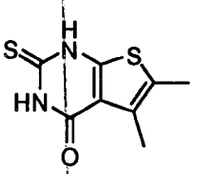
Example 49: 5,7-Dihydrothieno[3,4-d]pyrimidine-2,4(1H,3H)-dione



205

Prepared as in Example 48 from 4-oxotetrahydrothiophene-3-carbonitrile as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.74 (t, J = 3.6 Hz, 2H), 3.96 (t, J = 3.6 Hz, 2H), 11.06(s, 1H), 11.21 (s, 1H). MS 171 (MH^+).

Example 50: 5,6-Dimethyl-2-thioxo-2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-one



9

To a suspension of ethyl 4,5-dimethyl-2-thioureidothiophene-3-carboxylate (Example 50a) (37 mg, 0.17 mmol) in dry EtOH (10 mL) was added sodium hydroxide (21 mg, 0.52 mmol). The reaction mixture was then stirred at room temperature for 5 minutes and refluxed for 10 minutes. The reaction mixture was cooled to room temperature, neutralized with 10% AcOH and then concentrated to dryness. The residue was purified by chromatography on silica gel (Gradient 0-50 % EtOAc in Hexanes) to give the title compound (8 mg) in 24 % yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.25 (s, 6H), 12.24 (s, 1H), 13.27 (s, 1H). MS 202 (MH^+).

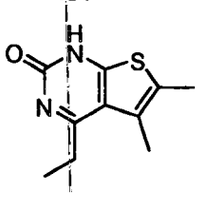
Example 50a: Ethyl 4,5-dimethyl-2-thioureidothiophene-3-carboxylate

To a solution of ethyl 2-isothiocyanato-4,5-dimethylthiophene-3-carboxylate (Example 50b) (1.21 g, 5.27 mmol) in dichloromethane (10 mL) was added ammonia (7 M in MeOH, 1.12 mL, 7.91 mmol) at 0 °C. The reaction mixture was then stirred at room temperature for 3 h, quenched with water and extracted with dichloromethane (3 X). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The dark orange residue was purified by chromatography on silica gel (Gradient 0-50 % EtOAc in Hexanes) to give the title compound (37.1 mg, 3 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (t, 3H, J = 7.1 Hz), 2.18 (s, 3H), 2.19 (s, 3H), 4.30 (q, 2H, J = 7.1 Hz), 8.43 (s, 2H), 11.38 (s, 1H). MS 259 (MH^+).

Example 50b: Ethyl 2-isothiocyanato-4,5-dimethylthiophene-3-carboxylate

To a mixture of thiophosgene (5.10 mL, 7.64 mmol) and calcium carbonate (1.05 g, 10.54 mmol) in $CHCl_3/H_2O$ (1/2 by volume, 6 mL) was added dropwise a solution of ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate (1.05 g, 5.27 mmol) in $CHCl_3$ (7 mL) at 0 °C over a period of 1 h. The reaction mixture was the stirred for 2.5 h at 0 °C, washed with water (3 X). The organic layer was dried over $MgSO_4$, filtered and concentrated to give the title compound (1.21 g, 100 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (t, 3H, J = 7.1 Hz), 2.19 (s, 3H), 2.30 (s, 3H), 4.28 (q, 2H, J = 7.1 Hz).

Example 51: 4-Ethyl-5,6-dimethylthieno[2,3-d]pyrimidin-2(1H)-one



135

To a solution of 1-(4,5-dimethyl-3-propionylthiophen-2-yl)urea (Example 51a) (15.4 mg, 0.068 mmol) in dry EtOH (10 mL) was added sodium hydroxide (8.4 mg, 0.20 mmol). The reaction mixture was then stirred at RT for 30 minutes under nitrogen. The reaction mixture was neutralized with 10 % AcOH and then concentrated to dryness. The residue was purified by chromatography on silica gel (Gradient 0-10 % MeOH in dichloromethane) to give the title compound (2.7 mg, 19 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, J = 7.6 Hz, 3H), 2.31 (s, 3H), 2.33 (s, 3H), 3.06 (q, J = 7.6 Hz, 2H). MS 209 (MH^+).

Example 51a: 1-(4,5-Dimethyl-3-propionylthiophen-2-yl)urea

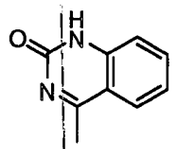
To a solution of triphosgene (68 mg, 0.224 mmol) in dry dichloromethane (2 mL) was added dropwise a mixture of 1-(2-amino-4,5-dimethylthiophen-3-yl)propan-1-one (Example 51b) (111 mg, 0.605 mmol) and DIEA (0.24 mL, 1.344 mmol) in dry dichloromethane (3.5 mL) over a period of 20 minutes. After the reaction mixture was stirred for 5 minutes, a mixture of ammonia (7 M in MeOH, 0.086 mL, 0.605 mmol) and DIEA (0.24 mL, 1.344 mmol) in dry dichloromethane (2mL) was added in one portion. The reaction mixture was then stirred at room temperature for 1 h under nitrogen. The reaction mixture was concentrated to dryness. The residue was dissolved in EtOAc (50 mL) and then washed with 10 % $NaHSO_4$, 5 % $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The yellow residue was purified by chromatography on silica gel (Gradient 0-50 % EtOAc in Hexanes) to give the title compound (15.4 mg, 30 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (t, 3H, J = 7.2 Hz), 2.25 (s, 3H), 2.30 (s, 3H), 2.87 (q, 2H, J = 7.2 Hz), 4.77 (s, 2H), 11.99 (s, 1H). MS 227 (MH^+).

Example 51b: 1-(2-Amino-4,5-dimethylthiophen-3-yl)propan-1-one

To a solution of 3-oxopentanenitrile (971 mg, 10 mmol) in dry EtOH (100 mL) was added sulfur (2.57 g, 10 mmol), butanone (0.91 mL, 10 mmol) and morpholine (0.88 mL, 10 mmol) at room temperature under nitrogen. The reaction mixture was then refluxed at 90 °C for 6 h, and then stirred overnight at room temperature under nitrogen. The orange brown reaction mixture was concentrated. The residue was diluted with water, and extracted with EtOAc (2 X).

The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified twice: first by chromatography on silica gel (Gradient 0-25 % EtOAc in hexanes), and then by Prep HPLC (0-90% acetonitrile in water) to give the title compound (123 mg, 7 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (t, 3H, J = 7.2 Hz), 2.17 (s, 3H), 2.24 (s, 3H), 2.78 (q, 2H, J = 7.2 Hz), 6.81 (s, 2H). MS 184 (MH^+).

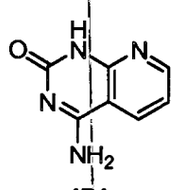
Example 52: 4-Ethyl-5,6-dimethylthieno[2,3-d]pyrimidin-2(1H)-one



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To a solution of methylmagnesium bromide (3.0 M in ether, 4.0 mL, 12.0 mmol) in dry ether (5 mL) was added dropwise a solution of 2-aminobenzonitrile (723 mg, 6.0 mmol) in dry ether (5 mL) at RT under nitrogen. After it was refluxed for 2 h under nitrogen, the reaction mixture was cooled down to 0 °C and methyl chloroformate (0.7 mL, 9.0 mmol) was added dropwise. Dry THF (5 mL) was added to dissolve the resultant precipitate. The reaction mixture was then refluxed overnight under nitrogen. The reaction mixture was acidified with 1N HCl and then neutralized with 5% $NaHCO_3$ aqueous solution. The water mixture was washed with EtOAc and the water layer was concentrated. The residue was purified by Prep HPLC ((0-90 % acetonitrile in water) to give the title compound (15.2 mg). ^{1}H NMR (400 MHz, CD_3OD) δ 2.79 (s, 3H), 7.33 (d, J = 7.1 Hz, 1H), 7.34 (t, J = 7.1 Hz, 1H), 7.75 (td, J = 1.2, 7.8 Hz, 1H), 8.03 (dd, J = 1.2 8.4 Hz, 1H). MS 161 (MH^+).

Example 53: 4-aminopyrido[2,3-*d*]pyrimidin-2(1*H*)-one



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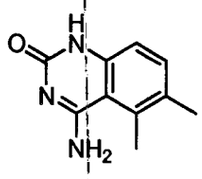
A solution of *N*-(3-cyanopyridin-2-ylcarbamoyl)benzamide (example 53a) (360 mg, 1.35 mmol) and NaOH (2 N, 1.85mL) in EtOH (5mL) was stirred at 100 °C under nitrogen for half an hour. After cooling to room temperature, the clear reaction solution was filtered and the filtrate was carefully neutralized with 10 % AcOH with vigorous stirring at 0 °C. The

resultant precipitate was collected by filtration, and washed with warm 20 % EtOH in water to give the final product 4-aminopyrido[2,3-d]pyrimidin-2(1 H)-one (120mg, 55 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.22 (dd, J = 4.4 Hz, 4.8 Hz, 1H), 7.29 (dd, J = 4.8 Hz, 1H), 8.24 (dd, J = 2 Hz, 1.6 Hz, 1H), 8.59 (dd, J = 2 Hz, 1.6 Hz, 1H), 8.66-8.71 (m, 2H), 8.70 (d, J = 1.2 Hz, 1H). MS 162 (MH^+).

Example 53a: *N*-(3-cyanopyridin-2-ylcarbamoyl)benzamide

To a solution of 2-amino-3-cyanopyridine (300 mg, 2.5 mmol) in 1.4-dioxane (5 mL) was added benzoyl isocyanate (370 mg, 2.5 mmol). The reaction mixture was then stirred at room temperature under nitrogen overnight. The precipitation was collected by filtration, washed with EtOAc/Hexanes (1:4), and dried under vacuum to give N-(3-cyanopyridin-2-ylcarbamoyl)benzamide as a white solid (360mg, 54%). MS 266 (MH^+).

Example 54: 5,6-dimethylquinazoline-2,4(1*H*,3*H*)-dione



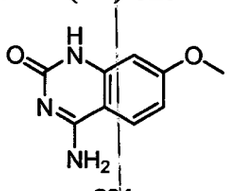
172

Prepared as in Example 53 from *N*-(2-cyano-3,4-dimethylphenylcarbamoyl)benzamide (Example 54a) as a white solid (90mg, 66%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.24 (s, 3H), 2.54 (s, 3H), 6.87 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 10.51 (s, 1H). MS 189 (MH^+).

Example 54a: *N*-(2-cyano-3,4-dimethylphenylcarbamoyl)benzamide:

Prepared as in Example 53a from 6-amino-2,3-dimethylbenzonitrile and benzoyl isocyanate as a off-white solid (210mg, 72%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.27 (s, 3H), 2.43 (s, 3H), 7.48 (d, J = 6.4 Hz, 2H), 7.53 (t, J = 8 Hz, 7.6 Hz, 2H), 7.65 (t, J = 7.2 Hz, 1H), 7.94 (d, J = 8 Hz, 1H), 8.03 (d, J = 7.6 Hz, 2H), 11.29 (s, 1H), 11.37 (s, 1H). MS 293 (MH^+).

Example 55: 4-amino-7-methoxyquinazolin-2(1*H*)-one



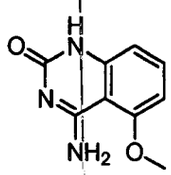
204

Prepared as in example 53 from *N*-(2-cyano-5-methoxyphenylcarbamoyl)benzamide (Example 55a) as a white solid (24mg, 37%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.79 (s, 3H), 6.63 (d, J = 4 Hz, 1H), 6.67 (dd, J = 2.4 Hz, 2.8 Hz, 1H), 7.67 (br, 2H), 7.89 (d, J = 8.8 Hz, 1H), 10.61 (s, 1H). MS 191 (MH^+).

Example 55a: *N*-(2-cyano-5-methoxyphenylcarbamoyl)benzamide:

Prepared as in Example 53a from 2-amino-4-methoxybenzonitrile and benzoyl isocyanate as white solid (99mg, 45%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.86 (s, 3H), 6.87 (dd, J = 2.5 Hz, 2.4 Hz, 1H), 7.54 (t, J = 8 Hz, 2H), 7.66 (t, J = 1.2 Hz, 1H), 7.77 (d, J = 7.2 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 2.8 Hz, 2H), 11.35 (s, 1H), 11.52 (s, 1H). MS 295 (MH^+).

Example 56: 4-amino-5-methoxyquinazolin-2(1*H*)-one



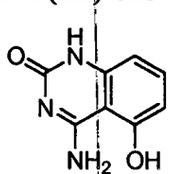
170

Prepared as in example 53 from *N*-(2-cyano-3-methoxyphenylcarbamoyl)benzamide (Example 56a) as a light yellow solid (35mg, 51%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.93 (s, 3H), 6.67 (dd, J = 7.6 Hz, 8.4 Hz, 2H), 7.45 (t, J = 8 Hz, 1H), 7.75 (s, 1H), 7.93-7.97 (br, 1H), 10.69 (s, 1H). MS 191 (MH^+).

Example 56a: *N*-(2-cyano-3-methoxyphenylcarbamoyl)benzamide:

Prepared as in Example 53a from 2-amino-6-methoxybenzonitrile and benzoyl isocyanate as light orange solid (118mg, 41%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.94 (s, 3H), 6.98 (d, J = 8 Hz, 1H), 7.54 (t, J = 8 hz, 2H), 7.64 (t, J = 8.4 Hz, 2H), 7.88 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 5.6 Hz, 2H), 11.35 (s, 1H), 11.51 (s, 1H). MS 295 (MH^+).

Example 57: 4-amino-5-hydroxyquinazolin-2(1*H*)-one



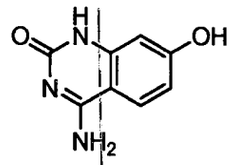
178

Prepared as in example 53 from *N*-(2-cyano-3-hydroxyphenylcarbamoyl)benzamide (Example 57a) as a green solid (50mg, 53%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.66 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 7.6 Hz, 1H), 7.57 (t, J = 8.8 Hz, 1H), 9.47 (s, 1H), 9.68 (s, 1H), 11.84 (s, 1H). MS 177 (MH^+).

Example 57a: *N*-(2-cyano-3-hydroxyphenylcarbamoyl)benzamide:

Prepared as in Example 53a from 2-amino-6-hydroxybenzonitrile and benzoyl isocyanate as an off-white solid (166mg, 46%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.76 (d, J = 8.4 Hz, 1H), 7.46 (t, J = 8 Hz, 1H), 7.54 (t, J = 8 Hz, 2H), 7.66-7.73 (m, 2H), 8.04-8.06 (d, J = 8 Hz, 2H), 11.24 (s, 1H), 11.30 (s, 1H), 11.42 (s, 1H). MS 281 (MH^+).

Example 58: 4-amino-7-hydroxyquinazolin-2(1*H*)-one



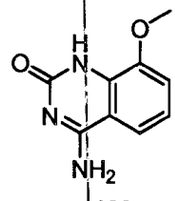
180

Prepared as in example 53 from *N*-(2-cyano-5-hydroxyphenylcarbamoyl)benzamide (Example 58a) as a light grey solid (104mg, 41%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.51 (s, 2H), 6.52 (d, J = 2.4 Hz, 1H), 7.69-7.72 (br, 1H), 7.82 (d, J = 9.2 Hz, 2H), 10.57 (br, 1H). MS 177 (MH^+).

Example 58a: *N*-(2-cyano-5-hydroxyphenylcarbamoyl)benzamide:

Prepared as in Example 53a, but refluxed in acetone instead of 1,4-dioxane, from 2-amino-4-hydroxybenzonitrile and benzoyl isocyanate as a yellow solid (399mg, 94%). MS 281 (MH^+).

Example 59: 4-amino-8-methoxyquinazolin-2(1*H*)-one



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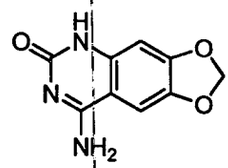
Prepared as in example 53 from *N*-(2-cyano-6-methoxyphenylcarbamoyl)benzamide (Example 59a) as a dark white solid (75mg, 39%). ^{1}H

NMR (400 MHz, DMSO-d_6) δ 3.86 (s, 3H), 7.02 (t, J = 8.4 Hz, 1H), 7.17 (d, J = 7.2 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.85 (br, 2H), 9.73(s, 1H). MS 191 (MH^+).

Example 59a: *N*-(2-cyano-6-methoxyphenylcarbamoyl)benzamide:

Prepared as in Example 53a from 2-amino-3-methoxybenzonitrile and benzoyl isocyanate as a light orange solid (280mg, 95%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.89 (s, 3H), 7.42 (t, J = 3.2 Hz, 2H), 7.46 (d, J = 3.6 Hz, 1H), 7.54 (t, J = 8 Hz, 2H), 7.66 (t, J = 7.6 Hz, 1H), 8.05 (d, J = 8.6 Hz, 2H), 10.55 (s, 1H), 11.32 (s, 1H). MS 295 (MH^+).

Example 60: 8-amino-[1,3]dioxolo[4,5-*g*]quinazolin-6(5*H*)-one



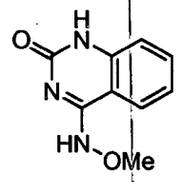
184

Prepared as in example 53 from *N*-(6-cyanobenzo[*d*][1,3]dioxol-5-ylcarbamoyl)benzamide (Example 60a) as a light yellow solid (80mg, 77%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.24 (s, 2H), 6.74 (s, 1H), 7.75 (s, 1H), 9.36 (d, J = 10.4 Hz, 1H), 9.80 (d, J = 7.2 Hz, 1H), 12.01(s, 1H). MS 205 (MH^+).

Example 60a: *N*-(6-cyanobenzo[*d*][1,3]dioxol-5-ylcarbamoyl)benzamide:

Prepared as in Example 53a from 6-aminobenzo[*d*][1,3]dioxole-5-carbonitrile and benzoyl isocyanate as a yellow solid (157mg, 82%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.19 (s, 2H), 7.42 (s, 1H), 7.54 (t, J = 8 Hz, 2H), 7.66 (t, J = 7.6 Hz, 1H), 7.74 (s, 1H), 8.03 (d, J =9.2 Hz, 2H), 11.32 (d, J = 12.8 Hz, 2H). MS 309 (MH^+).

Example 61: 4-(Methoxyamino)quinazolin-2(1*H*)-one

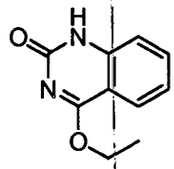


166

To a suspension of 2,4-dichloroquinazoline (995 mg, 5.0 mmol) in dry EtOH (100 mL), were added methoxyamine hydrochloride (569 mg, 5.5 mmol) and NaOH (227 mg, 5.5 mmol) in one portion at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour, then placed in a refrigerator at 4 °C for 72 h. Upon completion, the reaction was concentrated, and the residue

was dissolved in EtOAc and washed with saturated $NaHCO_3$ (1x) and brine (1x). The organic phase was dried over $MgSO_4$, filtered and concentrated. The crude product was purified by preparative HPLC (10-90 % CH_3CN in H_2O) to provide 4-(methoxyamino)quinazolin-2(1*H*)-one (556 mg, 36%) as an off-white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 3.68 (s, 3H), 7.02 (t, J = 7.4 Hz, 1H), 7.35 (d, J = 7.9 Hz, 1H), 7.52 (ddd, J = 8.1, 7.0, 1.5 Hz, 1H), 7.77 (dd, J = 7.8, 1.4 Hz, 1H), 10.13 (br s, 1H), 10.89 (br s, 1H). MS 192.2 (MH^+).

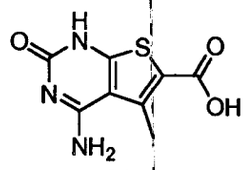
Example 62: 4-Ethoxyquinazolin-2(1*H*)-one



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Purification by preparative HPLC (10-90 % CH_3CN in H_2O) of the crude reaction of example 61 also provided 4-ethoxyquinazolin-2(1*H*)-one (90 mg, 9%) as an off-white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 1.35 (t, J = 7.0 Hz, 3H), 4.44 (q, J = 7.0 Hz, 2H), 7.34 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H), 7.46 (dd, J = 8.2, 1.0 Hz, 1H), 7.71 (ddd, J = 8.5, 7.0, 1.2 Hz, 1H), 8.01 (dd, J = 8.2, 1.5 Hz, 1H), 12.25 (br s, 1H). MS 191.1 (MH^+).

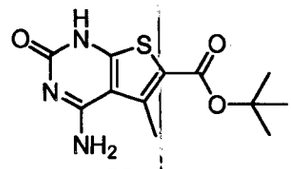
Example 63: 4-Amino-5-methyl-2-oxo-1,2-dihydrothieno[2,3-*d*]pyrimidine-6-carboxylic acid



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To a solution of *tert*-butyl 4-amino-5-methyl-2-oxo-1,2-dihydrothieno[2,3-*d*]pyrimidine-6-carboxylate (example 64a) (10.7 g, 38.03 mmol) in CH_2Cl_2 (25 mL), was added trifluoroacetic acid (25 mL, 324.5 mmol). The reaction mixture was stirred at rt overnight. The precipitated solid was collected by filtration, and washed with CH_2Cl_2 to yield 4-Amino-5-methyl-2-oxo-1,2-dihydrothieno[2,3-*d*]pyrimidine-6-carboxylic acid (6.98 g, 82 %) as a light brown solid. ^1H NMR (400 MHz, DMSO-d_6) δ 2.78 (s, 3H). MS 226.0 (MH^+).

Example 64: *tert*-Butyl 4-amino-5-methyl-2-oxo-1,2-dihydrothieno[2,3-*d*]pyrimidine-6-carboxylate



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To a suspension of *tert*-butyl 5-(3-benzoylureido)-4-cyano-3-methylthiophene-2-carboxylate (example 64a) (18 g, 60.52 mmol) in EtOH (200 mL) was added NaOH (75 mL, 2N). The suspension became clear, and the mixture was heated to reflux for 30 min. After cooling to rt, the reaction was filtered, and the filtrate was cooled to 0 °C in an ice/water bath. The solution was neutralized with 10 % acetic acid. The precipitated solid was collected by filtration, and heated in EtOH at 80 °C under N_2 for 20 min. After cooling to rt, the product was collected by filtration and washed with 10 % EtOH in H_2O to yield *tert*-Butyl 4-amino-5-methyl-2-oxo-1,2-dihydrothieno[2,3-*d*]pyrimidine-6-carboxylate (10.73 g, 63 %) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.51 (s, 9H), 2.73 (s, 3H), 3.18 (s, 2H). MS 282.2 (MH^+).

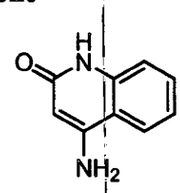
Example 64a: *tert*-butyl 5-(3-benzoylureido)-4-cyano-3-methylthiophene-2-carboxylate

To a solution of *tert*-butyl 5-amino-4-cyano-3-methylthiophene-2-carboxylate (example 64b) (16 g, 67.14 mmol) in dioxane (200 mL), was added benzoyl isocyanate (10 g, 67.14 mmol). The reaction mixture was stirred at rt overnight, and upon completion was diluted with EtOAc, washed with $NaHCO_3$, water, brine, dried over $MgSO_4$, filtered and concentrated to yield *tert*-butyl 5-(3-benzoylureido)-4-cyano-3-methylthiophene-2-carboxylate (21.78 g, 84 %) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.54 (s, 9H), 3.58 (s, 3H), 7.58 (t, J = 7.5 Hz, 2H), 7.71 (t, J = 7.5 Hz, 1H), 7.88 (d, J = 7.5 Hz, 1H), 8.05 (d, J = 7.5 Hz, 2H), 12.25 (br s, 1H).

Example 64b: *tert*-butyl 5-amino-4-cyano-3-methylthiophene-2-carboxylate

To a solution of tert-butyl 3-oxobutanoate (30 mL, 183.94 mmol) in dry EtOH (360 mL), were added elemental sulfur (5.90 g, 183.94 mmol), malononitrile (12.16 g, 183.94 mmol) and triethylamine (25.6 mL, 183.94 mmol). The reaction mixture was heated to 80 °C, and stirred for 2 h. After cooling to rt, the mixture was concentrated under reduced pressure. The resulting residue was dissolved in EtOAc, washed with $NaHCO_3$, water, brine, dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel (20 % EtOAc in hexane) to yield *tert*-butyl 5-amino-4-cyano-3-methylthiophene-2-carboxylate (31.2 g, 73 %) as a brown solid.

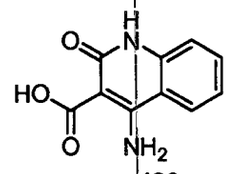
Example 65: 4-Aminoquinolin-2(1H)-one



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4-Amino-2-*oxo*-1,2-dihydroquinoline-3-carboxylic acid (Example 64) (0.030 g, 0.15 mmol) was heated neat at 295°C for 10 minutes, then cooled to room temperature to give 4-aminoquinolin-2(1H)-one (0.023 g, 99%) as a light yellow solid. M.p.: > 250°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.42 (s, 1H), 6.55 (s, 2H), 7.07 (t, J = 7.6 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.42 (t, J = 7.2 Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H), 10.71 (s, 1H). MS 161 (MH^+).

Example 66: 4-Amino-2-oxo-1,2-dihydroquinoline-3-carboxylic acid



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Benzyl 4-amino-2-oxo-1,2-dihydroquinoline-3-carboxylate (Example 66a) (0.6 g, 2.04 mmol) was dissolved in DMF (8 mL) and heated at 70°C under a hydrogen balloon in the presence of 10% Pd/C (0.15g) for 1 hour. The Pd/C was filtered out and washed with dichloromethane and the solvents were removed under vacuum. The residue was dissolved/suspended in NaOH (2M, 40 mL), stirred at room temperature for 30 minutes and the solution washed with dischloromethane. The aqueous layer was cooled to 0°C and acidified to pH 1 with 2M HCl. The resultant precipitate was collected and washed with dichloromethane to give 4-amino-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (0.050 g, 12%) as a light yellow solid. M.p.: > 250°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.32 (m, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.69 (m, 1H), 8.27 (d, J = 8.4 Hz, 1H), 8.86 (s, 1H), 9.87 (s, 1H), 11.95 (s, 1H). MS 205 (MH^+).

Example 66a: Benzyl 4-amino-2-oxo-1,2-dihydroquinoline-3-carboxylate

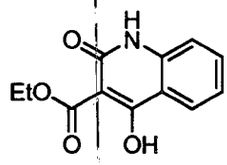
Benzyl 4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylate (Example 66b) (0.55 g, 1.75 mmol) was dissolved in DMF (8 mL) and 4-methoxybenzylamine (0.56 mL, 4.31 mmol) was added. The reaction was heated at 115°C for 30 minutes, then cooled to room temperature and poured into ice water. The resultant precipitate was dissolved in 10 mL TFA and stirred at

room temperature for 15 minutes, then the mixture was poured into ice water. The resultant precipitate was collected, dissolved in dichloromethane, dried over $MgSO_4$, filtered and evaporated to give the crude benzyl 4-amino-2-oxo-1,2-dihydroquinoline-3-carboxylate (600 mg) which was used as this without further purification. MS 295 (MH^+).

Example 66b: Benzyl 4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylate

Dibenzylmalonate (7.75 mL, 31.6 mmol) was added slowly to a suspension of 60% sodium hydride in mineral oil (1.41 g, 35.3 mmol) in anhydrous DMF (100 mL) at -20°C under nitrogen. After stirring at room temperature for 30 minutes, isatoic anhydride (5.0 g, 30.7 mmol) was added, and the reaction was heated at 120°C for 1 hour. The reaction was then cooled to -50°C and oxalyl chloride (10.7 mL, 123 mmol) was slowly added. The reaction mixture was stirred at room temperature for 2 hours then poured into aqueous NaCl (10%, 750 mL) at 0°C, and the resultant precipitate was filtered out. The precipitate was dissolved in dichloromethane, dried over $MgSO_4$, filtered and evaporated under reduced pressure. Diethyl ether was added to the residue, and the resultant solid was collected to give benzyl 4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylate (3.56 g, 37% yield) which was used without further purification. MS 314 (MH^+).

Example 67: Ethyl 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate

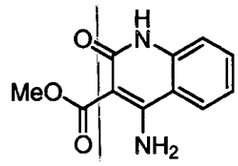


188

Diethylmalonate (11.4 mL, 75.1 mmol) was added slowly to a suspension of 60% sodium hydride in mineral oil (3.09 g, 77.3 mmol) in anhydrous DMF (100 mL) at -10°C under nitrogen. After stirring at room temperature for 30 minutes, isatoic anhydride (12.0 g, 73.6 mmol) was added, and the reaction was heated at 115°C for 2.5 hours. The reaction was cooled to room temperature, then poured into ice water (1.4 L) and acidified to pH 4 with 2M HCl. The resultant precipitate was collected, then dissolved/suspended in dichloromethane (450 mL). The dichloromethane solution was filtered out then evaporated to provide a residue that was vigorously triturated with diethyl ether (150 mL) for 1 hour. The solid was collected to give ethyl 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (3.63 g, 21%) as a white solid. M.p.:

190°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (t, J = 7.2 Hz, 3H), 4.35 (q, J = 7.2 Hz, 2H), 7.21 (m, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.63 (m, 1H), 7.93 (dd, J = 0.8, 8.4 Hz, 1H), 11.51 (s, 1H), 13.40 (s, 1H). MS 234 (MH^+).

Example 68: Methyl 4-amino-2-oxo-1,2-dihydroquinoline-3-carboxylate



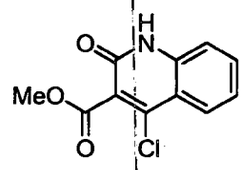
210

Methyl 4-(4-methoxybenzylamino)-2-oxo-1,2-dihydroquinoline-3-carboxylate (Example 68a) (0.841 g, 2.49 mmol) was dissolved in TFA (5 mL) and stirred at room temperature for 30 minutes. The TFA was removed under reduced pressure, and the residue was dissolved in dichloromethane, then precipitated out by adding excess diethyl ether. The resultant solid was collected by filtration, suspended in dichloromethane, and washed with concentrated sodium bicarbonate. The solid was collected to give methyl 4-amino-2-oxo-1,2-dihydroquinoline-3-carboxylate (0.230 g, 42%) as a white solid. M.p.: 236°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.73 (s, 3H), 7.12 (t, J = 8.0 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 8.38 (bs, 2H), 10.88 (bs, 1H). MS 219 (MH^+).

Example 68a: methyl 4-(4-methoxybenzylamino)-2-oxo-1,2-dihydroquinoline-3-carboxylate

Methyl 4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylate (Example 69) (0.928 g, 3.91 mmol) was dissolved in DMF (6 mL), and 4-methoxybenzylamine (1.14 mL, 8.78 mmol) was added. The reaction was heated at 90°C for 30 minutes, then cooled to room temperature and poured into a stirred mixture of 50 mL hexanes and 100 mL ice water. The resultant precipitate was collected by filtration and further chromatographed on silica gel (0% to 20% MeOH in dichloromethane) to give methyl 4-(4-methoxybenzylamino)-2-oxo-1,2-dihydroquinoline-3-carboxylate as an off white solid (0.841 g, 64%). MS 339 (MH^+).

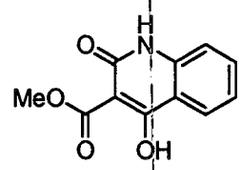
Example 69: Methyl 4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylate



190

Dimethylmalonate (2.2 mL, 19.2 mmol) was added slowly to a suspension of 60% sodium hydride in mineral oil (0.81 g, 20.3 mmol) in anhydrous DMF (100 mL) at -10°C under nitrogen. After stirring at room temperature for 30 minutes, isatoic anhydride (3.0 g, 18.4 mmol) was added, and the reaction mixture was heated at 115°C for 2.5 hours. The reaction was then cooled to -40°C and oxalyl chloride (6 mL, 68.8 mmol) was slowly added. The reaction was stirred at room temperature for 20 minutes, and was then poured into 1200 mL of 10% NaCl at 0°C. The resultant precipitate was collected by filtration to give crude methyl 4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylate (1.40 g, 32%), which was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.87 (s, 3H), 7.39 (m, 2H), 7.70 (m, 1H), 7.92 (d, J = 8.4 Hz, 1H), 12.49 (s, 1H). MS 238 (MH^+).

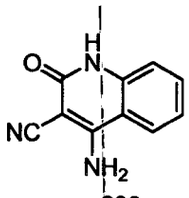
Example 70: Methyl 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate



192

Dimethylmalonate (2.2 mL, 19.2 mmol) was added slowly to a suspension of 60% sodium hydride in mineral oil (0.81 g, 20.3 mmol) in anhydrous DMF (50 mL) at -10°C under nitrogen. After stirring at room temperature for 30 minutes, isatoic anhydride (3.0 g, 18.4 mmol) was added, and the reaction was heated at 115°C for 2.5 hours. The reaction was cooled to room temperature, then poured into ice water (500 mL) and acidified to pH 2 with 2M HCl. The resultant precipitate was collected by filtration to give crude methyl 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (2.89 g, 72%), which was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.86 (s, 3H), 7.23 (m, 2H), 7.63 (m, 1H), 7.94 (dd, J = 0.8, 8.0 Hz, 1H), 11.55 (s, 1H), 13.33 (s, 1H). MS 220 (MH^+).

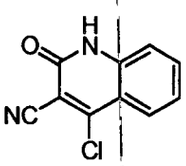
Example 71: 4-Amino-2-oxo-1,2-dihydroquinoline-3-carbonitrile



200

4-chloro-2-oxo-1,2-dihydroquinoline-3-carbonitrile (example 72) (0.66 g, 3.23 mmol) was suspended in DMF (7 mL), and 4-methoxybenzylamine (0.94 mL, 7.26 mmol) was added. The reaction was heated at 100°C for 1 hour and the DMF was removed under vacuum. The residue was dissolved in TFA (6 mL) and stirred at room temperature for 30 minutes and dichloromethane (10 mL) was added. The solid product that formed was collected, suspended in water and the solution stirred overnight. The solid was collected by filtration to give 4-amino-2-oxo-1,2-dihydroquinoline-3-carbonitrile (0.150 g, 25%) as a white solid. M.p.: > 250°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.19 (m, 2H), 7.57 (m, 1H), 7.88 (bs, 2H), 8.12 (d, J = 7.6 Hz, 1H), 11.23 (s, 1H). MS 186 (MH^+).

Example 72: 4-chloro-2-oxo-1,2-dihydroquinoline-3-carbonitrile



198

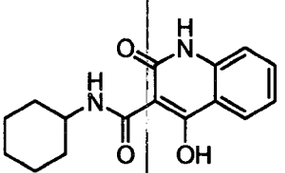
2,4-dichloroquinoline-3-carbonitrile (Example 72a) (0.95 g, 4.26 mmol) and ammonium acetate (0.36 g, 4.67 mmol) were heated in acetic acid (20 mL) at 140°C for 4 hours, then cooled to room temperature. The reaction was poured into ice water (400 mL), and the resultant precipitate was collected by filtration to give 4-chloro-2-oxo-1,2-dihydroquinoline-3-carbonitrile (0.668 g, 77%) as a light yellow solid. M.p.: > 250°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42 (m, 2H), 7.79 (m, 1H), 7.96 (d, J = 8.4 Hz, 1H), 12.72 (s, 1H). MS 205 (MH^+).

Example 72a: 2,4-dichloroquinoline-3-carbonitrile

N-cyclohexyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamide (Example 73) (1.18 g, 4.12 mmol) was dissolved in phosphorus oxychloride (15 mL) and triethylamine (1.72 mL, 12.4 mmol) was slowly added. The reaction was heated at 120°C for 7 hours, then cooled to room temperature and poured carefully into ice water (300 mL). The resultant

precipitate was collected by filtration to give 2,4-dichloroquinoline-3-carbonitrile (0.848 g, 92%), which was used without further purification. MS 223 (MH^+).

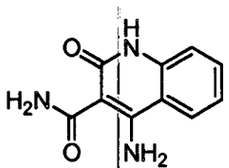
Example 73: N-cyclohexyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamide



194

Methyl 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (Example 70) (2.70 g, 12.3 mmol) was suspended in toluene (27 mL), and cyclohexylamine (1.40 g, 14.1 mmol) was added. The reaction was heated at 115°C for 5 hours, then cooled to room temperature. Diethyl ether (50 mL) was added, and the resultant precipitate was collected by filtration to give N-cyclohexyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamide (1.22 g, 35%) as an off white solid. M.p.: 221°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.37 (m, 4H), 1.55 (m, 1H), 1.68 (m, 2H), 1.88 (m, 2H), 3.86 (m, 1H), 7.28 (t, J = 8.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.68 (t, J = 7.6 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 10.35 (d, J = 7.6 Hz, 1H), 11.83 (bs, 1H). MS 287 (MH^+).

Example 74: 4-amino-2-oxo-1,2-dihydroquinoline-3-carboxamide



202

N,N-bis(4-methoxybenzyl)-4-(4-methoxybenzylamino)-2-oxo-1,2-dihydroquinoline-3-carboxamide (Example 74a) (2.0 g, 3.55 mmol) was dissolved in TFA (15 mL) and the solution was stirred at room temperature for 6 hours. The TFA was removed under vacuum, and the resultant solid was stirred in water overnight, then collected by filtration to give 1.8 grams of crude final product. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.18 (m, 2H), 7.25 (d, J = 7.2 Hz, 1H), 7.56 (t, J = 8.0 Hz, 1H), 8.09 (d, J = 7.6 Hz, 2H), 9.83 (d, J = 4.8 Hz, 1H), 10.85 (bs, 1H), 11.12 (s, 1H). MS 204 (MH^+).

Example 74a: *N,N*-bis(4-methoxybenzyl)-4-(4-methoxybenzylamino)-2-oxo-1,2-dihydroquinoline-3-carboxamide

4-chloro-*N,N*-bis(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-3-carboxamide (Example 74b) (4.25 g, 9.18 mmol) was dissolved in DMF (20 mL), and 4-methoxybenzylamine (2.68 mL, 20.6 mmol) was added. The reaction was heated at 100°C for 1.5 hours, then cooled to room temperature and poured into ice water (300 mL). The resultant precipitate was collected by filtration and further chromatographed on silica gel (0% to 20% MeOH in dichloromethane) to give crude *N,N*-bis(4-methoxybenzyl)-4-(4-methoxybenzylamino)-2-oxo-1,2-dihydroquinoline-3-carboxamide (3.65g, 71%), which was used without further purification. MS 564 (MH^+).

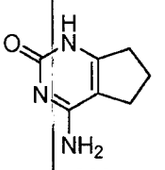
Example 74b: 4-chloro-*N,N*-bis(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-3-carboxamide

Triethylamine (5.73 mL, 41.2 mmol) was added to phosphorus oxychloride (60 mL), followed by 4-hydroxy-*N,N*-bis(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-3-carboxamide (Example 74c) (6.11 g, 13.7 mmol). The reaction was heated at 65°C for 4 hours, then cooled to room temperature and carefully poured into ice water (1200 mL). The solution was extracted dichloromethane (2x200 mL. The organic layers were combined and washed with water, dried over $MgSO_4$, filtered and evaporated. The residue was dissolved in dichloromethane (18 mL) and poured into 200 mL of 30% hexanes in diethyl ether. The resultant precipitate was collected by filtration to give crude 4-chloro-*N,N*-bis(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-3-carboxamide (4.25 g, 67%) which was used without further purification. MS 463 (MH^+).

Example 74c: 4-Hydroxy-*N,N*-bis(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-3-carboxamide

Ethyl 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (Example 67) (3.58 g, 15.4 mmol) and bis(4-methoxybenzyl)amine (4.54 g, 17.6 mmol) were suspended in toluene (36 mL) and heated at 115°C for 5 hours, then cooled to room temperature. Diethyl ether was added (50 mL), and the resultant precipitate was collected by filtration to give crude 4-hydroxy-*N,N*-bis(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-3-carboxamide (6.45 g, 95%) which was used without further purification.

Example 75 : 4-Amino-6,7-dihydro-1H-cyclopenta[d]pyrimidin-2(5H)-one



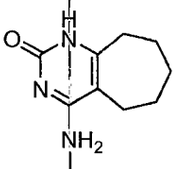
206

A solution of N-(2-cyanocyclopent-1-enylcarbamoyl) benzamide (example 75a) (500 mg, 1.96 mmol) and NaOH (2 N, 2.7 mL) in EtOH (20 mL) was stirred at 100 °C under nitrogen for 2 hours. After cooling to room temperature, the clear reaction solution was filtered and the filtrate was carefully neutralized with 10 % AcOH with vigorous stirring at 0 °C. The resultant precipitate was collected by filtration, washed with warm water and then 20 % EtOH in water to give the final product 4-amino-6,7-dihydro-1H-cyclopenta[d]pyrimidin-2(5H)-one (200 mg, 68 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.57 (brs, 1H), 6.93 (brs, 1H), 6.65 (brs, 1H), 2.56 (t, J = 7.2 Hz, 2H), 2.43 (t, J = 7.6 Hz, 2H) 1.96-1.89 (m, 2H). MS 152 (MH^+).

Example 75a: N-(2-cyanocyclopent-1-enylcarbamoyl)benzamide

To a solution of 2-aminocyclopent-1-enecarbonitrile (400 mg, 3.7 mmol) in 1.4-dioxane (20 mL) was added benzoyl isocyanate (545 g, 3.7 mmol). The reaction mixture was then stirred at room temperature under nitrogen overnight. The precipitate was collected by filtration, washed with 1.4-dioxane, and dried to give N-(2-cyanocyclopent-1-enylcarbamoyl) benzamide (720 mg, 76 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.33 (s, 1H), 11.22 (brs, 1H), 7.99-7.97 (m, 2H), 7.67-7.63 (m, 1H), 7.54-7.51 (m, 2H), 3.04-3.0 (m, 2H), 2.51-2.47 (m, 2H) 1.95-1.90 (m, 2H). MS 256 (MH^+).

Example 76: 4-amino-6,7,8,9-tetrahydro-1H-cyclohepta[d]pyrimidin-2(5H)-one



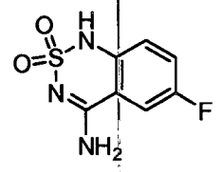
208

Prepared as in example 75 from (Z)-N-(2-cyanocyclohept-1-enylcarbamoyl) benzamide (Example 76a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (brs, 1H), 6.72 (brs, 2H), 2.49-2.46 (m, 2H), 2.38-2.36 (m, 2H) 1.72-1.66 (m, 2H), 1.52-1.48 (m, 2H) 1.41-1.36 (m, 2H). MS 180 (MH^+).

Example 76a: (Z)-N-(2-cyanocyclohept-1-enylcarbamoyl)benzamide:

Prepared as in Example 75a from (Z)-2-aminocyclohept-1-enecarbonitrile and benzoyl isocyanate as a white solid. MS 284 (MH^+).

Example 77: 6-Fluoro-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



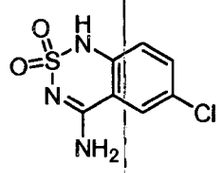
500

A solution of N-(2-cyano-4-fluorophenyl)sulfamide (Example 77a) (211 mg, 1.0 mmol) in EtOH (1 mL) was treated with NaOH (2.0 N, 1.0 mL, 2.0 mmol), and the resultant solution was heated to 100 °C for 0.5 h. After it was cooled down to room temperature the solution was neutralized with 10 % AcOH. The resultant precipitate was collected by filtration, washed with water to give 6-fluoro-1H-benzo[c][1,2,6]thiadiazin-4-amine4-2,2-dioxide as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.01-7.05 (dd, J = 8.8Hz, 5.2Hz, 1H), 7.45-7.5 (m, 1H), 7.80-7.83 (dd, J = 9.6Hz, 2.4Hz, 1H), 8.24 (s, 1H), 11.03 (s, 1H).

Example 77a: N-(2-Cyano-4-fluorophenyl)sulfamide

A solution of 2-amino-5-fluorobenzonitrile (136 mg, 1 mmol) and sulfamoyl chloride (114 mg, 1 mmol) in DMA (2 mL) was stirred at room temperature for 2 hours. The reaction was purified by Varian HPLC (10% Acetonitrile/Water) to give N-(2-Cyano-4-fluorophenyl)sulfamide as a pale-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) 7.18 (m, 2H), 7.56-7.60 (dd J = 8.8 Hz, 2.8Hz 2H), 9.44 (s, 1H).

Example 78: 6-Chloro-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



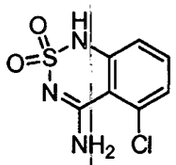
501

Prepared as in Example 77 from N-(2-cyano-4-chlorophenyl)sulfamide (Example 78a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.00-7.03 (d, J = 8.8Hz, 1H), 7.59-7.62 (dd, J = 8.8Hz, 4Hz, 1H), 8.05-8.06 (d, J = 2.4Hz, 1H), 8.27-8.33 (d, J = 25Hz,1H), 11.19 (s, 1H).

Example 78a: N-(2-cyano-4-chlorophenyl)sulfamide

Prepared as in Example 77a from 2-amino-5-chlorobenzonitrile and sulfamoyl chloride. ^{1}H NMR (400 MHz, DMSO-d_6) 7.3 (S, 2H), 7.54-7.56 (d J = 9.2 Hz, 1H), 7.74-7.77 (dd J = 8.4Hz, 2 Hz, 1H), 9.67 (s, 1H).

Example 79: 5-Chloro-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



502

Prepared as in Example 77 from 5-chloro-(2-Cyano-3-chlorophenyl)sulfamide (Example 79a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.00-7.03 (m,1H), 7.20-7.23 (dd, J = 8.4Hz, 1.2Hz, 1H), 7.48-7.52 (m, 1H), 7.75 (s,1H), 8.61 (s,1H), 11.22 (s, 1H).

Example 79a: N-(2-Cyano-3-chlorophenyl)sulfamide

Prepared as in Example 77a from 2-amino-6-chlorobenzonitrile and sulfamoyl chloride.

Example 80: 5-Fluoro-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



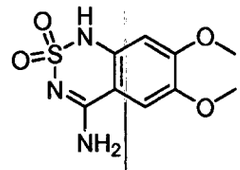
503

Prepared as in Example 77 from N-(2-Cyano-3-fluorophenyl)sulfamide (Example 80a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.84-6.97 (m, 2H), 7.53-7.57 (m, 1H), 7.59 (s, 1H), 8.42 (s,1H), 11.29 (s, 1H).

Example 80a: N-(2-Cyano-3-fluorophenyl)sulfamide

Prepared as in Example 77a from 2-amino-6-fluorobenzonitrile and sulfamoyl chloride

Example 81: 6,7-Dimethoxy-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



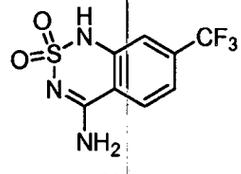
504

Prepared as in Example 77 from N-(2-Cyano-4,5-dimethoxyphenyl)sulfamide (Example 81a).^{1}H NMR (400 MHz, DMSO-d_6) δ 3.75-3.79 (d, J = 14.4, 6H), 6.48 (s, 1H), 7.38 (s, 1H), 7.89 (b,1H), 8.04 (b,1H), 0.64 (s, 1H).

Example 81a: N-(2-Cyano-4,5-dimethoxyphenyl)sulfamide

Prepared as in Example 77a from 2-amino-4,5-dimethoxybenzonitrile and sulfamoyl chloride. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.77-3.80 (d, J = 14.8, 6H), 7.05 (s, 1H), 7.06 (s, 1H), 7.29 (s,1H), 9.15 (s, 1H).

Example 82: 7-Trifluoromethyl-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



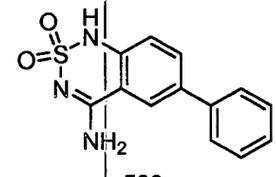
505

Prepared as in Example 77 from N-(2-Cyano-5-trifluoromethylphenyl)sulfamide (Example 82a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.28 (s, 1H), 7.43-7.45 (dd, J = 8.8Hz, 1.6Hz, 1H), 8.14-8.16 (d, J = 7.6Hz, 1H), 8.41-8.52 (b, 2H), 11.40 (s, 1H).

Example 82a: N-(2-Cyano-5-trifluoromethylphenyl)sulfamide

Prepared as in Example 77a from 2-amino-4-trifluoromethylbenzonitrile and sulfamoyl chloride.^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53(s, 1H), 7.74-7.76 (d, J = 8.4Hz, 1H), 8.01-8.03 (dd, J = 8.4Hz, 1.6Hz, 1H), 8.23 (s,1H), 10.16 (b, 1H).

Example 83: 6-Phenyl-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



506

Prepared as in Example 77 from N-(2-Cyano-4-phenylphenyl)sulfamide (Example 83a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.72-6.70(d, J = 8Hz1H), 6.97-7.0 (m, 1H),

7.08-7.12 (m, 2H), 7.34-7.36 (m,2H), 7.50-7.53 (dd, J = 8.4Hz, 1.6Hz, 1H), 7.83 (b, 1H), 7.87 (s, 1H), 8.07(b, 1H) 10.75 (s, 1H).

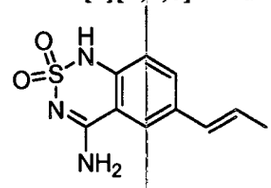
Example 83a: N-(2-Cyano-4-phenylphenyl)sulfamide

In a 2mL microwave vial, phenyl boronic acid (75 mg, 0.6 mmol), N-(2-cyano-4-bromophenyl)sulfamide (Example 83b) (137 mg, 0.5 mmol), and potassium carbonate (400 mg, 1.5 mmol) were dissolved in DME/Water mixture (1.5 mL, DME/Water 4:1). The solution was degassed by bubbling N_2 gas into the reaction solution for 5 minutes and Palladium tetrakis triphenylphospine (25 mg, 0.025 mmol) was added. The reaction was placed in a microwave reactor for 5 minutes at 150°C. The crude reaction was dissolved in water and washed with ethyl acetate. The aqueous solution was evaporated under vacuum to give N-(2-Cyano-4-phenylphenyl)sulfamide.

Example 83b: N-(2-cyano-4-bromolphenyl)sulfamide

Prepared as in Example 77a from 2-amino-5-bromobenzonitrile and sulfamoyl chloride. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31(s, 2H), 7.48-7.50 (d, J = 8 Hz, 1H), 7.85-7.88 (dd, J = 9.3Hz, 1.2Hz, 1H), 8.05-8.06 (d, J = 2.4Hz, 1H), 9.67 (s, 1H).

Example 84: 6-(E)-prop-1-enyl-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



507

Prepared as in Example 77 from N-(2-cyano-4-(E)-prop-1-enylphenyl)sulfamide (Example 84a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83-1.82(d, J = 5.6Hz 3H), 6.29-6.25 (m, 2H), 6.85-6.87 (d, J = 8.4Hz, 1H), 7.5-7.53 (dd, J = 8.4Hz, 1.6Hz, 1H), 7.86 (s, 1H), 7.96 (b, 2H), 10.95 (b, 1H).

Example 84a: N-(2-Cyano-4-(E)-prop-1-enylphenyl)sulfamide

Prepared as in Example 77a from N-(2-cyano-4-bromolphenyl)sulfamide (Example 83b) and (*E*)-prop-1-enylboronic acid.

Example 85: 6-(2-methylprop-1-enyl)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



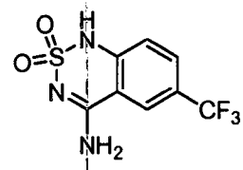
508

Prepared as in Example 77 from N-(2-Cyano-4-(2-methylprop-1-enyl) phenyl)sulfamide (Example 85a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.8-1.85(dd, J = 22.4Hz, 1.2Hz, 6H), 6.18 (s, 1H), 6.84-6.86 (d, J = 8.4Hz, 1H), 7.31-7.33 (d, J = 8.4Hz, 1H), 7.66 (s, 1H), 7.78 (b, 2H), 10.91 (b, 1H).

Example 85a: N-(2-Cyano-4-(2-methylprop-1-enyl) phenyl)sulfamide

Prepared as in Example 77a from N-(2-cyano-4-bromolphenyl)sulfamide (Example 83b) and 2-methylprop-1-enylboronic acid.

Example 86: 6-Trifluoromethyl-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



509

Prepared as in Example 77 from N-(2-cyano-4-trifluorophenyl)sulfamide (Example 86a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.14-7.16 (d, J = 8.8Hz, 1H), 7.85-7.88 (dd, J = 8.8Hz, 1.6Hz, 1H), 8.37-8.39 (d, J = 9.6Hz, 1H), 8.52 (b, 2H), 11.56 (s, 1H).

Example 86a: N-(2-Cyano-4-trifluoromethylphenyl)sulfamide

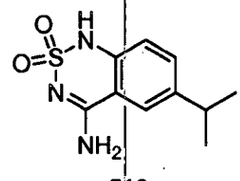
Prepared as in Example 77a from 2-amino-5-(trifluoromethyl)benzonitrile (Example 86b) and sulfamoyl chloride. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53(s, 2H), 7.74-7.76 (d, J = 8.4 Hz, 1H), 8.01-8.03 (dd, J = 8.4Hz, 1.6Hz, 1H), 8.23-8.233 (d, J = 1.2Hz, 1H), 10.16 (b, 1H).

Example 86b: 2-Amino-5-(trifluoromethyl)benzonitrile

In a 20mL microwave vial, 2-bromo-4-(trifluoromethyl)aniline (238 mg, 1 mmol) and copper cyanide (90 mg, 1 mmol) were dissolved in N-methylpyrrolidone (NMP) (10 mL). The reaction was placed in a microwave reactor for 5 minutes at 200°C. The crude was dissolved in ethyl acetate and the precipitate was removed by filtration. The clear solution was washed with water. The organic layer was collected, dried over sodium sulfate, and evaporated under

vacuum. The residue was purified by Varia HPLC (10% acetonitrile/water) to give the title compound.

Example 87: 6-Isopropyl-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



510

Prepared as in Example 77 from N-(2-cyano-4-isopropylphenyl)sulfamide (Example 87a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.18-1.2(d, J = 6.4Hz, 6H), 2.85 (m, 1H), 6.91-6.93 (d, J = 8.8Hz, 1H), 7.42-7.45 (dd, J = 8.8Hz, 2Hz 1H), 7.768-7.773 (d, J = 2Hz, 1H), 8.13 (b, 2H), 10.8 (s, 1H).

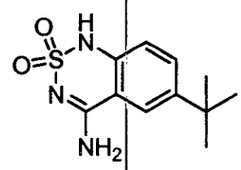
Example 87a: N-(2-Cyano-4-isopropylphenyl)sulfamide

Prepared as in Example 77a from 2-Amino-5-isopropylbenzonitrile (Example 87b) and sulfamoyl chloride.

Example 87b: 2-Amino-5-isopropylbenzonitrile

Prepared as in Example 86b from 2-bromo-4-isopropylaniline.

Example 88: 6-Isobutyl-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



511

Prepared as in Example 77 from N-(2-cyano-4-isobutylphenyl)sulfamide (Example 88a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.27(s, 9H), 6.92-6.94 (d, J = 8.4Hz, 1H), 7.58-7.61 (dd, J = 8.8Hz, 2.4Hz 1H), 7.84-7.85 (d, J = 2.4Hz, 1H), 8.06 (b, 1H), 8.33 (b, 1H), 10.8 (s, 1H).

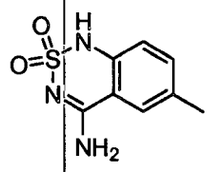
Example 88a: N-(2-Cyano-4-isobutylphenyl)sulfamide

Prepared as in Example 77a from 2-Amino-5-isobutylbenzonitrile (Example 88b) and sulfamoyl chloride.

Example 88b: 2-Amino-5-isobutylbenzonitrile

Prepared as in Example 86b from 2-bromo-4-isobutylaniline.

Example 89: 6-Methyl-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



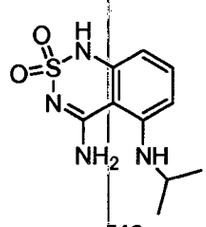
512

Prepared as in Example 77 from N-(2-cyano-4-methylphenyl)sulfamide (Example 89a). MS 212 (MH^+).

Example 89a: N-(2-cyano-4-methylphenyl)sulfamide

Prepared as in Example 77a from 2-amino-5-methylbenzonitrile (Example 14b) and sulfamoyl chloride.

Example 90: N^5-isopropyl-1H-benzo[c][1,2,6]thiadiazine-4,5-diamine-2,2-dioxide



513

A solution of 2-amino-6-(isopropylamino)benzonitrile sulfamide (Example 90a) (0.14 g, 0.54 mmol) and NaOH (2 N, 0.54 mL) in EtOH (3 mL) was stirred at 90 °C under nitrogen for 0.5 hour. The reaction mixture was cooled to room temperature, and concentrated under vacuum. H_2O (1 mL) was added and the reaction mixture was neutralized to pH ~ 3 with 10% AcOH. The resultant precipitate was extracted with EtOAc, and after evaporation of solvents the residue was purified by preparative thin layer chromatography using a DCM/EtOAc (4:1) solution as eluant, to give N^5-isopropyl-1H-benzo[c][1,2,6]thiadiazine-4,5-diamine-2,2-dioxide (0.02 g). ^1H NMR (400 MHz, DMSO-d_6) δ 1.11 (d, J = 6.4 Hz, 6H), 1.84 (bs, 1H), 5.24 (bs, NH), 6.22-6.19 (m, 2H, NH), 7.09 (t, J = 8.0 Hz, 1H), 7.48 (bs, 2H). MS 255 (MH^+).

Example 90a: 2-amino-6-(isopropylamino)benzonitrile sulfamide

To a solution of 2-amino-6-(isopropylamino)benzonitrile (Example 90b) (0.09 g, 0.54 mmol) in DMA (3 mL) was added sulfamoyl chloride (0.19 g, 1.62 mmol). The reaction mixture was stirred at room temperature under nitrogen for 2 hours, diluted with H_2O (5 mL) and extracted with EtOAc. Solvents of the combined organic phases were evaporated and the residue

was purified by preparative thin layer chromatography using a Hexane/EtOAc (3:2) solution as eluant, to give 2-amino-6-(isopropylamino)benzonitrile sulfamide (0.14 g). MS 255 (MH^+).

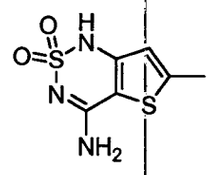
Example 90b: 2-amino-6-(isopropylamino)benzonitrile

To a solution of 2-(isopropylamino)-6-nitrobenzonitrile (Example 90c) (0.21 g, 1.02 mmol) in MeOH (9 mL) was added concentrated HCl (2 mL). Then Fe (0.17 g, 3.07 mmol) was added portionwise, and the reaction mixture was refluxed at 90°C for 15 minutes. After cooling to room temperature, dilution with H_2O (50 mL) and extraction with DCM (3x 50 mL), the combined organic phases were washed with brine, dried over $MgSO_4$ and the solvents were evaporated to give 2-amino-6-(isopropylamino)benzonitrile (0.19 g, 100 %) as a brown oil which was used in the next step without any further purification. MS 176 (MH^+).

Example 90c: 2-(isopropylamino)-6-nitrobenzonitrile

To a solution of 2,6-dinitrobenzonitrile (0.58 g, 3.00 mmol) in DMF (6 mL) was added isopropylamine (0.71 g, 12.00 mmol) and the reaction mixture was stirred at 50 °C under nitrogen for ten minutes. After cooling to room temperature, dilution with H_2O and extraction with EtOAc, solvents of the combined organic phases were evaporated and the residue was purified by flash chromatography (Biotage system, 80 g silicagel column) using a Hexane/EtOAc (3:2) solution as eluant, to give 2-(isopropylamino)-6-nitrobenzonitrile (0.22 g, 35 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.20 (d, J = 6.4 Hz, 6H), 3.85-3.80 (m, 1H), 5.94 (d, J = 8.0 Hz, NH), 7.26 (d, J = 9.0 Hz, 1H), 7.42 (d, J = 9.0 Hz, 1H), 7.60 (t, J = 8.8 Hz, 1H).

Example 91: 6-methyl-1H-thieno[3,2-c][1,2,6]thiadiazin-4-amine-2,2-dioxide

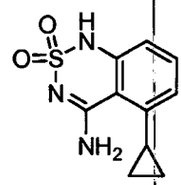


514

A solution of 3-amino-5-methylthiophene-2-carbonitrile (250 mg, 1.0 eq., 1.81 mmol) and sulfamoyl chloride (2.71 mmol, 1.5 eq., 314 mg) in DMA (5 mL) was stirred at room temperature overnight. Water (30 mL) and NaOH (1.5 eq., 10 N, 2.71 mmol, 271 µL) were added and the mixture was frozen in a dry ice/acetone bath and the volatiles were removed on the lyophilizer. The resulting solid was washed with water and then suspended in EtOH (25 mL, 200 proof). To this suspension was added NaOH (1 N, 2.5 eq., 4.52 mmol, 4.52 mL) and the

mixture heated to reflux for 45 minutes. The reaction mixture was cooled to room temperature and quenched with HCl (1 N, 2.5 eq., 4.52 mmol, 4.52 mL). The pH was adjusted to ~ 1-2 with 1 N HCl and the volatiles removed on a rotary evaporator. The resulting solid was suspended in water (10 mL), stirred, filtered off, and washed with water. The crude product was dried in a vacuum oven to give 6-methyl-1H-thieno[3,2-c][1,2,6]thiadiazin-4-amine-2,2-dioxide (257 mg) as an off-white powder ^{1}H NMR (400 MHz, DMSO-d_6) δ2.46 (d, J = 0.8 Hz, 3H), 6.53 (q, J = 0.8 Hz, 1H), 7.75 (br. s, 2H), 11.34 (s, 1H). ^{1}H NMR (400 MHz, CD_3OD) δ2.52 (d, J = 0.8 Hz, 3H), 6.55 (q, J = 0.8 Hz, 1H). MS 218 (MH^+).

Example 92: 5-cyclopropyl-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



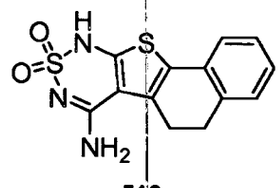
515

A solution of 2-amino-6-cyclopropylbenzonitrile (Example 92a) (1.0 eq., 626 µmol, 99 mg) and sulfamoyl chloride (1.5 eq., 939 µmol, 109 mg) in DMA (1 mL) was stirred in a scintillation vial at room temperature. After 2 hours, NaOH (1.5 eq., 939 µmol, 1N, 939 µL) and water (18 mL) were added and the resulting precipitated product stirred overnight at room temperature. The precipitate was filtered off and washed with water (3 X 5 mL). The wet precipitate was dissolved in EtOH (5 mL, 200 proof) and NaOH (2.5 eq., 1565 µmol, 1N, 1565 µL) was added. The reaction was heated to 80 ° C with stirring overnight. The reaction mixture was cooled to room temperature and HCl (2.5 eq., 1565 µmol, 1N, 1565 µL) was added to the reaction vial. The ethanol and most of the water was removed on the rotary evaporator. The resulting precipitate was suspended in water (5 mL), stirred, filtered off, and washed with water (20 mL). The product was dried in a vacuum oven to give 5-cyclopropyl-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide (41 mg, 28%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ0.71 (m, 2H), 1.04 (m, 2H), 2.401 (m, 1H), 6.85 (d, J = 8 Hz, 2H), 7.37 (t + br. s, J = 8 Hz, 2H), 8.40 (br. s, 1H), 10.80 (s, 1H). ^{1}H NMR (400 MHz, CD_3OD) δ0.89 (m, 2H), 1.15 (m,2H), 2.36 (m, 1H), 6.90 (d, J = 8 Hz, 1H), 6.97 (d, J = 8 Hz, 1H), 7.41 (t, J = 8 Hz, 1H). MS 238 (MH^+).

Example 92a: 2-amino-6-cyclopropylbenzonitrile

A 2-5 mL microwave vial containing 2-amino-6-bromobenzonitrile (1.0 eq., 1.0 mmol, 197 mg), cyclopropylboronic acid (1.3 eq., 1.3 mmol, 112 mg), and K_3PO_4 (3.5 eq., 3.5 mmol, 743 mg) was flushed with nitrogen. To this vial was added toluene (4 mL, Sure-Seal), water (200 µL), tricyclohexylphosphine (0.018 eq., 18.1 µmol, 88% pure, 20% in hexanes, 32 µL), and palladium (II) acetate (0.05 eq. "Pd," trimer, 0.0167 mmol, 12 mg), all under nitrogen. The reaction vial was flushed with nitrogen, capped with a crimp-top septum, and microwaved for 30 minutes at 130 ° C. The reaction mixture was cooled to room temperature, partitioned between EtOAc (3 mL) and water (1 mL). The layers were separated, the water layer extracted EtOAc (2 X 3 mL), the combined organic layers dried over sodium sulfate. The EtOAc was filtered through a 0.45 µm PTFE frit to remove finely divided solids and concentrated on a rotary evaporator. The crude product was purified on silica gel (SiliaPrep 80g cartridge, gradient elution from 10% EtOAc/hexanes to 40% EtOAc/hexanes, loaded in solution in 1:1 hexanes:DCM). The fractions containing product were concentrated on a rotary evaporator to give 2-amino-6-cyclopropylbenzonitrile (99 mg, 62.7%) as a waxy yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ0.668 (m, 2H), 0.979 (m, *2*H), 1.978 (m, 1H), 5.882 (br. s, 2H), 6.128 (d, J = 8 Hz, 1H), 6.546 (d, J = 8 Hz, 1H), 7.129 (t, J = 8 Hz, 1H).

Example 93: 5,6-[4',5'-dihydronaphtho[1',2'-b]]-1H-thieno[2,3-c][1,2,6]thiadiazin-4-amine-2,2-dioxide



516

A solution of 2-sulfamoylamino-4,5-dihydronaphtho[1,2-b]thiophene-3-carbonitrile (Example 93a) (336 mg, 1.11 mmol) in EtOH (5 mL) was treated with NaOH (2.0 N, 1.1 mL, 2.22 mmol), and the resultant solution was heated to 100 °C and stirred at that temperature for 1.5 h. After it was cooled down to room temperature, the clear solution was filtered, and the filtrate was carefully neutralized with 10 % AcOH while it was vigorously stirred at 0 °C. The resultant precipitate was collected by filtration, washed with warm water, and 20 % EtOH in water to give 105 mg of the title product as an off-white solid in 31% yield. ^{1}H

NMR (400 MHz, DMSO-d_6) δ 2.48 (m, 4H), 5.70 (s, 2H), 6.87-6.89 (d, J = 7.6 Hz, 1H), 6.96 (t, 1H), 7.06-7.10 (m, 2H). MS 306 (MH^+).

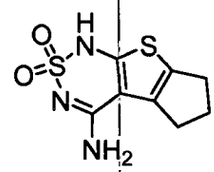
Example 93a: 2-sulfamoylamino-4,5-dihydronaphtho[1,2-b]thiophene-3-carbonitrile

To a solution of 2-amino-4,5-dihydronaphtho[1,2-b]thiophene-3-carbonitrile (Example 93b) (250 mg, 1.11 mmol) in dimethylacetamide (5 mL) was added sulfamoyl chloride (385 mg, 3.33 mmol). The reaction mixture was stirred at room temperature under nitrogen for about 1 hr, then it was diluted with water and extracted with EtOAc, the organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated to give the crude product which was carried on for next step.

Example 93b: 2-amino-4,5-dihydronaphtho[1,2-b]thiophene-3-carbonitrile

A solution of 3,4-dihydronaphthalen-2(1H)-one (2.2 g, 15.05 mmol), malononitrile (994 mg, 15.05 mmol), sulfur (482 mg, 15.05 mmol), and triethylamine (1.52 g, 15.05 mmol) in EtOH (100 mL) was refluxed for 2 hr under nitrogen. The solvent was then removed under reduced pressure and the residue was crystallized from EtOAc/Hexanes to give 2.91 g of the title product as a brown solid in 86% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.59 (t, 2H), 2.86 (t, 2H), 6.94 (d, 1H), 7.03 (t, 1H), 7.11-7.16 (m, 2H), 7.48 (s, 2H).

Example 94: 5,6-(dihydro-4'H-cyclopenta-1'H)thieno[2,3-c][1,2,6]thiadiazin-4-amine-2,2-dioxide



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Prepared as in Example 93 from 2-sulfamoylamino-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carbonitrile (Example 94a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.15 (m, 2H), 2.53 (m, 2H), 2.68 (m, 2H), 5.39 (s, 2H). MS 244 (MH^+).

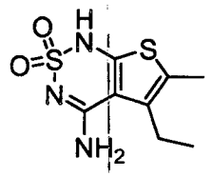
Example 94a: 2-sulfamoylamino-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carbonitrile

Prepared as in Example 93a from 2-amino-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carbonitrile (Example 94b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (m, 2H), 2.82 (m, 2H), 2.89 (m, 2H), 5.46 (s, 1H).

Example 94b : 2-amino-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carbonitrile

Prepared as in Example 93b from cyclopentanone. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.23 (m, 2H), 2.53 (m, 2H), 2.63 (m, 2H), 7.00 (s, 2H).

Example 95: 5-ethyl-6-methyl-1H-thieno[2,3-c][1,2,6]thiadiazin-4-amine-2,2-dioxide



518

Prepared as in Example 93 from 2-sulfamoylamino-4-ethyl-5-methylthiophene-3-carbonitrile (Example 95a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.01 (t, 3H), 2.06 (s, 3H), 2.53 (q, 2H), 5.50 (s, 2H). MS 246 (MH^+).

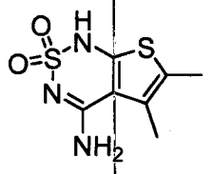
Example 95a : 2-sulfamoylamino-4-ethyl-5-methylthiophene-3-carbonitrile

Prepared as in Example 93a from 2-amino-4-ethyl-5-methylthiophene-3-carbonitrile (Example 95b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (t, 3H), 2.31 (s, 3H), 2.59 (q, 2H), 5.45 (s, 2H).

Example 95b : 2-amino-4-ethyl-5-methylthiophene-3-carbonitrile

Prepared as in Example 93b from pentan-3-one. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.01 (t, 3H), 2.06 (s, 3H), 2.33 (q, 2H), 6.84 (s, 2H). MS 167 (MH^+).

Example 96: 5,6-dimethyl-1H-thieno[2,3-c][1,2,6]thiadiazin-4-amine-2,2-dioxide



577

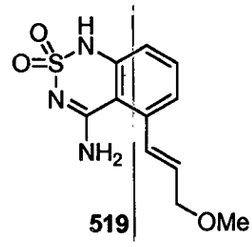
Prepared as in Example 93 from 2-sulfamoylamino-4,5-dimethylthiophene-3-carbonitrile (Example 96a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.04 (s, 3H), 2.10 (s, 3H), 5.48 (s, 2H). MS 232 (MH^+).

Example 96a: 2-sulfamoylamino-4,5-dimethylthiophene-3-carbonitrile

To a solution of 2-amino-4,5-dimethylthiophene-3-carbonitrile (Example 4b) (1.0 g, 6.57 mmol) in 1,4-dioxane (50 mL) was added sulfamide (3.87 g, 40.30 mmol). The reaction mixture was heated to reflux for 24 hr, after cooled to room temperature, the solvent was

removed under reduced pressure and the residue was purified by chromatography on silica gel eluting with EtOAc/Hexanes (2:3) to give 300 mg of product as a dark red oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.09 (3, 3H), 2.26 (s, 3H), 7.32 (s, 2H), 10.17 (s, 1H).

Example 97: (*E*)-5-(3-Methoxyprop-1-enyl)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



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A solution of (*E*)-2-sulfamoylamino-6-(3-methoxyprop-1-enyl)benzonitrile (Example 97a) (139 mg, 0.5 mmol) in EtOH was treated with NaOH (2.0 N, 0.5 mL, 1.0 mmol), and the resultant solution was heated to 100 °C, and stirred at that temperature for 4 h. After it was cooled down to room temperature, the clear reaction solution was filtered, and the filtrate was carefully neutralized with 10 % AcOH while it was vigorously stirred at 0 °C. The resultant precipitate was collected by filtration, washed with warm water, and 20 % EtOH in water to give the title product (*E*)-5-(3-Methoxyprop-1-enyl)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide (108 mg, 78 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.29 (s, 3H), 4.06 (dd, J = 4.8, 1.2 Hz, 2H), 6.26 (dt, J = 16.2, 5.0 Hz, 1H), 6.91-6.95 (m, 2H), 6.97 (bs, 1H), 7.16 (d, J = 7.2 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 8.31 (s, 1H), 10.93 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 58.4, 72.5, 111.6, 117.0, 122.4, 129.0, 132.5, 134.0, 138.1, 143.7, 162.9. MS 268 (MH^+).

Example 97a: (*E*)-2-sulfamoylamino-6-(3-methoxyprop-1-enyl)benzonitrile

To a solution of (*E*)-2-amino-6-(3-methoxyprop-1-enyl)benzonitrile (Example 97b) (188 mg, 1.0 mmol) in DMA was added NH_2SO_2Cl (347 mg, 3.0 mmol) at 0 °C under nitrogen. The reaction mixture was then stirred at room temperature for 6 hrs, diluted with EtOAc, washed with brine (5X), and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give (*E*)-2-sulfamoylamino-6-(3-methoxyprop-1-enyl)benzonitrile as a pale-yellow solid, which was used in the next step without further purification.

Example 97b: (*E*)-2-amino-6-(3-methoxyprop-1-enyl)benzonitrile

To a solution of 2-amino-6-bromobenzonitrile (1.0 g, 5.0 mmol), (*E*)-2-(3-methoxypropenyl)-4,4,5,5-tetramethyl-(1,3,2)-dioxaboroane (1.2 g, 6.0 mmol), and K_2CO_3 (1.38

g, 10.0 mmol) in DME/H_2O (4:1, 20 mL) was added $Pd(PPh_3)_4$ (289 mg) at room temperature under nitrogen. The reaction mixture was warmed to 85 °C and stirred at that temperature under nitrogen overnight. After it was cooled down to room temperature, the reaction solution was diluted with EtOAc, washed with brine (2X), and dried over Na_2SO_4. After removal of the solvent, the residue was purified by chromatography on silica gel eluting with 30 % EtOAc in hexanes to give the title compound as a pale-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.40 (s, 3H), 4.12 (dd, J = 6.0, 1.8 Hz, 2H), 4.42 (s, 2H), 6.42 (dt, J = 16.0, 5.8 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 6.85 (d, J = 16.0 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 7.26 (t, J = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 58.2, 72.7, 95.4, 113.6, 115.0, 116.6, 128.5, 130.9, 133.4, 140.3, 150.1. MS 189 (MH^+).

Example 98: 5-(3-Methylbut-2-en-2-yl)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



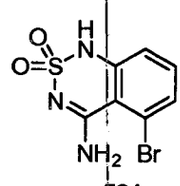
520

Prepared as in Example 97 from 2-amino-6-(3-methylbut-2-en-2-yl)benzonitrile (Example 98a) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (s, 3H), 1.80 (s, 3H), 1.86 (s, 3H), 6.70 (dd, J = 7.2, 1.0 Hz, 1H), 6.82 (s, 1H), 6.93 (dd, J = 7.2, 1.0 Hz, 1H), 7.46 (t, J = 7.2 Hz, 1H), 8.28 (s, 1H), 10.98 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 20.8, 21.4, 22.6, 109.4, 116.8, 124.4, 129.7, 132.0, 134.3, 144.1, 144.6, 162.1. MS 266 (MH^+).

Example 98a: 2-Amino-6-(3-methylbut-2-en-2-yl)benzonitrile

Prepared as in Example 1a from 2-amino-6-bromobenzonitrile and 3-Methyl-2-buten-2-ylboronic acid as an orange oil. MS 187 (MH^+).

Example 99: 5-Bromo-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide

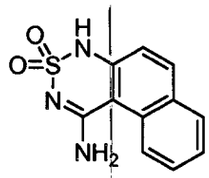


521

Prepared as in Example 97 from 2-amino-6-bromobenzonitrile as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.03-7.07 (m, 1H), 7.37-7.42 (m, 2H), 7.65 (s, 1H), 8.60 (s,

1H), 11.19 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 113.3, 118.0, 121.0, 129.0, 135.0, 145.5, 161.3. MS 275, 277 (MH^+).

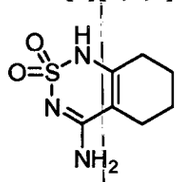
Example 100: 4H-Naphtho[2,1-c][1,2,6]thiadiazin-1-amine-2,2-dioxide



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Prepared as in Example 97 from 2-amino-1-naphthonitrile as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.17 (d, J = 8.0 Hz, 1H), 7.48 (dt, J = 1.2, 8.0 Hz, 1H), 7.63 (dt, J = 1.2, 8.0 Hz, 1H), 7.90 (s, 1H), 7.93 (dd, J = 1.2, 8.0 Hz, 1H), 8.24 (s, 1H), 8.39 (d, J = 8.0 Hz, 1H), 11.42 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 106.3, 118.2, 124.9, 125.4, 129.2, 129.8, 130.0, 130.2, 135.9, 143.7, 163.2. MS 248 (MH^+).

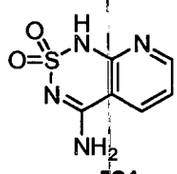
Example 101: 5,6,7,8-Tetrahydro-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



523

Prepared as in Example 97 from 2-aminocyclohex-1-enecarbonitrile (Example 10b) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.54-1.62 (m, 4H), 2.08 (t, J = 5.4 Hz, 2H), 2.20 (t, J = 5.4 Hz, 2H), 6.94 (s, 1H), 7.41 (s, 1H), 10.53 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 21.6, 22.5, 28.3, 97.6, 150.3, 163.4. MS 202 (MH^+).

Example 102: 1H-pyrido[2,3-c][1,2,6]thiadiazin-4-amine-2,2-dioxide

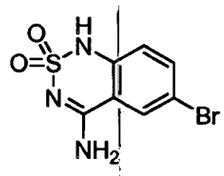


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A stirred mixture of 2-aminonicotinonitrile (238 mg, 2.0 mmol), sulfamide (192 mg, 2.0 mmol), and 1 mL of DBU was heated at 160 °C under nitrogen overnight. After it was cooled down to room temperature, the reaction mixture was diluted with water, and extracted three times with EtOAc. The aqueous layer was dried down under vacuum, and the residue was

purified by chromatography on silica gel eluting with 15 % MeOH in dichloromethane to give the title compound as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.87 (t, J = 5.6 Hz, 1H), 7.95 (brs, 2H), 8.22 (d, J = 5.2 Hz, 1H), 8.39-8.37 (m, 1H), 12.58 (brs, 1H). MS 199 (MH^+).

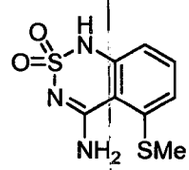
Example 103: 6-Bromo-1H-benzo[c][1,2,6]thiadiazin-4-amine



525

Prepared as in Example 97 from 2-amino-5-bromobenzonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.95 (d, J = 8.8 Hz, 1H). 7.73-7.70 (m, 1H), 8.17 (d, J = 1.6 Hz, 1H), 8.28 (brs, 2H), 11.9 (s, 1H). MS 275, 277 (MH^+).

Example 104: 5-(Methylthio)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



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Prepared as in Example 97 from 2-sulfamoylamino-6-(methylthio)benzonitrile (Example 104a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.39 (s, 3H), 6.38-6.36 (m, 1H), 6.47-6.45 (m, 1H), 6.59 (brs, 2H), 6.97-6.93 (m, 1H). MS 244 (MH^+).

Example 104a: 2-sulfamoylamino-6-(methylthio)benzonitrile

Prepared as in Example 1 from 2-amino-6-(methylthio)benzonitrile (Example 8b) and sulfamoyl chloride. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.56 (s, 3H), 7.18 (d, J = 8.4 Hz, 1H), 7.26 (s, 2H), 7.33 (d, J = 8.0 Hz, 1H), 7.59 (t, J = 8.40 Hz, 1H), 9.51 (s, 1H).

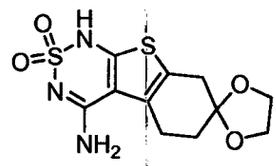
Example 104b: 2-amino-6-(methylthio)benzonitrile

To a solution of 2-(methylthio)-6-nitrobenzonitrile (Example 104c) (1.5 g, 7.73 mmol) in EtOH (150 ml)/THF (50 ml)/EtOAc (50 ml) was added 200 mg of 10 % Pd/C. The reaction mixture was hydrogenated on part shaker overnight. After the filtration, the filtered solution was dried down under vacuum, and the residue was purified by chromatography on silica gel eluting with EtOAc/Hexane to give the title compound (79 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.51 (s, 3H), 4.47 (s, 2H), 6.53-6.51 (m, 1H), 6.58 (d, J = 8.0 Hz, 1H), 7.27-7.21 (m, 1H).

Example 104c: 2-(methylthio)-6-nitrobenzonitrile

To a suspension of 2,6-dinitrobenzonitrile (5.0 g, 25.89 mmol) in 100 mL of anhydrous MeOH was added NaSMe (2.0 g in 100 mL of MeOH) dropwise through addition funnel under nitrogen at 0 °C. After the completion of addition, the reaction mixture was stirred at 0 °C for 1 hr. Then 250 mL of water was added to the reaction mixture, the resultant precipitate was collected by filtration and dried in the air to give the title product as a yellow solid (93 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64 (s, 3H), 7.60-7.57 (m, 1H), 7.70 (t, J = 8.4 Hz, 1H), 8.01-7.99 (m, 1H).

Example 105: 5,6-(1',2',3',4'-tetrahydro-2',2'-ethylenedioxide-benzo)-1H-thieno[2,3-c][1,2,6] thiadiazin-4-amine-2,2-dioxide



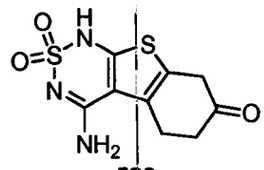
527

Prepared as in Example 97 from 2-amino-5,7-dihydro-4H-spiro[benzo[b]thiophene-6,2'-[1,3]dioxolane]-3-carbonitrile (Example 105a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.80 (t, J = 6.0 Hz, 2H), 2.65 (s, 2H), 2.79 (t, J = 6.0 Hz, 2H), 3.94-3.91 (m, 4H), 5.99 (brs, 2H). MS 316 (MH^+).

Example 105a: 2-amino-5,7-dihydro-4H-spiro[benzo[b]thiophene-6,2'-[1,3] dioxolane]-3-carbonitrile

A solution of 1,4-dioxaspiro[4.5]decan-8-one (5.0 g, 32.0 mmol), malononitrile (2.11 g, 32.01 mmol), sulfur (1.03 g, 32.0 mmol), and triethylamine (4.5 mL, 32.0 mmol) in EtOH (100 mL) was stirred at room temperature for 1 h under nitrogen. The solvent was then removed under reduced pressure and the residue was treated with EtOAc. The resultant precipitate was collected by filtration and dried in the air to give the title product as a light green solid (44 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.77 (t, J = 6.8 Hz, 2H), 2.43 ((t, J = 6.4 Hz, 2H), 2.57 (s, 2H), 3.88 (s, 4H), 6.99 (s, 2H). MS 237 (MH^+).

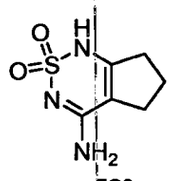
Example 106: 5,6-(1',2',3',4'-tetrahydro-2'-oxide-benzo)-1H-thieno[2,3-c][1,2,6] thiadiazin-4-amine-2,2-dioxide



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A stirred mixture of 5,6-(1',2',3',4'-tetrahydro-2',2'-ethylenedioxide-benzo)-1H-thieno[2,3-c][1,2,6] thiadiazin-4-amine-2,2-dioxide (Example 105) (130 mg, 0.41 mmol), 5 mL of THF and 1 mL of 2 N HCl was refluxed under nitrogen for 2 hrs. After it was cooled down to room temperature, the resultant precipitate was collected by filtration and dried in the air to give the title product as a pink solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.57 (t, J = 6.8 Hz, 2H), 3.10 (t, J = 6.4 Hz, 2H), 3.50 (s, 2H), 6.91 (brs, 1H), 7.88 (brs, 1H), 11.81 (brs, 1H). MS 272 (MH^+).

Example 107: 1,5,6,7-tetrahydrocyclopenta[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



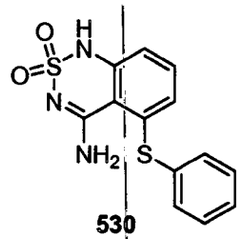
529

A solution of 2-sulfamoylaminocyclopent-1-enecarbonitrile (Example 107a) (108 mg, 0.57 mmol) in EtOH was treated with NaOH (2.0 N, 0.5 mL), and the resultant solution was heated to 100 °C and stirred at that temperature for 4 h. After it was cooled down to room temperature, the reaction solution was carefully neutralized with 2N HCl while it was vigorously stirred at 0 °C. The reaction solution was dried down under vacuum, and the residue was purified by chromatography on silica gel eluting with 10 % MeOH in dichloromethane to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.69-1.63 (m, 2H), 2.2 (t, J = 7.6 Hz, 2H), 2.3 (t, J = 6.8 Hz, 2H), 5.12 (s, 2H). MS 188 (MH^+).

Example 107a: 2-sulfamoylaminocyclopent-1-enecarbonitrile

To a solution of 2-aminocyclopent-1-enecarbonitrile (440 mg, 4.07 mmol) in 10 mL of DMA was added sulfamoyl chloride (941.3 mg, 8.15 mmol), and the resultant mixture was stirred at room temperature under nitrogen for 2 h. Then it was diluted with EtOAc, the organic layer was washed with brine and dried down under vacuum, and the residue was purified by chromatography on silica gel eluting with EtOAc/Hexane to give the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04-1.97 (m, 2H), 2.61-2.57(m, 2H), 2.9-2.86 (m, 2H), 5.66 (s, 2H), 8.04 (s, 1H).

Example 108: 5-(Phenylthio)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



530

Prepared as in Example 97 from 2-sulfamoylamino-6-(phenylthio)benzonitrile (Example 108a) ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.43-6.40 (m, 1H), 6.64-6.62 (m, 1H), 6.75 (brs, 2H), 7.01-6.97 (m, 1H), 7.22-7.15 (m, 3H), 7.3-7.26 (m, 2H). MS 306 (MH^+)

Example 108a: 2-sulfamoylamino-6-(phenylthio)benzonitrile

Prepared as in Example 104a from 2-amino-6-(phenylthio)benzonitrile (Example 108b). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.85-6.82 (m, 1H), 7.32 (s, 2H), 7.47-7.42 (m, 6H), 7.53 (t, J = 8.0 Hz, 1H), 9.63 (s, 1H).

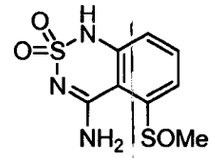
Example 108b: 2-amino-6-(phenylthio)benzonitrile

Prepared as in Example 104b from 2-nitro-6-(phenylthio)benzonitrile (Example 108c). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.20 (brs, 2H), 6.32-6.30 (m, 1H), 6.69-6.67 (m, 1H), 7.19 (t, J = 8.0 Hz, 1H), 7.4-7.34 (m, 5H).

Example 108c: 2-nitro-6-(phenylthio)benzonitrile

To a mixture of 2, 6-dinitrobenzonitrile (2.0 g, 10.36 mmol) and K_2CO_3 (1.43 g, 10.36 mmol) in 5 mL of anhydrous DMF was added PhSH (1.14 ml in 5 mL of DMF) dropwise under nitrogen at 0 °C. After the completion of addition, the reaction mixture was stirred at 0 °C for 0.5 hr. Then the reaction mixture was poured into 50 mL of water, the resultant precipitation was collected by filtration, washed with water and dried in the air to give the title product.

Example 109: 5-(Methylsulfinyl)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



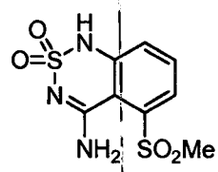
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Prepared as in Example 107 from 2-sulfamoylamino-6-(methylsulfinyl)benzonitrile (Example 109a) ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.58 (s, 3H), 6.51 (brs, 2H), 6.78-6.76 (m, 1H), 6.94-6.92 (m, 1H), 7.23-7.19 (m, 1H). MS 260 (MH^+)

Example 109a: 2-sulfamoylamino-6-(methylsulfinyl)benzonitrile

The mixture of 2-sulfamoylamino-6-(methylthio)benzonitrile (Example 104a) (48 mg, 0.2 mmol) and MCPBA (69 mg, 0.4 mmol) in dichloromethane (16 mL) was heated refluxed overnight. After cooling down, the precipitation was collected by filtration, rinsed with dichloromethane, dried in the air to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.83 (s, 3H), 7.35 (brs, 2H), 7.72-6.69 (m, 2H), 7.92 (t, J = 8.0 Hz, 1H), 9.87 (brs, 1H).

Example 110: 5-(Methylsulfonyl)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



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Prepared as in Example 107 from 2-sulfamoylamino-6-(methylsulfonyl)benzonitrile (Example 110a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.30 (s, 3H), 6.95-6.93 (m, 1H), 7.01 (bs, 2H), 7.17-7.17 (m, 1H), 7.24-7.21 (m, 1H).MS 276 (MH^+)

Example 110a: 2-sulfamoylamino-6-(methylsulfonyl)benzonitrile

Prepared as in Example 107a from 2-amino-6-(methylsulfonyl)benzonitrile (Example 109b) ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.37 (s, 3H), 7.46 (s, 2H), 7.85-7.83 (m, 1H), 7.93-7.91 (m, 2H), 9.92 (s, 1H).

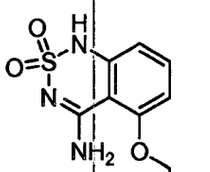
Example 110b: 2-amino-6-(methylsulfonyl)benzonitrile

Prepared as in Example 107b from 2-(methylsulfonyl)-6-nitrobenzonitrile (Example 110c). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.26 (s, 3H), 6.63 (brs, 2H), 7.15-7.09 (m, 2H), 7.51-7.47 (m, 1H).

Example 110c: 2-(methylsulfonyl)-6-nitrobenzonitrile

Prepared as in Example 109a from 2-(methylthio)-6-nitrobenzonitrile (Example 104c) ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.48 (s, 3H), 8.21 (d, J = 7.6 Hz, 1H), 8.49-8.47 (m, 1H), 8.66-8.64 (m, 1H).

Example 111: 4-Amino-5-(propyloxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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To a suspension of 2-sulfamoylamino-6-propoxybenzonitrile (Example 111a) (4.73 g, 18.53 mmol) in ethanol (65 mL), was added aqueous NaOH (2N, 18.6 ml, 37.06 mmol). The resulting clear solution was refluxed for 3 hours under nitrogen. After cooling to room temperature, the resulting solution was filtered, the filtrate was cooled to 0 °C and neutralized with 10% acetic acid. The resulting precipitate was collected by filtration, suspended in 50 ml of ethanol/water (1:1) and warmed to 40 °C for 20 min. The solid was collected by filtration to provide 4-Amino-5-(propyloxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide (4 g, 85%) as a pale yellow powder. M.p.: 229-230 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.96 (t, J = 7.3 Hz, 3H), 1.81 (sext, J = 7.3 Hz, 2H), 4.10 (t, J = 6.7 Hz, 2H), 6.60 (d, J = 8.6 Hz, 1H), 6.73 (d, J = 8.6 Hz, 1H), 7.44 (t, J = 8.6 Hz, 1H), 7.81 (br s, 1H), 8.35 (br s, 1H), 10.93 (br s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 11.07, 22.18, 71.41, 100.93, 105.64, 110.21, 135.53, 145.16, 158.47, 161.10. MS 256 (MH^+).

Example 111a: 2-Sulfamoylamino-6-propoxybenzonitrile

To a solution of 2-amino-6-propoxybenzonitrile (Example 111b) (4.23 g, 24.01 mmol) in dimethylacetamide (20 mL) under N_2 was added sulfamoyl chloride (5.56 g, 48.02 mmol). The reaction mixture was then stirred at room temperature under nitrogen for 4 hours. Upon completion, the reaction was quenched by addition of ice/water (250 mL). The resulting precipitate was collected by filtration, rinsed with water and dried to yield 2-sulfamoylamino-6-propoxybenzonitrile (4.73 g, 77%) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.01 (d, J = 7.2 Hz, 3H), 1.76 (sext, J = 7.2 Hz, 2H), 4.08 (t, J = 6.8 Hz, 2H), 6.96 (d, J = 8.5 Hz, 1H), 7.15 (t, J = 8.5 Hz, 1H), 7.28 (br s, 2H), 7.57 (d, J = 8.5 Hz, 1H), 9.46 (s, 1H). MS 256 (MH^+).

Example 111b: 2-Amino-6-propoxybenzonitrile

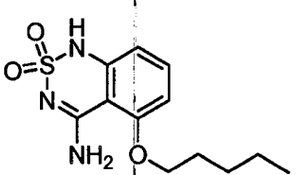
2-Nitro-6-propoxybenzonitrile (Example 111c) (4.95 g, 24.01 mmol) was dissolved in EtOH (50 mL) and THF (15 mL). 10% Pd/C (255 mg, 2.4 mmol) was added, and the reaction was hydrogenated using a Parr apparatus for 12 hours at 40 psi. Upon completion, the reaction was filtered through celite and the filtrate concentrated to provide 2-nitro-6-

propoxybenzonitrile (4.3 g, 100%) as a light brown gel. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (d, J = 7.4 Hz, 3H), 1.83 (sext, J = 7.0 Hz, 2H), 3.96 (t, J = 7.0 Hz, 2H), 4.38 (br s, 2 H), 6.20 (d, J = 8.5 Hz, 1H), 6.28 (t, J = 8.5 Hz, 1H), 7.19 (d, J = 8.5 Hz, 1H).

Example 111c: 2-Nitro-6-propoxybenzonitrile

To a solution of 2,6-dinitrobenzonitrile (6 g, 31.07 mmol) in dry DMF (45 mL) at 0 °C, was added a solution of sodium (815 mg, 35.42 mmol) in n-propanol (23.5 mL) dropwise over 30 minutes. After compete addition, the reaction mixture was warmed to room temperature and stirred for 2.5 hours. The reaction was poured into an ice/water mixture (250 mL), and the precipitate was collected by filtration and dried to yield 2-nitro-6-propoxybenzonitrile (4.95 g, 77%) as a light brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (d, J = 7.5 Hz, 3H), 1.93 (sext, J = 7.5 Hz, 2H), 4.14 (t, J = 7.0 Hz, 2H), 7.31 (d, J = 8.6 Hz, 1H), 7.69 (t, J = 8.6 Hz, 1H), 7.82 (d, J = 8.6 Hz, 1H).

Example 112: 4-Amino-5-(pentoxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-pentoxybenzonitrile (Example 112a) to provide 4-amino-5-(pentoxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide (59 mg, 43%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.88 (t, J = 7.3 Hz, 3H), 1.35 (m, 4H), 1.80 (quint, J = 6.8 Hz, 2H), 4.14 (t, J = 6.4 Hz, 2H), 6.59 (d, J = 8.2 Hz, 1H), 6.73 (d, J = 8.56 Hz, 1H), 7.44 (t, J = 8.5 Hz, 1H), 7.81 (br s, 1H), 8.34 (br s, 1H), 10.92 (br s, 1H). MS 284 (MH^+).

Example 112a: 2-Sulfamoylamino-6-pentoxybenzonitrile

Prepared as in Example 1a from 2-amino-6-pentoxybenzonitrile to provide 2-sulfamoylamino-6-pentoxybenzonitrile.

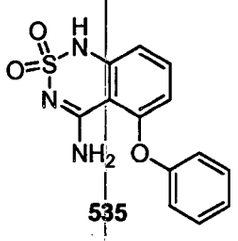
Example 112b: 2-Amino-6-(pentyloxy)benzonitrile

Prepared as in Example 111b from 2-nitro-6-(pentyloxy)benzonitrile to provide 2-Amino-6-(pentyloxy)benzonitrile. MS 205 (MH^+).

Example 112c: 2-Nitro-6-(pentyloxy)benzonitrile

Prepared as in Example 111c from 2,6-dinitrobenzonitrile and pentanol to provide 2-nitro-6-(pentyloxy)benzonitrile.

Example 113: 4-Amino-5-(phenoxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-phenoxybenzonitrile (Example 113a) to provide 4-Amino-5-(phenoxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide (29 mg, 50%). ^{1}H NMR (400 MHz, MeOD) δ 6.39 (dd, J = 8.3, 0.8 Hz, 1H), 6.75 (dd, J = 8.2, 1.1 Hz, 1H), 7.18 (m, 2H), 7.30 (m, 1H), 7.40 (t, J = 8.5 Hz, 1H), 7.48 (m, 2H). MS 290 (MH^+).

Example 113a: 2-Sulfamoylamino-6-phenoxybenzonitrile

Prepared as in Example 111a from 2-amino-6-phenoxybenzonitrile (Example 113b) to provide 2-sulfamoylamino-6-phenoxybenzonitrile (250 mg, 100%). ^{1}H NMR (400 MHz, MeOD) δ 6.60 (d, J = 8.6 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 7.26 (t, J = 7.5 Hz, 1H), 7.39 (d, J = 8.3 Hz, 1H), 7.45 (m, 2H), 7.50 (t, J = 8.6 Hz, 1H). MS 290 (MH^+).

Example 113b: 2-Amino-6-phenoxybenzonitrile

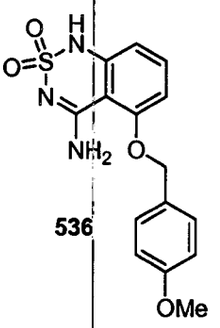
To a solution of 2-nitro-6-(phenoxy)benzonitrile (Example 113c) (1.94 g, 8.08 mmol) in MeOH (164 mL) was slowly added concentrated HCl (7.23 mL) followed by iron powder (1.58 g, 28.3 mmol). The reaction was refluxed for 30 min and concentrated in vacuo. The residue was dissolved in EtOAc and washed with 1N NaOH, water and brine. The organic layer was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography 1:1 Hexane:EtOAc to yield 2-amino-6-phenoxybenzonitrile (384 mg, 22.6%). ^{1}H NMR (400 MHz, MeOD) δ 5.97 (d, J = 8.3 Hz, 1H), 6.50 (d, J = 8.6 Hz, 1H), 7.06 (m, 2H), 7.18 (m, 2H), 7.40 (m, 2H). MS 210 (MH^+).

Example 113c: 2-Nitro-6-phenoxybenzonitrile

A solution of 2,6-dinitrobenzonitrile (2.0 g, 10.5 mmol), phenol (1.42 g, 15.1 mmol) and K_2CO_3 (1.45 g, 10.5 mmol) in DMF (20 mL) was stirred at rt under N_2 for 4.5 hours. Upon completion, the reaction was diluted with EtOAc (100 mL), washed with H_2O, dried over $MgSO_4$, filtered and concentrated. The residue was recrystallized from Hexane/EtOAc to provide 2-nitro-6-phenoxybenzonitrile (1.94 g, 77%). ^{1}H NMR (400 MHz, MeOD) δ 7.20 (m, 2H), 7.28

(dd, J = 8.6, 1.1 Hz, 1H), 7.34 (m, 1H), 7.51 (m, 2H), 7.78 (t, J = 8.7 Hz, 1H), 8.05 (dd, J = 8.2, 0.8 Hz, 1H).

Example 114: 4-Amino-5-(4-methoxybenzyloxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-(4-methoxybenzyloxy) benzonitrile (Example 114a) to provide 4-amino-5-(4-methoxy benzyloxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide (12 mg, 10%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.76 (s, 3H), 6.72 (d, J = 8.4, 1H), 6.80 (d, J = 8.1, 1H), 6.95 (m, 2H), 7.48 (m, 3H), 10.89 (br s, 1H), 11.0 (br s, 1H). MS 334 (MH^+).

Example 114a: 2-Sulfamoylamino-6-(4-methoxybenzyloxy) benzonitrile

To a solution of chlorosulfonyl isocyanate (212 mg, 1.50 mmol) in CH_2Cl_2 (0.55 mL) at 0 °C, was added formic acid (0.575 mL) under N_2. The reaction was stirred for 30 min, and a solution of 2-amino-6-(4-methoxybenzyloxy) benzonitrile (Example 114b) (191 mg, 0.75 mmol) in CH_2Cl_2 (4 mL) was added at 0 °C, followed by Et_3N (0.627 mL, 4.50 mmol). After 30 min, the reaction was concentrated in vacuo and diluted with water. The pH was adjusted to 7 with concentrated HCl, and purified by reverse phase HPLC (10-90% acetonitrile in water) to provide 2-sulfamoylamino-6-(4-methoxybenzyloxy) benzonitrile (130 mg, 52%). ^{1}H NMR (400 MHz, MeOD) δ 3.80 (s, 3H), 5.15 (s, 2H), 6.88 (d, J = 8.1 Hz 1H), 6.94 (m, 2H), 7.40 (m, 2H), 7.48 (t, J = 8.7 Hz, 1H), 7.75 (dd, J = 8.6, 0.8 Hz, 1H).

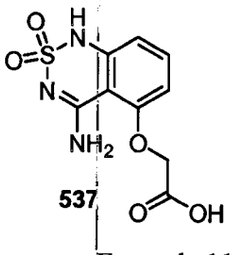
Example 114b: 2-Amino-6-(4-methoxybenzyloxy) benzonitrile

Prepared as in Example 113b from 2-nitro-6-(4-methoxybenzyloxy) benzonitrile (Example 114c) to provide 2-amino-6-(4-methoxybenzyloxy) benzonitrile (451 mg, 22%). ^{1}H NMR (400 MHz, MeOD) δ 3.80 (s, 3H), 5.06 (s, 2H), 6.33 (dd, J = 8.3, 0.8 Hz, 1H), 6.38 (m, 1H), 6.93 (m, 2H), 7.19 (t, J = 8.2 Hz, 1H), 7.38 (m, 2H).

Example 114c: 2-Nitro-6-(4-methoxybenzyloxy) benzonitrile

Prepared as in Example 112c from 2,6-dinitrobenzonitrile and 4-methoxybenzyl alcohol to provide 2-nitro-6-(4-methoxybenzyloxy) benzonitrile (2.40 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 5.26 (s, 2H), 6.93 (m, 2H), 7.35 (dd, J = 8.6, 0.7 Hz, 1H), 7.38 (m, 2H), 7.65 (t, J = 8.6 Hz, 1H), 7.83 (dd, J = 8.2, 0.8 Hz, 1H).

Example 115: 4-Amino-5-oxyacetic acid-1*H*-benzo[*c*][1,2,3]thiadiazine-2,2-dioxide



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Prepared in a similar manner as Example 111 from ethyl 2-(2-cyano-3-(sulfamoylamino)phenoxy)acetate (Example 115a) to provide 4-Amino-5-oxyacetic acid-1*H*-benzo[*c*][1,2,3]thiadiazine-2,2-dioxide (74.9 mg, 15%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.88 (s, 2H), 6.65 (dd, J = 8.3, 0.8 Hz, 1H), 6.69 (dd, J = 8.5, 0.7 Hz, 1H), 7.46 (t, J = 8.3 Hz, 1H), 8.42 (br s, 1H), 8.53 (br s, 1H) 11.02 (br s, 1H), 13.49 (br s, 1H). MS 272 (MH^+).

Example 115a: Ethyl 2-(2-cyano-3-(sulfamoylamino)phenoxy)acetate

Prepared in a similar manner as Example 111a from ethyl 2-(3-amino-2-cyanophenoxy)acetate (Example 5b) to provide ethyl 2-(2-cyano-3-(sulfamoylamino)phenoxy)acetate (567 mg, 79%) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.22 (t, J =7.0 Hz, 3H), 4.19 (q, J = 7.0 Hz, 2H), 5.01 (s, 2H), 6.87 (d, J = 8.6 Hz, 1H), 7.20 (d, J = 8.3 Hz, 1H), 7.32 (s, 2H), 7.56 (t, J = 8.6 Hz, 1H), 9.53 (br s, 1H).

Example 115b: Ethyl 2-(3-amino-2-cyanophenoxy)acetate

Prepared in a similar manner as Example 111b from ethyl 2-(3-amino-2-nitrophenoxy)acetate (Example 115c) to provide ethyl 2-(3-amino-2-cyanophenoxy)acetate (539 mg, 56%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.21 (t, J =7.6 Hz, 3H), 4.17 (q, J = 7.6 Hz, 2H), 4.85 (s, 2H), 6.06 (br s, 2H), 6.10 (d, J = 8.0 Hz, 1H), 6.38 (dd, J = 8.6, 0.8 Hz, 1H), 7.17 (t, J = 8.4 Hz, 1H).

Example 115c: Ethyl 2-(3-amino-2-nitrophenoxy)acetate

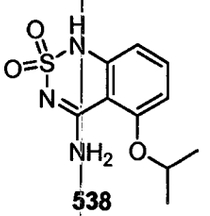
To a solution of 2-hydroxy-6-nitrobenzonitrile (Example 115d) (616 mg, 4.33 mmol) and K_2CO_3 (718 mg, 5.20 mmol) in acetone (8 mL), was added ethyl bromoacetate (0.576 mL, 5.20 mmol). The reaction was refluxed under N_2 for 4.5 hours. Upon completion, the

reaction was filtered, and the filtrate was concentrated and dried to yield ethyl 2-(3-amino-2-nitrophenoxy). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.23 (t, J =7.0 Hz, 3H), 4.20 (q, J = 7.1 Hz, 2H), 5.19 (s, 2H), 7.69 (dd, J = 8.6, 0.8 Hz, 1H), 7.89 (t, J = 8.4 Hz, 1H), 7.97 (dd, J = 8.3, 0.8 Hz, 1H).

Example 115d: 2-Hydroxy-6-nitrobenzonitrile

To a solution of 2,6-dinitrobenzonitrile (10.0 g, 52.3 mmol) in MeOH (215 mL), was added a solution of Na (1.32 g, 57.5 mmol) in MeOH (23.3 mL). The reaction was refluxed under N_2 for 2.5 hours, cooled to rt and the precipitate was collected by filtration. The resulting residue was combined with pyridine hydrochloride (15.1 g, 130 mmol), and the solids were melted at 200 °C for 18 hours. Upon completion, the reaction was cooled to rt, washed with brine (1 x 300 mL) and extracted with EtOAc (2 x 500 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to provide 2-hydroxy-6-nitrobenzonitrile (6.70 g, 87%). ^{1}H NMR (400 MHz, MeOD) δ 7.35 (dd, J = 8.3, 0.8 Hz, 1H), 7.67 (t, J = 8.2 Hz, 1H), 7.77 (dd, J = 8.2, 1.1 Hz, 1H).

Example 116: 4-Amino-5-(isopropoxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared in a similar manner as Example 111 from 2-sulfamoylamino-6-isopropoxybenzonitrile (Example 116a) to provide 4-amino-5-(isopropoxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide (50 mg, 171%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.38 (d, J = 5.8 Hz, 6H), 4.84 (sept, J = 5.9 Hz, 1H), 6.59 (d, J = 8.7 Hz, 1H), 6.77 (d, J = 8.7 Hz, 1H), 7.45 (d, J = 8.7 Hz, 1H), 7.81 (br s, 1H), 8.32 (br s, 1H), 10.94 (br s, 1H). MS 256 (MH^+).

Example 116a: 2-Sulfamoylamino-6-isopropoxybenzonitrile

Prepared in a similar manner as Example 111a from 2-amino-6-isopropoxybenzonitrile (Example 6b) to provide 2-sulfamoylamino-6-isopropoxybenzonitrile (21 mg, 8%). ^{1}H NMR (400 MHz, MeOD) δ 1.37 (d, J = 5.6 Hz, 6H), 4.67 (sept, J = 6.0 Hz, 1H), 6.29 (d, J = 8.2 Hz, 1H), 6.36 (dd, J = 8.1, 0.8 Hz, 1H), 7.07 (t, J = 8.2 Hz, 1H).

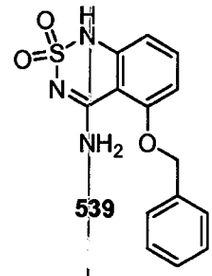
Example 116b: 2-Amino-6-isopropoxybenzonitrile

Prepared in a similar manner as Example 113b from 2-nitro-6-isopropoxybenzonitrile (Example 116c) to provide 2-amino-6-isopropoxybenzonitrile (201 mg, 76%) as a yellow oil. ^{1}H NMR (400 MHz, MeOD) δ 1.34 (d, J = 6.0 Hz, 6H), 4.64 (sept, J = 6.1 Hz, 1H), 6.25 (d, J = 8.1 Hz, 1H), 6.34 (dd, J = 8.2, 0.8 Hz, 1H), 7.18 (t, J = 8.3 Hz, 1H).

Example 116c: 2-Nitro-6-isopropoxybenzonitrile

Prepared in a similar manner as Example 115c from 2-hydroxy-6-nitrobenzonitrile (Example 115d) and isopropyl bromide to provide 2-nitro-6-isopropoxybenzonitrile (324 mg, 64%). ^{1}H NMR (400 MHz, MeOD) δ 1.43 (d, J = 6.2 Hz, 6H), 4.89 (sept, J = 6.2 Hz, 1H), 7.61 (dd, J = 8.0, 1.0 Hz, 1H), 7.80 (t, J = 8.2 Hz, 1H), 7.85 (dd, J = 8.2, 1.2 Hz, 1H).

Example 117: 4-Amino-5-(benzyloxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-(benzyloxy)benzonitrile (Example 117a) to provide 4-amino-5-(benzyloxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide (42 mg, 61%). ^{1}H NMR (400 MHz, MeOD) δ 5.32 (s, 2H), 6.65 (dd, J = 8.3, 1.2 Hz, 1H), 6.85 (dd, J = 8.6, 1.0 Hz, 1H), 7.36-7.52 (m, 6H). MS 304 (MH^+).

Example 117a: 2-Sulfamoylamino-6-(benzyloxy)benzonitrile

Prepared as in Example 111a from 2-amino-6-(benzyloxy)benzonitrile (Example 117b) to provide 2-sulfamoylamino-6-(benzyloxy)benzonitrile (74 mg, 30%). ^{1}H NMR (400 MHz, MeOD) δ 5.22 (s, 2H), 6.94 (d, J = 8.5 Hz, 1H), 7.26 (d, J = 8.2 Hz, 1H), 7.32 (m, 1H), 7.38 (t, J = 7.2 Hz, 2H), 7.47 (d, J = 7.4 Hz, 2H), 7.51 (t, J = 8.2 Hz, 1H).

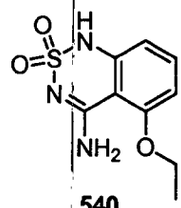
Example 117b: 2-Amino-6-(benzyloxy)benzonitrile

Prepared as in Example 113b from 2-nitro-6-(benzyloxy)benzonitrile (Example 117c) to provide 2-amino-6-(benzyloxy)benzonitrile (215 mg, 63%). ^{1}H NMR (400 MHz, MeOD) δ 5.15 (s, 2H), 6.32 (d, J = 8.2 Hz, 1H), 6.39 (d, J = 8.2 Hz, 1H), 7.20 (t, J = 8.4 Hz, 1H), 7.38 (t, J = 7.6 Hz, 2H), 7.46 (d, J = 7.4 Hz, 2H). MS 225 (MH^+).

Example 117c: 2-Nitro-6-(benzyloxy)benzonitrile

To a solution of 2-hydroxy-6-nitrobenzonitrile (Example 115) (1.0 g, 6.09 mmol) and Cs_2CO_3 (2.16 g, 6.64 mmol) in acetone (14 mL) was added benzyl bromide (1.16 g, 6.76 mmol). The reaction was refluxed under N_2 for 1.5 hours, then filtered and the filtrate concentrated. The residue was purified by flash chromatography 3:2 Hexane:EtOAc to provide 2-nitro-6-(benzyloxy)benzonitrile (500 mg, 32%). ^{1}H NMR (400 MHz, MeOD) δ 5.40 (s, 2H), 7.34-7.45 (m, 3H), 7.53 (m, 2H), 7.69 (dd, J = 8.6, 0.8 Hz, 1H), 7.82 (t, J = 8.4 Hz, 1H), 7.91 (t, J = 8.2, 0.8 Hz, 1H).

Example 118: 4-Amino-5-(ethoxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-ethoxybenzonitrile (Example 118a) to provide 4-amino-5-ethoxy-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide (120 mg, 50%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.37 (t, J = 6.9 Hz, 3H), 4.18 (q, J = 6.9 Hz, 2H), 6.96 (d, J = 8.8 Hz, 1H), 7.16 (d, J = 8.8 Hz, 1H), 7.27 (br s, 2H), 7.57 (t, J = 8.4 Hz, 1H), 9.44 (br s, 1H). MS 242 (MH^+).

Example118a: 2-Sulfamoylamino-6-ethoxybenzonitrile

Prepared in a similar manner as Example 111a from 2-amino-6-ethoxybenzonitrile (Example 8b) to provide 2-sulfamoylamino-6-ethoxybenzonitrile (161 mg, 67%). MS 242 (MH^+).

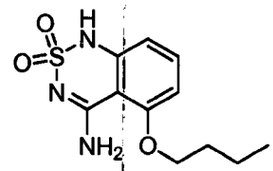
Example 118b: 2-Amino-6-ethoxybenzonitrile

Prepared in a similar manner as Example 111b from 2-nitro-6-ethoxybenzonitrile (Example 8c) to provide 2-amino-6-ethoxybenzonitrile (162 mg, 100%). MS 163 (MH^+).

Example 118c: 2-Nitro-6-ethoxybenzonitrile

Prepared in a similar manner as Example 115c from 2-hydroxy-6-nitrobenzonitrile (Example 115d) and ethyl bromide to provide 2-nitro-6-ethoxybenzonitrile (192 mg, 50%).

Example 119: 4-Amino-5-(butoxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared in a similar manner as Example 111 from 2-sulfamoylamino-6-butoxybenzonitrile (Example 119a) to provide 4-amino-5-butoxy-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide (67 mg, 50%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.95 (t, J = 7.4 Hz, 3H), 1.44 (sext, J = 7.4 Hz, 2H), 1.81 (quint, J = 7.9 Hz, 2H), 4.17 (t, J = 6.7 Hz, 2H), 6.61 (d, J = 8.2 Hz, 1H), 6.76 (d, J = 8.2 Hz, 1H), 7.46 (t, J = 8.2 Hz, 1H), 7.82 (br s, 1H), 8.35 (br s, 1H), 10.96 (br s, 1H). MS 270 (MH^+).

Example 119a: 2-Sulfamoylamino-6-butoxybenzonitrile

Prepared in a similar manner as Example 111a from 2-amino-6-butoxybenzonitrile (Example 9b) to provide 2-sulfamoylamino-6-butoxybenzonitrile. MS 270 (MH^+).

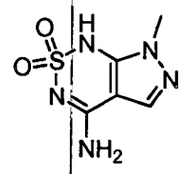
Example 119b: 2-Amino-6-butoxybenzonitrile

Prepared in a similar manner as Example 111b from 2-nitro-6-butoxybenzonitrile (Example 9c) to provide 2-amino-6-butoxybenzonitrile (190 mg, 71%). MS 191 (MH^+).

Example 119c: 2-nitro-6-butoxybenzonitrile

Prepared in a similar manner as Example 115c from 2-hydroxy-6-nitrobenzonitrile (Example 115d) and butyl bromide to provide 2-nitro-6-butoxybenzonitrile.

Example 120: 4-Amino-1-methyl-*1H*-pyrazolo[*c*][1,2,6]thiadiazine-2,2-dioxide



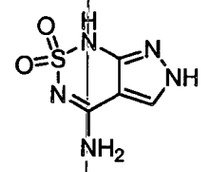
542

Prepared in a similar manner as Example 111 from 5-sulfamoylamino-1-methyl-*1H*-pyrazole-4-carbonitrile (Example 120a) to provide 4-Amino-1-methyl-*1H*-pyrazolo[c][1,2,6]thiadiazine-2,2-dioxide (100 mg, 50%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.76 (s, 3H), 7.43 (s, 2H), 7.98 (s, 1H), 9.84 (s, 1H).

Example 120a: 5-sulfamoylamino-1-methyl-*1H*-pyrazole-4-carbonitrile

Prepared in a similar manner as Example 111a from 5-amino-1-methyl-*1H*-pyrazole-4-carbonitrile to provide 5-sulfamoylamino-1-methyl-*1H*-pyrazole-4-carbonitrile.

Example 121: 4-Amino-*2H*-pyrazolo[*c*][1,2,6]thiadiazine-2,2-dioxide



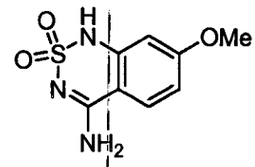
543

Prepared in a similar manner as Example 111 from 3-sulfamoylamino-*1H*-pyrazole-4-carbonitrile (Example 11a) to provide 4-amino-*2H*-pyrazolo[*c*][1,2,6]thiadiazine-2,2-dioxide (90 mg, 48%).^{1}H NMR (400 MHz, DMSO-d_6) δ 6.97 (s, 2H), 8.47 (s, 1H), 9.71 (s, 1H), 13.36 (s, 1H).

Example 121a: 3-Sulfamoylamino-*1H*-pyrazole-4-carbonitrile

Prepared in a similar manner as Example 111a from 3-amino-*1H*-pyrazole-4-carbonitrile to provide 3-sulfamoylamino-*1H*-pyrazole-4-carbonitrile.

Example 122: 4-Amino-7-methoxy-*1H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared in a similar manner as Example 111 from 2-sulfamoylamino-4-methoxybenzonitrile (Example 122a) to provide 4-amino-7-methoxy-*1H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide (49 mg, 65%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.81 (s, 3H), 6.58 (d, J = 2.3 Hz, 1H), 6.75 (dd, J = 9.1, 2.7 Hz, 1H), 7.82 (d, J = 8.8 Hz, 1H), 10.85 (br s, 1H), 10.99 (br s, 1H). MS 228 (MH^+).

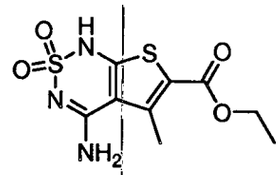
Example 122a: 2-Sulfamoylamino-4-methoxybenzonitrile

Prepared in a similar manner as Example 114a from 2-amino-4-methoxybenzonitrile (Example 122b) to provide 2-sulfamoylamino-4-methoxybenzonitrile as white crystals (111 mg, 44%). ^{1}H NMR (400 MHz, MeOD) δ 3.85 (s, 3H), 6.73 (dd, J = 9.0, 2.8 Hz, 1H), 7.54 (d, J = 9.0 Hz, 1H), 7.84 (d, J = 2.4 Hz, 1H). MS 228 (MH^+).

Example 122b: 2-Amino-4-methoxybenzonitrile

Prepared in a similar manner as Example 111b from 2-nitro-4-methoxybenzonitrile to provide 2-amino-4-methoxybenzonitrile (910 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 4.73 (br s, 2H), 6.20 (m, 1H), 6.31 (m, 1H), 7.30 (d, J = 8.7 Hz, 1H).

Example 123: Ethyl 4-amino-5-methyl-2-oxo-1,2-dihydrothieno[*c*][1,3,6]thiadiazine-2,2-dioxide-6-carboxylate



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Prepared in a similar manner as Example 111 from ethyl 5-sulfamoylamino-4-cyano-3-methylthiophene-2-carboxylate (Example 123a) to provide ethyl 4-amino-5-methyl-2-oxo-1,2-dihydrothieno[*c*][1,3,6]thiadiazine-2,2-dioxide-6-carboxylate (1.22 g, 72%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.26 (t, J = 6.9 Hz, 3H), 2.73 (s, 3H), 4.17 (q, J = 7.0 Hz, 2H). MS 290 (MH^+).

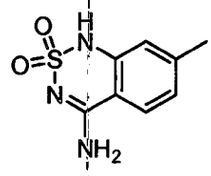
Example 123a: Ethyl 5-sulfamoylamino-4-cyano-3-methylthiophene-2-carboxylate

Prepared in a similar manner as Example 114a from ethyl 5-amino-4-cyano-3-methylthiophene-2-carboxylate (Example 123b) to provide ethyl 5-sulfamoylamino-4-cyano-3-methylthiophene-2-carboxylate (1.73 g, 80%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.28 (t, J = 7.0 Hz, 3H), 2.36 (s, 3H), 4.24 (q, J = 7.1 Hz, 2H).

Example 123b: Ethyl 5-amino-4-cyano-3-methylthiophene-2-carboxylate

To a solution of ethyl 3-oxobutanoate (3.0 mL, 23.5 mmol), malononitrile (1.55 g, 23.5 mmol) and sulfur (753 mg, 23.5 mmol) in EtOH (39 mL), was added Et_3N (3.28 mL, 23.5 mmol). The reaction was refluxed under N_2 for 3 hours, then directly purified by flash chromatography (99:1 CH_2Cl_2:EtOAc) to provide ethyl 5-amino-4-cyano-3-methylthiophene-2-carboxylate (2.18 g, 44%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.21 (t, J = 7.0 Hz, 3H), 2.36 (s, 3H), 4.15 (q, J = 7.2 Hz, 2H).

Example 124: 4-Amino-7-methyl-1H-benzo[c][1,2,6]thiadiazine-2,2-dioxide



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Prepared in a similar manner as Example 111 from 2-sulfamoylamino-4-methylbenzonitrile (Example 124a) to provide 4-amino-7-methyl-*1H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide (50 mg, 50%). ^{1}H NMR (400 MHz, MeOD) δ 2.40 (s, 3H), 6.92 (s, 1H), 7.03 (m, 1H), 7.70 (d, J = 8.2 Hz, 1H). MS 212 (MH^+).

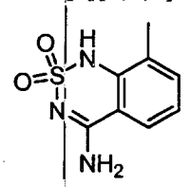
Example 124a: 2-Sulfamoylamino-4-methylbenzonitrile

Prepared in a similar manner as Example 114a from 2-amino-4-methylbenzonitrile (Example 14b) to provide 2-sulfamoylamino-4-methylbenzonitrile (205 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 6.88 (m, 1H), 7.38 (d, J = 7.7 Hz, 1H), 7.72 (br s, 1H), 7.97 (s, 1H), 9.37 (s, 1H),. MS 212 (MH^+).

Example 124b: 2-Amino-4-methylbenzonitrile

A solution of 2-bromo-4-methylbenzonitrile (2.0 g, 10.7 mmol) and CuCN (1.92 g, 21.4 mmol) in NMP (10 mL) was reacted in a microwave for 20 min at 200 °C. Upon completion the reaction was cooled to 0 °C, and 15% aqueous NH_4OH (215 mL) was slowly added. The mixture was stirred at rt for 30 min, then extracted with CH_2Cl_2. The organic layer was washed with H_2O, brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (3:1 Hexane:EtOAc) to provide 2-amino-4-methylbenzonitrile (1.24 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 3H), 5.70 (m, 1H), 5.84 (m, 1H), 6.41 (d, J = 8.0 Hz, 1H).

Example 125: 4-Amino-8-methyl-*1H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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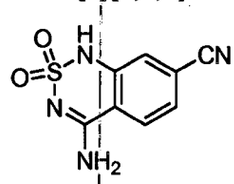
Prepared in a similar manner as Example 111 from 2-sulfamoylamino-3-methylbenzonitrile (Example 125a) to provide 4-amino-8-methyl-*1H*-benzo[*c*][1,2,6]thiadiazine-

2,2-dioxide (9 mg, 8%). ^{1}H NMR (400 MHz, MeOD) δ 2.37 (s, 3H), 7.09 (t, J = 7.7 Hz, 1H), 7.45 (d, J = 7.3 Hz, 1H), 8.04 (d, J = 7.7 Hz, 1H). MS 212 (MH^+).

Example 125a: 2-Sulfamoylamino-3-methylbenzonitrile

Prepared in a similar manner as Example 114a from 2-amino-3-methylbenzonitrile (Example 15b) to provide 2-sulfamoylamino-3-methylbenzonitrile (115 mg, 46%). ^{1}H NMR (400 MHz, MeOD) δ 2.34 (s, 3H), 7.31 (t, J = 7.5 Hz, 1H), 7.57 (m, 2H). MS 212 (MH^+).

Example 126: 4-Amino-7-cyano-*1H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



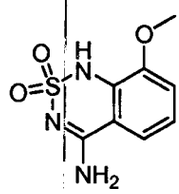
548

Prepared in a similar manner as Example 114a from 2-aminoterephthalonitrile (Example 126a) to provide 4-amino-7-cyano-*1H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide (40 mg, 16%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.37 (d, J = 1.5 Hz, 1H), 7.57 (dd, J = 8.2, 1.6 Hz, 1H), 8.12 (d, J = 8.5 Hz, 1H), 8.51 (br s, 2H), 11.51 (s, 1H). MS 223 (MH^+).

Example 126a: 2-Aminoterephthalonitrile

Prepared in a similar manner as Example 124b from 2,5-dibromoaniline to provide 2-aminoterephthalonitrile (1.14 g, 100%). ^{1}H NMR (400 MHz, MeOD) δ 6.91 (dd, J = 8.2, 1.6 Hz, 1H), 7.12 (d, J = 1.6 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H).

Example 127: 4-Amino-8-methoxy-*1H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared in a similar manner as Example 111 from 2-sulfamoylamino-3-methoxybenzonitrile (Example 127a) to provide 4-amino-8-methoxy-*1H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide (11 mg, 15%). ^{1}H NMR (400 MHz, MeOD) δ 3.97 (s, 3H), 7.14 (t, J = 7.9 Hz, 1H), 7.22 (dd, J = 7.8, 1.2 Hz, 1H), 7.72 (d, J = 8.2, 1.2 Hz, 1H). MS 228 (MH^+).

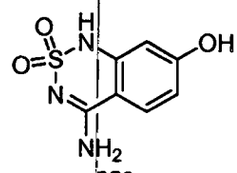
Example 127a: 2-Sulfamoylamino-3-methoxybenzonitrile

Prepared in a similar manner as Example 114a from 2-amino-3-methoxybenzonitrile (Example 127b) to provide 2-sulfamoylamino-3-methoxybenzonitrile (113 mg, 45%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.85 (s, 3H), 7.27 (m, 1H), 7.30 (dd, J = 7.7, 1.7 Hz, 1H), 7.35 (dd, J = 7.9, 1.7 Hz, 1H), 8.87 (s, 1H), 9.09 (br s, 1H). MS 228 (MH^+).

Example 127b: 2-Amino-3-methoxybenzonitrile

Prepared in a similar manner as Example 111b from 3-methoxy-2-nitrobenzonitrile to provide 2-amino-3-methoxybenzonitrile (346 mg, 60%). ^{1}H NMR (400 MHz, MeOD) δ 3.87 (s, 3H), 6.65 (t, J = 7.7 Hz, 1H), 6.95 (dd, J = 7.7, 1.2 Hz, 1H), 7.00 (dd, J = 8.2, 1.2 Hz, 1H). MS 149 (MH^+).

Example 128: 4-Amino-7-hydroxy-*1H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared in a similar manner as Example 111 from 2-sulfamoylamino-4-hydroxybenzonitrile (Example 128a) to provide 4-amino-7-hydroxy-*1H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide (7 mg, 14%). ^{1}H NMR (400 MHz, MeOD) δ 6.50 (d, J = 2.0 Hz, 1H), 6.65 (dd, J = 9.0, 2.4 Hz, 1H), 7.82 (d, J = 8.8 Hz, 1H). MS 214 (MH^+).

Example 128a: 2-Sulfamoylamino-4-hydroxybenzonitrile

Prepared in a similar manner as Example 114a from 2-amino-4-hydroxybenzonitrile (Example 18b) to provide 2-sulfamoylamino-4-hydroxybenzonitrile (51 mg, 22%). ^{1}H NMR (400 MHz, MeOD) δ 6.56 (dd, J = 8.6, 2.4 Hz, 1H), 7.43 (d, J = 8.6 Hz, 1H), 7.68 (d, J = 2.2 Hz, 1H). MS 214 (MH^+).

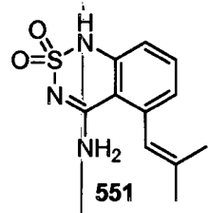
Example 128b: 2-Amino-4-hydroxybenzonitrile

Prepared in a similar manner as Example 111b from 4-hydroxy-2-nitrobenzonitrile (Example 128c) to provide 2-Amino-4-hydroxybenzonitrile (286 mg, 100%). ^{1}H NMR (400 MHz, MeOD) δ 6.15 (dd, J = 8.5, 2.3 Hz, 1H), 6.20 (d, J = 1.9 Hz, 1H), 7.18 (d, J = 8.6 Hz, 1H).

Example 128c: 4-Hydroxy-2-nitrobenzonitrile

A mixture of 4-methoxy-2-nitrobenzonitrile (820 mg, 4.6 mmol) and pyridine hydrochloride (755 mg, 4.6 mmol) was heated at 200 °C under N_2 for 18 hours. Upon completion, the reaction was cooled to room temperature, washed with brine and extracted with EtOAc (2 x 100 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (1:1 Hexane:EtOAc) to provide 4-hydroxy-2-nitrobenzonitrile (200 mg, 26%). ^{1}H NMR (400 MHz, MeOD) δ 7.24 (dd, J = 8.6, 2.4 Hz, 1H), 7.70 (d, J = 2.4 Hz, 1H), 7.83 (d, J = 8.6 Hz, 1H).

Example 129: 4-Amino-5-(2-methylprop-1-enyl)-1H-benzo[c] [1,2,3] thiadiazine-2,2-dioxide



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To a stirred solution of 2-sulfamoylamino-6-(2-methylprop-1-enyl)benzonitrile (Example 129a) (1.69 g, 6.73 mmol) in EtOH (29.0 mL), under a nitrogen atmosphere, an aqueous solution of NaOH (2.0M, 6.73 mL, 13.45 mmol) was added at room temperature. The obtained mixture was heated at reflux for 4 h, cooled to room temperature and neutralized with 10% AcOH (pH ~ 6). The neutralized mixture was kept in an ice bath for 30 min. The obtained precipitate was filtered, washed with cold water and dried, to give 1.49 g (88%) of the title compound as a white solid. The product was purified by crystallization from ethanol. m.p.: > 260 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ10.91 (broad s, 1H), 8.30 (broad s, 1H), 7.46 (t, J = 8.00 Hz, 1H), 6.96 (broad s, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 7.2 Hz, 1H), 6.46 (broad s, 1H), 1.89-1.87 (m, 3H), 1.65-1.63 (m, 3H). ^{13}C-NMR (100MHz, DMSO-d_6) δ162.1, 143.1, 138.8, 137.6, 132.9, 124.4, 123.3, 115.7, 110.7, 25.8 and 19.2. MS 252 (MH^+).

Example 129a: 2-Sulfamoylamino-6-(2-methylprop-1-enyl)benzonitrile

A solution of 2-amino-6-(2-methylprop-1-enyl)benzonitrile (Example 129b) (1.24 g; 7.23 mmol) in N,N-dimethylacetamide (DMA) (20.0 mL), under a nitrogen atmosphere, was treated with sulfamoyl chloride (1.67 g; 14.45 mmol) at room temperature. The obtained mixture was stirred at room temperature for 2 h and the reaction was quenched with water (40 mL). The mixture was extracted with EtOAc (4 x 80 mL), the combined extract was washed with water (2 x 20 mL) and brine, and dried with $MgSO_4$. The filtrate was evaporated and the residue was purified by chromatography on silica gel using gradient (Hexanes/EtOAc 1:0 to 1:1), to give 1.69

g (93%) of the title compound as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ9.42 (broad s, 1H), 7.61 (t, J = 8.0 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.24 (broad s, 2H), 7.19 (d, J = 8.0 Hz, 1H), 6.35 (broad s, 1H), 1.92-1.95 (m, 3H), 1.76-1.79 (m, 3H).

Example 129b: 2-Amino-6-(2-methylprop-1-enyl)benzonitrile

Concentrated HCl (65.5 mL) was added slowly to a solution of 2-nitro-6-(2-methylprop-1-enyl)benzonitrile (Example 129c) (2.00 g; 9.89 mmol) in EtOH (120.2 mL) at room temperature. Then, the obtained mixture was treated with iron powder (5.52 g; 98.91 mmol), added in small portions at the same temperature. The mixture was stirred at room temperature for 15 min, and then heated at reflux for 30 min. The mixture was cooled to room temperature, EtOH was evaporated and the pH was adjusted to pH~10 with aqueous NaOH (2.0M). The basified mixture was extracted with EtOAc (4x100 mL) and the combined extract was dried with anhydrous $MgSO_4$. The filtrate was evaporated and the residue was purified by chromatography on silica gel using gradient hexanes to hexanes/EtOAc (8:2), to afford 1.32 g (77%) of the title compound as yellow oil. ^{1}H-NMR (400 MHz, DMSO-d_6) δ7.19-7.25 (m, 1H), 6.62 (d, J = 8.4 Hz, 1H), 6.46 (d, J = 7.2 Hz, 1H), 6.23 (broad s, 1H), 5.91 (broad s, 2H), 1.86-1.88 (m, 3H), 1,72-1.74 (m, 3H).

Example 129c: 2-Nitro-6-(2-methylprop-1-enyl)benzonitrile

A suspension of 2-cyano-3-nitrophenyl trifluoromethanesulfonate (Example 129d) (4.80 g; 16.21 mmol), 2-methy-1-propenylboronic acid (2.43 g; 24.32 mmol), tetrakis(tiphenylphosphine)palladium(0) (1.87 g; 1.62 mmol), sodium carbonate (1.89 g; 17.83 mmol) and water (33.0 mL) in dimethoxyethane (DME) (132.0 mL) was heated at reflux for 4 h, under a nitrogen atmosphere. The reaction mixture was cooled to room temperature and diluted with water (100 mL) and EtOAc (250 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined extract was washed with brine and dried with anhydrous $MgSO_4$. The filtrate was evaporated and the residue was purified by chromatography on silica gel using gradient hexanes to hexanes/EtOAc (7:3), to give 2.01 g (61%) of the title compound as a yellow solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ8.19-8.23 (m, 1H), 7.83-7.93 (m, 2H), 6.45 (broad s, 1H), 1.95-1.98 (m, 3H), 1.75-1.79 (m, 3H).

Example 129d: 2-Cyano-3-nitrophenyl trifluoromethanesulfonate

To a solution of 2-hydroxy-6-nitrobenzonitrile (Example 129e) (2.90 g, 17.67 mmol) in CH_2Cl_2 (90.0 mL), at 0 °C and under a nitrogen atmosphere, triethylamine (3.58 g, 4.93

mL, 35.34 mmol) was added, followed by drop wise addition of trifluoromethanesulfonic anhydride (7.48 g, 4.46 mL, 26.51 mmol). The reaction mixture was stirred at 0 °C for 30 min and the reaction was quenched with saturated aqueous Na_2CO_3 solution (100 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL). The combined extract was dried with anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by chromatography on silica gel using gradient hexanes to hexanes/EtOAc (6:4), to afford 5.23 g (100%) of the title compound as a brown solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.49-8.53 (m, 1H), 8.23-8.27 (m, 1H), 8.13-8.19 (m, 1H).

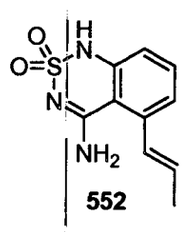
Example 129e: 2-Hydroxy-6-nitrobenzonitrile

2-Methoxy-6-nitrobenzonitrile (Example 129f) (10.73 g, 60.2 mmol) and pyridine hydrochloride (16.0 g, 138 mmol) were mixed together as solids under nitrogen, and then heated in a preheated oil bath at 200°C for 40 min. After cooling to room temperature, water (200 mL) and CH_2Cl_2 (200 mL) were added and stirred vigorously for 1 hour. Then, the precipitated product was collected by filtration and recrystallized from water, to give 8.2 g, (83%) of 2-hydroxy-6-nitrobenzonitrile as a brown solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ12.13 (broad s, 1H), 7.68-7.79 (m, 2H), 7.39-7.44 (m, 1H).

Example 129f: 2-Methoxy-6-nitrobenzonitrile

A solution of sodium methoxide, obtained by adding sodium (1.68 g, 73.1 mmol) to anhydrous MeOH (73 mL), was added to 2,6-dinitrobenzonitrile (13.20 g, 68.4 mmol) in dry MeOH (284 mL) under nitrogen at room temperature over 10 min. The reaction was refluxed for 1 hour, and then MeOH was removed under vacuum. Dichloromethane (400 mL) was added, and the insoluble solids were filtered out. The organic layer was washed with brine (100 mL), dried with $MgSO_4$, and removed under vacuum to give 11.45 g (94%) of 2-methoxy-6-nitrobenzonitrile, which was used without further purification. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.87-7.94 (m, 2H), 7.68-7.75 (m, 1H), 4.01 (s, 3H).

Example 130: 4-Amino-5-((*E*)-prop-1-enyl)-1H-benzo[c][1,2,3]thiadiazine-2,2-dioxide



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To a stirred solution of (*E*)-2-sulfamoylamino-6-(prop-1-enyl)benzonitrile (Example 130a) (0.82 g, 3.45 mmol) in EtOH (15.0 mL), under a nitrogen atmosphere, an aqueous solution of NaOH (2.0 M, 3.45 mL, 6.90 mmol) was added at room temperature. The obtained mixture was heated at reflux for 4 h. The mixture was cooled to room temperature and neutralized (pH ~ 6) with 10% AcOH. The neutralized mixture was kept in an ice bath for 30 min. The obtained precipitate was filtered, washed with water and dried to afford 0.70 g (86%) of the title compound. The product was purified by crystallization from ethanol. m.p.: > 260 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ10.90 (broad s, 1H), 8.32 (broad s, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.11 (d, J = 7.6 Hz, 1H), 6.95 (broad s, 1H), 6.91 (d, J = 7.2 Hz, 1H), 6.75 (dd, J = 15.6 Hz, J = 1.2 Hz, 1H), 6.23 (dq, J = 15.6 Hz, J = 6.8 Hz, 1H), 1.88 (dd, J = 6.8 Hz, J = 1.6 Hz, 3H). ^{13}C-NMR (100MHz, DMSO-d_6) δ162.2, 142.9, 138.3, 133.2, 131.2, 128.8, 121.7, 115.8, 110.4, and 18.7. MS 238 (MH^+).

Example 130a: (*E*)-2-Sulfamoylamino-6-(prop-1-enyl)benzonitrile

A solution of (*E*)-2-amino-6-(prop-1-enyl)benzonitrile (Example 130b) (0.60 g, 3.82 mmol) in N,N-dimethylacetamide (DMA) (15.5 mL), under a nitrogen atmosphere, was treated with sulfamoyl chloride (0.88 g, 7.63 mmol) at room temperature. The obtained mixture was stirred at room temperature for 2 h and the reaction was quenched with water (20 mL). The mixture was extracted with EtOAc (4 x 80 mL), the combined extract was washed with water (2 x 20 mL) and brine, and dried with $MgSO_4$. The filtrate was evaporated and the residue was purified by chromatography on silica gel using gradient hexanes to hexanes/EtOAc (1:1) to give 0.83 g (92%) of the title compound as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ9.39 (broad s, 1H), 7.48-7.60 (m, 2H), 7.38-7.43 (m, 1H), 7.21 (broad s, 2H), 6.51-6.65 (m, 2H), 1.88-1.94 (m, 3H).

Example 130b: (*E*)-2-Amino-6-(prop-1-enyl)benzonitrile

Concentrated HCl (34.5 mL) was added slowly to a solution of (*E*)-2-nitro-6-(prop-1-enyl)benzonitrile (Example 2c) (0.98 g, 5.21 mmol) in EtOH (63.5 mL) at room temperature. Then, the obtained mixture was treated with iron powder (2.91 g, 52.08 mmol), added in small portions at the same temperature. The mixture was stirred at room temperature for 15 min. and then heated at reflux for 30 min. The mixture was cooled to room temperature, EtOH was evaporated and the pH was adjusted to pH~10 with aqueous solution of NaOH (2.0M). The basified mixture was extracted with EtOAc (4x100 mL) and the combined extract

was dried with anhydrous $MgSO_4$. The filtrate was evaporated and the residue was purified by chromatography on silica gel using gradient hexanes to hexanes/EtOAc (8:2), to afford 0.67 g (81%) of the title compound as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ7.16-7.23 (m, 1H), 6.78 (d, J = 7.2 Hz, 1H), 6.59-6.64 (m, 1H), 6.35-6.53 (m, 2H), 5.92 (broad s, 2H), 1.83-1.89 (m, 3H).

Example 130c: (*E*)-2-Nitro-6-(prop-1-enyl)benzonitrile

A suspension of 2-iodo-6-nitrobenzonitrile (Example 130d) (1.52 g, 5.53 mmol), tetrakis(tiphenylphosphine)palladium(0) (0.64 g, 0.55 mmol), *trans*-1-propen-1-ylboronic acid (0.95 g, 11.06 mmol), sodium carbonate (0.65 g, 6.08 mmol) and water (10.0 mL) in dimethoxyethane (DME) (40.0 mL) was heated at reflux for 15 h, under a nitrogen atmosphere. The reaction mixture was cooled to room temperature and diluted with water (20 mL) and EtOAc (100 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 50 mL).The combined extract was washed with brine and dried with anhydrous $MgSO_4$. The filtrate was evaporated and the residue was purified by chromatography on silica gel using gradient hexanes to hexanes/EtOAc (7:3), to give 0.98 g (94%) of the title compound as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ8.16-8.24 (m, 2H), 7.83-7.89 (m, 1H), 6.71-6.84 (m, 2H), 1.90-2.02 (m, 3H).

Example 130d: 2-Iodo-6-nitrobenzonitrile

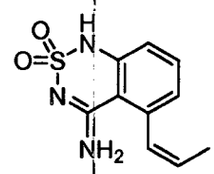
2-Amino-6-nitrobenzonitrile (Example 130e) (4.32 g, 26.5 mmol) was added in small portions to a suspension of sodium nitrite (2.19 g, 31.7 mmol) in concentrated H_2SO_4 (43 mL) and acetic acid (43 mL) at 45°C. The reaction was heated at 45°C for 1 h and then added in small portions to a solution of potassium iodide (7.47 g, 45.0 mmol) in H_2SO_4 (1 M, 43 mL). After stirring at room temperature for 1.5 h, iced water was added to the reaction and the precipitated product was collected by filtration. The product was purified by chromatography on silica gel eluting with CH_2Cl_2, to give 2-iodo-6-nitrobenzonitrile (3.86 g, 53%) as a yellow solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ8.46-8.52 (m, 1H), 8.34-8.38 (m, 1H), 7.66-7.71 (m, 1H).

Example 130e: 2-Amino-6-nitrobenzonitrile

Concentrated HCl (39 mL) was added to a solution of 2,6-dinitrobenzonitrile (11.3 g, 58.5 mmol) in MeOH (235 mL) and 1,4-dioxane (145 mL) at 70°C. External heating was removed, and iron powder (11.44 g, 205 mmol) was added slowly in portions at a rate which maintained a temperature of 70°C. After the addition of iron was complete, the reaction was

heated at reflux for a further 30 min, then cooled to room temperature and poured into EtOAc (400 mL) and water (400 mL). The solids were filtered out and extracted twice with boiling EtOAc (300 mL). The combined organic extract was dried with $MgSO_4$, filtered and evaporated to give 2-amino-6-nitrobenzonitrile (6.5 g, 68%) as a red solid, which was used without further purification. ^{1}H-NMR (400 MHz, DMSO-d_6) δ7.48-7.54 (m, 1H), 7.41-7.45 (m, 1H), 7.18-7.22 (m, 1H), 6.74 (broad s, 2H).

Example 131: 4-Amino-5-((*Z*)-prop-1-enyl)-1H-benzo[c][1,2,3]thiadiazine-2,2-dioxide



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Prepared as in Example 129 from (*Z*)-2-sulfamoylamino-6-(prop-1-enyl)benzonitrile (Example 131a) to provide 4-Amino-5-((*Z*)-prop-1-enyl)-1H-benzo[c][1,2,3]thiadiazine-2,2-dioxide (28.2 mg, 91%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.92 (broad s, 1H), 8.30 (broad s, 1H), 7.44-7.51 (m, 1H), 6.90-7.00 (m, 2H), 6.83-6.89 (m, 1H), 6.65-6.73 (m, 1H), 5.88-5.99 (m, 1H), 1.60-1.66 (m, 3H).

Example 131a: (*Z*)-2-Sulfamoylamino-6-(prop-1-enyl)benzonitrile

Prepared as in Example 129a from (*Z*)-2-amino-6-(prop-1-enyl)benzonitrile (Example 3b) in amount of 32.7 mg (92%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.45 (broad s, 1H), 7.59-7.65 (m, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.18-7.28 (m, 3H), 6.50-6.57 (m, 1H), 5.99-6.09 (m, 1H), 1.74-1.79 (m, 3H).

Example 131b: (*Z*)-2-Amino-6-(prop-1-enyl)benzonitrile

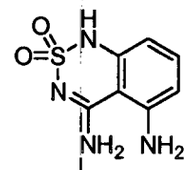
Concentrated HCl (1.54 mL) was added to a suspension of (Z)-2-nitro-6-(prop-1-enyl)benzonitrile (Example 3c) (0.35 g, 1.86 mmol) in MeOH (30 mL) and 1,4-dioxane (15 mL) at room temperature, followed by portion wise addition of iron powder (0.73 g, 13.0 mmol). The obtained mixture was heated at refluxed for 2.5 h, cooled to 0°C and the pH was adjusted to pH~10 with aqueous 50% solution of NaOH. The mixture was extracted with EtOAc (3 x 50 mL), the combined extract was dried with $MgSO_4$, filtered and concentrated. The residue was purified by chromatography on silica gel eluting with gradient 0% to 100% DCM in hexanes, to give 0.24 g (80%) of (Z)-2-amino-6-(prop-1-enyl)benzonitrile as a yellow oil. ^{1}H NMR (400

MHz, DMSO-d_6) δ 7.24-7.30 (m, 1H), 6.68 (d, J = 8.4 Hz, 1H), 6.55 (d, J = 7.2 Hz, 1H), 6.42-6.48 (m, 1H), 5.98 (broad s, 2H), 5.89-5.97 (m, 1H), 1.74-1.78 (m, 3H). MS 159 (MH^+).

Example 131c: (*Z*)-2-Nitro-6-(prop-1-enyl)benzonitrile

Prepared as in Example 129c from 2-cyano-3-nitrophenyl trifluoromethanesulfonate Example (129d) and *cis*-1-propen-1-ylboronic acid. The crude product was purified by chromatography on silica gel eluting with solvent gradient 0% to 100% DCM in hexanes, to give 0.80 g (97%) of (Z)-2-nitro-6-(prop-1-enyl)benzonitrile (97%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25-8.30 (m, 1H), 7.90-7.98 (m, 2H), 6.25-6.70 (m, 1H), 6.17-6.28 (m, 1H), 1.78-1.82 (m, 3H).

Example 132: 4,5-Diamino-1H-benzo[c][1,2,3]thiadiazine-2,2-dioxide



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Prepared as in Example 129 from 2-sulfamoylamino-6-aminobenzonitrile (Example 132a) in amount of 95.3 mg (84%) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 (broad s, 1H), 7.80 (broad s, 2H), 7.09-7.16 (t, J = 8.0 Hz, 1H), 6.42 (d, J = 8.4 Hz, 1H), 6.22 (d, J = 8.4 Hz, 1H), 5.79 (broad s, 2H).

Example 132a: 2-Sulfamoylamino-6-aminobenzonitrile

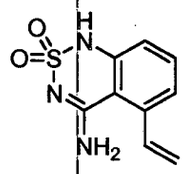
Prepared as in Example 129a from 2,6-diaminobenzonitrile (Example 132b) in amount of 129.4 mg (60%) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.00 (broad s, 1H), 7.18 (t, J = 8.0 Hz, 1H), 7.08 (broad s, 2H), 6.62-6.67 (m, 1H), 6.49-6.54 (m, 1H), 5.95 (broad s, 2H).

Example 132b: 2,6-Diamonobenzonitrile

Concentrated HCl (44.3 mL) was added to a solution of 2,6-dinitrobenzonitrile (12.9 g, 67.1 mmol) in MeOH (269 mL) and 1,4-dioxane (166 mL) at 70°C. External heating was removed, and iron powder (13.1 g, 235 mmol) was added slowly in portions at a rate which maintained a temperature of 70°C. After the addition of iron was complete, the reaction was heated at reflux for a further 30 min, then cooled to room temperature and poured into EtOAc (400 mL) and water (400 mL). The solids were filtered out and extracted twice with boiling EtOAc (300 mL). The organic layers were combined, dried with $MgSO_4$, filtered and

concentrated. The crude product was purified by reverse phase chromatography (0-100 % CH_3CN in H_2O) to give the title compound (1.0 g, 11%), which was used without further purification. MS 134 (MH^+).

Example 133: 4-Amino-5-vinyl-1H-benzo[c][1,2,3]thiadiazine-2,2-dioxide



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Prepared as in Example 129 from 2-sulfamoylamino-6-vinylbenzonitrile (Example 133a) in amount of 30.0 mg (48%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.95 (broad s, 1H), 8.33 (broad s, 1H), 7.48 (t, J = 8.0 Hz, 1H), 7.18 (d, J = 7.6 Hz, 1H), 7.09 (dd, J = 17.6, 10.8 Hz, 1H), 6.90-6.99 (m, 2H), 5.78 (dd, J = 17.6, 1.6 Hz, 1H), 5.47 (dd, J = 11.2, 1.2 Hz, 1H).

Example 133a: 2-Sulfamoylamino-6-vinylbenzonitrile

Prepared as in Example 129a from 2-amino-6-vinylbenzonitrile (Example 133b) in amount of 63.0 mg (81%), as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.46 (broad s, 1H), 7.59-7.67 (m, 2H), 7.46-7.52 (m, 1H), 7.23 (broad s, 2H), 6.93 (dd, J = 17.2, 10.8 Hz, 1H), 6.08 (d, J = 17.2 Hz, 1H), 5.59 (d, J = 11.2 Hz, 1H).

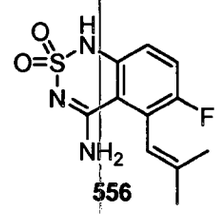
Example 133b: 2-Amino-6-vinylbenzonitrile

Prepared as in Example 129b from 2-nitro-6-vinylbenzonitrile (Example 133c) in amount of 123.9 mg (71%), as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.25 (t, J = 8.0 Hz, 1H), 6.87 (d, J = 7.2 Hz, 1H), 6.80 (dd, J = 17.2, 11.6 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 6.00 (broad s, 2H), 5.92 (d, J = 17.2 Hz, 1H), 5.44 (d, J = 10.8 Hz, 1H).

Example 133c: 2-Nitro-6-vinylbenzonitrile

Prepared as in Example 129c from 2-cyano-3-nitrophenyl trifluoromethanesulfonate Example (129d) in amount of 0.61 g (86%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26-8.34 (m, 2H), 7.90-7.98 (m, 1H), 7.09 (dd, J = 17.6, 11.2 Hz, 1H), 6.26 (d, J = 17.6 Hz, 1H), 5.80 (d, J = 11.6 Hz, 1H).

Example 134: 4-Amino-6-fluoro-5-(2-methylprop-1-enyl)-1H-benzo[c][1,2,3]thiadiazine-2,2-dioxide



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Prepared as in Example 129 from 3-fluoro-2-(2-methylprop-1-enyl)-6-sulfamoylaminobenzonitrile (Example 134a) in amount of 125.0 mg (86%) as a white solid. m.p.:>250°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.51 (s, 3H), 1.90 (s, 3H), 6.27 (s, 1H), 7.00 (m, 1H), 7.10 (broad s, 1H), 7.45 (m, 1H), 8.35 (broad s, 1H), 10.95 (broad s, 1H). MS 270 (MH^+).

Example 134a: 3-Fluoro-2-(2-methylprop-1-enyl)-6-sulfamoylaminobenzonitrile

Prepared as in Example 129a from 6-amino-3-fluoro-2-(2-methylprop-1-enyl)benzonitrile (Example 134b) in amount of 156.0 mg (88%), as a white solid. MS 270 (MH^+).

Example 134b: 6-Amino-3-fluoro-2-(2-methylprop-1-enyl)benzonitrile

Prepared as in Example 129b from 3-fluoro-2-(2-methylprop-1-enyl)-6-nitrobenzonitrile (Example 134c) in amount of 0.38 g, (84%) as a white solid. MS 191 (MH^+).

Example 134c: 3-Fluoro-2-(2-methylprop-1-enyl)-6-nitrobenzonitrile

2-Bromo-3-fluoro-6-nitrobenzonitrile (Example 134d) (0.62 g, 2.53 mmol), 2-methylprop-1-enylboronic acid (0.50 g, 5.05 mmol), palladium(II) acetate (0.023 g, 0.102 mmol), K_3PO_4 (1.61 g, 7.58 mmol), and dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (0.083 g, 0.202 mmol) were suspended in anhydrous THF (16 mL) under nitrogen and heated at 70°C for 4.5 h. Solvent was removed under vacuum, and the product was purified by chromatography on silica gel eluting with gradient 0% to 100% ethyl acetate in hexanes, to give 3-fluoro-2-(2-methylprop-1-enyl)-6-nitrobenzonitrile 0.44 g (78%) as a yellow solid. MS 221 (MH^+).

Example 134d: 2-Bromo-3-fluoro-6-nitrobenzonitrile

Triethylamine (2.53 mL, 18.2 mmol) was added to a suspension of 2-bromo-3-fluoro-6-nitrobenzamide (Example 6e) (1.60 g, 6.08 mmol) in $POCl_3$ (32 mL), and the mixture was heated at 75°C for 1.5 h. The mixture was carefully poured into a mixture of ice and water (400 mL) and extracted twice with CH_2Cl_2. The combined extract was dried $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by chromatography on silica gel eluting

with solvent gradient 0% to 100% EtOAc in hexanes, to give 2-bromo-3-fluoro-6-nitrobenzonitrile 0.95 g, (64%) as a yellow solid.

Example 134e: 2-Bromo-3-fluoro-6-nitrobenzamide

2-Bromo-3-fluoro-6-nitrobenzoic acid (Example 134f) (24.83 g, 94.0) mmol, (mixture of two regioisomers) was dissolved in anhydrous THF (200 mL) under a nitrogen atmosphere at room temperature. Anhydrous DMF (0.75 mL) was added and the obtained mixture was cooled to 0°C. Oxalyl chloride (12.3 mL, 141 mmol) was slowly added and the reaction mixture was stirred at 0°C for 10 min, and at room temperature for a further 2 h. The reaction was evaporated to dryness, suspended in anhydrous THF (100 mL) and added slowly to concentrated ammonium hydroxide (350 mL) at 0°C. After stirring for 45 minutes at 0°C the mixture was extracted with CH_2Cl_2 (5 x 100 mL), and the organic extractions were then discarded. At this point the desired regioisomer existed as an insoluble precipitate in the aqueous layer, which was collected by filtration to give 10.3 g (42%) of 2-bromo-3-fluoro-6-nitrobenzamide which was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (dd, J = 8.8, 4.4 Hz, 1H), 8.10 (broad s, 1H), 7.95 (broad s, 1H), 7.66 (dd, J = 9.6, 7.6 Hz, 1H).

Example 134f: 2-Bromo-3-fluoro-6-nitrobenzoic acid

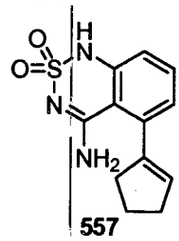
In a 1L, three necked flask fitted with a dropping funnel and a thermometer were charged 2-bromo-3-fluorobenzoic acid (Example 134g) (28.23 g, 0.13 mol) and concentrated H_2SO_4 (200 mL). After cooling to 0 °C, HNO_3 (70%, 16.0 mL) was added dropwise over 30 min, keeping the temperature between 0 to 10 °C. After 1 h, the reaction mixture was poured into the crushed ice keeping the temperature below 20 °C. The mixture was extracted with EtOAc (2 x 200 mL), the combined extract was washed with brine and dried with $MgSO_4$. The filtrate was evaporated to give 27.27 g (77%) of a mixture of 2-bromo-3-fluoro-6-nitrobenzoic acid and 2-bromo-3-fluoro-5-nitrobenzoic acid (1:0.4) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (dd, J = 9.6, 4.8 Hz, 1H), 7.21 (dd, J = 10.0, 8.0 Hz, 1H).

Example 134g : 2-Bromo-3-fluorobenzoic acid

In a 1L, three necked flask fitted with a dropping funnel and thermometer, were charged 2-amino-3-fluorobenzoic acid (20.0 g, 0.13 mol) and acetonitrile (160 mL). After cooling to 0 °C, HBr (47%, 160 mL) was added drop wise over 10 min. To the resulting solution a solution of $NaNO_2$ (10.0 g, 0.14 mol) in water (20.0 mL) was added drop wise over 1 h. After

addition, the reaction mixture was stirred at 0 °C for 5 min, and cupper(I) bromide (22.0 g, 0.15 mol) was added portionwise over 30 min. Stirring was continued at 70 °C ina an oil bath for 1 h. After cooling to 0 °C, 700 mL of water was added and the precipitate was filtered, washed with cold water and dried under vacuum to give 28.23 g (100%) of the title compound as a white solid. The crude product was used in the next step without purification.

Example 135: 4-Amino-5-(cyclopenten-1-yl)-1H-benzo[c][1,2,3]thiadiazine-2,2-dioxide



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Prepared as in Example 129 from 2-sulfamoylamino-6-(cyclopenten-1-yl)benzonitrile (Example 135a) in amount of 36.0 mg (33%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.97 (m, 2H), 2.48 (m, 2H), 2.58 (m, 2H), 5.94 (m, 1H), 6.83 (broad s, 1H), 6.92 (m, 2H), 7.46 (m, 1H), 8.25 (broad s, 1H), 11.02 (broad s, 1H). MS 264 (MH^+).

Example 135a: 2-Sulfamoylamino-6-(cyclopenten-1-yl)benzonitrile

Prepared as in Example 129a from 2-amino-6-(cyclopenten-1-yl)benzonitrile (Example 135b) in amount of 156.0 mg (88%), as a white solid.

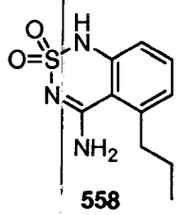
Example 135b: 2-Amino-6-(cyclopenten-1-yl)benzonitrile

Prepared as in Example 129b from 2-(cyclopenten-1-yl)-6-nitrobenzonitrile (Example 135c) in amount of 0.44 g, (84%) as a white solid. MS 185 (MH^+).

Example 135c: 2-(Cyclopenten-1-yl)-6-nitrobenzonitrile

Prepared as in Example 129c from 2-cyano-3-nitrophenyl trifluoromethanesulfonate (Example 129d) in amount of 0.62 g (84%) as a white solid.

Example 136: 4-Amino-5-*n*-propyl-1H-benzo[c][1,2,3]thiadiazine-2,2-dioxide



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Prepared as in Example 129 from 2-sulfamoylamino-6-*n*-propylbenzonitrile (Example 136a) in amount of 144.3 mg (66%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6)

δ 10.73 (broad s, 1H), 8.14 (broad s, 1H), 7.44 (broad s, 1H), 7.38 (t, J = 8.0 Hz, 1H), 6.97 (d, J = 6.8 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 2.97 (t, J = 7.6 Hz, 2H), 1.51 (hex, J = 7.6 Hz, 2H), 0.81 (t, J = 7.6 Hz, 3H).

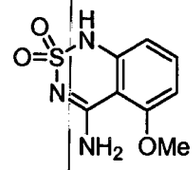
Example 136a: 2-Sulfamoylamino-6-*n*-propylbenzonitrile

Prepared as in Example 129a from 2-amino-6-*n*-propylbenzonitrile (Example 136b) in amount of 238.4 mg (91%), as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.37 (broad s, 1H), 7.55 (t, J = 8.4 Hz, 1H), 7.39- 7.44 (m, 1H), 7.17-7.23 (m, 3H), 2.71 (t, J = 8.0 Hz, 2H), 1.60 (hex, J = 7.6 Hz, 2H), 0.90 (t, J = 7.6 Hz, 3H).

Example 136b: 2-Amino-6-*n*-propylbenzonitrile

(Z)-2-Amino-6-(prop-1-enyl)benzonitrile (Example 131b) (0.45 g, 2.82 mmol) and 10% Pd/C (0.17 g) were stirred in EtOH (15 mL) under a hydrogen atmosphere for 4 h. The catalyst was filtered out, and the organic layer was concentrated under vacuum to give 0.43 g (96%) of 2-amino-6-*n*-propylbenzonitrile as yellow oil, which was used without further purification. MS 161 (MH^+).

Example 137: 4-Amino-5-methoxy-1H-benzo[c][1,2,3]thiadiazine-2,2-dioxide



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Prepared as in Example 129 from 2-sulfamoylamino-6-methoxybenzonitrile (Example 137a) in amount of 138.9 mg (93%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (broad s, 1H), 8.28 (broad s, 1H), 8.03 (broad s, 1H), 7.44 (t, J = 8.0 Hz, 1H), 6.70 (d, J = 8.4 Hz, 1H), 6.58 (d, J = 8.0 Hz, 1H), 3.89 (s, 3H).

Example 137a: 2-Sulfamoylamino-6-methoxybenzonitrile

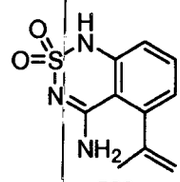
Prepared as in Example 129a from 2-amino-6-methoxybenzonitrile (Example 137b) in amount of 175.9 mg (84%), as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.44 (broad s, 1H), 7.56 (t, J = 8.4 Hz, 1H), 7.25 (broad s, 2H), 7.14 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 8.8 Hz, 1H), 3.87 (s, 3H).

Example 137b: 2-Amino-6-methoxybenzonitrile

A solution of 2-methoxy-6-nitrobenzonitrile (1.01 g, 5.69 mmol), cyclohexene (2.84 g, 3.51 mL, 34.58 mmol) and 10% Pd/C (0.58 g) in EtOH (25 mL) was refluxed for 1.5 h.

The mixture was cooled to room temperature, filtered and evaporated, to afford the title compound 0.83 g (98%). The crude product was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.17 (t, J = 8.0 Hz, 1H), 6.31- 6.35 (m, 1H), 6.17-6.21 (m, 1H), 5.97 (broad s, 2H), 3.76 (s, 3H).

Example 138: 4-Amino-5-(prop-1-en-2-yl)-1H-benzo[c][1,2,3]thiadiazine-2,2-dioxide



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Prepared as in Example 129 from 2-sulfamoylamino-6-(prop-1-en-2-yl)benzonitrile (Example 138a) in amount of 63.8 mg (82%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (broad s, 1H), 8.32 (broad s, 1H), 7.44- 7.52 (m, 1H), 6.94-7.00 (m, 1H), 6.84-6.89 (m, 1H), 6.82 (broad s, 1H), 5.16-5.19 (m, 1H), 5.31-5.35 (m, 1H), 2.00 (s, 3H).

Example 138a: 2-Sulfamoylamino-6-(prop-1-en-2-yl)benzonitrile

Prepared as in Example 129a from 2-amino-6-(prop-1-en-2-yl)benzonitrile (Example 138b) in amount of 80.5 mg (100%), as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.40 (broad s, 1H), 7.58-7.64 (m, 1H), 7.48-7.52 (m, 1H), 7.25 (broad s, 2H), 7.18-7.24 (m, 1H), 5.34-5.40 (m, 1H), 5.10-5.14 (m, 1H), 2.10 (s, 3H).

Example 138b: 2-Amino-6-(prop-1-en-2-yl)benzonitrile

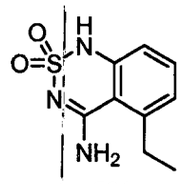
Prepared as in Example 129b from 2-nitro-6-(prop-1-en-2-yl)benzonitrile (Example 138c) in amount of 303.4 mg (83%), as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.18-7.25 (m, 1H), 6.67-6.72 (m, 1H), 6.47-6.51 (m, 1H), 5.97 (broad s, 2H), 5.24-5.27 (m, 1H), 5.07-5.10 (m, 1H), 2.03-2.06 (m, 3H)

Example 138c: 2-Nitro-6-(prop-1-en-2-yl)benzonitrile

A suspension of 2-cyano-3-nitrophenyl trifluoromethanesulfonate (Example 129d) (0.93 g, 3.15 mmol), potassium trifluoro(prop-1-en-2-yl)borate (0.70 g, 4.73 mmol), dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium(II) (0.26 g, 0.32 mmol), cesium carbonate (3.08 g, 9.45 mmol) and water (5.6 mL) in THF (56 mL) was heated at reflux for 25 min, under a nitrogen atmosphere. The reaction mixture was cooled to room temperature and diluted with water (100 mL) and EtOAc (100 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 100 mL).The combined extract was washed with

diluted HCl (1.5M), brine and dried with anhydrous $MgSO_4$. The filtrate was evaporated and the residue was purified by chromatography on silica gel using gradient hexanes to hexanes/EtOAc (7:3), to give 0.30 g (49%) of the title compound as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24-8.29 (m, 1H), 7.86-7.95 (m, 2H), 5.47-5.52 (m, 1H), 5.20-5.23 (m, 1H), 2.12-2.15 (m, 3H).

Example 139: 4-Amino-5-ethyl-1H-benzo[c][1,2,3]thiadiazine-2,2-dioxide



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Prepared as in Example 129 from 2-sulfamoylamino-6-vinylbenzonitrile (Example 139a) in amount of 84.2 mg (80%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.74 (broad s, 1H), 8.16 (broad s, 1H), 7.24-7.52 (m, 2H), 6.99 (d, J = 7.2 Hz, 1H), 6.84-6.88 (m, 1H), 3.00 (q, J = 7.6 Hz, 2H), 1.12 (t, J = 7.6 Hz, 3H).

Example 139a: 2-Sulfamoylamino-6-vinylbenzonitrile

Prepared as in Example 129a from 2-amino-6-ethylbenzonitrile (Example 139b) in amount of 280.3 mg (98%), as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (broad s, 1H), 7.52-7.60 (t, J = 8.4 Hz, 1H), 7.38-7.43 (m, 1H), 7.19 7.24 (m, 1H), 7.19 (broad s, 2H), 2.75 (q, J = 8.0, 2H), 1.18 (t, J = 7.6 Hz, 3H).

Example 139b: 2-Amino-6-ethylbenzonitrile

Prepared as in Example 129b from 2-ethyl-6-nitrobenzonitrile (Example 139c) in amount of 0.46 g (74%), as a orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.18 (t, J = 8.0 Hz, 1H), 6.59 (d, J = 8.0 Hz, 1H), 6.47 (d, J = 7.2 Hz, 1H), 5.89 (broad s, 2H), 2.60 (q, J = 7.6 Hz, 2H), 1.15 (t, J = 7.6 Hz, 3H).

Example 139c: 2-Ethyl-6-nitrobenzonitrile

A suspension of 2 ethyl-6-nitroaniline (Example 139d) (1.96 g, 11.80 mmol) in a solution of HCl (3.0M, 24.5 mL) was stirred at room temperature for 20 min. After cooling to 0-5 °C, a solution of $NaNO_2$ (1.63 g, 23.6 mmol) in water (12.25 mL) was added over a period of 10 min. The obtained mixture was stirred at 0-5 °C for 30 min, and the obtained homogeneous solution was transferred to a solution of CuCN (2.63 g, 29.5 mmol) and KCN (5.06 g, 77.8 mmol) in water (60 mL) and EtOH (31.0 mL). The resulting mixture was stirred vigorously at

room temperature for 30 min, and then heated at 70 °C for another 30 min to complete the reaction. The cold mixture was filtered and extracted with EtOAc (3 x 100 mL). The combined extract was washed with NaOH (0.5M) and brine, and dried with anhydrous $MgSO_4$. The filtrate was evaporated and the residue was purified by chromatography on silica gel eluting with 30% EtOAc in hexanes, to afford 0.66 g (33%) of the title compound as an orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18-8.24 (m, 1H), 7.85-7.97 (m, 2H), 2.93 (q, J = 7.2 Hz, 2H), 1.24 (t, J = 7.2 Hz, 3H).

Example 139d: 2 Ethyl-6-nitroaniline

A solution of N-(2-ethyl-6-nitrophenyl)actamide (Example 139e) (0.62 g, 2.98 mmol) in EtOH (21 mL) and concentrated HCl (13 mL) was refluxed for 24 h. EtOH was evaporated, the residue was diluted with water (10 mL) and the pH was adjusted to pH~8 with NaOH (2.0M aqueous solution). The neutralized solution was extracted with EtOAc (3 x 50 mL), the combined extract was washed with water and brine, and dried with anhydrous $MgSO_4$. The filtrate was evaporated and the residue was purified on HPLC to give 0.32 g (64%) of 2-ethyl-6-nitroaniline as an orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82-7.87 (m, 1H), 7.27-7.32 (m, 1H), 7.16 (broad s, 2H), 6.55-6.62 (m, 1H), 2.55 (q, J = 7.2 Hz, 2H), 1.13 (t, J = 7.2 Hz, 3H).

Example 139e: N-(2-ethyl-6-nitrophenyl)acetamide

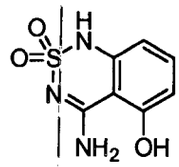
A solution of nitric acid (4.2 mL) in glacial acetic acid (5.2 mL)) was added drop wise to solution of N-(2-ethylphenyl)acetamide (Example 139f) (1.00 g, 6.13 mmol) in AcOH (22 mL) and acetic anhydride (18 mL) at 0 °C. The reaction was stirred at 0 °C for 1 h, diluted with water (50 mL) and neutralized with Na_2CO_3 (pH~8). The neutralized mixture was extracted with EtOAc (3 x 50 mL), the combined extract was washed with water and brine, and dried with anhydrous $MgSO_4$. The filtrate was evaporated and the residue was purified on HPLC to give 0.62 g (48%) of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.81 (broad s, 1H), 7.68-7.73 (m, 1H), 7.57-7.62 (m, 1H), 7.39 (t, J = 8.0 Hz, 1H), 2.64 (q, J = 8.0 Hz, 2H), 2.00 (s, 3H), 1.10 (t, J = 8.0 Hz, 3H).

Example 139f: N-(2-ethylphenyl)acetamide

2-Ethylaniline (9.70 g, 80.0 mmol) was added to a mixture of glacial AcOH (30 mL) and actic anhydride (20 mL), and the resulting mixture was refluxed at 120 °C for 3h. The reaction mixture was then cooled to room temperature and poured into a boiling mixture of water and EtOH (20 mL each). The mixture was stirred at rt for 1 h and then cooled (0-5 °C) overnight.

EtOH was evaporated and the remainder of the mixture was diluted with water (100 mL). The obtained mixture was neutralized with Na_2CO_3 and extracted with EtOAc. The combined extract was washed with brine, dried with anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by chromatography on silica gel eluting with 5% MeOH in CH_2Cl_2, to afford 5.50 g (42%) of the title compound as a pink solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (broad s, 1H), 7.05-7.40 (m, 4H), 2.55 (q, J = 7.6 Hz, 2H), 2.02 (s, 3H), 1.09 (t, J = 7.6 Hz, 3H).

Example 140: 4-Amino-5-hydroxy-1H-benzo[c][1,2,3]thiadiazine-2,2-dioxide



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Prepared as in Example 129 from 2-sulfamoylamino-6-hydroxybenzonitrile (Example 140a) in amount of 50.6 mg (20%) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.00 (broad s, 1H), 9.24 (broad s, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.18 (broad s, 2H), 6.97 (d, J = 8.4 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H).

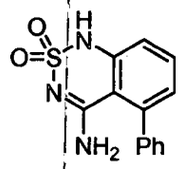
Example 140a: 2-Sulfamoylamino-6-hydroxybenzonitrile

Prepared as in Example 129a from 2-amino-6-hydroxybenzonitrile (Example 140b) in amount of 0.25 g (99%), as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.01 (broad s, 1H), 9.25 (broad s, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.18 (broad s, 2H), 6.95-6.99 (m, 1H), 6.69-6.74 (m, 1H).

Example 140b: 2-Amino-6-hydroxybenzonitrile

A solution of 2-methoxy-6-nitrobenzonitrile (Example 129f) (1.11 g, 6.76 mmol) in EtOH (120 mL) was hydrogenated over a catalytic amount of 10% Pd/C (0.15 g) at room temperature under hydrogen (1 atm). After 2 h, the mixture was filtered and the catalyst was washed with EtOAc (150 mL). The combined extract was evaporated, to give 1.11 g (100%) of the title compound as a brown solid. The crude product was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.39 (broad s, 1H), 7.00 (t, J = 8.0 Hz, 1H), 6.12-6.17 (m, 1H), 6.01-6.05 (m, 1H), 5.77 (broad s, 2H).

Example 141: 4-Amino-5-phenyl-1H-benzo[c][1,2,3]thiadiazine-2,2-dioxide



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Prepared as in Example 129 from 2-sulfamoylamino-6-phenylbenzonitrile (Example 141a) in amount of 114.7 mg (90%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.12 (broad s, 1H), 8.04 (broad s, 1H), 7.52-7.58 (m, 1H), 7.39-7.50 (m, 3H), 7.32-7.38 (m, 2H), 7.02-7.07 (m, 1H), 6.97-7.01 (m, 1H), 5.61 (broad s, 1H).

Example 141a: 2-Sulfamoylamino-6-phenybenzonitrile

Prepared as in Example 129a from 3-aminobiphenyl-2-carbonitrile (Example 141b) in amount of 142.3 mg (94%), as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.49 (broad s, 1H), 7.68-7.74 (m, 1H), 7.58-7.62 (m, 1H), 7.44-7.53 (m, 5H), 7.30-7.34 (m, 1H), 7.29 (broad s, 2H).

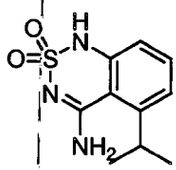
Example 141b: 3-Aminobiphenyl-2-carbonitrile

Prepared as in Example 129b from 3-nitrobiphenyl-2-carbonitrile (Example 141c) in amount of 117.0 mg (80%), as a white solid. MS 195 (MH^+).

Example 141c: 3-Nitrobiphenyl-2-carbonitrile

Prepared as in Example 129c from 2-cyano-3-nitrophenyl trifluoromethanesulfonate (Example 129d) and phenilboronic acid .

Example 142: 4-Amino-5-isopropyl-1H-benzo[c][1,2,3]thiadiazine-2,2-dioxide



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Prepared as in Example 129 from 2-sulfamoylamino-6-isopropylbenzonitrile (Example 142a) in amount of 53.7 mg (49%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.74 (broad s, 1H), 8.19 (broad s, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.15 (broad s, 1H), 7.07-7.13 (m, 1H), 6.83-6.88 (m, 1H), 3.71 (hep, J = 6.4 Hz, 1H), 1.18 (d, J = 6.8 Hz, 6H).

Example 142a: 2-Sulfamoylamino-6-isopropylbenzonitrile

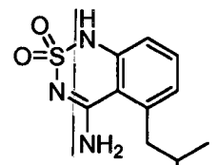
Prepared as in Example 129a from 2-amino-6-isopropylbenzonitrile (Example 142b) in amount of 112.0 mg (97%), as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.35

(broad s, 1H), 7.60 (t, J = 8.4 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 7.20 (broad s, 2H), 3.20 (hep, J = 6.8 Hz, 1H), 1.23 (d, J = 6.8 Hz, 6H).

Example 142b: 2-Amino-6-isopropylbenzonitrile

Prepared as in Example 136b from 2-Amino-6-(prop-1-en-2-yl)benzonitrile (Example 138b) in amount of 112.0 mg (97%), as a white solid. . ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.21 (t, J = 8.0 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1H), 6.52 (d, J = 7.2 Hz, 1H), 5.87 (broad s, 2H), 3.03 (hep, J = 6.8 Hz, 1H), 1.18 (d, J = 6.8 Hz, 6H).

Example 143: 4-Amino-5-isobutyl-1H-benzo[c][1,2,3]thiadiazine-2,2-dioxide



565

Prepared as in Example 129 from 2-sulfamoylamino-6-isobutylbenzonitrile (Example 143a) in amount of 32.5 mg (63%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.70 (broad s, 1H), 8.08 (broad s, 1H), 7.55 (broad s, 1H), 7.36 (t, J = 8.0 Hz, 1H), 6.89-6.94 (m, 1H), 6.84-6.88 (m, 1H), 2.87 (d, J = 6.8 Hz, 2H), 1.69-1.81 (m, 1H), 0.72 (d, J = 6.8 Hz, 6H).

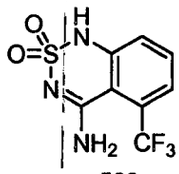
Example 143a: 2-Sulfamoylamino-6-isobutylbenzonitrile

Prepared as in Example 129a from 2-amino-6-isobutylbenzonitrile (Example 143b) in amount of 52.0 mg (91%), as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (broad s, 1H), 7.55 (t, J = 8.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.21 (broad s, 2H), 7.16 (d, J = 6.8 Hz, 1H), 2.62 (d, J = 7.6 Hz, 2H), 1.82-1.96 (m, 1H), 0.88 (d, J = 6.4 Hz, 6H).

Example 143b: 2-Amino-6-isobutylbenzonitrile

Prepared as in Example 136b from 2-Amino-6-(2-methylprop-1-enyl)benzonitrile (Example 129b) in amount of 76.4 mg (98%), as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.17 (t, J = 8.0 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1H), 6.42 (d, J = 7.6 Hz, 1H), 5.88 (broad s, 2H), 2.47 (d, J = 7.6 Hz, 2H), 1.78-1.92 (m, 1H), 0.86 (d, J = 6.4 Hz, 6H).

Example 144: 4-Amino-5-trifluoromethyl-1H-benzo[c][1,2,3]thiadiazine-2,2-dioxide



566

Prepared as in Example 129 from 2-sulfamoylamino-6-trifluoromethylbenzonitrile (Example 144a) in amount of 114.8 mg (96%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.41 (broad s, 1H), 7.64-7.72 (m, 1H), 7.50 (d, J = 7.2 Hz, 1H), 7.38-7.68 (broad s, 1H), 7.31 (d, J = 8.4 Hz, 1H), 3.10-3.60 (broad s, 1H).

Example 144a: 2-Sulfamoylamino-6-trifluoromethylbenzonitrile

Prepared as in Example 129a from 2-amino-6-trifluoromethylbenzonitrile (Example 144b) in amount of 138.5 mg (82%), as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (broad s, 1H), 7.84-7.92 (m, 2H), 7.69-7.76 (m, 1H), 7.42 (broad s, 2H).

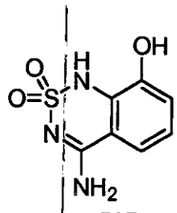
Example 144b: 2-Amino-6-trifluorobenzonitrile

2-(4-Methoxybenzylamino)-6-(trifluoromethyl)benzonitrile (Example 144c) (3.49 g, 11.4 mmol) was treated with trifluoroacetic acid (TFA) (35 mL) at 0°C, and then stirred at room temperature for 20 min. The TFA was removed under vacuum, and the residue was dissolved in CH_2Cl_2 (150 mL) and washed with 1M NaOH. The organic layer was dried with $MgSO_4$, filtered and removed under vacuum. The crude product was purified by chromatography on silica gel eluting with CH_2Cl_2 to give 2.12 g (99%) 2-amino-6-(trifluoromethyl)benzonitrile as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (m, 1H), 7.07 (m, 1H), 6.96 (m, 1H), 6.60 (br s, 2H).

Example 144c: 2-(4-Methoxybenzylamino)-6-(trifluoromethyl)benzonitrile

2-Fluoro-6-(trifluoromethyl)benzonitrile (2.44 g, 12.9 mmol) and 4-methoxybenzylamine (7.09 g, 51.7 mmol) were suspended in 1,4-dioxane (10 mL) and heated in a microwave at 180°C for 30 min. The 1,4-dioxane was removed under vacuum, and the crude material was purified by chromatography on silica gel eluting with CH_2Cl_2 to give 3.71 g of 2-(4-methoxybenzylamino)-6-(trifluoromethyl)benzonitrile (94%) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.71 (s, 3H), 4.42 (d, J = 5.6 Hz, 2H), 6.89 (m, 2H), 6.97 (m, 2H), 7.29 (m, 3H), 7.48 (m, 1H).

Example 145: 4-Amino-8-hydroxy-1H-benzo[c][1,2,3]thiadiazine-2,2-dioxide



567

Prepared as in Example 129 from 2-sulfamoylamino-3-hydroxybenzonitrile (Example 145a) in amount of 53.9 mg (66%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.14 (broad s, 2H), 8.04 (broad s, 2H), 7.31-7.39 (m, 1H), 6.97-7.03 (m, 1H), 6.88 (t, J = 7.6 Hz, 1H).

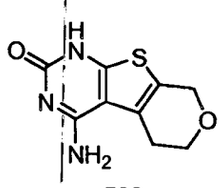
Example 145a: 2-Sulfamoylamino-3-hydroxybenzonitrile

Prepared as in Example 129a from 2-amino-3-hydroxybenzonitrile (Example 145b) in amount of 83.5 mg (39%), as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.23 (broad s, 1H), 8.66 (broad s, 1H), 7.14-7.27 (m, 3H), 6.71 (broad s, 2H).

Example 145b: 2-Amino-3-hydroxybenzonitrile

To a solution of 2-amino-3-methoxybenzonitrile (Example 127b) (0.98 g, 6.59 mmol) in CH_2Cl_2 (25.0 mL), a solution of BBr_3 in CH_2Cl_2 (1.0M, 19.8 mL, 19.77 mmol) was added drop wise at -78 °C under a nitrogen atmosphere. The obtained mixture was stirred at -78 °C for 30 min, and then at room temperature overnight. The reaction was quenched with water, basified with saturated aqueous $NaHCO_3$ (pH~8) and extracted with CH_2Cl_2. The combined extract was dried with $MgSO_4$, filtered and evaporated. The title compound was obtained in amount of 0.80 g (91%) as orange solid and was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86 (broad s, 1H), 6.82-6.87 (m, 2H), 6.46 (t, J = 8.0 Hz, 1H), 5.34 (broad s, 2H).

Example 146: 4-Amino-5,6-(5',7'-dihydro-4'H-[2',3'-c]pyrano)thieno[2,3-d]-pyrimidine-2(1H)-one



568

A solution of N-(3-cyano-5,7-dihydro-4H-thieno[2,3-c]pyran-2-ylcarbamoyl) benzamide (Example 146a) (500 mg, 1.53 mmol) and NaOH (2 N, 2.1 mL) in EtOH (40 mL) was stirred at 100 °C under nitrogen overnight. After cooling to room temperature, the clear reaction solution was filtered, and the filtrate was carefully neutralized with 10 % AcOH with vigorous stirring at 0 °C. The resultant precipitate was collected by filtration, washed with water and then 20 % EtOH in water to give the final product (280 mg, 82 %) as an off-white solid, which was dried under vacuum overnight. M.p.: > 260 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.83 (t, J = 5.6 Hz, 2H), 3.86 (t, J = 5.6 Hz, 2H), 4.58 (s, 2H), 7.23 (brs, 2H), 11.56 (brs, 1H). MS 224 (MH^+).

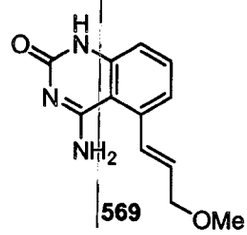
Example 146a: N-(3-cyano-5,7-dihydro-4H-thieno[2,3-c]pyran-2-ylcarbamoyl) benzamide

To a solution of 2-amino-5,7-dihydro-4H-thieno[2,3-c]pyran-3-carbonitrile (Example 146b) (400 mg, 2.22 mmol) in 1.4-dioxane (30 mL) was added benzoyl isocyanate (327 mg, 2.22 mmol). The reaction mixture was then stirred at room temperature under nitrogen overnight. The precipitate was collected by filtration, washed with 1.4-dioxane, and dried in the air to give the title compound (577 mg, 80 %) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.62 (t, J = 5.2 Hz, 2H), 3.87 (t, J = 5.2 Hz, 2H), 4.62 (s, 2H), 7.56-7.53 (m, 2H), 7.67-7.65 (m, 1H), 8.04-8.01 (m, 2H), 11.60 (brs, 1H), 12.13 (brs, 1H).

Example 146b: 2-amino-5,7-dihydro-4H-thieno[2,3-c]pyran-3-carbonitrile

To a mixture of dihydro-2H-pyran-4(3H)-one (820 mg, 8.19 mmol), malononitrile (541 mg, 8.19 mmol) and sulfur (263 mg, 8.19 mmol) in Ethanol (50 mL) was added triethylamine (1.14 mL, 8.19 mmol). The reaction mixture was then refluxed under nitrogen overnight. After cooling to room temperature, the precipitate was collected by filtration, washed with ethanol, and dried in the air to give the title compound (1.15 g, 78 %) as a light brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.43-2.40 (m, 2H), 3.80 (t, J = 5.6 Hz, 2H), 4.40 (t, J = 2.0 Hz, 2H), 7.09 (s, 2H). MS 181 (MH^+).

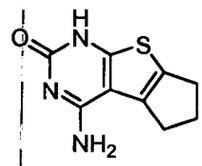
Example 147: (E)-4-amino-5-(3-methoxyprop-1-enyl)quinazolin-2(1H)-one



569

Prepared as in Example 146 from (*E*)-2-amino-6-(3-methoxyprop-1-enyl)benzonitrile (Example 97a) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.28 (s, 3H), 4.02 (dd, J = 6.0, 1.2 Hz, 2H), 6.13 (dt, J = 16.0, 3.8 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.80 (d, J = 16.0 Hz, 1H), 11.07 (s, 1H), 11.13 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 58.0, 72.9, 111.4, 115.5, 121.9, 129.9, 131.2, 134.7, 140.2, 142.7, 150.6, 164.1.

Example 148: 4-Amino-5,6-(2',3'-dihydro-1'H-cyclopenta[b])-thieno[2,3-d]pyrimidin-2(1H)-one-2,2-dioxide



570

Prepared as in Example 4 from N-(3-cyano-5,6-dihydro-4H-cyclopenta[b]thiophen-2-ylcarbamoyl)benzamide (Example 148a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.33 (m, 2H), 2.76 (t, 2H), 2.87 (t, 2H), 7.51 (br-s, 2H), 11.56 (br-s, 1H). MS 208 (MH^+).

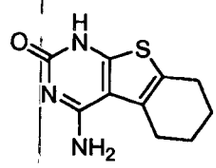
Example 148a : N-(3-cyano-5,6-dihydro-4H-cyclopenta[b]thiophen-2-ylcarbamoyl)benzamide

Prepared as in Example 4a from 2-amino-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carbonitrile (Example 148b). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.34 (m, 2H), 2.72 (t, 2H), 2.82 (t, 2H), 7.52 (t, 2H), 7.65 (t, 1H), 8.01 (d, 2H), 11.56 (s, 1H), 12.06 (s, 1H)

Example 148b : 2-amino-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carbonitrile

Prepared as in Example 5b from cyclopentanone. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.23 (m, 2H), 2.53 (m, 2H), 2.63 (m, 2H), 7.00 (s, 2H)^{1}H NMR (400 MHz, DMSO-d_6) δ 2.23 (m, 2H), 2.53 (t, 2H), 2.62 (t, 2H), 7.00 (s, 2H).

Example 149: 4-amino-5,6-(1',2',3',4'-tetrahydrobenzo[b])-thieno[2,3-d]pyrimidin-2(1H)-one-2,2-dioxide



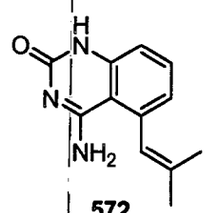
571

Prepared as in Example 4 from N-(3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-ylcarbamoyl)benzamide (Example 149a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.73 (m, 4H), 2.57 (t, 2H), 2.72 (t, 2H). MS 222 (MH^+).

Example 149a: N-(3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-ylcarbamoyl)benzamide

Prepared as in Example 4a from 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (Example 5b). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.75 (m, 4H), 2.51 (t, 2H), 2.60 (t, 2H), 7.54 (t, 2H), 7.66 (t, 1H), 8.02 (d, 2H), 11.57 (s, 1H), 12.06 (s, 1H).

Example 150: 4-Amino-5-(2-methylprop-1-enyl)quinazolin-2(1*H*)-one



572

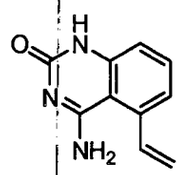
A suspension of *N*-(2-cyano-3-(2-methylprop-1-enyl) phenyl carbamoyl) benzamide (Example 150a) (0.133 g, 0.416 mmol) in EtOH (3 mL) was treated with a solution of NaOH (2 M, 0.416 mL, 0.832 mmol) at room temperature. The obtained mixture was heated at 90°C for 30 min, cooled to room temperature and neutralized with 10% AcOH. The precipitated product was collected by filtration to give 69.0 mg (77%) of 4-amino-5-(2-methylprop-1-enyl)quinazolin-2(1*H*)-one as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.60 (d, J = 1.2 Hz, 3H), 1.93 (d, J = 1.2 Hz, 3H), 6.58 (s, 1H), 6.67 (broad s, 1H), 6.73 (m, 1H), 7.05 (m, 1H), 7.48 (m, 1H), 7.93 (broad s, 1H), 10.72 (broad s, 1H). MS 216 (MH^+).

Example 150a: *N*-(2-cyano-3-(2-methylprop-1-enyl)phenylcarbamoyl)benzamide

Benzoyl isocyanate (88.1 mg, 0.60 mmol) was added to a solution of 2-amino-6-(2-methylprop-1-enyl)benzonitrile (Example 129b) (75.2 mg, 0.44 mmol) in anhydrous 1,4-

dioxane under nitrogen, and was stirred at room temperature for 12 h. The mixture was concentrated under vacuum, and purified by chromatography on silica gel eluting with solvent gradient 0% to 15% MeOH in CH_2Cl_2, to give 125.0 mg (86%) of *N*-(2-cyano-3-(2-methylprop-1-enyl)phenylcarbamoyl)benzamide as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.80 (d, J = 1.2 Hz, 3H), 1.95 (d, J = 1.2 Hz, 3H), 6.40 (s, 1H), 7.19 (m, 1H), 7.55 (m, 2H), 7.67 (m, 2H), 8.03 (m, 2H), 8.13 (m, 1H), 11.33 (s, 1H), 11.48 (s, 1H).

Example 151: 4-Amino-5-vinylquinazolin-2(1*H*)-one



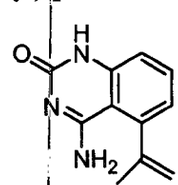
573

Prepared as in Example 150 from N-(2-cyano-3-vinylphenylcarbamoyl)benzamide (Example 151a) in amount of 20.0 mg (33%), as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.53 (m, 1H), 5.64 (m, 1H), 6.50 (broad s, 1H), 6.98 (m, 1H), 7.08 (m, 1H), 7.37 (m, 1H), 7.50 (m, 1H), 8.0 (broad s, 1H), 10.75 (broad s, 1H). MS 188 (MH^+).

Example 151a: N-(2-cyano-3-vinylphenylcarbamoyl)benzamide

Prepared as in Example 150a from 2-amino-6-vinylbenzonitrile (Example 133b) in amount of 99.3 mg (83%), as a white solid.

Example 152: 4-Amino-5-(prop-1-en-2-yl)quinazolin-2(1*H*)-one



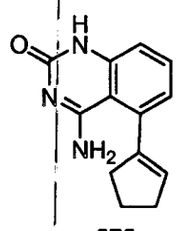
574

Prepared as in Example 150 from N-(2-Cyano-3-(prop-1-en-2-yl)phenylcarbamoyl)benzamide (Example 152a) in amount of 30.0 mg (47%), as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.07 (s, 3H), 5.14 (m, 1H), 5.43 (m, 1H), 6.67 (broad s, 1H), 6.80 (m, 1H), 7.11 (m, 1H), 7.50 (m, 1H), 7.99 (broad s, 1H), 10.81 (broad s, 1H). MS 202 (MH^+).

Example 152a: N-(2-Cyano-3-(prop-1-en-2-yl)phenylcarbamoyl)benzamide

Prepared as in Example 150a from 2-amino-6-(prop-1-en-2-yl)benzonitrile (Example 138b) in amount of 96.0 mg (72%), as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.15 (s, 3H), 5.23 (m, 1H), 5.43 (m, 1H), 7.25 (m, 1H), 7.55 (m, 2H), 7.68 (m, 2H), 8.04 (m, 2H), 8.19 (m, 1H), 11.35 (s, 1H), 11.54 (s, 1H).

Example 153: 4-Amino-5-cyclopentenylquinazolin-2(1*H*)-one



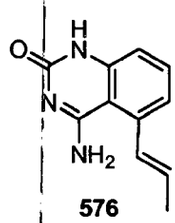
575

Prepared as in Example 150 from N-(Cyano-3-cyclopentenylphenylcarbamoyl)benzamide (Example 153a) in amount of 60.0 mg (75%), as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.01 (m, 2H), 2.55 (m, 2H), 2.61 (m, 2H), 5.91 (s, 1H), 6.49 (broad s, 1H), 6.81 (m, 1H), 7.08 (m, 1H), 7.48 (m, 1H), 7.88 (broad s, 1H), 10.76 (s, 1H). MS 228 (MH^+).

Example 153a: N-(Cyano-3-cyclopentenylphenylcarbamoyl)benzamide

Prepared as in Example 150a from 2-amino-6-(cyclopenten-1-yl)benzonitrile (Example 135b) in amount of 117.0 mg (93%), as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.99 (m, 2H), 2.57 (m, 2H), 2.78 (m, 2H), 6.45 (m, 1H), 7.26 (m, 1H), 7.57 (m, 2H), 7.68 (m, 2H), 8.06 (m, 2H), 8.15 (m, 1H), 11.34 (br s, 1H), 11.51 (s, 1H).

Example 154: (*E*)-4-Amino-5-(prop-1-enyl)quinazolin-2(1*H*)-one



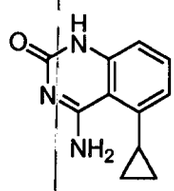
576

Prepared as in Example 150 from (*E*)-N-(2-Cyano-3-(prop-1-enyl)phenylcarbamoyl)benzamide (Example 154a) in amount of 13.0 mg (8%), as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.91 (m, 3H), 6.09 (m, 1H), 6.40 (broad s, 1H), 6.91 (m, 2H), 7.03 (m, 1H), 7.45 (m, 1H), 7.9 (broad s, 1H), 10.70 (s, 1H). MS 202 (MH^+).

Example 154a: (*E*)-N-(2-Cyano-3-(prop-1-enyl)phenylcarbamoyl)benzamide

Prepared as in Example 150a from (*E*)-2-amino-6-(prop-1-enyl)benzonitrile (Example 130b) in amount of 0.22 g (88%), as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.50 (broad s, 1H), 11.34 (broad s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 8.02-8.08 (m, 2H), 7.64-7.70 (m, 2H), 7.52-7.59 (m, 2H), 7.20 (d, J = 8.0 Hz, 1H), 5.50-5.18 (m, 2H), 3.55-3.59 (m, 3H).

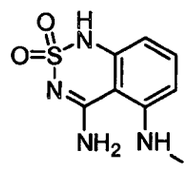
Example 155: 4-amino-5-cyclopropylquinazolin-2(1H)-one



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A solution of 2-amino-6-cyclopropylbenzonitrile (Example 92a) (1.0 eq., 1.0 mmol, 158 mg) and benzoyl isocyanate (90% pure, 1.0 eq., 1.0 mmol, 1.171 g/mL, 140 µL) in dioxane (15 mL) was stirred at room temperature. After 2 hours, the volatiles were removed on a rotary evaporator. The resulting crude N-benzoyl urea was suspended in EtOH (10 mL, 200 proof) and NaOH (2.5 eq., 2.5 mmol, 1N, 2.50 mL) was added. The reaction was heated to 75 ° C with stirring for 7 hours. The solvent were evaporated and the residue diluted with water (10 mL). The reaction mixture was acidified with 10% citric acid/water solution and carefully titrated to pH 7-8 with saturated $NaHCO_3$ solution. The precipitated product was collected by vacuum filtration, washing with water. The residue was suspended in EtOH (3 mL, 200 proof) and HCl was added (12.1N, 3 mL). The mixture was heated to 90 ° C for 1 hour. The reaction mixture was cooled to room temperature and diluted with water (20 mL), filtered (0.45 µm PTFE frit), and the filtrate concentrated on a rotary evaporator. The residue was further purified by preparative TLC (1000 µm, 10/90 MeOH/DCM) and trituration with methanol at room temperature. The reaction gives 25 mg (12.4%) of the title compound as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ0.802 (m, 2H), 1.086 (m, 2H), 2.345 (m, 1H), 6.922 (d, J = 8 Hz, 1H), 7.000 (d, J = 8 Hz, 1H), 7.253 (br. s, 1H), 7.397 (t, J = 8 Hz, 1H), 8.022 (br. s, 1H), 10.644 (s, 1H). MS 202 (MH^+).

Example 156: N^5-methyl-1H-benzo[c][1,2,6]thiadiazine-4,5-diamine-2,2-dioxide



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Prepared as in Example 90 from 2-amino-6-(methylamino)benzonitrile sulfamide (Example 156a) to give N^5-methyl-1H-benzo[c][1,2,6]thiadiazine-4,5-diamine-2,2-dioxide (27.7 mg, 45 %). ^{1}H NMR (400MHz, DMSO-d_6) δ 2.67 (d, J = 2 Hz, 3H), 5.91 (bs, NH), 6.21-6.17 (m, 2H), 7.17 (t, J = 8 Hz, 1H), 7.51 (bs, 2H), 10.6 (bs, NH). MS 227 (MH^+).

Example 156a: 2-amino-6-(methylamino)benzonitrile sulfamide

Prepared as in Example 90a from 2-amino-6-(methylamino)benzonitrile (Example 156b) to give 2-amino-6-(methylamino)benzonitrile sulfamide (65 mg, 30 %). ^{1}H NMR (400MHz, $CDCl_3$) δ 2.88 (d, J = 5.2 Hz, 3H), 4.23 (bs, NH), 4.66 (bs, NH), 4.87 (bs, 2H), 6.44 (d, J = 8 Hz, 1H), 6.90 (d, J = 8 Hz, 1H), 7.39 (t, J = 8 Hz, 1H). MS 227 (MH^+).

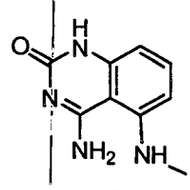
Example 156b: 2-amino-6-(methylamino)benzonitrile

Prepared as in Example 90b from 2-methylamino-6-nitrobenzonitrile (example 156b) to give 2-amino-6-(methylamino)benzonitrile (0.30 g, 85%) as a brown oil which was used in the next step without any further purification. ^{1}H NMR (400MHz, $CDCl_3$) δ 2.87 (d, J = 5.2 Hz, 3H), 4.25 (bs, 2H), 4.47 (bs, NH), 5.96 (d, J = 8.8 Hz, 1H), 6.02 (d, J = 8.4 Hz, 1H), 7.13 (t, J = 8 Hz, 1H). Ms 148 (MH^+).

Example 156c: 2-methylamino-6-nitrobenzonitrile

Prepared as in Example 90c from 2,6-dinitrobenzonitrile and methylamine to give 2-methylamino-6-nitrobenzonitrile (0.42 g, 79%). ^{1}H NMR (400MHz, DMSO-d_6) δ 2.85 (d, J = 5.2 Hz, 3H), 6.75 (d, J = 4.8 Hz, NH), 7.16 (d, J = 8.4 Hz, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.64 (t, J = 8.4 Hz, 1H).

Example 157: 4-amino-5-(methylamino)quinazolin-2(1H)-one



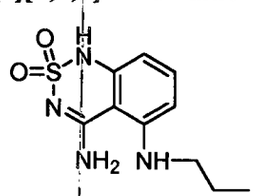
579

A solution of N-(2-cyano-3-(methylamino)phenylcarbamoyl)benzamide (Example 157a) (0.05 g, 0.17 mmol) and NaOH (2N, 0.17 mL) in EtOH (6 mL) was stirred at 90 °C under nitrogen for half an hour. The reaction mixture was cooled down to room temperature, and concentrated under vacuum. H_2O (1 mL) was added and the reaction mixture was neutralized to pH ~ 4 with 10% AcOH. The resultant precipitation was filtered and dried under vacuum. The crude product was purified by preparative thin layer chromatography using a DCM/MeOH (9:1) solution as eluant, to give 4-amino-5-(methylamino)quinazolin-2(1H)-one (18.2 mg, 56 %). ^{1}H NMR (400MHz, DMSO-d_6) δ 2.76 (s, 3H), 6.10 (d, J = 7.6 Hz, 1H), 6.12 (d, J = 8 Hz, 1H), 7.13 (t, J = 8 Hz, 1H), 7.25 (bs, NH), 9.66 (bs, NH,) 10.13 (bs, 2H). MS 191 (MH^+).

Example 157a: N-(2-cyano-3-(methylamino)phenylcarbamoyl)benzamide

To a solution of 2-amino-6-(methylamino)benzonitrile (example 156b) (0.14 g, 0.97 mmol) in 1,4-dioxane (3mL) was added benzoyl isocyanate (0.17 g, 1.17 mmol). The reaction mixture was stirred at room temperature under nitrogen overnight. The obtained precipitate was filtered and dried under vacuum to give N-(2-cyano-3-(methylamino)phenylcarbamoyl)benzamide (57 mg, 20%). ^{1}H NMR (400MHz, DMSO-d_6) δ 2.75 (d, J = 4.4 Hz, 3H), 6.26 (d, J = 4.8 Hz, NH), 6.43 (d, J = 9.6 Hz, 1H), 7.40-7.43 (m, 2H), 7.51-7.55 (m, 2H), 7.63-7.65 (m, 1H), 8.01 (d, J = 8.4 Hz, 2H), 11.23 (s, NH), 11.30 (s, NH). MS 295 (MH^+).

Example 158: N^5-propyl-1H-benzo[c][1,2,6]thiadiazine-4,5-diamine-2,2-dioxide



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Prepared as in Example 90 from 2-amino-6-(propylamino)benzonitrile sulfamide (Example 158a) to give N^5-propyl-1H-benzo[c][1,2,6]thiadiazine-4,5-diamine-2,2-dioxide (183 mg, 74 %). ^{1}H NMR (400MHz, DMSO-d_6) δ 0.91 (t, J = 7.2 Hz, 3H), 1.57-1.63 (m, 2H), 2.48 (q, J = 7.2, 2H), 5.85-5.88 (m, NH), 6.27 (d, J = 8 Hz, 1H), 6.37 (d, J = 8.4 Hz, 1H), 7.24 (t, J = 8 Hz, 1H), 7.87 (bs, 2H), 10.65 (bs, NH). MS 255 (MH^+).

Example 158a: 2-amino-6-(propylamino)benzonitrile sulfamide

Prepared as in Example 90a from 2-amino-6-(propylamino)benzonitrile (Example 158b) to give 2-amino-6-(propylamino)benzonitrile sulfamide (254 mg, 43 %). ^{1}H NMR

(400MHz, $CDCl_3$) δ 0.87 (t, J = 7.2 Hz, 3H), 1.48-1.57 (m, 2H), 3.10 (q, J = 6, J = 5.6, 2H), 5.86-5.89 (m, NH), 6.49 (d, J = 8.4 Hz, 1H), 6.69 (d, J = 7.6 Hz, 1H), 7.13 (s, 2H), 7.29 (t, J = 8 Hz, 1H), 9.06 (s, NH). MS 255 (MH^+).

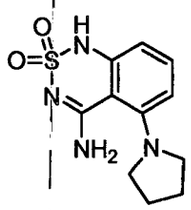
Example 158b: 2-amino-6-(propylamino)benzonitrile

Prepared as in Example 90b from 2-propylamino-6-nitrobenzonitrile (example 158c) to give 2-amino-6-(propylamino)benzonitrile (0.41 g, 91%) as a brown oil which was used in the next step without any further purification. MS 175 (MH^+).

Example 158c: 2-propylamino-6-nitrobenzonitrile

Prepared as in Example 90c from 2,6-dinitrobenzonitrile and propylamine 2-propylamino-6-nitrobenzonitrile (0.53 g, 86%). ^1H NMR (400MHz, DMSO-d_6) δ 0.88 (t, J = 7.2 Hz, 3H), 1.51-1.57 (m, 2H), 3.22 (q, J = 5.6, J = 6.4, 2H), 6.60-6.63 (m, NH), 7.22 (d, J = 8.8 Hz, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.58 (t, J = 8.4 Hz, 1H).

Example 159: 5-(pyrrolidin-1-yl)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



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Prepared as in Example 90 from 2-amino-6-(pyrrolidin-1-yl)benzonitrile sulfamide (example 159a) to give 5-(pyrrolidin-1-yl)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide (14.2 mg, 11 %). ^1H NMR (400 MHz, DMSO-d_6) δ 1.88-1.86 (m, 4H), 3.16-3.10 (m, br, 4H), 6.45 (d, J = 7.6 Hz, 1H), 6.64 (d, J = 8.4 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.83 (s, 1H, NH2), 8.14 (s, 1H, NH2), 10.79 (s, 1NH). MS 267 (MH^+).

Example 159a: 2-amino-6-(pyrrolidin-1-yl)benzonitrile sulfamide

Prepared as in Example 90a from 2-amino-6-(pyrrolidin-1-yl)benzonitrile (Example 159b) to give 2-amino-6-(pyrrolidin-1-yl)benzonitrile sulfamide (0.34 g, 100%). ^1H NMR (400 MHz, DMSO-d_6) δ 1.94-1.91 (m, 4H), 3.48-3.45 (m, 4H), 6.55 (d, J = 7.6 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 7.15 (s, 2H, NH_2), 7.32 (t, J = 8.0 Hz, 1H), 8.9 (s, 1NH). MS 267 (MH^+).

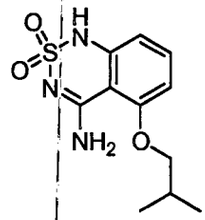
Example 159b: 2-amino-6-(pyrrolidin-1-yl)benzonitrile

Prepared as in Example 90b from 2-nitro-6-(pyrrolidin-1-yl)benzonitrile (example 159c) to give 2-amino-6-(pyrrolidin-1-yl)benzonitrile (0.48 g, 85 %) as a brown oil which was used in the next step without any further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.91-1.88 (m, 4H), 3.43-3.40 (m, 4H), 5.61 (s, 2H, NH_2), 5.86 (d, J = 8.8 Hz, 1H), 6.06 (d, J = 8.0 Hz, 1H), 6.99 (t, J = 8.0 Hz, 1H). MS 188 (MH^+).

Example 159c: 2-nitro-6-(pyrrolidin-1-yl)benzonitrile

Prepared as in Example 90c from 2,6-dinitrobenzonitrile and pyrrolidin to give 2-nitro-6-(pyrrolidin-1-yl)benzonitrile which was used in the next step without any further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.97-1.94 (m, 4H), 3.60-3.57 (m, 4H), 7.22 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 6.8 Hz, 1H), 7.58 (t, J = 8.0 Hz, 1H). MS 218 (MH^+).

Example 160: 4-Amino-5-isobutoxy-*1H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared in the same manner as example 111 from 2-sulfamoylamino-6-isobutoxybenzonitrile (example 160a) to provide 4-amino-5-isobutoxy-*1H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide (65 mg, 50%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.01 (d, J = 6.7 Hz, 6H), 2.06 (sept, J = 6.6 Hz, 1H), 3.90 (d, J = 6.2 Hz, 2H), 6.96 (d, J = 8.3 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 7.27 (br s, 2H), 7.56 (t, J = 8.7 Hz, 1H), 9.46 (s, 1H). MS 270 (MH^+).

Example 160a: 2-Sulfamoylamino-6-isobutoxybenzonitrile

Prepared in a similar manner as example 111a from 2-amino-6-isobutoxybenzonitrile (example 160b) to provide 2-sulfamoylamino-6-isobutoxybenzonitrile (130 mg, 50%). MS 191 (MH^+-NH_2SO_2).

Example 160b: 2-Amino-6-isobutoxybenzonitrile

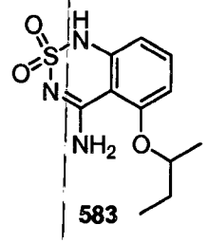
Prepared in a similar manner as example 111b from 2-isobutoxy-6-nitrobenzonitrile (example 160c) to provide 2-amino-6-isobutoxybenzonitrile. MS 191 (MH^+).

Example 160c: 2-Isobutoxy-6-nitrobenzonitrile

Prepared in a similar manner as example 160c from 2,6-dinitrobenzonitrile and isobutanol to provide 2-isobutoxy-6-nitrobenzonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.05 (d,

J = 6.4 Hz, 6H), 2.11 (sept, J = 6.6 Hz, 1H), 4.07 (d, J = 6.5 Hz, 2H), 7.75 (dd, J = 8.0, 1.9 Hz, 1H), 7.91 (t, J = 8.2 Hz, 1H), 7.94 (dd, J = 8.2, 1.9 Hz, 1H).

Example 161: 4-Amino-5-*sec*-butoxy-*1H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared in a similar manner as example 111 from 2-sulfamoylamino-6-*sec*-butoxybenzonitrile (example 161a) to provide 4-amino-5-*sec*-butoxy-*1H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide (57 mg, 44%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.95 (t, J = 7.9 Hz, 3H), 1.28 (d, J = 5.9 Hz, 3H), 1.67 (m, J = 7.4 Hz, 2H), 4.57 (sext, J = 5.9 Hz, 1H), 6.98 (d, J = 8.7 Hz, 1H), 7.13 (d, J = 8.3 Hz, 1H), 7.27 (br s, 2H), 7.55 (t, J = 8.3 Hz, 1H), 9.41 (s, 1H). MS 270 (MH^+).

Example 161a: 2-Sulfamoylamino-6-*sec*-butoxybenzonitrile

Prepared in a similar manner as example 1a from 2-amino-6-*sec*-butoxybenzonitrile (example 20b) to provide 2-sulfamoylamino-6-*sec*-butoxybenzonitrile. MS 191 (MH^+-NH_2SO_2).

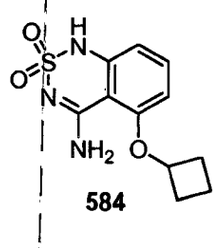
Example 161b: 2-Amino-6-*sec*-butoxybenzonitrile

Prepared in a similar manner as example 111b from 2-*sec*-butoxy-6-nitrobenzonitrile (example 161c) to provide 2-amino-6-*sec*-butoxybenzonitrile. MS 191 (MH^+).

Example 161c: 2-*sec*-Butoxy-6-nitrobenzonitrile

Prepared in a similar manner as example 161c from 2,6-dinitrobenzonitrile and *sec*-butanol to provide 2-*sec*-butoxy-6-nitrobenzonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.98 (t, J = 7.5 Hz, 3H), 1.33 (d, J = 5.9 Hz, 3H), 1.73 (m, 2H), 4.76 (sext, J = 5.9 Hz, 1H), 7.78 (dd, J = 6.8, 2.8 Hz, 1H), 7.90 (m, 2H).

Example 162: 4-Amino-cyclobutoxy-*1H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared in a similar manner as example 111 from 2-sulfamoylamino-6-cyclobutoxybenzonitrile (example 162a) to provide 4-amino-cyclobutoxy-*1H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide (19.4 mg, 10%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.65 (m, 1H), 1.79 (m, 1H), 2.19 (m, 2H), 2.43 (m, 2H), 4.82 (m, 1H), 6.52 (d, J = 7.9 Hz, 1H), 6.58 (d, J = 8.2 Hz, 1H), 7.40 (t, J = 8.1 Hz, 1H), 7.78 (br s, 1H), 8.31 (br s, 1H), 10.92 (br s). MS 268 (MH^+).

Example 162a: 2-Sulfamoylamino-6-cyclobutoxybenzonitrile

Prepared in a similar manner as example 111a from 2-amino-6-cyclobutoxybenzonitrile (example 162b) to provide 2-sulfamoylamino-6-cyclobutoxybenzonitrile (231 mg, 100%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.67 (m, 1H), 1.82 (m, 1H), 2.08 (m, 2H), 2.47 (m, 2H), 4.83 (pent, J = 7.2 Hz, 1H), 6.79 (d, J = 8.2 Hz, 1H), 7.15 (d, J = 8.2 Hz, 1H), 7.28 (br s, 1H), 7.54 (t, J = 8.2 Hz, 1H), 9.46 (br s, 1H). MS 268 (MH^+).

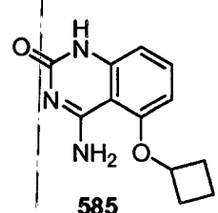
Example 162b: 2-Amino-6-cyclobutoxybenzonitrile

Prepared in a similar manner as example 111b from 2-cyclobutoxy-6-nitrobenzonitrile (example 162c) to provide 2-amino-6-cyclobutoxybenzonitrile (174 mg, 70%) as white needles. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.65 (m, 1H), 1.81 (m, 1H), 2.06 (m, 2H), 2.44 (m, 2H), 4.72 (pent, J = 7.3 Hz, 1H), 6.00 (br s, 2H), 6.07 (d, J = 7.8 Hz, 1H), 6.34 (dd, J = 8.2, 0.8 Hz, 1H), 7.17 (t, J = 8.1 Hz, 1H). MS 189 (MH^+).

Example 162c: 2-Cyclobutoxy-6-nitrobenzonitrile

Prepared in a similar manner as example 111c from 2,6 dinitrobenzonitrile and cyclobutanol to provide 2-amino-6-cyclobutoxybenzonitrile (298 mg, 34%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.69 (m, 1H), 1.85 (m, 1H), 2.14 (m, 2H), 2.52 (m, 2H), 4.98 (pent, J = 7.3 Hz, 1H), 7.55 (dd, J = 8.2, 1.1 Hz, 1H), 7.87 (t, J = 8.2 Hz, 1H), 7.92 (dd, J = 8.4, 1.3 Hz, 1H).

Example 163: 4-Amino-5-cyclobutoxyquinazolin-2(*1H*)-one



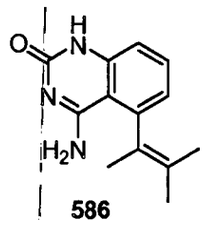
585

Prepared in a similar manner as example 111 from *N*-(2-cyano-3-cyclobutoxyphenylcarbamoyl)benzamide (example 163a) to provide 4-amino-5-cyclobutoxyquinazolin-2(*1H*)-one (19.4 mg, 76%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.68 (m, 1H), 1.84 (m, 1H), 2.20 (m, 2H), 2.49 (m, 2H), 4.87 (pent, J = 7.2 Hz, 1H), 7.52 (d, J = 8.2 Hz, 1H), 6.71 (d, J = 8.2 Hz, 1H), 7.92 (t, J = 8.2 Hz, 1H), 7.48 (br s, 1H), 7.88 (br s, 1H), 10.65 (br s, 1H). MS 232 (MH^+).

Example 163a: *N*-(2-Cyano-3-cyclobutoxyphenylcarbamoyl)benzamide

To a solution of 2-amino-6-cyclobutoxybenzonitrile (example 162b) (30 mg, 0.16 mmol) in 1,4-dioxane (2 mL) was added benzoyl isocyanate (23 mg, 0.16 mmol). The reaction was stirred at rt under N_2 for 19 hours. Upon completion, the reaction was diluted with EtOAc, washed with saturated $NaHCO_3$ (2x), water, brine, dried over $MgSO_4$, filtered and concentrated to provide *N*-(2-cyano-3-cyclobutoxyphenylcarbamoyl)benzamide (38 mg, 71%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.64 (m, 1H), 1.81 (m, 2H), 2.05 (m, 1H), 2.42 (m, 2H), 4.71 (pent, J = 7.1 Hz, 1H), 6.05 (d, J = 8.2 Hz, 1H), 6.33 (d, J = 8.3 Hz, 1H), 7.15 (t, J = 8.5 Hz, 1H), 7.45 (m, 1H), 7.56 (m, 2H), 7.87 (m, 1H), 8.05 (m, 1H), 11.35 (s, 1H).

Example 164: 4-Amino-5-(3-methylbut-2-en-2-yl)quinazolin-2(1H)-one



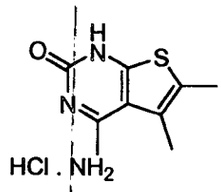
586

Prepared in a similar manner to example 146 from 1N-(2-cyano-3-(3-methylbut-2-en-2-yl)phenylcarbamoyl)benzamide (example 164a) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 3H), 1.83 (s, 3H), 1.89 (s, 3H), 6.65 (dd, J = 7.2, 1.0 Hz, 1H), 6.69 (bs, 2H), 7.04 (dd, J = 7.2, 1.0 Hz, 1H), 7.48 (t, J = 7.2 Hz, 1H), 10.74 (s, 1H). MS 230 (MH^+).

Example 164a: N-(2-cyano-3-(3-methylbut-2-en-2-yl) phenyl carbamoyl) benzamide

Prepared in a similar manner to example 146a from 2-amino-6-(3-methylbut-2-en-2-yl)benzonitrile (Example 98a) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.47 (s, 3H), 1.81 (s, 3H), 1.92 (s, 3H), 7.01-7.04 (m, 1H), 7.51-7.56 (m, 1H), 7.62-7.69 (m. 3H), 8.01-8.04 (m, 2H), 8.12-8.15 (m, 1H), 11.32 (s, 1H), 11.49 (s, 1H). MS 334 (MH^+).

Example 165: Improved synthesis of 4-Amino-5,6-dimethylthieno[2,3-d] pyrimidine-2(1H)-one hydrochloride



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This example describes an improved method for preparing the HCl salt of compound 1. Specifically, the improved method involves a particular washing protocol and formation of the HCl salt as the final step. When compared to the general method for preparing HCl salt, this method provides significantly more pure material with improved solubility and ease of handling.

To a solution of 4-amino-5,6-dimethylthieno[2,3-d]pyrimidine-2(1H)-one (Example 165a) (1082 g, 5.54 moles) in water (8.1 L) was added an ethanolic solution of HCl (1.25 N in 200 proof ethanol). The resulting slurry was heated to reflux for 15 minutes to afford a clear solution. (In some cases additional 1:1 H_2O:1.25 N HCl in ethanol must be added to obtain a clear solution). The solution was filtered while hot and the filtrate cooled to 0 °C while stirring. The resulting precipitate was collected by filtration, and washed with acetone (3 x 5.4 L) and heptane (3 x 5.4 L). The solids were placed in drying trays and dried under vacuum overnight to give 4-amino-5,6-dimethylthieno[2,3-d]pyrimidine-2(1H)-one hydrochloride as an off white powder (1176 g, 92% yield). > 99% pure as determined by HPLC. M.p.: > 260 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.30 (s, 6H), 8.56 (bs, 1H), 9.54 (bs, 1H), 12.92 (bs, 2H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 12.2, 13.3, 106.5, 125.5, 125.7, 146.1, 154.9, 155.3. MS 196.2 (MH^+). Purity as determined by HPLC, 99.64%.

Example 165a: 4-amino-5,6-dimethylthieno[2,3-d]pyrimidine-2(1H)-one.

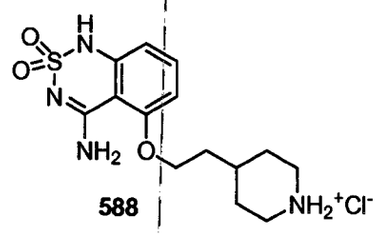
Ethanol was added to a 50 L three neck flask (30.8 L) and stirring was initiated. N-(3-cyano-4,5-dimethylthiophen-2-ylcarbamoyl)benzamide (Example 165b) (933 g, 3.12 mol) was added followed by the addition of NaOH (2 N, 4.5 L) The reaction mixture was heated to reflux (~77 °C) and stirred under nitrogen for 2.5 hours. The solution was then cooled to 65 °C and treated with charcoal (233 g). After stirring for 30 minutes the hot solution was filtered and the filtrate was slowly cooled to room temperature. The filtrate was carefully neutralized with 4 N HCl with vigorous stirring, then further cooled to -5 °C to 5 °C. The resulting precipitate was collected by filtration, washed with water (3 x 14 L), DMF (1 x 18.7 L), acetone (3 x 14 L) and

water (3 x 14 L). The solids were placed in drying trays and dried under vacuum overnight to give 4-amino-5,6-dimethylthieno[2,3-d]pyrimidine-2(1H)-thione (573 g, 87 %) as an off-white solid. M.p.: > 260 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (bs, 1H), 2.25 (s, 3H), 2.16 (s, 3H). MS 196(MH^+). Purity as determined by HPLC, 99.64%

Example 165b: N-(3-Cyano-4,5-dimethylthiophen-2-ylcarbamoyl)benzamide

To a solution of 2-amino-4,5-dimethylthiophene-3-carbonitrile (1680 g, 11.04 mol) in 1.4-dioxane (42 L) was added benzoylisocyanate (1624 g, 11.04 mol). The reaction mixture was then stirred at room temperature under nitrogen overnight. The resulting precipitate was collected by filtration, washed with 1.4-dioxane (3 x 1.7 l) and heptane (3 x 1.7 L), and dried under vacuum overnight to give N-(3-Cyano-4,5-dimethylthiophen-2-ylcarbamoyl)benzamide as a white solid (2800 g, 84.7% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.10 (s, 3H), 2.24 (s, 3H), 7.52-7.56 (m, 2H), 7.64-7.69 (m, 1H), 8.01-8.03 (m, 2H), 11.57 (brs, 1H), 12.05 (brs, 1H). MS 300 (MH^+).

Example 166: 4-(2-(4-Amino-*1H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide-5-yloxy)ethyl)piperidinium chloride



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tert-Butyl-4-(2-(4-Amino-*1H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide-5-yloxy)ethyl)piperidine-1-carboxylate (Example 166a) (20 mg, 0.047 mmol) was dissolved in a solution of HCl in EtOH (1 mL, 1.25 M). The reaction was stirred at reflux under N_2. Upon completion, the precipitate was collected by vacuum filtration to provide the desired product (17 mg, 100%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.38 (m, 2H), 1.73 (m, 1H), 1.81 (m, 2H), 1.87 (m, 2H), 2.84 (m, 2H), 3.24 (m, 2H), 4.21 (t, J = 6.4 Hz, 2H), 6.64 (d, J = 8.1 Hz, 1H), 6.78 (d, J = 8.3 Hz, 1H), 7.47 (t, J = 8.3 Hz, 1H), 7.81 (br s, 1H), 8.35 (br s, 1H), 8.59 (m, 1H), 8.85 (m, 1H), 10.99 (br s, 1H). MS 325 (MH^+).

Example 166a: *tert*-Butyl 4-(2-(4-amino-*1H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide-5-yloxy)ethyl)piperidine-1-carboxylate

Prepared as in Example 111 from *tert*-butyl 4-(2-(2-cyano-3-(sulfamoylamino)phenoxy)ethyl)piperidine-1-carboxylate (Example 166b) in 15% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.07 (qd, J = 12.8, 4.6 Hz, 2H), 1.40 (s, 9H), 1.60 (m, 1H), 1.70 (m, 2H), 1.79 (q, J = 6.7 Hz, 2H), 2.70 (m, 2H), 3.93 (m, 2H), 4.21 (t, J = 6.7 Hz, 2H), 6.62 (d, J = 8.1 Hz, 1H), 6.78 (d, J = 8.3 Hz, 1H), 7.46 (t, J = 8.3 Hz, 1H), 7.82 (br s, 1H), 8.34 (br s, 1H), 10.96 (br s, 1H).

Example166b: *tert*-Butyl-4-(2-(2-cyano-3-(sulfamoylamino)phenoxy) ethyl) piperidine-1-carboxylate

Prepared as in Example 111a from *tert*-butyl 4-(2-(3-amino-2-cyanophenoxy)ethyl)piperidine-1-carboxylate (Example 166c) in 72% yield as a clear syrup. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.08 (m, 2H), 1.40 (s, 9H), 1.71 (m, 5H), 2.70 (m, 2H), 3.93 (m, 2H), 4.17 (t, J = 6.3 Hz, 2H), 6.98 (d, J = 8.6 Hz, 1H), 7.16 (d, J = 8.3 Hz, 1H), 7.28 (br s, 2H), 7.57 (t, J = 8.3 Hz, 1H), 9.45 (br s, 1H).

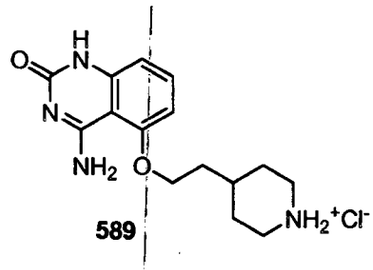
Example 166c: *tert*-Butyl 4-(2-(3-amino-2-cyanophenoxy)ethyl)piperidine-1-carboxylate:

Prepared as in Example 111b from *tert*-butyl 4-(2-(2-cyano-3-nitrophenoxy)ethyl)piperidine-1-carboxylate (Example 166d) in 36% as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (m, 2H), 1.40 (s, 9H), 1.68 (m, 5H), 2.70 (m, 2H), 3.93 (m, 2H), 4.05 (t, J = 6.0 Hz, 2H), 5.98 (br s, 2H), 6.23 (d, J = 8.4 Hz, 1H), 6.34 (d, J = 8.4 Hz, 1H), 7.18 (t, J = 8.2 Hz, 1H).

Example 166d: *tert*-Butyl-4-(2-(2-cyano-3-nitrophenoxy)ethyl)piperidine-1-carboxylate:

To a suspension of *tert*-butyl-4-(2-hydroxyethyl)piperidine-1-carboxylate (769 µL, 3.50 mmol) and NaH (118 mg, 3.50 mmol, 60% dispersion in mineral oil) in dry DMF (5 mL) at 0 °C, was added a solution of 2,6-dinitrobenzonitrile (614 mg, 3.18 mmol) in dry DMF (4 mL). The reaction was stirred under N_2, warming to rt. Upon completion, the reaction was quenched with H_2O (50 mL), and the precipitate was collected by vacuum filtration to provide *tert*-butyl-4-(2-(2-cyano-3-nitrophenoxy)ethyl)piperidine-1-carboxylate (955 mg, 80%) as a tan solid ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (m, 2H), 1.40 (s, 9H), 1.73 (m, 5H), 2.70 (m, 2H), 3.94 (m, 2H), 4.32 (t, J = 6.8 Hz, 2H), 7.75 (m, 1H), 7.92 (m, 2H).

Example 167: 4-(2-(4-Amino-2-oxo-1,2-dihydroquinazolin-5-yloxy) ethyl) piperidinium chloride



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Prepared as in Example 166 from *tert*-butyl 4-(2-(4-amino-2-oxo-1,2-dihydroquinazolin-5-yloxy)ethyl)piperidine-1-carboxylate (Example 167a) in 92% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.36 (m, 2H), 1.70 (m, 1H), 1.83 (q, J = 6.5 Hz, 2H), 1.88 (m, 2H), 2.84 (m, 2H), 3.26 (m, 2H), 4.36 (t, J = 6.4 Hz, 2H), 6.86 (d, J = 8.3 Hz, 1H), 6.99 (d, J = 8.3 Hz, 1H), 7.76 (t, J = 8.3 Hz, 1H), 8.50 (br s, 1H), 8.74 (br s, 1H), 8.98 (br s, 1H), 9.46 (br s, 1H), 11.99 (br s, 1H). MS 289 (MH^+).

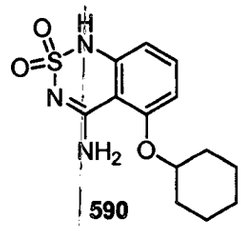
Example 167a: *tert*-Butyl 4-(2-(4-amino-2-oxo-1,2-dihydroquinazolin-5-yloxy)ethyl)piperidine-1-carboxylate

Prepared as in Example 111 from *tert*-butyl 4-(2-(3-(3-benzoylureido)-2-cyanophenoxy)ethyl)piperidine-1-carboxylate (Example 167b) in 31% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.08 (qd, J = 12.8, 4.6 Hz, 2H), 1.40 (s, 9H), 1.60 (m, 1H), 1.70 (m, 2H), 1.79 (q, J = 6.4 Hz, 2H), 2.69 (m, 2H), 3.93 (m, 2H), 4.23 (t, J = 6.9 Hz, 2H), 6.73 (m, 2H), 7.47 (t, J = 8.2 Hz, 1H), 7.57 (br s, 1H), 7.93 (br s, 1H), 10.73 (br s, 1H).

Example 167b: *tert*-Butyl 4-(2-(3-(3-benzoylureido)-2-cyanophenoxy)ethyl) piperidine-1-carboxylate

Prepared as in Example 146a from *tert*-butyl 4-(2-(3-amino-2-cyanophenoxy)ethyl)piperidine-1-carboxylate (Example 167c) in 100% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.09 (m, 2H), 1.40 (s, 9H), 1.60 (m, 1H), 1.71 (m, 5H), 2.71 (m, 2H), 3.94 (m, 2H), 4.21 (t, J = 6.5 Hz, 2H), 7.01 (d, J = 8.5 Hz, 1H), 7.56 (t, J = 7.4 Hz, 2H), 7.47 (t, J = 8.2 Hz, 1H), 7.64 (t, J = 8.5 Hz, 1H), 7.68 (tt, J = 7.3, 1.5 Hz, 1H), 7.87 (d, J = 8.3 Hz, 1H), 8.05 (m, 2H), 11.35 (br s, 1H), 11.49 (br s, 1H) .

Example 168: 4-Amino-5-(cyclohexyloxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-hexyloxybenzonitrile (Example 168a) in 63% yield as a white crystalline solid. M.p.: 215-216 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30-1.71 (m, 8H), 1.99 (m, 2H), 4.63 (m, 1H), 6.60 (dd, J = 8.2, 0.8 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 7.45 (t, J = 8.3 Hz, 1H), 7.83 (br d, J = 2.0 Hz, 1H), 8.40 (br d, J = 2.4 Hz, 1H), 10.95 (br s, 1H). MS 296 (MH^+).

Example 168a: 2-Sulfamoylamino-6-cyclohexyloxybenzonitrile:

Prepared as in Example 111a from 2-amino-6-cyclohexyloxybenzonitrile (Example 168b) in 91% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.37 (m, 3H), 1.51 (m, 3H), 1.70 (m, 2H), 1.85 (m, 2H), 4.55 (m, 1H), 6.98 (d, J = 8.1 Hz, 1H), 7.10 (d, J = 8.5 Hz, 1H), 7.24 (br s, 2H), 7.51 (t, J = 8.5 Hz, 1H), 9.39 (s, 1H).

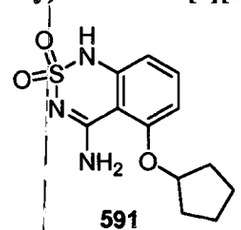
Example 168b: 2-Amino-6-cyclohexyloxybenzonitrile:

Prepared as in Example 111b from 2-Nitro-6-cyclohexyloxybenzonitrile to provide 2-amino-6-cyclohexyloxybenzonitrile (420 mg, 27%) as a green syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (m, 3H), 1.50 (m, 3H), 1.71 (m, 2H), 1.85 (m, 2H), 4.43 (m, 1 H), 5.94 (br s, 2H), 6.26 (d, J = 8.6 Hz, 1H), 6.31 (d, J = 8.1 Hz, 1H), 7.16 (t, J = 8.1 Hz, 1H). MS 215 (MH^+).

Example 168c: 2-Nitro-6-cyclohexyloxybenzonitrile:

Prepared as in Example 166d from 2-nitro-6-cyclohexyloxybenzonitrile and cyclohexanol in 100% yield as a light tan solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (m, 4H), 1.60 (m, 2H), 1.74 (m, 2H), 1.90 (m, 2H), 4.76 (m, 1H), 7.79 (m, 1H), 7.89 (m, 2H).

Example 169: 4-Amino-5-(cyclopentoxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-pentoxybenzonitrile (Example 169a) in 38% yield as off-white needles M.p.: >260 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.67 (m, 4H), 1.85 (m, 2H), 1.98 (m, 2H), 5.05 (m, 1H), 6.61 (d, J = 7.8 Hz, 1H), 6.76 (d, J = 7.8 Hz, 1H), 7.46 (t, J = 7.8 Hz, 1H), 7.72 (br s, 1H), 8.35 (br s, 1H), 10.96 (br s, 1H). MS 282 (MH^+).

Example 169a: 2-Sulfamoylamino-6-cyclopentoxybenzonitrile:

Prepared as in Example 111a from 2-amino-6-cyclopentoxybenzonitrile (Example 169b) in 100% yield as a light brown syrup. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.61 (m, 2H), 1.74 (m, 4H), 1.93 (m, 2H), 4.98 (m, 1H), 6.96 (d, J = 9.0 Hz, 1H), 7.14 (d, J = 8.2 Hz, 1H), 7.28 (br s, 2H), 7.55 (t, J = 8.2 Hz, 1H), 9.43 (s, 1H).

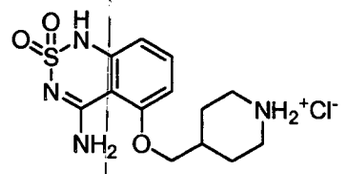
Example 169b: 2-Amino-6-cyclopentoxybenzonitrile:

Prepared as in Example 111b from 2-Nitro-6-cyclopentoxybenzonitrile (Example 169c) in 84% yield as a green syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (m, 2H), 1.71 (m, 4H), 1.89 (m, 2H), 4.84 (m, 1 H), 5.94 (br s, 2H), 6.20 (d, J = 8.0 Hz, 1H), 6.31 (d, J = 8.3 Hz, 1H), 7.17 (t, J = 8.3 Hz, 1H).

Example 169c: 2-Nitro-6-cyclopentoxybenzonitrile:

Prepared as in Example 166d from 2,6-dinitrobenzonitrile and cyclopentanol in 78% yield as a light tan solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64 (m, 2H), 1.77 (m, 4H), 1.97 (m, 2H), 5.14 (m, 1H), 7.73 (m, 1H), 7.88 (m, 2H).

Example 170: 4-(2-(4-Amino-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide-5-yloxy)methyl)piperidinium chloride



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Prepared as in Example 166 from *tert*-butyl 4-(2-(4-amino-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide-5-yloxy)methyl)piperidine-1-carboxylate (Example 170a) in 89% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.49 (m, 2H), 1.90 (d, J = 13.1 Hz, 2H), 2.23 (m, 1H), 2.89 (q, J = 11.6 Hz, 2H), 3.30 (d, J = 12.3 Hz, 2H), 4.09 (br s, J = 6.6

Hz, 2H), 6.65 (d, J = 8.2 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 7.48 (t, J = 8.2 Hz, 1H), 7.74 (br s, 1H), 8.33 (br s, 1H), 8.69 (m, 1H), 8.92 (m, 1H), 11.01 (s, 1H). MS 272 (MH^+).

Example 170a: *tert*-Butyl 4-(2-(4-amino-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide-5-yloxy)methyl)piperidine-1-carboxylate

Prepared as in Example 111 from *tert*-butyl 4-((2-cyano-3-(sulfamoylamino)phenoxy)methyl)piperidine-1-carboxylate (Example 170b) in 91% as a white solid. MS 355 (MH^+ - $C(CH_3)_3$).

Example 170b: *tert*-Butyl 4-((2-cyano-3-(sulfamoylamino) phenoxy)methyl) piperidine-1-carboxylate

Prepared as in Example 111a from *tert*-butyl 4-((3-amino-2-cyanophenoxy)methyl)piperidine-1-carboxylate (Example 170c) in 56% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.20 (m, 2H), 1.41 (s, 9H), 1.76 (d, J = 13.2 Hz, 2H), 1.97 (m, 2H), 4.00 (m, 4H), 6.96 (d, J = 8.6 Hz, 1H), 7.16 (d, J = 8.3 Hz, 1H), 7.28 (s, 2H), 7.57 (t, J = 8.3 Hz, 1H), 9.47 (s, 1H).

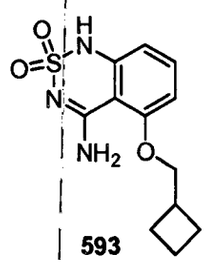
Example 170c: *tert*-Butyl 4-((3-amino-2-cyanophenoxy)methyl)piperidine-1-carboxylate

Prepared as in Example 111b from *tert*-butyl 4-((2-cyano-3-nitrophenoxy)methyl)piperidine-1-carboxylate (Example 170d) in 74% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.18 (qd, J = 12.6, 3.8 Hz, 2H), 1.41 (s, 9H), 1.74 (d, J = 12.6 Hz, 2H), 1.93 (m, 2H), 2.75 (m, 2H), 3.88 (d, J = 6.6 Hz, 2H), 3.99 (br d, J = 12.1 Hz, 2H), 6.00 (br s, 2H), 6.21 (d, J = 8.2 Hz, 1H), 6.34 (d, J = 8.3 Hz, 1H), 7.18 (t, J = 8.2 Hz, 1H).

Example 170d: *tert*-Butyl 4-((2-cyano-3-nitrophenoxy)methyl)piperidine-1-carboxylate

Prepared as in Example 111c from 2,6-dinitrobenzonitrile and *tert*-butyl 4-(hydroxymethyl)piperidine-1-carboxylate in 73% as a tan solid. ^{1}H NMR (400 MHz, MeOD) δ 1.24 (qd, J = 12.8, 4.4 Hz, 2H), 1.41 (s, 9H), 1.78 (br d, J = 12.1 Hz, 2H), 2.02 (m, 2H), 2.77 (m, 2H), 4.00 (br d, J = 13.1 Hz, 2H), 4.15 (d, J = 6.3 Hz, 2H), 7.74 (dd, J = 7.5, 1.5 Hz, 1H), 7.91 (m, 2H).

Example 171: 4-Amino-5-(cyclobutylmethoxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-cyclobutylmethoxybenzonitrile (Example 171a) in 21% yield as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.88 (m, 4H), 2.08 (m, 2H), 2.86 (sept, J = 7.9 Hz, 1H), 4.16 (d, J = 6.9 Hz, 2H), 6.62 (dd, J = 8.2, 1.2 Hz, 1H), 6.77 (dd, J = 8.6, 0.7 Hz, 1H), 7.47 (t, J = 8.2 Hz, 1H), 7.76 (br s, 1H), 8.39 (br s, 1H), 10.98 (br s, 1H). MS 282 (MH^+).

Example 171a: 2-Sulfamoylamino-6- cyclobutylmethoxybenzonitrile

Prepared as in Example 111a from 2-amino-6-cyclobutylmethoxybenzonitrile (Example 171b) in 94% yield as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.94 (m, 4H), 2.12 (m, 2H), 2.86 (sept, J = 7.5 Hz, 1H), 4.13 (d, J = 6.3 Hz, 2H), 7.00 (d, J = 8.4 Hz, 1H), 7.19 (d, J = 8.2 Hz, 1H), 7.31, (br s, 2H), 7.60 (t, J = 8.4 Hz, 1H), 9.48 (br s, 1H).

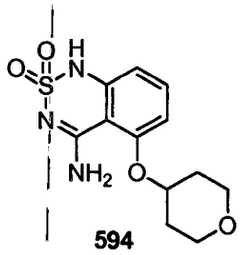
Example 171b: 2-Amino-6-cyclobutylmethoxybenzonitrile

Prepared as in Example 111b from 2-nitro-6-cyclobutylmethoxybenzonitrile (Example 171c) in 41% yield as a yellow oil. MS 203 (MH^+).

Example 171c: 2-Nitro-6-cyclobutylmethoxybenzonitrile

Prepared as in Example 166d from 2,6-dinitrobenzonitrile and cyclobutylmethanol in 68% as a tan solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.93 (m, 4H), 2.10 (m, 2H), 2.79 (m, 1H), 4.25 (d, J = 6.3 Hz, 2H), 7.74 (dd, J = 8.5, 2.2 Hz, 1H), 7.91 (m, 2H).

Example 172: 4-Amino-5-(tetrahydro-2*H*-pyran-4-yloxy)-1*H*-benzo[*c*][1,2,6] thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-(tetrahydro-2*H*-pyran-4-yloxy)benzonitrile (Example 172a) in 69% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-

d_6) δ 1.77 (m, 2H), 2.05 (m, 2H), 3.51 (td, J = 11.6, 2.1 Hz, 2H), 3.85 (dt, J = 11.4, 3.9 Hz, 2H), 4.83 (sept, J =4.1 Hz, 1H), 6.62 (d, J = 8.0 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 7.46 (t, J = 8.2 Hz, 1H), 7.78 (br s, 1H), 8.39 (br s, 1H), 10.96 (br s, 1H). MS 298 (MH^+).

Example 172a: 2-Sulfamoylamino-6-(tetrahydro-2*H*-pyran-4-yloxy)benzonitrile

Prepared as in Example 111a from 2-amino-6-(tetrahydro-2*H*-pyran-4-yloxy)benzonitrile (Example 172b) in 58% as a light orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.64 (m, 2H), 1.99 (m, 2H), 3.53 (ddd, J = 11.6, 8.3, 3.1 Hz, 2H), 3.85 (m, 2H), 4.80 (sept, J = 4.0 Hz, 1H), 7.07 (d, J = 8.3 Hz, 1H), 7.16 (d, J = 8.1 Hz, 1H), 7.28 (br s, 2H), 7.56 (t, J = 8.5 Hz, 1H), 9.47 (br s, 1H).

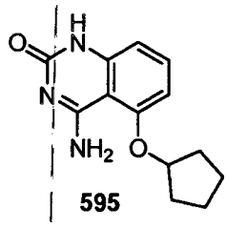
Example 172b: 2-Amino-6-(tetrahydro-2*H*-pyran-4-yloxy)benzonitrile

Prepared as in Example 111b from 2-nitro-6-(tetrahydro-2*H*-pyran-4-yloxy)benzonitrile (Example 172c) in 49% as an orange syrup. MS 219 (MH^+).

Example 172c: 2-Nitro-6-(tetrahydro-2*H*-pyran-4-yloxy)benzonitrile

Prepared as in Example 166d from 2,6-dinitrobenzonitrile and tetrahydro-2*H*-pyran-4-ol in 100% yield as a tan solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.69 (m, 2H), 2.03 (m, 2H), 3.56 (m, 2H), 3.87 (m, 2H), 4.98 (sept, J = 3.8 Hz, 1H), 7.90 (m, 3H).

Example 173: 4-Amino-5-(cyclopentyloxy)quinazolin-2(1*H*)-one



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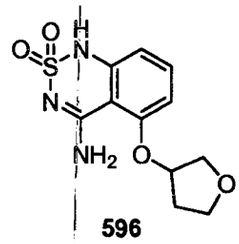
Prepared as in Example 111 from *N*-(2-cyano-3-(cyclopentyloxy)phenylcarbamoyl)benzamide (Example 173a) in 45% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.68 (m, 4H), 1.84 (m, 2H), 1.99 (m, 2H), 5.06 (m, 1H), 6.70 (d, J = 8.3 Hz, 2H), 7.43 (s, 1H), 7.45 (t, J = 8.2 Hz, 1H), 7.85 (br s, 1H), 10.65 (br s, 1H).

Example 173a: *N*-(2-Cyano-3-(cyclopentyloxy)phenylcarbamoyl)benzamide

Prepared as in Example 146a from 2-amino-6-cyclopentoxybenzonitrile (Example 173b) in 70% yield as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.63 (m, 2H), 1.77 (m, 4H), 1.98 (m, 2H), 5.03 (m, 1H), 6.98 (d, J = 8.6 Hz, 1H), 7.55 (t, J = 7.6 Hz, 2H), 7.62 (t, J =

8.6 Hz, 1H), 7.67 (tt, J = 7.4, 1.2 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 8.06 (m, 2H), 11.37 (br s, 1H), 11.54 (br s, 1H).

Example 174: 4-Amino-5-(tetrahydrofuran-3-yloxy)-1*H*-benzo[*c*][1,2,6] thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-(tetrahydrofuran-3-yloxy)benzonitrile (Example 174a) in 33% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.07 (m, 1H), 2.26 (m, 1H), 3.74 (td, J = 8.4, 4.7 Hz, 1H), 3.84 (m, 2H), 3.95 (d, J = 10.4 Hz, 1H), 5.23 (m, 1H), 6.61 (d, J = 8.1 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 7.45 (t, J = 8.1 Hz, 1H), 7.64 (br s, 1H), 8.33 (br s, 1H), 10.97 (br s, 1H). MS 284 (MH^+).

Example 174a: 2-Sulfamoylamino-6-(tetrahydrofuran-3-yloxy)benzonitrile

Prepared as in Example 111a from 2-amino-6-(tetrahydrofuran-3-yloxy)benzonitrile (Example 174b) in 40% yield as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.99 (m, 1H), 2.28 (m, 1H), 3.77 (td, J = 8.3, 4.7 Hz, 1H), 3.83 (m, 1H), 3.87 (d, J = 7.3 Hz, 1H), 3.92 (dd, J = 10.2, 4.4 Hz, 1H), 5.19 (m, 1H), 6.96 (d, J = 8.3 Hz, 1H), 7.18 (d, J = 8.3 Hz, 1H), 7.29 (s, 2H), 7.58 (t, J = 8.3 Hz, 1H), 9.49 (br s, 1H).

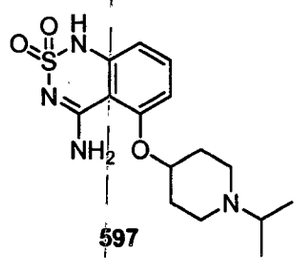
Example 174b: 2-Amino-6-(tetrahydrofuran-3-yloxy)benzonitrile

Prepared as in Example 111b from 2-nitro-6-(tetrahydrofuran-3-yloxy)benzonitrile (Example 174c) in 97% yield as a light brown syrup. MS 205 (MH^+).

Example174c: 2-Nitro-6-(tetrahydrofuran-3-yloxy)benzonitrile

Prepared as in Example 166d from 2,6-dinitrobenzonitrile and tetrahydrofuran-3-ol in 50% yield as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.04 (m, 1H), 2.32 (m, 1H), 3.81 (td, J = 8.3, 4.6 Hz, 1H), 3.89 (m, 2H), 3.98 (dd, J = 10.8, 4.5 Hz, 1H), 5.36 (m, 1H), 7.75 (dd, J = 8.1, 1.5 Hz, 1H), 7.91 (t, J = 8.2 Hz, 1H), 7.95 (dd, J = 8.2, 1.6 Hz, 1H).

Example 175: 4-Amino-5-(1-isopropylpiperidin-4-yloxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-(1-isopropylpiperidin-4-yloxy)benzonitrile (Example 175b) in 12% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.24 (d, J = 6.7 Hz, 6H), 2.11 (m, 2H), 2.28 (m, 2H), 3.13 (m, 4H), 4.87 (m, 1H), 6.67 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 8.6 Hz, 1H), 7.49 (t, J = 8.3 Hz, 1H), 7.67 (br s, 1H), 8.43 (br s, 1H), 10.79 (br s, 1H). MS 339 (MH^+).

Example 175a: 2-Sulfamoylamino-6-(1-isopropylpiperidin-4-yloxy)benzonitrile

Prepared as in Example 111a from 2-amino-6-(1-isopropylpiperidin-4-yloxy)benzonitrile (Example 175b). The product was carried onto the next step without further purification.

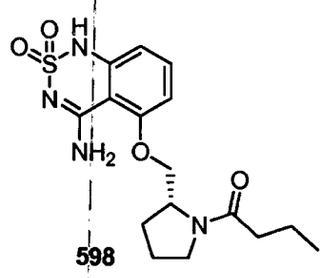
Example 175b: 2-Amino-6-(1-isopropylpiperidin-4-yloxy)benzonitrile

Prepared as in Example 111b from 2-nitro-6-(1-isopropylpiperidin-4-yloxy)benzonitrile (Example 175c) in 80% yield as a brown syrup. MS 260 (MH^+).

Example 175c: 2-Nitro-(1-isopropylpiperidin-4-yloxy)-6-benzonitrile

Prepared as in Example 166d from 2,6-dinitrobenzonitrile and 1-isopropylpiperidin-4-ol in 90% yield as a tan solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.99 (d, J = 6.8 Hz, 6H), 1.72 (m, 2H), 1.95 (m, 2H), 2.41 (m, 2H), 2.71 (m, 3H), 4.80 (m, 1H), 7.81 (dd, J = 8.2, 1.3 Hz, 1H), 7.89 (m, 2H).

Example 176: (*R*)-4-Amino-5-((1-butyrylpyrrolidin-2-yl)methoxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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To a solution of (*R*)-2-amino-6-((1-butyrylpyrrolidin-2-yl)methoxy)benzonitrile (84 mg, 0.29 mmol) (Example 176a) in acetonitrile (9 mL), was added sulfamoyl chloride (70 mg, 0.60 mmol). The reaction was stirred at rt for 20 h, and upon completion was concentrated *in vacuo*. The resulting residue was dissolved in EtOH (1 mL), and 2N aqueous NaOH (4 mL) was added. The mixture was refluxed for 2 h, and upon completion was cooled to rt, neutralized with 1N HCl and stirred at 0 °C. The resulting precipitate was collected by vacuum filtration to provide the desired product (38 mg, 35%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.89 (t, J = 7.3 Hz, 3H), 1.54 (sext, J = 7.3 Hz, 2H), 1.94 (m, 4H), 2.26 (t, J = 7.3 Hz, 2H), 3.49 (m, 2H), 4.10 (m, 1H), 4.25 (m, 1H), 4.43 (m, 1H), 6.62 (d, J = 8.2 Hz, 1H), 6.90 (d, J = 8.2 Hz, 1H), 7.45 (t, J = 8.2 Hz, 1H), 8.08 (br s, 1H), 8.34 (br s, 1H), 10.93 (br s, 1H). MS 367 (MH^+).

Example 176a: (*R*)-2-Amino-6-((1-butyrylpyrrolidin-2-yl)methoxy)benzonitrile

Prepared as in Example 111b from (*R*)-2-((1-butyrylpyrrolidin-2-yl)methoxy)-6-nitrobenzonitrile (Example 176b) in 77% yield. MS 274 (MH^+).

Example 176b: (*R*)-2-((1-Butyrylpyrrolidin-2-yl)methoxy)-6-nitrobenzonitrile

To a suspension of (*R*)-2-((2-cyano-3-nitrophenoxy)methyl)pyrrolidinium chloride (140 mg, 0.49 mmol) (Example 176c) in THF (3 mL) were added Et_3N (143 µL, 1.03 mmol) and butyryl chloride (56 µL, 0.54 mmol). The reaction was stirred for 72 h at rt under N_2. Upon completion, the reaction was filtered, and the filtrate was concentrated to provide (*R*)-2-((1-butyrylpyrrolidin-2-yl)methoxy)-6-nitrobenzonitrile (127 mg, 82%) as a yellow syrup. MS 318 (MH^+).

Example176c: (*R*)-2-((2-Cyano-3-nitrophenoxy)methyl)pyrrolidinium chloride

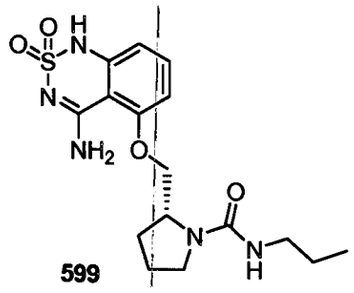
Prepared as in Example 166 from (*R*)-*tert*-butyl 2-((2-cyano-3-nitrophenoxy)methyl)pyrrolidine-1-carboxylate (Example 176d) in 71% yield as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.92 (m, 2H), 2.14 (m, 2H), 3.28 (m, 2H), 4.07 (m, 2H), 4.50 (dd, J = 710.6, 6.4 Hz, 1H), 4.57 (dd, J = 10.9, 3.5 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.98 (m, 2H), 9.36 (br s, 1H), 9.74 (br s, 1H).

Example 176d: (*R*)-*tert*-Butyl 2-((2-cyano-3-nitrophenoxy)methyl)pyrrolidine-1-carboxylate

Prepared as in Example 166d from 2,6-dinitrobenzonitrile and (*R*)-*tert*-butyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate in 87% yield as a tan solid. ^{1}H NMR (400 MHz,

DMSO-d_6) δ 1.39 (s, 9H), 1.82 (m, 1H), 2.02 (m, 3H), 3.32 (m, 2H), 4.08 (m, 1H), 4.32 (m, 2H), 7.79 (d, J = 8.0 Hz, 1H), 7.91 (m, 2H).

Example 177: (*R*)-2-((4-Amino-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide-5-yloxy)methyl)-*N*-propylpyrrolidine-1-carboxamide



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Prepared as in Example 176 from (*R*)-2-((3-amino-2-cyanophenoxy)methyl)-*N*-propylpyrrolidine-1-carboxamide (Example 177a) in 57% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.83 (t, J = 7.6 Hz, 3H), 1.42 (sext, J = 7.3 Hz, 2H), 1.90 (m, 4H), 3.00 (m, 2H), 3.20 (m, 1H), 3.43 (m, 2H), 4.01 (m, 1H), 4.16 (m, 1H), 4.33 (m, 1H), 6.27 (m, 1H), 6.61 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 8.3 Hz, 1H), 7.45 (t, J = 8.2 Hz, 1H), 8.19 (br s, 1H), 8.27 (br s, 1H), 10.91 (s, 1H). MS 382 (MH^+).

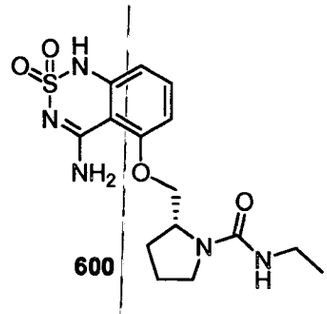
Example 177a: (*R*)-2-((3-Amino-2-cyanophenoxy)methyl)-*N*-propylpyrrolidine-1-carboxamide

Prepared as in Example 111b from (*R*)-2-((2-cyano-3-nitrophenoxy)methyl)-*N*-propylpyrrolidine-1-carboxamide (Example 177b) in 14% yield. MS 303 (MH^+).

Example 177b: (*R*)-2-((2-Cyano-3-nitrophenoxy)methyl)-*N*-propylpyrrolidine-1-carboxamide

Prepared as in Example 176b from (*R*)-2-((2-cyano-3-nitrophenoxy)methyl)pyrrolidinium chloride (Example 176c) and propyl isocyanate in 100% yield as a light yellow solid. MS 333 (MH^+).

Example 178: (*R*)-2-((4-Amino-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide-5-yloxy)methyl)-*N*-ethylpyrrolidine-1-carboxamide



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Prepared as in Example 176 from (*R*)-2-((3-amino-2-cyanophenoxy)methyl)-*N*-ethylpyrrolidine-1-carboxamide (Example 178a) in 60% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.02 (t, J = 6.8 Hz, 3H), 1.90 (m, 4H), 3.08 (quint, J = 6.8 Hz, 2H), 3.20 (m, 2H), 4.01 (m, 1H), 4.16 (m, 1H), 4.33 (m, 1H), 6.27 (m, 1H), 6.62 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 7.46 (t, J = 8.4 Hz, 1H), 8.20 (br s, 1H), 8.27 (br s, 1H), 10.91 (s, 1H). MS 368 (MH^+).

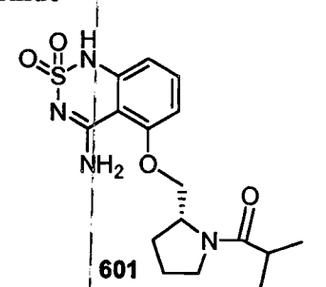
Example 178a: (*R*)-2-((3-Amino-2-cyanophenoxy)methyl)-*N*-ethylpyrrolidine-1-carboxamide

Prepared as in Example 111b from (*R*)-2-((2-cyano-3-nitrophenoxy)methyl)-*N*-ethylpyrrolidine-1-carboxamide (Example 178b) in 62% yield. MS 289 (MH^+).

Example 178b: (*R*)-2-((2-Cyano-3-nitrophenoxy)methyl)-*N*-ethylpyrrolidine-1-carboxamide

Prepared as in Example 176b from (*R*)-2-((2-cyano-3-nitrophenoxy)methyl)pyrrolidinium chloride (Example 176c) and ethyl isocyanate in 95% yield as a light yellow solid. MS 319 (MH^+).

Example 179: (*R*)-4-Amino-5-((1-isobutyrylpyrrolidin-2-yl)methoxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 176 from (*R*)-2-amino-6-((1-isobutyrylpyrrolidin-2-yl)methoxy)benzonitrile (Example 179b) in 100% yield as a white solid. ^{1}H NMR (400 MHz,

DMSO-d_6) δ 1.02 (d, J = 6.3 Hz, 6H), 1.94 (m, 4H), 2.70 (m, 1H), 3.55 (m, 2H), 4.12 (m, 1H), 4.24 (m, 1H), 4.43 (m, 1H), 6.62 (d, J = 7.9 Hz, 1H), 6.91 (d, J = 8.1 Hz, 1H), 7.47 (t, J = 8.1 Hz, 1H), 8.04 (br s, 1H), 8.34 (br s, 1H), 10.93 (br s, 1H). MS 367 (MH^+).

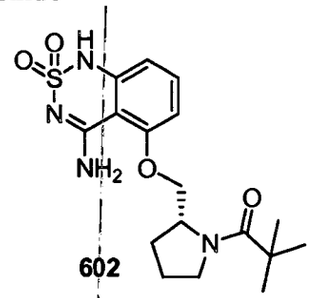
Example 179a: (*R*)-2-Amino-6-((1-isobutyrylpyrrolidin-2-yl) methoxy) benzonitrile

Prepared as in Example 111b from (*R*)-2-((1-isobutyrylpyrrolidin-2-yl)methoxy)-6-nitrobenzonitrile (Example 179b) in 80% yield as a clear syrup. MS 288 (MH^+).

Example 179b: (*R*)-2-((1-Isobutyrylpyrrolidin-2-yl)methoxy)-6-nitrobenzonitrile

Prepared as in Example 176b from (*R*)-2-((2-cyano-3-nitrophenoxy)methyl)pyrrolidinium chloride and isobutyryl chloride in 100% yield as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.96 (dd, J = 6.6, 3.5 Hz, 6H), 1.93 (m, 4H), 2.14 (m, 1H), 2.66 (sept, J = 6.6 Hz, 1H), 3.55 (m, 1H), 4.28 (m, 3H), 7.79 (dd, J = 7.6, 1.8 Hz, 1H), 7.89 (m, 2H).

Example 180: (*R*)-4-Amino-5-((1-pivaloylpyrrolidin-2-yl)methoxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 176 from (*R*)-2-amino-6-((1-pivaloylpyrrolidin-2-yl)methoxy)benzonitrile (Example 180a) in 64% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.18 (s, 9H), 1.92 (m, 4H), 3.55 (m, 1H), 3.73 (m, 1H), 4.13 (m, 1H), 4.27 (m, 1H), 4.48 (m, 1H), 6.62 (d, J = 8.2 Hz, 1H), 6.92 (d, J = 8.2 Hz, 1H), 7.47 (t, J = 8.2 Hz, 1H), 7.95 (br s, 1H), 8.37 (br s, 1H), 10.95 (br s, 1H). MS 381 (MH^+).

Example 180a: (*R*)-2-Amino-6-((1-pivaloylpyrrolidin-2-yl)methoxy)benzonitrile

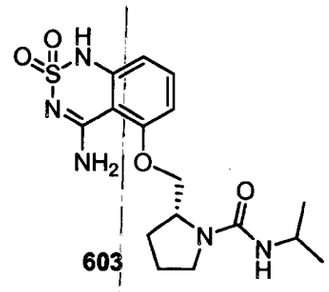
Prepared as in Example 111b from (*R*)-2-((1-pivaloylpyrrolidin-2-yl)methoxy)-6-nitrobenzonitrile (Example 180bW) in 91% yield as a clear syrup. MS 302 (MH^+).

Example 180b: (*R*)-2-((1-Pivaloylpyrrolidin-2-yl)methoxy)-6-nitrobenzonitrile

Prepared as in Example 176b from (*R*)-2-((2-cyano-3-nitrophenoxy)methyl)pyrrolidinium chloride and pivaloyl chloride in 99%. ^{1}H NMR (400 MHz,

DMSO-d_6) δ 1.16 (s, 9H), 1.91 (m, 3H), 2.13 (m, 1H), 3.70 (m, 2H), 4.35 (m, 3H), 7.81 (dd, J = 7.5, 2.1 Hz, 1H), 7.92 (m, 2H).

Example 181: (*R*)-2-((4-Amino-1*H*-benzo[*e*][1,2,6]thiadiazine-2,2-dioxide-5-yloxy)methyl)-*N*-isopropylpyrrolidine-1-carboxamide



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Prepared as in Example 176 from (*R*)-2-((3-amino-2-cyanophenoxy)methyl)-*N*-isopropylpyrrolidine-1-carboxamide (Example 181a) in 23% yield as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.05 (d, J = 6.4 Hz, 6H), 1.87 (m, 4H), 3.17 (m, 1H), 3.79 (m, 1H), 3.98 (m, 1H), 4.15 (m, 1H), 4.31 (m, 1H), 5.88 (d, J = 7.4 Hz, 1H), 6.59 (d, J = 8.2 Hz, 1H), 6.86 (d, J = 8.5 Hz, 1H), 7.43 (t, J = 8.2 Hz, 1H), 8.18 (br s, 1H), 8.23 (br s, 1H), 10.88 (s, 1H). MS 382 (MH^+).

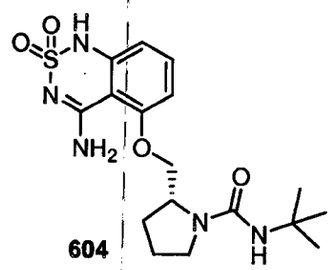
Example 181a: (*R*)-2-((3-Amino-2-cyanophenoxy)methyl)-*N*-isopropylpyrrolidine -1-carboxamide

Prepared as in Example 111b from (*R*)-2-((2-cyano-3-nitrophenoxy)methyl)-*N*-isopropylpyrrolidine-1-carboxamide (Example 181b) in 86% yield as a clear syrup. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.07 (d, J = 5.9 Hz, 6H), 1.89 (m, 3H), 2.10 (m, 1H), 3.16 (m, 1H), 3.45 (m, 1H), 3.78 (m, 1H), 3.91 (m, 1H), 4.06 (m, 1H), 4.12 (m, 1H), 5.85 (d, J = 7.7 Hz, 1H), 6.00 (br s, 2H), 6.31 (d, J = 8.4 Hz, 1H), 6.34 (d, J = 8.4 Hz, 1H), 7.18 (t, J = 8.4 Hz, 1H).

Example 181b: (*R*)-2-((2-Cyano-3-nitrophenoxy)methyl)-*N*-isopropylpyrrolidine-1-carboxamide

Prepared as in Example 176b from (*R*)-2-((2-cyano-3-nitrophenoxy)methyl)pyrrolidinium chloride (Example 176c) and isopropyl isocyanate in 100% yield as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.07 (d, J = 6.5 Hz, 6H), 1.91 (m, 3H), 2.13 (m, 1H), 3.17 (m, 1H), 3.79 (m, 1H), 4.19 (m, 2H), 4.32 (d, J = 8.8 Hz, 1H), 5.91 (d, J = 8.1 Hz, 1H), 7.89 (m, 3H).

Example 182: (*R*)-2-((4-Amino-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide-5-yloxy)methyl)-*N*-*tert*-butylpyrrolidine-1-carboxamide



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Prepared as in Example 176 from (*R*)-2-((3-amino-2-cyanophenoxy)methyl)-*N*-*tert*-butylpyrrolidine-1-carboxamide (Example 182a) in 56% yield as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.27 (s, 9H), 1.89 (m, 4H), 3.21 (m, 1H), 4.02 (m, 1H), 4.19 (m, 1H), 4.34 (m, 1H), 5.35 (s, 1H), 6.62 (m, 1H), 6.86 (m, 1H), 7.46 (m, 1H), 8.23 (br s, 1H), 8.25 (br s, 1H), 10.91 (s, 1H). MS 396 (MH^+).

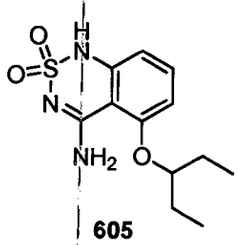
Example 182a: (*R*)-2-((3-Amino-2-cyanophenoxy)methyl)-*N*-*tert*-butylpyrrolidin-1-carboxamide

Prepared as in Example 111b from (*R*)-2-((2-cyano-3-nitrophenoxy)methyl)-*N*-*tert*-butylpyrrolidine-1-carboxamide (Example 182b) in 96% yield as a white solid. MS 317 (MH^+).

Example 182b: (*R*)-2-((2-Cyano-3-nitrophenoxy)methyl)-*N*-*tert*-butylpyrrolidine-1-carboxamide

Prepared as in Example 176b from (*R*)-2-((2-cyano-3-nitrophenoxy)methyl)pyrrolidinium chloride (Example 176c) and *tert*-butyl isocyanate in 100% yield as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.s7 (s, 9H), 1.86 (m, 1H), 1.95 (m, 2H), 2.12 (m, 1H), 3.18 (m, 1H), 3.37 (m, 1H), 4.20 (m, 1H), 4.23 (dd, J = 16.0, 6.3 Hz, 1H), 4.31 (dd, J = 9.7, 2.7 Hz, 1H), 5.36 (s, 1H), 7.84 (dd, J = 7.4, 0.9 Hz, 1H), 7.91 (m, 2H).

Example 183: 4-Amino-5-(pentan-3-yloxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-(pentan-3-yloxy) benzonitrile (Example 183a) in 48.7% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.91 (t, J = 7.6 Hz, 6H), 1.73 (m, 4H), 4.54 (m, 1H), 6.59 (dd, J = 8.4, 1.2 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 7.45 (t, J = 8.4 Hz, 1H), 7.84 (br d, J = 2.8 Hz, 1H), 8.38 (br d, J = 1.6 Hz, 1H), 10.96 (s, 1H). MS 284 (MH^+).

Example 183a: 2-Sulfamoylamino-6-(pentan-3-yloxy)benzonitrile:

Prepared as in Example 111a from 2-amino-6-(pentan-3-yloxy)benzonitrile (Example 183b) in 68.1% yield. MS 284 (MH^+).

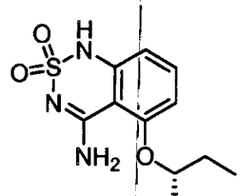
Example 183b: 2-Amino-6-(pentan-3-yloxy)benzonitrile:

Prepared as in Example 111b from 2-nitro-6-(pentan-3-yloxy)benzonitrile (Example 183c) in 100% yield. MS 205 (MH^+).

Example 183c: 2-Nitro-6-(pentan-3-yloxy)benzonitrile:

Prepared as in Example 111c from pentan-3-ol and 2,6-dinitrobenzonitrile in 86.5% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.94 (t, J = 7.6 Hz, 6H), 1.70 (m, 4H), 4.62 (m, 1H), 7.78 (dd, J = 7.2, 2.4 Hz, 1H), 7.88 (m, 2H).

Example 184: (*S*)-4-Amino-5-(*sec*-butoxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from (*S*)-2-sulfamoylamino-6-*sec*-butoxybenzonitrile (Example 184a) in 43.2% yield. ^{1}H NMR (400 MHz, DMSO-d_6) 0.94 (t, J = 7.6 Hz, 3H), 1.29 (d, J = 6.4 Hz, 1H), 1.69 (m, 2H), 4.72 (m, 1H), 6.59 (dd, J = 8.4, 1.2 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 7.45 (t, J = 8.4 Hz, 1H), 7.84 (br d, J = 2.8 Hz, 1H), 8.38 (br d, J = 1.6 Hz, 1H), 10.96 (s, 1H). MS 270 (MH^+).

Example 184a: (*S*)-2-Sulfamoylamino-6-*sec*-butoxybenzonitrile:

Prepared as in Example 111a from (*S*)-2-amino-6-*sec*-butoxybenzonitrile (Example 184b) in 69.1% yield. MS 270 (MH^+).

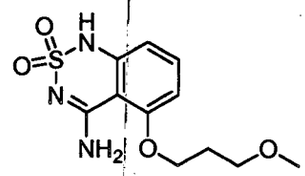
Example 184b: (*S*)-2-Amino-6-*sec*-butoxybenzonitrile:

Prepared as in Example 111b from (*S*)-2-*sec*-butoxy-6-nitrobenzonitrile (Example 184c) in 100% yield. MS 191(MH^+).

Example 184c: (*S*)-2-*sec*-Butoxy-6-nitrobenzonitrile:

Prepared as in Example 111c from (*S*)-butan-2-ol and 2,6-dinitrobenzonitrile in 85.2% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.94 (t, J = 7.6 Hz, 3H), 1.29 (d, J = 6.4 Hz, 1H), 1.69 (m, 2H), 4.72 (m, 1H), 7.74 (dd, J = 6.8, 2.4 Hz, 1H), 7.86 (m, 1H).

Example 185: (*S*)-4-Amino-5-(methoxypropoxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-(3-methoxypropoxy)benzonitrile (Example 185a) in 69.3% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.03 (m, 2H), 3.23 (s, 3H), 3.50 (t, J = 5.4 Hz, 2H), 4.18 (t, J = 5.6 Hz, 2H), 6.58 (dd, J = 8.0, 0.8 Hz, 1H), 6.70 (dd, J = 8.4, 0.8 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 78.22 (br s, 1H), 8.31 (br s, 1H), 10.90 (s, 1H). MS 286 (MH^+).

Example 185a: 2-Sulfamoylamino-6-(3-methoxypropoxy)benzonitrile:

Prepared as in Example 111a from 2-amino-6-(3-methoxypropoxy)benzonitrile (Example 185b) in 69.7% yield. MS 286 (MH^+).

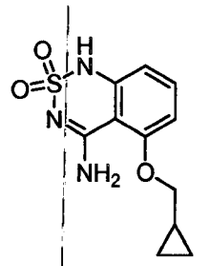
Example 185b: 2-Amino-6-(3-methoxypropoxy)benzonitrile:

Prepared as in Example 111b from 2-(3-methoxypropoxy)-6-nitrobenzonitrile (Example 185c) in 100% yield. MS 207 (MH^+).

Example 185c: 2-(3-Methoxypropoxy)-6-nitrobenzonitrile:

Prepared as in Example 111c from 3-methoxypropan-1-ol and 2,6-dinitrobenzonitrile in 63.6% yield. ^{1}H NMR (400 MHz, CDCl3) δ 2.16 (m, 2H), 3.36 (s, 3H), 3.63 (t, J = 5.6 Hz, 2H), 4.29 (t, J = 6.4 Hz, 2H), 7.35 (dd, J = 8.8, 0.8 Hz, 1H), 7.69 (t, J = 8.8 Hz, 1H), (dd, J = 8.4, 0.8 Hz, 1H).

Example 186: (*S*)-4-Amino-5-(cyclopropylmethoxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-(cyclopropylmethoxy)benzonitrile (Example 186a) in 49.4% yield. M.P.: 246-247 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.39 (m, 2H), 1.60 (m, 2H), 1.36 (m, 1H), 4.02 (d, J = 7.2 Hz, 2H), 6.60 (dd, J = 8.4, 0.8 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 7.45 (t, J = 8.8 Hz, 1H), 7.99 (br d, J = 1.6 Hz, 1H), 8.41 (br d, J = 1.6 Hz, 1H), 10.96 (br s, 1H). MS 268 (MH^+).

Example 186a: 2-Sulfamoylamino-6-(cyclopropylmethoxy)benzonitrile:

Prepared as in Example 111a from 2-amino-6-(cyclopropylmethoxy)benzonitrile (Example 186b) in 87.5% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.18 (m, 2H), 0.41 (m, 2H), 1.07 (m, 1H), 3.80 (d, J = 7.2 Hz, 2H), 6.76 (d, J = 8.0 Hz, 1H), 6.96 (d, J = 7.6 Hz, 1H), 7.09 (br s, 2H), 7.37 (t, 8.0 Hz, 1H). MS 268 (MH^+).

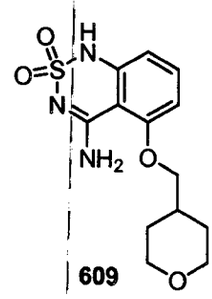
Example 186b: 2-Amino-6-(cyclopropylmethoxy)benzonitrile:

Prepared as in Example 111b from 2-(cyclopropylmethoxy)-6-benzonitrile (Example 186c) in 100% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.35 (m, 2H), 0.58 (m, 2H), 1.23 (m, 1H), 3.86 (d, J = 7.6 Hz, 2H), 5.98 (br s, 2H), 6.20 (d, J = 8.0 Hz, 1H), 6.32 (dd, J = 8.8, 0.8 Hz, 1H), 7.17 (t, 8.8 Hz, 1H) MS 189 (MH^+).

Example 186c: 2-(Cyclopropylmethoxy)-6-benzonitrile:

Prepared as in Example 111c from 2,6-dinitrobenzonitrile and cyclopropylmethanol in 90%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.40 (m, 2H), 0.62 (m, 2H), 1.29 (m, 1H), 4.14 (d, J = 7.2 Hz, 2H), 7.71 (dd, J = 7.2, 1.2 Hz, 1H), 7.9 (m, 2H).

Example 187: 4-Amino-5-(methoxytetrahydro-2*H*-pyran-4-yl)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-(tetrahydro-2*H*-pyran-4-yl)benzonitrile (Example 187a) in 92% yield as a cream colored solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (m, 4H), 1.63 (br m, 4H), 3.31 (br m, 2H), 3.86 (br m, 2H), 4.01 (d, J = 6.8 Hz, 2H), 6.57 (d, J = 8.4 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.68 (br, 1H), 8.24 (s, 1H), 10.90 (br, 1H). MS 312 (MH^+).

Example 187a: 2-Sulfamoylamino-6-(tetrahydro-2*H*-pyran-4-yl)benzonitrile

Prepared as in Example 111a from 2-amino-6-((tetrahydro-2*H*-pyran-4-yl)methoxy)benzonitrile (Example 187b) in 51% yield as an orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.35 (m, 2H), 1.66 (br, 2H), 2.01 (br, 1H), 3.32 (br, 2H), 3.87 (br m, 2H), 3.96 (d, J = 6.4 Hz, 2H), 6.92 (d, J = 8.4 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.19 (br s, 2H), 7.52 (t, J = 8.4 Hz, 1H), 9.44 (br s, 1H).

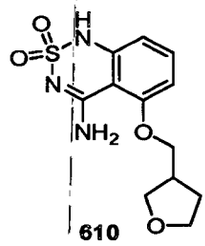
Example 187b: 2-Amino-6-((tetrahydro-2*H*-pyran-4-yl)methoxy)benzonitrile

Prepared as in Example 111b from 2-nitro-6-((tetrahydro-2*H*-pyran-4-yl)methoxy)benzonitrile (Example 187c) in 80% yield as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 1.32 (m, 2H), 1.64 (m, 2H), 1.97 (br, 1H), 3.31 (m, 2H), 3.86 (m, 4H), 5.97 (s, 2H), 6.19 (d, J = 8.4 Hz, 1H), 6.31 (d, 1H), 7.15 (t, J = 8.4 Hz, 1H).

Example 187c: 2-Nitro-6-((tetrahydro-2*H*-pyran-4-yl)methoxy)benzonitrile:

To a solution of tetrahydropyran-4-methanol (782 mg, 6.73 mmol) in THF (25 mL), was added slowly 1.38M nBuLi (4.13 mL, 5.70mmol) in hexane at -78 °C under nitrogen. At one hour a solution of 2,6-dinitrobenzonitrile (1.00 g, 5.18 mmol) in THF (25 mL) was added. The reaction was stirred under N_2 overnight at rt, then was quenched with water (100mL). The precipitate was collected by filtration to provide 2-nitro-6-((tetrahydro-2*H*-pyran-4-yl)methoxy)benzonitrile (1.13g, 83%) as a light brown solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 1.68 (m, 2H), 2.06 (br, 1H), 3.33 (m, 2H), 3.88 (m, 2H), 4.11 (d, J = 6.0 Hz, 2H), 7.72 (d, J = 6.0 Hz, 1H), 7.89-7.85 (m, 2H).

Example 188: 4-Amino-5-(methoxytetrahydrofuran-3-yl)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-(methoxytetrahydrofuran-3-yl)benzonitrile (Example 188a) in 26% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.64 (m, 1H), 1.99 (m, 1H), 2.73 (m, 1H), 3.56 (m, 2H), 3.67 (m, 1H), 3.75 (m, 1H), 4.04 (m, 2H), 6.51 (d, J = 8.4 Hz, 1H), 6.62 (d, J= 8.4 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 7.70 (br s, 1H), 8.09 (br s, 1H), 10.92 (br s, 1H), MS 298 (MH^+).

Example 188a: 2-Sulfamoylamino-6-(methoxytetrahydrofuran-3-yl)benzonitrile

Prepared as in Example 111a from 2-amino-6-((tetrahydrofuran-3-yl)mehtoxy)benzonitrile (Example 188b) in 14% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.62 (m, 1H), 1.96 (m, 1H), 2.43 (m, 1H), 2.61 (m, 1H), 3.48 (m, 1H), 3.60 (m, 1H), 3.71 (m, 2H), 3.99 (m, 2H), 6.90 (d, J = 8.8 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 7.19 (s, 1H), 7.49 (t, J = 8.4 Hz, 1H), 9.42 (s, 1H).

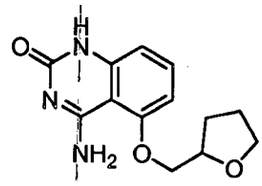
Example 188b: 2-Amino-6-((tetrahydrofuran-3-yl)mehtoxy)benzonitrile:

Prepared as in Example 111b from 2-nitro-6-((tetrahydrofuran-3-yl)methoxy)benzonitrile (Example 188c) in 99% yield as a golden brown oil. MS 219 (MH^+).

Example 188c: 2-Nitro-6-((tetrahydrofuran-3-yl)methoxy)benzonitrile:

Prepared as in Example 166d from 2,6-dinitrobenzonitrile and 3-hydroxymethyltetrahydrofuran in 48% yield as an orange-red solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.68 (m, 1H), 2.00 (m, 1H), 2.70 (m, 1H), 3.54 (m, 1H), 3.66 (m, 1H), 3.76 (m, 2H), 4.03 (m, 1H), 4.19 (m, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.90-7.95 (m, 2H).

Example 189: 4-Amino-5-((tetrahydrofuran-2-yl)methoxy)quinazolin-2(1*H*)-one



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Prepared as in Example 111 from *N*-(2-cyano-3-((tetrahydrofuran-2-yl)methoxy)phenylcarbamoyl)benzamide (Example 189a) in 39% yield. ^{1}H NMR (400 MHz, *d*-DMSO) δ 1.65 (br m, 1H), 1.85 (br m, 2H), 1.99 (br m, 1H), 3.71 (m, 2H), 3.78 (m, 1H), 3.98 (m, 1H), 6.70-6.67 (m, 2H), 7.42 (t, J = 8.0 Hz, 1H), 7.62 (s, 1H), 7.88 (s, 1H), 10.62 (s, 1H).

Example 189a: *N*-(2-Cyano-3-((tetrahydrofuran-2-yl)methoxy) phenyl carbamoyl)benzamide

Prepared as in Example 146a from 2-amino-6-((tetrahydrofuran-2-yl)methoxy)benzonitrile (Example 189b) in 45% yield as a white solid. ^{1}H NMR (400 MHz, *d*-DMSO) δ 1.98-1.74 (m, 4H), 3.54 (m, 1H), 3.69 (m, 1H), 4.20-4.07 (m, 3H), 6.97 (d, J = 8.8 Hz, 1H), 7.67-7.51 (m, 4H).

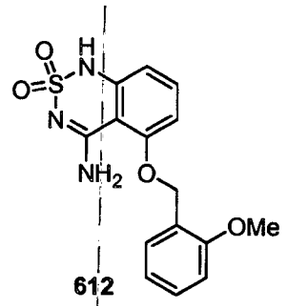
Example 189b: 2-Amino-6-((tetrahydrofuran-2-yl)methoxy)benzonitrile

Prepared as in Example 111b from 2-nitro-6-((tetrahydrofuran-2-yl)methoxy)benzonitrile (Example 189c) in 92% yield as a light blue clear oil. ^{1}H NMR (400 MHz, MeOD) δ 1.97-1.68 (m, 4H), 3.75-3.64 (m, 1H), 3.80-3.75 (m, 1H), 3.98-3.90 (m, 2H), 4.15-4.12 (m, 1H), 5.96 (s, 1H), 6.18 (d, J = 8.0 Hz, 1H), 6.31 (d, J = 8.0 Hz, 1H), 7.14 (t, J = 8.4 Hz, 1H).

Example 189c: 2-Nitro-6-((tetrahydrofuran-2-yl)methoxy)benzonitrile:

Prepared as in Example 166d from 2,6-dinitrobenzonitrile and tetrafurfuryl alcohol in 68% yield. ^{1}H NMR (400 MHz, MeOD) δ 2.10-1.70 (m, 7H), 3.68-3.66 (m, 1H), 3.80-3.78 (m, 1H), 4.29-4.20 (m, 3H), 7.72 (d, J = 6.0 Hz, 1H), 7.90-7.84 (m, 2H).

Example 190: 4-Amino-5-(2-methoxybenzyloxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-(4-methoxybenzyloxy) benzonitrile (Example 190a) in 85% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.81 (s, 3H), 5.25 (s, 2H), 6.59 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.96 (t, J = 7.2 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.46-7.42 (m, 2H), 7.91 (s, 1H), 8.31 (s, 1H), 10.96 (s, 1H). MS 334 (MH^+).

Example 190a: 2-Sulfamoylamino-6-(2-methoxybenzyloxy) benzonitrile

Prepared as in Example 111a from 2-amino-6-((tetrahydrofuran-2-yl)methoxy)benzonitrile (Example 190b) in 23% yield. ^{1}H NMR (400 MHz, d-DMSO) δ 3.80 (s, 3H), 6.88 (d, J = 8.4 Hz, 1H), 6.88 (d, J = 8.1 Hz 1H), 6.96 (t, J = 7.6 Hz, 1H), 7.06 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.4 Hz, 1H), 7.39-7.33 (m, 5H), 7.45 (d, J = 7.2 Hz, 1H), 11.20 (s, 1H).

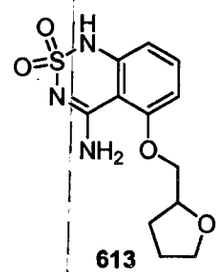
Example 190b: 2-Amino-6-(2-methoxybenzyloxy) benzonitrile

Prepared as in Example 111b from 2-nitro-6-(2-methoxybenzyloxy) benzonitrile (example 190c) in 56% yield. ^{1}H NMR (400 MHz, MeOD) δ 3.79 (s, 3H), 5.04 (s, 2H), 6.30-6.26 (m, 2H), 7.06-6.94 (m, 3H), 7.33-7.28 (m, 3H), 7.54 (s, 1H).

Example 190c: 2-Nitro-6-(2-methoxybenzyloxy) benzonitrile

Prepared as in Example 111c from 2,6-dinitrobenzonitrile and 2-methoxybenzyl alcohol in 58% yield. ^{1}H NMR (400 MHz, DMSO) δ 3.82 (s, 3H), 5.34 (s, 2H), 6.99 (t, J = 7.6 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 7.37 (t, J = 8.4 Hz, 1H), 7.46 (d, J = 6.0 Hz, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.93-7.87 (m, 2H).

Example 191: 4-Amino-5-(methoxytetrahydrofuran-2-yl)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



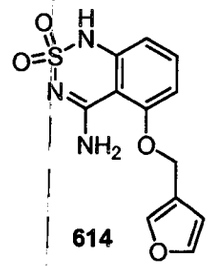
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Prepared as in Example 111 from 2-sulfamoylamino-6-(methoxytetrahydrofuran-2-yl)benzonitrile (Example 191a) in 100% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.65 (m, 1H), 1.86 (m, 1H), 1.98 (m, 1H), 3.69 (m, 1H), 3.78 (m, 1H), 3.98 (m, 1H) 4.25 (m, 1H), 6.61 (d, J = 7.2 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H).

Example 191a: 2-Sulfamoylamino-6-(methoxytetrahydrofuran-2-yl)benzonitrile

Prepared as in Example 111a from 2-amino-6-((tetrahydrofuran-2-yl)methoxy)benzonitrile (Example 189b) in 79% yield as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.02-1.68 (m, 2H), 3.66 (m, 1H), 3.81-3.76 (m, 1H), 4.20-4.03 (m, 3H), 6.93 (d, J = 8.4 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.23 (s, 1H), 7.53 (t, J = 8.4 Hz, 1H), 9.34 (br s, 1H).

Example 192: 4-Amino-5-(furan-3-ylmethoxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-(furan-3-ylmethoxy)benzonitrile (Example 192a) in 45% yield as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.11 (s, 2H), 6.54 (d, J = 0.4 Hz, 1H), 6.56 (s, 1H), 6.80 (d, J = 8.8 Hz, 1H), 7.39 (t, J = 8.4 Hz, 1H), 7.64 (s, 1H), 7.74 (s, 1H), 7.81 (s, 1H), 8.23 (s, 1H), 10.90 (s, 1H). MS 294 (MH^+).

Example 192a: 2-Sulfamoylamino-6-(furan-3-ylmethoxy)benzonitrile

Prepared as in Example 111a from 2-amino-6-(furan-3-ylmethoxy)benzonitrile (Example 192b) in 57% yield as an off white solid. ^{1}H NMR (400 MHz, *d*-DMSO) δ 5.04 (s,

2H), 6.62 (s, 1H), 6.88 (d, J = 8.8 Hz, 1H), 7.15 (d, J = 8.1, 0.8 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 7.39-7.32 (m, 2H), 7.67 (s, 1H), 7.79 (s, 1H), 7.86 (s. 1H), 7.93 (s, 1H), 10.91 (s, 1H).

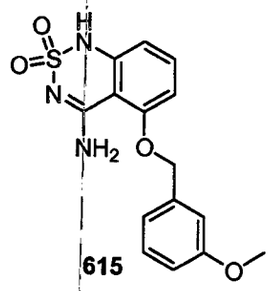
Example 192b: 2-Amino-6-(furan-3-ylmethoxy)benzonitrile

Prepared as in Example 111b from 2-nitro-6-(furan-3-ylmethoxy)benzonitrile (Example 192c) in 21% yield as a light yellow oil. ^{1}H NMR (400 MHz, *d*-DMSO) δ 4.92 (s, 2H), 6.31-6.26 (m, 2H), 6.59 (s, 1H), 6.99 (t, J = 8.4 Hz, 1H), 7.27 (s, 1H), 7.45 (s, 1H), 7.66 (s, 1H), 7.76 (s, 1H).

Example 192c: 2-Nitro-6-(furan-3-ylmethoxy)benzonitrile

Prepared as in Example 111c from 2,6-dinitrobenzonitrile and 3-furanmethanol in 100% yield. ^{1}H NMR (400 MHz, *d*-DMSO) δ 5.27 (s, 2H), 6.59 (s, 1H), 7.69 (s, 1H), 7.91-7.84 (m, 4H).

Example 193: 4-Amino-5-(3-methoxybenzyloxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-(3-methoxybenzyloxy)benzonitrile (Example 193a) in 54% yield. ^{1}H NMR (400 MHz, *d*-DMSO) δ 3.74 (s, 3H), 5.27 (s, 2H), 6.59 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 7.04 (d, J = 7.2 Hz, 1H), 7.08 (s, 1H), 7.31 (t, J = 8.4 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.89 (br s, 1H), 8.32 (br s, 1H), 10.96 (br s, 1H). MS 334 (MH^+).

Example193a: 2-Sulfamoylamino-6-(3-methoxybenzyloxy)benzonitrile

Prepared as in Example 111a from 2-amino-6-(3-methoxybenzyloxy)benzonitrile (Example 193b) in17% yield as a white solid. MS 334 (MH^+).

Example 193b: 2-Amino-6-(3-methoxybenzyloxy)benzonitrile

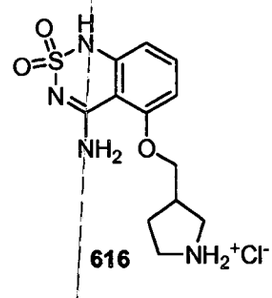
To a mixture of 2-nitro-6-(3-methoxybenzyloxy)benzonitrile (Example 193c) (480mg, 1.69 mmol) in 5:1 acetone:water (9 mL) was added zinc (552mg, 8.44 mmol) and ammonium chloride (911mg, 16.9 mmol). The reaction was stirred at room temperature for 30 minutes, then filtered and concentrated. The residue was purified by flash chromatography

(55:45 EtOAc:Hexane) to provide 2-amino-6-(benzyloxy)benzonitrile (337 mg, 78%). ^{1}H NMR (400 MHz, *d*-DMSO) δ 3.73 (s, 3H), 5.04 (s, 1H), 6.27 (d, J = 8.0 Hz, 1H), 6.31 (d, J = 8.4 Hz, 1H), 7.06-6.97 (m, 3H), 7.27 (t, J = 8.0 Hz, 1H), 7.36 (s, 1H), 7.55 (s, 1H).

Example 193c: 2-(3-Methoxybenzyloxy)-6-nitrobenzonitrile

Prepared as in Example 111c from 2,6-dinitrobenzonitrile and 3-methoxybenzylalcohol in 83% yield. ^{1}H NMR (400 MHz, *d*-DMSO) δ 3.75 (s, 3H), 5.38 (s, 2H), 6.91 (d, J = 8.0 Hz, 1H), 7.04 (d, J = 7.6 Hz, 1H), 7.07 (s, 1H), 7.33 (t, J=8.0 Hz, 1H), 7.78 (d, J = 8.8 Hz, 4H), 7.93-7.87 (m, 2H).

Example 194: 4-(2-(4-Amino-*1H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide-5-yloxy)methyl)pyrrolidinium chloride



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Prepared as in Example 166 from *tert*-Butyl 3-(2-(4-amino-*1H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide-5-yloxy)methyl)pyrrolidine-1-carboxylate (Example 194a) in 27% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.72 (m, 1H), 2.07 (m, 1H), 2.52 (m, 1H), 2.64 (m, 1H), 2.94-2.74 (m, 3H), 3.79 (m, 2H), 6.26 (d, J = 8.0 Hz, 1H), 6.37 (d, J = 8.8 Hz, 1H), 7.09 (t, J = 8.0 Hz, 1H), 7.31 (br s, 1H), 7.96 (br s, 1H), 9.03 (br s, 1H).

Example 194a: *tert*-Butyl 3-(2-(4-amino-*1H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide-5-yloxy)methyl)pyrrolidine-1-carboxylate

Prepared as in Example 111 from *tert*-butyl-3-((2-cyano-3-(sulfamoylmethyl)phenoxy)methyl) pyrrolidine-1-carboxylate (Example 194b) in 94% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.37 (s, 9H), 1.66 (br m, 1H), 1.97 (br m, 1H), 2.78 (br m, 1H), 3.48-3.20 (br m, 4H), 4.12 (br, m 2H), 6.60 (d, J = 8.0 Hz, 1H), 6.74 (d, J = 8.4Hz, 1H), 7.44 (t, J = 8.4 Hz, 1H), 7.70 (s, 1H), 8.33 (s, 1H), 10.95 (s, 1H).

Example 194b: *tert*-Butyl 3-((2-cyano-3-(sulfamoylamino)phenoxy)methyl) pyrrolidine -1-carboxylate

Prepared as in Example 111a from *tert*-butyl 3-((3-amino-2-cyanophenoxy)methyl)pyrrolidine-1-carboxylate (Example 194c) in 47% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.37 (s, 9H), 1.70 (br, 1H), 1.97 (br, 1H), 2.63 (br, 1H), 3.47-2.98 (br m, 4H), 4.08 (br m, 2H), 6.94 (d, J = 8.8 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 7.24 (s, 1H), 7.48 (s, 1H), 7.54 (t, J = 8.0, 1H), 9.48 (br s, 1H).

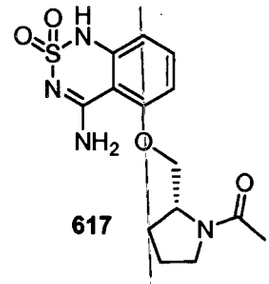
Example 194c: *tert*-Butyl 3-((3-amino-2-cyanophenoxy)methyl)pyrrolidine-1-caroxylate

Prepared as in Example 111b from *tert*-butyl–((2-cyano-3-nitorphenoxy)methyl)pyrrolidine-1-carboxylate (Example 194d) in 100% yield as a clear oil. ^{1}H NMR (400MHz, DMSO-d_6) δ 1.37 (s, 9H), 1.69 (br, 1H), 1.96 (br, 1H), 2.59 (br, 1H), 3.07 (br, 1H), 3.23 (br, 1H), 3.35 (br, 1H), 3.40 (br, 1H), 3.96 (m, 2H), 5.98 (s, 2H), 6.20 (d, J = 8.0 Hz, 1H), 6.32 (d, J = 8.0 Hz, 1H), 7.15 (t, J = 8.4 Hz, 1H).

Example 194d: *tert*-Butyl –((2-cyano-3-nitorphenoxy)methyl)pyrrolidine-1-carboxylate

Prepared as in Example 166d from 2,6-dinitrobenzonitrile and *tert*-butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate in 69% yield as a yellow solid. MS 347 (MH^+).

Example 195: (*R*)-4-Amino-5-((1-acetylpyrrolidin-2-yl)methoxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 176 from (*R*)-2-amino-6-((1-acetylpyrrolidin-2-yl)methoxy)benzonitrile (Example 195a) in 31% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.90 (m, 4H), 2.00 (s, 3H), 3.49 (m, 2H), 4.09 (dd, J = 9.7, 6.1 Hz, 1H), 4.24 (dd, J = 9.8, 5.7 Hz, 1H), 4.41 (m, 1H), 6.62 (d, J = 8.2 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 7.46 (t, J = 8.3 Hz, 1H), 8.12 (br s, 1H), 8.33 (br s, 1H), 10.93 (br s, 1H). MS 339 (MH^+).

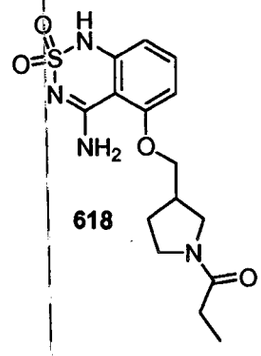
Example 195a: (*R*)-2-Amino-6-((1-acetylpyrrolidin-2-yl)methoxy)benzonitrile

Prepared as in Example 111b from (*R*)-2-((1-acetylpyrrolidin-2-yl)methoxy)-6-nitrobenzonitrile (Example 195b) in 77% yield as a clear syrup. MS 260 (MH^+).

Example 195b: (*R*)-2-((1-Acetylpyrrolidin-2-yl)methoxy)-6-nitrobenzonitrile

Prepared as in Example 176b from (*R*)-2-((2-cyano-3-nitrophenoxy)methyl)pyrrolidinium chloride and acetyl chloride in 100% yield as a yellow syrup. MS 290 (MH^+).

Example 196: 4-Amino-5-(methoxy-3-pyrolidine-1-propionyl)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-((1-propionylpyrrolidin-3-yl)methoxybenzonitrile (Example 196a) in 29% yield as an off-white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 0.95 (t, J = 7.6 Hz, 3H), 1.66 (m, 1H), 1.77 (m, 1H), 1.97 (m, 1H), 2.05 (m, 1H), 2.21 (q, J = 8.0 Hz, 2H), 2.74 (m, 1H), 2.86 (m, 1H), 3.63-3.23 (m, 4H), 4.13 (m, 2H), 6.60 (d, J = 8.0 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.72 (s, 1H), 8.37-8.32 (m, 1H), 10.94 (s, 1H).

Example 196a: 2-Sulfamoylamino-6-((1-propionylpyrrolidin-3-yl) methoxybenzonitrile

Prepared as in Example 111a from 2-amino-6-((1-propionylpyrrolidin-3-yl)methoxy)benzonitrile (Example 196b) in 27% yield as a white solid. MS 353 (MH^+).

Example 196b: 2-Amino-6-((1-propionylpyrrolidin-3-yl)methoxy)benzonitrile:

Prepared as in Example 111b from 2-nitro-6-((1-propionylpyrrolidin-3-yl)methoxy)benzonitrile (Example 196c) in 100% yield as a clear oil. MS 274 (MH^+).

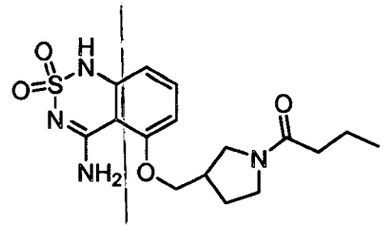
Example 196c: 2-Nitro-6-((1-propionylpyrrolidin-3-yl)methoxy)benzonitrile:

Prepared as in Example 176b from 2-nitro-6-(pyrrolidin-3-ylmethoxy)benzonitrile hydrochloride (Example 196d) and propionyl chloride in 51% as a yellow solid. MS 304 (MH^+).

Example 196d: 2-Nitro-6-(pyrrolidin-3-ylmethoxy)benzonitrile hydrochloride:

Prepared as in Example 166 from *tert*-butyl–((2-cyano-3-nitorphenoxy)methyl)pyrrolidine-1-carboxylate (Example 194d) in 100% yield as a yellow solid. MS 248 (MH^+).

Example 197: 4-Amino-5-(methoxy-3-pyrolidine-1-butyryl)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-((1-butyrylpyrrolidin-3-yl)methoxybenzonitrile (Example 197a) in 73% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.86 (t, J = 7.6 Hz, 3H), 1.48 (q, J = 7.6 Hz, 2H), 1.65 (m, 1H), 1.76 (m, 1H), 1.97 (m, 1H), 2.05 (m, 1H), 2.17 (t, J = 7.2 Hz, 2H), 2.74 (m, 1H), 2.85 (m, 1H), 3.10 (m, 1H), 3.64-3.23 (m, 4H), 4.12 (m, 1H), 6.60 (d, J = 8.0 Hz, 1H), 6.75 (d, J = 8.8 Hz, 1H), 7.44 (t, J = 8.4 Hz, 1H), 7.71 (s, 1H), 8.35-8.32 (m, 1H), 10.94 (s, 1H).

Example 197a: 2-Sulfamoylamino-6-((1-butyrylpyrrolidin-3-yl)methoxybenzonitrile:

Prepared as in Example 111a from 2-amino-6-((1-butyrylpyrrolidin-3-yl)methoxy)benzonitrile (Example 197b) in 19% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.85 (t, J = 7.6 Hz, 3H), 1.48 (q, J = 7.6 Hz, 2H), 2.13-1.64 (m, 2H), 2.17 (m, 2H), 2.75-2.53 (m, 2H), 3.65-3.18 (m, 4H), 4.09 (m, 2H), 6.94 (m, 1H), 7.13 (m, 1H), 7.25 (s, 1H), 7.54 (m, 1H), 9.45 (m, 1H).

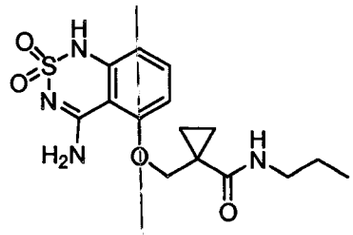
Example 197b: 2-Amino-6-((1-butyrylpyrrolidin-3-yl)methoxy)benzonitrile:

Prepared as in Example 111b from 2-nitro-6-((1-butyrylpyrrolidin-3-yl)methoxy)benzonitrile (Example 197c) in 100% yield as a brown oil. MS 288 (MH^+).

Example 197c: 2-Nitro-6-((1-butyrylpyrrolidin-3-yl)methoxy)benzonitrile:

Prepared as in Example 176b from 2-nitro-6-(pyrrolidin-3-ylmethoxy)benzonitrile hydrochloride (Example 196d) and butyryl chloride in 100% yield as an orange solid. MS 318 (MH^+).

Example 198: (E)-4-Amino-5-(1-(propylcarbamoyl)cyclopropylmethoxy)-1H-benzo[c][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 1-((2-cyano-3-(sulfamoylamino)phenoxy)methyl)-N-propylcyclopropanecarboxamide (Example 198a) in 94% yield as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ10.95 (broad s, 1H), 8.35 (broad s, 1H), 7.95 (broad s, 1H), 7.76 (t, J = 5.2 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 6.61 (d, J = 7.6 Hz, 1H), 4.22 (s, 2H), 3.01 (q, J = 6.4 Hz, 2H), 1.40 (hex, J = 6.8 Hz, 2H), 1.12-1.18 (m, 2H), 0.88-0.95 (m, 2H), 0.80 (t, J = 7.6 Hz, 3H). MS 353 (MH^+).

Example 198a: 1-((2-Cyano-3-(sulfamoylamino)phenoxy)methyl)-N-propylcyclopropanecarboxamide

Prepared as in Example 111a from 1-((3-amino-2-cyanophenoxy)methyl)-N-propylcyclopropanecarboxamide (Example 198b) and sulfamoyl chloride in 78% yield as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ9.45 (broad s, 1H), 7.51-7.61 (m, 2H), 7.26 (broad s, 2H), 7.16 (d, J = 8.0 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 4.24 (s, 2H), 3.04 (q, J = 6.4 Hz, 2H), 1.43 (hex, J = 7.6 Hz, 2H), 1.08-1.14 (m, 2H), 0.83-0.88 (m, 2H), 0.82 (t, J = 7.2 Hz, 3H).

Example 198b: 1-((3-Amino-2-cyanophenoxy)methyl)-N-propylcyclopropanecarboxamide

A solution of 1-(hydroxymethyl)-N-propylcyclopropanecarboxamide (Example 198c) (0.67 g, 4.25 mmol) in anhydrous THF (10 mL) was treated with NaH (0.17 g, 4.25 mmol, 60% suspension in mineral oil) at 0 °C, under a nitrogen atmosphere. The obtained mixture was stirred at 0 °C for 10 min and at rt over 30 min. Then, a solution of 2-amino-6-fluorobenzonitrile (0.53 g, 3.86 mmol) in THF (5.0 mL) was added and the obtained mixture was heated at reflux overnight. The cold mixture was quenched with saturated aqueous solution of NH_4Cl (20 mL) and extracted with EtOAc (3x50 mL). The combined extract was washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by chromatography on silica gel using gradient hexanes → hexanes/EtOAc (4:6), to give 0.75 g (71%) of the title compound as a yellow solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ7.51 (t, J = 6.0 Hz, 1H), 7.17 (t, J

= 8.0 Hz, 1H), 6.34 (d, J = 8.4 Hz, 1H), 6.19 (d, J = 8.4 Hz, 1H), 5.97 (broad s, 2H), 4.13 (s, 2H), 3.04 (q, J = 6.4 Hz, 2H), 1.43 (hex, J = 6.8 Hz, 2H), 1.05-1.11 (m, 2H), 0.78-0.86 (m, 5H).

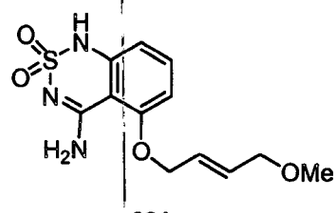
Example 198c: 1-(Hydroxymethyl)-N-propylcyclopropanecarboxamide

To a solution of ethyl 1-(propylcarbamoyl)cyclopropanecarboxylate (Example 198d) (1.65 g, 8.27 mmol) in EtOH (70 mL) was added $NaBH_4$ (0.97 g, 25.64 mmol) at rt. The obtained mixture was stirred at rt over 2 days, quenched with 1.5M HCl and concentrated under reduced pressure. The concentrated mixture was extracted with EtOAc (4x70 mL), the combined extract was washed with saturated $NaHCO_3$ and brine, and was dried over $MgSO_4$. The filtrate was evaporated and the residue was purified by chromatography on silica gel using the solvent gradient hexanes → hexanes/EtOAc (1:9), to furnish 1.14 g (88%) of the product as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ7.49 (broad s, 1H), 5.09 (broad s, 1H), 3.49 (s, 2H), 3.05 (q, J = 6.4 Hz, 2H), 1.41 (hex, J = 7.6 Hz, 2H), 0.86-0.91 (m, 2H), 0.83 (t, J = 7.2 Hz, 3H), 0.55-0.60 (m, 2H).

Example 198d: Ethyl 1-(propylcarbamoyl)cyclopropanecarboxylate

To a solution of 1-(ethoxycarbonyl)cyclopropanecarboxylic acid (Wheeler, T. N.; Ray, J. A. *Synthetic Communications* **1988**, *18(2)*, 141) (1.52 g, 9.62 mmol) and *n*-propylamine (0.63 g, 10.58 mmol) in anhydrous DMF (65 mL) at rt, were added $NaHCO_3$ (4.04 g, 48.11 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (2.21 g, 11.54 mmol) and 1-hydroxybenzotriazole hydrate (1.77 g, 11.54 mmol) under a nitrogen atmosphere. After being stirred at rt overnight, the mixture was partitioned between water (100 mL) and EtOAc (300 mL). The organic phase was separated, washed with water and brine, and was dried over anhydrous $MgSO_4$. The filtrate was evaporated to give 1.65 g (86%) of the crude product which was used in the next step without purification. ^{1}H-NMR (400 MHz, DMSO-d_6) δ8.33 (broad s, 1H), 4.08 (q, J = 6.8 Hz, 2H), 3.07 (q, J = 6.4 Hz, 2H), 1.43 (hex, J = 6.4 Hz, 2H), 1.31 (s, 4H), 1.17 (t, J = 6.4 Hz, 3H), 0.85 (t, J = 7.2 Hz, 3H).

Example 199: (*E*)-4-Amino-5-(4-methoxybut-2-enyloxy)-1H-benzo[c][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-(4-methoxybut-2-enyloxy)benzonitrile (Example 199a) in 91% yield as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ10.94 (broad s, 1H), 8.34 (broad s, 1H), 7.90 (broad s, 1H), 7.45 (t, J = 8.4 Hz, 1H), 6.75 (d, J = 7.6 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 5.88-6.02 (m, 2H), 4.75-4.81 (m, 2H), 3.88-3.93 (m, 2H), 3.22 (s, 3H). MS 298 (MH^+).

Example 199a: 2-Sulfamoylamino-6-(4-methoxybut-2-enyloxy)benzonitrile

Prepared as in Example 111a from (*E*)-2-amino-6-(4-methoxybut-2-enyloxy)benzonitrile (Example 199b) in 93% yield as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ9.46 (broad s, 1H), 7.56 (t, J = 8.4 Hz, 1H), 7.26 (broad s, 2H), 7.15 (d, J = 8.0 Hz, 1H), 6.96 (d, J = 8.8 Hz, 1H), 5.84-6.00 (m, 2H), 4.68-4.76 (m, 2H), 3.89-3.95 (m, 2H), 3.23 (s, 3H).

Example 199b: (*E*)-2-Amino-6-(4-methoxybut-2-enyloxy)benzonitrile

To a solution of (*E*)-2-(4-methoxybut-2-enyloxy)-6-nitrobenzonitrile (Example 199c) (0.25 g, 1.00 mmol) in a mixture of AcOH, EtOH and water (33 mL, 1:1:1) was added iron powder (0.56 g, 10.00 mmol) at rt. The obtained mixture was stirred at rt for 20 min, then was heated to 50 °C for a further 15 min, and allowed to cool. The suspension was concentrated under reduced pressure; the residue was treated with water (50 mL) and extracted with EtOAc (4x50 mL). The combined extract was washed with saturated aqueous $NaHCO_3$ and brine, and was dried over anhydrous $MgSO_4$. The filtrate was evaporated and the residue was purified by silica gel flash chromatography using gradient hexanes → hexanes/EtOAc (1:1), to give 0.19 g (86%) of the title compound as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) 7.17 (t, J = 8.4 Hz, 1H), 6.34 (d, J = 8.8 Hz, 1H), 6.22 (d, J = 8.4 Hz, 1H), 6.00 (broad s, 2H), 5.82-5.96 (m, 2H), 4.56-4.62 (m, 2H), 3.88-3.93 (m, 2H), 3.23 (s, 3H).

Example 199c: (*E*)-2-(4-Methoxybut-2-enyloxy)-6-nitrobenzonitrile

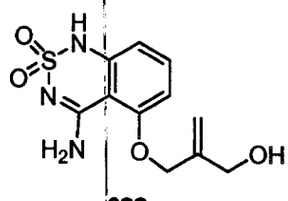
To a solution of (*E*)-2-(4-hydroxybut-2-enyloxy)-6-nitrobenzonitrile (Example 199d) (0.50 g, 2.13 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (2.18 g, 10.65 mmol) in

CH_2Cl_2 (15.0 mL) at rt, was added trimethyloxonium tetrafluoroborate (1.58 g, 10.65 mmol) under a nitrogen atmosphere. After 1 h at rt, the reaction was quenched with water (50 mL) and extracted with EtOAc (4x50 mL). The combined extract was washed with water, 1.5M HCl, saturated aqueous $NaHCO_3$ and brine, and was dried over anhydrous $MgSO_4$. The filtrate was evaporated and the residue was purified by chromatography on silica gel using the solvent gradient hexanes → hexanes/EtOAc (3:7), to give 0.25 g (72%) of the title compound as a yellow solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ7.84-7.92 (m, 2H), 7.68-7.73 (m, 1H), 5.82-6.03 (m, 2H), 4.82-4.88 (m, 2H), 3.87-3.93 (m, 2H), 3.21 (s, 3H).

Example 199d: (*E*)-2-(4-Hydroxybut-2-enyloxy)-6-nitrobenzonitrile

Prepared as in Example 166d from (*E*)-but-2-ene-1,4-diol (Miller, A. E. G.; Biss, J. W.; Schwartzman, L. H. *J. Org. Chem.* **1959**, *24*, 627 in 30% yield as a yellow solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ7.83-7.94 (m, 2H), 7.67-7.74 (m, 1H), 5.97-6.07 (m, 1H), 5.78-5.89 (m, 1H), 4.80-89 (m, 3H), 3.94-4.02 (m, 2H).

Example 200: 4-Amino-5-(2-(hydroxymethyl)allyloxy)-1H-benzo[c][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-((2-cyano-3-(sulfamoylamino)phenoxy)methyl)allyl acetate (Example 200a) in 44% yield as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ10.95 (broad s, 1H), 8.34 (broad s, 1H), 8.01 (broad s, 1H), 7.45 (t, J = 8.0 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 5.26 (s, 1H), 5.20 (s, 1H), 5.14 (t, J = 5.2 Hz, 1H), 4.78 (s, 2H), 4.03 (d, J = 5.2 Hz, 2H). MS 284 (MH^+).

Example 200a: 2-((2-Cyano-3-(sulfamoylamino)phenoxy)methyl)allyl acetate

Prepared as in Example 111a from 2-((3-amino-2-cyanophenoxy)methyl)allyl acetate (Example 200b) in 87% yield as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ9.50 (broad s, 1H), 7.57 (t, J = 8.4 Hz, 1H), 7.28 (broad s, 2H), 7.17 (d, J = 8.0 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 5.39 (broad s, 1H), 5.33 (broad s, 1H), 4.74 (s, 2H), 4.63 (s, 2H), 2.05 (s, 3H).

Example 200b: 2-((3-Amino-2-cyanophenoxy)methyl)allyl acetate

Prepared as in Example 199b from 2-((2-cyano-3-nitrophenoxy)methyl)allyl acetate (Example 200c) in 76% yield as a yellow oil. ^{1}H-NMR (400 MHz, DMSO-d_6) δ7.18 (t, J = 8.4 Hz, 1H), 6.35 (d, J = 8.8 Hz, 1H), 6.23 (d, J = 8.0 Hz, 1H), 6.03 (broad s, 2H), 5.34-5.38 (m, 1H), 5.28-5.31 (m, 1H), 4.61 (s, 4H), 2.05 (s, 3H).

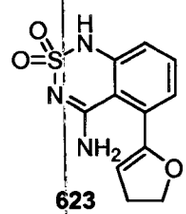
Example 200c: 2-((2-Cyano-3-nitrophenoxy)methyl)allyl acetate

To a solution of 2-(2-(hydroxymethyl)allyloxy)-6-nitrobenzonitrile (Example 200d) (0.40 g, 1.73 mmol), 4-dimethylaminopyridine (0.21 g, 1.73 mmol) and pyridine (0.68 g, 8.64 mmol) in CH_2Cl_2 (10.0 mL) at 0 °C, was added Ac_2O (0.53 g, 5.19 mmol) under a nitrogen atmosphere. After being stirred at 0 °C for 10 min, the mixture was stirred at rt overnight. The reaction mixture was diluted with EtOAc (100 mL), washed with 1.5M HCl, saturated aqueous $NaHCO_3$ and brine, and was dried over $MgSO_4$. The filtrate was evaporated and the residue was purified by chromatography on silica gel using the solvent gradient hexanes → hexanes/EtOAc (3:7), to furnish 0.40 g (84%) of the title compound as a yellow solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ7.95 (dd, J = 8.4 Hz, J = 1.2 Hz, 1H), 7.91 (t, J = 8.4 Hz, 1H), 7.74 (dd, J = 8.4 Hz, J = 1.2 Hz, 1H), 5.43-5.46 (m, 1H), 5.36-5.40 (m, 1H), 4.90 (s, 2H), 4.66 (s, 2H), 2.05 (s, 3H).

Example 200d: 2-(2-(Hydroxymethyl)allyloxy)-6-nitrobenzonitrile

Prepared as in Example 166d from 2,6-dinitrobenzonitrile and 2-methylenepropane-1,3-diol in 55% yield as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ7.93 (dd, J = 8.4 Hz, J = 0.8 Hz, 1H), 7.89 (t, J = 8.0 Hz, 1H), 7.73 (dd, J = 7.6 Hz, J = 0.8 Hz, 1H), 5.23-5.29 (m, 2H), 5.03 (t, J = 5.6 Hz, 1H), 4.85 (s, 2H), 4.06 (d, J = 5.2 Hz, 2H). |ΠατΑππ1009_Α1|ZZΜΠΤΑΓ|

Example 201: 4-Amino-5-(4,5-dihydrofuran-2-yl)-1H-benzo[c][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-(4,5-dihydrofuran-2-yl)benzonitrile (Example 201a) in 31% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.75-2.81 (m, 2H), 4.43 (t, J = 9.2 Hz, 2H), 5.35-5.36 (m, 1H), 7.07 (dd, J = 1.2, 8.0 Hz, 1H),

7.12 (dd, J = 1.2, 7.2 Hz, 1H), 7.50-7.54 (m, 1H), 8.2-8.4 (broad s, 1H), 11.09 (s, 1H). MS 266 (MH^+).

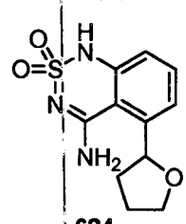
Example 201a: 2-Sulfamoylamino-6-(4,5-dihydrofuran-2-yl)benzonitrile

Prepared as in Example 111a from 2-amino-6-(4,5-dihydrofuran-2-yl)benzonitrile (Example 201b) in 19% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.82-2.88 (m, 2H), 4.45 (t, J = 9.6 Hz, 2H), 5.89 (t, J = 3.2 Hz, 1H), 7.29 (s, 2H), 7.47 (d, J = 7.2 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.67 (t, J = 8.0 Hz, 1H), 9.42 (s, 1H). MS 266 (MH^+).

Example 201b: 2-amino-6-(4,5-dihydrofuran-2-yl)benzonitrile

2-Amino-6-bromobenzonitrile (0.75 g, 3.81 mmol), (4,5-dihydrofuran-2-yl)trimethylstannane (Menez, P.; Fargeas, V.; Poisson, J.; Ardisson, J.; Lallemand, J.-Y.; Pancrazi, A. *Tetrahedron Letters* **1994**, *35(42)*, 7767) (1.02 g, 4.38 mmol), and palladium tetrakis(triphenylphosphine) (0.33 g, 0.28 mmol) were refluxed in toluene (10.0 mL) under nitrogen for 1.5 h. Saturated ammonium chloride (12 mL) and ammonium hydroxide (4 mL) were added, and the mixture was extracted with EtOAc. The organic layer was concentrated under vacuum and the residue was purified by chromatography on silica using 35% EtOAc/hexanes to give 0.48 g (68%) of the title compound as yellow oil. ^{1}H NMR (400 MHz, Acetone-d_6) δ 2.78-2.83 (m, 2H), 4.40 (t, J = 9.2 Hz, 2H), 5.76 (t, J = 3.2 Hz, 1H), 6.04 (s, 2H), 6.77-6.80 (m, 2H), 7.28 (t, J = 8.0 Hz, 1H). MS 187 (MH^+).

Example 202: 4-Amino-5-(tetrahydrofuran-2-yl)-1H-benzo[c][1,2,6]thiadiazine-2,2-dioxide



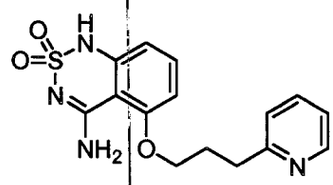
624

Prepared as in Example 111 from 2-sulfamoylamino-6-(tetrahydrofuran-2-yl)benzonitrile (Example 202a) in 52% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.94-2.05 (m, 3H), 2.21-2.28 (m, 1H), 3.81-3.87 (m, 1H), 3.92-3.97 (m, 1H), 5.23-5.27 (m, 1H), 7.02 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.9-8.5 (broad, 2H), 10.94 (s, 1H). MS 268 (MH^+).

Example 202a: 2-Sulfamoylamino-6-(tetrahydrofuran-2-yl)benzonitrile

2-Amino-6-(4,5-dihydrofuran-2-yl)benzonitrile (Example 202b) (0.24 g, 1.28 mmol), 10% Pd/C (0.24 g), and ammonium formate (2.40 g, 38.1 mmol) were refluxed in MeOH (25 mL) under nitrogen for 1.5 h. The insoluble solids were filtered out and discarded, and the solvent was removed under vacuum. The resultant residue was dissolved in EtOAc, washed with saturated Na_2CO_3 and brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was dissolved in anhydrous DMA (2.0 mL) and was treated with sulfamoyl chloride (0.11 g, 0.97 mmol). The reaction mixture was stirred under nitrogen for 30 minutes, quenched with water (5.0 mL) and extracted with EtOAc (3x50 mL). The combined extract was dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by silica gel prep-TLC using 65% EtOAc/hexanes to give 45.0 mg (13%) of the title compound as a white solid. ^{1}H NMR (400 MHz, Acetone-d_6) δ 1.71-1.78 (m, 1H), 2.02-2.07 (m, 2H), 2.45-2.52 (m, 1H), 3.90-3.95 (m, 1H), 4.10-4.15 (m, 1H), 5.08 (t, J = 6.8 Hz, 1H), 6.6-6.8 (broad, 2H), 7.36-7.39 (m, 1H), 7.62-7.63 (m, 2H), 8.22 (broad s, 1H). MS 268 (MH^+).

Example 203: 4-Amino-5-(3-(pyridin-2-yl)propoxy)-1H-benzo[c][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-(3-(pyridin-2-yl)propoxy)benzonitrile (Example 203a) in 58% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.37 (quint, J = 6.8 Hz, 2H), 2.89 (t, J = 7.2 Hz, 2H), 4.19 (t, J = 6.0 Hz, 2H), 6.60 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 8.8 Hz, 1H), 7.19-7.22 (m, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.44 (t, J = 8.4 Hz, 1H), 7.68-7.72 (m, 1H), 7.92 (s, 1H), 8.36 (s, 1H), 8.49 (d, J = 4.0 Hz, 1H), 10.94 (broad s, 1H). MS 333 (MH^+).

Example 203a: 2-Sulfamoylamino-6-(3-(pyridin-2-yl)propoxy)benzonitrile

Prepared as in Example 111a from 2-amino-6-(3-(pyridin-2-yl)propoxy)benzonitrile (Example 203b) in 97% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.15 (quint, J = 6.4 Hz, 2H), 2.92 (t, J = 7.6 Hz, 2H), 4.15 (t, J = 6.0 Hz, 2H), 6.93

(d, J = 8.4 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 7.20-7.29 (m, 4H), 7.55 (t, J = 8.4 Hz, 1H), 7.68-7.72 (m, 1H), 8.48 (d, J = 4.8 Hz, 1H), 9.49 (broad s, 1H). MS 333 (MH^+).

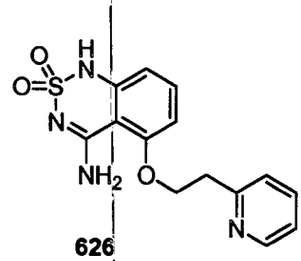
Example 203b: 2-Amino-6-(3-(pyridin-2-yl)propoxy)benzonitrile

Prepared as in Example 199b from 2-nitro-6-(3-(pyridin-2-yl)propoxy)benzonitrile (Example 203c) in 85% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.12 (quint, J = 6.8 Hz, 2H), 2.90 (t, J = 7.2 Hz, 2H), 4.02 (t, J = 6.4 Hz, 2H), 5.99 (s, 2H), 6.18 (d, J = 8.0 Hz, 1H), 6.33 (d, J = 8.8 Hz, 1H), 7.14-7.22 (m, 2H), 7.26 (d, J = 8.0 Hz, 1H), 7.67-7.71 (m, 1H), 8.49 (d, J = 3.6 Hz, 1H). MS 254 (MH^+).

Example 203c: 2-Nitro-6-(3-(pyridin-2-yl)propoxy)benzonitrile

Prepared as in Example 187c from 3-(pyridin-2-yl)propan-1-ol 2,6-dinitrobenzonitrile in 86% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.21 (quint, J = 6.4 Hz, 2H), 2.95 (t, J = 7.2 Hz, 2H), 4.31 (t, J = 6.4 Hz, 2H), 7.19-7.22 (m, 1H), 7.28 (d, J = 7.6 Hz, 1H), 7.67-7.74 (m, 2H), 7.86-7.92 (m, 2H), 8.48 (d, J = 4.8 Hz, 1H). MS 284 (MH^+).

Example 204: 4-Amino-5-(2-(pyridin-2-yl)ethoxy)-1H-benzo[c][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-(2-(pyridin-2-yl)ethoxy)benzonitrile (Example 204a) in 22% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.29 (t, J = 5.6 Hz, 2H), 4.46 (t, J = 5.6 Hz, 2H), 6.59 (d, J = 8.0 Hz, 1H), 6.75 (d, J = 8.8 Hz, 1H), 7.28-7.31 (m, 1H), 7.40-7.46 (m, 2H), 7.75-7.80 (m, 1H), 8.33-8.52 (m, 3H), 10.91 (s, 1H). MS 319 (MH^+).

Example 204a: 2-Sulfamoylamino-6-(2-(pyridin-2-yl)ethoxy)benzonitrile

Prepared as in Example 111a from 2-amino-6-(2-(pyridin-2-yl)ethoxy)benzonitrile (Example 204b) in 67% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.22 (t, J = 6.4 Hz, 2H), 4.48 (t, J = 6.4 Hz, 2H), 7.00 (d, J = 8.8 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 7.23-7.26 (m, 3H), 7.39 (d, J = 7.6 Hz, 1H), 7.55 (t, J = 8.4 Hz, 1H), 7.73 (t, J = 7.2 Hz, 1H), 8.51 (d, J = 4.4 Hz, 1H), 9.42 (s, 1H). MS 319 (MH^+).

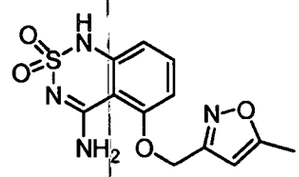
Example 204b: 2-Amino-6-(2-(pyridin-2-yl)ethoxy)benzonitrile

Prepared as in Example 2b from 2-nitro-6-(2-(pyridin-2-yl)propoxy)benzonitrile (Example 221c) in 60% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.18 (t, J = 6.8 Hz, 2H), 4.36 (t, J = 6.8 Hz, 2H), 5.97 (s, 2H), 6.25 (d, J = 8.4 Hz, 1H), 6.32 (d, J = 8.4 Hz, 1H), 7.17 (t, J = 8.0 Hz, 1H), 7.22-7.26 (m, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.70-7.75 (m, 1H), 8.51 (d, J = 4.4 Hz, 1H). MS 240 (MH^+).

Example 204c: 2-Nitro-6-(2-(pyridin-2-yl)ethoxy)benzonitrile

Prepared as in Example 187c from 2-(pyridin-2-yl)ethanol and 2,6-dinitrobenzonitrile in 82% yield as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.27 (t, J = 6.4 Hz, 2H), 4.64 (t, J = 6.4 Hz, 2H), 7.23-7.27 (m, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.71-7.79 (m, 2H), 7.86-7.91 (m, 2H), 8.50-8.52 (m, 1H). MS 270 (MH^+).

Example 205: 4-Amino-5-((5-methylisoxazol-3-yl)methoxy)-1H-benzo[c][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-((5-methylisoxazol-3-yl)methoxy)benzonitrile (Example 205a) in 83% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.42 (s, 3H), 5.40 (s, 2H), 6.36 (s, 1H), 6.65 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 7.48 (t, J = 8.4 Hz, 1H), 8.06 (s, 1H), 8.40 (s, 1H), 11.02 (s, 1H). MS 309 (MH^+).

Example 205a: 2-Sulfamoylamino-6-((5-methylisoxazol-3-yl)methoxy)benzonitrile

Prepared as in Example 111a from 2-amino-6-((5-methylisoxazol-3-yl)methoxy)benzonitrile (Example 222b) in 85% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.42 (s, 3H), 5.32 (s, 2H), 6.34 (s, 1H), 7.07 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.30 (s, 2H), 7.59 (t, J = 8.8 Hz, 1H), 9.53 (s, 1H). MS 309 (MH^+).

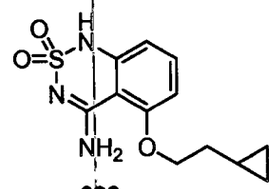
Example 205b: 2-Amino-6-((5-methylisoxazol-3-yl)methoxy)benzonitrile

Prepared as in Example 199b from 2-((5-methylisoxazol-3-yl)methoxy)-6-nitrobenzonitrile (Example 205c) in 52% yield as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.42 (s, 3H), 5.19 (s, 2H), 6.07 (s, 2H), 6.31-6.33 (m, 2H), 6.37 (d, J = 8.4 Hz, 1H), 7.20 (t, J = 8.4 Hz, 1H). MS 230 (MH^+).

Example 205c: 2-((5-Methylisoxazol-3-yl)methoxy)-6-nitrobenzonitrile

Prepared as in Example 187c from (5-methylisoxazol-3-yl)methanol and 2,6-dinitrobenzonitrile in 86% yield as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.43 (d, J = 0.8 Hz, 3H), 5.50 (s, 2H), 6.38 (d, J = 0.4 Hz, 1H), 7.83 (dd, J = 1.2, 8.4 Hz, 1H), 7.91-7.98 (m, 2H). MS 260 (MH^+).

Example 206: 4-Amino-5-(2-cyclopropylethoxy)-1H-benzo[c][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-(2-cyclopropylethoxy)benzonitrile (Example 206a) in 94% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.11-0.15 (m, 2H), 0.43-0.48 (m, 2H), 0.77-0.81 (m, 1H), 1.73 (q, J = 6.8 Hz, 2H), 4.21 (t, J = 6.8 Hz, 2H), 6.61 (d, J = 8.0 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 7.46 (t, J = 8.4 Hz, 1H), 7.87 (s, 1H), 8.39 (s, 1H), 10.96 (s, 1H). MS 282 (MH^+).

Example 206a: 2-Sulfamoylamino-6-(2-cyclopropylethoxy)benzonitrile

Prepared as in Example 111a from 2-amino-6-(2-cyclopropylethoxy)benzonitrile (Example 206b) in 80% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.13-0.17 (m, 2H), 0.41-0.46 (m, 2H), 0.82-0.87 (m, 1H), 1.64 (q, J = 6.4 Hz, 2H), 4.16 (t, J = 6.4 Hz, 2H), 6.96 (d, J = 8.0 Hz, 1H), 7.14 (d, J = 8.8 Hz, 1H), 7.27 (s, 2H), 7.56 (t, J = 8.8 Hz, 1H), 9.44 (s, 1H). MS 282 (MH^+).

Example 206b: 2-Amino-6-(2-cyclopropylethoxy)benzonitrile

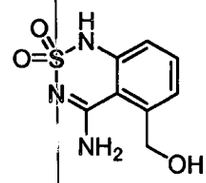
Prepared as in Example 199b from 2-(2-cyclopropylethoxy)-6-nitrobenzonitrile (Example 206c) in 90% yield as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.13-0.16 (m, 2H), 0.40-0.45 (m, 2H), 0.81-0.85 (m, 1H), 1.61 (q, J = 6.8 Hz, 2H), 4.04 (t, J = 6.4 Hz, 2H), 5.97 (s, 2H), 6.21 (d, J = 8.0 Hz, 1H), 6.32 (d, J = 8.8 Hz, 1H), 7.17 (t, J = 8.4 Hz, 1H). MS 203 (MH^+).

Example 206c: 2-(2-Cyclopropylethoxy)-6-nitrobenzonitrile

Prepared as in Example 187c from 2-cyclopropylethanol and 2,6-dinitrobenzonitrile in 85% yield as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.15-0.20 (m,

2H), 0.43-0.47 (m, 2H), 0.84-0.89 (m, 1H), 1.69 (q, J = 6.8 Hz, 2H), 4.31 (t, J = 6.4 Hz, 2H), 7.73-7.76 (m, 1H), 7.86-7.93 (m, 2H). MS 233 (MH^+).

Example 207: 4-Amino-5-(hydroxymethyl)-1H-benzo[c][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-cyano-3-(sulfamoylamino)benzyl acetate (Example 207a) in 53% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.60 (s, 2H), 6.62-6.63 (m, 1H), 7.04 (d, J = 8.0 Hz, 1H), 7.09 (d, J = 7.2 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 8.33 (broad s, 1H), 8.86 (broad s, 1H), 10.92 (s, 1H). MS 228 (MH^+).

Example 207a: 2-Cyano-3-(sulfamoylamino)benzyl acetate

Prepared as in Example 111a from 3-amino-2-cyanobenzyl acetate (Example 207b) in 90% yield as a white solid. ^{1}H NMR (400 MHz, Acetone-d_6) δ 2.09 (s, 3H), 5.24 (s, 2H), 6.76 (broad s, 2H), 7.38 (dd, J = 0.8, 7.2 Hz, 1H), 7.66-7.75 (m, 2H), 8.40 (broad s, 1H). MS 270 (MH^+).

Example 207b: 3-Amino-2-cyanobenzyl acetate

Prepared as in Example 199b from 2-cyano-3-nitrobenzyl acetate (Example 207c) in 84% yield as yellow oil. ^{1}H NMR (400 MHz, Methanol-d_4) δ 2.10 (s, 3H), 5.11 (s, 2H), 6.70 (d, J = 7.2 Hz, 1H), 6.78 (d, J = 8.8 Hz, 1H), 7.28 (t, J = 8.4 Hz, 1H). MS 191 (MH^+).

Example 207c: 2-Cyano-3-nitrobenzyl acetate

Acetic anhydride (0.84 mL, 8.87 mmol) was added to a solution of 2-(hydroxymethyl)-6-nitrobenzonitrile (Example 207d) (0.31 g, 1.77 mmol), pyridine (0.86 mL, 10.6 mmol), and DMAP (0.22 g, 1.77 mmol) in CH_2Cl_2 (10 mL), and stirred for 24 h at rt. The mixture was washed once with AcOH (1 M, 20 mL), dried with $MgSO_4$, concentrated, and purified by chromatography on silica using CH_2Cl_2, to give the title compound in amount of 0.36 g (92%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.12 (s, 3H), 5.35 (s, 2H), 7.99 (t, J = 8.0 Hz, 1H), 8.06 (dd, J = 0.8, 8.0 Hz, 1H), 8.37 (dd, J = 0.8, 8.0 Hz, 1H).

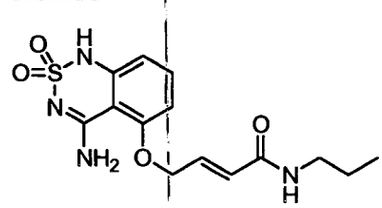
Example 207d: 2-(Hydroxymethyl)-6-nitrobenzonitrile

Sodium borohydride (92.0 mg, 2.43 mmol) was added to a solution of 2-formyl-6-nitrobenzonitrile (Example 207e) (0.86 g, 4.88 mmol) in MeOH (38 mL) and THF (38 mL) at -8°C, and was stirred at that temperature for no more than 30 min. The reaction was quenched with HCl (6 M, 4.88 mL), followed by addition of water (50 mL), and brine (50 mL). The mixture was extracted with EtOAc, the combined extract was dried over $MgSO_4$, filtered and concentrated. The crude product was purified by chromatography on silica using the solvent gradient $CH_2Cl_2 \rightarrow CH_2Cl_2$/MeOH (8:2) to give the title compound in amount of 0.32 g, (37%), which was used immediately in the next step. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.77 (d, J = 5.6 Hz, 2H), 5.87 (t, J = 5.6 Hz, 1H), 7.97 (t, J = 8.0 Hz, 1H), 8.07 (dd, J = 0.4, 8.0 Hz, 1H), 8.28 (dd, J = 0.8, 8.0 Hz, 1H).

Example 207e: 2-Formyl-6-nitrobenzonitrile

1,1-Dimethoxy-*N*,*N*-dimethylmethanamine (13.56 mL, 102 mmol) was added to a solution of 2-methyl-6-nitrobenzonitrile (15.0 g, 92.5 mmol) in anhydrous DMF (60 mL) under nitrogen and was heated at 130°C for 15 h. Ice water (300 mL) was added, and the resultant dark precipitate was collected by filtration and dried under vacuum. Phosphate buffer (pH 7, 350 mL) and then $NaIO_4$ (40 g, 187 mmol) were added to a solution of the dark precipitate in THF (350 mL) and stirred at rt for 3 h. The mixture was extracted with EtOAc, the combined extract was washed with brine and dried with $MgSO_4$. The filtrate was concentrated and the residue was purified by chromatography on silica using the solven gradient hexanes→EtOAc, to give 3.07 g (19%) of the title compound as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (t, J = 8.4 Hz, 1H), 8.41 (dd, J = 1.2, 7.6 Hz, 1H), 8.62 (dd, J = 1.2, 8.4 Hz, 1H), 10.25 (s, 1H).

Example 208: (*E*)-4-Amino-5-(4-oxo-4-(propylamino)but-2-enyloxy)-1H-benzo[c][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from (*E*)-4-(2-cyano-3-(sulfamoylamino)phenoxy)-N-propylbut-2-enamide (Example 208a) in 19% yield as a white solid. ^{1}H NMR (400 MHz, Acetone-d_6) δ 0.87 (t, J = 7.2 Hz, 3H), 1.47 (hex, J = 7.6 Hz, 2H), 3.11-3.17 (m, 4H), 5.35 (q, J

= 7.2 Hz, 1H), 6.70 (d, J = 6.0 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 7.2-7.5 (broad s, 2H), 7.51 (t, J = 8.0 Hz, 1H), 8.19 (broad s, 1H), 9.5-10.5 (broad s, 1H). MS 339 (MH^+).

Example 208a: (*E*)-4-(2-Cyano-3-(sulfamoylamino)phenoxy)-N-propylbut-2-enamide

Prepared as in Example 111a from (*E*)-4-(3-amino-2-cyanophenoxy)-N-propylbut-2-enamide (Example 208b) in 87% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.84 (t, J = 7.2 Hz, 3H), 1.43 (hex, J = 6.8 Hz, 2H), 3.06 (q, J = 6.8 Hz, 2H), 4.90 (d, J = 2.8 Hz, 2H), 6.15 (d, J = 15.6 Hz, 1H), 6.70-6.77 (m, 1H), 6.91 (d, J 8.8 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 7.27 (broad s, 2H), 7.57 (t, J = 8.8 Hz, 1H), 8.13-8.16 (m, 1H), 9.52 (broad s, 1H). MS 339 (MH^+).

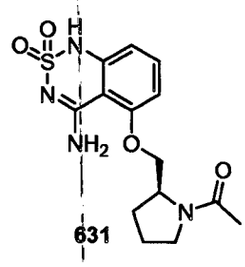
Example 208b: (*E*)-4-(3-Amino-2-cyanophenoxy)-N-propylbut-2-enamide

Prepared as in Example 199b from (*E*)-4-(2-cyano-3-nitrophenoxy)-N-propylbut-2-enamide (Example 208c) in 73% yield as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.84 (t, J = 7.2 Hz, 3H), 1.42 (hex, J = 7.2 Hz, 2H), 3.06 (q, J = 6.8 Hz, 2H), 4.77-4.79 (m, 2H), 6.04 (s, 2H), 6.11-6.20 (m, 2H), 6.35 (d, J = 8.4 Hz, 1H), 6.67-6.74 (m, 1H), 7.18 (t, J = 8.0 Hz, 1H), 8.11-8.14 (m, 1H). MS 260 (MH^+).

Example 208c: (*E*)-4-(2-Cyano-3-nitrophenoxy)-N-propylbut-2-enamide

(*E*)-4-Bromo-N-propylbut-2-enamide (Elliott, M.; Farnham, A. W.; Janes, N. F.; Johnson, D. M.; Pulman, D. A. *Pesticide Science* **1987** *18(4)* 229) (0.14 g, 0.70 mmol), 2-hydroxy-6-nitrobenzonitrile (0.14 g, 0.88 mmol), potassium carbonate (0.39 g, 2.81 mmol), and 18-crown-6 (0.11 g, 0.42 mmol) were refluxed in acetone (6 mL) for 2 h, and then poured into ice water (45 mL). The resultant precipitate was collected by filtration to give 0.16 g (79%) of the title compound as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.84 (t, J = 7.2 Hz, 3H), 1.42 (hex, J = 7.2 Hz, 2H), 3.06 (q, J = 6.8 Hz, 2H), 5.07 (d, J = 2.8 Hz, 2H), 6.16 (d, J = 16.0 Hz, 1H), 6.71-6.78 (m, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.88-7.96 (m, 2H), 8.11-8.14 (m, 1H).

Example 209: (*S*)-4-Amino-5-((1-acetylpyrrolidin-2-yl)methoxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 176 from (*S*)-2-amino-6-((1-acetylpyrrolidin-2-yl)methoxy)benzonitrile (Example 209a) in 10% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.93 (m, 4H), 2.00 (s, 3H), 3.50 (m, 2H), 4.09 (dd, J = 10.0, 6.2 Hz, 1H), 4.24 (dd, J = 10.0, 5.6 Hz, 1H), 4.41 (m, 1H), 6.62 (d, J = 8.2 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 7.46 (t, J = 8.5 Hz, 1H), 8.12 (br s, 1H), 8.33 (br s, 1H), 10.93 (br s, 1H). MS 339 (MH^+).

Example 209a: (*S*)-2-Amino-6-((1-acetylpyrrolidin-2-yl)methoxy)benzonitrile

To a suspension of (*S*)-2-((2-cyano-3-nitrophenoxy)methyl)pyrrolidinium chloride (130 mg, 0.46 mmol) (Example 209b) in THF (5 mL) were added Et_3N (135 µL, 0.97 mmol) and acetyl chloride (36 µL, 0.50 mmol). The reaction was stirred at rt for 18 h, filtered and diluted with EtOH (20 mL). The resulting solution was hydrogenated (20 Bar) using 10% Pd/C as the catalyst. Upon completion, the reaction mixtrue was concentrated to provide the title compound (61 mg, 51%) as a clear syrup. MS 260 (MH^+).

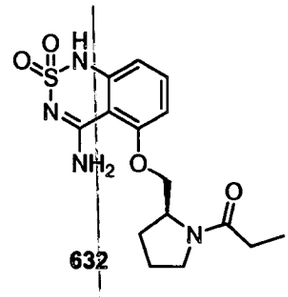
Example 209b: (*S*)-2-((2-Cyano-3-nitrophenoxy)methyl)pyrrolidinium chloride

Prepared as in Example 166 from (*S*)-*tert*-butyl-2-((2-cyano-3-nitrophenoxy)methyl)pyrrolidine-1-carboxylate (Example 209c) in 81% yield as an off-white solid. MS 248 (MH^+-HCl).

Example 209c: (*S*)-*tert*-Butyl 2-((2-cyano-3-nitrophenoxy)methyl)pyrrolidine-1-carboxylate

Prepared as in Example 166d from 2,6-dinitrobenzonitrile and (*S*)-*tert*-butyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate in 89% yield as a tan solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.40 (s, 9H), 1.81 (m, 1H), 2.03 (m, 3H), 3.32 (m, 2H), 4.08 (m, 1H), 4.33 (m, 2H), 7.79 (d, J = 7.8 Hz, 1H), 7.93 (m, 2H).

Example 210: (*S*)-4-Amino-5-((1-propionylpyrrolidin-2-yl)methoxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



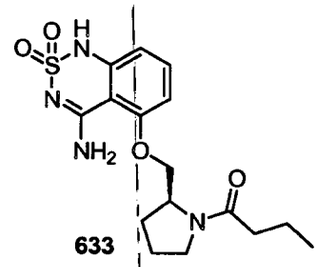
632

Prepared as in Example 176 from (*S*)-2-amino-6-((1-propionylpyrrolidin-2-yl)methoxy)benzonitrile (Example 210a) in 17% yield as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.01 (t, J = 7.8 Hz, 3H), 1.95 (m, 4H), 2.31 (m, 2H), 3.48 (m, 2H), 4.11 (dd, J = 10.0, 6.4 Hz, 1H), 4.27 (dd, J = 9.8, 5.0 Hz, 1H), 4.43 (m, 1H), 6.64 (d, J = 7.9 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 7.48 (t, J = 8.2 Hz, 1H), 8.09 (br s, 1H), 8.34 (br s, 1H), 10.95 (br s, 1H). MS 353 (MH^+).

Example 210a: (*S*)-2-Amino-6-((1-propionylpyrrolidin-2-yl)methoxy)benzonitrile

Prepared as in Example 209a from (*S*)-2-((2-cyano-3-nitrophenoxy)methyl)pyrrolidinium chloride (Example 210b) and propionyl chloridein 90% yield as a clear syrup. MS 274 (MH^+).

Example 211: (*S*)-4-Amino-5-((1-butyrylpyrrolidin-2-yl)methoxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



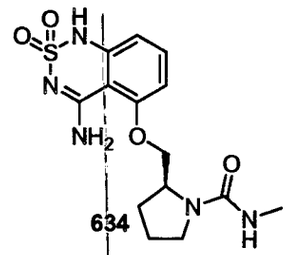
633

Prepared as in Example 176 from (*S*)-2-amino-6-((1-butyrylpyrrolidin-2-yl)methoxy)benzonitrile (Example 211a) in 78% yield as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.88 (t, J = 7.5 Hz, 3H), 1.54 (q, J = 7.5 Hz), 1.94 (m, 4H), 2.26 (t, J = 7.5 Hz, 2H), 3.48 (m, 2H), 4.10 (m, 1H), 4.25 (m, 1H), 4.43 (m, 1H), 6.62 (d, J = 8.1 Hz, 1H), 6.89 (d, J = 8.6 Hz, 1H), 7.47 (t, J = 8.3 Hz, 1H), 8.08 (br s, 1H), 8.32 (br s, 1H), 10.93 (br s, 1H). MS 367 (MH^+).

Example 211a: (*S*)-2-Amino-6-((1-butyrylpyrrolidin-2-yl)methoxy)benzonitrile

Prepared as in Example 209a from (*S*)-2-((2-cyano-3-nitrophenoxy)methyl)pyrrolidinium chloride (Example 209b) and butyryl chloride to in 90% yield as a white solid. MS 288 (MH^+).

Example 212: (*S*)-2-((4-Amino-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide-5-yloxy)methyl)-*N*-methylpyrrolidine-1-carboxamide



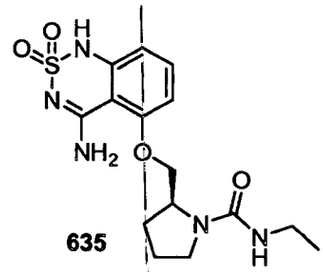
634

Prepared as in Example 176 from (*S*)-2-((3-amino-2-cyanophenoxy)methyl)-*N*-methylpyrrolidine-1-carboxamide (Example 212a) in 30% yield as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.89 (m, 4H), 2.60 (d, J = 3.9 Hz, 3H), 3.20 (m, 2H), 4.01 (m, 1H), 4.16 (m, 1H), 4.32 (m, 1H), 6.23 (m, 1H), 6.62 (d, J = 8.2 Hz, 1H), 6.89 (d, J = 8.5 Hz, 1H), 7.46 (t, J = 8.2 Hz, 1H), 8.19 (br s, 1H), 8.27 (br s, 1H), 10.92 (s, 1H). MS 354 (MH^+).

Example 212a: (*S*)-2-((3-Amino-2-cyanophenoxy)methyl)-*N*-methylpyrrolidine-1-carboxamide

Prepared as in Example 209a from (*S*)-2-((2-cyano-3-nitrophenoxy)methyl)pyrrolidinium chloride (Example 209b) and methyl isocyanate in 53% yield as a white solid. MS 275 (MH^+).

Example 213: (*S*)-2-((4-Amino-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide-5-yloxy)methyl)-*N*-ethylpyrrolidine-1-carboxamide



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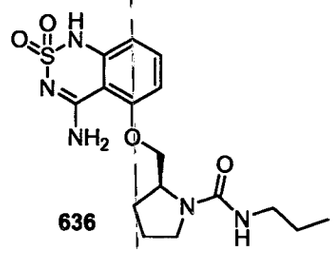
Prepared as in Example 276 from (*S*)-2-((3-amino-2-cyanophenoxy)methyl)-*N*-ethylpyrrolidine-1-carboxamide (Example 213a) in 68% yield as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.03 (t, J = 6.9 Hz, 6H), 1.90 (m, 4H), 3.08 (quint, J = 6.6 Hz, 2H), 3.20

(m, 1H), 3.31 (m, 1H), 4.00 (dd, J = 9.7, 6.7 Hz, 1H), 4.17 (dd, J = 9.7, 6.0 Hz, 1H), 4.33 (m, 1H), 6.27 (d, J = 5.7 Hz, 1H), 6.62 (d, J = 8.2 Hz, 1H), 6.89 (d, J = 8.3 Hz, 1H), 7.46 (t, J = 8.2 Hz, 1H), 8.20 (br s, 1H), 8.26 (br s, 1H), 10.91 (s, 1H). MS 368 (MH^+).

Example 213a: (*S*)-2-((3-Amino-2-cyanophenoxy)methyl)-*N*-ethylpyrrolidine-1-carboxamide

Prepared as in Example 209a from (*S*)-2-((2-cyano-3-nitrophenoxy)methyl)pyrrolidinium chloride (Example 209bW) and ethyl isocyanate in 100% yield as a white solid. MS 289 (MH^+).

Example 214: (*S*)-2-((4-Amino-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide-5-yloxy)methyl)-*N*-propylpyrrolidine-1-carboxamide



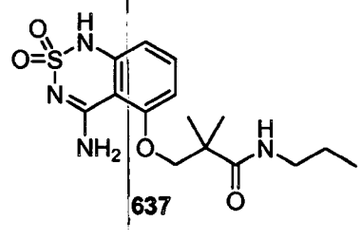
636

Prepared as in Example 276 from (*S*)-2-((3-amino-2-cyanophenoxy)methyl)-*N*-propylpyrrolidine-1-carboxamide (Example 214a) in 37% yield as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.84 (t, J = 7.6 Hz, 6H), 1.43 (sext, J = 7.4 Hz, 2H), 1.92 (m, 4H), 3.01 (m, 2H), 3.21 (m, 1H), 3.33 (m, 1H), 4.02 (dd, J = 9.7, 6.4 Hz, 1H), 4.18 (dd, J = 9.7, 5.9 Hz, 1H), 4.34 (m, 1H), 6.27 (d, J = 5.6 Hz, 1H), 6.62 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 8.6 Hz, 1H), 7.46 (t, J = 8.3 Hz, 1H), 8.20 (br s, 1H), 8.27 (br s, 1H), 10.91 (s, 1H). MS 382 (MH^+).

Example 214a: (*S*)-2-((3-Amino-2-cyanophenoxy)methyl)-*N*-propylpyrrolidine-1-carboxamide

Prepared as in Example 209a from (*S*)-2-((2-cyano-3-nitrophenoxy)methyl)pyrrolidinium chloride (Example 209b) and propyl isocyanate in100% yield as a white solid. MS 303 (MH^+).

Example 215: 3-(4-Amino-2,2-dioxide-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)-2',2'-dimethyl-N-propylpropanamide



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To a stirred solution of 3-(3-sulfamoylamino-2-cyanophenoxy)-2,2-dimethyl-N-propylpropanamide (18.52 g, 52.55 mmol) (Example 215a) in EtOH (150 mL) was added NaOH solution (2.0 N, 52.3 mL) at room temperature. The reaction mixture was then refluxed for 2 hrs until the reaction was complete by TLC. The solution was cooled to 0 °C and neutralized carefully with 10% acetic acid and the precipitate was collected by filtration and washed with water. The product was further purified by recrystallization from EtOH/H_2O (1:4), dried under vacuum to give the title compound as a white solid (13.5 g, 73%). M.p.: 225-226 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.75 (t, J = 7.4 Hz, 3H), 1.22 (s, 6H), 1.38 (m, 2H), 3.01 (q, J = 6.5 Hz, 2H), 4.07 (s, 2H), 6.59 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.82 (t, J = 5.6 Hz, 1H), 7.92 (s, 1H), 8.33 (s, 1H), 10.93 (s, 1H). MS 355 (MH^+).

Example 215a: 3-(3-sulfamoylamino-2-cyanophenoxy)-2,2-dimethyl-N-propyl-propanamide

To a solution of 3-(3-amino-2-cyanophenoxy)-2,2-dimethyl-N-propylpropanamide (16.5 g, 59.92 mmol) (Example 215b) in DMA (50 mL) was added sulfamoyl chloride (13.85 g, 119.84 mmol) at 0 °C under nitrogen. The reaction mixture was then stirred at room temperature under nitrogen for 3 hrs then diluted with EtOAc, washed successively with $NaHCO_3$, brine, dried over Na_2SO_4, filtered and evaporated to give the title compound as a off white solid (18.52 g,87%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.79 (t, J = 7.6 Hz, 3H), 1.20 (s, 6H), 1.38 (m, 2H), 3.01 (q, J = 6.5 Hz, 2H), 4.05 (s, 2H), 6.92 (d, J = 8.4 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 7.24 (s, 2H), 7.53 (t, J = 8.4 Hz, 1H), 7.55 (t, J = 5.6 Hz, 1H), 9.42 (s, 1H). MS 355 (MH^+).

Example 215b: 3-(3-amino-2-cyanophenoxy)-2,2-dimethyl-N-propylpropanamide

Method A: To a solution of 3-(2-cyano-3-nitrophenoxy)-2,2-dimethyl-N-propylpropanamide (305 mg, 1.0 mmol) (Example 215c) in EtOAc (20.0 mL) was added 10% Pd/C (50 mg). The suspension was stirred under an atmosphere of H_2 at room temperature overnight. The Pd/C was filtered off, and washed with EtOAc. The filtrate was concentrated

under reduced pressure and the residue was purified by chromatography on silica gel eluting with 50% EtOAc in hexanes to give the title compound (267 mg, 97%) as a white solid. MS 276 (MH^+).

Method B: To a solution of 3-hydroxy-2,2-dimethyl-N-propylpropanamide (20.2 g, 0.127 mol) (Example 215d) in dry THF (500 mL) was carefully added NaH (60% in mineral oil, 7.64 g, 0.191 mol) in small portions at 0 °C under nitrogen. The reaction mixture was then warmed to room temperature and stirred under nitrogen for 1 hr. To this solution was slowly added at room temperature 2-amino-6-fluorobenzonitrile (17.3 g, 0.127 mol) in THF (100 mL) and the reaction mixture refluxed overnight under nitrogen then cooled down to room temperature, quenched with brine, and extracted with EtOAc (3X). The combined organic layers were washed with brine, dried over Na_2SO_4, evaporated and the residue was crystallized from EtOAc/Hexane to give the compound as a white solid (16.5 g, 48%). MS 276 (MH^+).

Example 215c: 3-(2-cyano-3-nitrophenoxy)-2,2-dimethyl-N-propylpropanamide

To a solution of 3-hydroxy-2,2-dimethyl-N-propylpropanamide (1.59 g, 10.0 mmol) (Example 215d) in dry THF (30 mL) was carefully added NaH (60% in mineral oil, 400 mg, 10.0 mmol) in small portions at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C under nitrogen for 2 hrs. To this solution was added 2,6-dinitrobenzonitrile (1.93, 10.0 mmol), and the reaction solution was stirred at 0 °C – RT under nitrogen overnight. The reaction mixture was quenched with brine, and extracted with EtOAc (3X). The combined organic layers were washed with brine, dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by chromatography on silica gel eluting with 60% EtOAc in hexanes to give the title compound as a pale yellow solid (2.21 g, 72%). MS 306 (MH^+).

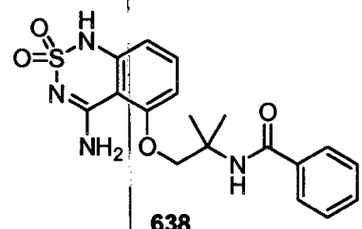
Example 215d: 3-hydroxy-2,2-dimethyl-N-propylpropanamide

Method A: A solution of methyl 3-hydroxy-2,2-dimethylpropanoate (2.64 g, 20 mmol) and n-propylamine (1.81 g, 30 mmol) was heated at 190 °C under microwave for 10 hrs. The excessive amine was removed under vacuum to give the title compound as colorless oil (3.18 g, 100%). MS 160 (MH^+).

Method B: To a solution of 3-hydroxy-2,2-dimethylpropanoic acid (20.0 g, 0.169 mol), propylamine (15.3 mL, 0.186 mol), and HOBt (25.1 g, 0.186 mol) in dry dichloromethane (500 mL) was added EDCI (35.6 g, 0.186 mmol) at room temperature under nitrogen. The reaction mixture was then stirred at room temperature under nitrogen overnight. The reaction

quenched with brine, and extracted EtOAc (8X). The combined organic layers were washed with saturated $NaHCO_3$ solution, dilute HCl, brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave the title compound as colorless oil (19.2 g, 71%). MS 160 (MH^+).

Example 216: N-(1-(4-amino-2,2-dioxide-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)-2'-methylpropan-2'-yl)benzamide



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Prepared as in Example 215 from N-(1-(3-sulfamoylamino-2-cyanophenoxy)-2-methylpropan-2-yl)benzamide (Example 216a) in 93% yield as a white solid. M.p.: 235-236 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 1.47 (s, 6H), 4.38 (s, 2H), 6.61 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 7.39-7.51 (m, 4H), 7.75 (d, J = 7.6 Hz, 2H), 7.90 (s, 1H), 8.17 (s, 1H), 8.47 (s, 1H), 10.97 (s, 1H). MS 389 (MH^+).

Example 216a: N-(1-(3-sulfamoylamino-2-cyanophenoxy)-2-methylpropan-2-yl)benzamide

Prepared as in Example 215a from N-(1-(3-amino-2-cyanophenoxy)-2-methylpropan-2-yl)benzamide (Example 216b) in 98% yield as a white solid. MS 389 (MH^+).

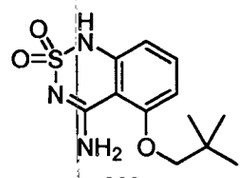
Example 216b: N-(1-(3-amino-2-cyanophenoxy)-2-methylpropan-2-yl)benzamide

Prepared as in Example 215b (Method A) from N-(1-(2-cyano-3-nitrophenoxy)-2-methylpropan-2-yl)benzamide (Example 216c) in 96% yield as a white solid. MS 310 (MH^+).

Example 216c: N-(1-(2-cyano-3-nitrophenoxy)-2-methylpropan-2-yl)benzamide

Prepared as in Example 215c from N-(1-hydroxy-2-methylpropan-2-yl)benzamide (Boyd, R.N.; Hansen, R.H. *J. Am. Chem. Soc.* **1953**, *75*, 5896) and 2,6-dinitrobenzonitrile in 91% yield as a pale yellow solid. MS 340 (MH^+).

Example 217: 5-(neopentyloxy)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



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Prepared as in Example 215 from 2-sulfamoylamino-6-(neopentyloxy)benzonitrile (Example 217a) in 73% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.01 (s, 9H), 3.86 (s, 2H), 6.61 (d, J = 8.0 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.66 (s, 1H), 8.49 (s, 1H), 10.99 (s, 1H). MS 284 (MH^+).

Example 217a: 2-sulfamoylamino-6-(neopentyloxy)benzonitrile

Prepared as in Example 215a from 2-amino-6-(neopentyloxy)benzonitrile (Example 217b) in 92% yield. MS 284 (MH^+).

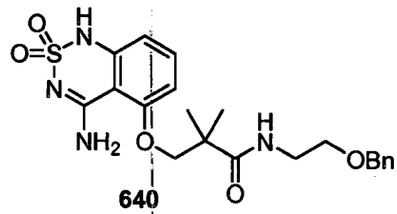
Example 217b: 2-amino-6-(neopentyloxy)benzonitrile

Prepared as in Example 215b (Method A) from 2-(neopentyloxy)-6-nitrobenzonitrile (Example 217c) in 96% yield. MS 205 (MH^+).

Example 217c: 2-(neopentyloxy)-6-nitrobenzonitrile

Prepared as in Example 215c from 2,2-dimethylpropan-1-ol and 2,6-dinitrobenzonitrile in 80% yield. MS 235 (MH^+).

Example 218: 3-(4-amino-2,2-dioxide-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)-N-(2''-(benzyloxy)ethyl)-2',2'-dimethylpropanamide



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Prepared as in Example 215 from 3-(3-sulfamoylamino-2-cyanophenoxy)-N-(2-(benzyloxy)ethyl)-2,2-dimethylpropanamide (Example 218a) in 92% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.22 (s, 6H), 3.26 (q, J = 5.8 Hz, 2H), 3.41 (t, J = 5.8 Hz, 2H), 4.07 (s, 2H), 4.36 (s, 2H), 6.60 (d, J = 7.6 Hz, 1H), 6.71 (d, J = 7.6 Hz, 1H), 7.19-7.28 (m, 4H), 7.43 (t, J = 8.0 Hz, 2H), 7.91 (s, 1H), 7.97 (t, J = 5.8 Hz, 1H), 8.34 (s, 1H), 10.93 (s, 1H). MS 447 (MH^+).

Example 218a: 3-(3-sulfamoylamino-2-cyanophenoxy)-N-(2-(benzyloxy)ethyl)-2,2-dimethylpropanamide

Prepared as in Example 215a from 3-(3-amino-2-cyanophenoxy)-N-(2-(benzyloxy)ethyl)-2,2-dimethylpropanamide (Example 218b) in 100% yield. MS 447 (MH^+).

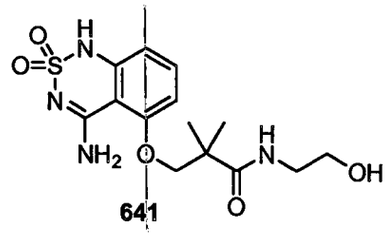
Example 218b: 3-(3-amino-2-cyanophenoxy)-N-(2-(benzyloxy)ethyl)-2,2-dimethyl-propanamide

Prepared as in Example 215b (Method B) from N-(2-(benzyloxy)ethyl)-3-hydroxy-2,2-dimethylpropanamide (Example 218c) and 2-amino-6-fluorobenzonitrile in 82% yield. MS 368 (MH^+).

Example 218c: N-(2-(benzyloxy)ethyl)-3-hydroxy-2,2-dimethylpropanamide

To a solution of 3-hydroxy-2,2-dimethylpropanoic acid (2.36 g, 20 mmol), 2-(benzyloxy)ethanamine (3.02 g, 20 mmol), and HOBt (2.71 g, 20 mmol) in dry dichloromethane (100 mL) was added EDCI (3.82 g, 20 mmol) at room temperature under nitrogen. The reaction mixture was then stirred at room temperature under nitrogen overnight. The reaction was quenched with brine, and extracted with EtOAc (3X). The combined organic layers were washed with saturated $NaHCO_3$ solution, dilute HCl, brine, and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by chromatography on silica gel eluting with 40% EtOAc in hexanes to give the title compound as colorless oil (4.89 g) in 97% yield. MS 252 (MH^+).

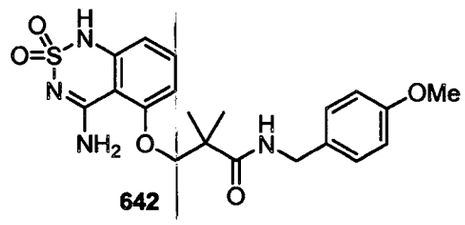
Example 219: 3-(4-amino-2,2-dioxide-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)-N-(2''-hydroxyethyl)-2',2'-dimethylpropanamide



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To a solution of 3-(4-amino-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)-2,2-dioxide-N-(2'-(benzyloxy)ethyl)-2',2'-dimethylpropanamide (Example 218, 112 mg, 0.25 mmol) in EtOAc/EtOH/THF (1:1:1, 20.0 mL) was added 10 % Pd/C (50 mg). And the suspension was stirred under an atmosphere of H_2 at room temperature for 2 hrs. The Pd/C was filtered off, and washed with MeOH. The filtration was concentrated under reduced pressure, and the residue was purified by recrystallization from EtOH to give the title compound as a white solid (81 mg) in 90% yield. ^1H NMR (400 MHz, DMSO-d_6) δ 1.22 (s, 6H), 3.11 (q, J = 6.0 Hz, 2H), 3.35 (q, J = 6.0 Hz, 2H), 4.05 (s, 2H), 4.61 (t, J = 6.0 Hz, 1H), 6.59 (d, J = 8.0 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.78 (t, J = 6.0 Hz, 1H), 7.93 (s, 1H), 8.29 (s, 1H), 10.93 (s, 1H). MS 357 (MH^+).

Example 220: 3-(4-amino-2,2-dioxide-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)-N-(4''-methoxybenzyl)-2',2'-dimethylpropanamide



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Prepared as in Example 215 from 3-(3-sulfamoylamino-2-cyanophenoxy)-N-(4-methoxybenzyl)-2,2-dimethylpropanamide (Example 220a) in 92% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.25 (s, 6H), 3.66 (s, 3H), 4.12 (s, 2H), 4.21 (d, J = 5.6 Hz, 2H), 6.61 (d, J = 8.4 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 7.44 (t, J = 8.4 Hz, 1H), 7.87 (s, 1H), 8.31 (s, 1H), 8.35 (t, J = 5.6 Hz, 1H), 10.95 (s, 1H). MS 433 (MH^+).

Example 220a: 3-(3-sulfamoylamino-2-cyanophenoxy)-N-(4-methoxybenzyl)-2,2-dimethylpropanamide

Prepared as in Example 215a from 3-(3-amino-2-cyanophenoxy)-N-(4-methoxybenzyl)-2,2-dimethylpropanamide (Example 220b) in 100% yield. MS 433 (MH^+).

Example 220b: 3-(3-amino-2-cyanophenoxy)-N-(4-methoxybenzyl)-2,2-dimethyl-propanamide

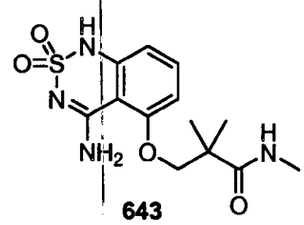
To a solution of 3-(2-cyano-3-nitrophenoxy)-N-(4-methoxybenzyl)-2,2-dimethyl-propanamide (1.15 g, 3.0 mmol) (Example 220c) in diglyme (30 mL) was added dropwise a solution of $SnCl_2 \cdot 2H_2O$ (2.03 g, 9.0 mmol) in concentrated HCl (15 mL) at 0 °C. The reaction mixture was then stirred at 0 °C for another 1 hr. The reaction solution was neutralized with 2 N NaOH at 0 °C, and extracted with EtOAc (2X). The combined organic layers were washed with brine, dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by chromatography on silica gel eluting with 50% EtOAc in hexanes to give the title compound as a white solid (0.91 g) in 86% yield. MS 354 (MH^+).

Example 220c: 3-(2-cyano-3-nitrophenoxy)-N-(4-methoxybenzyl)-2,2-dimethyl-propanamide

Prepared as in Example 215c from 3-hydroxy-N-(4-methoxybenzyl)-2,2-dimethylpropanamide (Example 220d) and 2,6-dinitrobenzonitrile in 95% yield as a pale yellow solid. MS 384 (MH^+).

Example 220d: 3-hydroxy-N-(4-methoxybenzyl)-2,2-dimethylpropanamide Prepared as in Example 4c from 3-hydroxy-2,2-dimethylpropanoic acid and 4-methoxybenzylamine in 97% yield as a white solid. MS 238 (MH^+).

Example 221: 3-(4-amino-2,2-dioxide-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)-N,2',2'-trimethylpropanamide



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Prepared as in Example 215 from 3-(3-sulfamoylamino-2-cyanophenoxy)-N,2,2-trimethylpropanamide (Example 221a) in 62% yield as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 1.21 (s, 6H), 2.58 (d, J = 1.2 Hz, 3H), 4.05 (s, 2H), 6.60 (d, J = 8.0 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.80 (q, J = 1.2 Hz, 1H), 7.96 (s, 1H), 8.33 (s, 1H), 10.93 (s, 1H). MS 327 (MH^+).

Example 221a: 3-(3-sulfamoylamino-2-cyanophenoxy)-N,2,2-trimethylpropanamide

Prepared as in Example 215a from 3-(3-amino-2-cyanophenoxy)-N,2,2-trimethylpropanamide (Example 221b) in 69% yield. MS 327 (MH^+).

Example 221b: 3-(3-amino-2-cyanophenoxy)-N,2,2-trimethylpropanamide

Prepared as in Example 215b (Method A) from 3-(2-cyano-3-nitrophenoxy)-N,2,2-trimethylpropanamide (Example 221c) in 95% yield as a white solid. MS 248 (MH^+).

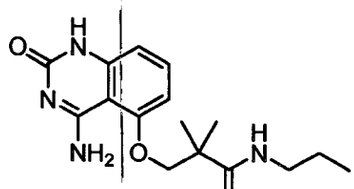
Example 221c: 3-(2-cyano-3-nitrophenoxy)-N,2,2-trimethylpropanamide

Prepared as in Example 215c from 3-hydroxy-N,2,2-trimethylpropanamide (Example 221d) and 2,6-dinitrobenzonitrile in 77% yield as a pale yellow solid. MS 378 (MH^+).

Example 221d: 3-hydroxy-N,2,2-trimethylpropanamide

Prepared as in Example 215d from methyl 3-hydroxy-2,2-dimethylpropanoate and methylamine in 51% yield. MS 132 (MH^+).

Example 222: 3-(4-amino-2-oxo-1,2-dihydroquinazolin-5-yloxy)-2,2-dimethyl-N-propylpropanamide



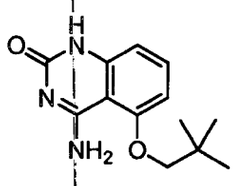
644

A solution of N-(2-cyano-3-(2,2-dimethyl-3-oxo-3-(propylamino)propoxy)-phenylcarbamoyl)benzamide (example 222a) (141 mg, 0.3 mmol) and NaOH (2 N, 0.3 mL) in EtOH (5 mL) was stirred at 100 °C under nitrogen for 2 hrs. After cooling to room temperature, the clear reaction solution was filtered, and the filtrate was carefully neutralized with 10 % AcOH with vigorous stirring at 0 °C. The resultant precipitate was collected by filtration, washed with water and then 20 % EtOH in water to give the final product (81 mg) in 76% yield as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.73 (t, J = 7.4 Hz, 3H), 1.21 (s, 6H), 1.33-1.41 (m, 2H), 3.01 (q, J = 7.4 Hz, 2H), 4.08 (s, 2H), 6.64 (d, J = 8.0 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.47 (s, 1H), 7.79 (t, J = 7.4 Hz, 1H), 7.84 (s, 1H), 10.60 (s, 1H). MS 319 (MH^+).

Example 222a: N-(2-cyano-3-(2,2-dimethyl-3-oxo-3-(propylamino)propoxy)phenyl-carbamoyl)benzamide

Prepared as in Example 146a from 3-(3-amino-2-cyanophenoxy)-2,2-dimethyl-N-propyl-propanamide (Example 215b, Method A) and benzoyl isocyanate in 85% yield as a white solid. MS 423 (MH^+).

Example 223: 4-amino-5-(neopentyloxy)quinazolin-2(1H)-one



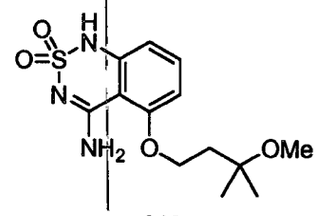
645

Prepared as in Example 222 from N-(2-cyano-3-(neopentyloxy)phenylcarbamoyl)benzamide (Example 223a) in 90% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.03 (s, 9H), 3.90 (s, 2H), 5.96 (s, 2H), 6.15 (d, J = 7.6 Hz, 1H), 6.30 (d, J = 7.6 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 11.22 (s, 1H). MS 248 (MH^+).

Example 223a: N-(2-cyano-3-(neopentyloxy)phenylcarbamoyl)benzamide

Prepared as in Example 146a from 2-amino-6-(neopentyloxy)-benzonitrile (Example 217b) and benzoyl isocyanate in 96% yield as a white solid. MS 352 (MH^+).

Example 224: 5-(3-methoxy-3-methylbutoxy)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



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Prepared as in Example 215 from 2-sulfamoylamino-6-(3-methoxy-3-methylbutoxy)benzonitrile (Example 224a) in 52% yield as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 1.16 (s, 6H), 1.98 (t, J = 6.2 Hz, 2H), 3.09 (s, 3H), 4.18 (t, J = 6.2 Hz, 2H), 8.57 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 8.25 (s, 1H), 8.30 (s, 1H), 10.89 (s, 1H). MS 314 (MH^+).

Example 224a: 2-sulfamoylamino-6-(3-methoxy-3-methylbutoxy)benzonitrile

Prepared as in Example 215a from 2-amino-6-(3-methoxy-3-methylbutoxy)benzonitrile (Example 224b) in 95% yield. MS 314 (MH^+).

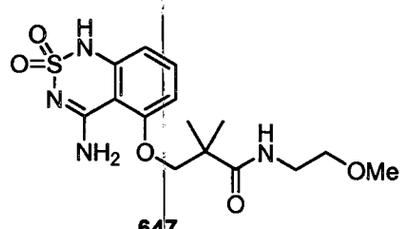
Example 224b: 2-amino-6-(3-methoxy-3-methylbutoxy)benzonitrile

Prepared as in Example 215b (Method A) from 2-(3-methoxy-3-methylbutoxy)-6-nitrobenzonitrile (Example 224c) in 62% yield. MS 235 (MH^+).

Example 224c: 2-(3-methoxy-3-methylbutoxy)-6-nitrobenzonitrile

Prepared as in Example 215c from 3-methoxy-3-methylbutan-1-ol and 2,6-dinitrobenzonitrile in 52% yield. MS 265 (MH^+).

Example 225: 3-(4-amino-2,2-dioxide-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)-N-(2''-methoxyethyl)-2',2'-dimethylpropanamide



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Prepared as in Example 215 from 3-(3-sulfamoylamino-2-cyanophenoxy)-N-(2-methoxyethyl)-2,2-dimethylpropanamide (Example 225a) in 12% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.21 (s, 6H), 3.13 (s, 3H), 3.17-3.22 (m, 2H), 3.28 (t, J = 6.0 Hz, 2H), 4.07 (s, 2H), 6.59 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.87 (s, 1H), 7.91 (t, J = 5.6 Hz, 1H), 8.33 (s, 1H), 10.92 (s, 1H). MS 371 (MH^+).

Example 225a: 3-(3-sulfamoylamino-2-cyanophenoxy)-N-(2-methoxyethyl)-2,2-dimethylpropanamide

Prepared as in Example 215a from 3-(3-amino-2-cyanophenoxy)-N-(2-methoxyethyl)-2,2-dimethylpropanamide (Example 225b) in 41% yield. MS 371 (MH^+).

Example 225b: 3-(3-amino-2-cyanophenoxy)-N-(2-methoxyethyl)-2,2-dimethyl-propanamide

Prepared as in Example 215b (Method A) from 3-(2-cyano-3-nitrophenoxy)-N-(2-methoxyethyl)-2,2-dimethylpropanamide (Example 225c) in 91% yield. MS 292 (MH^+).

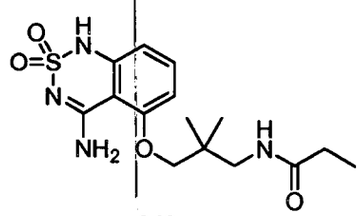
Example 225c: 3-(2-cyano-3-nitrophenoxy)-N-(2-methoxyethyl)-2,2-dimethyl-propanamide

Prepared as in Example 215c from 3-hydroxy-N-(2-methoxyethyl)-2,2-dimethylpropanamide (Example 225d) and 2,6-dinitrobenzonitrile in 55% yield. MS 322 (MH^+).

Example 225d: 3-hydroxy-N-(2-methoxyethyl)-2,2-dimethylpropanamide

Prepared as in Example 215d (Method A) from methyl 3-hydroxy-2,2-dimethylpropanoate and 2-methoxyethanamine in 100% yield. MS 176 (MH^+).

Example 226: N-(3-(4-amino-)-2,2-dioxide-1H-benzo[c][1,2,6]thiadiazin-5-yloxy-2',2'-dimethylpropyl)propionamide



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Prepared as in Example 215a from N-(3-(3-amino-2-cyanophenoxy)-2,2-dimethylpropyl)propionamide (Example 226a) and sulfamoyl chloride in 17% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.93-0.96 (m, 9H), 2.06-2.11 (m, 2H), 3.07 (d, J = 6.0

Hz, 2H), 3.74 (s, 2H), 6.58 (t, J = 8.4 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 7.41 (t, J = 8.4 Hz, 1H), 7.93-7.98 (m, 2H), 8.35 (brs, 1H), 10.91 (brs, 1H). MS 355 (MH^+).

Example 226a: N-(3-(3-amino-2-cyanophenoxy)-2,2-dimethylpropyl)propionamide

Prepared as in Example 215b (Method A) from N-(3-(2-cyano-3-nitrophenoxy)-2,2-dimethylpropyl)propionamide (Example 226b) in 100% yield. MS 276 (MH^+).

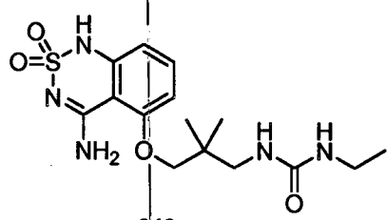
Example 226b: N-(3-(2-cyano-3-nitrophenoxy)-2,2-dimethylpropyl)propionamide

Prepared as in Example 215c from N-(3-hydroxy-2,2-dimethylpropyl)propionamide (Example 226c) and 2,6-dinitrobenzonitrile in 68% yield. MS 306 (MH^+).

Example 226c: N-(3-hydroxy-2,2-dimethylpropyl)propionamide

Prepared according to the literature (Boyd, R.N.; Hansen, R.H. *J. Am. Chem. Soc.* **1953**, *75*, 5896) from 2-amino-2-methylpropan-1-ol and benzoyl chloride in 84% yield as a white solid. MS 160 (MH^+).

Example 227: 1-(3-(4-amino-2,2-dioxide-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)-2',2'-dimethylpropyl)-3'-ethylurea



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Prepared as in Example 215 from 1-(3-(3-sulfamoylamino-2-cyanophenoxy)-2,2-dimethylpropyl)-3-ethylurea (Example 227a) in 55% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.88-0.96 (m, 9H), 2.90-2.97 (m, 2H), 3.01 (d, J = 6.4 Hz, 2H), 3.72 (s, 2H), 5.75 (t, J = 5.6 Hz, 1H), 6.07 (t, J = 6.4 Hz, 1H), 6.56 (d, J = 8.4 Hz, 1H), 6.67 (d, J = 8.8 Hz, 1H), 7.39 (t, J = 8.4 Hz, 1H), 8.05 (brs, 1H), 8.25 (brs, 1H), 10.89 (s, 1H). MS 370 (MH^+).

Example 227a: 1-(3-(3-sulfamoylamino-2-cyanophenoxy)-2,2-dimethylpropyl)-3-ethylurea

Prepared as in Example 215a from 1-(3-(3-amino-2-cyanophenoxy)-2,2-dimethylpropyl)-3-ethylurea (Example 227b) in 100% yield. MS 370 (MH^+).

Example 227b: 1-(3-(3-amino-2-cyanophenoxy)-2,2-dimethylpropyl)-3-ethylurea

Prepared as in Example 215b (Method A) from 1-(3-(2-cyano-3-nitrophenoxy)-2,2-dimethylpropyl)-3-ethylurea (Example 227c) in 90% yield. MS 291 (MH^+).

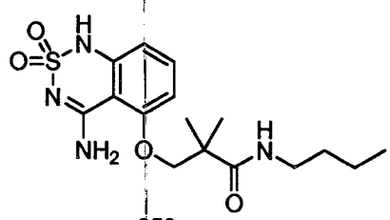
Example 227c: 1-(3-(2-cyano-3-nitrophenoxy)-2,2-dimethylpropyl)-3-ethylurea

Prepared as in Example 215c from 1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)urea (Example 227d) and 2,6-dinitrobenzonitrile in 47% yield. MS 321 (MH^+).

Example 227d: 1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)urea

To a solution of 3-amino-2,2-dimethylpropan-1-ol (1.03 g, 10 mmol) in dry 1,4-dioxane (20 mL) was added dropwise ethyl isocyanate (0.71 g, 10 mmol) at room temperature under nitrogen. The reaction mixture was then stirred at room temperature under nitrogen overnight. The solvent was removed under reduced pressure to give the title compound as colorless oil (1.74 g, 100%). MS 175 (MH^+).

Example 228: 3-(4-amino-2,2-dioxide-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)-N-butyl-2',2'-dimethylpropanamide



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Prepared as in Example 215 and 1a from 3-(3-amino-2-cyanophenoxy)-N-butyl-2,2-dimethylpropanamide (Example 228a) and sulfamoyl chloride in 14% yield as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 0.78 (t, J = 7.2 Hz, 3H), 1.14-1.22 (m, 8H), 1.33- 1.37 (m, 2H), 3.02-3.07 (m, 2H), 4.07 (s, 2H), 6.60 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 7.44 (t, J = 8.4 Hz, 1H), 7.80 (t, J = 5.6 Hz, 1H), 7.91 (s, 1H), 8.33 (s, 1H), 10.92 (s, 1H). MS 369 (MH^+).

Example 228a: 3-(3-amino-2-cyanophenoxy)-N-butyl-2,2-dimethylpropanamide .

Prepared as in Example 215b (Method A) from N-butyl-3-(2-cyano-3-nitrophenoxy)-2,2-dimethylpropanamide (Example 228b) in 89% yield. MS 290 (MH^+).

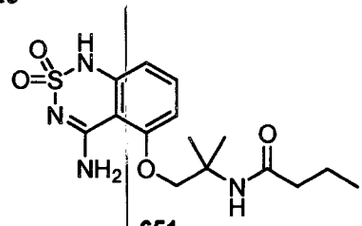
Example 228b: N-butyl-3-(2-cyano-3-nitrophenoxy)-2,2-dimethylpropanamide

Prepared as in Example 215c from N-butyl-3-hydroxy-2,2-dimethylpropanamide (Example 228c) and 2,6-dinitrobenzonitrile in 66% yield. MS 320 (MH^+).

Example 228c: N-butyl-3-hydroxy-2,2-dimethylpropanamide

Prepared as in Example 215d (Method A) from methyl 3-hydroxy-2,2-dimethylpropanoate and n-butyl amine in 100% yield. MS 174 (MH^+).

Example 229: N-(1-(4-amino-2,2-dioxide-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)-2'-methylpropan-2'-yl)butyramide



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Prepared as in Example 215 from N-(1-(3-sulfamoylamino-2-cyanophenoxy)-2-methylpropan-2-yl)butyramide (Example 229a) and sodium hydroxide in 54% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.78 (t, J = 7.2 Hz, 3H), 1.32 (s, 6H), 1.43- 1.44 (m, 2H), 2.00 (t, J = 7.2 Hz, 2H), 4.24 (s, 2H), 6.60 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 7.44 (t, J = 8.4 Hz, 1H), 7.77 (s, 1H), 7.82 (s, 1H), 8.42 (s, 1H), 10.97 (s, 1H). MS 355 (MH^+).

Example 229a: N-(1-(3-sulfamoylamino-2-cyanophenoxy)-2-methylpropan-2-yl)-butyramide

Prepared as in Example 215a from N-(1-(3-amino-2-cyanophenoxy)-2-methylpropan-2-yl)butyramide (Example 229b) and sulfamoyl chloride in 100% yield. MS 355 (MH^+).

Example 229b: N-(1-(3-amino-2-cyanophenoxy)-2-methylpropan-2-yl)butyramide

Prepared as in Example 215b (Method A) from N-(1-(2-cyano-3-nitrophenoxy)-2-methylpropan-2-yl)butyramide (Example 229c) in 100% yield. MS 276 (MH^+).

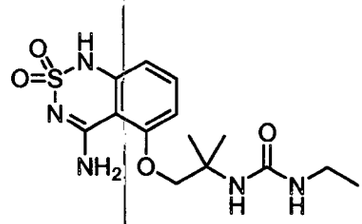
Example 229c: N-(1-(2-cyano-3-nitrophenoxy)-2-methylpropan-2-yl)butyramide

Prepared as in Example 215c from N-(1-hydroxy-2-methylpropan-2-yl)butyramide (Example 229d) and 2,6-dinitrobenzonitrile in 72% yield. MS 306 (MH^+).

Example 229d: N-(1-hydroxy-2-methylpropan-2-yl)butyramide

Prepared according to the literature (Boyd, R.N.; Hansen, R.H. *J. Am. Chem. Soc.* **1953**, *75*, 5896) from 2-amino-2-methylpropan-1-ol and butyryl chloride in 32% yield. MS 160 (MH^+).

Example 230: 1-(1-(4-amino-2,2-dioxide-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)-2'-methylpropan-2'-yl)-3'-ethylurea



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Prepared as in Example 215 from 1-(1-(3-sulfamoylamino-2-cyanophenoxy)-2-methylpropan-2-yl)-3-ethylurea (Example 230a) in 37% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.92 (t, J = 7.2 Hz, 3H), 1.27 (s, 6H), 2.90-2.93 (m, 2H), 4.21 (s, 2H), 5.63 (t, J = 5.2 Hz, 1H), 5.95 (s, 1H), 6.59 (d, J = 8.0 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 7.42 (t, J = 8.4 Hz, 1H), 7.94 (s, 1H), 8.34 (s, 1H), 10.94 (s, 1H). MS 356 (MH^+).

Example 230a: 1-(1-(3-sulfamoylamino-2-cyanophenoxy)-2-methylpropan-2-yl)-3-ethylurea

Prepared as in Example 215a from 1-(1-(3-amino-2-cyanophenoxy)-2-methylpropan-2-yl)-3-ethylurea (Example 230b) and sulfamoyl chloride in 100% yield. MS 356 (MH^+).

Example 230b: 1-(1-(3-amino-2-cyanophenoxy)-2-methylpropan-2-yl)-3-ethylurea

Prepared as in Example 215b (Method A) from 1-(1-(2-cyano-3-nitrophenoxy)-2-methylpropan-2-yl)-3-ethylurea (Example 230c) in 86% yield. MS 277 (MH^+).

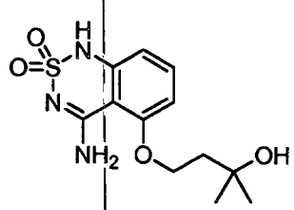
Example 230c: 1-(1-(2-cyano-3-nitrophenoxy)-2-methylpropan-2-yl)-3-ethylurea

Prepared as in Example 215c from 1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)urea (Example 230d) and 2,6-dinitrobenzonitrile in 65% yield. MS 307 (MH^+).

Example 230d: 1-ethyl-3-(1-hydroxy-2-methylpropan-2-yl)urea

Prepared as in Example 227d from 2-amino-2-methylpropan-1-ol and ethyl isocyanate in 94% yield. MS 161 (MH^+).

Example 231: 4-(4-amino-2,2-dioxide-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)-2'-methylbutan-2'-ol



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Prepared as in Example 215 from 4-(2-cyano-3-(sulfamoylamino)phenoxy)-2-methylbutan-2-yl acetate (Example 231a) in 20% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.15 (s, 6H), 1.89 (t, J = 6.4 Hz, 2H), 4.22 (t, J = 6.4 Hz, 2H), 4.62 (s,1H), 6.57 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 7.43 (t, J = 8.4 Hz, 1H), 8.22 (s, 1H), 8.30 (s, 1H), 10.87 (s, 1H). MS 300 (MH^+).

Example 231a: 4-(2-cyano-3-(sulfamoylamino)phenoxy)-2-methylbutan-2-yl acetate

Prepared as in Example 215a from 4-(3-amino-2-cyanophenoxy)-2-methylbutan-2-yl acetate (Example 231b) and sulfamoyl chloride in 100% yield. MS 342 (MH^+).

Example 231b: 4-(3-amino-2-cyanophenoxy)-2-methylbutan-2-yl acetate

Prepared as in Example 215b (Method A) from 4-(2-cyano-3-nitrophenoxy)-2-methylbutan-2-yl acetate (Example 231c). MS 263 (MH^+).

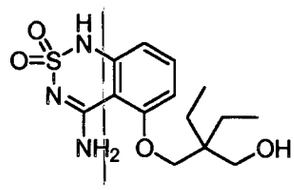
Example 231c: 4-(2-cyano-3-nitrophenoxy)-2-methylbutan-2-yl acetate

To a solution of 2-(3-hydroxy-3-methylbutoxy)-6-nitrobenzonitrile (Example 231d) (250 mg, 1 mmol), triethylamine (3 equiv.), and DMAP (0.1 equiv.) in dry dichloromethane (20 mL) was added dropwise acetyl chloride (1.5 equiv.) at 0 °C under nitrogen. The reaction mixture was then stirred at 0 °C – room temperature overnight. The reaction was diluted with EtOAc, washed with brine, and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by chromatography on silica gel eluting with 20% EtOAc in hexanes to give the title compound (137 mg, 47%). MS 293 (MH^+).

Example 231d: 2-(3-hydroxy-3-methylbutoxy)-6-nitrobenzonitrile

Prepared as in Example 215c from 3-methylbutane-1,3-diol and 2,6-dinitrobenzonitrile in 81% yield. MS 251 (MH^+).

Example 232: 2-((4-amino-2,2-dioxide-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)methyl)-2'-ethylbutan-1'-ol



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Prepared as in Example 215 from 2-ethyl-2-((2-methyl-3-(sulfamoylamino)phenoxy)methyl)butyl acetate (Example 232a) in 20% yield as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 0.73-0.80 (m, 6H), 1.21-1.37 (m, 4H), 3.31-3.33 (m, 2H), 3.89 (s, 2H), 4.92 (brs, 1H), 6.56 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 7.40 (t, J = 8.4 Hz, 1H), 8.16 (brs, 2H), 10.91 (brs, 1H). MS 328 (MH^+).

Example 232a: 2-((2-cyano-3-(sulfamoylamino)phenoxy)methyl)-2-ethylbutyl acetate

Prepared as in Example 215a from 2-((3-amino-2-cyanophenoxy)methyl)-2-ethylbutyl acetate (Example 232b) and sulfamoyl chloride in 90% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.80 (t, J = 7.6 Hz, 6H), 1.37-1.43 (m, 4H), 1.98 (s, 3H), 3.87 (s, 2H), 3.96 (s, 2H), 6.98 (d, J = 8.8 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 7.25 (s, 2H), 7.54 (t, J = 8.4 Hz, 1H), 9.46 (s, 1H).

Example 232b: 2-((3-amino-2-cyanophenoxy)methyl)-2-ethylbutyl acetate

Prepared as in Example 215b (Method A) from 2-((2-cyano-3-nitrophenoxy)methyl)-2-ethylbutyl acetate (Example 232c) in 91% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.79 (t, J = 7.6 Hz, 6H), 1.34-1.41 (m, 4H), 1.97 (s, 3H), 3.76 (s, 2H), 3.94 (s, 2H), 5.97 (s, 2H), 6.21 (d, J = 8.0 Hz, 1H), 6.31 (d, J = 8.4 Hz, 1H), 7.15 (t, J = 8.0 Hz, 1H). MS 291 (MH^+).

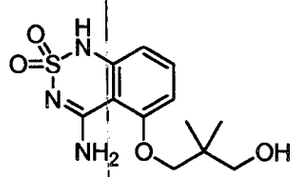
Example 232c: 2-((2-cyano-3-nitrophenoxy)methyl)-2-ethylbutyl acetate

Prepared as in Example 231c from 2-(2-ethyl-2-(hydroxymethyl)butoxy)-6-nitrobenzonitrile (Example 232d) and acetyl chloride in 82% yield. MS 321 (MH^+).

Example 232d: 2-(2-ethyl-2-(hydroxymethyl)butoxy)-6-nitrobenzonitrile

Prepared as in Example 215c from 2,2-diethylpropane-1,3-diol and 2,6-dinitrobenzonitrile in 86% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.80 (t, J = 7.6 Hz, 6H), 1.34 (q, J = 7.6 Hz, 4H), 3.33 (d, J = 5.6 Hz, 2H), 3.96 (s, 2H), 4.57 (t, J = 5.2 Hz, 1H), 7.74-7.76 (m, 1H), 7.84-7.90 (m, 2H).

Example 233: 3-(4-amino-2,2-dioxide-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)-2',2'-dimethylpropan-1'-ol



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Prepared as in Example 215 from 3-(2-cyano-3-(sulfamoyl-amino)phenoxy)-2,2-dimethylpropyl acetate (Example 233a) in 30% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.94 (s, 6H), 3.29-3.31 (m, 2H), 3.88 (s, 2H), 5.01 (t, J = 4.4 Hz, 1H), 6.58 (d, J = 8.4 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 8.14 (s, 1H), 8.32 (s, 1H), 10.92 (s, 1H). MS 300 (MH^+).

Example 233a: 3-(2-cyano-3-(sulfamoylamino)phenoxy)-2,2-dimethylpropyl acetate

Prepared as in Example 215a from 3-(3-amino-2-cyanophenoxy)-2,2-dimethylpropyl acetate (Example 233b) and sulfamoyl chloride in 60% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.99 (s, 6H), 1.98 (s, 3H), 3.85 (s, 2H), 3.91 (s, 2H), 6.91 (d, J = 8.4 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.23 (s, 2H), 7.52 (t, J = 8.0 Hz, 1H), 9.45 (s, 1H).

Example 233b: 3-(3-amino-2-cyanophenoxy)-2,2-dimethylpropyl acetate

Prepared as in Example 215b (Method A) from 3-(2-cyano-3-nitrophenoxy)-2,2-dimethylpropyl acetate (Example 233c) in 77% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.98 (s, 6H), 2.00 (s, 3H), 3.75 (s, 2H), 3.90 (s, 2H), 5.99 (s, 2H), 6.17 (d, J = 8.4 Hz, 1H), 6.31 (d, J = 8.4 Hz, 1H), 7.15 (t, J = 8.0 Hz, 1H).

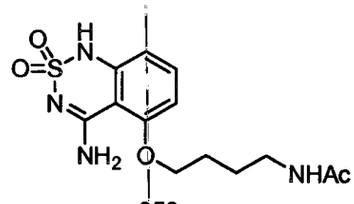
Example 233c: 3-(2-cyano-3-nitrophenoxy)-2,2-dimethylpropyl acetate

Prepared as in Example 231c from 2-(3-hydroxy-2,2-dimethylpropoxy)-6-nitrobenzonitrile (Example 233d) and acetyl chloride in 66% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.04 (s, 6H), 2.00 (s, 3H), 3.95 (s, 2H), 4.02 (s, 2H), 7.70-7.72 (m, 1H), 7.85-7.92 (m, 2H).

Example 233d: 2-(3-hydroxy-2,2-dimethylpropoxy)-6-nitrobenzonitrile

Prepared as in Example 215c from 2,2-dimethylpropane-1,3-diol and 2,6-dinitrobenzonitrile in 73% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.94 (s, 6H), 3.29-3.31 (m, 2H), 3.95 (s, 2H), 4.69 (t, J = 5.6 Hz, 1H), 7.69-7.71 (m, 1H), 7.84-7.90 (m, 2H).

Example 234: N-(4-(4-amino-2,2-dioxide-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)butyl)-acetamide



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Prepared as in Example 215 from N-(4-(2-cyano-3-(sulfamoylamino)phenoxy)butyl)acetamide (Example 234a) in 30% yield. ^{1}H NMR (400 MHz,

DMSO-d_6) δ 1.48-1.51 (m, 2H), 1.77-1.81 (m, 5H), 3.03-3.08 (m, 2H), 4.14 (t, J = 6.0 Hz, 2H), 6.59 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 7.43 (t, J = 8.4 Hz, 1H), 7.78 (s,1H). 7.84 (brs, 1H), 8.32 (s,1H), 10.93 (s, 1H). MS 327 (MH^+).

Example 234a: N-(4-(2-cyano-3-(sulfamoylamino)phenoxy)butyl)acetamide

Prepared as in Example 215a from N-(4-(3-amino-2-cyanophenoxy)butyl)acetamide (Example 234b) and sulfamoyl chloride in 100% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.51-1.54 (m, 2H), 1.70-1.73 (m, 2H), 1.77 (s, 3H), 3.04-3.09 (m, 2H), 4.09 (t, J = 6.4 Hz, 2H), 6.93 (d, J = 8.4 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.25 (s, 2H), 7.54 (t, J = 8.0 Hz, 1H), 7.85 (brs,1H), 9.42 (s, 1H).

Example 234b: N-(4-(3-amino-2-cyanophenoxy)butyl)acetamide

Prepared as in Example 215b (Method A) from N-(4-(2-cyano-3-nitrophenoxy)butyl)acetamide (Example 234c) in 85% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.49-1.54 (m, 2H), 1.66-1.70 (m, 2H), 1.77 (s, 3H), 3.03-3.08 (m, 2H), 3.97 (t, J = 6.8 Hz, 2H), 5.95 (s, 2H), 6.18 (d, J = 8.0 Hz, 1H), 6.31 (d, J = 7.6 Hz, 1H), 7.15 (t, J = 8.4 Hz, 1H), 7.83 (brs,1H).

Example 234c: N-(4-(2-cyano-3-nitrophenoxy)butyl)acetamide

To a solution of 2-(4-aminobutoxy)-6-nitrobenzonitrile (Example 234d) (235 mg, 1.0 mmol), triethylamine (3 equiv.), and DMAP (0.1 equiv.) in dry dichloromethane (20 mL) was added dropwise acetyl chloride (1.5 equiv.) at 0 °C under nitrogen. The reaction mixture was then stirred at 0 °C – RT overnight. The reaction was diluted with EtOAc, washed with brine, and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by chromatography on silica gel eluting with 50% EtOAc in hexanes to give the title compound (158 mg, 57%). MS 278 (MH^+).

Example 234d: 2-(4-aminobutoxy)-6-nitrobenzonitrile

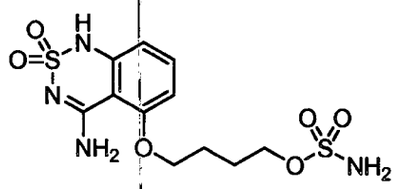
A solution of tert-butyl 4-(2-cyano-3-nitrophenoxy)butylcarbamate (Example 234e) (671 mg, 2 mmol) in DCM/TFA (1:1, 20 mL) was stirred at room temperature for 2 hrs. The solvent was removed under vacuum to give the title compound (698 mg, 100%). MS 236 (MH^+).

Example 234e: tert-butyl 4-(2-cyano-3-nitrophenoxy)butylcarbamate

Prepared as in Example 215c from tert-butyl 4-hydroxybutylcarbamate and 2,6-dinitrobenzonitrile in 7% yield as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.35 (s,

9H), 1.52-1.55 (m, 2H), 1.72-1.76 (m, 2H), 2.94-2.99 (m, 2H), 4.24 (t, J = 6.8 Hz, 2H), 6.86 (brs, 1H), 7.69-7.72 (m, 1H), 7.85-7.90 (m,2H).

Example 235: 4-(4-amino-2,2-dioxide-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)butyl sulfamate



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Prepared as in Example 215 from 4-(2-cyano-3-(sulfamoylamino)phenoxy)butyl sulfamate (Example 235a) in 31% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.74-1.79 (m, 2H), 1.85-1.91 (m, 2H), 4.07 (t, J = 6.4 Hz, 2H), 4.18 (t, J = 6.8 Hz, 2H), 6.58-6.60 (m, 1H), 6.74 (d, J = 8.4 Hz, 1H), 7.42-7.46 (m, 3H), 7.79 (s,1H), 8.32 (s, 1H), 10.93 (s,1H). MS 365 (MH^+).

Example 235a: 4-(2-cyano-3-(sulfamoylamino)phenoxy)butyl sulfamate

Prepared as in Example 215a from 2-amino-6-(4-(tert-butyldimethylsilyloxy)butoxy)benzonitrile (Example 235b) and sulfamoyl chloride in 63% yield. MS 382 (M^++H_2O).

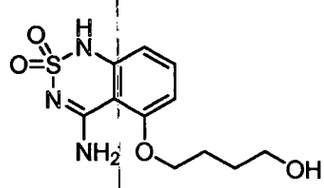
Example 235b: 2-amino-6-(4-(tert-butyldimethylsilyloxy)butoxy)benzonitrile

Prepared as in Example 215b (Method A) from 2-(4-(tert-butyldimethylsilyloxy)butoxy)-6-nitrobenzonitrile (Example 235c) in 76% yield. MS 321 (MH^+).

Example 235c: 2-(4-(tert-butyldimethylsilyloxy)butoxy)-6-nitrobenzonitrile

Prepared as in Example 215c from 4-(tert-butyldimethyl-silyloxy)butan-1-ol and 2,6-dinitrobenzonitrile in 25% yield as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.01 (s, 6H), 0.81-0.83 (m, 9H), 1.61-1.66 (m, 2H), 1.76-1.81 (m, 2H), 3.63 (t, J = 6.8 Hz, 2H), 4.26 (t, J = 6.4 Hz, 2H), 7.68-7.70 (m, 1H), 7.84-7.89 (m, 2H).

Example 236: 4-(4-amino-2,2-dioxide-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)-butan-1'-ol

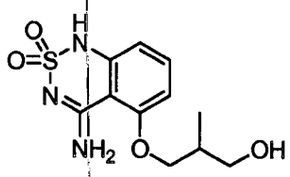


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Prepared as in Example 215 from 4-(2-cyano-3-(sulfamoylamino)phenoxy)butyl sulfamate (Example 235a) in 2% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 1.69-1.73 (m, 2H), 1.95-

1.99 (m, 2H), 3.63 (t, J = 6.4 Hz, 2H), 4.24 (t, J = 6.4 Hz, 2H), 6.61-6.63 (m, 1H), 6.75-6.77 (m, 1H), 7.45 (m, J = 8.0 Hz, 1H). MS 286 (MH^+).

Example 237: 3-(4-amino-2,2-dioxide-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)-2'-methylpropan-1'-ol



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Prepared as in Example 215 from 3-(2-cyano-3-(sulfamoylamino)phenoxy)-2-methylpropyl acetate (Example 237a) in 41% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.94 (d, J = 6.4 Hz, 3H), 2.09-2.13 (m, 1H), 3.36-3.42 (m, 1H), 3.46-3.50 (m, 1H), 4.05 (d, J = 6.4 Hz, 2H), 4.84 (t, J = 5.6 Hz, 1H), 6.57 (d, J = 7.6 Hz, 1H), 6.70 (d, J = 8.4 Hz, 1H), 7.42 (t, J = 8.4 Hz, 1H), 8.05 (brs, 1H), 8.24 (brs, 1H), 10.91 (s, 1H). MS 286 (MH^+).

Example 237a: 33-(2-cyano-3-(sulfamoylamino)phenoxy)-2-methylpropyl acetate

Prepared as in Example 215a from 3-(3-amino-2-cyanophenoxy)-2-methylpropyl acetate (Example 237b) and sulfamoyl chloride in 78% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.02 (d, J = 6.8 Hz, 3H), 2.01 (s, 3H), 2.23-2.27 (m, 1H), 3.99-4.07 (m, 4H), 6.94 (d, J = 8.8 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.26 (s, 2H), 7.55 (t, J = 8.0 Hz, 1H), 9.47 (s, 1H).

Example 237b: 3-(3-amino-2-cyanophenoxy)-2-methylpropyl acetate

Prepared as in Example 215b (Method A) from 3-(2-cyano-3-nitrophenoxy)-2-methylpropyl acetate (Example 237c) in 73% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.99 (d, J = 7.2 Hz, 3H), 2.00 (s, 3H), 2.19-2.24 (m, 1H), 3.91 (d, J = 5.2 Hz, 2H), 3.97-4.06 (m, 2H), 5.98 (s, 2H), 6.19 (d, J = 8.0 Hz, 1H), 6.32 (d, J = 8.4 Hz, 1H), 7.16 (t, J = 8.0 Hz, 1H).

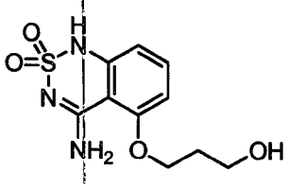
Example 237c: 3-(2-cyano-3-nitrophenoxy)-2-methylpropyl acetate

Prepared as in Example 231c from 2-(3-hydroxy-2-methylpropoxy)-6-nitrobenzonitrile (Example 237d) and acetyl chloride in 41% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.04 (d, J = 6.8 Hz, 3H), 2.00 (s, 3H), 2.28-2.33 (m, 1H), 4.05-4.08 (m, 2H), 4.18 (d, J = 6.0 Hz, 2H), 7.71-7.73 (m, 1H), 7.86-7.92 (m, 2H).

Example 237d: 2-(3-hydroxy-2-methylpropoxy)-6-nitrobenzonitrile

Prepared as in Example 215c from 2-methylpropane-1,3-diol and 2,6-dinitrobenzonitrile in 37% yield. MS 237 (MH^+).

Example 238: 3-(4-amino-2,2-dioxide-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)propan-1'-ol



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Prepared as in Example 215 from 3-(2-cyano-3-(sulfamoylamino)phenoxy)propyl sulfamate (Example 238a) in 6% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.92-1.97 (m, 2H), 3.55-3.59 (m, 2H), 4.20 (t, J = 6.4 Hz, 2H), 4.79 (t, J = 4.8 Hz, 1H), 6.57-6.59 (m, 1H), 6.71-6.73 (m, 1H), 7.43 (t, J = 8.4 Hz, 1H), 8.12 (brs, 1H), 8.28 (brs, 1H), 10.90 (s, 1H). MS 272 (MH^+).

Example 238a: 3-(2-cyano-3-(sulfamoylamino)phenoxy)propyl sulfamate

Prepared as in Example 215a from 2-amino-6-(3-hydroxypropoxy)benzonitrile (Example 238b) and sulfamoyl chloride in 30% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.11-2.14 (m, 2H), 4.16-4.21 (m, 4H), 6.96 (d, J = 8.0 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H), 7.26 (s, 2H), 7.49 (s, 2H), 7.56 (t, J = 8.4 Hz, 1H), 9.46 (s, 1H).

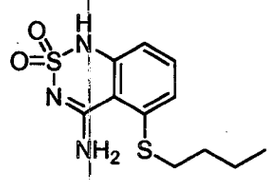
Example 238b: 2-amino-6-(3-hydroxypropoxy)benzonitrile

Prepared as in Example 215b (Method A) from 2-(3-hydroxypropoxy)-6-nitrobenzonitrile (Example 238c) in 100% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.79-1.85 (m, 2H), 3.52-3.56 (m, 2H), 4.04 (t, J = 6.4 Hz, 2H), 4.54 (t, J = 5.2 Hz, 1H), 5.93 (s, 2H), 6.19 (d, J = 8.0 Hz, 1H), 6.30 (d, J = 8.4 Hz, 1H), 7.15 (t, J = 8.0 Hz, 1H).

Example 238c: 2-(3-hydroxypropoxy)-6-nitrobenzonitrile

Prepared as in Example 215c from propane-1,3-diol and 2,6-dinitrobenzonitrile in 61% yield as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.89-1.93 (m, 2H), 3.56-3.61 (m, 2H), 4.30 (t, J = 6.4 Hz, 2H), 4.61 (t, J = 5.2 Hz, 1H), 7.71-7.74 (m, 1H), 7.85-7.91 (m, 2H).

Example 239: 5-(butylthio)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



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Prepared as in Example 215 from 2-sulfamoylamino-6-(butylthio)benzonitrile (Example 239a) in 12% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.85 (t, J = 7.6 Hz, 3H), 1.34-1.41 (m, 2H), 1.49-1.56 (m, 2H), 2.97 (t, J = 7.2 Hz, 2H), 6.87 (d, J = 8.4 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 8.12 (brs, 2H), 11.02 (brs, 1H). MS 286 (MH^+).

Example 239a: 2-sulfamoylamino-6-(butylthio)benzonitrile

Prepared as in Example 215a from 2-amino-6-(butylthio)benzonitrile (Example 239b) in 76% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.88 (t, J = 7.2 Hz, 3H), 1.36-1.45 (m, 2H), 1.54-1.61 (m, 2H), 3.07 (t, J = 7.6 Hz, 2H), 7.25-7.27 (m, 3H), 7.33-7.36 (m, 1H), 7.57 (t, J = 8.4 Hz, 1H), 9.50 (s, 1H).

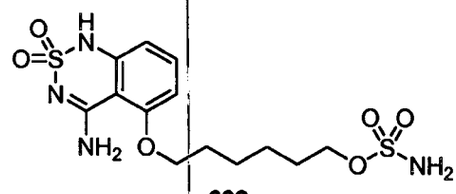
Example 239b: 2-amino-6-(butylthio)benzonitrile

Prepared as in Example 215b (Method A) from 2-nitro-6-(butylthio)benzonitrile (Example 239c) in 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, J = 7.2 Hz, 3H), 1.42-1.52 (m, 2H), 1.63-1.70 (m, 2H), 2.97 (t, J = 6.8 Hz, 2H), 4.43 (brs, 2H), 6.52-6.54 (m, 1H), 6.67-6.69 (m, 1H), 7.21 (t, J = 8.0 Hz, 1H).

Example 239c: 2-nitro-6-(butylthio)benzonitrile

Prepared as in Example 215c from butane-1-thiol and 2,6-dinitrobenzonitrile in 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, J = 7.2 Hz, 3H), 1.42-1.55 (m, 2H), 1.70-1.77 (m, 2H), 3.09 (t, J = 7.2 Hz, 2H), 7.63-7.69 (m, 2H), 7.99-8.01 (m, 1H).

Example 240: 6-(4-amino-2,2-dioxide-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)hexyl sulfamate



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Prepared as in Example 215 from 6-(2-cyano-3-(sulfamoylamino)phenoxy)hexyl sulfamate (Example 240a) in 46% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.03-1.05 (m, 4H), 1.28 (m, 2H), 1.45 (m, 2H), 3.64 (t, J = 6.4 Hz, 2H), 3.78 (t, J = 6.4 Hz, 2H), 6.22 (d, J = 7.6 Hz,

1H), 6.37 (d, J = 7.6 Hz, 1H), 7.02 (s, 2H), 7.07 (t, J = 7.6 Hz, 1H), 7.44 (s, 1H), 7.96 (s, 1H), 10.56 (s, 1H). MS 393 (MH^+).

Example 240a: 6-(2-cyano-3-(sulfamoylamino)phenoxy)hexyl sulfamate

Prepared as in Example 215a from 2-amino-6-(6-hydroxy-hexyloxy)benzonitrile (Example 240b) and sulfamoyl chloride in 20% yield. MS 393 (MH^+).

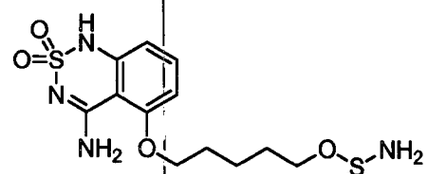
Example 240b: 2-amino-6-(6-hydroxyhexyloxy)benzonitrile

Prepared as in Example 215b (Method A) from 2-(6-hydroxyhexyloxy)-6-nitrobenzonitrile (Example 240c) in 99% yield. MS 235 (MH^+).

Example 240c: 2-(6-hydroxyhexyloxy)-6-nitrobenzonitrile

Prepared as in Example 215c from hexane-1,6-diol and 2,6-dinitrobenzonitrile in 88% yield as a pale yellow solid. MS 265 (MH^+).

Example 241: 5-(4-amino-2,2-dioxide-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)pentyl sulfamate



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Prepared as in Example 215 from 5-(2-cyano-3-(sulfamoylamino)-phenoxy)pentyl sulfamate (Example 241a) in 44% yield. ^1H NMR (400 MHz, DMSO-d_6) δ 1.09 (m, 2H), 1.33 (m, 2H), 1.47 (m, 2H), 3.66 (t, J = 6.6 Hz, 2H), 3.79 (t, J = 6.6 Hz, 2H), 6.22 (d, J = 8.0 Hz, 1H), 6.37 (d, J = 8.0 Hz, 1H), 7.03 (s, 2H), 7.07 (t, J = 8.0 Hz, 1H), 7.43 (s, 1H), 7.95 (s, 1H), 10.57 (s, 1H). MS 379 (MH^+).

Example 241a: 5-(2-cyano-3-(sulfamoylamino)phenoxy)pentyl sulfamate

Prepared as in Example 215a from 2-amino-6-(5-(tert-butyldimethylsilyloxy)pentyloxy)benzonitrile (Example 241b) and sulfamoyl chloride in 26% yield. MS 379 (MH^+).

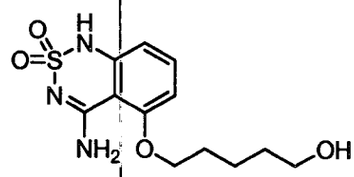
Example 241b: 2-amino-6-(5-(tert-butyldimethylsilyloxy)pentyloxy)benzonitrile

Prepared as in Example 215b (Method A) from 2-(5-(tert-butyldimethyl-silyloxy)pentyloxy)-6-nitrobenzonitrile (Example 241c) in 93% yield. MS 335 (MH^+).

Example 241c: 2-(5-(tert-butyldimethylsilyloxy)pentyloxy)-6-nitrobenzonitrile

Prepared as in Example 215c from 5-(tert-butyldimethyl-silyloxy)pentan-1-ol and 2,6-dinitrobenzonitrile as a pale yellow solid in 46% yield. MS 365 (MH^+).

Example 242: 5-(4-amino-2,2-dioxide-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)pentan-1'-ol



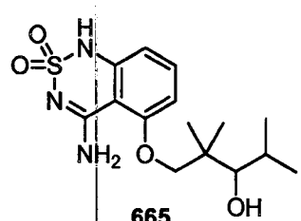
664

Prepared as in Example 215 from 2-sulfamoylamino-6-(5-hydroxy-pentyloxy)benzonitrile (Example 242a) in 32% yield. ^1H NMR (400 MHz, DMSO-d_6) δ 1.39-1.49 (m, 4H), 1.77-1.84 (m, 2H), 3.31-3.44 (m, 2H), 4.14 (t, J = 6.4 Hz, 2H), 4.35 (m, 1H), 6.59 (d, J = 8.0 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.81 (s, 1H), 8.34 (s, 1H), 10.93 (s, 1H). MS 300 (MH^+).

Example 242a: 2-sulfamoylamino-6-(5-hydroxypentyloxy)benzonitrile

Prepared as in Example 215a from 2-amino-6-(5-(tert-butyldimethylsilyloxy)pentyloxy)benzonitrile (Example 241b) and sulfamoyl chloride in 4% yield. MS 300 (MH^+).

Example 243: 1-(4-amino-2,2-dioxide-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)-2',2',4'-trimethylpentan-3'-ol



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Prepared as in Example 215 from 1-(2-cyano-3-(sulfamoylamino)-phenoxy)-2,2,4-trimethylpentan-3-yl acetate (Example 243a) in 35% yield as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 0.76-0.78 (d, 3H), 0.93 (s, 6H), 1.05 (s, 3H), 1.86-1.89 (m, 1H), 3.18-3.19 (d, 1H), 3.73-3.75 (d, 1H), 3.99-4.02 (d, 1H), 4.98-4.99 (d, 1H), 6.57-6.59 (d, J = 8 Hz, 1H), 6.70-6.72 (d, J = 8 Hz,1H), 7.43 (t, J = 8 Hz, 1H), 8.29 (s, 1H), 8.43 (s, 1H), 10.88 (s, 1H). MS 342 (MH^+).

Example 243a: 1-(2-cyano-3-(sulfamoylamino)phenoxy)-2,2,4-trimethylpentan-3-yl acetate

Prepared as in Example 215a from 1-(3-amino-2-cyanophenoxy)-2,2,4-trimethylpentan-3-yl acetate (Example 243b) and sulfamoyl chloride in 90% yield. MS 384 (MH^+).

Example 243b: 1-(3-amino-2-cyanophenoxy)-2,2,4-trimethylpentan-3-yl acetate

Prepared as in Example 215b (Method A) from 1-(2-cyano-3-nitrophenoxy)-2,2,4-trimethylpentan-3-yl acetate (Example 243c) in 83% yield. MS 305 (MH^+).

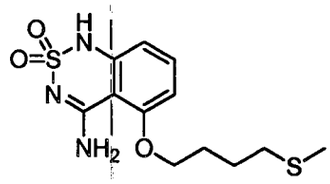
Example 243c: 1-(2-cyano-3-nitrophenoxy)-2,2,4-trimethylpentan-3-yl acetate

Prepared as in Example 231c from 2-(3-hydroxy-2,2,4-trimethylpentyloxy)-6-nitrobenzonitrile (Example 243d) and acetyl chloride in 50% yield. MS 335 (MH^+).

Example 243d: 2-(3-hydroxy-2,2,4-trimethylpentyloxy)-6-nitrobenzonitrile

Prepared as in Example 215c from 2,2,4-trimethylpentane-1,3-diol and 2,6-dinitrobenzonitrile in 90% yield. MS 293 (MH^+).

Example 244: 5-(4-(methylthio)butoxy)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



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Prepared as in Example 215 from 2-sulfamoylamino-6-(4-(methylthio)butoxy)benzonitrile (Example 244a) in 79% yield. ^1H NMR (400 MHz, DMSO-d_6) δ 1.63-1.67 (m, 2H), 1.86-1.90 (m, 2H), 2.02 (s, 3H), 2.48-2.53 (m, 2H), 4.16 (t, 2H), 6.57-6.60 (d, J=8.4 Hz, 1H), 6.72-6.74 (d, J = 8.4 Hz, 1H), 7.43 (t, J=8 Hz, 1H), 7.80 (s, 1H), 8.35 (s, 1H), 10.92 (s, 1H). MS 316 (MH^+).

Example 244a: 2-sulfamoylamino-6-(4-(methylthio)butoxy)benzonitrile

Prepared as in Example 215a from 2-amino-6-(4-(methylthio)-butoxy)benzonitrile (Example 244b) and sulfamoyl chloride in 66% yield. MS 316 (MH^+).

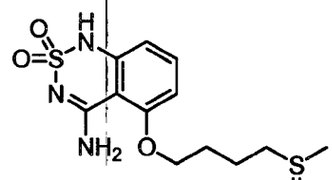
Example 244b: 2-amino-6-(4-(methylthio)butoxy)benzonitrile

Prepared as in Example 215b (Method A) from 2-(4-(methylthio)butoxy)-6-nitrobenzonitrile (Example 244c) in 95% yield. MS 237 (MH^+).

Example 244c: 2-(4-(methylthio)butoxy)-6-nitrobenzonitrile

Prepared as in Example 215c from 4-(methylthio)butan-1-ol and 2,6-dinitrobenzonitrile in 89% yield. MS 267 (MH^+).

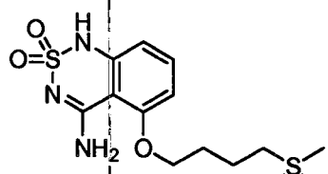
Example 245: 5-(4-(methylsulfinyl)butoxy)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



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To a solution of 5-(4-(methylthio)butoxy)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide (Example 244) (79 mg, 0.25 mmol) in DCM/CH_3CO_2H (20:1, 20 mL) was added MCPBA (1.0 equiv.) at room temperature. The reaction mixture was then stirred at room temperature overnight. The solvent was evaporated under reduced pressure, and the residue was purified by chromatography on silica gel eluting with 15% MeOH in dichloromethane to give the title compound (74 mg, 90%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.74-1.77 (m, 2H), 1.88-1.95 (m, 2H), 2.50 (s, 3H), 2.68-2.73 (m, 1H), 2.77-2.83(m,1H), 4.19 (t, 2H), 6.58-6.60 (d, J = 8.4 Hz, 1H), 6.73-6.75 (d, J = 8.0 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.79 (s, 1H), 8.33 (s, 1H), 10.92 (s, 1H). MS 332 (MH^+).

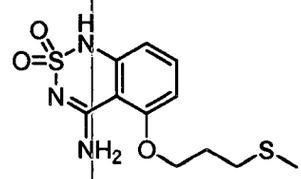
Example 246: 5-(4-(methylsulfonyl)butoxy)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



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Prepared as in Example 245 from 5-(4-(methylthio)butoxy)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide (Example 244) by the reaction with 3 equivalent of MCPBA as a white solid in 88% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.80-1.82 (m, 2H), 1.91-1.95 (m, 2H), 2.93 (s, 3H),3.18 (t, 2H), 4.18 (t, 2H), 6.58-6.60 (d, J = 8.4 Hz, 1H), 6.73-6.75 (d, J = 8.0 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.79 (s, 1H), 8.34 (s, 1H), 10.92 (s, 1H). MS 348 (MH^+).

Example 247: 5-(3-(methylthio)propoxy)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



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Prepared as in Example 215 from 2-sulfamoylamino-6-(3-(methylthio)propoxy)benzonitrile (Example 247a) in 69% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.05 (s, 3H), 2.08 (m, 2H), 2.59 (t, J = 7.2 Hz, 2H), 4.21 (t, J = 6.4 Hz, 2H), 6.59-6.61 (d, J = 8.0 Hz, 1H), 673-6.75 (d, J = 8.8 Hz,1H), 7.44 (t, J = 8.0 Hz, 1H), 7.79 (s, 1H), 8.33 (s, 1H), 10.93 (s, 1H). MS 302 (MH^+).

Example 247a: 2-sulfamoylamino-6-(3-(methylthio)propoxy)benzonitrile Prepared as in Example 215a from 2-amino-6-(3-(methylthio)propoxy)benzonitrile (Example 247b) and sulfamoyl chloride in 69% yield. MS 302 (MH^+).

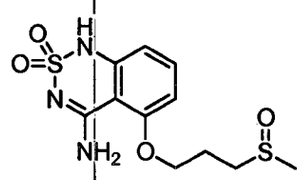
Example 247b: 2-amino-6-(3-(methylthio)propoxy)benzonitrile

Prepared as in Example 215b (Method A) from 2-(3-(methylthio)propoxy)-6-nitrobenzonitrile (Example 247c) in 98% yield. MS 223 (MH^+).

Example 247c: 2-(3-(methylthio)propoxy)-6-nitrobenzonitrile

Prepared as in Example 215c from 4-(methylthio)butan-1-ol and 2,6-dinitrobenzonitrile in 89% yield. MS 253 (MH^+).

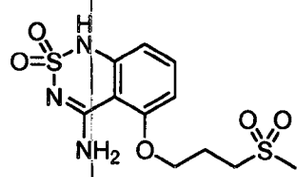
Example 248: 5-(3-(methylsulfinyl)propoxy)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



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Prepared as in Example 245 from 5-(3-(methylthio)propoxy)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide (Example 247) by the reaction with 1.0 equivalent of MCPBA as a white solid in 90% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.18-2.22 (m, 2H), 2.54 (s, 3H), 2.75-2.78 (m, 1H), 2.89-2.93 (m, 1H), 4.26 (t, J = 6.4Hz, 2H), 6.60-6.61 (d, J = 8.4 Hz, 1H), 6.73-6.75 (d, J = 8.0 Hz,1H), 7.44 (t, J = 8.0 Hz, 1H), 7.83 (s, 1H), 8.30 (s, 1H), 10.92 (s, 1H). MS 318 (MH^+).

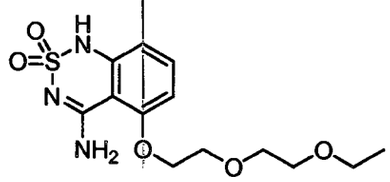
Example 249: 5-(3-(methylsulfonyl)propoxy)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



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Prepared as in Example 245 from 5-(3-(methylthio)propoxy)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide (Example 247) by the reaction with 3.0 equivalent of MCPBA in 87% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.24-2.27 (m, 2H), 3.00 (s, 3H), 3.26 (t, J = 7.6 Hz, 2H), 4.24 (t, J = 6.4 Hz, 2H), 6.60-6.62 (d, J = 8.0 Hz, 1H), 6.72-6.74 (d, J = 8.0 Hz,1H), 7.45 (t, J = 8.0 Hz, 1H), 7.79 (s, 1H), 8.31 (s, 1H), 10.93 (s, 1H). MS 334 (MH^+).

Example 250: 5-(2-(2-ethoxyethoxy)ethoxy)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



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Prepared as in Example 215 from 2-sulfamoylamino-6-(2-(2-ethoxyethoxy)ethoxy)benzonitrile (Example 250a) in 52% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.05 (t, J = 7.2 Hz, 3H), 3.37-3.43 (m, 2H), 3.47 (t, 2H), 3.58 (t, 2H), 3.81 (t, 2H), 4.26 (t, 2H), 6.60-6.62 (d, J = 8.0 Hz, 1H), 673-6.75 (d, J = 8.0 Hz, 1H), 7.45 (t, J = 8.4 Hz, 1H), 7.99 (s, 1H), 8.32 (s, 1H), 10.97 (s, 1H). MS 330 (MH^+).

Example 250a: 2-sulfamoylamino-6-(2-(2-ethoxyethoxy)ethoxy)benzonitrile

Prepared as in Example 215a from 2-amino-6-(2-(2-ethoxyethoxy)ethoxy)benzonitrile (Example 250b) and sulfamoyl chloride in 69% yield. MS 330 (MH^+).

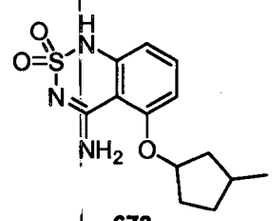
Example 250b: 2-amino-6-(2-(2-ethoxyethoxy)ethoxy)benzonitrile

Prepared as in Example 215b (Method A) from 2-(2-(2-ethoxyethoxy)ethoxy)-6-nitrobenzonitrile (Example 250c) in 98% yield. MS 251 (MH^+).

Example 250c: 2-(2-(2-ethoxyethoxy)ethoxy)-6-nitrobenzonitrile

Prepared as in Example 215c from 2-(2-ethoxyethoxy)ethanol and 2,6-dinitrobenzonitrile in 66% yield. MS 281 (MH^+).

Example 251: 5-(3-methylcyclopentyloxy)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



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Prepared as in Example 215 from 2-sulfamoylamino-6-(3-methylcyclopentyloxy)benzonitrile (Example 251a) in 45% yield. ^1H NMR (400 MHz, DMSO-d_6) δ 0.97-1.04 (m, 3H), 1.28-1.37 (m, 2H), 1.75-2.03 (m, 4H), 2.31-2.38 (m, 1H), 4.95-5.02 (m, 1H), 6.56-6.58 (d, J = 7.6 Hz,1H), 6.67-6.69 (d, J = 8.4 Hz, 1H),7.42 (t, J = 8.4 Hz, 1H), 7.69-7.72 (m, 1H), 8.30-8.36 (m, 1H), 10.92 (s, 1H). MS 296 (MH^+).

Example 251a: 2-sulfamoylamino-6-(3-methylcyclopentyloxy)benzonitrile

Prepared as in Example 215a from 2-amino-6-(3-methylcyclopentyloxy)benzonitrile (Example 251b) and sulfamoyl chloride in 52% yield. MS 296 (MH^+).

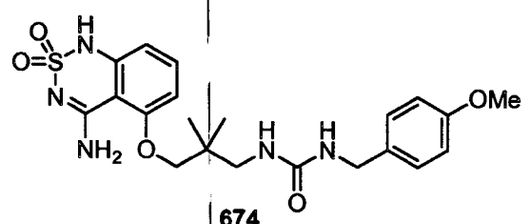
Example 251b: 2-amino-6-(3-methylcyclopentyloxy)benzonitrile

Prepared as in Example 215b (Method A) from 2-(3-methylcyclopentyloxy)-6-nitrobenzonitrile (Example 251c) in 98% yield. MS 217 (MH^+).

Example 251c: 2-(3-methylcyclopentyloxy)-6-nitrobenzonitrile

Prepared as in Example 215c from 3-methylcyclopentanol and 2,6-dinitrobenzonitrile in 70% yield. MS 247 (MH^+).

Example 252: 1-(3-(4-amino-2,2-dioxide-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)-2',2'-dimethylpropyl)-3'-(4''-methoxybenzyl)urea



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Prepared as in Example 215 from 1-(3-(3-sulfamoylamino-2-cyanophenoxy)-2,2-dimethylpropyl)-3-(4-methoxybenzyl)urea (Example 252a) in 77% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.92 (s, 6H), 3.06 (d, J = 6.4 Hz, 2H), 3.32 (s, 2H), 3.67 (s, 3H), 4.06 (d, J = 6.0 Hz, 2H), 6.29 (t, J = 6.0 Hz, 2H), 6.61 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.74 (d, J = 8.8 Hz, 2H), 7.06 (d, J = 8.8 Hz, 2H), 7.44 (t, J = 8.0 Hz, 1H), 8.12 (s, 1H), 8.34 (s, 1H), 10.90 (s, 1H). MS 462 (MH^+).

Example 252a: 1-(3-(3-sulfamoylamino-2-cyanophenoxy)-2,2-dimethylpropyl)-3-(4-methoxybenzyl)urea

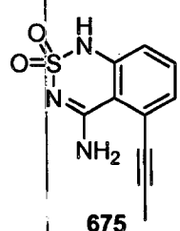
Prepared as in Example 215a from 1-(3-(3-amino-2-cyanophenoxy)-2,2-dimethylpropyl)-3-(4-methoxybenzyl)urea (Example 252b) and sulfamoyl chloride in 100% yield. MS 462 (MH^+).

Example 252b: 1-(3-(3-amino-2-cyanophenoxy)-2,2-dimethylpropyl)-3-(4-methoxybenzyl)urea

Prepared as in Example 215b (Method B) from 1-(3-hydroxy-2,2-dimethylpropyl)-3-(4-methoxybenzyl)urea (Example 252c) and 2-amino-6-fluorobenzonitrile in 60% yield. MS 383 (MH^+).

Example 252c: 1-(3-hydroxy-2,2-dimethylpropyl)-3-(4-methoxybenzyl)urea Prepared as in Example 227d from 3-amino-2,2-dimethylpropan-1-ol and 4-methoxybenzyl isocyanate in 100% yield. MS 267 (MH^+).

Example 253: 5-(prop-1-ynyl)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



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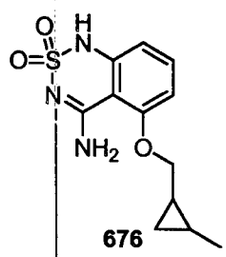
Prepared as in Example 215 from 2-sulfamoylamino-6-(3-(trimethylsilyl)prop-1-ynyl)benzonitrile (Example 253a) in 10% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.28 (s, 2H), 2.16 (s, 3H), 6.99-7.01 (d, J = 8.4 Hz, 1H), 7.21-7.23 (d, J = 7.8 Hz, 1H), 7.45 (t, J = 7.8 Hz, 1H). MS 236 (MH^+).

Example 253a: 2-sulfamoylamino-6-(3-(trimethylsilyl)prop-1-ynyl)benzonitrile

A solution of 2-amino-6-(3-(trimethylsilyl)prop-1-ynyl)benzonitrile (Example 253b) (557 mg, 2.0 mmol) and $NH_2SO_2NH_2$ (0.96 g, 10 mmol) in dry 1,4-dioxane (50 mL) was refluxed under nitrogen for 2 days. The solvent was evaporated under reduced pressure, and the residue was purified by chromatography on silica gel eluting with 70% EtOAc in hexanes to give the title compound (31 mg, 5%) as a white solid. MS 308 (MH^+).

Example 253b: 2-amino-6-(3-(trimethylsilyl)prop-1-ynyl)benzonitrile To a stirred solution of trimethyl(prop-2-ynyl)silane (1.12 g, 10 mmol), 2-amino-6-bromobenzonitrile (Klaubert, D. H.; Sellstedt, J. H.; Guinosso, C. J.; Capetola, R. J.; Bell, S. C. *J. Med. Chem.* **1981**, *24*, 742) (1.0 g, 5 mmol), CuI (0.01 equiv.) in triethylamine (50 mL) was added $Pd(PPh_3)_4$ (0.1 equiv.) at room temperature under nitrogen. The reaction mixture was then refluxed under nitrogen overnight. The solvent was evaporated, and the residue was titrated with EtOAc/water. The organic layer was separated, were washed with brine, and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by chromatography on silica gel eluting with 15% EtOAc in hexanes to give the title compound (1.43 g, 63%) as a as a liquid. MS 229 (MH^+).

Example 254: 5-((2-methylcyclopropyl)methoxy)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



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Prepared as in Example 111 from 2-amino-6-((2-methylcyclopropyl)methoxy)benzonitrile sulfamide (example 254a) in 68 % yield (mixture of diastereoisomers).^{1}H NMR (400 MHz, DMSO-d_6) δ 0.17-0.40 (m, 1H), 0.54-0.58 (m, 1H), 0.76-

0.85 (m, 1H), 0.99-1.12 (m, 4H), 3.96-4.33 (m, 2H), 6.58-6.61 (m, 1H), 6.67-6.77 (m, 1H), 7.41-7.47 (m, 1H), 7.97 (s, NH), 8.38 (s, NH), 10.97 (s, NH). MS 282 (MH^+).

Example 254a: 2-amino-6-((2-methylcyclopropyl)methoxy)benzonitrile sulfamide

Prepared as in example 90a from 2-amino-6-((2-methylcyclopropyl)methoxy)benzonitrile (Example 254b) in 100% yield. ^1H NMR (400 MHz, DMSO-d_6) δ 0.34-0.36 (m, 1H), 0.51-0.53 (m, 1H), 0.77-0.79 (m, 1H), 0.95-0.97 (m, 1H), 1.04-1.09 (m, 3H), 3.92-4.03 (m, 2H), 6.86-6.88 (bm, 1H), 7.11-7.18 (bm, 3H), 7.48-7.52 (bm, 1H), 9.53 (bs, NH). MS 282 (MH^+).

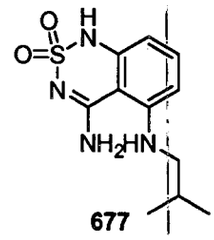
Example 254b: 2-amino-6-((2-methylcyclopropyl)methoxy)benzonitrile

A solution of 2-((2-methylcyclopropyl)methoxy)-6-nitrobenzonitrile (example 254c) (0.29 g, 1.25 mmol) in EtOAc/EtOH 1:1 (30 mL) was hydrogenated in an H-cube apparatus using 10% Pd/C as catalyst. The solution was evaporated to give 2-amino-6-((2-methylcyclopropyl)methoxy)benzonitrile (0.20 g, 79 %) as a yellow oil. MS 203 (MH^+).

Example 254c: 2-((2-methylcyclopropyl)methoxy)-6-nitrobenzonitrile

Prepared as in Example 166d from (2-methylcyclopropyl)methanol and 2,6-dinitrobenzonitrile in 81 % yield. MS 233 (MH^+).

Example 255: N5-isobutyl-1H-benzo[c][1,2,6]thiadiazine-4,5-diamine-2,2-dioxide



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Prepared as in Example 111 from 2-amino-6-(isobutylamino)benzonitrile sulfamide (Example 255a) in 23 % yield.1H NMR (400 MHz, DMSO-d_6) δ 0.95 (d, J = 6.8 Hz, 6H), 1.88-1.95 (m, 1H), 2.84 (t, J = 6.8 Hz, 2H), 5.87 (t, J = 6.4 Hz, NH), 6.31 (dd, J = 0.8 Hz, J = 8.0 Hz, 1H), 6.40 (d, J = 8.0 Hz, 1H), 7.26 (t, J = 8.4 Hz, 1H), 7.88 (s, NH_2), 10.70 (s, NH). MS 269 (MH^+).

Example 255a: 2-amino-6-(isobutylamino)benzonitrile sulfamide

Prepared as in Example 90a from 2-amino-6-(isobutylamino)benzonitrile (Example 255b) and used in the next step without any further purification. MS 269 (MH^+).

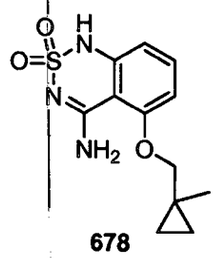
Example 255b: 2-amino-6-(isobutylamino)benzonitrile

Prepared as in Example 90b from 2-(isobutylamino)-6-nitrobenzonitrile (Example 255 in 66% yield. MS 190 (MH^+).

Example 255c: 2-(isobutylamino)-6-nitrobenzonitrile

Prepared as in Example 90c from 2,6-dinitrobenzonitrile and methylamine in 92% yield. MS 220 (MH^+).

Example 256: 5-((1-methylcyclopropyl)methoxy)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



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Prepared as in Example 111 from 2-amino-6-((1-methylcyclopropyl)methoxy)benzonitrile sulfamide (Example 256a), in 39 % yield. ^1H NMR (400 MHz, DMSO-d_6) δ 0.44-0.46 (m, 2H), 0.59-0.62 (m, 2H), 1.2 (s, 3H), 3.96 (s, 2H), 6.59 (d, J = 8.4 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.83 (bs, NH), 8.40 (bs, NH), 9.45 (bs, NH). MS 282 (MH^+).

Example 256a: 2-amino-6-((1-methylcyclopropyl)methoxy)benzonitrile sulfamide

Prepared as in example 90a from 2-amino-6-((1-methylcyclopropyl)methoxy)benzonitrile (Example 256b) in 100% yield.. ^1H NMR (400 MHz, DMSO-d_6) δ 0.40-0.43 (m, 2H), 0.53-0.56 (m, 2H), 1.20 (s, 3H), 3.89 (s, 2H), 6.85 (d, J = 8.0 Hz, 1H), 7.11-7.23 (bs, NH_2), 7.12 (d, J = 8.0 Hz, 1H), 7.51 (t, J = 8.4 Hz, 1H), 9.45 (bs, NH). MS 282 (MH^+).

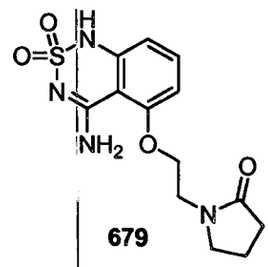
Example 256b: 2-amino-6-((1-methylcyclopropyl)methoxy)benzonitrile

Prepared as in Example 254b from 2-((1-methylcyclopropyl)methoxy)-6-nitrobenzonitrile (Example 256c) in 88% yield as a yellow oil. MS 203 (MH^+).

Example 256c: 2-((1-methylcyclopropyl)methoxy)-6-nitrobenzonitrile

Prepared as in Example 166d from (1-methylcyclopropyl)methanol and 2,6-dinitrobenzonitrile in 65% yield. ^1H NMR (400 MHz, DMSO-d_6) δ 0.44-0.46 (m, 2H), 0.57-0.59 (m, 2H), 1.22 (s, 3H), 4.06 (s, 2H), 7.67 (dd, J = 1.6 Hz, J = 8.0 Hz, 1H), 7.85-7.92 (m, 2H).

Example 257: 1-(2-(4-amino-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)ethyl)pyrrolidin-2-one-2,2-dioxide



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Prepared as in Example 111 from 2-amino-6-(2-(2-oxopyrrolidin-1-yl)ethoxy)benzonitrile sulfamide (Example 257a) in 45 % yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.94 (q, J = 7.2 Hz, 2H), 2.26 (t, J = 7.6 Hz, 2H), 3.43 (t, J = 7.2 Hz, 2H), 3.68 (t, J = 4.4 Hz, 2H), 4.23 (t, J = 4.4 Hz, 2H), 6.59 (d, J = 7.6 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 7.43 (t, J = 8.4 Hz, 1H), 7.82 (bs, NH), 8.21 (bs, NH), 10.98 (bs, NH). MS 325 (MH^+).

Example 257a: 2-amino-6-(2-(2-oxopyrrolidin-1-yl)ethoxy)benzonitrile sulfamide

Prepared as in example 90a from 2-amino-6-(2-(2-oxopyrrolidin-1-yl)ethoxy)benzonitrile (Example 257b) in 100% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.94 (q, J = 8.4 Hz, 2H), 2.22 (t, J = 8.4 Hz, 2H), 3.50-3.58 (m, 4H), 4.21 (t, J = 4.8 Hz, 2H), 6.94 (bs, 1H), 7.17 (d, J = 7.6 Hz, 1H), 7.24 (bs, NH_2), 7.54 (t, J = 7.2 Hz, 1H), 9.49 (bs, NH). MS 325 (MH^+).

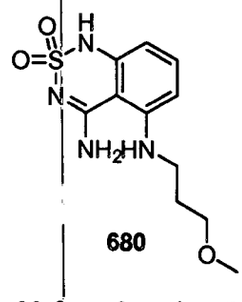
Example 257b: 2-amino-6-(2-(2-oxopyrrolidin-1-yl)ethoxy)benzonitrile

Prepared as in example 254b from 2-nitro-6-(2-(2-oxopyrrolidin-1-yl)ethoxy)benzonitrile (Example 257c) using trifluoroethanol/hexafluoroisopropanol (1:1) as solvent in 100% yield MS 246 (MH^+).

Example 257c: 2-nitro-6-(2-(2-oxopyrrolidin-1-yl)ethoxy)benzonitrile

Prepared as in Example 166d from 1-(2-hydroxyethyl)pyrrolidin-2-one and 2,6-dinitrobenzonitrile in 74 % yield. MS 276 (MH^+).

Example 258: N5-(3-methoxypropyl)-1H-benzo[c][1,2,6]thiadiazine-4,5-diamine-2,2-dioxide



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Prepared as in Example 90 from 2-amino-6-(3-methoxypropylamino)benzonitrile sulfamide (Example 258a) in 69 % yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.79-1.85 (m, 2H), 3.06 (q, J = 6.8 Hz, J = 6.8 Hz, 2H), 3.22 (s, 3H), 3.42 (t, , J = 6.0 Hz, 2H), 5.94 (t, J = 5.0 Hz, NH), 6.26 (d, J = 8.4 Hz, 1H), 6.34 (d, J = 8.0 Hz, 1H), 7.23 (t, J = 8.0 Hz, 1H),7.88 (s, NH_2), 10.64 (s, NH). MS 285 (MH^+).

Example 258a: 2-amino-6-(3-methoxypropylamino)benzonitrile sulfamide

Prepared as in Example 90a from 2-amino-6-(3-methoxypropylamino)benzonitrile in 65% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.74-1.79 (m, 2H), 3.19 (q, J = 6.8 Hz, J = 7.2 Hz, 2H), 3.22 (s, 3H), 3.39 (t, , J = 6.2 Hz, 2H), 5.96 (t, J = 5.6 Hz, NH), 6.47 (d, J = 8.8 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 7.09 (s, NH_2), 7.31 (t, J = 8.0 Hz, 1H), 9.09 (s, NH). MS 285 (MH^+).

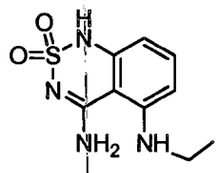
Example 258b: 2-amino-6-(3-methoxypropylamino)benzonitrile

To a solution of 2-(3-methoxypropylamino)-6-nitrobenzonitrile (Example 258c) (0.58 g, 2.48 mmol) in EtOH (20 mL) was added cyclohexene (1.26 mL, 12.4 mmol). Then 10% Pd/C (1.32 g) was added, and the reaction mixture was refluxed at 100°C for 20 minutes, cooled to room temperature, filtered trough Celite which was washed with EtOH (3x20 mL), and evaporated to give 2-amino-6-(3-methoxypropylamino)benzonitrile (0.43 g, 84 %) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.71-1.77 (m, 2H), 3.10 (q, J = 6.8 Hz, J = 6.8 Hz, 2H), 3.22 (s, 3H), 3.37 (t, , J = 3.2 Hz, 2H), 5.55 (t, J = 5.2 Hz, NH), 5.63 (s, NH_2), 5.79 (d, J = 7.6 Hz, 1H), 5.93 (d, J = 8.0 Hz, 1H), 6.98 (t, J = 8.0 Hz, 1H). MS 206 (MH^+).

Example 258c: 2-(3-methoxypropylamino)-6-nitrobenzonitrile

Prepared as in Example 90c from 2,6-dinitrobenzonitrile and 3-methoxypropylamine in 83 % yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.76-1.81 (m, 2H), 3.23 (s, 3H), 3.28-3.33 (m, 2H), 3.40 (t, J = 5.6 Hz, 2H), 6.66 (t, J = 4.8 Hz, NH), 7.30 (d, J = 8.8 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.60 (t, J = 8.0 Hz, 1H).

Example 259: N5-ethyl-1H-benzo[c][1,2,6]thiadiazine-4,5-diamine-2,2-dioxide



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Prepared as in Example 111 from 2-amino-6-(ethylamino)benzonitrile sulfamide (Example 259a) in 57% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.18 (t, J = 6.8 Hz, 3H), 2.99-3.06 (m, 2H), 5.87 (t, J = 5.2 Hz, NH), 6.30 (d, J = 7.6 Hz, 1H), 6.38 (d, J = 7.6 Hz, 1H), 7.26 (t, J = 8.0 Hz, 1H), 7.90 (s, NH_2), 10.68 (s, NH). MS 241 (MH^+).

Example 259a: 2-amino-6-(ethylamino)benzonitrile sulfamide

Prepared as in Example 90a from 2-amino-6-(ethylamino)benzonitrile (Example 259b) in 47% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.14 (t, J = 7.2 Hz, 3H), 3.15-3.22 (m, 2H), 5.84 (bs, NH), 6.48 (d, J = 8.8 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 7.02 (bs, NH_2), 7.31 (t, J = 8.0 Hz, 1H), 9.14 (bs, NH). MS 241 (MH^+).

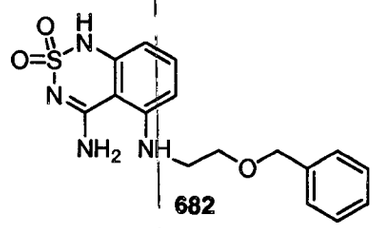
Example 259b: 2-amino-6-(ethylamino)benzonitrile

Prepared as in Example 254b from 2-(ethylamino)-6-nitrobenzonitrile (Example 259c) using Trifluoroethanol/Hexafluoroisopropanol (2:1) as solvent, in 81% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.14 (t, J = 7.2 Hz, 3H), 3.15-3.22 (m, 2H), 5.41 (bt, J = 5.2 Hz, NH), 5.64 (s, NH_2), 5.82 (d, J = 8.0 Hz, 1H), 5.96 (d, J = 8.0 Hz, 1H), 7.00 (t, J = 8.4 Hz, 1H). MS 162 (MH^+).

Example 259c: 2-(ethylamino)-6-nitrobenzonitrile

Prepared as in Example 90c from 2,6-dinitrobenzonitrile and a 2M ethylamine solution in THF in 88 % yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.13 (t, J = 7.6 Hz, 3H), 3.26-3.33 (m, 2H), 6.59 (bt, J = 5.2 Hz, NH), 7.22 (d, J = 9.2 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.60 (t, J = 8.4 Hz, 1H). MS 162 (M-Et).

Example 260: N5-(2-(benzyloxy)ethyl)-1H-benzo[c][1,2,6]thiadiazine-4,5-diamine-2,2-dioxide



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Prepared as in example 90 from 2-amino-6-(2-(benzyloxy)ethylamino)benzonitrile sulfamide (Example 260a) in 68 % yield. ^{1}H NMR (400MHz, DMSO-d_6) δ 3.25 (q, J = 5.2 Hz, J = 6.4 Hz, 2H), 3.64 (t, J = 5.6 Hz, 2H), 4.49 (s, 2H), 5.91 (t, J = 5.2 Hz, NH), 6.28 (d, J = 8.4 Hz, 1H), 6.40 (d, J = 8.4 Hz, 1H), 7.23 (t, J = 8.0 Hz, 1H), 7.25-7.35 (m, 5H), 7.90 (s, NH_2), 10.68 (s, NH). MS 347 (MH^+).

Example 260a: 2-amino-6-(2-(benzyloxy)ethylamino)benzonitrile sulfamide

Prepared as in Example 90a from 2-amino-6-(2-(benzyloxy)ethylamino)benzonitrile (Example 260b) in45%. ^{1}H NMR (400MHz, $CDCl_3$) δ 3.36 (q, J = 5.2 Hz, J = 5.6 Hz, 2H), 3.57 (t, J = 5.6 Hz, 2H), 4.49 (s, 2H), 5.76 (t, J = 5.6 Hz, NH), 6.55 (d, J = 8.4 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 7.12 (s, NH_2), 7.25-7.32 (m, 6H), 9.12 (s, NH). MS 347 (MH^+).

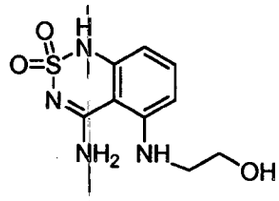
Example 260b: 2-amino-6-(2-(benzyloxy)ethylamino)benzonitrile

Prepared as in Example 90b from 2-(2-(benzyloxy)ethylamino)-6-nitrobenzonitrile (Example 260c) in 100% yield as a brown oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 3.27 (q, J = 5.2 Hz, J = 6.0 Hz, 2H), 3.56 (t, J = 5.6 Hz, 2H), 4.49 (s, 2H), 5.34 (t, J = 5.6 Hz, NH), 5.67 (s, NH_2), 5.84 (d, J = 8.0 Hz, 1H), 5.95 (d, J = 8.4 Hz, 1H), 6.98 (t, J = 8.2 Hz, 1H), 7.30-7.34 (m, 5H). Ms 268 (MH^+).

Example 260c: 2-(2-(benzyloxy)ethylamino)-6-nitrobenzonitrile

Prepared as in Example 90c from 2-(benzyloxy)ethanamine and 2,6-dinitrobenzonitrile in 77% yield. ^{1}H NMR (400MHz, DMSO-d_6) δ 3.49 (q, J = 5.2 Hz, J = 5.6 Hz, 2H), 3.59 (t, J = 5.6 Hz, 2H), 4.49 (s, 2H), 6.47 (t, J = 5.8 Hz, NH), 7.23-7.31 (m, 6H), 7.43 (d, J = 8.0 Hz, 1H), 7.58 (t, J = 8.4 Hz, 1H).

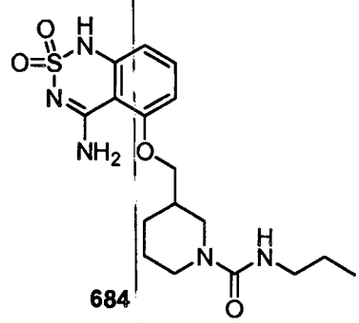
Example 261: 2-(4-amino-1H-benzo[c][1,2,6]thiadiazin-5-ylamino)ethanol-2,2-dioxide



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A solution of N^5-(2-(benzyloxy)-ethylamino)-1H-benzo[c][1,2,6]thiadiazine-4,5-diamine-2,2-dioxide (Example 260) (0.10 g, 0.29 mmol) in EtOH (20 mL) was charged with 30 mg of 10% Pd/C and H_2 balloon and stirred at room temperature for 24 hours. The reaction mixture was filtered trough Celite which was washed with EtOH, the combined organic phases were evaporated, and the residue was purified by flash chromatography using a DCM/MeOH (9:1) solution as eluant, to give 2-(4-amino-1H-benzo[c][1,2,6]thiadiazin-5-ylamino)ethanol-2,2-dioxide (64.8 mg, 87 %). ^{1}H NMR (400MHz, DMSO-d_6) δ 3.11 (q, J = 5.6 Hz, J = 5.6 Hz, 2H), 3.58-3.59 (m, 2H), 4.84 (bs, 1H), 5.84 (t, J = 5.2 Hz, NH), 6.26 (d, J = 8.0 Hz, 1H), 6.37 (d, J = 8.4 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 7.86 (s, NH_2), 10.65 (bs, NH). MS 257 (MH^+).

Example 262: 3-((4-Amino-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)methyl)-N-propylpiperidine-1-carboxamide-2,2-dioxide



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Prepared as in Example 111 from 3-((3-amino-2-cyanophenoxy)methyl)-N-propylpiperidine-1-carboxamide sulfamide (Example 262a) in 88 % yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.81 (t, J = 6.8 Hz, 3H), 1.23-1.43 (m, 4H), 1.60-1.63 (bm, 1H), 1.81-1.84 (bm, 1H), 1.99-2.05 (bm, 1H), 2.67-2.75 (m, 1H), 2.80-2.85 (m, 1H), 2.93-2.98 (m, 2H), 3.71 (bd, J = 12.8, 1H), 3.90 (bd, J = 10.8, 1H), 3.98-4.08 (m, 2H), 6.44 (d, J = 6.0 Hz, NH), 6.62 (d, J = 8.0 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 7.46 (t, J = 8.4 Hz, 1H), 7.80 (s, NH), 8.37 (s, NH), 10.95 (s, NH). MS 396 (MH^+).

Example 262a: 3-((3-amino-2-cyanophenoxy)methyl)-N-propylpiperidine-1 carboxamide sulfamide

Prepared as in Example 90a from 3-((3-amino-2-cyanophenoxy)methyl)-N-propylpiperidine-1-carboxamide (Example 262b) in 100% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.81 (t, J = 7.2 Hz, 3H), 1.31-1.44 (m, 4H), 1.61-1.64 (bm, 1H), 1.85-1.87 (bm, 2H), 2.60-2.75 (m, 2H), 2.94-2.98 (m, 2H), 3.78 (bd, J = 12.8 Hz, 1H), 3.93-3.97 (m, 1H), 4.01-4.10 (m, 2H), 6.38 (d, J = 6.0 Hz, NH), 6.96 (d, J = 8.8 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.27 (s, NH), 7.41 (s, NH), 7.57 (t, J = 8.4 Hz, 1H), 9.48 (s, NH). MS 396 (MH^+).

Example 262b: 3-((3-amino-2-cyanophenoxy)methyl)-N-propylpiperidine-1-carboxamide

Prepared as in Example 254b from 3-((2-cyano-3-nitrophenoxy)methyl)-N-propylpiperidine-1-carboxamide (Example 262c) in 94 % yield. MS 317 (MH^+).

Example 262c: 3-((2-cyano-3-nitrophenoxy)methyl)-N-propylpiperidine-1-carboxamide

To a solution of 2-nitro-6-(piperidin-3-ylmethoxy)benzonitrile hydrochloride (Example 262d) (0.10 g, 0.34 mmol) in THF (6 mL) were added triethylamine (0.10 mL, 0.76 mmol) and propylisocyanate (0.05 mL, 0.52 mmol) and the reaction mixture was stirred at r.t. under nitrogen for 3 hour then filtered and evaporated, to give 3-((2-cyano-3-nitrophenoxy)methyl)-N-propylpiperidine-1-carboxamide (0.13 g, 100 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.81 (t, J = 7.2 Hz, 3H), 1.34-1.41 (m, 4H), 1.62-1.64 (bm, 1H), 1.87-1.95 (bm, 2H), 2.64-2.77 (m, 2H), 2.93-2.98 (m, 2H), 3.77 (bd, J = 12.8 Hz, 1H), 3.98 (bd, J = 12.8 Hz, 1H), 4.09-4.13 (m, 1H), 4.17-4.20 (m, 1H), 6.38 (d, J = 5.6 Hz, NH), 7.74 (bdd, J = 1.6 Hz, J = 8.0 Hz, 1H), 7.88-7.94 (m, 2H). MS 347 (MH^+).

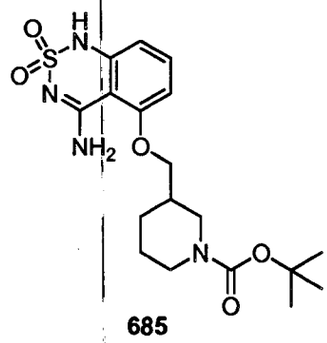
Example 262d: 2-nitro-6-(piperidin-3-ylmethoxy)benzonitrile hydrochloride

Prepared as in example 166 from tert-butyl 3-((2-cyano-3-nitrophenoxy)methyl)piperidine-1-carboxylate (Example 262e) in 98 % yield. MS 262 (MH^+).

Example 262e: tert-butyl 3-((2-cyano-3-nitrophenoxy)methyl)piperidine-1-carboxylate

Prepared as in Example 215c from tert-butyl 3-(hydroxymethyl)piperidine-1-carboxylate and 2,6-dinitrobenzonitrile in 58 % yield. MS 263 $[M+H\text{-}Boc]^+$.

Example 263: Tert-butyl 3-((4-amino-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)methyl)piperidine-1-carboxylate-2,2-dioxide



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Prepared as in Example 111 from tert-butyl 3-((3-amino-2-cyanophenoxy)methyl)piperidine-1-carboxylate sulfamide (Example 263a), keeping the pH above 3 upon acidification, to give tert-butyl 3-((4-amino-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)methyl)piperidine-1-carboxylate-2,2-dioxide (33 mg, 23 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.27-1.40 (bs, 11H), 1.62-1.66 (bm, 1H), 1.78-1.83 (bm, 1H), 2.05-2.12 (bm, 1H), 2.87-2.94 (m, 2H), 3.64-3.71 (bm, 1H), 3.83-3.86 (bm, 1H), 4.04 (bd, J = 7.2 Hz, 2H), 6.62 (d, J = 8.0 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 7.46 (t, J = 8.4 Hz, 1H), 7.76 (bs, NH), 8.37 (bs, NH), 10.95 (s, NH). MS 311 $[M+H\text{-}Boc]^+$.

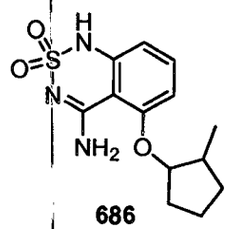
Example 263a: tert-butyl 3-((3-amino-2-cyanophenoxy)methyl)piperidine-1-carboxylate sulfamide

Prepared as in Example 90a from tert-butyl 3-((3-amino-2-cyanophenoxy)methyl)piperidine-1-carboxylate (Example 263b). Upon extraction, NaOH 1M (1.56 mL, 1.56 mmol) was added to the ice-cooled reaction medium triggering formation of a sticky orangy material. Water was poured away and the residue diluted in EtOAc, and extracted, to give tert-butyl 3-((3-amino-2-cyanophenoxy)methyl)piperidine-1-carboxylate sulfamide (0.15 g, 84 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.35-1.40 (bs, 11H), 1.63-1.66 (bm, 1H), 1.79-1.83 (bm, 1H), 1.88-1.93 (bm, 1H), 2.78-2.85 (m, 2H), 3.74-3.78 (bm, 1H), 3.92-4.04 (m, 3H), 6.96 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 7.27 (s, NH_2), 7.56 (t, J = 8.8 Hz, 1H), 9.47 (s, NH). MS 311 $[M+H\text{-}Boc]^+$.

Example 263b: tert-butyl 3-((3-amino-2-cyanophenoxy)methyl)piperidine-1-carboxylate

Prepared as in example 254b from tert-butyl 3-((2-cyano-3-nitrophenoxy)methyl)piperidine-1-carboxylate (Example 262e) in 100% yield as an oil. MS 232 $[M+H\text{-}Boc]^+$.

Example 264: 4-Amino-5-(*trans*-2-methylcyclopentyloxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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To a solution of 2-amino-6-(*trans*-2-methylcyclopentyloxy)benzonitrile (Example 264a) (150 mg, 0.694 mmol) in dimethylacetamide (3 mL) under N_2 was added sulfamoyl chloride (3 equiv.). The reaction mixture was stirred at room temperature under N_2 for 2 hours, diluted with ethyl acetate (50 mL) and quenched with water (20 mL). The layers were separated. The organic extract was evaporated. Ethanol (3 mL) and aqueous NaOH (2N, 2.5 equiv.) were consecutively added to the residue. The resulting mixture was heated at 90 °C for 16 hours. The workup was performed as in Example 111 to provide the desired product (160 mg, 78%) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.02 (d, J = 6.4 Hz, 3H), 1.26 (m, 1H), 1.71 (br s, 3H), 1.89 (m, 1H), 2.12 (m, 1H), 2.24 (m, 1H), 4.55 (br s, 1H), 6.60 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.73 (br s, 1H), 8.35 (br s, 1H), 10.96 (br s, 1H). MS 296 (MH^+).

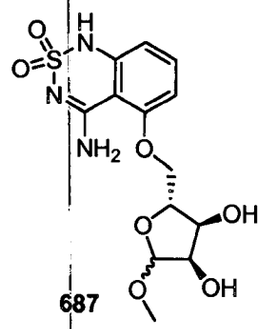
Example 264a: 2-Amino-6-(*trans*-2-methylcyclopentyloxy)benzonitrile

Prepared as in Example 111b from 2-(*trans*-2-methylcyclopentyloxy)-6-nitrobenzonitrile (Example 264b) to give the title compound in quantitative yield as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (d, J = 7.2 Hz, 3H), 1.23 (m, 1H), 1.72 (m, 1H), 1.81 (m, 2 H), 1.99 (m, 2H), 2.26 (m, 1H), 4.28 (m, 1H), 4.36 (br s, 2H), 6.18 (d, J = 8.4 Hz, 1H), 6.18 (d, J = 8.4 Hz, 1H), 7.18 (t, J = 8.4 Hz, 1H). MS 296 (MH^+)

Example 264b: 2-(*trans*-2-Methylcyclopentyloxy)-6-nitrobenzonitrile

Prepared as in Example 111c from 2,6 dinitrobenzonitrile and *trans*-2-methylcyclopentanol in 65% as a yellow solid. MS 247 (MH^+).

Example 265: 4-Amino-5-(((2*R*,3*S*,4*R*)-3,4-dihydroxy-5-methoxytetrahydrofuran-2-yl)methoxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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To a solution of 4-Amino-5-(((2*R*,3*S*,4*R*)-3,4,5-trihydroxytetrahydrofuran-2-yl)methoxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide (Example 265a) (7 mg, 0.020 mmol) in dry methanol (1 mL) was added trifluoroacetic acid 0.2 mL) and the mixture was refluxed overnight. The resulting solution was evaporated to dryness to provide the title compound as a white powder (7.28 mg, 100%, mixture of diastereomers ~ 4/1). ^{1}H NMR (400 MHz, DMSO-d_6): δ [3.17 (s, ¾H)], 3.22 (s, 3H), 3.81 (d, J = 4.0 Hz, 1H), [3.93 (m, ½H)], 4.12 (m, 3H), 4.39 (m, 1H), 4.71 (s, 1H), [4.85 (d , J = 4.0 Hz, ¼H)], 5.44 (br s, 2H), 6.65 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H), 7.95 (s, 1H), 8.41 (s, 1H), 11.00 (s, 1H), [11.01 (s, ¼H)].

Example 265a: 4-Amino-5-(((2*R*,3*S*,4*R*)-3,4,5-trihydroxytetrahydrofuran-2-yl)methoxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide

To a suspension of 4-Amino-5-(((3a*R*,4*R*,6*R*,6a*R*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide (Example 265b) (15 mg, 0.038 mmol) in water (1 mL) was added trifluoroacetic acid (0.2 mL) and the mixture was heated overnight at 80 °C. The reaction mixture was evaporated to dryness to furnish the title compound as a white solid in quantitative yield (mixture of diastereomers ~ 10/1). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.71 (m, 4H), 4.12 (m, 3H), 4.35 (m, 1H), 5.02 (s, 1H), 6.63 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 8.03 (br s, 1H), 8.31 (br s, 1H), 10.96 (br s, 1H), [11.00 (br s, 0.1H)].

Example 265b: 4-Amino-5-(((3a*R*,4*R*,6*R*,6a*R*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide

Prepared as in Example 111 from 2-sulfamoylamino-6-(((3a*R*,4*R*,6*R*,6a*R*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy)benzonitrile (Example 265c) in 78% yield as a beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.28 (s, 3H), 1.41 (s, 3H),

3.18 (s, 3H), 4.00 (t, J = 9.2 Hz, 1H), 4.32 (dd, J = 5.2, 10.0 Hz, 1H), 4.59 (dd, J = 5.2, 8.8 Hz, 1H), 4.63 (d, J = 6.0 Hz, 1H), 4.82 (d, J = 6.0 Hz, 1H), 5.02 (s, 1H), 6.64 (d, J = 8.4 Hz, 1H), 6.70 (d, J = 8.4 Hz, 1H), 7.48 (t, J = 8.4 Hz, 1H), 7.98 (br s, 1H), 8.43 (br s, 1H), 11.02 (br s, 1H).

Example 265c: 2-Sulfamoylamino-6-(((3a*R*,4*R*,6*R*,6a*R*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy)benzonitrile

Prepared as in Example 111a from 2-amino-6-(((3a*R*,4*R*,6*R*,6a*R*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy)benzonitrile (Example 265d) in 77% yield as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.50 (s, 3H), 3.33 (s, 3H), 4.08 (m, 2H), 4.51 (dd, J = 6.4, 7.6 Hz, 1H), 4.65 (d, J = 6.0 Hz, 1H), 4.79 (d, J = 6.0 Hz, 1H), 5.01 (s, 1H), 5.25 (br s, 2H), 6.70 (d, J = 8.4 Hz, 1H), 7.28 (br s, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.51 (t, J = 8.4 Hz, 1H).

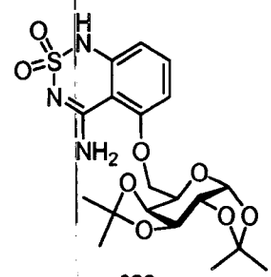
Example 265d: 2-Amino-6-(((3a*R*,4*R*,6*R*,6a*R*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy)benzonitrile

Prepared as in Example 111b from 2-(((3a*R*,4*R*,6*R*,6a*R*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methoxy)-6-nitrobenzonitrile (Example 252e) in 40% yield as colorless sticky material. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.49 (s, 3H), 3.33 (s, 3H), 4.05 (m, 2H), 4.45 (br s, 2H), 4.56 (dd, J = 6.0, 8.0 Hz, 1H), 4.65 (d, J = 6.0 Hz, 1H), 4.82 (br d, J = 6.0 Hz, 1H), 5.00 (s, 1H), 6.21 (dd, J = 0.8, 8.4 Hz, 1H), 6.33 (dd, J = 0.8, 8.4 Hz, 1H), 7.20 (t, J = 8.4 Hz, 1H).

Example 265e: 2-(((3a*R*,4*R*,6*R*,6a*R*)-6-Methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy)-6-nitrobenzonitrile

Prepared as in Example 111c from 2,6 dinitrobenzonitrile and *(*(3a*R*,4*R*,6*R*,6a*R*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methanol in 70% yield as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.49 (s, 3H), 3.32 (s, 3H), 4.23 (d, J = 2.0 Hz, 1H), 4.24 (s, 1H), 4.60 (br t, J = 6.0 Hz, 1H), 4.67 (d, J = 6.0 Hz, 1H), 4.86 (br d, J = 6.0 Hz, 1H), 5.01 (s, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.72 (t, J = 8.4 Hz, 1H), 7.87 (dd, J = 0.8, 8.4 Hz, 1H).

Example 266: 4-Amino-5-(((3a*R*,5a*S*,8a*S*,8b*S*)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis[1,3]dioxolo[4,5-*b*:4',5'-*d*]pyran-5-yl)methoxy)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 264 from 2-amino-6-(((3a*R*,5a*S*,8a*S*,8b*S*)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis[1,3]dioxolo[4,5-*b*:4',5'-*d*]pyran-5-yl)methoxy)benzonitrile (Example 266a) in 72% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (s, 3H), 1.31 (s, 3H), 1.38 (s, 3H), 1.43 (s, 3H), 4.07 (m, 2H), 4.19 (br d, J = 8.4 Hz, 1H), 4.36 (dd, J = 1.2, 8.0 Hz, 1H), 4.41 (dd, J = 2.4, 5.2 Hz, 1H), 4.44 (dd, J = 2.4, 10.0 Hz, 1H), 4.67 (dd, J = 2.4, 8.0 Hz, 1H), 5.51 (d, J = 4.8 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 7.45 (t, J = 8.4 Hz, 1H), 7.86 (br s, 1H), 8.41 (br s, 1H), 10.98 (br s, 1H). MS 456 (MH^+).

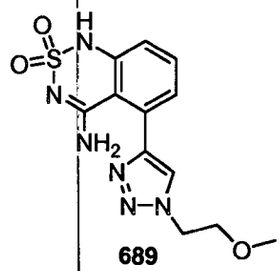
Example 266a: 2-Amino-6-(((3a*R*,5a*S*,8a*S*,8b*S*)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis[1,3]dioxolo[4,5-*b*:4',5'-*d*]pyran-5-yl)methoxy)benzonitrile

Prepared as in Example 111b from 2-nitro-6-(((3a*R*,5a*S*,8a*S*,8b*S*)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis[1,3]dioxolo[4,5-*b*:4',5'-*d*]pyran-5-yl)methoxy)benzonitrile (Example 266b) in quantitative yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.28 (s, 3H), 1.31 (s, 3H), 1.37 (s, 3H), 1.39 (s, 3H), 4.05 (m, 2H), 4.16 (dd, J = 4.0, 8.8 Hz, 1H), 4.37 (m, 2H), 4.67 (dd, J = 2.4, 8.0 Hz, 1H), 5.47 (d, J = 4.8 Hz, 1H), 6.01 (br s, 2H), 6.23 (d, J = 8.0 Hz, 1H), 6.35 (d, J = 8.4 Hz, 1H), 7.17 (t, J = 8.4 Hz, 1H).

Example 266b: 2-Nitro-6-(((3a*R*,5a*S*,8a*S*,8b*S*)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis[1,3]dioxolo[4,5-*b*:4',5'-*d*]pyran-5-yl)methoxy)benzonitrile

Prepared as in Example 111c from 2,6 dinitrobenzonitrile and ((3a*R*,5a*S*,8a*S*,8b*S*)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis[1,3]dioxolo[4,5-*b*:4',5'-*d*]pyran-5-yl)methanol in 59 % yield as white sticky material. MS 408 (MH^+), 424 (MH_2O^+).

Example 267: 4-Amino-5-(1-(2-methoxyethyl)-1*H*-1,2,3-triazol-4-yl)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-(1-(2-methoxyethyl)-1*H*-1,2,3-triazol-4-yl)benzonitrile (Example 267a) in 78% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.27 (s, 3H), 3.78 (t, J = 5.2 Hz, 2H), 4.59 (t, J = 5.2 Hz, 2H), 6.90 (br s, 1H), 7.09 (dd, J = 0.8, 8.0 Hz, 1H), 7.20 (dd, J = 0.8, 7.6 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 8.15 (br s, 1H), 8.32 (s, 1H), 11.09 (br s, 1H). MS 323 (MH^+).

Example 267a: 2-Sulfamoylamino-6-(1-(2-methoxyethyl)-1*H*-1,2,3-triazol-4-yl)benzonitrile

Prepared as in Example 111a from 2-amino-6-(1-(2-methoxyethyl)-1*H*-1,2,3-triazol-4-yl)benzonitrile (Example 267b) in 90 % yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.28 (s, 3H), 3.79 (t, J = 5.2 Hz, 2H), 4.66 (t, J = 5.2 Hz, 2H), 7.32 (br s, 2H), 7.60 (dd, J = 1.2, 8.0 Hz, 1H), 7.76 (t, J = 8.0 Hz, 1H), 7.82 (dd, J = 1.2, 8.0 Hz, 1H), 8.64 (s, 1H), 9.52 (br s, 1H).

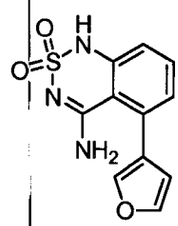
Example 267b: 2-Amino-6-(1-(2-methoxyethyl)-1*H*-1,2,3-triazol-4-yl)benzonitrile

To a solution of 1-bromo-2-methoxyethane (5.00 g, 35.97 mmol) in DMF (25 mL), was added sodium azide (3 equiv.) and the mixture was heated at 50 °C for 48 hours. The reaction mixture was diluted with water (75 mL) and extracted with diethyl ether. The organic extract was dried over $MgSO_4$ and concentrated to furnish 1-azido-2-methoxyethane as a yellow liquid. This azide (200 mg, 1.94 mmol) was added to a solution of 2-Amino-6-ethynylbenzonitrile (250 mg, 1.76 mmol) (Example 267c) in H_2O/*tert*-BuOH = 1:2 (15 mL) and the solution was treated consecutively with sodium ascorbate (0.264 mmol) and $CuSO_4$ (0.035 mmol). The reaction mixture was stirred at room temperature for 48 hours, diluted with water and extracted with ethyl acetate. The organic extract was dried over $MgSO_4$ and purified over silica gel (ethyl acetate/hexane 6:4) to furnish the title compound as a white solid in 88 % yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.26 (s, 3H), 3.78 (t, J = 5.2 Hz, 2H), 4.23 (t, J = 5.2 Hz, 2H), 6.13 (br s, 2H), 6.80 (dd, J = 1.2, 8.4 Hz, 1H), 7.09 (dd, J = 1.2, 7.6 Hz, 1H), 7.36 (t, J = 8.4 Hz, 1H), 8.52 (s, 1H). MS 244 (MH^+).

Example 267c: 2-Amino-6-ethynylbenzonitrile

To a solution of 2-amino-6-bromobenzonitrile (1.25 g, 6.34 mmol) and ethynyltrimethylsilane (2.42 g, 12.7 mmol) in dry Et_3N (15 mL) was added under N_2 Cu(I) (60 mg), $Pd(PPh_3)_4$ (360 mg) and the mixture was stirred at 80 °C for 20 hours. The reaction mixture was cooled down to room temperature, diluted with ethyl acetate and washed with brine. The organic layer was evaporated and the residue was dissolved in methanol (20 mL), treated with 1M aqueous NaOH solution (1.05 equiv.) and stirred at room temperature for 1 hour. Methanol was evaporated off and the aqueous residue was extracted with CH_2Cl_2, dried over $MgSO_4$, and purified over silica gel (ethyl acetate/hexanes 75/25) to furnish the desired product in 93% yield as light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.54 (s, 1H), 6.24 (br s, 2H), 6.76 (dd, J = 0.8, 7.6 Hz, 1H), 6.82 (dd, J = 0.8, 8.4 Hz, 1H), 7.28 (dd, J = 7.6, 8.4 Hz, 1H). MS 143 (MH^+).

Example 268: 4-Amino-5-(furan-3-yl)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-(furan-3-yl)benzonitrile (Example 268a) in 47% yield as a beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.34 (br s, 1H), 6.51 (dd, J = 0.8, 2.0 Hz, 1H), 7.03 (m, 2H), 7.52 (dd, J = 7.6, 8.0 Hz, 1H), 7.79 (t, J = 1.6 Hz, 1H), 7.93 (dd, J = 0.8, 1.6 Hz, 1H), 8.23 (br s, 1H), 11.09 (s,1H). MS 264 (MH^+)

Example 268a: 2-Sulfamoylamino-6-(furan-3-yl)benzonitrile

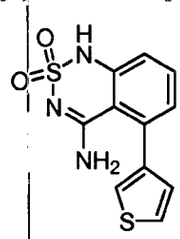
Prepared as in Example 111a from 2-amino-6-(furan-3-yl)benzonitrile (Example 268b)in 63% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.97 (dd, J = 0.8, 2.0 Hz, 1H), 7.29 (br s, 2H), 7.46 (dd, J = 0.8, 7.6 Hz, 1H), 7.54 (dd, J = 0.8, 8.0 Hz, 1H), 7.69 (t, J = 8.0 Hz, 1H), 7.85 (t, J = 1.6 Hz, 1H), 8.21 (dd, J = 0.8, 1.6 Hz, 1H), 9.48 (br s, 1H).

Example 268b: 2-Amino-6-(furan-3-yl)benzonitrile

Prepared as in Example 129c from furan-3-ylboronic acid and 2-amino-6-bromobenzonitrile in 74% yield as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.51 (br s, 2H),

6.66 (dd, J = 1.2, 8.4 Hz, 1H), 6.78 (dd, J = 1.2, 2.0 Hz, 1H), 6.82 (dd, J = 1.2, 8.0 Hz, 1H), 7.31 (t, J = 8.0 Hz, 1H), 7.50 (t, J = 1.6 Hz, 1H), 7.95 (dd, J = 1.2, 1.6 Hz, 1H).

Example 269: 4-Amino-5-(thiophen-3-yl)-1*H*-benzo[*c*][1,2,6]thiadiazine-2,2-dioxide



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Prepared as in Example 111 from 2-sulfamoylamino-6-(thiophen-3-yl)benzonitrile (Example 269a) in 52% yield as a beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.82 (br s, 1H), 7.05 (m, 3H), 7.54 (t, J = 8.0 Hz, 1H), 7.67 (m, 1H), 8.15 (br s, 1H), 11.13 (s,1H). MS 280 (MH^+).

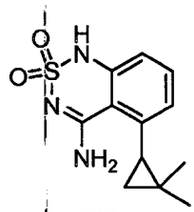
Example 269a: 2-Sulfamoylamino-6-(thiophen-3-yl)benzonitrile

Prepared as in Example 111a from 2-amino-6-(thiophen-3-yl)benzonitrile (Example 269b) in 60% yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31 (br s, 2H), 7.42 (dd, J = 1.2, 2.8 Hz, 1H), 7.43 (d, J = 1.6 Hz, 1H), 7.57 (dd, J = 0.8, 8.0 Hz, 1H), 7.70 (t, J = 8.0 Hz, 1H), 7.73 (dd, J = 2.8, 4.8 Hz, 1H), 7.88 (dd, J = 1.2, 2.8 Hz, 1H), 9.48 (br s, 1H).

Example 269b: 2-Amino-6-(thiophen-3-yl)benzonitrile

Prepared as in Example 129c from thiophen-3-ylboronic acid and 2-amino-6-bromobenzonitrile in 94 % yield as a beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.08 (br s, 2H), 6.70 (dd, J = 1.2, 7.6 Hz, 1H), 6.77 (dd, J = 1.2, 8.4 Hz, 1H), 7.31 (dd, J = 7.6, 8.4 Hz, 1H), 7.38 (dd, J = 1.2, 4.8 Hz, 1H), 7.66 (dd, J = 2.8, 4.8 Hz, 1H), 7.78 (dd, J = 1.2, 2.8 Hz, 1H).

Example 270: 5-(2,2-dimethylcyclopropyl)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



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A solution of 2-amino-6-(2,2-dimethylcyclopropyl)benzonitrile (381 µmol, 71 mg) (Example 270a) and sulfamoyl chloride (572 µmol, 66 mg) in DMA (1 mL) was stirred at room temperature. After 1 hour, the reaction mixture was diluted with NaOH (1N, 572 µmol, 572 µL) and water (~30 mL). The precipitate was filtered off, washed with water (3 X 5 mL) then dissolved in EtOH (10 mL) and NaOH (1N, 953 µL) was added. The reaction was heated to 80 ° C with stirring. After completion the solvent were evaporated and the residue was partitioned between water (20 mL) and ether (5 mL) .The aqueus layer was extracted with ether (2 X 5 mL), then acidified to pH ~3 with 1N HCl. The precipitate was collected, washed with water, dried in vacuo to give the desired product (59 mg, 58%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ0.610 (m, 1H), 0.63 (s, 3H), 0.89 (m, 1H), 1.20 (s, 3H), 2.48 (m, 1H), 6.88 (d, J = 8 Hz, 1H), 6.92 (d, J = 8 Hz, 1H), 7.21 (br. s, 1H), 7.39 (t, J = 8 Hz, 1H), 8.42 (br. s, 1H), 10.74 (s, 1H). MS 266 (MH^+).

Example 270a: 2-amino-6-cyclopropylbenzonitrile

To a degazed solution of 2-amino-6-bromobenzonitrile (851 µmol, 168 mg), 2,2-dimethylcyclopropylboronic acid (1.106 µmol, 126 mg) (Example 270b), and Cs_2CO_3 (2.979 mmol, 970 mg) in DME (3.4 mL) and water (850 µL) was added tetrakis(triphenylphosphino)palladium(0) (43 µmol, 50 mg) under nitrogen and the reaction mixture microwaved for 2 hours at 160 ° C. The reaction mixture was cooled to room temperature and extracted with EtOAc (3 X 5 mL). The combined organic layers was washed once with brine (5 mL), dried over sodium sulfate, filtered and evaporated. The crude product was purified on silica gel (EtOAc/hexanes 10%-40%) to give the desired product (71 mg, 45%) as a waxy, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ0.82 (m, 1H), 0.82 (s, 3H), 0.85 (m, 1H), 1.33 (s, 3H), 1.92 (m, 1H), 4.36 (br. s, 2H), 6.47 (d, J = 8 Hz, 1H), 6.56 (d, J = 8 Hz, 1H), 7.20 (t, J = 8 Hz, 1H).

Example 270b: 2,2-dimethylcyclopropylboronic acid

To a solution of 1-bromo-2,2-dimethylcyclopropane (7.48 mmol, 1.115 g) (Example 270c) in anhydrous THF (20 mL) was added tBuLi (8.23 mmol, 1.7 M in pentane, 4.85 mL) dropwise at -78 ° C under nitrogen. After 1 hour at -78 ° C, trimethylborate (8.23 mmol, 920 µL) was added and the reaction mixture was stirred for 2 hours at -78 ° C, warmed to room temperature, stirred for 1 hour, and quenched with sat. NH_4Cl solution (20 mL). The

reaction mixture was diluted to a total volume of 100 mL with DCM and treated with HCl (6N in water, 22.45 mmol, 3.74 mL). The layers were separated, the aqueous layer extracted with dicholrometane (2 X 50 mL), the combined organic layers were washed with brine (25 mL), dried over sodium sulfate, filtered and evaporated. The residue was diluted with acetone (50 mL) and a few drops of water, then carefully concentrated in vacuo to give 214 mg (25.1%) of product as an off-white solid. ^{1}H NMR (400 MHz, acetone-d_6) δ0.00 (m, 1H), 0.13 (m, 1H), 0.755 (d of d, J = 4 Hz, 8 Hz, 1H), 0.865 (d of d, J = 4 Hz, 8 Hz, 1H), 1.39 (s, 3H), 1.46 (s, 3H), 6.81 (s, 2H).

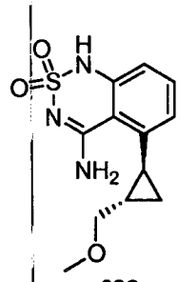
Example 270c: 1-bromo-2,2-dimethylcyclopropane

To a suspension of Zinc (dust, 319.4 mmol, 20.88 g) in EtOH (20 mL) was added HCl (12 N, 5 mL) at 0 ° C. A solution of 1,1-dibromo-2,2-dimethylcyclopropane (18.2 g) (example 270d) in EtOH (20 mL) was added to the mixture over 5 minutes with stirring. The reaction mixture was allowed to warm slowly to room temperature overnight. The zinc salts were filtered off through a pad of Celite, the Celite washed with EtOH (50 mL), and the resulting solution partitioned between water (200 mL) and pentane (200 mL). The aqueous layer was further extracted with pentane (2 X 100 mL), and the combined organic extracts successively washed with water (4 X 75 mL), brine (25 mL), dried over sodium sulfate, filtered, and evaporated to gives the product (1.115 g , 9.4%) as a volatile, colorless liquid. ^{1}H NMR (400 MHz, acetone-d_6) δ0.602 (d of d, J = 4 Hz, 6 Hz, 1H), 1.025 (d of d, J = 6 Hz, 8 Hz, 1H), 1.116 (s, 3H), 1.233 (s, 3H), 2.963 (d of d, J = 4 Hz, 8 Hz, 1H).

Example 270d: 1,1-dibromo-2,2-dimethylcyclopropane

To a solution of pentane (200 mL) cooled to -5 ° C was added isobutylene (457.7 mmol, 25.68 g) followed by potassium tert-butoxide (549.2 mmol, 61.63 g). Then bromoform (457.7 mmol, 40.0 mL) was added dropwise with vigorous stirring over about 1 hour at -5 ° C. The reaction mixture was allowed to warm slowly to room temperature and then partitioned between pentane (100 mL) and water (200 mL). The aqueous layer was extracted with pentane (2 X 50 mL) and the combined organic layers washed with water (4 X 75 mL), brine (50 mL), dried over sodium sulfate, filtered and evaporated. The orange residue was pushed through a silica plug eluting with pentane. The solvent was evaporated to give the desired product (65.70 g, 57.3%) as a colorless oil. ^{1}H NMR (400 MHz, acetone-d_6) δ1.392 (s, 6H), 1.505 (s, 2H).

Example 271: (±)-trans-5-(2-(methoxymethyl)cyclopropyl)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



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Prepared as in Example 270 from (±)-trans-2-amino-6-(2-(methoxymethyl)cyclopropyl)benzonitrile (example 271a) and sulfamoyl chloride in 34% as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ0.976 (m, 1H), 1.172 (m, 1H), 1.340 (m, 1H), 2.282 (m, 1H), 3.175 (d of d, J = 8 Hz, 10 Hz, 1H), 3.252 (s, 3H), 3.576 (d of d, J = 5 Hz, 10 Hz, 1H), 6.802 (d, J = 8 Hz, 1H), 6.855 (d, J = 8 Hz, 1H), 7.376 (t, J = 8 Hz, 1H), 8.396 (br. s, 1H), 8.473 (br. s, 1H), 10.823 (s, 1H). MS 282 (MH^+).

Example 271a: (±)-trans-2-amino-6-(2-(methoxymethyl)cyclopropyl)benzonitrile

Prepared as in Example 270a from (±)-trans-2-(methoxymethyl)cyclopropylboronic acid (example 271b) and 2-amino-6-bromobenzonitrile in 64% yield as a yellowish brown waxy solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ0.932 (m, 2H), 1.341 (m, 1H), 1.879 (m, 1H), 2.324 (s, 3H), 3.351 (d, J = 6 Hz, 2H), 5.896 (br. s, 2H), 6.148 (d, J = 8 Hz, 1H), 6.550 (d, J = 8 Hz, 1H), 7.130 (t, J = 8 Hz, 1H).

Example 271b: (±)-trans-2-(methoxymethyl)cyclopropylboronic acid

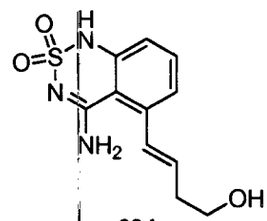
To a solution of (±)-trans-2-(methoxymethyl)cyclopropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10.0 mmol, 2.121 g) (example 271c) dissolved in THF (64 mL) was added $NaIO_4$ (30.0 mmol, 6.417 g) and water (16 mL). The reaction mixture was stirred at room temperature for 3 minutes then treated with aqueous HCl (2N, 3.33 mL). The reaction mixture was stirred for one hour at room temperature, partitioned with EtOAc (100 mL), the aqueous layer extracted with EtOAC (2 X 50 mL), the combined organic layers washed with brine (25 mL), dried over sodium sulfate, filtered, and evaporated. The mixture was taken up in acetone, treated with a few drops of water, and carefully evaporated to a viscous oil, which slowly solidified at room temperature to give the desired product in quantritative yield. ^{1}H NMR (400

MHz, DMSO-d_6) δ-0.467 (m, 1H), 0.324 (m, 1H), 0.532 (m, 1H), 1.055 (m, 1H), 3.099 (d of d, J = 7 Hz, 10 Hz, 1H), 3.186 (d of d, J = 7 Hz, 10 Hz, 1H), 3.206 (s, 3H), 7.344 (s, 2H).

Example 271c: (±)-trans-2-(methoxymethyl)cyclopropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

To a solution of (E)-2-(3-methoxyprop-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (32.2 mmol, 6.3710 g) in anhydrous toluene (50 mL) under nitrogen was added diethyl zinc (0.59 M in hexanes, 32.2 mmol, 54.6 mL), followed by CH_2I_2 (45.08 mmol, 3.63 mL). The flask was heated to 50 ° C under nitrogen. After 4 hours, another portion of diethyl zinc (54.6 mL) and CH_2I_2 (3.63 mL) was added and heated overnight under nitrogen. The reaction mixture was cooled to room temperature and quenched with saturated aqueous NH_4Cl (50 mL). The reaction mixture was partitioned with ether (200 mL), the layers separated, the organic layer washed with brine (25 mL), dried over sodium sulfate, filtered and evaporated. The residue was purified on silica gel (EtOAc/hexanes 1% to 15%) to give the desired product (5.552 g , 81.3%) as a light-yellow oil. ^{1}H NMR (400 MHz, acetone) δ0.012 (m, 1H), 0.804 (m, 1H), 0.944 (m, 1H), 1.172 (m, 1H), 3.484 (dd, J = 6 Hz, 10 Hz, 1H), 3.553 (dd, J = 6 Hz, 10 Hz, 1H), 3.570 (s, 3H).

Example 272: (E)-4-(4-amino-2,2-dioxo-1H-benzo[c][1,2,6]thiadiazin-5-yl)but-3-en-1-ol

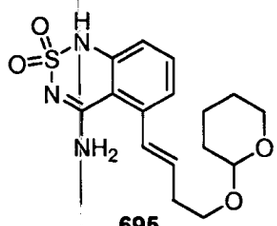


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To a solution of (E)-5-(4-(tetrahydro-2H-pyran-2-yloxy)but-1-enyl)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide (322 µmol, 43 mg) (Example 273) in THF (860 µL) was added AcOH (1.7 mL) and water (430 µL) and the solution heated overnight at 45 ° C. The solution was cooled to room temperature and the solvent evaporated. The residue was triturated with boiling water then cooled to room temperature. The resulting solid was collected and washed with water to give the desired product (69 mg, 80%) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ2.365 (q, J = 6 Hz, 2H), 3.568 (q, J = 6 Hz, 2H), 4.681 (t, J = 6 Hz, 1H), 6.186 (d of t, J = 7 Hz, 16 Hz, 1H), 6.786 (d, J = 16 Hz, 1H), 6.922 (d, J = 8 Hz, 1H),

7.022 (br. s, 1H), 7.088 (d, J = 8 Hz, 1H), 7.468 (t, J = 8 Hz, 1H), 8.388 (br. s, 1H), 10.935 (s, 1H). MS 268 (MH^+).

Example 273: (E)-5-(4-(tetrahydro-2H-pyran-2-yloxy)but-1-enyl)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



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Prepared as in Example 270 from (E)-2-amino-6-(4-(tetrahydro-2H-pyran-2-yloxy)but-1-enyl)benzonitrile (example 273a) and sulfamoyl chloride in 61% yield as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ1.459 (m, 4H), 1.610 (m, 2H), 1.700 (m, 2H), 2.479 (q, J = 6 Hz, 2H), 3.428 (m, 1H), 3.528 (m, 1H), 3.765 (m, 2H), 4.579 (m, 1H), 6.200 (d of t, J = 7 Hz, 16 Hz, 1H), 6.823 (d, J = 16 Hz, 1H), 6.867 (br. s, 1H), 6.931 (d, J = 8 Hz, 1H), 7.087 (d, J = 8 Hz, 1H), 7.472 (t, J = 8 Hz, 1H), 8.401 (br. s, 1H), 10.945 (s, 1H). MS 352 (MH^+).

Example 273a: (E)-2-amino-6-(4-(tetrahydro-2H-pyran-2-yloxy)but-1-enyl)benzonitrile

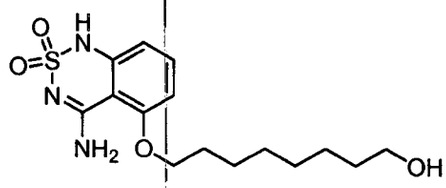
Prepared as in Example 270a from (E)-4,4,5,5-tetramethyl-2-(4-(tetrahydro-2H-pyran-2-yloxy)but-1-enyl)-1,3,2-dioxaborolane (Example 273b) and 2-amino-6-bromobenzonitrile in 47% yield as a yellow gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ1.570 (m, 4H), 1.727 (m, 2H), 1.837 (m, 2H), 2.565 (q, J = 6 Hz, 2H), 3.541 (m, 2H), 3.879 (m, 2H), 4.387 (br. s, 2H), 4.635 (m, 1H), 6.423 (d of t, J = 7 Hz, 16 Hz, 1H), 6.586 (d, J = 8 Hz, 1H), 6.710 (d, J = 16 Hz, 1H), 6.905 (d, J = 8 Hz, 1H), 7.237 (t, J = 8 Hz, 1H).

Example 273b: (E)-4,4,5,5-tetramethyl-2-(4-(tetrahydro-2H-pyran-2-yloxy)but-1-enyl)-1,3,2-dioxaborolane

Neat 2-(but-3-ynyloxy)tetrahydro-2H-pyran (12.8 mmol, 2.0 mL) was treated with pinacolborane (19.1 mmol, 2.78 mL) at 60 ° C under nitrogen. After 2 hours, another portion of pinacolborane (12.8 mmol, 1.86 mL) was added and continued heating at 60 ° C. After 8 hours, the reaction mixture was diluted with hexanes (30 mL) and treated dropwise with water (1 mL), stirring until gas evolution ceased. The layers were separated, the water layer

extracted with hexanes (2 X 5 mL), the combined organic layers washed with brine (5 mL), dried over magnesium sulfate, filtered, and evaporated. The crude product was purified on silica gel (EtOAc/hexanes 10% to 30%) to give the product (1.73 g, 48% yield) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.262 (s, 3H), 1.531 (m, 2H), 1.699 (m, 1H), 1.812 (m, 1H), 2.469 (d of q, J = 2 Hz, 7 Hz, 2H), 3.495 (m, 1H), 3.832 (m, 2H), 4.593 (d of d, J = 3 Hz, 4 Hz, 1H), 5.523 (d of t, J = 2 Hz, 18 Hz, 1H), 6.634 (d of t, J = 7 Hz, 18 Hz, 1H).

Example 274: 8-(4-amino-2,2-dioxo-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)octan-1-ol



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To a solution of 8-(3-amino-2-cyanophenoxy)octyl acetate (746 µmol, 227 mg) in DMA (3 mL) was added sulfamoyl chloride (1.492 mmol, 172 mg) and pyridine (4.476 mmol, 362 µL). The reaction mixture was stirred at room temperature until completion, then quenched with sat. $NaHCO_3$ (15 mL) and solid NaCl added.. The precipate was collected and washed with water. The wet precipitate was suspended in EtOH (15 mL) and treated with NaOH (8.952 mmol, 1N, 8.95 mL). The reaction mixture was refluxed until completion then cooled to room temperature. Most of the EtOH and water were removed in vacuo, then the reaction mixture was dissolved in water (15 mL), extracted with ether (3 X 5 mL), filtered through a 0.45 µm PTFE frit, then acidified with 10% citric acid/water solution to pH 4-5. The precipitate was filtered off, washed with water and dried to give the desired product 146 mg (57.3%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.265 (m, 6H), 1.380 (m, 4H), 1.785 (pentet, J = 7 Hz, 2H), 3.348 (q, J = 6 Hz, 2H), 4.303 (t, J = 5 Hz, 2H), 6.580 (d, J = 8 Hz, 1H), 6.724 (d, J = 8 Hz, 1H), 7.428 (t, J = 8 Hz, 1H), 7.796 (br. s, 1H), 8.329 (br. s, 1H), 10.922 (s, 1H). MS 342 (MH^+).

Example 274a: 8-(3-amino-2-cyanophenoxy)octyl acetate

A solution of 8-(2-cyano-3-nitrophenoxy)octyl acetate (802 µmol, 268 mg) (Example 274c) in EtOH (15 mL) was hydrogenated in an H-cube apparatus using 10% Pd/C as catalyst. The solution was evaporated to give 8-(3-amino-2-cyanophenoxy)octyl acetate (244 mg, 244 mg). MS 305 (MH^+)

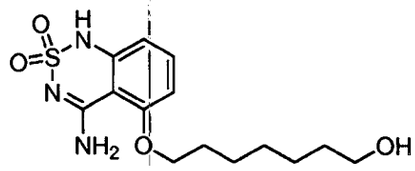
Example 274b: 8-(2-cyano-3-nitrophenoxy)octyl acetate

2-(8-hydroxyoctyloxy)-6-nitrobenzonitrile (804 μmol, 235 mg) (Example 274c) was dissolved in dry DCM (10 mL), cooled to 0 ° C, and treated successively with pyridine (3.216 mmol, 260 μL) and acetyl chloride (1.608 mmol, 114 μL). The reaction mixture was stirred and allowed to warm slowly to room temperature. When the reaction was complete, the volatiles were removed in vacuo and the crude product purified on silica gel (10% to 50% EtOAc in hexanes) to give the desired product (268 mg, 100%). MS 335 (MH^+).

Example 274c: 2-(8-hydroxyoctyloxy)-6-nitrobenzonitrile

To a solution of 1,8-octanediol (3.87 mmol, 566 mg) in THF (dry, 10 mL) was added 2,6-dinitrobenzonitrile (1.29 mmol, 250 mg) and DBU (1.30 mmol, 194 μL). The reaction mixture was stirred for 24 hours at room temperature an evaporated. The oily residue was triturated with 10% citric acid/water and solid NaCl added. The precipitate was collected , washed with water, dried in vacuo and purified on silica gel (40% to 100% EtOAc in hexanes) to give the desired product (235 mg, 62.3%) asa pinkish solid. MS 293 (MH^+).

Example 275: 7-(4-amino-2,2-dioxo-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)heptan-1-ol



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Prepared as in Example 274 from 7-(3-amino-2-cyanophenoxy)heptyl acetate (Example 275a) and sulfamoyl chloride in 79.4% yield. ^1H NMR (400 MHz, DMSO-d_6) δ 1.320 (m, 4H), 1.405 (m, 4H), 1.811 (pentet, J = 7 Hz, 2H), 3.378 (q, J = 6 Hz, 2H), 4.154 (t, J = 6 Hz, 2H), 4.331 (t, J = 5 Hz, 1H), 6.605 (d, J = 8 Hz, 1H), 6.752 (d, J = 8 Hz, 1H), 7.454 (t, J = 8 Hz, 1H), 7.823 (br. s, 1H), 8.358 (br. s, 1H), 10.946 (s, 1H). MS 328 (MH^+).

Example 275a: 7-(3-amino-2-cyanophenoxy)heptyl acetate

Prepared as in Example 274a from 7-(2-cyano-3-nitrophenoxy)heptyl acetate (Example 275b) in 89% yield. MS 291 (MH^+)

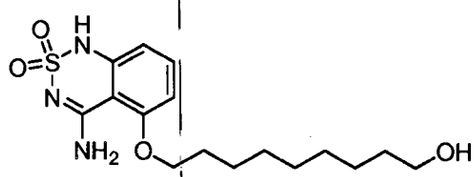
Example 275b: 7-(2-cyano-3-nitrophenoxy)heptyl acetate

Prepared as in Example 274b from 2-(7-hydroxyheptyloxy)-6-nitrobenzonitrile (Example 275c) in 100% yield. MS 321 (MH^+).

Example 275c: 2-(7-hydroxyheptyloxy)-6-nitrobenzonitrile

Prepared as in Example 274c (except DBU was replaced with KOtBu) from 1,7-heptanediol in 65% yield. MS 279 (MH^+).

Example 276: 9-(4-amino-2,2-dioxo-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)nonan-1-ol



698

Prepared as in Example 274 from 9-(3-amino-2-cyanophenoxy)nonyl acetate (Example 276a) and sulfamoyl chloride in 62.3% yield. ^1H NMR (400 MHz, DMSO-d_6) δ 1.250 (m, 8H), 1.381 (m, 4H), 1.791 (pentet, J = 7 Hz, 2H), 3.349 (q, J = 6 Hz, 2H), 4.135 (t, J = 6 Hz, 2H), 4.301 (t, J = 5 Hz, 1H), 6.585 (d, J = 8 Hz, 1H), 6.728 (d, J = 8 Hz, 1H), 7.434 (t, J = 8 Hz, 1H), 7.798 (br. s, 1H), 8.329 (br. s, 1H), 10.924 (s, 1H). MS 356 (MH^+).

Example 276a: 9-(3-amino-2-cyanophenoxy)nonyl acetate

Prepared as in Example 274a from 9-(2-cyano-3-nitrophenoxy)nonyl acetate (Example 276b) in 99.3% yield. MS 319 (MH^+)

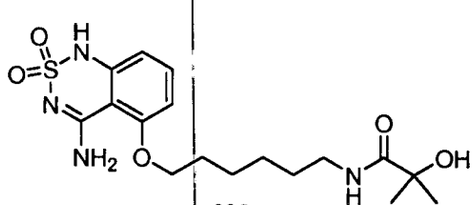
Example 276b: 9-(2-cyano-3-nitrophenoxy)nonyl acetate

Prepared as in Example 274b from 2-(9-hydroxynonyloxy)-6-nitrobenzonitrile (Example 276c) in100% yield. MS 349 (MH^+).

Example 276c: 2-(9-hydroxynonyloxy)-6-nitrobenzonitrile

Prepared as in Example 274c (except DBU was replaced with 1,1,3,3-tetramethylguanidine) from 1,9-nonanediol and 2,6-dinitrobenzonitrile in 30.7% yield. MS 307 (MH^+).

Example 277: N-(6-(4-amino-2,2-dioxo-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)hexyl)-2-hydroxy-2-methylpropanamide



699

Prepared as in Example 274 from 1-(6-(3-amino-2-cyanophenoxy)hexylamino)-2-methyl-1-oxopropan-2-yl acetate (Example 277a) in 65.5% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.201 (s, 6H), 1.289 (m, 2H), 1.399 (m, 4H), 1.790 (pentet, J = 7 Hz, 2H), 3.036 (q, J = 6 Hz, 2H), 4.130 (t, J = 6 Hz, 2H), 5.272 (s, 1H), 6.587 (d, J = 8 Hz, 1H), 6.728 (d, J = 8 Hz, 1H), 7.436 (t, J = 8 Hz, 1H), 7.594 (br. t, 1H), 7.804 (br. s, 1H), 8.326 (br. s, 1H), 10.924 (s, 1H). MS 399 (MH^+).

Example 277a: 1-(6-(3-amino-2-cyanophenoxy)hexylamino)-2-methyl-1-oxopropan-2-yl acetate

Prepared as in Example 274a from 1-(6-(2-cyano-3-nitrophenoxy)hexylamino)-2-methyl-1-oxopropan-2-yl acetate (Example 274b) in 94.4% yield. MS 362 (MH^+)

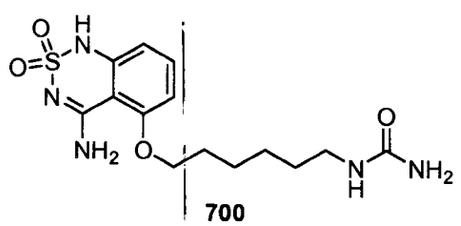
Example 277b: 1-(6-(2-cyano-3-nitrophenoxy)hexylamino)-2-methyl-1-oxopropan-2-yl acetate

To a solution of tert-butyl 6-(2-cyano-3-nitrophenoxy)hexylcarbamate (333 µmol, 121 mg) (Example 277c) in dixoane (2 mL) was added con. HCl (1 mL). After 15 minutes, the solution was concentrated in vacuo and dried on high vacuum. The crude HCl salt was suspended in DCM (dry, 10 mL) and treated with pyridine (2.664 mmol, 215 µL) and 1-chloro-2-methyl-1-oxopropan-2-yl acetate (1.332 mmol, 193 µL). The reaction mixture was refluxed under a nitrogen atmosphere until clear (6 h), then cooled to room temperature and the volatiles removed in vacuo. The residue was purified on silica gel (40% to 100% EtOAc in hexanes) to give the product (117 mg, 90%) as a light yellow heavy oil. MS 392 (MH^+).

Example 277c: tert-butyl 6-(2-cyano-3-nitrophenoxy)hexylcarbamate

Prepared as in Example 215c from tert-butyl 6-hydroxyhexylcarbamate in 53.8% yield as light yellow solid. MS 364 (MH^+).

Example 278: 1-(6-(4-amino-2,2-dioxo-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)hexyl)urea

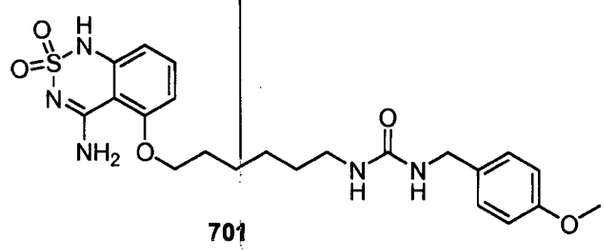


700

A solution of 1-(6-(4-amino-2,2-dioxo-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)hexyl)-3-(4-methoxybenzyl)urea (122 µmol, 58 mg) (Example 279) in DCM (2.5 mL) was

treated with TFA (2.5 mL). The reaction mixture was stirred at room temperature for 4 hours, then the volatiles were removed under a stream of nitrogen. The oily residue was triturated with ether, the precipitate collected, washed with ether, then dissolved in MeOH and evaporated to gives the desired product (44 mg,100% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ1.364 (m, 6H), 1.812 (pentet, J = 7 Hz, 2H), 2.943 (br t, 2H), 4.154 (d, J = 7 Hz, 2H), 4.131 (t, J = 7 Hz, 2H), 5.349 (br. s, 2H), 5.894 (br. s, 1H), 6.607 (d, J = 8 Hz, 1H), 6.752 (d, J = 8 Hz, 1H), 7.456 (t, J = 8 Hz, 1H), 7.824 (br. s, 1H), 8.351 (br. s, 1H), 10.945 (s, 1H). MS 356 (MH^+).

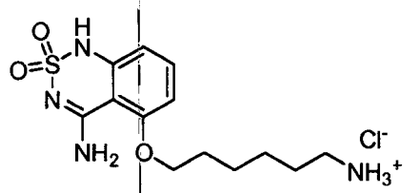
Example 279: 1-(6-(4-amino-2,2-dioxo-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)hexyl)-3-(4-methoxybenzyl)urea



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To a suspention of 6-(4-amino-2,2-dioxo-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)hexan-1-aminium chloride (166 µmol, 52 mg) (Example 280) in dry DCM (6 mL) was successively added Et_3N (332 µmol, 46 µL) and 1-(isocyanatomethyl)-4-methoxybenzene (183 µmol, 26 µL). The reaction was stirred for 48 hours at room temperature then concentrated in vacuo. The residue was washed with water, dried, then purified on silica gel (20% to 100% EtOAc in hexanes) to give the desired product (64 mg, 81.0% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ1.296 (m, 2H), 1.371 (m, 4H), 1.791 (pentet, J = 8 Hz, 2H), 2.980 (q, J = 6 Hz, 2H), 3.695 (s, 3H), 4.086 (d, J = 6 Hz, 2H), 4.131 (t, J = 6 Hz, 2H), 5.836 (br. t, J = 5 Hz, 1H), 6.141 (br. t, J = 6 Hz, 1H), 6.585 (d, J = 8 Hz, 1H), 6.727 (d, J = 8 Hz, 1H), 6.840 (d, J = 9 Hz, 2H), 7.137 (d, J = 9 Hz, 2H), 7.433 (t, J = 8 Hz, 1H), 7.803 (br. s, 1H), 8.321 (br. s, 1H), 10.926 (s, 1H). MS 476 (MH^+).

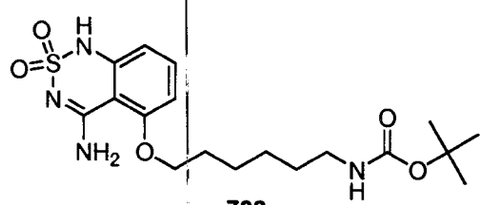
Example 280: 6-(4-amino-2,2-dioxo-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)hexan-1-aminium chloride



702

To a solution of tert-butyl 6-(4-amino-2,2-dioxo-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)hexylcarbamate (118 mg, 286 umol) (Example 281) in dioxane (2 mL) was added con. HCl (1 mL) and the solution stirred at room temperature for 15 minutes. The solvents were removed in vacuo and the residue triturated with hot ethanol. After cooling to room temperature, the precipitated was collected, washed with hot ethanol, and dried in vacuo to give the desired product 56 mg (62.9%) as an off-white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.367 (m, 4H), 1.529 (pentet, J = 7 Hz, 2H), 1.795 (pentet, J = 7 Hz, 2H), 2.741 (br m, 2H), 4.144 (t, J = 7 Hz, 2H), 6.596 (d, J = 8 Hz, 1H), 6.733 (d, J = 8 Hz, 1H), 7.440 (t, J = 8 Hz, 1H), 7.725 (br. s, 3H), 7.795 (br. s, 1H), 8.350 (br. s, 1H), 10.954 (s, 1H). MS 313 (MH^+).

Example 281: tert-butyl 6-(4-amino-2,2-dioxo-1H-benzo[c][1,2,6]thiadiazin-5-yloxy)hexylcarbamate



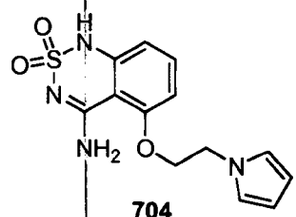
703

Prepared as in Example 274 from tert-butyl 6-(3-amino-2-cyanophenoxy)hexylcarbamate (Example 281a) and sulfamoyl chloride in 59.5% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.274 (m, 2H), 1.339 (s, 9H), 1.361 (m, 4H), 1.779 (pentet, J = 7 Hz, 2H), 2.878 (q, J = 6 Hz, 2H), 4.122 (t, J = 6 Hz, 2H), 6.580 (d, J = 8 Hz, 1H), 6.722 (d, J = 8 Hz, 1H), 6.75 (br t, J = 6 Hz, 1H), 7.428 (t, J = 8 Hz, 1H), 7.798 (br. s, 1H), 8.323 (br. s, 1H), 10.921 (s, 1H). MS 413 (MH^+).

Example 281a: tert-butyl 6-(3-amino-2-cyanophenoxy)hexylcarbamate

Prepared as in Example 274a from tert-butyl 6-(2-cyano-3-nitrophenoxy)hexylcarbamate (example 277c) in quantitative yield. MS 334 (MH^+).

Example 282: 5-(2-(1H-pyrrol-1-yl)ethoxy)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



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Prepared as in Example 274 from 2-(2-(1H-pyrrol-1-yl)ethoxy)-6-aminobenzonitrile (Example 282a) and sulfamoyl chloride in 66.6%yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ4.392 (m, 4H), 5.992 (t, J = 2 Hz, 2H), 6.595 (d, J = 8 Hz, 1H), 6.693 (d, J = 8 Hz, 1H), 6.816 (t, J = 2 Hz, 2H), 7.428 (t, J = 8 Hz, 1H), 7.482 (br. s, 1H), 8.288 (br. s, 1H), 10.930 (s, 1H). MS 307 (MH^+).

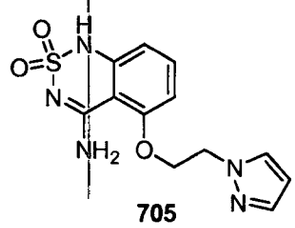
Example 282a: 2-(2-(1H-pyrrol-1-yl)ethoxy)-6-aminobenzonitrile

Prepared as in Example 274a from 2-(2-(1H-pyrrol-1-yl)ethoxy)-6-nitrobenzonitrile (Example 282b) in 85.2% yield. MS 228 (MH^+).

Example 282b: 2-(2-(1H-pyrrol-1-yl)ethoxy)-6-nitrobenzonitrile

Prepared as in Example 166d from 2-(1H-pyrrol-1-yl)ethanol and 2,6-dinitrobenzonitrile, in 42.5% yield. MS 258 (MH^+).

Example 283: 5-(2-(1H-pyrazol-1-yl)ethoxy)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



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Prepared as in Example 274 from 2-(2-(1H-pyrazol-1-yl)ethoxy)-6-aminobenzonitrile (Example 283a) and sulfamoyl chloride in 54.5% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ4.406 (t, J = 5 Hz, 2H), 4.630 (t, J = 5 Hz, 2H), 6.266 (t, J = 2 Hz, 1H), 6.593 (d, J = 8 Hz, 1H), 6.689 (d, J = 8 Hz, 1H), 7.445 (br s, 1H), 7.425 (t, J = 8 Hz, 1H), 7.805 (d, J = 2 Hz, 1H), 8.224 (br. s, 1H), 8.301 (br. s, 1H), 10.904 (s, 1H). MS 308 (MH^+).

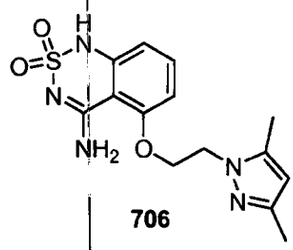
Example 283a: 2-(2-(1H-pyrazol-1-yl)ethoxy)-6-aminobenzonitrile

Prepared as in Example 274a from 2-(2-(1H- pyrazol -1-yl)ethoxy)-6-nitrobenzonitrile (Example 283b) in 46.2% yield. MS 229 (MH^+).

Example 283b: 2-(2-(1H- pyrazol -1-yl)ethoxy)-6-nitrobenzonitrile

Prepared as in Example 215c from 2-(1H-pyrazol-1-yl)ethanol and 2,6-dinitrobenzonitrile in 89.2% yield. MS 259 (MH^+).

Example 284: 5-(2-(3,5-dimethyl-1H-pyrazol-1-yl)ethoxy)-1H-benzo[c][1,2,6]thiadiazin-4-amine-2,2-dioxide



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Prepared as in Example 274 from 2-(2-(3,5-dimethyl-1H-pyrazol-1-yl)ethoxy)-6-aminobenzonitrile (Example 284a) and sulfamoyl chloride in 18.2% yield. ^1H NMR (400 MHz, DMSO-d_6) δ2.066 (s, 3H), 2.215 (s, 3H), 4.313 (t, J = 4 Hz, 2H), 4.397 (t, J = 4 Hz, 2H), 5.801 (s, 1H), 6.584 (d, J = 8 Hz, 1H), 6.645 (d, J = 8 Hz, 1H), 7.418 (t, J = 8 Hz, 1H), 8.395 (br. s, 1H), 8.677 (br. s, 1H), 10.885 (s, 1H). MS 336 (MH^+).

Example 284a: 2-(2-(3,5-dimethyl-1H-pyrazol-1-yl)ethoxy)-6-aminobenzonitrile

Prepared as in Example 274a from 2-(2-(3,5-dimethyl-1H- pyrazol -1-yl)ethoxy)-6-nitrobenzonitrile (example 284b) in 69.3% yield. MS 257 (MH^+).

Example 284b: 2-(2-(3,5-dimethyl-1H- pyrazol -1-yl)ethoxy)-6-nitrobenzonitrile

Prepared as in Example 215c from 2-(3,5-dimethyl-1H-pyrazol-1-yl)ethanol and 2,6-dinitrobenzonitrile in 90.7% yield. MS 287 (MH^+).

EXPERIMENT 4: Biological Assay

An HEK293 cell line derivative (Chandrashekar *et al.*, *Cell* 100, 703-711, 2000) which stably expresses Gα15 and hT1R2/hT1R3 (Li *et al.*, *Proc Natl Acad Sci USA* 99, 4692-4696, 2002) (see also, International Publication No. WO 03/001876) was used in biological assays in association with identifying compounds with sweet taste enhancing properties.

Compounds were initially selected based on their activity on the hT1R2/hT1R3-HEK293-Gα15 cell line Li *et al.*, *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 clone S-9) 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., 2002) (see also, International Publication No. WO 03/001876).

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 compounds at concentrations corresponding to three times the desired final level (Stimulation 1).

Cells were incubated with the compounds for 7.5 minutes and then another stimulation was performed in the FLIPR instrument by the addition of 25 µl of D-PBS supplemented with a sub-optimal concentration of sweeteners (producing about 5% to 20% receptor activity) (Stimulation 2).

Alternatively after replacement with 25 µl D-PBS per well, stimulation was performed in the FLIPR instrument at room temperature by addition of 25 µl D-PBS supplemented with different stimuli.

Typical sweeteners used include, but are not limited to D-Glucose, D-Fructose, Sucralose, Aspartame and Sucrose. Receptor activity was then 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. Compounds producing an increase in sweetener-mediated receptor activity were chosen for further characterization and quantification of potential enhancement properties.

In this follow assay, a fixed concentration of compounds was added in duplicates to 10 consecutive columns (20 wells total) during stimulation 1. Typical compound concentrations tested were 300 µM, 100 µM, 50 µM, 30 µM, 10 µM, 3 µM and 1 µM, 0.3 µM, 0.1 µM, or 0.03 µM. After the 7.5 minute incubation period, increasing concentrations of sweetener (to generate a dose-response curve) was presented in the same wells, in duplicates, during stimulation 2. The relative efficacy of compounds at enhancing the receptor was determined by the calculating the magnitude of a shift in the EC_{50} for the sweetener. Enhancement was defined as a ratio ($EC_{50}R$) corresponding to the EC_{50} of sweeteners,

determined in the absence of the test compound, divided by the EC_{50} of the sweetener, determined in the presence of the test compound. In some embodiments, compounds have an $EC_{50}R$ between about 1 (*e.g.*, >1) and about 1000. In other embodiments, compounds have an $EC_{50}R$ between about 1.25 and about 500. In still other embodiments, compounds have an $EC_{50}R$ between about 1.50 and about 100. In yet other embodiments, compounds have an $EC_{50}R$ between about 1 (*e.g.*, >1) and about 50.

In still other embodiment, compounds at about 50 μM have an $EC_{50}R$ between about 1 (*e.g.*, >1) and about 1000, between about 1.25 and about 500, between about 1.50 and about 100, or between about 1 (*e.g.*, >1) and about 50. Assay results for compounds are illustrated in Table A below.

In one illustrative example, the pre-incubated sucralose $EC_{50}R$ at 50 μM for one group of specific compounds of the present invention generally ranges from 0.73 to 5.20, while the co-stimulation sucralose $EC_{50}R$ at 50 μM for the same group of compounds generally ranges from 0.72 to 4.46. In another illustrative example, the co-stimulated sucrose $EC_{50}R$ at 50 μM for one group of specific compounds of the present invention generally ranges from 1.30 to 4.35, the co-stimulation sucralose $EC_{50}R$ at 50 μM for the same group of compounds generally ranges from 1.73 to 24.09, and the co-stimulation fructose $EC_{50}R$ at 50 μM for the same group of compounds generally ranges from 0.81 to 4.46. In another illustrative example, the co-stimulated sucrose $EC_{50}R$ at 50 μM for one group of specific compounds of the present invention generally ranges from 1.05 to 2.44, the co-stimulation sucralose $EC_{50}R$ at 50 μM for the same group of compounds generally ranges from 1.57 to 11.63, and the co-stimulation fructose $EC_{50}R$ at 50 μM for the same group of compounds generally ranges from 0.99 to 1.78. In another illustrative example, the co-stimulated sucrose $EC_{50}R$ at 50 μM for one group of specific compounds of the present invention generally ranges from 1.27 to 116.56, the co-stimulation sucralose $EC_{50}R$ at 50 μM for the same group of compounds generally ranges from 1.48 to 157.63, and the co-stimulation fructose $EC_{50}R$ at 50 μM for the same group of compounds generally ranges from 0.68 to 9.56. In another illustrative example, the co-stimulated sucrose $EC_{50}R$ at 50 μM for one group of specific compounds of the present invention generally ranges from 0.88 to 36.66, the co-stimulation sucralose $EC_{50}R$ at 50 μM for the same group of compounds generally ranges from 1.07 to 101.15, and the co-stimulation fructose $EC_{50}R$ at 50 μM for the same group of compounds generally ranges from 0.71 to 7.09. In another illustrative

example, the co-stimulated sucrose $EC_{50}R$ at 50 μM for one group of specific compounds of the present invention generally ranges from 1.39 to 17.17, the co-stimulation sucralose $EC_{50}R$ at 50 μM for the same group of compounds generally ranges from 3.80 to 49.89, and the co-stimulation fructose $EC_{50}R$ at 50 μM for the same group of compounds generally ranges from 0.92 to 6.07. In another illustrative example, the co-stimulated sucrose $EC_{50}R$ at 50 μM for one group of specific compounds of the present invention generally ranges from 1.30 to 56.27, the co-stimulation sucralose $EC_{50}R$ at 50 μM for the same group of compounds generally ranges from 1.26 to 204.98, and the co-stimulation fructose $EC_{50}R$ at 50 μM for the same group of compounds generally ranges from 1.14 to 8.37.

EXPERIMENT 5: Sweet Flavor and Sweet Flavor Enhancement Measurement Using Human Panelists Conducting a Scaling Test

Test samples containing experimental compounds were compared to a dose-response curve for perceived sweetness intensity of sweeteners (such as, for example, sucralose, sucrose, fructose and other sweeteners) concentrations to determine equivalent sweetness intensity.

A group of eight or more panelists tasted solutions including sweeteners at various concentrations, as well as the experimental compound both with and without added sweetener. Panelists then rated sweetness intensity of all samples on a structured horizontal line scale, anchored from 0 to 15, where 0 equals no sweetness and 15 equals equivalent sweetness to a 15% sucrose sample. Scores for sweetness intensity were averaged across panelists. Then using the average scores and/or equation of the line for the sweetener dose-response curve, equivalent sweetness concentrations were determined for the samples containing experimental compounds.

Subjects had been previously familiarized with the key attribute taste and were trained to use the 0 to 15 point line scale. Subjects refrained from eating or drinking (except water) for at least 1 hour prior to the test. Subjects ate a cracker and rinsed with water several times to clean the mouth.

Sweetener solutions are provided at a wide range of concentrations such as 100 ppm, 200 ppm, 300 ppm, 400 ppm, and 500 ppm for sucralose, or between 0% and 12% for sucrose or fructose, in order to create a dose-response curve. Samples containing experimental

compound were prepared both alone and in a 100 ppm sucralose solution or a 6% sucrose or fructose solution. All samples were made up in low sodium buffer pH 7.1. In order to aid dispersion, solutions can be made up in 0.1% ethanol.

The solutions were dispensed in 20 ml volumes into 1 oz. sample cups and served to the subjects at room temperature. All samples were presented in randomized counterbalanced order to reduce response bias. Further, two sessions of testing may be used to check panel precision.

Subjects tasted each sample individually and rate sweetness intensity on the line scale prior to tasting the next sample. All samples were expectorated. Subjects may retaste the samples but can only use the volume of sample given. Subjects must rinse with water between samples. Eating an unsalted cracker between samples may be required depending on the samples tasted.

The scores for each sample were averaged across subjects and standard error was calculated. The dose-response curve was plotted graphically, and this may be used to ensure the panel is rating accurately; *i.e.*, increasing the concentration of sucralose should correspond to increased average scores for sweetness. A 2-way ANOVA (factors being samples and panelists) and multiple comparison tests (such as Tukey's Honestly Significant Difference test) can be used to determine differences among samples and/or panelists. A 3-way ANOVA, with sessions as the third factor, can be used to determine if there is any difference in the ratings between sessions.

The compounds tested in this Experiment, namely, compounds C1 to C21, are representative compounds of the present invention including compounds of structural Formula (I) and its subgeneric formulas.

The results of human taste tests with a compound **C1** are found below. Table 1 indicates that 100 μM compound **C1** in 100 ppm sucralose has sweetness equivalent to 200 ppm sucralose. Table 2 indicates that 100 μM compound **C1** alone has no sweetness, and therefore can be defined as a true sweet enhancer.

Table 1. Average sweetness scores for various sucralose samples, including 100 ppm sucralose with 100 μM compound **C1**, n = 32 (16 Panelists x 2 replicates). Tukey's value = 1.409 (α = 0.05).

Sample	Average	Standard	Tukey's HSD

		Error	Significance (5%)
100 ppm Sucralose	6.3	0.3	A
100 ppm Sucralose + 100 μM C1	10.2	0.5	B
200 ppm Sucralose	10.4	0.5	B
300 ppm Sucralose	11.5	0.4	Bc
400 ppm Sucralose	12.3	0.4	C

Table 2. Average sweetness scores for 100 μM compound **C1** and low sodium buffer, n = 15 (15 Panelists x 1 rep). Tukey's value = 0.186 (α = 0.05).

Sample	Average	Standard Error	Tukey's HSD Significance (5%)
Low Sodium Buffer (contains no sweeteners)	0.1	0.1	A
100 μM 7	0.1	0.1	A

The results of human taste tests with compound **C2** are found below. Table 3 indicates that 100 μM compound in 100 ppm sucralose has sweetness equivalent to about 600 ppm sucralose. Table 4 shows a dose response curve of compound **C2** with 100 ppm sucralose which shows that the sweetness of sucralose is significantly enhanced by addition of increasing amounts of compound **C2**. Table 5 indicates that 100 μM compound **C2** alone has little or no sweetness, and therefore can be defined as a true sweet enhancer.

Table 3. Average sweetness scores, n = 12 (12 Panelists x 1 rep). Tukey's value = 2.449 (α = 0.05), 2.209 (α = 0.10).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
100ppm Sucralose	7.4	1.7	0.5	a	a
200ppm Sucralose	10.4	1.9	0.6	b	b
300ppm Sucralose	10.5	2.8	0.8	b	b
400ppm Sucralose	11.2	2.4	0.7	bc	bc

600ppm Sucralose	13.0	1.4	0.4	c	c
100 µM C2 + 100ppm Sucralose	13.3	1.6	0.5	c	c

Table 4. Average sweetness scores, n = 26 (14 Panelists x 1 rep; 12 panelists x 1 rep). Tukey's value = 1.584 ($\alpha = 0.05$), 1.452 ($\alpha = 0.10$).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
100 ppm sucralose	6.3	1.5	0.3	a	a
100 ppm sucralose + 3.12 µM C2	7.4	1.7	0.3	ab	ab
100 ppm sucralose + 6.25 µM C2	8.4	1.8	0.4	bc	bc
100 ppm sucralose + 12.5 µM C2	9.1	1.9	0.4	cd	cd
200 ppm sucralose	9.5	2.0	0.4	cd	cd
300 ppm sucralose	10.3	2.7	0.5	d	d
100 ppm sucralose + 25 µM C2	10.3	1.6	0.3	d	d
400 ppm sucralose	12.1	1.9	0.4	e	e
100 ppm sucralose + 50 µM C2	12.3	1.5	0.3	e	e

Table 5. Average sweetness scores, n = 12 (12 Panelists x 1 rep). Tukey's value = 0.809 (α = 0.05), 0.723 (α = 0.10).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
0% Sucrose	0.0	0.0	0.0	a	a
100 μM C2 in LSB	0.2	0.3	0.1	a	a
2% Sucrose	2.4	1.0	0.3	b	b

The results of human taste tests with compound **C3** are found below. Table 6 indicates that 100 μM compound in 100 ppm sucralose has sweetness equivalent to about between 200 and 300 ppm sucralose. Table 7 indicates that 100 μM compound **C3** alone has no sweetness, and therefore can be defined as a true sweet enhancer.

Table 6. Average sweetness scores, n = 13 (13 Panelists x 1 rep). Tukey's value = 2.333 (α = 0.05), 2.087 (α = 0.10).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
100 ppm Sucralose	6.5	1.3	0.4	a	a
200 ppm Sucralose	9.1	2.0	0.6	b	b
100 ppm Sucralose + 100 μM C3	9.8	1.8	0.5	b	bc
300 ppm Sucralose	10.8	2.8	0.8	b	bc
400 ppm Sucralose	11.2	2.3	0.6	b	c

Table 7. Average sweetness scores, n = 13 (13 Panelists x 1 rep). Tukey's value = 0.906 (α = 0.05), 0.811 (α = 0.10).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
100 μM C3 in LSB	0.0	0.0	0.0	a	a
0% Sucrose	0.0	0.1	0.0	a	a
2% Sucrose	1.8	1.0	0.3	b	b

The results of human taste tests with a compound **C4** are found below. Table 8 indicates that 100 μM compound **C4** in 6% sucrose has sweetness equivalent to 8% sucrose. Table 9 indicates that 100 μM compound **C4** alone has no sweetness, and therefore can be defined as a true sweet enhancer.

Table 8. Average sweetness scores for various sucrose samples, including 6% sucrose with 100 μM compound **C4**, n = 28 (14 Panelists x 2 replicates). Tukey's value = 1.091 (α = 0.05), 0.976 (α = 0.10).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
6% Sucrose	6.6	1.0	0.2	a	a
8% Sucrose	8.1	2.1	0.4	b	b
6% Sucrose+ 100 μM C4	8.1	1.1	0.2	b	b
9% Sucrose	8.6	1.9	0.4	bc	b
10% Sucrose	9.6	0.6	0.1	c	c

Table 9. Average sweetness scores, n = 14 (14 Panelists x 1 rep). Tukey's value = 0.876 (α = 0.05), 0.784 (α = 0.10).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
100 μM C4 in LSB	0.3	0.6	0.2	a	a
0% Sucrose	0.3	1.1	0.3	a	a
2% Sucrose	2.2	0.6	0.2	b	b
4% Sucrose	4.0	0.9	0.2	c	c
6% Sucrose	5.5	0.9	0.2	d	d

The results of human taste tests with a compound **C5** are found below. Table 10 indicates that 100 μM compound **C5** in 6% sucrose has sweetness equivalent to 9% sucrose. Table 11 indicates that 100 μM compound **C5** alone has no sweetness, and therefore can be defined as a true sweet enhancer.

Table 10. Average Sweetness, n = 24 (12 Panelists x 2 rep). Tukey's value = 0.832 ($\alpha = 0.05$), 0.744 ($\alpha = 0.10$).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
6% Sucrose	7.3	1.3	0.3	a	a
8% Sucrose	7.9	1.3	0.3	ab	ab
9% Sucrose	8.6	1.1	0.2	bc	bc
6% Sucrose + 100 µM C5	8.8	0.9	0.2	cd	c
10% Sucrose	9.6	0.7	0.1	d	d

Table 11. Average Sweetness, n = 14 (14 Panelists x 1 rep). Tukey's value = 0.981 ($\alpha = 0.05$), 0.877 ($\alpha = 0.10$).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
LSB + 100 µM C5	0.2	0.5	0.1	a	a
0% Sucrose	0.4	1.5	0.4	a	a
2% Sucrose	2.1	0.8	0.2	b	b
4% Sucrose	3.9	0.7	0.2	c	c
6% Sucrose	5.7	0.7	0.2	d	d

The results of human taste tests with a compound **C6** are found below. Table 12 indicates that 100 µM compound **C6** in 6% sucrose has sweetness equivalent to about 10% sucrose. Table 13 indicates that 100 µM compound **C6** alone has no sweetness, and therefore can be defined as a true sweet enhancer.

Table 12. Average Sweetness, n = 28 (14 Panelists x 2 rep). Tukey's value = 0.818 ($\alpha = 0.05$), 0.732 ($\alpha = 0.10$).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
6% Sucrose	6.8	1.2	0.2	a	a
8% Sucrose	8.3	1.1	0.2	b	b
9% Sucrose	8.6	1.3	0.3	bc	bc
6% Sucrose + 100 µM C6	9.3	1.0	0.2	cd	cd
10% Sucrose	9.5	0.7	0.1	d	d

Table 13. Average Sweetness, n = 14 (14 Panelists x 1 rep). Tukey's value = 1.238 ($\alpha = 0.05$), 1.107 ($\alpha = 0.10$).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
0% Sucrose	0.0	0.1	0.0	a	a
LSB + 100 μM C6	0.2	0.5	0.1	a	a
2% Sucrose	1.9	0.9	0.2	b	b
4% Sucrose	3.9	1.3	0.4	c	c
6% Sucrose	5.5	2.0	0.5	d	d

The results of human taste tests with a compound **C7** are found below. Table 14 indicates that 50 μM compound **C7** in 6% sucrose has sweetness equivalent to about 9% sucrose.

Table 14. Average Sweetness, n = 26 (13 Panelists x 2 rep). Tukey's value = 0.762 ($\alpha = 0.05$), 0.682 ($\alpha = 0.10$).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
6% Sucrose	6.5	1.0	0.2	a	a
8% Sucrose	8.5	1.3	0.2	b	b
9% Sucrose	8.7	1.4	0.3	b	b
6% Sucrose+ 50 μM C7	8.9	1.1	0.2	bc	b
10% Sucrose	9.7	0.9	0.2	c	c

The results of human taste tests with a compound **C8** are found below. Table 15 indicates that 100 μM compound **C8** in 6% sucrose has sweetness equivalent to about 8% sucrose. Table 16 indicates that 100 μM compound **C8** alone has no sweetness, and therefore can be defined as a true sweet enhancer.

Table 15. Average Sweetness, n = 28 (14 Panelists x 2 rep). Tukey's value = 0.859 ($\alpha = 0.05$), 0.768 ($\alpha = 0.10$).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
6% Sucrose	7.0	1.3	0.3	a	a
6% Sucrose + 100 µM C8	8.2	1.3	0.3	b	b
8% Sucrose	8.4	1.5	0.3	bc	bc
9% Sucrose	9.0	1.0	0.2	bc	c
10% Sucrose	9.1	1.0	0.2	c	c

Table 16. Average Sweetness, n = 14 (14 Panelists x 1 rep). Tukey's value = 1.029 ($\alpha = 0.05$), 0.921 ($\alpha = 0.10$).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
0% Sucrose	0.0	0.0	0.0	a	a
100 µM C8 in LSB	0.2	0.3	0.1	a	a
2% Sucrose	2.0	0.9	0.2	b	b
4% Sucrose	4.1	1.4	0.4	c	c
6% Sucrose	5.7	1.4	0.4	d	d

The results of human taste tests with a compound **C9** are found below. Table 17 indicates that from about 40 to about 55 µM compound **C9** in 100 ppm sucralose has sweetness equivalent to about 400 ppm sucralose. Table 18 indicates that from about 40 to about 55 µM compound **C9** alone has no sweetness, and therefore can be defined as a true sweet enhancer.

Table 17. Average Sweetness, n = 28 (14 Panelists x 2 rep). Tukey's value = 1.304 ($\alpha = 0.05$), 1.178 ($\alpha = 0.10$).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
100 ppm sucralose	6.5	2.0	0.4	a	a
200 ppm sucralose	9.0	1.8	0.3	b	b
300 ppm sucralose	10.9	1.6	0.3	c	c
100 ppm sucralose + 40-55 μM C9	12.2	1.3	0.3	cd	d
400 ppm sucralose	12.3	1.8	0.3	d	d

Table 18. Average Sweetness, n = 22 (11 Panelists x 2 rep). Tukey's value = 0.693 ($\alpha = 0.05$), 0.619 ($\alpha = 0.10$).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
LSB + 40-55 μM C9	0.1	0.4	0.1	a	a
0% Sucrose	0.2	0.6	0.1	a	a
2% Sucrose	2.4	0.8	0.2	b	b
4% Sucrose	4.2	1.1	0.2	c	c
6% Sucrose	5.9	1.1	0.2	d	d

The results of human taste tests with a compound **C10** are found below. Table 19 indicates that 25 μM compound **C10** in 6% sucrose has sweetness equivalent to about 8% sucrose.

Table 19. Average Sweetness, n = 28 (14 Panelists x 2 rep). Tukey's value = 0.747 ($\alpha = 0.05$), 0.668 ($\alpha = 0.10$).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
6% Sucrose	7.3	1.4	0.3	a	a
6% Sucrose + 25 μM C10	8.4	1.1	0.2	b	b
8% Sucrose	8.6	1.2	0.2	bc	bc
9% Sucrose	9.1	0.9	0.2	cd	cd
10% Sucrose	9.7	0.5	0.1	d	d

Table 20 indicates that 25 μM of compounds **C10** alone has no sweetness, and therefore can be defined as true sweet enhancers.

Table 20. Average Sweetness, n = 14 (14 Panelists x 1 rep). Tukey's value = 0.957(α = 0.05), 0.856 (α = 0.10).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
0% Sucrose	0.2	0.5	0.1	a	a
LSB+ 25 μM C10	0.2	0.6	0.1	a	a
2% Sucrose	2.8	1.5	0.4	b	b
4% Sucrose	4.7	1.0	0.3	c	c
6% Sucrose	5.9	0.5	0.1	d	d

The results of human taste tests with a compound **C11** are found below. Table 21 indicates that 50 μM compound **C11** in 6% sucrose has sweetness equivalent to about 8% sucrose.

Table 21. Average Sweetness, n = 15 (15 Panelists x 1 rep). Tukey's value = 0.905 (α = 0.05), 0.810 (α = 0.10).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
6% Sucrose	6.5	0.9	0.2	a	a
8% Sucrose	8.3	0.9	0.2	b	b
6% Sucrose + 50 μM C11	8.4	1.0	0.2	b	b
10% Sucrose	9.4	0.9	0.2	c	c
9% Sucrose	9.4	0.7	0.2	c	c

The results of human taste tests with a compound **C12** are found below. Table 22 indicates that 50 μM compound **C12** in 6% sucrose has sweetness equivalent to about 9% -10% sucrose.

Table 22. Average Sweetness, n = 26 (13 Panelists x 2 rep). Tukey's value = 0.492 ($\alpha = 0.05$), 0.440 ($\alpha = 0.10$).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
6% Sucrose	6.5	0.8	0.2	a	a
8% Sucrose	8.2	1.0	0.2	b	b
6% Sucrose + 50 μM C12	9.0	0.8	0.2	c	c
9% Sucrose	9.2	0.7	0.1	c	c
10% Sucrose	9.4	0.9	0.2	c	c

The results of human taste tests with a compound **C13** are found below. Table 23 indicates that 25 μM compound **C13** in 6% sucrose has sweetness equivalent to about 8% sucrose.

Table 23. Average Sweetness, n = 26 (13 Panelists x 2 rep). Tukey's value = 0.636 ($\alpha = 0.05$), 0.569 ($\alpha = 0.10$).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
6% Sucrose	6.8	1.0	0.2	a	a
6% Sucrose + 25 μM C13	8.6	1.1	0.2	b	b
8% Sucrose	8.7	1.0	0.2	b	b
9% Sucrose	9.5	0.7	0.1	c	c
10% Sucrose	9.5	0.8	0.2	c	c

The results of human taste tests with a compound **C14** are found below. Table 24 indicates that 50 μM compound **C14** in 6% sucrose has sweetness equivalent to about 8%-9% sucrose.

Table 24. Average Sweetness, n = 26 (12 Panelists x 1 rep; 14 Panelists x 1 rep). Tukey's value = 0.782 ($\alpha = 0.05$), 0.701 ($\alpha = 0.10$).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
6% Sucrose	6.5	1.0	0.2	a	a
8% Sucrose	8.4	1.2	0.2	b	b
6% Sucrose + 50 μM C14	8.7	1.3	0.2	bc	bc
9% Sucrose	9.2	1.2	0.2	c	cd
10% Sucrose	9.4	0.7	0.1	c	d

The results of human taste tests with a compound **C15** are found below. Table 25 indicates that 50 μM compound **C15** in 6% sucrose has sweetness equivalent to about 9%-10% sucrose.

Table 25. Average Sweetness, n = 25 (11 Panelists x 1 rep; 14 Panelists x 1 rep). Tukey's value = 0.688 ($\alpha = 0.05$), 0.617 ($\alpha = 0.10$).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
6% Sucrose	6.7	0.9	0.2	a	a
8% Sucrose	8.1	1.0	0.2	b	b
6% Sucrose + 50 μM C15	9.1	1.1	0.2	c	c
10% Sucrose	9.2	0.9	0.2	c	c
9% Sucrose	9.3	0.7	0.1	c	c

The results of human taste tests with compound **C16** are found below. Table 26 indicates that 25 μM compound **C16** in 6% sucrose has sweetness equivalent to about 10%-12% sucrose. Table 27 shows a dose response curve of compound **C16** with 6% sucrose which shows that the sweetness of sucrose is significantly enhanced by addition of increasing amounts of compound **C16**. Table 28 indicates that 14.11 μM compound **C16** in 50 ppm sucralose has sweetness equivalent to about 200 ppm-300 ppm sucralose. Table 29 indicates that 25 μM compound **C16** in 6% fructose has sweetness equivalent between 6% and 8% fructose. Table 29

indicates that 25 μM compound C16 alone has little or no sweetness, and therefore can be defined as a true sweet enhancer.

Table 26. Average Sweetness, n = 24 (12 Panelists x 2 rep). Tukey's value = 1.021 (α = 0.05), 0.974 (α = 0.10).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
6% Sucrose	6.2	1.5	0.3	a	
8% Sucrose	8.3	1.1	0.2	b	
9% Sucrose	9.3	1.4	0.3	bc	
10% Sucrose	9.8	1.2	0.2	cd	
6% Sucrose + 25 μM C16	10.6	1.7	0.3	de	
12% Sucrose	11.1	1.4	0.3	e	

Table 27. Average Sweetness, n = 30 (15 Panelists x 2 rep). Tukey's value = 1.038 (α = 0.05), 1.043 (α = 0.10).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
6% Sucrose	6.7	1.0	0.2	a	a
6% Sucrose + 2.82 μM C16	7.5	1.6	0.3	ab	ab
6% Sucrose + 5.64 μM C16	8.0	1.1	0.2	b	b
8% Sucrose	8.3	1.7	0.3	b	b
6% Sucrose + 11.29 μM C16	10.1	1.5	0.3	c	c
6% Sucrose + 19.75 μM C16	10.3	1.7	0.3	cd	cd
10% Sucrose	10.3	1.8	0.4	cd	cd
6% Sucrose 28.22 μM C16	10.9	1.4	0.3	cd	cd
12% Sucrose	11.2	1.0	0.2	d	d

Table 28. Average Sweetness, n = 28 (14 Panelists x 2 rep). Tukey's value = 0.969 ($\alpha = 0.05$), 0.881 ($\alpha = 0.10$).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
50 ppm sucralose	4.3	0.7	0.1	a	a
100 ppm sucralose	6.2	1.6	0.3	b	b
150 ppm sucralose	8.2	1.8	0.3	cd	cd
200 ppm sucralose	8.9	1.6	0.3	de	d
50 ppm sucralose + 14.11 µM C16	9.9	2.3	0.4	ef	e
300 ppm sucralose	10.3	1.7	0.3	f	e

Table 29. Average Sweetness, n = 26 (13 Panelists x 2 rep). Tukey's value = 0.714 ($\alpha = 0.05$), 0.639 ($\alpha = 0.10$).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
6% Fructose	6.9	1.0	0.2	a	a
6% Fructose+ 25 µM C16	7.8	1.1	0.2	b	b
8% Fructose	8.6	0.8	0.2	c	c
9% Fructose	9.3	0.7	0.1	cd	d
10% Fructose	9.5	0.7	0.1	d	d

Table 30. Average Sweetness, n = 30 (15 Panelists x 2 rep). Tukey's value = 0.535 ($\alpha = 0.05$), 0.479 ($\alpha = 0.10$).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
0% Sucrose	0.2	0.5	0.1	a	a
LSB + 25 µM C16	0.6	0.8	0.2	a	a
2% Sucrose	2.3	0.8	0.2	b	b
4% Sucrose	4.2	1.2	0.2	c	c
6% Sucrose	5.8	0.6	0.1	d	d

The results of human taste tests with compound **C17** are found below. Table 31 indicates that 8 μM compound **C17** in 6% sucrose has sweetness equivalent to about 9%-10% sucrose. Table 32 indicates that 8 μM compound **C17** alone has little or no sweetness, and therefore can be defined as a true sweet enhancer.

Table 31. Average Sweetness, n = 28 (14 Panelists x 2 rep). Tukey's value = 0.657 ($\alpha = 0.05$), 0.588 ($\alpha = 0.10$).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
6% Sucrose	6.8	1.2	0.2	a	a
8% Sucrose	8.5	0.9	0.2	b	b
9% Sucrose	8.6	0.8	0.2	b	b
6% Sucrose + 8 μM C17	9.0	1.1	0.2	bc	bc
10% Sucrose	9.6	0.6	0.1	c	c

Table 32. Average Sweetness, n = 28 (14 Panelists x 2 rep). Tukey's value = 0.467 ($\alpha = 0.05$), 0.425 ($\alpha = 0.10$).

Treatment	Average	SD	St Er	Tukey (5%)	Tukey (10%)
0% Sucrose	0.1	0.4	0.1	a	a
LSB + 8 μM C17	0.2	0.5	0.1	a	a
2% Sucrose	2.3	0.7	0.1	c	c
4% Sucrose	4.5	1.0	0.2	d	d
6% Sucrose	5.8	0.6	0.1	e	e

EXPERIMENT 6: Sweet Flavor and Sweet Flavor Enhancement Measurement Using Human Panelists Conducting a Paired Comparison Test

Test samples containing experimental compounds are presented in pairs to the panelist and they are asked to determine which of the sample is sweeter. A group of 10-16 or more panelists participated in each test. Subjects refrained from eating or drinking (except water) for at least 1 hour prior to the test. Subjects rinsed with water several times to clean the mouth.

All samples are prepared with ethanol to ensure dispersion of the compound in solution. This includes samples without compound; all solutions are balanced for 0.1% ethanol.

Samples are also prepared with low sodium buffer (pH 7.1) in place of water. Buffer contains 0.952 g of KCl, 5.444 g of Na_2HPO_4, and 0.952 g of KH_2PO_4 in 40 L of DIUF water. Sample volumes are usually 20 ml.

In one paired comparison test, the panelist is presented with two different samples and asked to identify the sample which is sweeter. The samples within a paired comparison test are presented in a randomized, counterbalanced order. Panelists have up to a 1 minute delay between taste tests to clear the mouth of any tastes.

Binomial probability tables are used to determine the probability of the correct number of responses occurring for each test at alpha=0.05.

The results of human taste tests with a compound **C18** are found below. Table 33 indicates that panelists perceived 6% Fructose + 100 μM **C18** as being significantly sweeter than a solution of 6% Fructose ($p<0.05$)

Table 33. Sample selected as more sweet by panelists: n = 26 (13 panelists x 2 reps).

Samples	Total
6% Fructose	6
6% Fructose + 100 μM 568	20
Total	26
Confidence	0.991
6% Fructose + 100 μM C18	0.009

(p-value)	

The results of human taste tests with a compound **C19** are found below. Table 34 indicates that panelists perceived 6% Fructose + 100 μM **C19** as being significantly sweeter than a solution of 6% Fructose ($p<0.05$)

Table 34. Sample selected as more sweet by panelists: n = 24 (12 panelists x 2 reps).

Samples	**Total**
6% Fructose	6
6% Fructose + 100 μM C19	18
Total	24
Confidence	0.977
6% Fructose + 100 μM C19 (p-value)	0.023

The results of human taste tests with a compound **C20** are found below. Table 34 indicates that panelists perceived 6% Fructose + 100 μM **C20** as being significantly sweeter than a solution of 6% Fructose ($p<0.05$). Table 36 indicates that 100 μM compound **C20** alone has little or no sweetness on its own (Experiment 5).

Table 35. Sample selected as more sweet by panelists: n = 19 (19 panelists x 1 rep).

Samples	**Test 1**	**Total**
6% Fructose	0	0
6% Fructose + 100 μM C20	19	19
Total	19	19

Table [illegible] 3 Panelists x 1 rep). [illegible] ($\alpha = 0.05$), 0.67

[illegible]	Average	SD	St Er	Tukey (5%)
0% [illegible]	.2	0.5	0.1	a
LSB+ [illegible]	2.2	0.5	0.1	a
2% Fructose	2.3	0.7	0.2	b
4% Fructose	4.2	1.1	0.3	c
6% [illegible]	5.9	0.3	0.1	d

The results of human taste tests with a compound C21 [illegible] below. Table 37 indicates that panelists perceived 6% Fructose + 25 µM **C21** as being [illegible] sweeter than a solution of [illegible] fructose ($p<0.05$). Table 38 indicates that panelists perceived 6% Fructose + 25 µM C21 has the same sweetness intensity than a solution of 7% Fructose.

Table 37. Sample selected as more sweet by panelists: n = 25 (25 panelists x 1 rep).

Samples	Test 1
6% Fructose	5
6% fructose + 25 µM C21	20
Total	25
Confidence	0.999
6% fructose + 25 µM C21 (p-value)	0.001

Table 38. Sample selected as more sweet by panelists: n = 25 (25 panelists x 1 rep).

Samples	Test 1
7% Fructose	13
6% fructose + 25 µM C21	12
Total	25
Confidence	0.166
6% fructose + 25 µM C21 (p-value)	0.834

EXPERIMENT 7. Solubility Determination of the Compounds of the Present Invention and Their HCl Salts in Propylene Glycol

The solubility of the present compounds and their HCl salts in propylene glycol was determined by shake flask method. Approximately 50 mg of the test compound was weighed out and added to a 4-mL glass vial, and then 1 mL of propylene glycol was added to the vial. The vial was sonicated for 10 minutes and then shaken for 24 hrs on an orbital shaker set at 300 rpm. An aliquot of 200 µL of the solution was transferred from the vial into a 1.5 mL centrifuge vial and centrifuged at 12,500 rpm for 10 min. An aliquot of 50 µL of the supernatant was diluted by 100 times with propylene glycol. Then 50 µL of this solution was further diluted 100 times with water and analyzed by liquid chromatography mass spectrometry (C18 column with gradient elution with a flow rate of 2.0 mL/min, water with 0.1% trifluoroacetic acid as mobile phase A and methanol with 0.1% trifluoraacetic acid as mobile phase B, mobile phase B % rising from 5% to 95% in 0.6 min and then being held at 95% for 1.4 min). The result of one exemplary solubility test is shown in Table A.

Table A. Solubility of Compound C2 and Its HCl Salt

Compound	Solubility Average (mM)	Standard Deviation (mM)
C2	6.2	1.7
C2.hydrochloride	45.7	3.0

All publications and patent applications herein are incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

The foregoing detailed description has been given for clearness of understanding only and no unnecessary limitations should be understood therefrom as modifications will be obvious to those skilled in the art. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed inventions, or that any publication specifically or implicitly referenced is prior art.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

Embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

We claim:

1. A method of screening for a candidate of a chemosensory receptor ligand modifier comprising

determining whether a test entity is suitable to interact with a chemosensory receptor *via* a first interacting site within the Venus flytrap domain of the chemosensory receptor.

2. The method of claim 1, wherein the first interacting site of the Venus flytrap domain of the chemosensory receptor includes one or more interacting residues of the Venus flytrap domain of the chemosensory receptor.

3. The method of claim 1, wherein the first interacting site of the Venus flytrap domain of the chemosensory receptor includes one or more interacting spaces of the Venus flytrap domain of the chemosensory receptor.

4. The method of claim 1, wherein the first interacting site of the Venus flytrap domain includes an interacting space identified based on one or more interacting residues.

5. The method of claim 1, wherein the first interacting site of the Venus flytrap domain of the chemosensory receptor includes one or more interacting residues, which are identified based on mutagenesis analysis of the Venus flytrap domain.

6. The method of claim 1, wherein the first interacting site of the Venus flytrap domain is identified based on computer modeling, X-ray crystallography, or a combination thereof.

7. The method of claim 1, wherein the first interacting site of the Venus flytrap domain is identified based on one or more known chemosensory receptor ligands.

8. The method of claim 1, wherein the first interacting site of the Venus flytrap domain is identified based on one or more known chemosensory receptor ligand modifiers.

9. The method of claim 1, wherein the first interacting site of the Venus flytrap domain is identified based on a predetermined chemosensory receptor ligand.

10. The method of claim 1, wherein the first interacting site of the Venus flytrap domain is predetermined.

11. The method of claim 1, wherein the first interacting site of the Venus flytrap domain is in the T1R2 Venus flytrap domain.

12. The method of claim 1, wherein the first interacting site of the Venus flytrap domain is in the T1R2 Venus flytrap domain and is identified in the presence of T1R3 Venus flytrap domain.

13. The method of claim 1, wherein the determination is carried out in silico.

14. A method of screening for a candidate of a chemosensory receptor ligand modifier comprising

determining whether a test entity is suitable to interact with a chemosensory receptor *via* a first interacting site within the Venus flytrap domain of the chemosensory receptor,

wherein the first interacting site is identified in light of a second interacting site identified based on the interaction between a chemosensory receptor ligand and the chemosensory receptor.

15. The method of claim 14, wherein the first and second interacting site are in the T1R2 Venus flytrap domain.

16. The method of claim 14, wherein the first and second interacting site are in the T1R2 Venus flytrap domain and identified in the presence of T1R3 Venus flytrap domain.

17. The method of claim 1, wherein the first interacting site includes an interacting residue selected from the group consisting of amino acid N143, S144, and I167 of a human T1R2 and a combination thereof.

18. The method of claim 1, wherein the first interacting site includes at least one residue selected from the group consisting of amino acid S40, S144, [illegible] P277 of a human T1R2 and a combination thereof.

19. The method of claim 1, wherein the first interacting site includes at least one residue selected from the group consisting of amino acid K65, R383, D307, [illegible] D278 of a human T1R2 and a combination thereof.

20. The method of claim 1, wherein the first interacting site includes at least one residue selected from the group consisting of amino acid I167, P185, T184, [illegible] V384, A305, I325, I306, E382, D307, E382, D278, I279, I67, V66, V309, D142, S165, S303, T242, F103, Q328 and S168 of a human T1R2 and a combination thereof.

21. The method of claim 1, wherein the first interacting site includes at least one residue selected from the group consisting of amino acid N143, S144, I167, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, P185, T184, T326, E302, V384, A305, I325, I306, D307, E382, I279, I67, V66, V309, S303, T242, F103, Q328, and S168 of a human T1R2 and a combination thereof.

22. The method of claim 1, wherein the first interacting site includes a group of interacting residues selected from the group consisting of 1) N143, S144, and I167 of a human T1R2, 2) S40, S144, S165, Y103, D142, P277 or a human T1R2, 3) K65, R383, D307, E302, and D278 of a human T1R2, 4) I167, P185, T184, T326, E302, V384, A305, I325, I306, R383, D307, E382, D278, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, and S168 of a human T1R2, 5) N143, S144, I167, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, and S168 of a human T1R2, and 6) a combination thereof.

23. The method of claim 1, wherein the first interacting site includes an interacting residue selected from the group consisting of amino acid K65, D278, L279, D307, R383 and V384 of a human T1R2 and a combination thereof and wherein a test entity suitable to interact with the first

interacting site of the chemosensory receptor is indicative of a candidate of a chemosensory receptor ligand enhancer.

24. The method of claim 1, wherein the first interacting site includes an interacting residue selected from the group consisting of amino acid S40, S144, Y103, D142, P277 of a human T1R2 and a combination thereof wherein a test entity suitable to interact with the first interacting site of the chemosensory receptor is indicative of a candidate of an enhancer for sucrose or sucralose.

25. The method of claim 1, wherein the test entity is a designed compound structure.

26. The method of claim 1, wherein the chemosensory receptor ligand is a sweet flavor entity selected from the group consisting of cyclamic acid, mogroside, tagatose, maltose, galactose, mannose, sucrose, fructose, lactose, aspartame, aspartame derivatives, neotame, saccharin, sucralose, acesulfame K, glucose, erythritol, D-tryptophan, glycine, mannitol, sorbitol, maltitol, lactitol, isomalt, hydroganeted glucose syrup (HGS), hydrogenated starch hydrolyzate (HSH), stevioside, rebaudioside A, sweet Ste*via*-based glycosides, alitame, carrelame, guanidine-based sweeteners, tagatose, xylitol, and high fructose corn syrup.

27. A method of screening for a candidate of a chemosensory receptor modifier comprising

determining whether a test entity is suitable to interact with a chemosensory receptor *via* an interacting site within the Venus flytrap domain of the chemosensory receptor,

wherein the interacting site includes an interacting residue selected from the group consisting of N143, S144, I167, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, P185, T184, T326, E302, V384, A305, I325, I306, D307, E382, I279, I67, V66, V309, S303, T242, F103, Q328, and S168 of a human T1R2 and a combination thereof,

wherein a test entity suitable to interact with the interacting site of the chemosensory receptor is indicative of a candidate of a chemosensory receptor modifier.

28. The method of claim 27, wherein the interacting site includes an interacting residue selected from the group consisting of amino acid N143, S144, and I167 of a human T1R2 and a combination thereof.

29. The method of claim 27, wherein the interacting site includes an interacting residue selected from the group consisting of amino acid S40, S144, Y103, D142, and P277 of a human T1R2 and a combination thereof.

30. The method of claim 27, wherein the interacting site includes an interacting residue selected from the group consisting of I167, P185, T184, T326, E302, V384, A305, I325, I306, R383, D307, E382, D278, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, and S168 of a human T1R2 and a combination thereof.

31. The method of claim 27, wherein the interacting site is in the T1R2 Venus flytrap domain.

32. The method of claim 27, wherein the interacting site is in the T1R2 Venus flytrap domain and identified in the presence of T1R3 Venus flytrap domain.

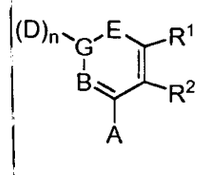
33. The method of claim 27, wherein the determination is carried out *in silico*.

34. The method of claim 27, wherein the test entity is a designed compound structure.

35. A chemosensory receptor ligand modifier identified by the method of claim 1.

36. A chemosensory receptor modifier identified by the method of claim 27.

37. A chemosensory receptor ligand enhancer identified by the method of claim 1 and having structural Formula (I):



(I)

or a tautomer, salt, solvate, and/or ester thereof, wherein:

G forms a single bond with either D or E and a double bond with the other of D or E;

R^1 is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, $-NO_2$, $-OR^3$, $-S(O)_aR^3$, $-NR^3R^4$, $-CONR^3R^4$, $-CO_2R^3$, $-NR^3CO_2R^4$, $-NR^3CONR^4R^5$, $-NR^3CSNR^4R^5$, $-NR^3C(=NH)NR^4R^5$, $-SO_2NR^3R^4$, $-NR^4SO_2R^3$, $-NR^3SO_2NR^4R^5$, $-B(OR^3)(OR^4)$, $-P(O)(OR^3)(OR^4)$ or $-P(O)(R^3)(OR^4)$;

R^2 is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, $-NO_2$, $-OR^6$, $-S(O)_bR^6$, $-NR^6R^7$, $-CONR^6R^7$, $-CO_2R^6$, $-NR^6CO_2R^7$, $-NR^6CONR^7R^8$, $-NR^6CSNR^7R^8$, $-NR^6C(=NH)NR^7R^8$, $-SO_2NR^5R^6$, $-NR^5SO_2R^6$, $-NR^5SO_2NR^6R^7$, $-B(OR^5)(OR^6)$, $-P(O)(OR^5)(OR^6)$, or $-P(O)(R^5)(OR^6)$; or alternatively, R^1 and R^2, together with the atoms to which they are bonded, form an aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring wherein the ring is optionally fused to another aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring;

with the proviso that R^1 and R^2 are not both hydrogen;

A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, halo, -CN, $-NO_2$, $-OR^9$, $-S(O)_cR^9$, $-NR^9COR^{10}$, $-NHOR^9$, $-NR^9R^{10}$, $-NOR^9$, $-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$, $-NR^9C(=NH)NR^{10}R^{11}$, $-B(OR^{10})(OR^{11})$, $-P(O)(OR^{10})(OR^{11})$ or $-P(O)(R^{10})(OR^{11})$;

B is -N- or $-C(R^{12})-$;

R^{12} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, $-NR^{13}R^{14}$, -CN, $-OR^{13}$, $-S(O)_dR^{13}$, $-CO_2R^{13}$ or $-CONR^{13}R^{14}$;

G is -C- or $-S(O)_2-$;

provided that when G is $-S(O)_2-$, then G forms a single bond with E;

when the bond between D and G is a single bond, then D is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, $-OR^{15}$, -NH-OR^{15}, $-S(O)_eR^{15}$, $-NR^{15}R^{16}$, -NH-NHR^{15}, $-CO_2R^{15}$, or $-CONR^{15}R^{16}$;

when G forms a double bond with D, then D is =O, =S , =N-OR^{15}, or =N-NHR^{15};

n is 0 when G is $-S(O)_2-$, and n is 1 when G is -C-;

E is $-NR^{17}-$, -N- or $-C(R^{18})-$;

provided that E is $-NR^{17}-$ only when G forms a single bond with E;

R^{17} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl or $-CO_2R^{19}$;

R^{18} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, $-NR^{20}R^{21}$, -CN, $-OR^{20}$, $-S(O)_fR^{20}$, $-CO_2R^{20}$ or $-CONR^{20}R^{21}$;

a, b, c, d, e and f are independently 0, 1 or 2; and

R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{13}, R^{14}, R^{15}, R^{16}, R^{18}, R^{20}, and R^{21} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl; or alternatively, R^3 and R^4, R^4 and R^5, R^6 and R^7, R^7 and R^8, R^9 and R^{10}, R^{10} and R^{11}, R^{13} and R^{14}, R^{15} and R^{16}, or R^{20} and R^{21}, together with the atoms to which they are bonded, form a cycloheteroalkyl or substituted cycloheteroalkyl ring.

38. A method of modulating the activity of a chemosensory receptor ligand comprising contacting a chemosensory receptor ligand modifier with a cell containing T1R2 Venus flytrap domain in the presence of a chemosensory receptor ligand, wherein the chemosensory receptor ligand modifier interacts with an interacting site of the chemosensory receptor.

39. The method of claim 38, wherein the interacting site of the chemosensory receptor includes an interacting residue selected from the group consisting of amino acid N143, S144, and I167 of a human T1R2 and a combination thereof.

40. The method of claim 38, wherein the interacting site of the chemosensory receptor includes an interacting residue selected from the group consisting of amino acid S40, S144, S165, Y103, D142, and P277 of a human T1R2 and a combination thereof.

41. The method of claim 38, wherein the interacting site of the chemosensory receptor includes an interacting residue selected from the group consisting of amino acid K65, R383, D307, E302, and D278 of a human T1R2 and a combination thereof.

42. The method of claim 38, wherein the interacting site of the chemosensory receptor includes an interacting residue selected from the group consisting of amino acid I167, P185, T184, T326, E302, V384, A305, I325, I306, R383, D307, E382, D278, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, and S168 of a human T1R2 and a combination thereof.

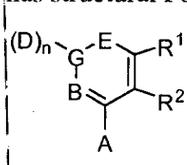
43. The method of claim 38, wherein the interacting site includes an interacting residue selected from the group consisting of amino acid N143, S144, I167, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, P185, T184, T326, E302, V384, A305, I325, I306, D307, E382, I279, I67, V66, V309, S303, T242, F103, Q328, and S168 of a human T1R2 and a combination thereof.

44. The method of claim 38, wherein the interacting site includes a group of interacting residues of K65, D278, L279, D307, R383, and V384 of a human T1R2 and wherein the chemosensory receptor ligand modifier enhances the activity of a chemosensory receptor ligand.

45. The method of claim 38, wherein the interacting site includes a group of interacting residues of S40, S144, Y103, D142, and P277 of a human T1R2 and wherein the chemosensory receptor ligand is selected from the group consisting of sucrose and sucralose.

46. The method of claim 38, wherein the chemosensory receptor ligand modifier stabilizes a close conformation within T1R2 Venus flytrap domain formed by the interaction between the chemosensory receptor ligand and the chemosensory receptor.

47. The method of claim 38, wherein the chemosensory receptor ligand modifier is a chemosensory receptor ligand enhancer and has structural Formula (I):



(I)

or a tautomer, salt, solvate, and/or ester thereof, wherein:

G forms a single bond with either D or E and a double bond with the other of D or E;

R^1 is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, $-NO_2$, $-OR^3$, $-S(O)_aR^3$, $-NR^3R^4$, $-CONR^3R^4$, $-CO_2R^3$, $-NR^3CO_2R^4$, $-NR^3CONR^4R^5$, $-NR^3CSNR^4R^5$, $-NR^3C(=NH)NR^4R^5$, $-SO_2NR^3R^4$, $-NR^4SO_2R^3$, $-NR^3SO_2NR^4R^5$, $-B(OR^3)(OR^4)$, $-P(O)(OR^3)(OR^4)$ or $-P(O)(R^3)(OR^4)$;

R^2 is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, $-NO_2$, $-OR^6$, $-S(O)_bR^6$, $-NR^6R^7$, $-CONR^6R^7$, $-CO_2R^6$, $-NR^6CO_2R^7$, $-NR^6CONR^7R^8$,

$-NR^6CSNR^7R^8$, $-NR^6C(=NH)NR^7R^8$, $-SO_2NR^5R^6$, $-NR^5SO_2R^6$, $-NR^5SO_2NR^6R^7$, $-B(OR^5)(OR^6)$, $-P(O)(OR^5)(OR^6)$, or $-P(O)(R^5)(OR^6)$; or alternatively, R^1 and R^2, together with the atoms to which they are bonded, form an aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring wherein the ring is optionally fused to another aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring;

with the proviso that R^1 and R^2 are not both hydrogen;

A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, halo, -CN, $-NO_2$, $-OR^9$, $-S(O)_cR^9$, $-NR^9COR^{10}$, $-NHOR^9$, $-NR^9R^{10}$, $-NOR^9$, $-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$, $-NR^9C(=NH)NR^{10}R^{11}$, $-B(OR^{10})(OR^{11})$, $-P(O)(OR^{10})(OR^{11})$ or $-P(O)(R^{10})(OR^{11})$;

B is -N- or $-C(R^{12})-$;

R^{12} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, $-NR^{13}R^{14}$, -CN, $-OR^{13}$, $-S(O)_dR^{13}$, $-CO_2R^{13}$ or $-CONR^{13}R^{14}$;

G is -C- or $-S(O)_2-$;

provided that when G is $-S(O)_2-$, then G forms a single bond with E;

when the bond between D and G is a single bond, then D is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, $-OR^{15}$, $-NH-OR^{15}$, $-S(O)_eR^{15}$, $-NR^{15}R^{16}$, $-NH-NHR^{15}$, $-CO_2R^{15}$, or $-CONR^{15}R^{16}$;

when G forms a double bond with D, then D is =O, =S , $=N-OR^{15}$, or $=N-NHR^{15}$;

n is 0 when G is $-S(O)_2-$, and n is 1 when G is -C-;

E is $-NR^{17}-$, -N- or $-C(R^{18})-$;

provided that E is $-NR^{17}-$ only when G forms a single bond with E;

R^{17} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl,

substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl or $-CO_2R^{19}$;

R^{18} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, $-NR^{20}R^{21}$, -CN, $-OR^{20}$, $-S(O)_fR^{20}$, $-CO_2R^{20}$ or $-CONR^{20}R^{21}$;

a, b, c, d, e and f are independently 0, 1 or 2; and

R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{13}, R^{14}, R^{15}, R^{16}, R^{18}, R^{20}, and R^{21} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl; or alternatively, R^3 and R^4, R^4 and R^5, R^6 and R^7, R^7 and R^8, R^9 and R^{10}, R^{10} and R^{11}, R^{13} and R^{14}, R^{15} and R^{16}, or R^{20} and R^{21}, together with the atoms to which they are bonded, form a cycloheteroalkyl or substituted cycloheteroalkyl ring.

48. The method of claim 38, wherein the cell contains T1R2 Venus flytrap domain within a GPCR pathway.

49. The method of claim 38, wherein the chemosensory receptor ligand modifier is provided in a comestible composition.

50. The method of claim 38, wherein the chemosensory receptor ligand modifier is provided in a medicinal composition.

51. The method of claim 38, wherein the chemosensory receptor ligand modifier is provided in a food or beverage product.

52. A chemosensory receptor ligand modifier, wherein in the presence of a chemosensory receptor ligand it interacts with T1R2 Venus flytrap domain *via* at least three interacting residues selected from the group consisting of N143, S144, I167, S40, S144, S165, Y103, D142, P277,

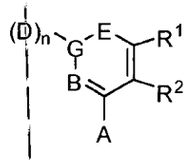
K65, R383, D307, E302, D278, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, and S168 of a human T1R2.

53. The chemosensory receptor ligand modifier of claim 52, wherein it interacts with T1R2 Venus flytrap domain *via* a group of amino acids selected from the group consisting of 1) N143, S144, and I167 of a human T1R2, 2) S40, S144, S165, Y103, D142, P277 or a human T1R2, 3) K65, R383, D307, E302, and D278 of a human T1R2, 4) I167, P185, T184, T326, E302, V384, A305, I325, I306, R383, D307, E382, D278, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, and S168 of a human T1R2, and 5) N143, S144, I167, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, and S168 of a human T1R2.

54. The chemosensory receptor ligand modifier of claim 52, wherein it interacts with T1R2 Venus flytrap domain *via* a group of amino acids K65, D278, L279, D307, R383, and V384 of a human T1R2 and wherein it enhances the activity of a chemosensory receptor ligand.

55. The chemosensory receptor ligand modifier of claim 52, wherein it interacts with T1R2 Venus flytrap domain *via* a group of amino acids of S40, S144, Y103, D142, P277 of a human T1R2 in the presence of sucrose or sucralose and wherein it enhances the activity of sucrose or sucralose.

56. The chemosensory receptor ligand modifier of claim 52 is a compound having structural Formula (I):



(I)

or a tautomer, salt, solvate, and/or ester thereof, wherein:

G forms a single bond with either D or E and a double bond with the other of D or E;

R^1 is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl,

substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, -NO_2, -OR^3, -$S(O)_aR^3$, -NR^3R^4, -$CONR^3R^4$, -CO_2R^3, -$NR^3CO_2R^4$, -$NR^3CONR^4R^5$, -$NR^3CSNR^4R^5$, -$NR^3C(=NH)NR^4R^5$, -$SO_2NR^3R^4$, -$NR^4SO_2R^3$, -$NR^3SO_2NR^4R^5$, -$B(OR^3)(OR^4)$, -$P(O)(OR^3)(OR^4)$ or -$P(O)(R^3)(OR^4)$;

R^2 is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, -NO_2, -OR^6, -$S(O)_bR^6$, -NR^6R^7, -$CONR^6R^7$, -CO_2R^6, -$NR^6CO_2R^7$, -$NR^6CONR^7R^8$, -$NR^6CSNR^7R^8$, -$NR^6C(=NH)NR^7R^8$, -$SO_2NR^5R^6$, -$NR^5SO_2R^6$, -$NR^5SO_2NR^6R^7$, -$B(OR^5)(OR^6)$, -$P(O)(OR^5)(OR^6)$, or -$P(O)(R^5)(OR^6)$; or alternatively, R^1 and R^2, together with the atoms to which they are bonded, form an aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring wherein the ring is optionally fused to another aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring;

with the proviso that R^1 and R^2 are not both hydrogen;

A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, halo, -CN, -NO_2, -OR^9, -$S(O)_cR^9$, -NR^9COR^{10}, -$NHOR^9$, -NR^9R^{10}, -NOR^9, -$CONR^9R^{10}$, -CO_2R^9, -$NR^9CO_2R^{10}$, -$NR^9CONR^{10}R^{11}$, -$NR^9CSNR^{10}R^{11}$, -$NR^9C(=NH)NR^{10}R^{11}$, -$B(OR^{10})(OR^{11})$, -$P(O)(OR^{10})(OR^{11})$ or -$P(O)(R^{10})(OR^{11})$;

B is -N- or -$C(R^{12})$-;

R^{12} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -$NR^{13}R^{14}$, -CN, -OR^{13}, -$S(O)_dR^{13}$, -CO_2R^{13} or -$CONR^{13}R^{14}$;

G is -C- or -$S(O)_2$-;

provided that when G is -$S(O)_2$-, then G forms a single bond with E;

when the bond between D and G is a single bond, then D is hydrogen, alkyl,

substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, $-OR^{15}$, $-NH-OR^{15}$, $-S(O)_eR^{15}$, $-NR^{15}R^{16}$, $-NH-NHR^{15}$, $-CO_2R^{15}$, or $-CONR^{15}R^{16}$;

when G forms a double bond with D, then D is =O, =S , $=N-OR^{15}$, or $=N-NHR^{15}$;

n is 0 when G is $-S(O)_2-$, and n is 1 when G is -C-;

E is $-NR^{17}-$, -N- or $-C(R^{18})-$;

provided that E is $-NR^{17}-$ only when G forms a single bond with E;

R^{17} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl or $-CO_2R^{19}$;

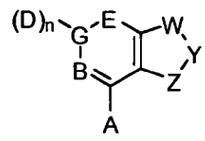
R^{18} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, $-NR^{20}R^{21}$, -CN, $-OR^{20}$, $-S(O)_fR^{20}$, $-CO_2R^{20}$ or $-CONR^{20}R^{21}$;

a, b, c, d, e and f are independently 0, 1 or 2; and

R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{13}, R^{14}, R^{15}, R^{16}, R^{18}, R^{20}, and R^{21} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl; or alternatively, R^3 and R^4, R^4 and R^5, R^6 and R^7, R^7 and R^8, R^9 and R^{10}, R^{10} and R^{11}, R^{13} and R^{14}, R^{15} and R^{16}, or R^{20} and R^{21}, together with the atoms to which they are bonded, form a cycloheteroalkyl or substituted cycloheteroalkyl ring.

57. The compound of claim 56, wherein R^1 and R^2, together with the atoms to which they are bonded, form an aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring where the ring is optionally fused to another aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring.

58. The compound of claim 56, having structural Formula (II),



(II)

wherein:

Y forms a single bond with either W or Z and a double bond with the other of W or Z;

W is $-C(R^{24})-$, -S-, -N-, $-N(R^{25})-$, or -O-;

Y is $-C(R^{26})-$ or -N-;

Z is $-C(R^{27})-$, -S-, -N-, $-N(R^{28})-$, or -O-;

R^{24} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, $-NO_2$, $-OR^{29}$, $-S(O)_gR^{29}$, $-NR^{29}R^{30}$, $-CONR^{29}R^{30}$, $-CO_2R^{29}$, $-SO_2NR^{29}R^{30}$, $-NR^{29}SO_2R^{30}$, $-B(OR^{29})(OR^{30})$, $-P(O)(OR^{29})(OR^{30})$ or $-P(O)(R^{29})(OR^{30})$;

R^{26} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, halo, -CN, $-NO_2$, $-OR^{31}$, $-S(O)_hR^{31}$, $-OCOR^{31}$, $-NR^{31}R^{32}$, $-CONR^{31}R^{32}$, $-CO_2R^{31}$, $-SO_2NR^{31}R^{32}$, $-NR^{31}SO_2R^{32}$, $-B(OR^{31})(OR^{32})$, $-P(O)(OR^{31})(OR^{32})$ or $-P(O)(R^{31})(OR^{32})$;

R^{27} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, halo, -CN, $-NO_2$, $-OR^{33}$, $-S(O)_iR^{33}$, $-OCOR^{33}$, $-NR^{33}R^{34}$, $-CONR^{33}R^{34}$, $-COR^{33}$, $-CO_2R^{33}$, $-SO_2NR^{33}R^{34}$, $-NR^{33}SO_2R^{34}$, $-B(OR^{33})(OR^{34})$, $-P(O)(OR^{33})(OR^{34})$ or $-P(O)(R^{33})(OR^{34})$ or alternatively R^{24} and R^{26} or R^{26} and R^{27} together with the atoms to which they are bonded form a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring;

g, h and i are independently 0 or 1;

R^{25} and R^{28} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl; and

R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, and R^{34} are independently hydrogen, alkyl, substituted alkyl, aryl,

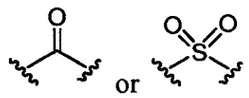
substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl; or alternatively R^{29} and R^{30}, R^{31} and R^{32} or R^{33} and R^{34} together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring; and

with the following provisos:

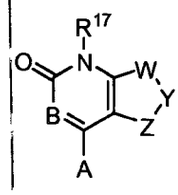
(a) when W is -O- or -S- or -NR^{25}, then Z is –$C(R^{27})$ or -N-; and

(b) when Z is -O- or -S- or -NR^{28}, then W is -$C(R^{24})$ or -N-.

59. The compound of claim 58, wherein $(D)_n$-G is



60. The compound of claim 58, having structural Formula (IIa):



(IIa)

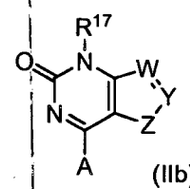
with the following provisos:

(a) when W is -O- or -S- or -NR^{25}, then Z is –$C(R^{27})$ or -N-;

(b) when Z is -O- or -S- or -NR^{28}, then W is -$C(R^{24})$ or -N-; and

(c) when B is -N-, then A is not halo.

61. The compound of claim 60, having structural Formula (IIb):



(IIb)

wherein:

W is -$C(R^{24})$- or -N-;

Y is -$C(R^{26})$- or -N-; and

Z is -S-, -N(R^{28})- or -O-.

62. The compound of claim 61, wherein

W is -C(R^{24})-, and

Y is -C(R^{26})-.

63. The compound of claim 62, wherein

R^{24} is hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, -CN, -NO_2, -OR^{29}, -$S(O)_gR^{29}$, -$OCOR^{29}$, -$NR^{29}R^{30}$, -$CONR^{29}R^{30}$ or -CO_2R^{29}; and

R^{26} is hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, -CN, -NO_2, -OR^{31}, -$OCOR^{31}$, -$S(O)_hR^{31}$, -$NR^{31}R^{32}$, -$CONR^{31}R^{32}$or -CO_2R^{31}.

64. The compound of claim 63, wherein

R^{24} is hydrogen, -CF_3, alkyl or substituted alkyl; and

R^{26} is hydrogen, -CF_3, alkyl or substituted alkyl.

65. The compound of claim 62, wherein

A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, -CN, -NO_2, -$S(O)_cR^9$, -NR^9R^{10}, -$CONR^9R^{10}$, -CO_2R^9 or -$NR^9CO_2R^{10}$;

R^{17} is hydrogen, alkyl, substituted alkyl, arylalkyl, or substituted arylalkyl;

R^{24} is hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, -CN, -NO_2, -OR^{29}, -$S(O)_gR^{29}$, -$OCOR^{29}$, -$NR^{29}R^{30}$, -$CONR^{29}R^{30}$ or -CO_2R^{29}; and

R^{26} is hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, -CN, -NO_2, -OR^{31}, -$S(O)_hR^{31}$, -$OCOR^{31}$, -$NR^{31}R^{32}$, -$CONR^{31}R^{32}$or -CO_2R^{31}.

66. The compound of claim 62, wherein

A is -NR^9COR^{10}, -$NHOR^9$, -NR^9R^{10}, -NOR^9, -$CONR^9R^{10}$, -CO_2R^9, -$NR^9CO_2R^{10}$, -OR^9, -$NR^9CONR^{10}R^{11}$, -$NR^9CSNR^{10}R^{11}$ or -$NR^9C(=NH)NR^{10}R^{11}$;

R^{17} is hydrogen, alkyl, substituted alkyl, arylalkyl, or substituted arylalkyl;

R^{24} is hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, -CN, -NO_2, -OR^{29}, -$S(O)_gR^{29}$, -$OCOR^{29}$, -$NR^{29}R^{30}$, -$CONR^{29}R^{30}$ or -CO_2R^{29}; and

R^{26} is hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, -CN, $-NO_2$, $-OR^{31}$, $-S(O)_hR^{31}$, $-OCOR^{31}$, $-NR^{31}R^{32}$, $-CONR^{31}R^{32}$or $-CO_2R^{31}$.

67. The compound of claim 66, wherein

A is -OH, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHOCH_3$, $-NOCH_3$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$ or $-CH_2NHC(O)CH_3$;

R^{17} is hydrogen, methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *t*-butyl, phenyl or benzyl;

R^{24} is hydrogen, $-CF_3$, methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl or *t*-butyl; and R^{26} is hydrogen, $-CF_3$, methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl or *t*-butyl.

68. The compound of claim 67, wherein

A is $-NH_2$,

R^{17} is hydrogen or methyl,

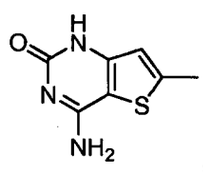
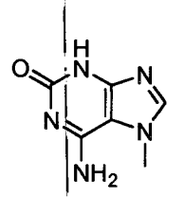
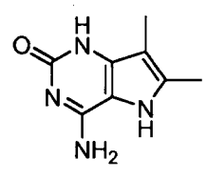
R^{24} is hydrogen, $-CF_3$, methyl or ethyl, and

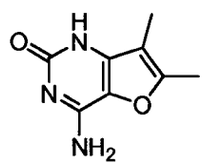
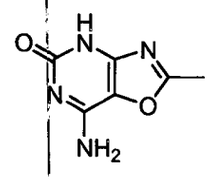
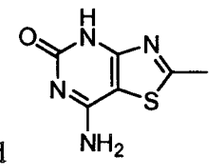
R^{26} is hydrogen, $-CF_3$, methyl or ethyl.

69. The compound of any of claims 62 to 68, wherein R^{28} is hydrogen, alkyl or arylalkyl.

70. The compound of any of claims 62 to 68, wherein R^{28} is hydrogen, methyl or benzyl.

71. The compound of claim 61 having structural formula selected from the group consisting of:

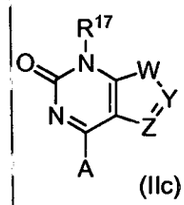






, and

;

or a tautomer, salt, solvate, and/or ester thereof.

72. The compound of claim 71, wherein the salt is hydrochloride or trifluoroacetate salt.

73. The compound of claim 60, having structural Formula (IIc):


(IIc)

wherein,

W is -S-, -N(R^{25})-, or -O-;

Y is -C(R^{26})- or -N-; and

Z is -C(R^{27})- or -N-.

74. The compound of claim 73, wherein

Y is -C(R^{26})-, and

Z is -C(R^{27})-.

75. The compound of claim 74, wherein

R^{27} is hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, -CN, -NO_2, -OR^{33}, -$S(O)_iR^{33}$, -$OCOR^{33}$, -$NR^{33}R^{34}$, -$CONR^{33}R^{34}$ or -CO_2R^{33}; and

R^{26} is hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, -CN, -NO_2, -$OR^{31,}$ -$S(O)_hR^{31,}$ -$OCOR^{31,}$ -$NR^{31}R^{32}$, -$CONR^{31}R^{32}$ or -CO_2R^{31}.

76. The compound of claim 74, wherein

R^{26} and R^{27} together with the atom to which they are bonded form a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring.

77. The compound of claim 74, wherein

A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, $-NR^9COR^{10}$, $-NHOR^9$, $-NOR^9$, $-OR^9$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$ or $-NR^9C(=NH)NR^{10}R^{11}$, -CN, $-NO_2$, $-S(O)_cR^9$, $-NR^9R^{10}$, $-C(O)NR^9R^{10}$, $-CO_2R^9$ or $-NR^9CO_2R^{10}$; and

R^{17} is hydrogen, alkyl, substituted alkyl, arylalkyl, or substituted arylalkyl.

78. The compound of claim 74, wherein

A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, $-NR^9COR^{10}$, $-NHOR^9$, $-NOR^9$, $-OR^9$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$ or $-NR^9C(=NH)NR^{10}R^{11}$, -CN, $-NO_2$, $-S(O)_cR^9$, $-NR^9R^{10}$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-CO_2R^9$ or $-NR^9CO_2R^{10}$;

R^{17} is hydrogen, alkyl, substituted alkyl, arylalkyl, or substituted arylalkyl;

R^{27} is hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, -CN, $-NO_2$, $-OR^{33}$, $-S(O)_iR^{33}$, $-OCOR^{33}$, $-NR^{33}R^{34}$, $-C(O)NR^{33}R^{34}$ or $-CO_2R^{33}$; and

R^{26} is hydrogen, alkyl, substituted alkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, -CN, $-NO_2$, $-OR^{31}$, $-S(O)_hR^{31}$, $-OC(O)R^{31}$, $-NR^{31}R^{32}$, $-C(O)NR^{31}R^{32}$or $-CO_2R^{31}$, or alternatively R^{26} and R^{27} together with the atom(s) to which they are bonded form a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring.

79. The compound of claim 78, wherein

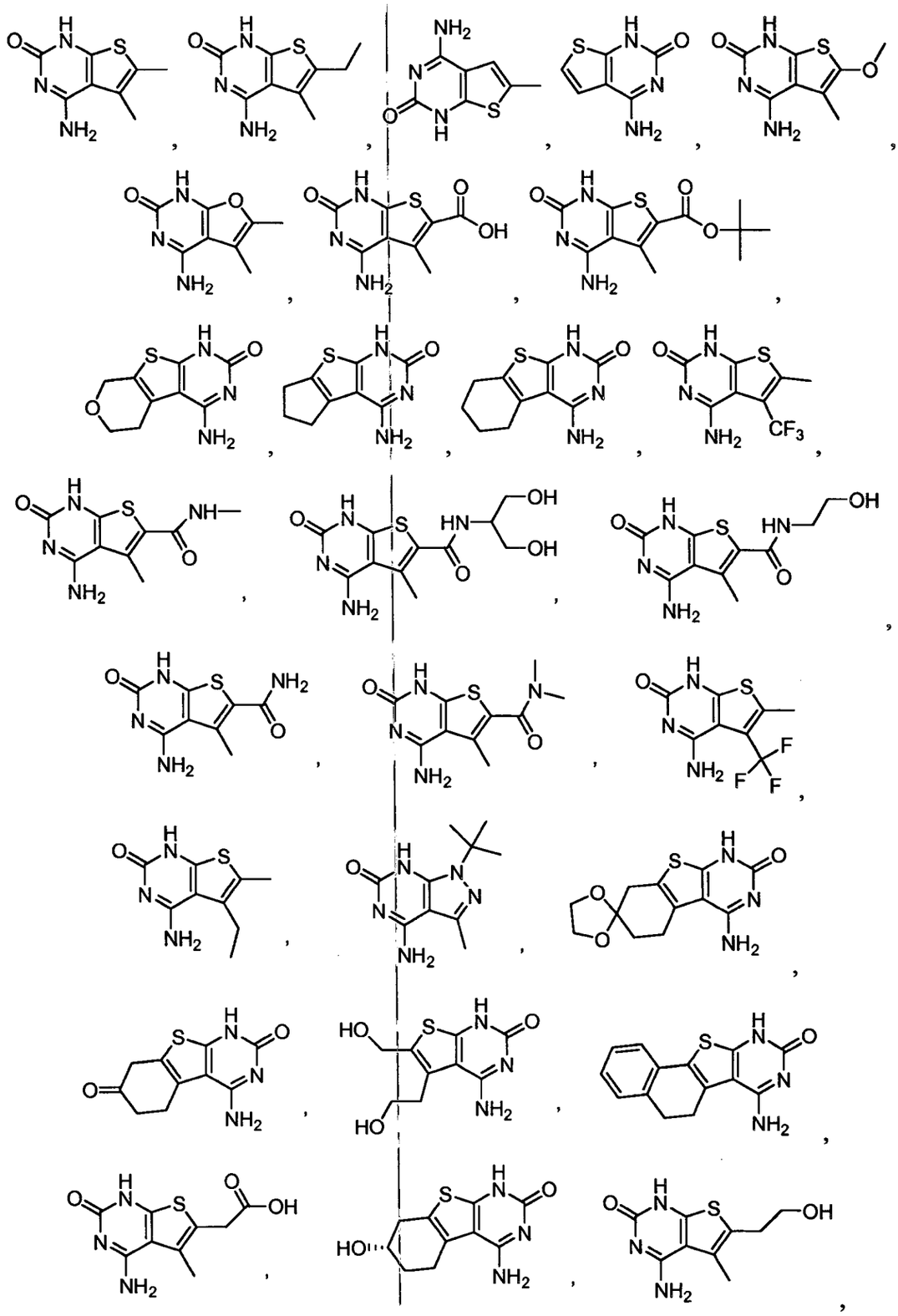
A is $-NH_2$;

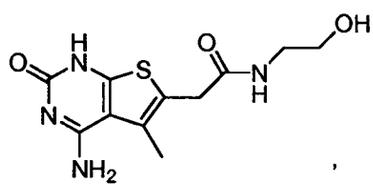
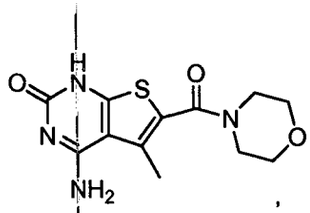
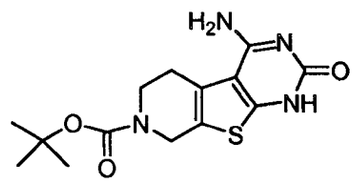
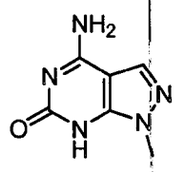
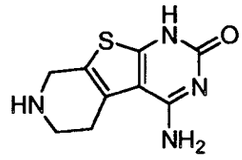
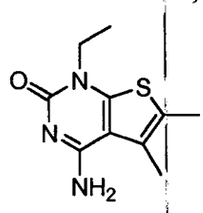
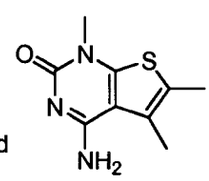
R^{17} is hydrogen, methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *t*-butyl, phenyl or benzyl;

R^{26} and R^{27} are independently hydrogen, alkanyl, substituted alkanyl, alkoxy, carboxylic acid, carboxylic acid amide, or carboxylic acid ester;

or alternatively, R^{26} and R^{27} together with the atom(s) to which they are bonded form a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring.

80. The compound of claim 73, having structural formula selected from the group consisting of:

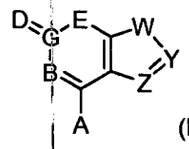



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, and

;

or a tautomer, salt, solvate, and/or ester thereof.

81. The compound of claim 80, wherein the salt is hydrochloride or trifluoroacetate salt.

82. The compound of claim 58, having structural Formula (IIe):


(IIe)

wherein,

G forms a single bond with E and a double bond with D;

B is -N-;

E is $-NR^{17}-$;

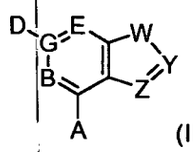
D is =S , $=N-OR^{15}$, or $=N-NHR^{15}$;

W is -S-, $-N(R^{25})-$ or -O-;

Y is $-C(R^{26})-$; and

Z is $-C(R^{27})-$.

83. The compound of claim 58, having structural Formula (IIf):



(IIf)

wherein,

G forms a double bond with E and a single bond with D;

B is -N-;

E is -N-;

D is $-OR^{15}$, $-NH-OR^{15}$, $-NH-NHR^{15}$, $-S(O)_eR^{15}$, or $-NR^{15}R^{16}$;

W is -S-, $-N(R^{25})-$ or -O-;

Y is $-C(R^{26})-$; and

Z is $-C(R^{27})-$.

84. The compound of claim 82 or 83, wherein A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, $-OR^9$, $-SR^9$, -CN, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$ or $-NR^9C(=NH)NR^{10}R^{11}$.

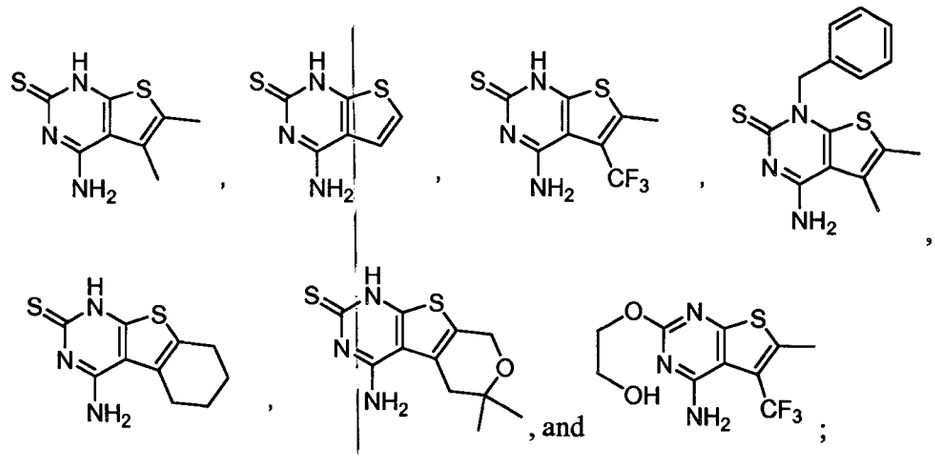
85. The compound of claim 84, wherein

R^{17} is hydrogen, alkyl, substituted alkyl, arylalkyl, or substituted arylalkyl;

R^{26} and R^{27} are independently hydrogen, alkanyl, substituted alkanyl, alkoxy;

or alternatively, R^{26} and R^{27} together with the atom(s) to which they are bonded form a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring.

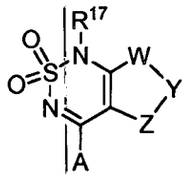
86. The compound of claim 82 or 83, having structural formula selected from the group consisting of



or a tautomer, salt, solvate, and/or ester thereof.

87. The compound of claim 86, wherein the salt is hydrochloride or trifluoroacetate salt.

88. The compound of claim 58, having structural Formula (IId):



(IId)

with the following provisos:

(a) when W is -O- or -S- or -NR^{25}, then Z is –$C(R^{27})$ or -N-; and

(b) when Z is -O- or -S- or -NR^{28}, then W is -$C(R^{24})$ or -N-.

89. The compound of claim 88, wherein

W is -S-, NR^{25}, -O-;

Y is -CR^{26}-;

Z is -$C(R^{27})$-; and

W and Y forms a single bond and Y and Z forms a double bond.

90. The compound of claim 88, wherein

W is -$C(R^{24})$-;

Y is -CR^{26}-;

Z is -S-, -NR^{28}-, -O-; and

W and Y forms a double bond and Y and Z forms a single bond.

91. The compound of claim 88, wherein

W is -S-, NR^{25}, -O-;

Y is -N-;

Z is -$C(R^{27})$-; and

W and Y forms a single bond and Y and Z forms a double bond.

92. The compound of claim 88, wherein

W is - NR^{25};

Y is -N-; and

Z is -$C(R^{27})$-; and

Y forms a single bond with each of W and a double bond with Z.

93. The compound of any of claims 88 to 92, wherein A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, -OR^9, -SR^9, -CN, -NR^9R^{10}, -$CONR^9R^{10}$, -CO_2R^9, -$NR^9CO_2R^{10}$, -$NR^9CONR^{10}R^{11}$, -$NR^9CSNR^{10}R^{11}$ or -$NR^9C(=NH)NR^{10}R^{11}$.

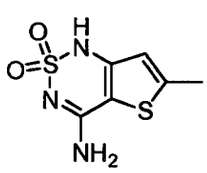
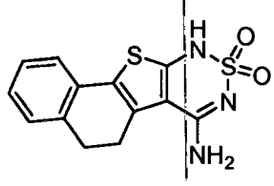
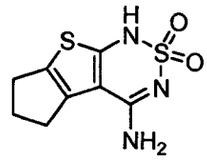
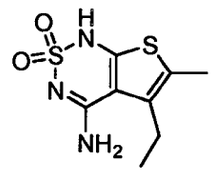
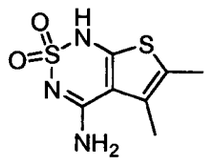
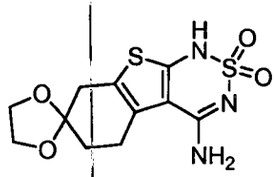
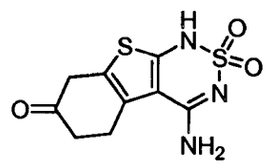
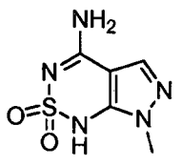
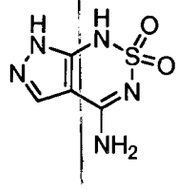
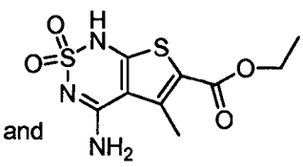
94. The compound of claim 93, wherein R^{17} is hydrogen.

95. The compound of claim 94, wherein

R^{26} and R^{27} are independently hydrogen, alkanyl, substituted alkanyl, alkoxy, carboxylic acid, carboxylic acid ester;

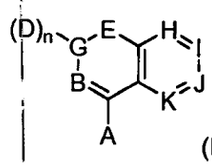
or alternatively, R^{26} and R^{27} together with the atom(s) to which they are bonded form a cycloalkyl or substituted cycloalkyl ring.

96. The compound of claim 88, having structural formula selected from the group consisting of:


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, and

;

or a tautomer, salt, solvate, and/or ester thereof.

97. The compound of claim 56 having structural Formula (III):


(III)

wherein:

H is -C(R^{35})- or -N-;

I is -C(R^{36}) or -N-;

J is -C(R^{37})- or -N-;

K is -C(R^{38})- or -N-;

R^{35} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, -NO_2, -OR^{39}, -$S(O)_jR^{39}$, -$OCOR^{39}$, -$NR^{39}R^{40}$, -$CONR^{39}R^{40}$, -CO_2R^{39}, -$SO_2NR^{39}R^{40}$, -$NR^{39}SO_2R^{40}$, -$B(OR^{39})(OR^{40})$, -$P(O)(OR^{39})(OR^{40})$ or -$P(O)(R^{39})(OR^{40})$;

R^{36} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, -NO_2, -OR^{41}, -$S(O)_kR^{41}$, -$OCOR^{41}$,

$-NR^{41}R^{42}$, $-CONR^{41}R^{42}$, $-CO_2R^{41}$, $-SO_2NR^{41}R^{42}$, $-NR^{41}SO_2R^{42}$, $-B(OR^{41})(OR^{42})$, $-P(O)(OR^{41})(OR^{42})$ or $-P(O)(R^{41})(OR^{42})$;

R^{37} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl ,-CN, $-NO_2$, $-OR^{43}$, $-S(O)_lR^{43}$, $-OCOR^{43}$, $-NR^{43}R^{44}$, $-CONR^{43}R^{44}$, $-CO_2R^{43}$, $-SO_2NR^{43}R^{44}$, $-NR^{43}SO_2R^{44}$, $-B(OR^{43})(OR^{44})$, $-P(O)(OR^{43})(OR^{44})$ or $-P(O)(R^{43})(OR^{44})$;

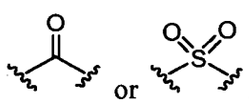
R^{38} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, $-NO_2$, $-OR^{45}$, $-S(O)_mR^{45}$, $-OCOR^{45}$, $-NR^{45}R^{46}$, $-CONR^{45}R^{46}$, $-COR^{45}$, $-CO_2R^{45}$, $-SO_2NR^{45}R^{46}$, $-NR^{45}SO_2R^{46}$, $-B(OR^{45})(OR^{46})$, $-P(O)(OR^{45})(OR^{46})$ or $-P(O)(R^{45})(OR^{46})$; or alternatively R^{36} and R^{37} or R^{37} and R^{38} taken together with the atom to which they are bonded, form a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, or substituted cycloheteroalkyl ring;

j, k, l and m are independently 0, 1 or 2; and

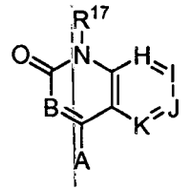
R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, and R^{46} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl or alternatively R^{39} and R^{40}, R^{41} and R^{42}, R^{43} and R^{44} or R^{45} and R^{46} together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

with the proviso that at most, two of H, I, J and K are -N-.

98. The compound of claim 97, wherein $(D)_n$-G is

 or .

99. The compound of claim 97, having structural Formula (IIIa):



(IIIa)

100. The compound of claim 99, wherein A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, $-OR^9$, $-NO_2$, $-S(O)_cR^9$, $-NHOR^9$, $-NR^9COR^{10}$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$, or $-NR^9C(=NH)NR^{10}R^{11}$.

101. The compound of claim 100, wherein A is -OH, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHOCH_3$, $-NOCH_3$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$ or $-CH_2NHC(O)CH_3$.

102. The compound of claim 99, wherein R^{17} is hydrogen, alkyl, substituted alkyl, arylalkyl, or substituted arylalkyl.

103. The compound of claim 102, wherein R^{17} is hydrogen, methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *t*-butyl, phenyl or benzyl.

104. The compound of claim 99, wherein

H is $-C(R^{35})-$;

I is $-C(R^{36})$;

J is $-C(R^{37})-$; and

K is $-C(R^{38})-$.

105. The compound of claim 99, wherein

A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, -CN, $-OR^9$, $-NO_2$, $-S(O)_cR^9$, $-NHOR^9$, $-NR^9COR^{10}$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$ or $-NR^9CO_2R^{10}$; and

R^{17} is hydrogen, alkyl, substituted alkyl, arylalkyl, or substituted arylalkyl.

106. The compound of claim 99, wherein

A is -OH, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHOCH_3$, $-NOCH_3$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$ or $-CH_2NHC(O)CH_3$; and

R^{17} is hydrogen, methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *t*-butyl, phenyl or benzyl.

107. The compound of claim 99, wherein

R^{35} is hydrogen, alkyl, substituted alkyl, halo, heteroalkyl, substituted heteroalkyl, -CN, $-NO_2$, $-OR^{39}$, $-S(O)_jR^{39}$, $-OCOR^{39}$, $-NR^{39}COR^{40}$, $-CONR^{39}R^{40}$, $-CO_2R^{39}$, $NR^{39}R^{40}$, $-SO_2NR^{39}R^{40}$, or-$NR^{39}SO_2R^{40}$;

R^{36} is hydrogen, alkyl, substituted alkyl, halo, heteroalkyl, substituted heteroalkyl, -CN, $-NO_2$, $-OR^{41}$, $-S(O)_jR^{41}$, $-OCOR^{41}$, $NR^{41}R^{42}$, $-NR^{41}COR^{42}$, $-CONR^{41}R^{42}$, $-CO_2R^{41}$, $-SO_2NR^{41}R^{42}$, or-$NR^{41}SO_2R^{42}$;

R^{37} is hydrogen, alkyl, substituted alkyl, halo, heteroalkyl, substituted heteroalkyl, -CN, $-NO_2$, $-OR^{43}$, $-S(O)_jR^{43}$, $-OCOR^{43}$, $NR^{43}R^{44}$, $-NR^{43}COR^{44}$, $-CONR^{43}R^{44}$, $-CO_2R^{43}$, $-SO_2NR^{43}R^{44}$, or $-NR^{43}SO_2R^{44}$; or alternatively R^{36} and R^{37}, together with the atoms to which they are bonded, form a cycloheteroalkyl or substituted cycloheteroalkyl ring; and

R^{38} is hydrogen, alkyl, substituted alkyl, halo, heteroalkyl, substituted heteroalkyl, -CN, $-NO_2$, $-OR^{45}$, $-S(O)_jR^{45}$, $-OCOR^{45}$, $NR^{45}R^{46}$, $-NR^{45}COR^{46}$, $-CONR^{45}R^{46}$, $-CO_2R^{45}$, $-SO_2NR^{45}R^{46}$, $-NR^{45}SO_2R^{46}$.

108. The compound of claim 107, wherein

R^{38} is hydrogen, alkanyl, substituted alkanyl, alkenyl, substituted alkenyl, cycloalkanyl, substituted cycloalkanyl, cycloalkenyl, substituted cyclcoalkenyl, halo, heteroalkyl, substituted heteroalkyl, -CN, $-NO_2$, $-OR^{45}$, $-S(O)_jR^{45}$, $-OCOR^{45}$, $NR^{45}R^{46}$, $-NR^{45}COR^{46}$, $-CONR^{45}R^{46}$, $-CO_2R^{45}$, $-SO_2NR^{45}R^{46}$, $-NR^{45}SO_2R^{46}$.

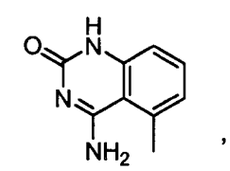
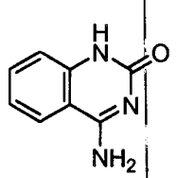
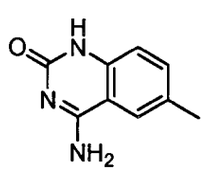
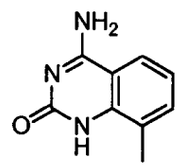
109. The compound of claim 107, wherein

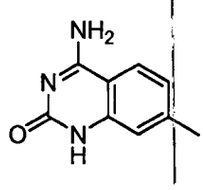
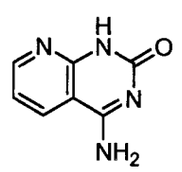
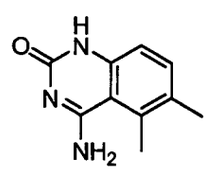
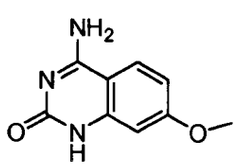
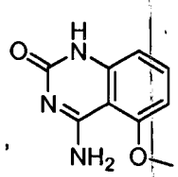
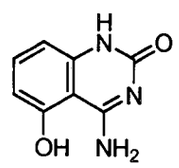
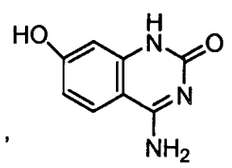
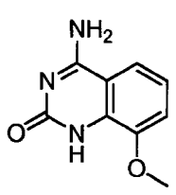
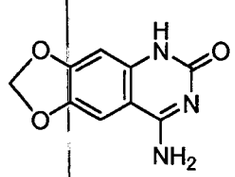
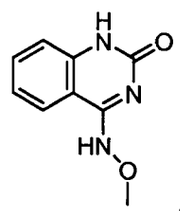
A is -NH_2,

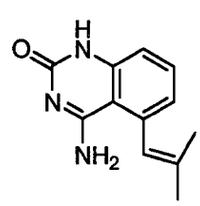
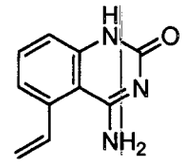
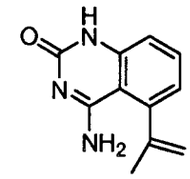
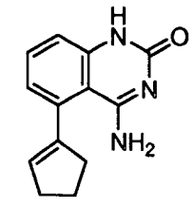
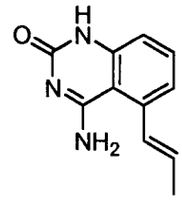
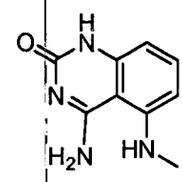
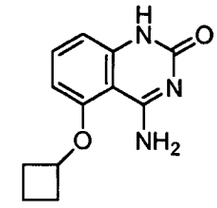
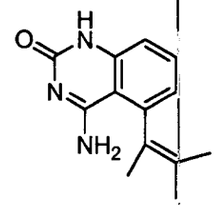
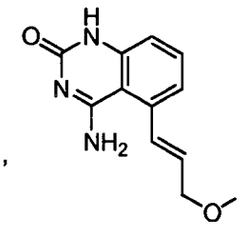
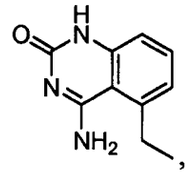
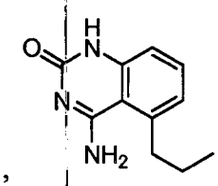
R^{17} is hydrogen, methyl, ethyl or benzyl; and

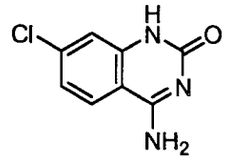
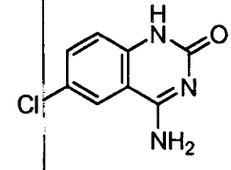
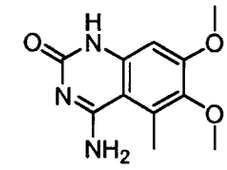
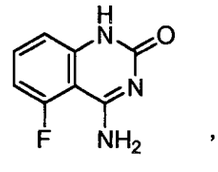
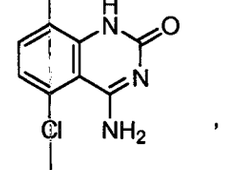
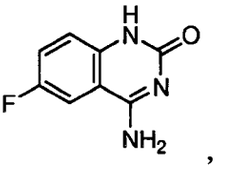
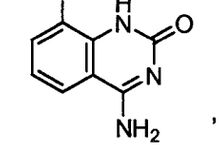
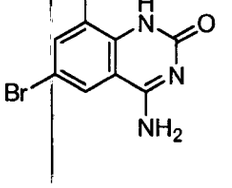
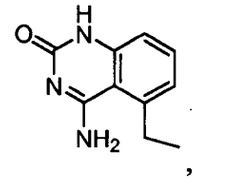
R^{35}, R^{36}, R^{37} and R^{38} are independently hydrogen, fluoro, chloro, bromo, methyl, trifluromethyl, ethyl, isopropyl, cyclopropyl, propenyl, methylpropenyl, butenyl, methylbutenyl, substituted propenyl, substituted methylpropenyl, substituted butenyl, substituted methylbutenyl, -NH-alkanyl, -NH-(substituted alkanyl), -OH, -OCH_3, -O-cycloalkanyl, –O-benzyl, -CO_2H.

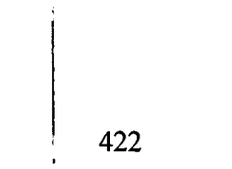
110. The compound of claim 99 having structural formula selected from the group consisting of


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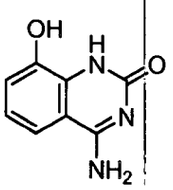
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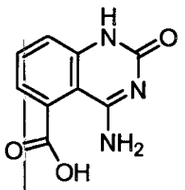
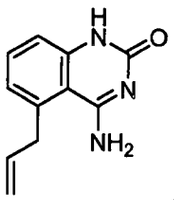
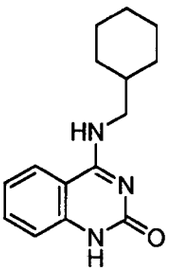
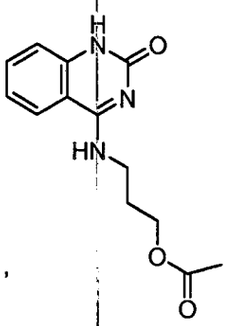
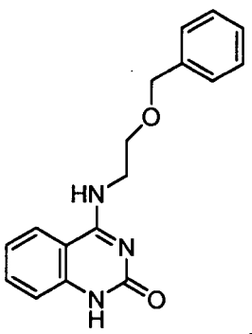
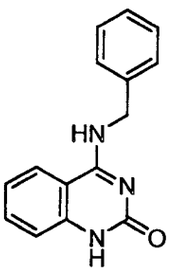
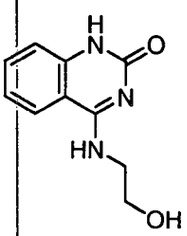
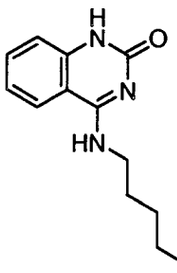
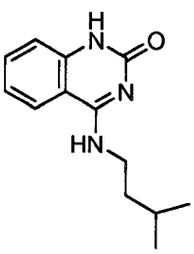
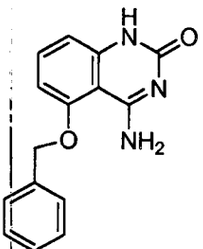
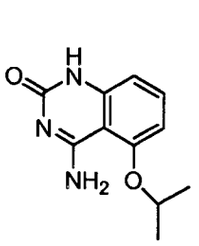

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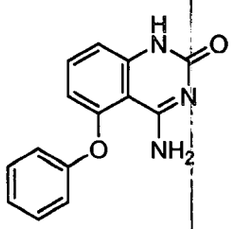
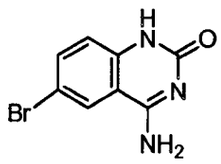
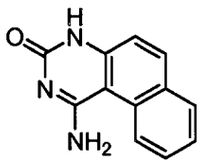
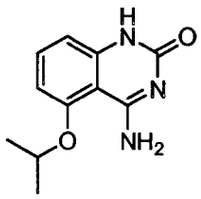
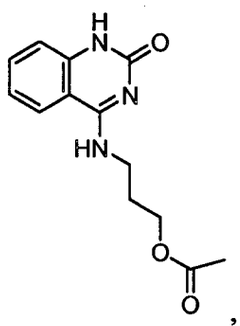
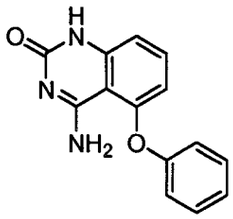
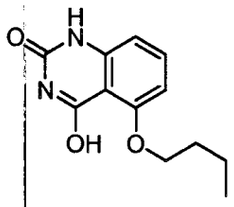
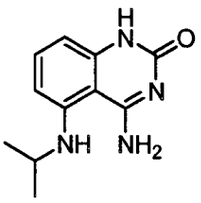
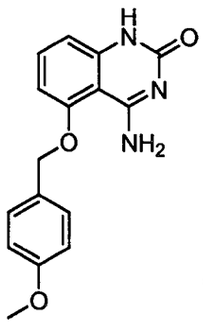
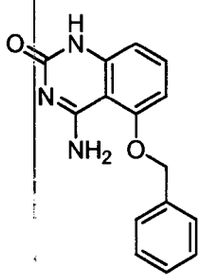
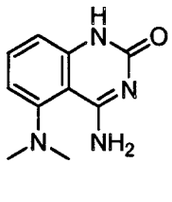
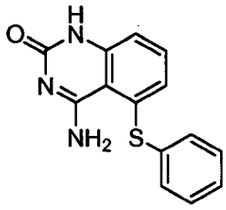
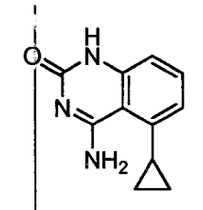
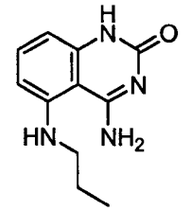
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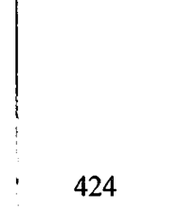
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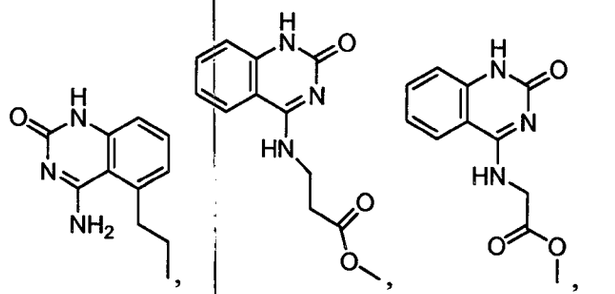



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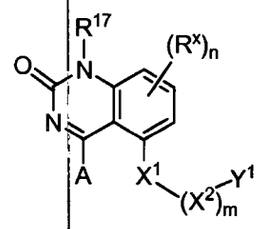


143 145 147 ;

or a tautomer, salt, solvate, and/or ester thereof.

111. The compound of claim 110, wherein the salt is hydrochloride or trifluoroacetate salt.

112. The compound of claim 99, having structural Formula (IIIa1):



(IIIa1)

wherein,

A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, $-OR^9$, $-NO_2$, $-S(O)_cR^9$, $-NOR^9$, $-NHOR^9$, $-NR^9COR^{10}$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$ or $-NR^9CO_2R^{10}$;

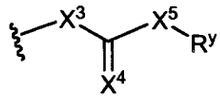
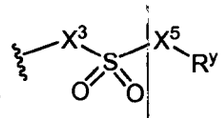
R^{17} is hydrogen, alkyl, substituted alkyl, arylalkyl, or substituted arylalkyl;

X^1 is $-CH_2-$, $-O-$, $-NR^9-$, $-S-$, $-S(O)-$, or $-S(O)_2-$;

X^2 is alkylene, substituted alkylene, heteroalkylene, or substituted heteroalkylene;

m is 0 or 1;

Y^1 is cycloheteroalkyl, substituted cycloheteroalkyl, or


, or

;

X^3 and X^5 are independently a covalent bond, –O– or $–NR^9–$;

X^4 is O, NR^9, N-OR^9, or S;

R^x is halo, -NO_2, -CN, -OH, -NH_2, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl;

n is 0, 1, 2, or 3;

R^y is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl, -NR^9R^{10}; and

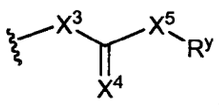
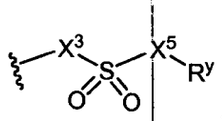
each R^9 and R^{10} is independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl;

with the proviso that when X^1 is –O– or –S–, and m is zero; then X^3 is not –O–.

113. The compound of claim 112, wherein

X^1 is $–CH_2-$; and

Y^1 is


, or

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114. The compound of claim 112, wherein

X^1 is –O–, $–NR^9–$, or –S–;

m is 0 or 1, and

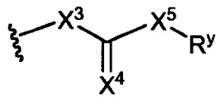
Y^1 is cycloheteroalkyl or substituted cycloheteroalkyl.

115. The compound of claim 112, wherein

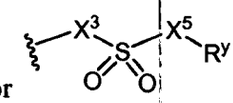
X^1 is –O–, $–NR^9–$, or –S–;

m is 1, and

Y^1 is



, or



.

116. The compound of any one of claims 112, 114, and 115, wherein

X^2 is methylene, ethylene, propylene, dimethylethylene, methylcyclopropylene, or cyclopropylmethylene.

117. The compound of any one of claims 112 to 116, wherein A is hydrogen, alkyl, substituted alkyl, -CN, $-OR^9$, $-NO_2$, $-S(O)_cR^9$, $-NOR^9$, $-NHOR^9$, $-NR^9COR^{10}$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$ or $-NR^9CO_2R^{10}$.

118. The compound of any one of claims 112 to 116, wherein R^{17} is hydrogen, alkyl, substituted alkyl.

119. The compound of claim 112, wherein Y^1 is cycloheteroalkyl or substituted cycloheteroalkyl.

120. The compound of claim 119, wherein Y^1 is piperidinyl, substituted piperidinyl, tetrahydrofuranyl, subsitituted tetrahydrofuranyl, tetrahydropyranyl, subsitituted tetrahydropyranyl, dihydrofuranyl, substituted dihydrofuranyl, pyrrolidinyl, substituted pyrrolidinyl, oxetanyl, or substituted oxetanyl.

121. The compound of claim 119 or 120, wherein the substituted cycloheteroalkyl comprises one or more substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, $-OR^9$, $-NO_2$, $-S(O)_cR^9$, $-NOR^9$, $-NHOR^9$, $-NR^9COR^{10}$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$, and $-NR^9CO_2R^{10}$.

122. The compound of claim 112, wherein X^4 is O.

123. The compound of claim 112, wherein $-X^3-C(X^4)-X^5-$ is –C(O)-, -C(O)-NH-, -NH-C(O)-, -NH-C(O)-NH-, -C(O)-O-, -O-C(O)-, -O-C(O)-O-, -NH-C(O)-O-, -O-C(O)-NH-, –C(NH)-, -C(NH)-NH-, -NH-C(NH)-, -NH-C(NH)-NH-, -C(NH)-O-, -O-C(NH)-, -O-C(NH)-O-, -NH-C(NH)-O-, -O-C(NH)-NH-, -C(N-OH)-, or -C(S)-.

124. The compound of claim 112, wherein

A is hydrogen, alkyl, substituted alkyl, or $-NR^9R^{10}$;

R^{17} is hydrogen; and

Y^1 is piperidinyl, substituted piperidinyl, tetrahydrofuranyl, subsitituted tetrahydrofuranyl, tetrahydropyranyl, subsitituted tetrahydropyranyl, dihydrofuranyl, substituted dihydrofuranyl, pyrrolidinyl, substituted pyrrolidinyl, oxetanyl, or substituted oxetanyl.

125. The compound of claim 112, wherein

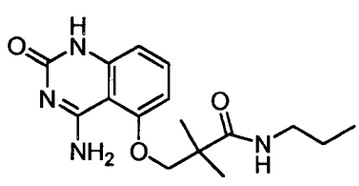
A is hydrogen, alkyl, substituted alkyl, or $-NR^9R^{10}$;

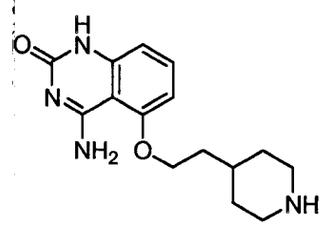
R^{17} is hydrogen;

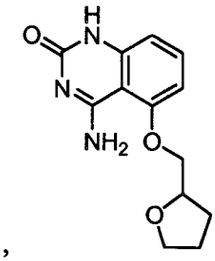
Y^1 is $-X^3-C(X^4)-X^5-$; and

$-X^3-C(X^4)-X^5-$ is –C(O)-, -C(O)-NH-, -NH-C(O)-, -NH-C(O)-NH-, -C(O)-O-, -O-C(O)-, -O-C(O)-O-, -NH-C(O)-O-, -O-C(O)-NH-, –C(NH)-, -C(NH)-NH-, -NH-C(NH)-, -NH-C(NH)-NH-, -C(NH)-O-, -O-C(NH)-, -O-C(NH)-O-, -NH-C(NH)-O-, -O-C(NH)-NH-, -C(N-OH)-, or -C(S)-.

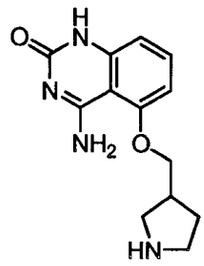
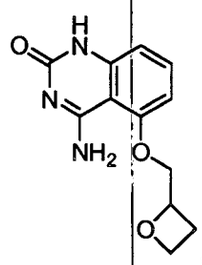
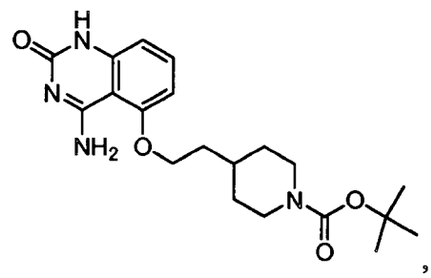
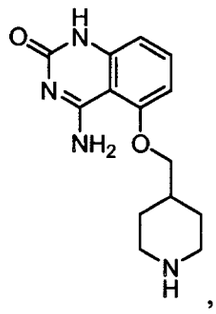
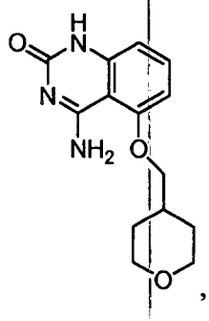
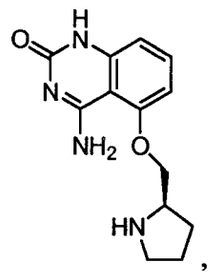
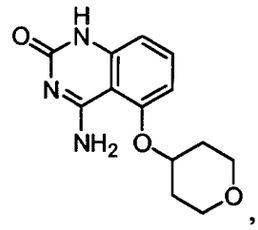
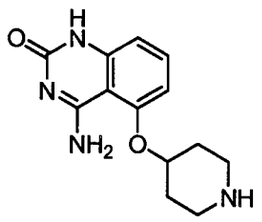
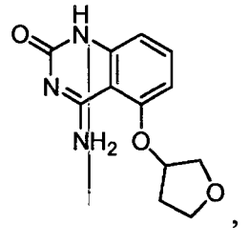
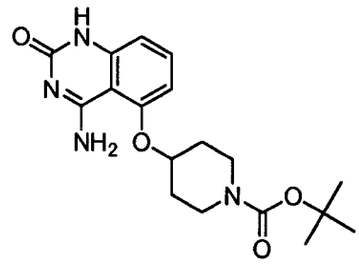
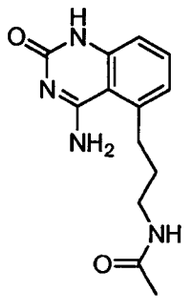
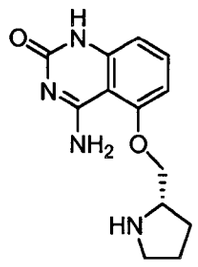
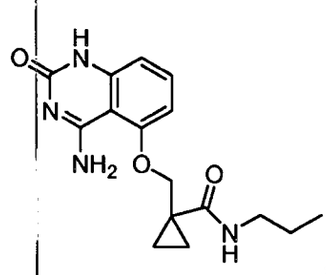
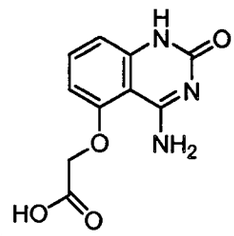
126. The compound of claim 112, having structural formula selected from the group consisting of



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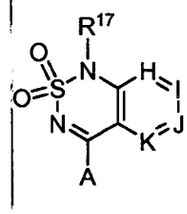
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or a tautomer, salt, solvate, and/or ester thereof.

127. The compound of claim 122, wherein the salt is hydrochloride or trifluoroacetate salt.

128. The compound of claim 97, having structural Formula (IIIb):



(IIIb).

129. The compound of claim 128, wherein A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, -CN, $-NO_2$, $-OR^9$, $-S(O)_cR^9$, $-NR^9COR^{10}$, $-NHOR^9$, $-NR^9R^{10}$, $-NOR^9$, $-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$, or $-NR^9C(=NH)NR^{10}R^{11}$.

130. The compound of claim 128, wherein R^{17} is hydrogen, alkyl, or substituted alkyl.

131. The compound of claim 128, wherein

A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, $-OR^1$, $-SR^1$, -CN, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$ or $-NR^9C(=NH)NR^{10}R^{11}$; and

R^{17} is hydrogen, alkyl, or substituted alkyl.

132. The compound of claim 128, wherein

H is $-C(R^{35})-$ or -N-;

I is $-C(R^{36})-$;

J is $-C(R^{37})-$; and

K is $-C(R^{38})-$ or -N-.

133. The compound of Claim 128, wherein

H is $-C(R^{35})-$;

I is $-C(R^{36})-$;

J is $-C(R^{37})-$; and

K is $-C(R^{38})-$.

134. The compound of Claim 128, wherein

R^{35} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl, -CN, $-NO_2$, $-OR^{39}$, $-S(O)_jR^{39}$, $-OCOR^{39}$, $-NR^{39}R^{40}$, $-CONR^{39}R^{40}$, $-CO_2R^{39}$, $-SO_2NR^{39}R^{40}$, $-NR^{39}SO_2R^{40}$;

R^{36} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl, -CN, $-NO_2$, $-OR^{41}$, $-S(O)_kR^{41}$, $-OCOR^{41}$, $-NR^{41}R^{42}$, $-CONR^{41}R^{42}$, $-CO_2R^{41}$, $-SO_2NR^{41}R^{42}$, $-NR^{41}SO_2R^{42}$;

R^{37} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl ,-CN, $-NO_2$, $-OR^{43}$, $-S(O)_lR^{43}$, $-OCOR^{43}$, $-NR^{43}R^{44}$, $-CONR^{43}R^{44}$, $-CO_2R^{43}$, $-SO_2NR^{43}R^{44}$, $-NR^{43}SO_2R^{44}$;

R^{38} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl, -CN, $-NO_2$, $-OR^{45}$, $-S(O)_mR^{45}$, $-OCOR^{45}$, $-NR^{45}R^{46}$, $-CONR^{45}R^{46}$, $-COR^{45}$, $-CO_2R^{45}$, $-SO_2NR^{45}R^{46}$, $-NR^{45}SO_2R^{46}$.

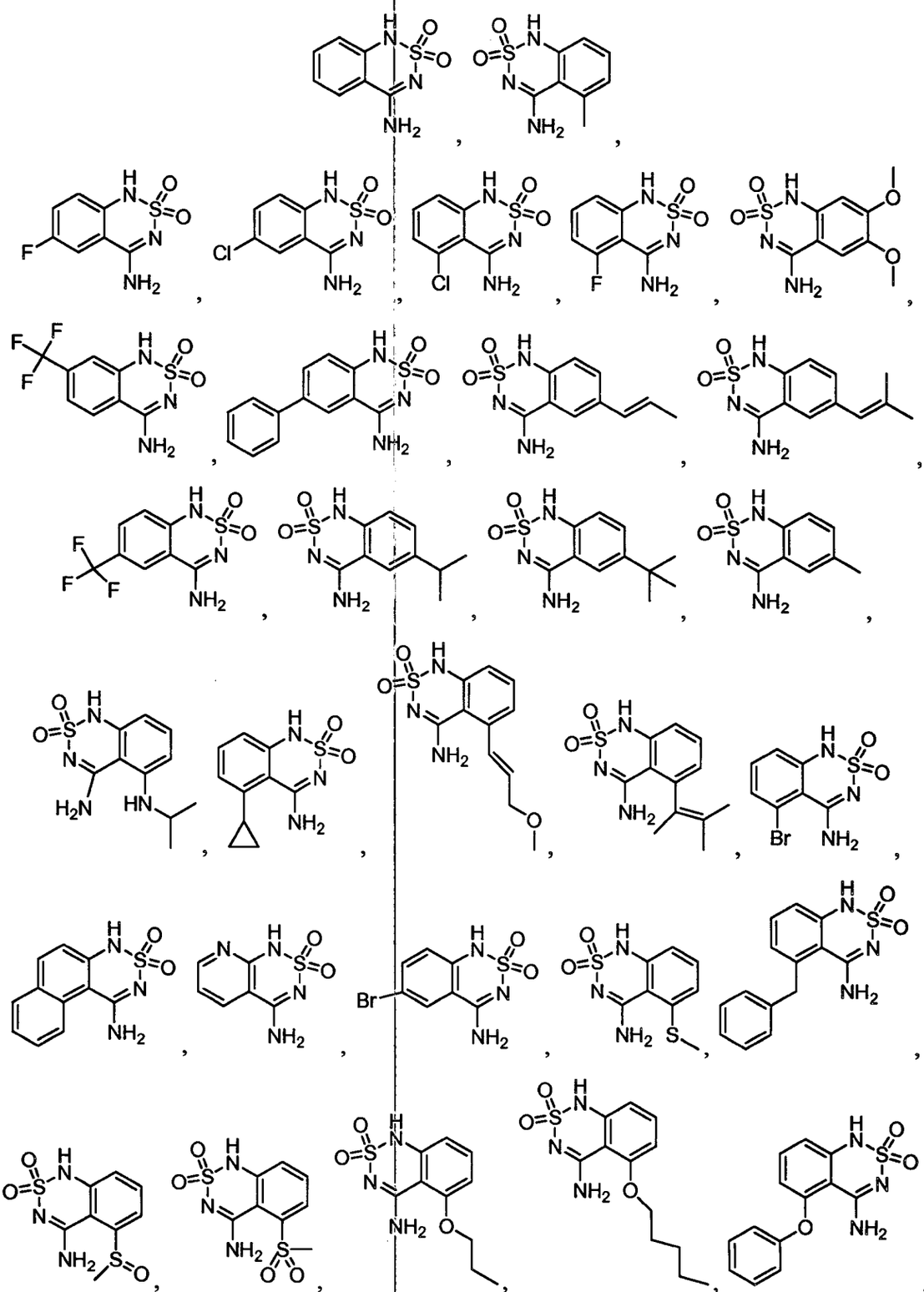
135. The compound of claim 128, wherein

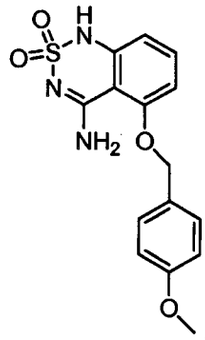
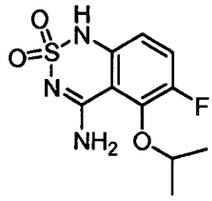
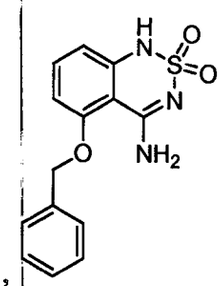
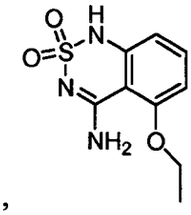
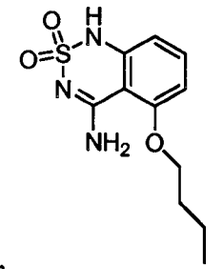
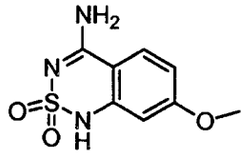
A is $-NH_2$,

R^{17} is hydrogen, methyl, ethyl or benzyl; and

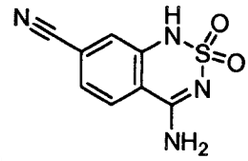
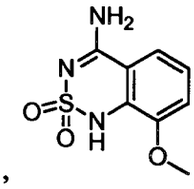
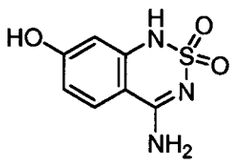
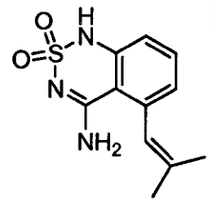
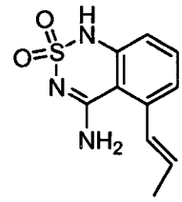
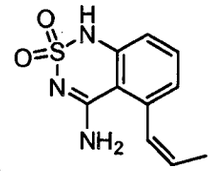
R^{35}, R^{36}, R^{37} and R^{38} are independently hydrogen, fluoro, chloro, bromo, -CN, alkanyl, substituted alkanyl, alkenyl, substitued alkenyl, alkynyl, substituted alkynyl, cycloalkanyl, substituted cycloalkanyl, cycloalkenyl, substitued cycloalkenyl, heteroalkanyl, substituted heteroalkanyl, cycloheteroalkyl, substituted cycloheteroalkyl, -O-alkanyl, -O-(substituted alkanyl), -O-alkenyl, -O-(substituted alkenyl), -NH-alkanyl, -NH-(substituted alkanyl), -NH-alkenyl, -NH-(substituted alkenyl), -S-alkanyl, -S-(substituted alkanyl), -S-alkenyl, or -S-(substituted alkenyl).

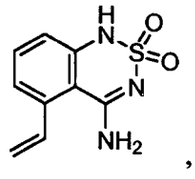
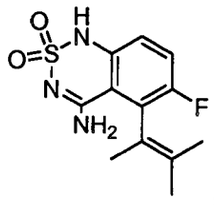
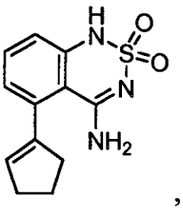
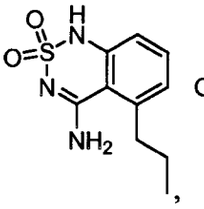
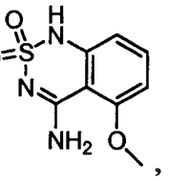
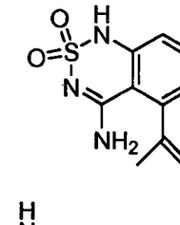
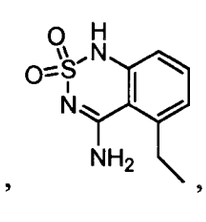
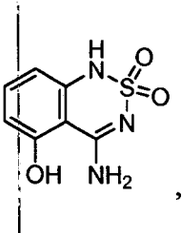
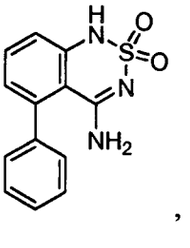
136. A compound of Claim 128 having structural formula selected from the group consisting of:

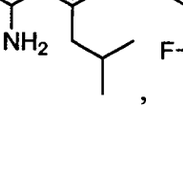
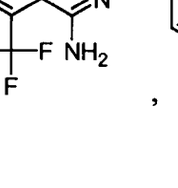
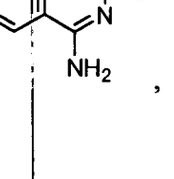
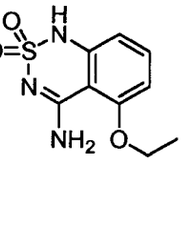
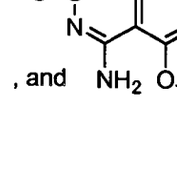



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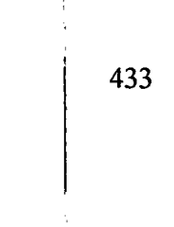
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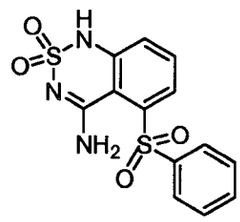
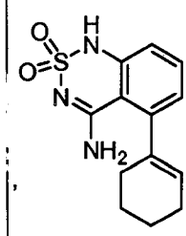
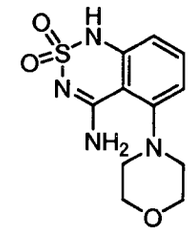
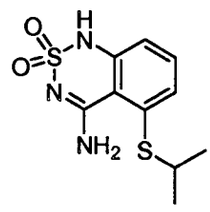
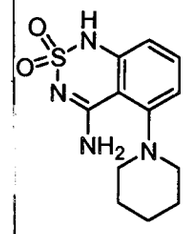
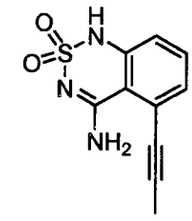
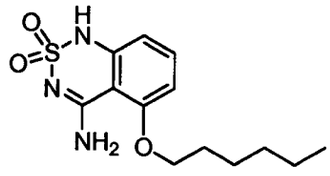
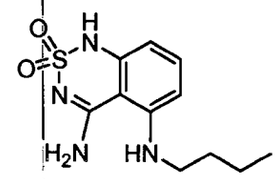
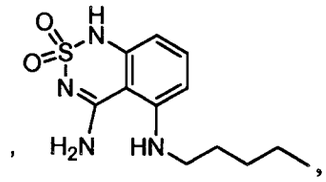
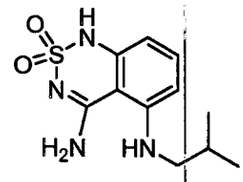
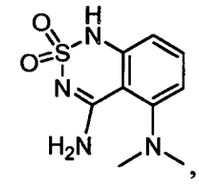
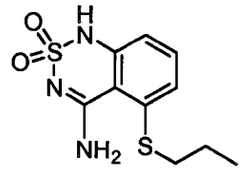
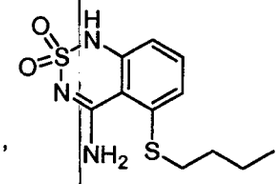
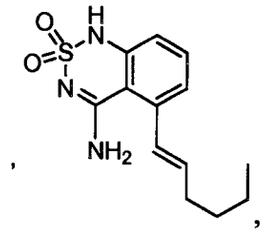
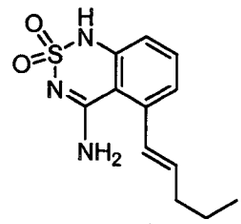
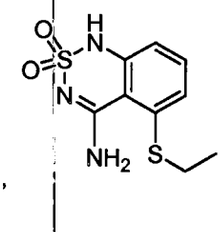
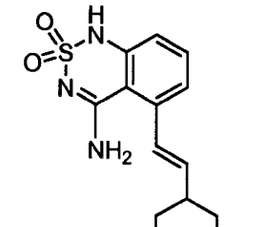
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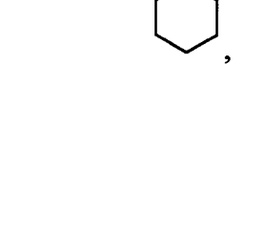
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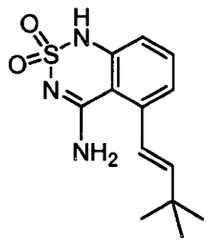
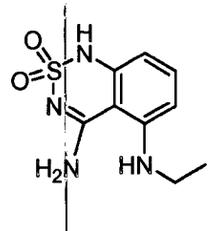
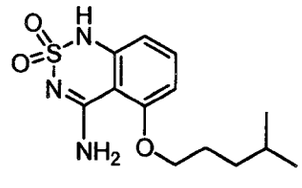
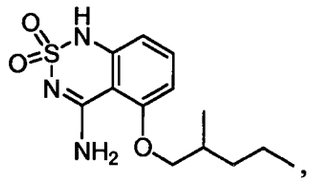
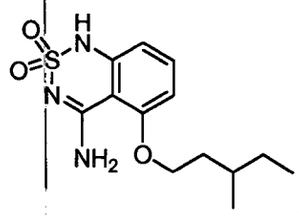
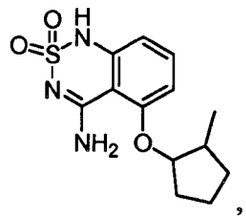
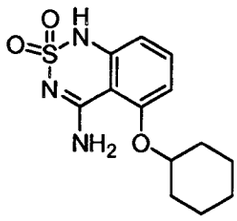
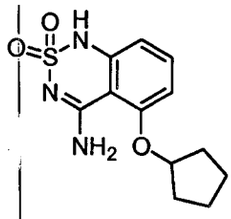
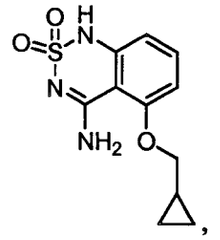
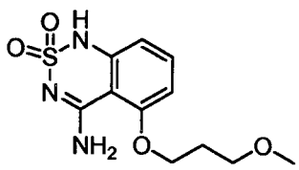
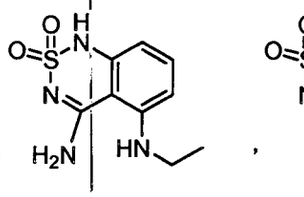
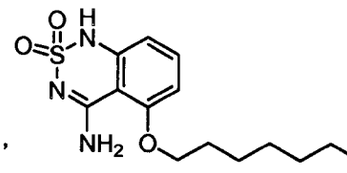
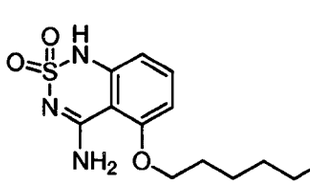
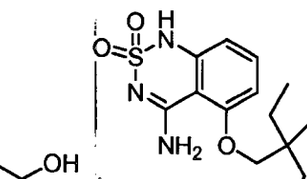
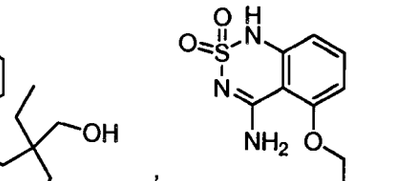
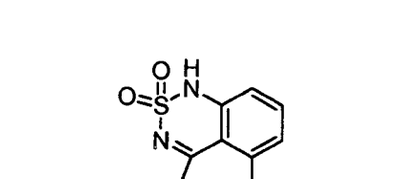
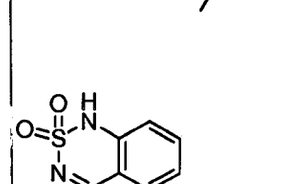
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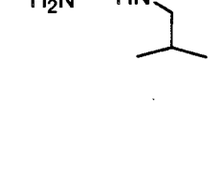
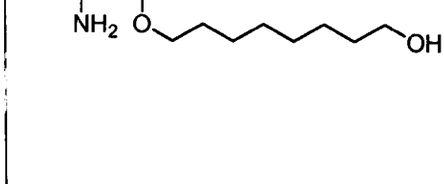
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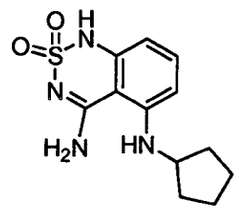
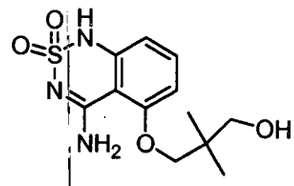
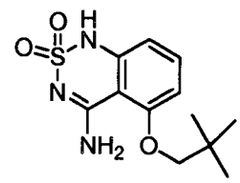
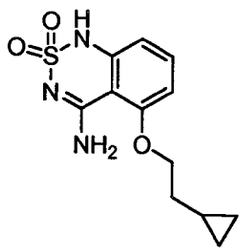
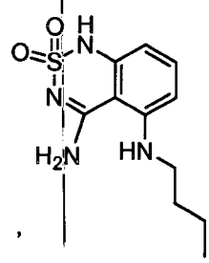
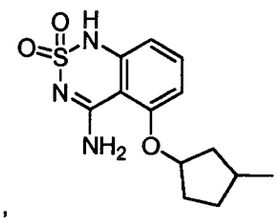
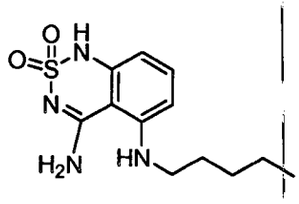
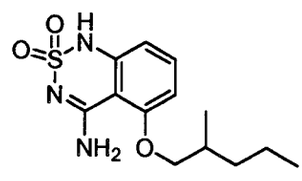
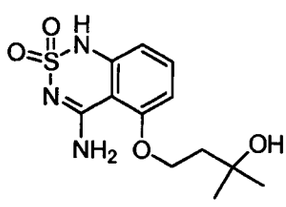
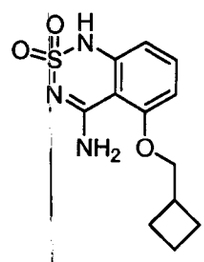
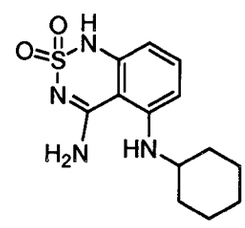
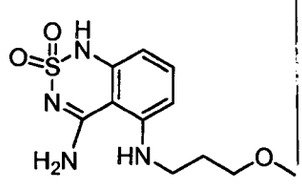
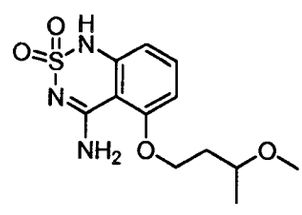
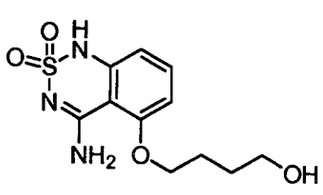
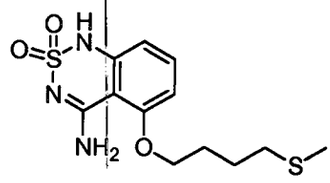
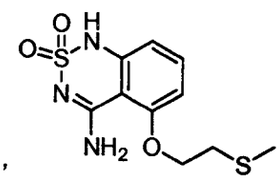
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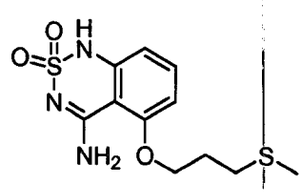
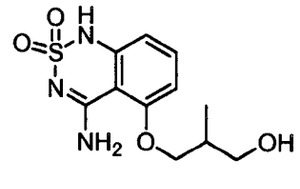
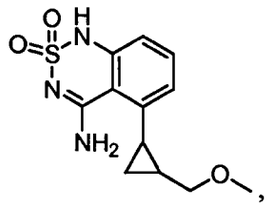
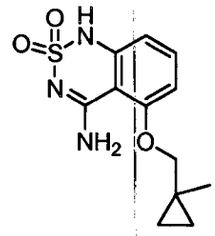
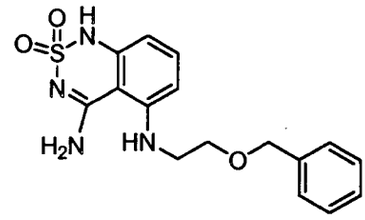
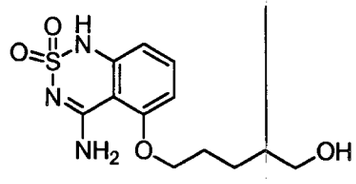
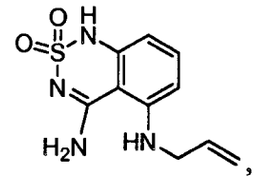
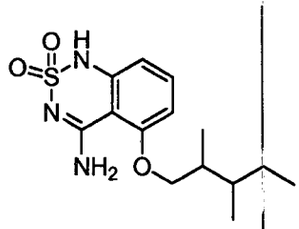
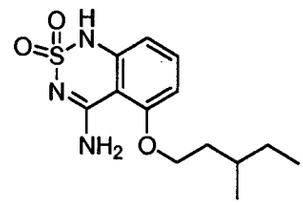
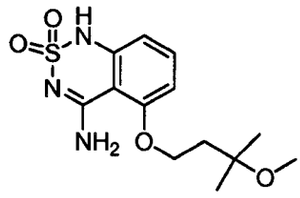
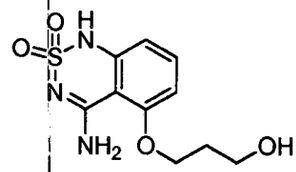
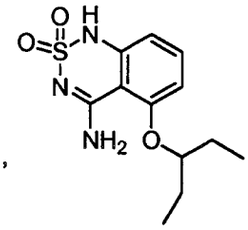
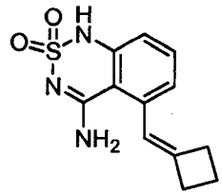
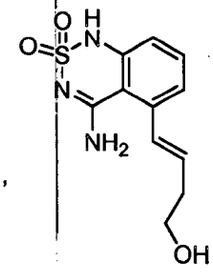
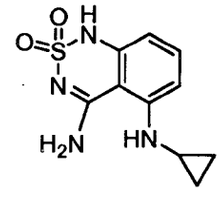


















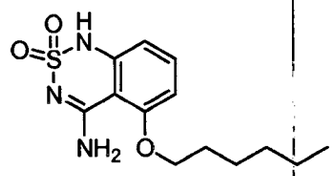
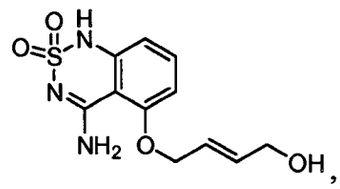
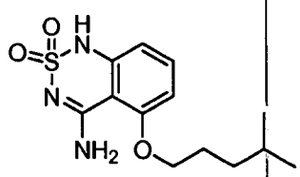
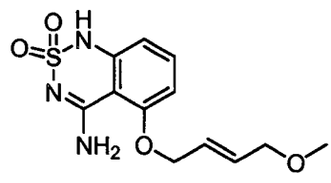
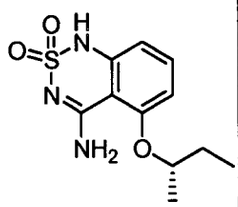
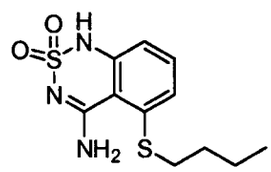
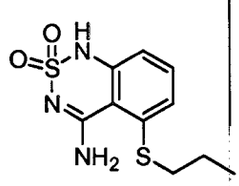
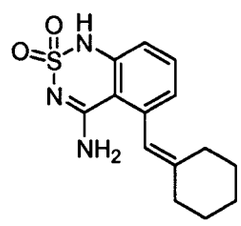
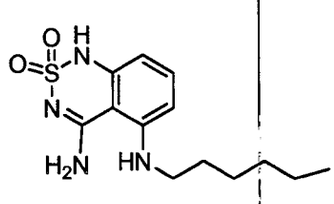
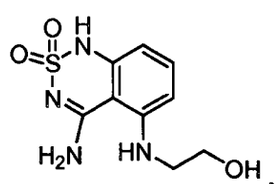
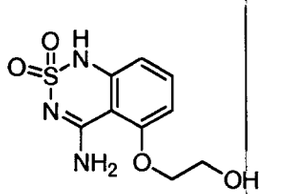
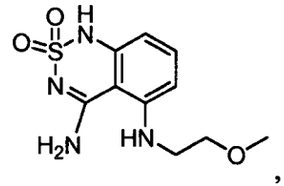
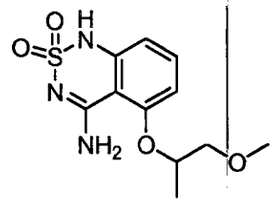
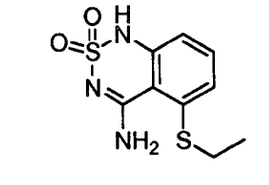



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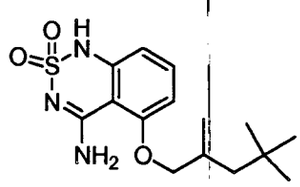
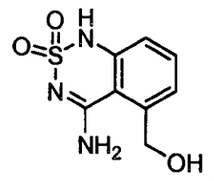
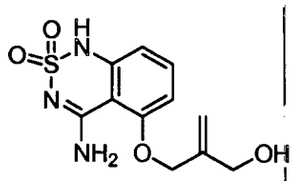
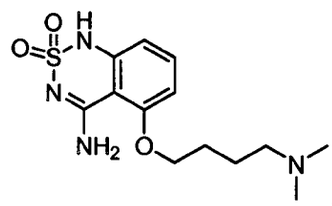
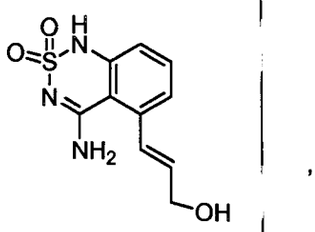
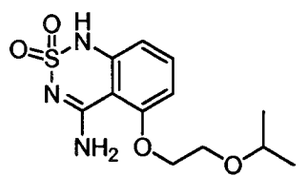
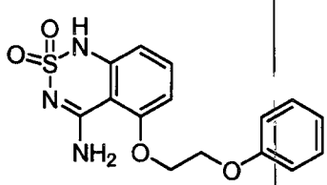
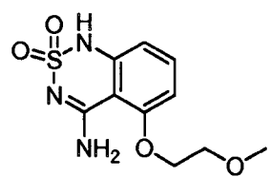
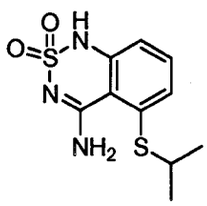
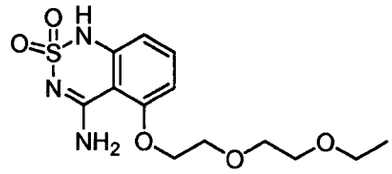
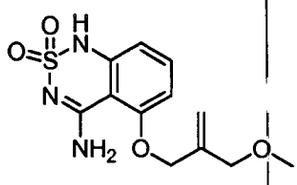
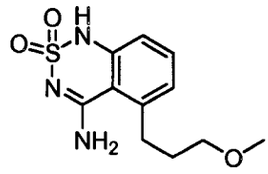
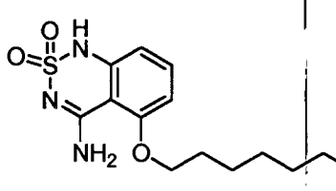
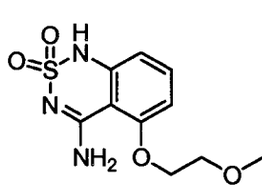

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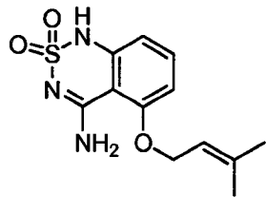
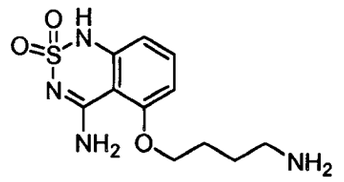
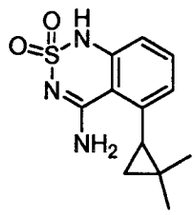
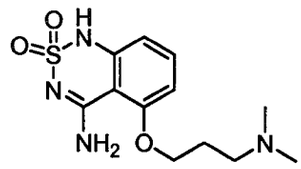
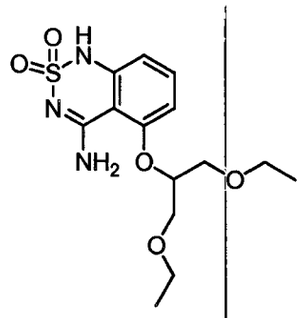
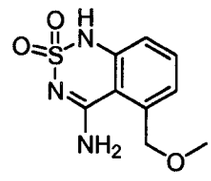
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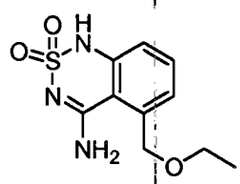
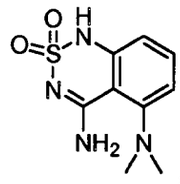
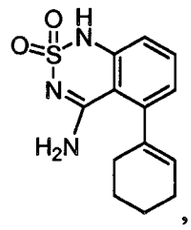
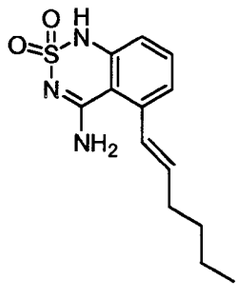
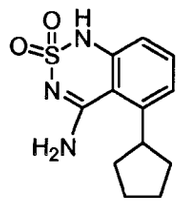
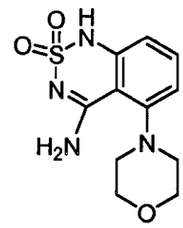
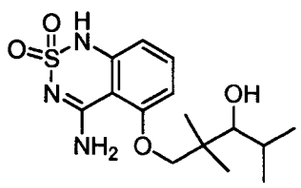
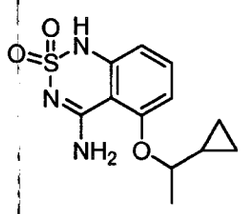
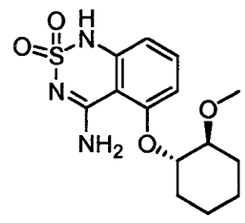
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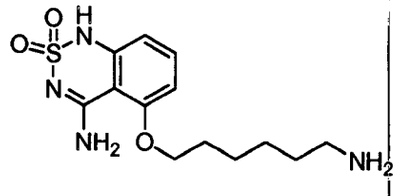
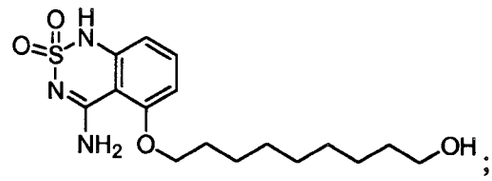

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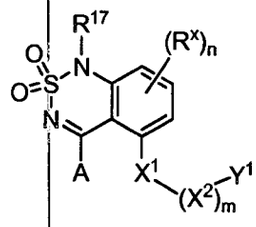
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or a tautomer, salt, solvate, and/or ester thereof.

137. The compound of claim 136, wherein the salt is hydrochloride or trifluoroacetate salt.

138. The compound of claim 128, having structural Formula (IIIb1):



(IIIb1)

wherein,

A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, -OR^9, -NO_2, -$S(O)_cR^9$, -NOR^9, -$NHOR^9$, -NR^9COR^{10}, -NR^9R^{10}, -$CONR^9R^{10}$, -CO_2R^9 or -$NR^9CO_2R^{10}$;

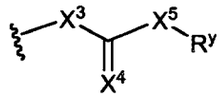
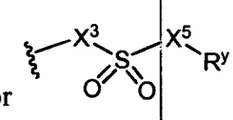
R^{17} is hydrogen, alkyl, substituted alkyl, arylalkyl, or substituted arylalkyl;

X^1 is $–CH_2–$, –O–, $–NR^9–$, –S–, –S(O)–, or $–S(O)_2–$;

X^2 is alkylene, substituted alkylene, heteroalkylene, or substituted heteroalkylene;

m is 0 or 1;

Y^1 is heteroaryl, substituted heteroaryl, cycloheteroalkyl, substituted cycloheteroalkyl, or


, or

;

X^3 and X^5 are independently a covalent bond, –O– or $–NR^9–$;

X^4 is O, NR^9, N-OR^9, or S;

R^x is halo, $-NO_2$, -CN, -OH, $-NH_2$, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl;

n is 0, 1, 2, or 3;

R^y is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl, $-NR^9R^{10}$; and

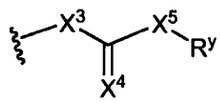
each R^9 and R^{10} is independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl;

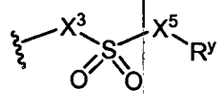
with the proviso that when X^1 is –O– or –S–, and m is zero; then X^3 is not –O–.

139. The compound of claim 138, wherein

X^1 is $-CH_2-$; and

Y^1 is



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140. The compound of claim 138, wherein

X^1 is –O–, $-NR^9-$, or –S–;

m is 0 or 1, and

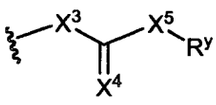
Y^1 is cycloheteroalkyl or substituted cycloheteroalkyl.

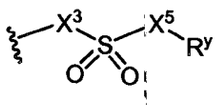
141. The compound of claim 138, wherein

X^1 is –O–, $-NR^9-$, or –S–;

m is 1, and

Y^1 is



, or


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142. The compound of any one of claims 138, 140, and 141, wherein

X^2 is alkanylene, substituted alkanylene, heteroalkanylene, substituted heteroalkanylene, alkenylene, substituted alkenylene, heteroalkenylene, or substituted heteroalkenylene.

143. The compound of any one of claims 138, 140, and 141, wherein

X^2 is methylene, ethylene, propylene, *iso*-propylene, butylene, *iso*-butylene, *sec*-butylene, pentylene, hexylene, heptylene, dimethylethylene, methylcyclopropylene, cyclopropylmethylene, ethenylene, propenylene, or butenylene.

144. The compound of claim 138, wherein A is hydrogen, alkyl, substituted alkyl, -CN, $-NO_2$, $-OR^9$, $-S(O)_cR^9$, $-NR^9COR^{10}$, $-NHOR^9$, $-NR^9R^{10}$, $-NOR^9$, $-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$, $-NR^9C(=NH)NR^{10}R^{11}$.

145. The compound of claim 138, wherein R^{17} is hydrogen, alkyl, or substituted alkyl.

146. The compound of claim 138, wherein Y^1 is cycloheteroalkanyl, substituted cycloheteroalkanyl, cycloheteroalkenyl, or substituted cycloheteroalkenyl.

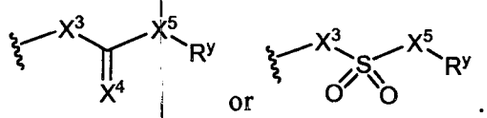
147. The compound of claim 146, wherein Y^1 is piperidinyl, substituted piperidinyl, tetrahydrofuranyl, subsitituted tetrahydrofuranyl, tetrahydropyranyl, subsitituted tetrahydropyranyl, dihydrofuranyl, substituted dihydrofuranyl, pyrrolidinyl, substituted pyrrolidinyl, oxetanyl, substituted oxetanyl, saccharide ring or its derivative, substituted saccharide ring or its derivative.

148. The compound of claim 138, wherein Y^1 is heteroaryl or substituted heteroaryl.

149. The compound of claim 148, wherein Y^1 is pyridinyl, substituted pyridinyl, pyrrolyl, substituted pyrrolyl, furanyl, substituted furanyl, pyrazolyl, substituted pyrazolyl, isoxazolyl, substituted isoxazolyl, oxazolyl, and substituted oxazolyl.

150. The compound of claim 146 or 147, wherein the substituted cycloheteroalkanyl or the substituted cycloheteroalkenyl comprises one or more substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, $-OR^9$, $-NO_2$, $-S(O)_cR^9$, $-NOR^9$, $-NHOR^9$, $-NR^9COR^{10}$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$, and $-NR^9CO_2R^{10}$.

151. The compound of claim 138, wherein Y is



or

.

152. The compound of claim 151, wherein X^4 is O.

153. The compound of claim 138, wherein $-X^3-C(X^4)-X^5-$ is –C(O)-, -C(O)-NH-, -NH-C(O)-, -NH-C(O)-NH-, -C(O)-O-, -O-C(O)-, -O-C(O)-O-, -NH-C(O)-O-, -O-C(O)-NH-, –C(NH)-, -C(NH)-NH-, -NH-C(NH)-, -NH-C(NH)-NH-, -C(NH)-O-, -O-C(NH)-, -O-C(NH)-O-, -NH-C(NH)-O-, -O-C(NH)-NH-, -C(N-OH)-, or -C(S)-.

154. The compound of claim 138, wherein

A is hydrogen, alkyl, substituted alkyl, or $-NR^9R^{10}$;

R^{17} is hydrogen; and

Y^1 is piperidinyl, substituted piperidinyl, tetrahydrofuranyl, subsitituted tetrahydrofuranyl, tetrahydropyranyl, subsitituted tetrahydropyranyl, dihydrofuranyl, substituted dihydrofuranyl, pyrrolidinyl, substituted pyrrolidinyl, oxetanyl, substituted oxetanyl, monosaccharide ring, substituted monosaccharide ring, pyridinyl, substituted pyridinyl, pyrrolyl, substituted pyrrolyl, furanyl, substituted furanyl, pyrazolyl, substituted pyrazolyl, isoxazolyl, substituted isoxazolyl, oxazolyl, or substituted oxazolyl.

155. The compound of claim 138, wherein

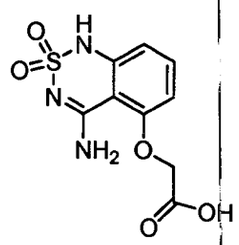
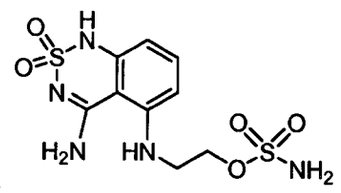
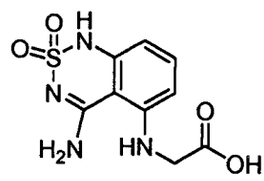
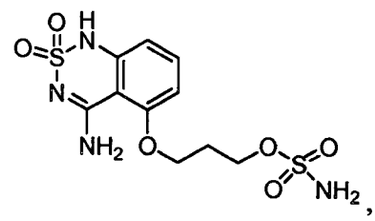
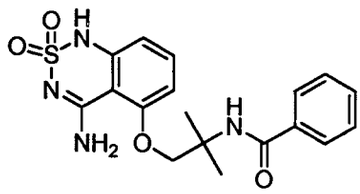
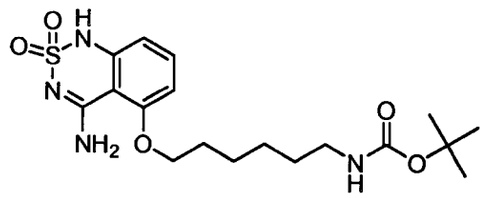
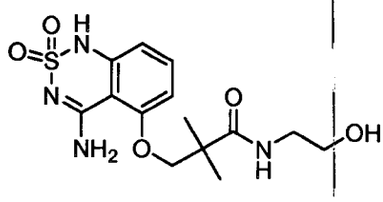
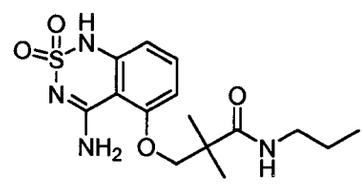
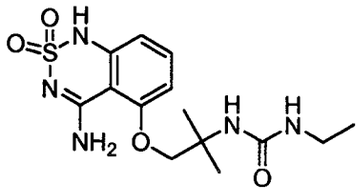
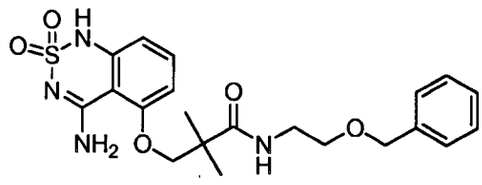
A is hydrogen, alkyl, substituted alkyl, or $-NR^9R^{10}$;

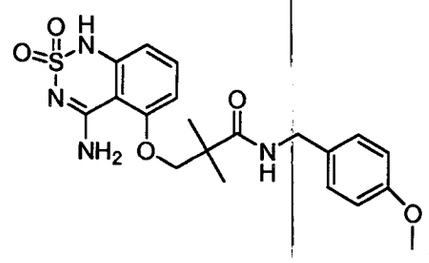
R^{17} is hydrogen;

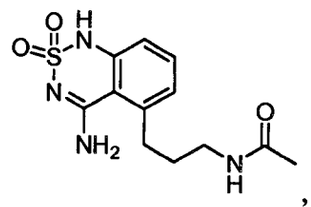
Y^1 is $-X^3-C(X^4)-X^5-$; and

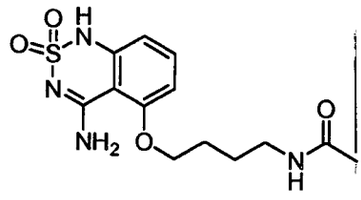
$-X^3-C(X^4)-X^5-$ is –C(O)-, -C(O)-NH-, -NH-C(O)-, -NH-C(O)-NH-, -C(O)-O-, -O-C(O)-, -O-C(O)-O-, -NH-C(O)-O-, -O-C(O)-NH-, –C(NH)-, -C(NH)-NH-, -NH-C(NH)-, -NH-C(NH)-NH-, -C(NH)-O-, -O-C(NH)-, -O-C(NH)-O-, -NH-C(NH)-O-, -O-C(NH)-NH-, $-S(O)_2-$, $-NH-S(O)_2-$, $-S(O)_2-NH-$, $-O-S(O)_2-$, $-S(O)_2-O-$, -C(N-OH)-, or -C(S)-.

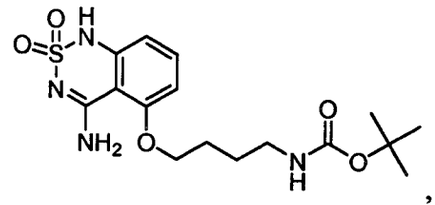
156. The compound of claim 138, having structural formula selected from the group consisting of

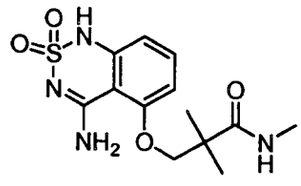

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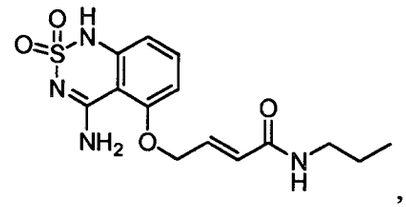


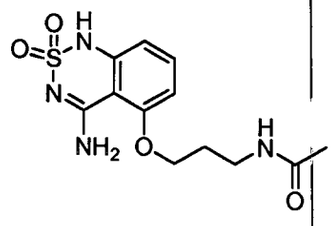


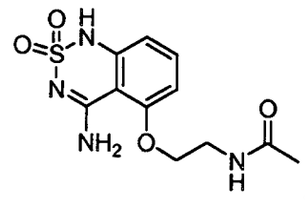


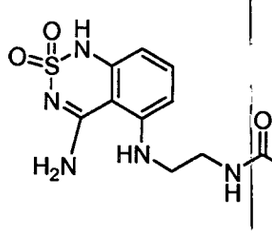


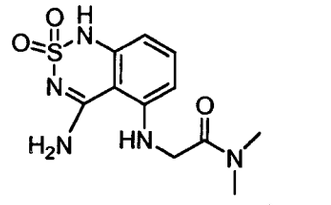


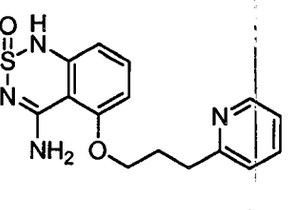


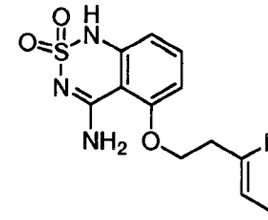


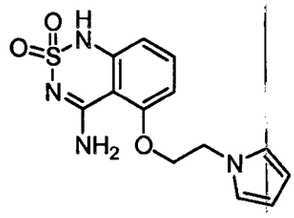
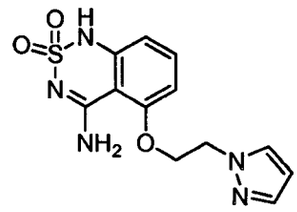
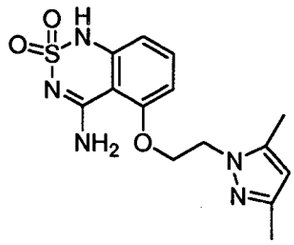
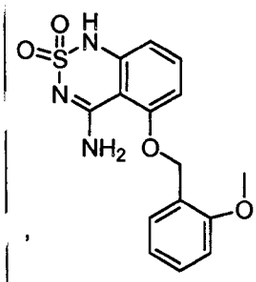
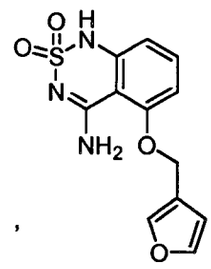
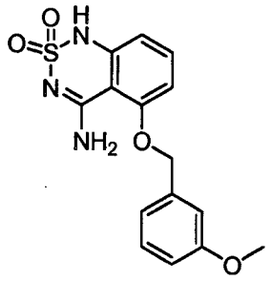
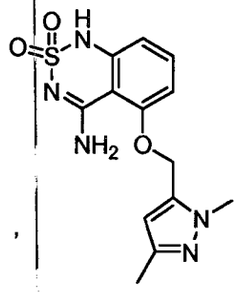
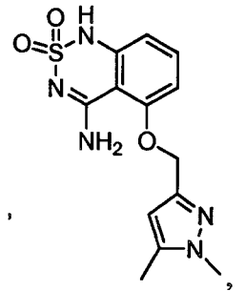
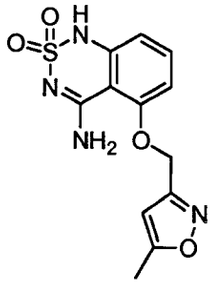
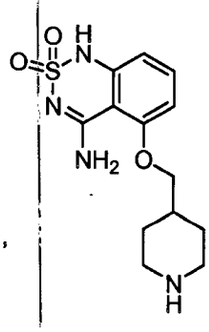
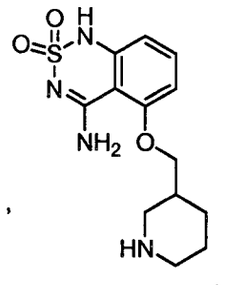
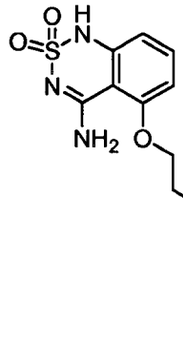
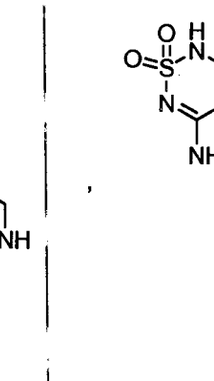
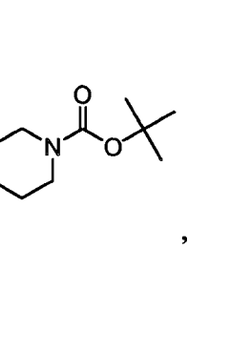






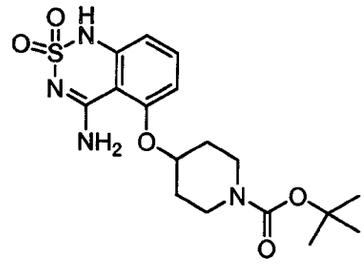
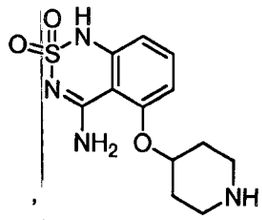
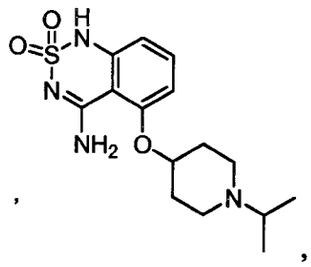
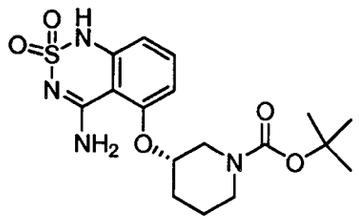
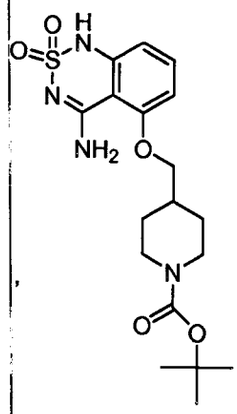
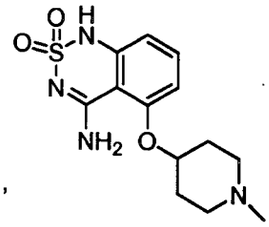
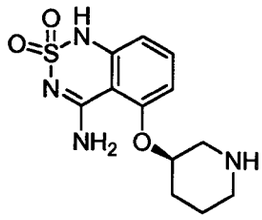
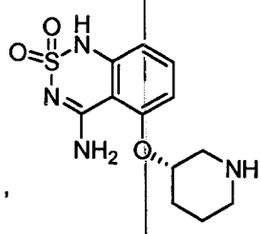
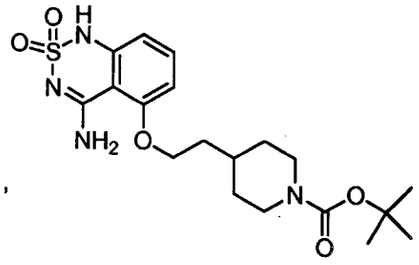
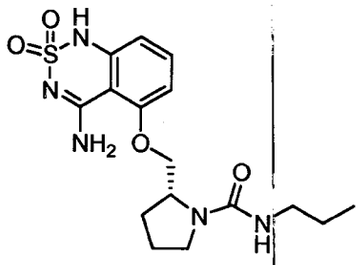
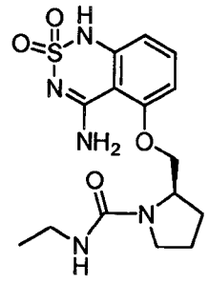


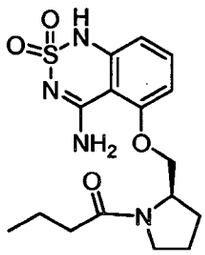
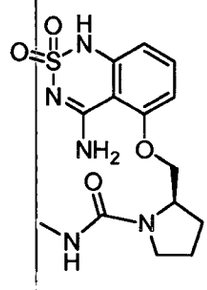
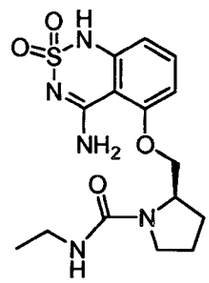
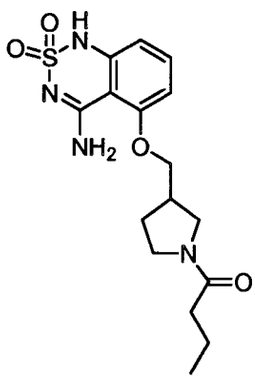
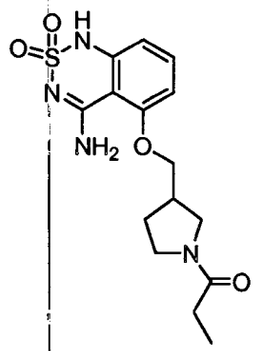
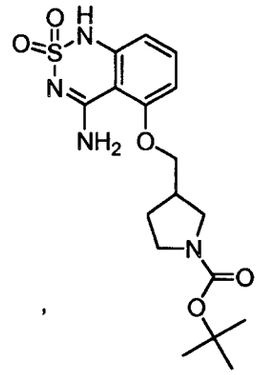
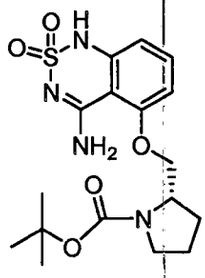
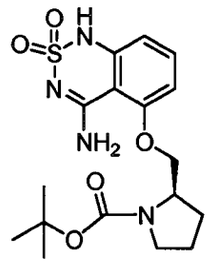
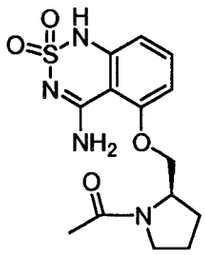
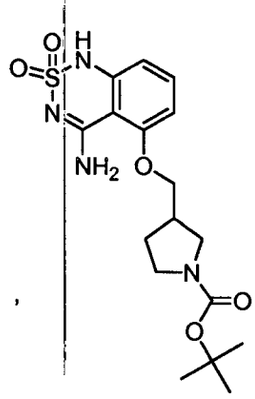
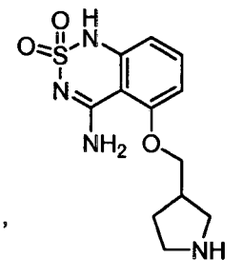


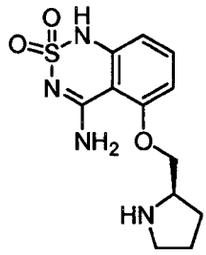
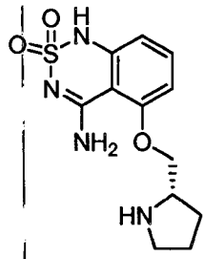
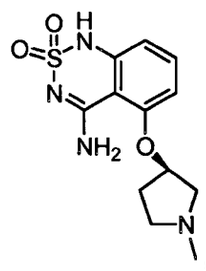
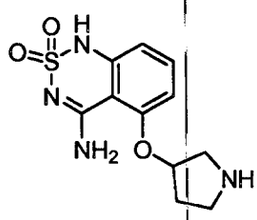
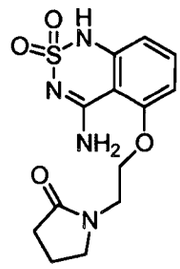
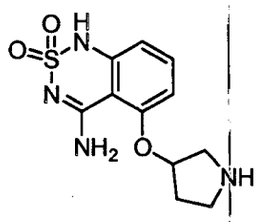
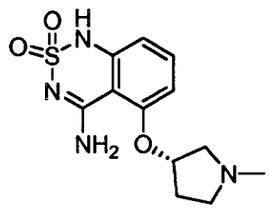
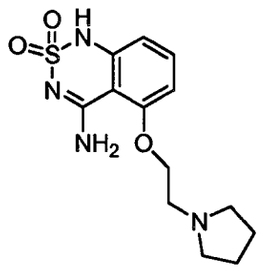
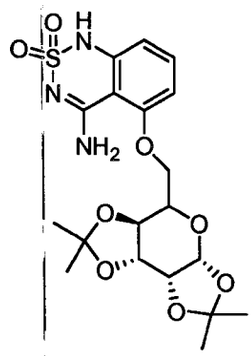
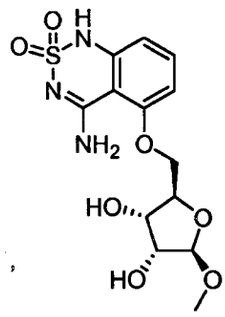
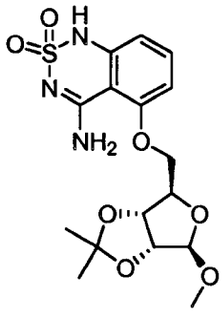
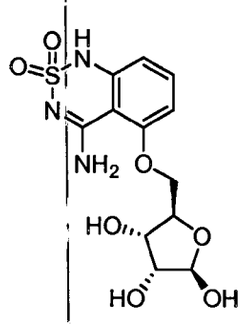
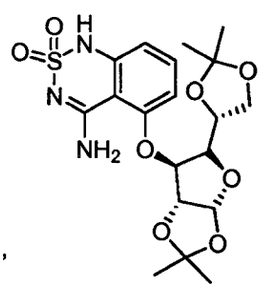

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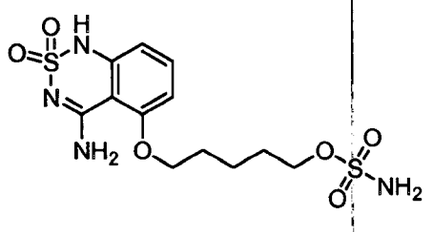
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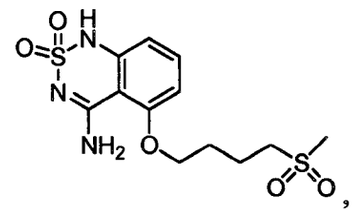
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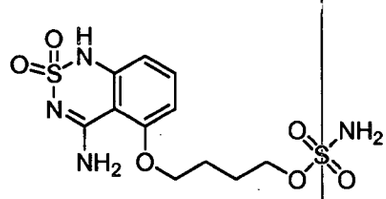

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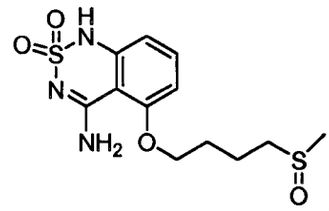

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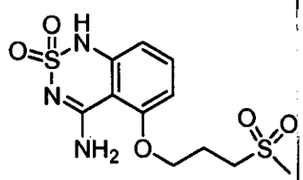

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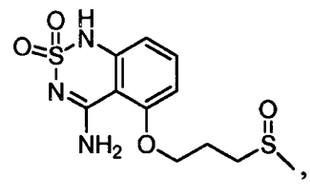


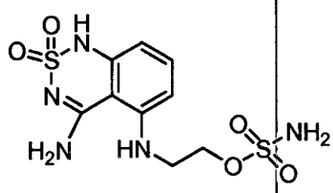


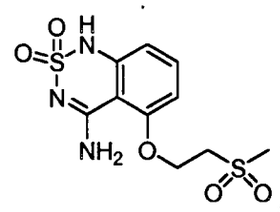


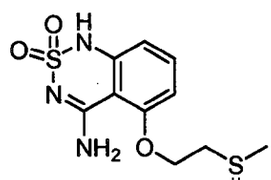


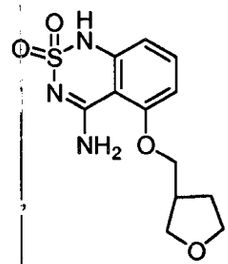


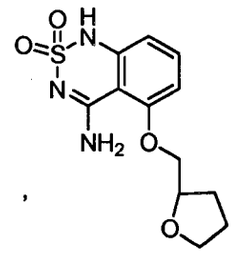


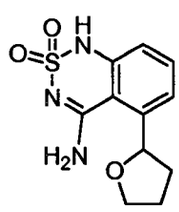


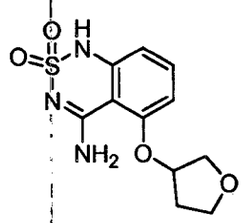


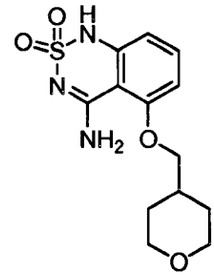


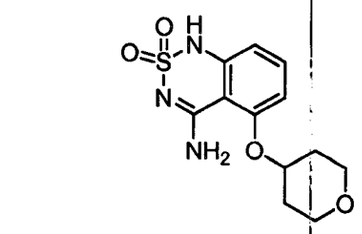
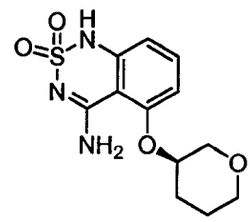
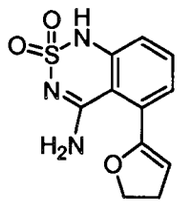
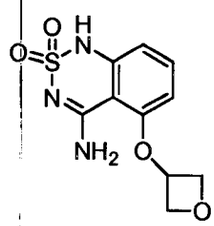
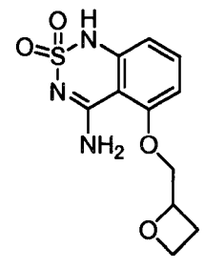
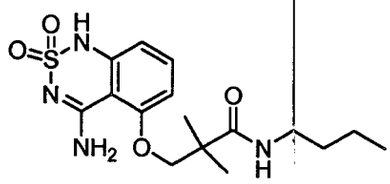
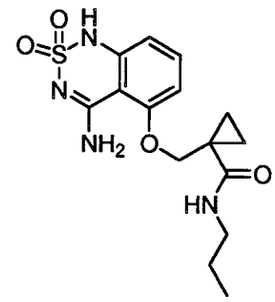
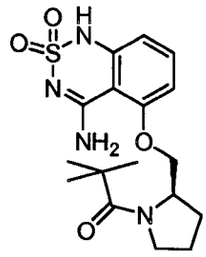
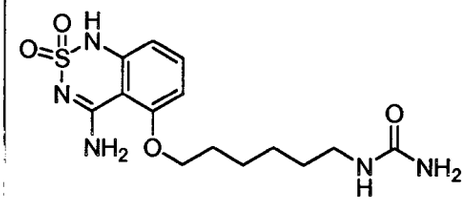
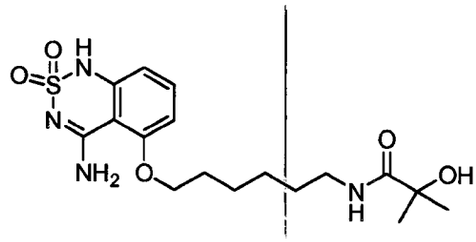
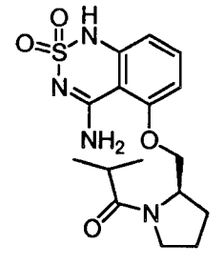


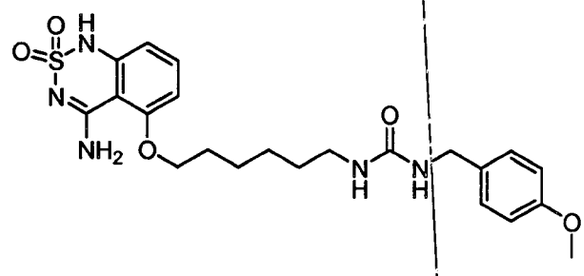


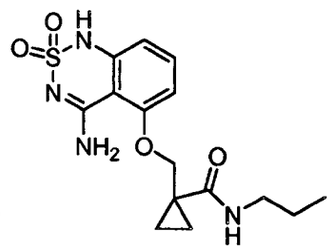


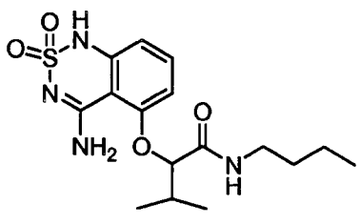


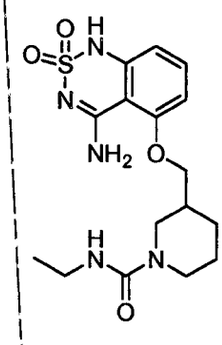


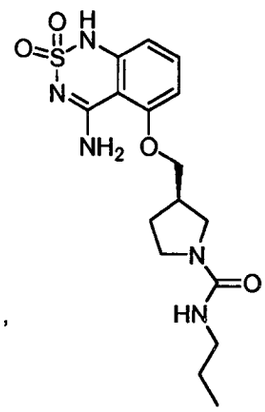

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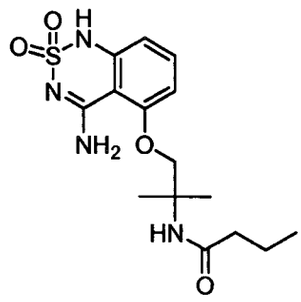


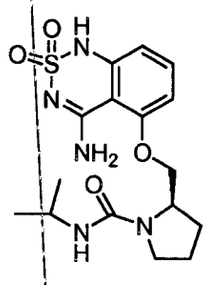


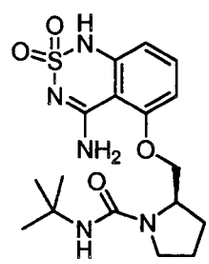


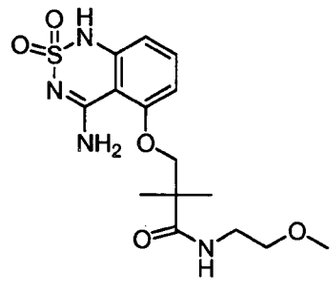


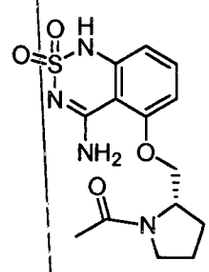


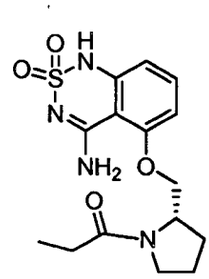


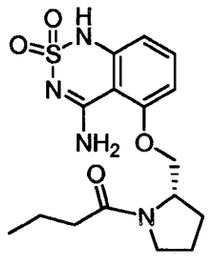
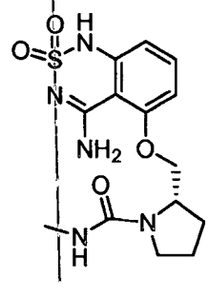
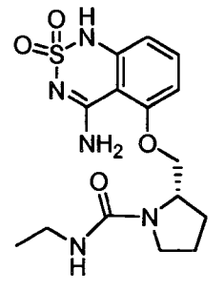
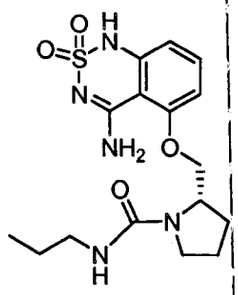
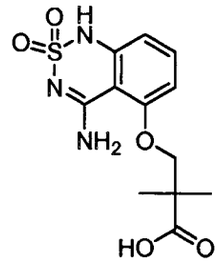
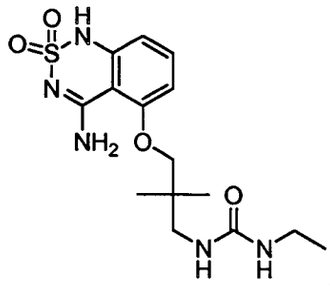
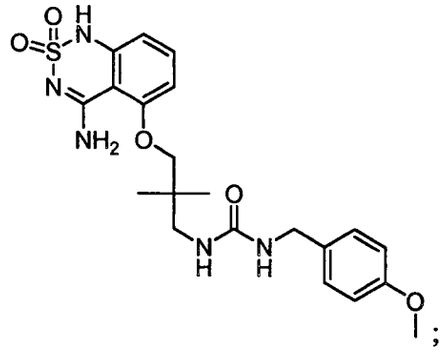








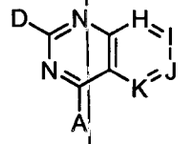



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, and

;

or a tautomer, salt, solvate, and/or ester thereof.

157. The compound of claim 156, wherein the salt is a hydrochloride or trifluoroacetate salt.

158. The compound of claim 97, having structural formula (IIIc)


(IIIc)

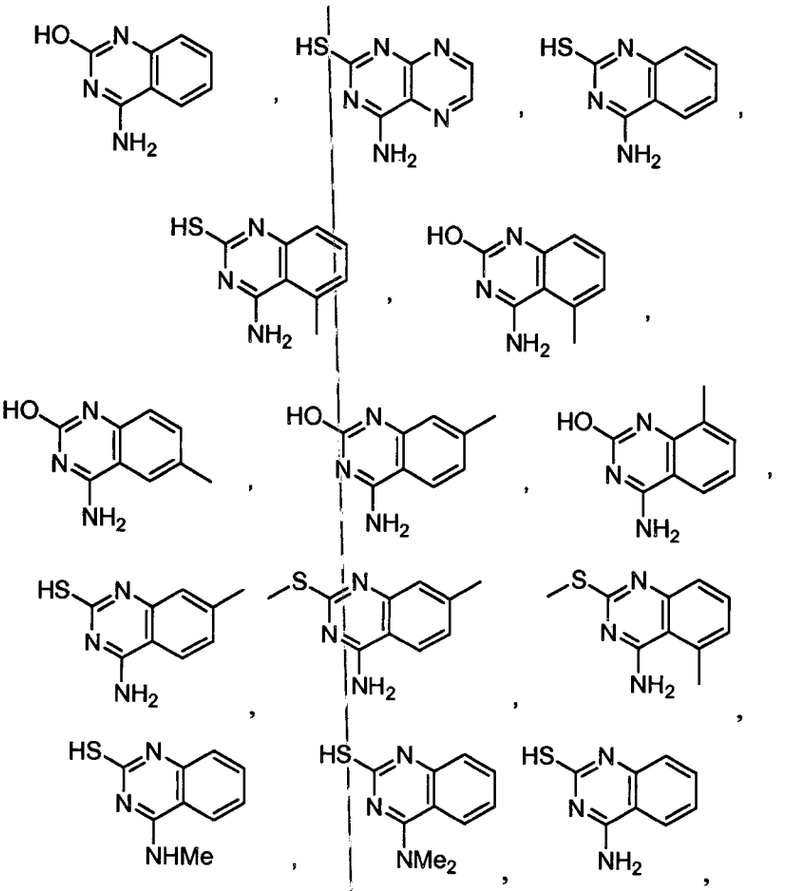
wherein:

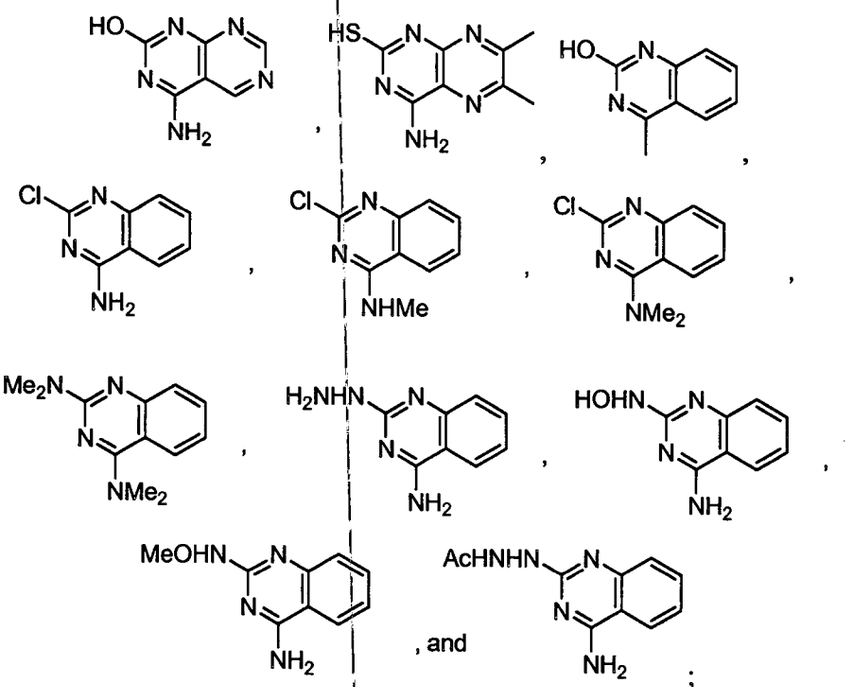
D is halo, $-OR^{15}$, $-NH-OR^{15}$, $-NH-NHR^{15}$, $-S(O)_eR^{15}$, or $-NR^{15}R^{16}$.

159. The compound of claim 158, wherein
R^{35}, R^{36}, R^{37}, and R^{38} are independently hydrogen, alkyl, or substituted alkyl.

160. The compound of claim 159, wherein
H is -C(R^{35})-;
I is -C(R^{36});
J is -C(R^{37})-; and
K is -C(R^{38})-.

161. The compound of claim 158, having strucutural formula selected from the group consisting of



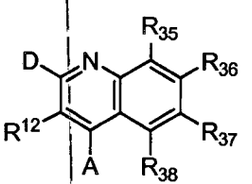


, and ;

or a tautomer, salt, solvate, and/or ester thereof.

162. The compound of claim 161, wherein the salt is hydrochloride or trifluoroacetate salt.

163. The compound of claim 97, having structural Formula (XI):



(XI)

wherein,

R^{12} is hydrogen, -OH, -SH, -CN, $-CH_2OH$ or $-CO_2H$;

D is -OH or -SH; and

A is -OH, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, or $-CH_2NHC(O)CH_3$;

provided that when R^{12} is hydrogen, then R^{35}, R^{36}, R^{37}, and R^{38} are not hydrogen.

164. The compound of claim 163, wherein

R^{12} is -OH, -SH, -CN, $-CH_2OH$ or $-CO_2H$; and

A is $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, or $-CH_2NHC(O)CH_3$.

165. The compound of claim 164, wherein

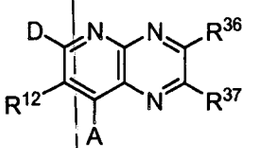
when R^{36}, R^{37}, R^{38} and R^{35} are hydrogen, D is –OH, and A is $-CO_2H$; then R^{12} is not $-CO_2H$ or -OH;

when R^{36}, R^{37}, R^{38} and R^{35} are hydrogen, D is –OH, and A is $–NH_2$; then R^{12} is not $-CO_2H$ or CN;

when R^{36}, R^{38} and R^{35} are hydrogen, R^{37} is -OMe, D is –OH, and A is $-CH_2OH$; then R^{12} is not $-CH_2OH$; and

when R^{36}, R^{38} and R^{35} are hydrogen; R^{37} is hydrogen or methyl, D is –OH, and A is $–CO_2H$; then R^{12} is not -SH.

166. The compound of claim 97, having structural Formula (XII):



(XII)

,

wherein

R^{12} is hydrogen, -OH, -SH, -CN, $-CH_2OH$ or $-CO_2H$;

D is -SH or –OH;

A is -OH, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, or $-CH_2NHC(O)CH_3$;

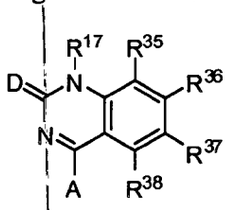
R^{36} is hydrogen, $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, $-CH_3$, $-C_2H_5$, $-CH(CH_3)_2$, $-CH_2OH$, $-CH_2OCH_3$, -CN, $-C(O)NR^{41}R^{42}$, $-CO_2R^{41}$, $-SO_2NR^{39}R^{40}$, $-NR^{39}SO_2R^{40}$, $-B(OR^{39})(OR^{40})$, $-P(O)(OR^{39})(OR^{40})$ or $-P(O)(R^{39})(OR^{40})$; and

R^{37} is hydrogen, $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, $-CH_3$, $-C_2H_5$, $-CH(CH_3)_2$, $-CH_2OH$,

$-CH_2OCH_3$, -CN, $-C(O)NR^{43}R^{44}$, $-CO_2R^{43}$, $-SO_2NR^{43}R^{44}$, $-NR^{43}SO_2R^{44}$, $-B(OR^{43})(OR^{44})$, $-P(O)(OR^{43})(OR^{44})$ or $-P(O)(R^{43})(OR^{44})$.

167. The ligand modifier of claim 166, wherein R^{12} is -OH, -SH, -CN, $-CH_2OH$ or $-CO_2H$.

168. The compound of claim 97, having structural Formula (XIII):



(XIII)

,

wherein:

D is =O or =S;

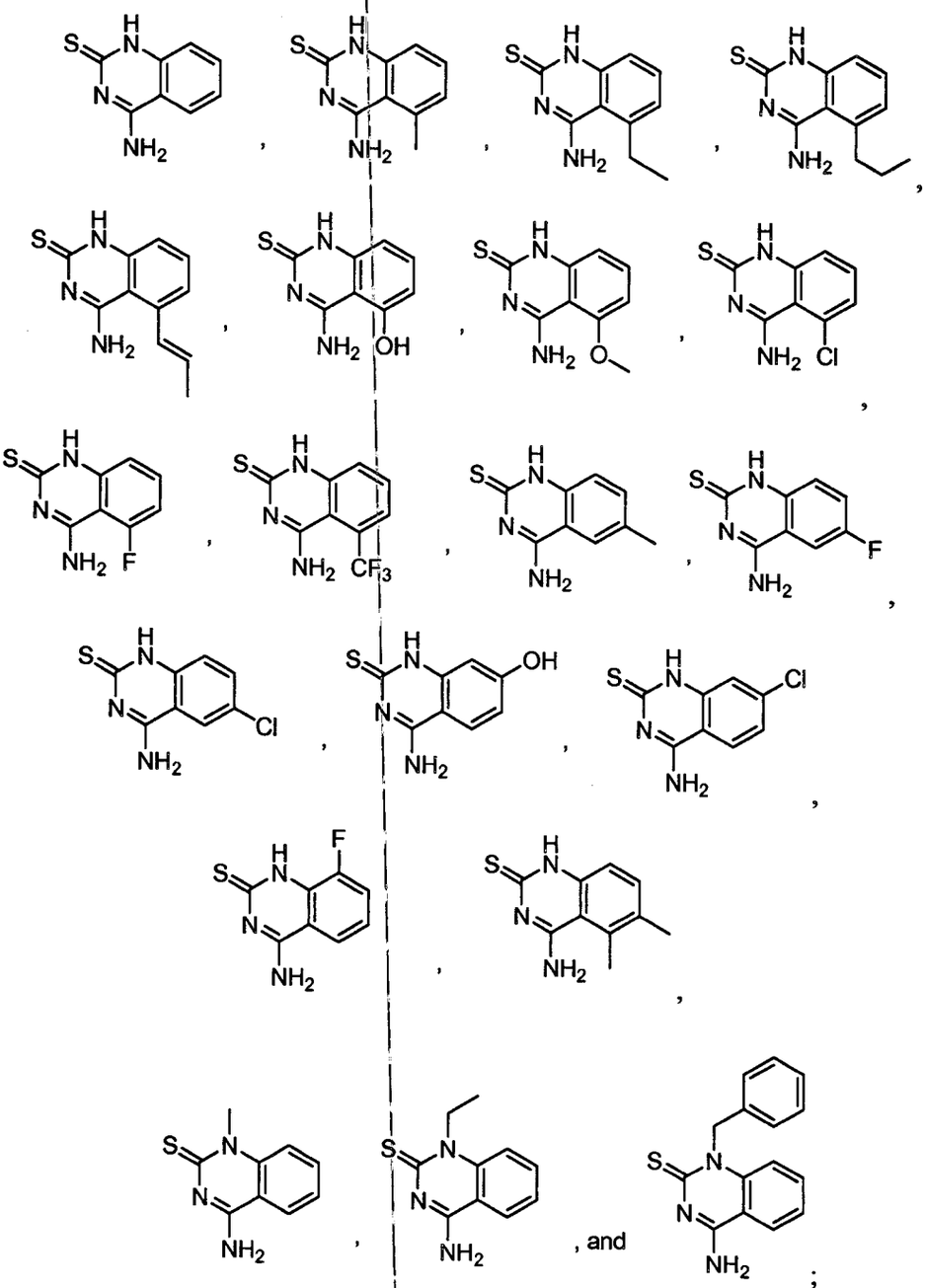
A is -OH, NH_2, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, or $-CH_2NHC(O)CH_3$;

R^{17} is hydrogen, alkyl, aryl, arylalkyl.

169. The compound of claim 168, wherein

when A is $-NH_2$, and R^{35}, R^{36}, R^{37} and R^{38} are hydrogen; then R^{17} is not methyl, ethyl or phenyl.

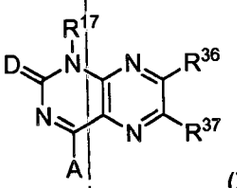
170. The compound of claim 168, having structural formula selected from the group consisting of



or a tautomer, salt, solvate, and/or ester thereof.

171. The compound of claim 170, wherein the salt is hydrochloride or trifluoroacetate salt.

172. The compound of claim 97, having structural Formula (XIV):



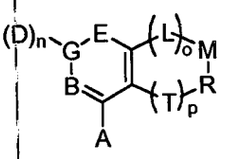
(XIV),

wherein:

A is -OH, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -$NHC(O)CH_3$, -$NHC(O)OCH_3$, -$NHC(O)NH_2$, -$NHC(S)NH_2$, -$NHC(NH)NH_2$, -CN, -CH_2OH, -CH_2NH_2, -CH_2NHCH_3, -$CH_2N(CH_3)_2$, -CO_2H, -$CONH_2$, -$CONHCH_3$, or -$CH_2NHC(O)CH_3$;

R^{17} is alkyl, aryl, or arylalkyl.

173. The compound of claim 56, having structural Formula (IV):



(IV),

wherein:

L is -CHR^{60}-, -NR^{47}, -O- or -S-;

M is -CHR^{61}-, -NR^{48}, -O- or -S-;

R is -CHR^{62}-, -NR^{49}, -O- or -S-;

T is -CHR^{63}-, -NR^{50}, -O- or -S-;

o and p are independently 0, 1, or 2;

R^{60} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl ,-CN, -NO_2, -OR^{64}, -$S(O)_tR^{64}$, -$OCOR^{64}$, -$NR^{64}COR^{65}$, -$NR^{64}R^{65}$, -$CONR^{64}R^{65}$, -CO_2R^{64}, -$SO_2NR^{64}R^{65}$, -$NR^{64}SO_2R^{65}$, -$B(OR^{64})(OR^{65})$, -$P(O)(OR^{64})(OR^{65})$ or -$P(O)(R^{64})(OR^{65})$;

R^{61} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl ,-CN, -NO_2, -OR^{66}, -$S(O)_uR^{66}$,

$-OCOR^{66}$, $-NR^{66}COR^{67}$, $-NR^{66}R^{67}$, $-CONR^{66}R^{67}$, $-CO_2R^{66}$, $-SO_2NR^{66}R^{67}$, $-NR^{66}SO_2R^{67}$, $-B(OR^{66})(OR^{67})$, $-P(O)(OR^{66})(OR^{67})$ or $-P(O)(R^{66})(OR^{67})$;

R^{62} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl ,-CN, $-NO_2$, $-OR^{68}$, $-S(O)_vR^{68}$, $-OCOR^{68}$, $-NR^{68}COR^{69}$, $-NR^{68}R^{69}$, $-CONR^{68}R^{69}$, $-CO_2R^{68}$, $-SO_2NR^{68}R^{69}$, $-NR^{68}SO_2R^{69}$, $-B(OR^{68})(OR^{69})$, $-P(O)(OR^{68})(OR^{69})$ or $-P(O)(R^{68})(OR^{69})$;

R^{63} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl ,-CN, $-NO_2$, $-OR^{70}$, $-S(O)_xR^{70}$, $-OCOR^{70}$, $-NR^{70}COR^{71}$, $-NR^{70}R^{71}$, $-CONR^{70}R^{71}$, $-CO_2R^{70}$, $-SO_2NR^{70}R^{71}$, $-NR^{70}SO_2R^{71}$, $-B(OR^{70})(OR^{71})$, $-P(O)(OR^{70})(OR^{71})$ or $-P(O)(R^{70})(OR^{71})$; or alternatively R^{60} and R^{61}, R^{61} and R^{62}, or R^{62} and R^{63} together with the atoms to which they are bonded form an aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring;

t, u, v and x are independently 0, 1 or 2;

R^{64} to R^{71} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl or alternatively R^{64} and R^{65}, R^{66} and R^{67}, R^{68} and R^{69}, or R^{70} and R^{71} together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring; and

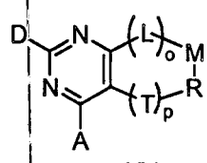
R^{47} to R^{50} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl;

with the proviso that at most only one of L, M, R and T is a heteroatom.

174. The compound of claim 173, wherein B is -N-, and E is $-NR^{17}-$ or -N-.

175. The compound of claim 174, wherein G is -C-.

176. The compound of claim 175, having structural Formula (XV):



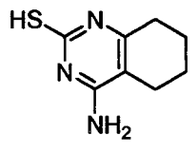
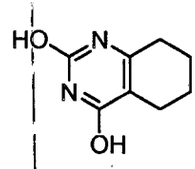
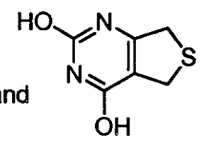
XV

wherein:

D is -SH or –OH; and

A is -OH, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -$NHC(O)CH_3$, -$NHC(O)OCH_3$, -$NHC(O)NH_2$, -$NHC(S)NH_2$, -$NHC(NH)NH_2$, -CN, -CH_2OH, -CH_2NH_2, -CH_2NHCH_3, -$CH_2N(CH_3)_2$, -CO_2H, -$CONH_2$, -$CONHCH_3$, or -$CH_2NHC(O)CH_3$.

177. The compound of claim 176, having structural formula selected from the group consisting of


,

, and

;

or a tautomer, salt, solvate, and/or ester thereof.

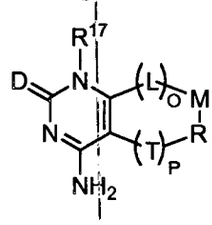
178. The compound of claim 177, wherein the salt is hydrochloride or trifluoroacetate salt.

179. The compound of claim 174, wherein

A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, -OR^9, -SR^9, -CN, -NR^9R^{10}, -$CONR^9R^{10}$, -CO_2R^9, -$NR^9CO_2R^{10}$, -$NR^9CONR^{10}R^{11}$, -$NR^9CSNR^{10}R^{11}$ or -$NR^9C(=NH)NR^{10}R^{11}$; and

D is =O, =S , =N-OR^{15}.

180. The compound of claim 174, having structural Formula (IVb):

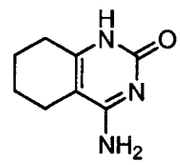
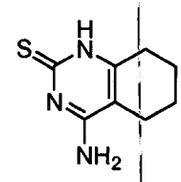
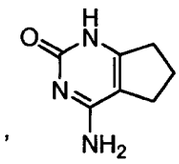
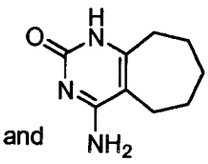


(IVb),

wherein,

L is -CHR^{60}-; M is -CHR^{61}-; R is -CHR^{62}-; T is -CHR^{63}-.

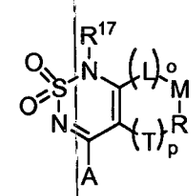
181. The compound of claim 180, having structural formula selected from the group consisting of:




, and

;

or a tautomer, salt, solvate, and/or ester thereof.

182. The compound of claim 181, wherein the salt is hydrochloride or trifluoroacetate salt.

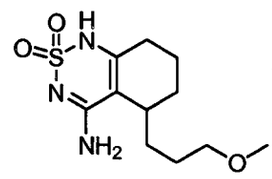
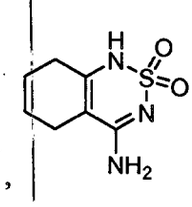
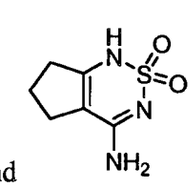
183. The compound of claim 173, having structural Formula (IVa):


(IVa).

184. The compound of Claim 183, wherein L is -CHR^{60}-; M is -CHR^{61}-; R is -CHR^{62}-; and T is -CHR^{63}-.

185. The compound of Claim 184, wherein A is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, -OR^9, -SR^9, -CN, -NR^{9}R^{10}, -CONR^{9}R^{10}, -CO$_2$R^9, -NR^{9}CO$_2$R^{10}, -NR^{9}CONR^{10}R^{11}, -NR^{9}CSNR^{10}R^{11} or -NR^{9}C(=NH)NR^{10}R^{11}.

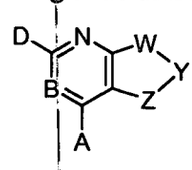
186. The compound of claim 183, having structural formula selected from the group consisting of:


,

, and

;

or a tautomer, salt, solvate, and/or ester thereof.

187. The compound of claim 186, wherein the salt is hydrochloride or trifluoroacetate salt.

188. The compound of claim 58, having structural Formula (Va):



(Va)

wherein:

D is hydrogen, alkyl, aryl, halo, -OH, $-NH_2$, $-SR^{15}$, $-CH_3$, $-CO_2H$ or $-CONH_2$;

A is $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, or $-CH_2NHC(O)CH_3$; and

R^{15} is hydrogen, alkyl, substituted alkyl, arylalkyl.

189. The compound of claim 188, wherein

Y forms a single bond with W and a double bond with Z;

W is $-C(R^{24})-$ or –N-;

Y is $-C(R^{26})-$ or –N-; and

Z is –S-, $-N(R^{28})$, or –O-.

190. The compound of claim 188, wherein

Y forms a double bond with W and a single bond with Z;

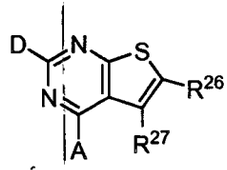
W is –S-, $-N(R^{25})$, or –O-

Y is $-C(R^{26})-$ or –N-; and

Z is $-C(R^{27})-$ or –N-.

191. The compound of claim 189 or 190, wherein B is $-C(R^{12})-$.

192. The compound of claim 188, having structural Formula (V):



(V)

wherein:

R^{26} is hydrogen, alkyl, halo, $-CO_2R^{54}$, $-CONR^{54}R^{55}$, $-SO_2NR^{54}R^{55}$, $-NR^{54}SO_2R^{55}$, $-B(OR^{54})(OR^{55})$, $-P(O)(OR^{54})(OR^{55})$ or $-P(O)(R^{54})(OR^{55})$;

R^{27} is hydrogen, alkoxy, alkyl, substituted alkyl, halo, -CN, $-C(O)NR^{56}R^{57}$, $-CO_2R^{56}$, $-SO_2NR^{56}R^{57}$, $-NR^{56}SO_2R^{57}$, $-B(OR^{56})(OR^{57})$, $-P(O)(OR^{56})(OR^{57})$ or $-P(O)(R^{56})(OR^{57})$; or alternatively R^{52} and R^{53} together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring and

R^{54}, R^{55}, R^{56}, and R^{57} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl; or alternatively R^{54} and R^{55} or R^{56} and R^{57} together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

provided that when R^{26} and R^{27} are hydrogen, and D is –SH; then A is $-NH_2$.

193. The compound of claim 192, wherein

when D is methyl, A is dimethylamino, and R^{53} is hydrogen; then R^{52} is not methyl, ethyl or carboxyl;

when D is methyl, A is dimethylamino, and R^{53} is methyl; then R^{52} is not methyl;

when D is $-SCH_3$, A is dimethylamino, and R^{53} is hydrogen; then R^{52} is not carboethoxy;

when D is hydrogen, A is dimethylamino, and R^{53} is hydrogen; then R^{52} is not carboxyl or carboethoxy;

when D is hydrogen, A is dimethylamino and R^{53} is methyl; then R^{52} is not methyl;

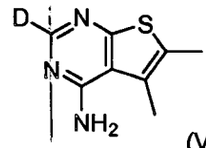
when D is hydrogen, A is methylamino and R^{53} is hydrogen; then R^{52} is not methyl, ethyl or carboethoxy;

when D is hydrogen, A is methylamino and R^{53} is methyl; then R^{52} is not methyl or carboethoxy;

when D is hydrogen, A is methylamino and R^{53} is $-CH_2NMe$; then R^{52} is not methyl or carboethoxy;

when D is phenyl, A is methylamino and R^{53} is hydrogen then R^{52} is not methyl; and when D is phenyl, A is -NH(CO)CH_3 and R^{53} is methyl then R^{52} is not carbomethoxy.

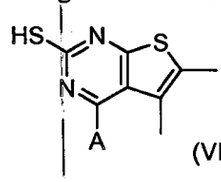
194. The ligand modifier of claim 192, having structural formula (VI):



(VI),

wherein D is hydrogen, -CH_3, -C_2H_5, phenyl or benzyl.

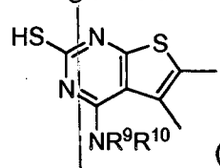
195. The compound of claim 192, having structural formula (VII):



(VII),

wherein A is hydrogen, -CH_3, -C_2H_5, phenyl or benzyl.

196. The compound of claim 192, having structural formula (VIII):

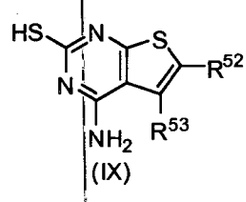


(VIII)

wherein

R^9 and R^{10} are independently hydrogen, -CH_3, -C_2H_5, phenyl or benzyl; and provided that both R^9 and R^{10} are not hydrogen.

197. The compound of claim 192, having structural formula (IX):



(IX)

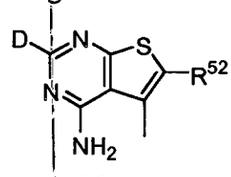
wherein

R^{52} is alkyl, substituted alkyl, -CN, $-C(O)NR^{54}R^{55}$, $-CO_2R^{54}$, $-SO_2NR^{54}R^{55}$, $-NR^{54}SO_2R^{55}$, $-B(OR^{54})(OR^{55})$, $-P(O)(OR^{54})(OR^{55})$, or $-P(O)(R^{54})(OR^{55})$;

R^{53} is alkyl, CO_2R^{56} or $-CONR^{56}R^{57}$, $-SO_2NR^{56}R^{57}$, $-NR^{56}SO_2R^{57}$, $-B(OR^{56})(OR^{57})$, $-P(O)(OR^{56})(OR^{57})$ or $-P(O)(R^{56})(OR^{57})$; and

R^{54} to R^{57} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl; or alternatively R^{52} and R^{53} together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring.

198. The compound of claim 192, having structural formula (X):



(X)

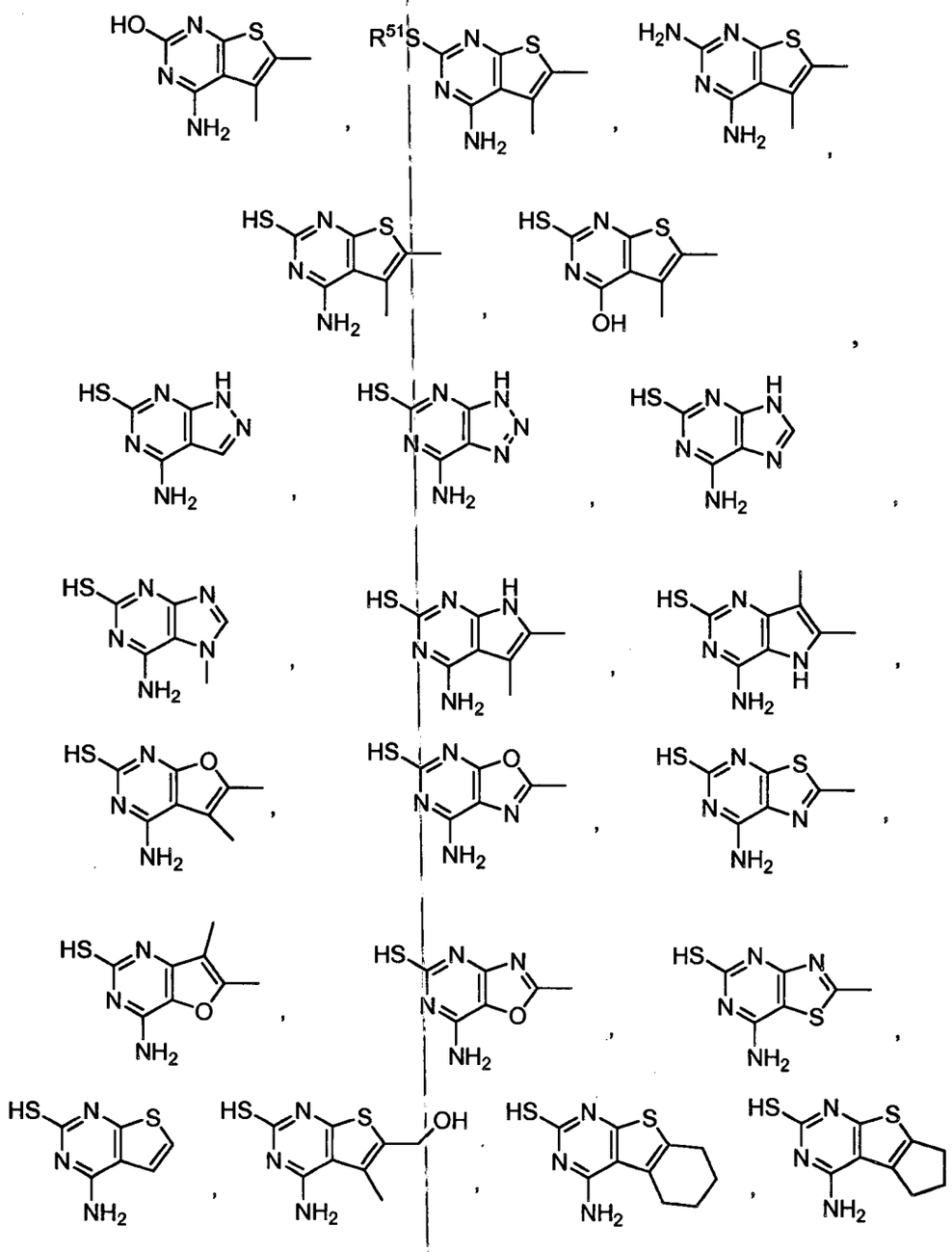
wherein,

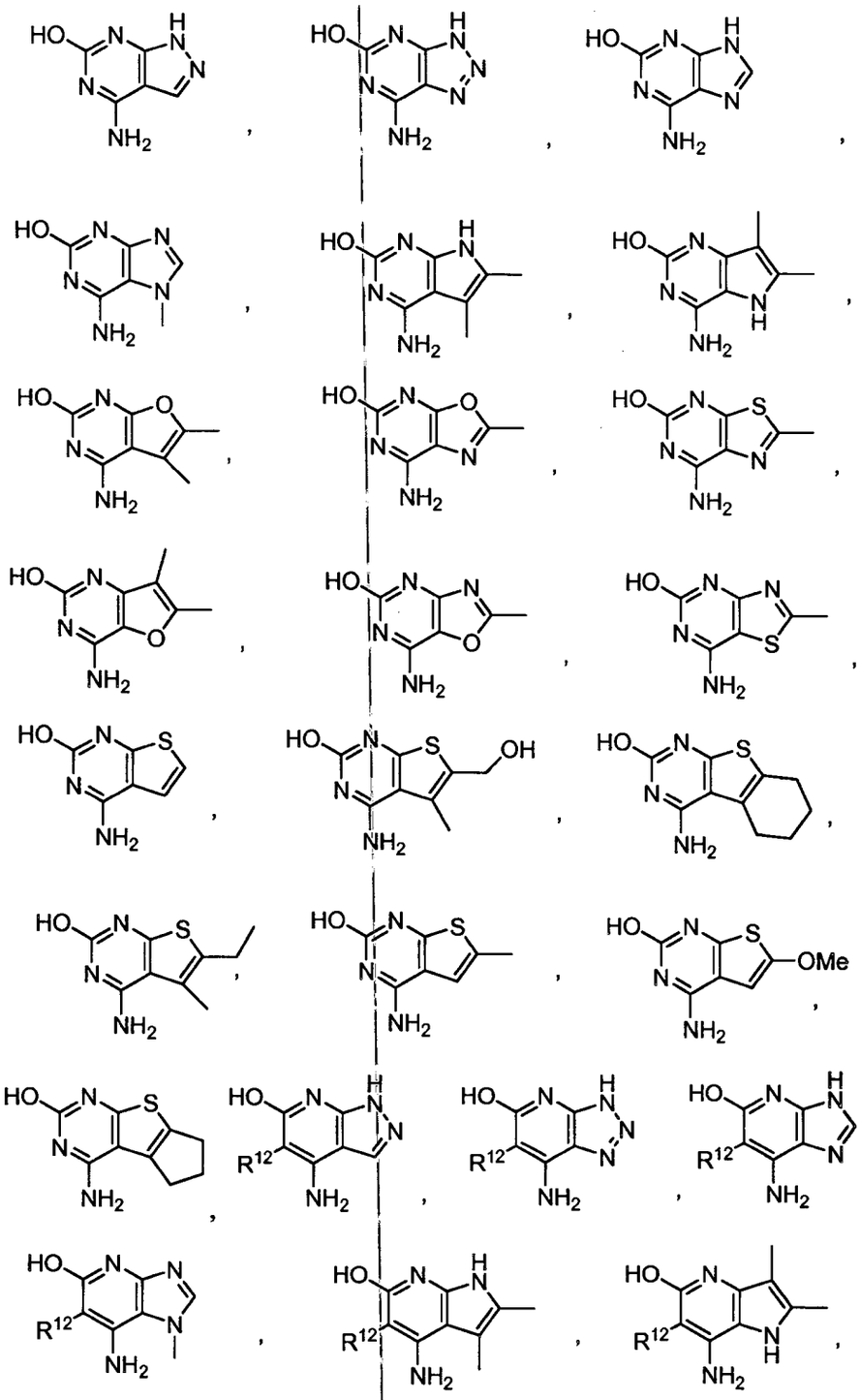
D is -OH, -SH or $-NH_2$,

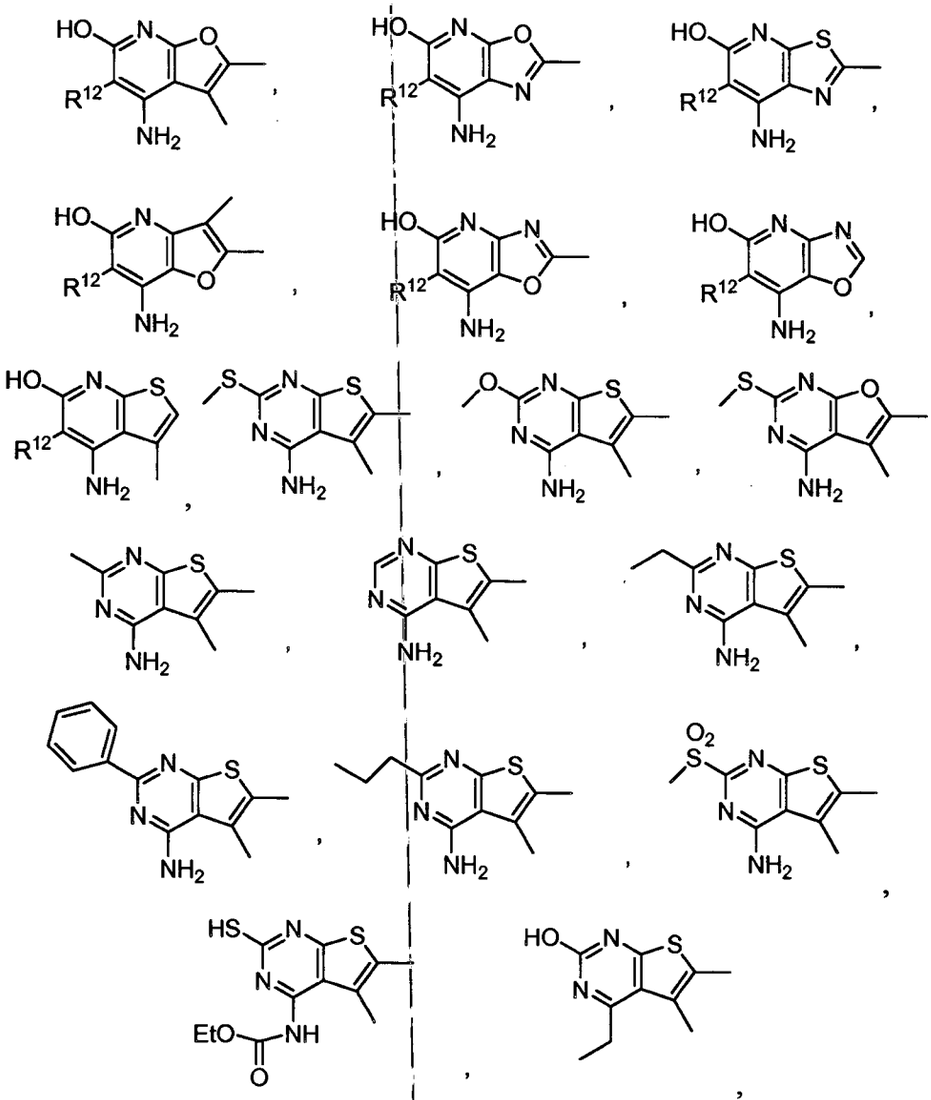
R^{52} is alkyl, substituted alkyl, alkoxy, -CN, $-C(O)NR^{54}R^{55}$, $-CO_2R^{54}$, $-SO_2NR^{54}R^{55}$, $-NR^{54}SO_2R^{55}$, $-B(OR^{54})(OR^{55})$, $-P(O)(OR^{54})(OR^{55})$, $-P(O)(R^{54})(OR^{55})$, and

R^{54} and R^{55} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl; or alternatively R^{54} and R^{55} together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring.

199. The compound of claim 188, having structural formula selected from the group consisting of







wherein,

R^{12} is –OH, -SH, -CN, $-CH_2OH$, or $-CO_2H$; and

R^{51} is $-CH_3$, $-CH_2CH_3$, benzyl, or $-CH_2CO_2CH_2CH_3$;

or a tautomer, salt, solvate, and/or ester thereof.

200. The compound of claim 199, wherein the salt is hydrochloride or trifluoroacetate salt.

201. An ingestible composition comprising the chemosensory receptor ligand modifier of claim 52.

202. The ingestible composition of claim 201, selected from the group consisting of a comestible composition, a medicinal composition, a pharmaceutical composition, and combinations thereof.

203. The ingestible composition of claim 201, selected from the group consisting of food or beverage product, non-edible product, and combinations thereof.

204. The ingestible composition of claim 203, wherein the food or beverage product is selected from the group consisting of the Soup category; the Dried Processed Food category; the Beverage category; the Ready Meal category; the Canned or Preserved Food category; the Frozen Processed Food category; the Chilled Processed Food category; the Snack Food category; the Baked Goods category; the Confectionary category; the Dairy Product category; the Ice Cream category; the Meal Replacement category; the Pasta and Noodle category; the Sauces, Dressings, Condiments category; the Baby Food category; the Spreads category; sweet coatings, frostings, or glazes; and combinations thereof.

205. The ingestible composition of claim 203, wherein the non-edible product is selected from the group consisting of nutritional products and dietary supplements, pharmaceuticals, over the counter medications, oral care products, and cosmetics.

206. The ingestible composition of claim 201, wherein the chemosensory receptor ligand modifier is a compound having structural Formula (I) as described in claim 56, or a tautomer, salt, solvate, and/or ester thereof.

207. The ingestible composition of claim 201, comprising at least about 0.0001 ppm of the chemosensory receptor ligand modifier.

208. The ingestible composition of claim 201, comprising from about 0.0001 ppm to about 10 ppm of the chemosensory receptor ligand modifier.

209. The ingestible composition of claim 201, comprising from about 0.01 ppm to about 100 ppm of the chemosensory receptor ligand modifier.

210. The ingestible composition of claim 201, comprising from about 10 ppm to about 100,000 ppm of the chemosensory receptor ligand modifier.

211. The ingestible composition of claim 201, further comprising one or more sweeteners.

212. The ingestible composition of claim 211, wherein the sweetener is selected from the group consisting of sucrose, fructose, glucose, galactose, mannose, lactose, tagatose, maltose, corn syrup (including high fructose corn syrup), D-tryptophan, glycine, erythritol, isomalt, lactitol, mannitol, sorbitol, xylitol, maltodextrin, maltitol, isomalt, hydrogenated glucose syrup (HGS), hydrogenated starch hydrolyzate (HSH), stevioside, rebaudioside A, other sweet Ste*via*-based glycosides, carrelame, other guanidine-based sweeteners, saccharin, acesulfame-K, cyclamate, sucralose, alitame, mogroside, neotame, aspartame, other aspartame derivatives, and combinations thereof.

213. The ingestible composition of claim 206, wherein the chemosensory receptor ligand modifier is a compound having structural Formula (II) as described in claim 58 or strutural Formula (III) as described in claim 97, or a tautomer, salt, solvate, and/or ester thereof.

214. The ingestible composition of claim 206, wherein the chemosensory receptor ligand modifier has structural Formula (IIa) as described in claim 60, structural Formula (IIc) as described in claim 73, structural Formula (IIIb) as described in claim 124, or structural Formula (IIIb1) as described in claim 133, or a tautomer, salt, solvate, and/or ester thereof.

215. The ingestible composition of claim 202, wherein the pharmaceutical composition comprises a compound having structural Formula (I) as described in claim 56, or a tautomer, salt, solvate, and/or ester thereof; and a pharmaceutically acceptable vehicle.

216. A method of enhancing the sweet taste of an ingestible composition comprising contacting the ingestible composition or precursors thereof with a chemosensory receptor ligand modifier to form a modified ingestible composition.

217. The method of claim 216, wherein the ingestible composition is selected from the group consisting of a comestible composition, a medicinal composition, a pharmaceutical composition, and compositions thereof.

218. The method of claim 216, wherein the ingestible composition is selected from the group consisting of food or beverage product, non-edible product, and combinations thereof.

219. The method of claim 216, wherein the modified ingestible composition comprises at least about 0.001 ppm of the chemosensory receptor ligand modifier.

220. The method of claim 216, wherein the modified ingestible composition comprises from about 0.001 ppm to about 100,000 ppm of the chemosensory receptor ligand modifier.

221. The method of claim 216, wherein the chemosensory receptor ligand modifier is a compound having structural Formula (I) as described in claim 56, or a tautomer, salt, solvate, and/or ester thereof.

222. The method of claim 216, wherein the chemosensory receptor ligand enchancer is a compound having structural Formula (II) as described in claim 58 or strutural Formula (III) as described in claim 97, or a tautomer, salt, solvate, and/or ester thereof.

223. The method of claim 216, wherein the chemosensory receptor ligand enchancer has structural Formula (IIa) as described in claim 60, structural Formula (IIc) as described in claim 73, structural Formula (IIIb) as described in claim 128, or structural Formula (IIIb1) as described in claim 138, or a tautomer, salt, solvate, and/or ester thereof.

224. A method of treating a condition associated with a chemosensory receptor comprising administering to a subject in need of such treatment an effective amount of an entity selected from the group consisting of a chemosensory receptor modifier, chemosensory receptor ligand modifier, and a combination thereof, wherein the entity interacts with an interacting site of the chemosensory receptor.

225. The method of claim 224, wherein the condition associated with a chemosensory receptor is taste.

226. The method of claim 224, wherein the condition associated with a chemosensory receptor is a condition associated with gastrointestinal system or metabolic disorders.

227. The method of claim 224, wherein the condition associated with a chemosensory receptor is a condition associated with a functional gastrointestinal disorder.

228. The method of claim 224, wherein the condition associated with a chemosensory receptor is a condition associated with cells expressing a T1R.

229. The method of claim 224, wherein the condition associated with a chemosensory receptor is a condition associated with hormone-producing cells that express a T1R.

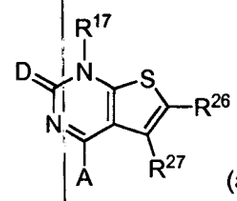
230. The method of claim 224, wherein the entity is a chemosensory receptor ligand modifier.

231. The method of claim 230, wherein the chemosensory receptor ligand modifier is a compound having structural Formula (I) as described in claim 56, or a tautomer, salt, solvate, and/or ester thereof.

232. The method of claim 230, wherein the chemosensory receptor ligand modifier is a compound having structural Formula (II) as described in claim 58 or strutural Formula (III) as described in claim 97, or a tautomer, salt, solvate, and/or ester thereof.

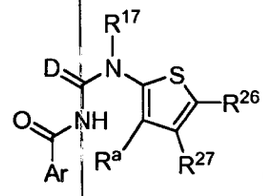
233. The method of claim 230, wherein the chemosensory receptor ligand modifier has structural Formula (IIa) as described in claim 60, structural Formula (IIc) as described in claim 73, structural Formula (IIIb) as described in claim 128, or structural Formula (IIIb1) as described in claim 138, or a tautomer, salt, solvate, and/or ester thereof.

234. A process of preparing a compound having structural Formula (a):



(a),

comprising reacting a compound having structural Formula (b)



(b)

with a base,

wherein:

D is oxygen or sulfur;

A is $-NH_2$ or $-OR^b$;

R^{17} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, or substituted arylalkyl;

R^{26} and R^{27} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, -CN, $-NO_2$, $-OR^{31}$, $-S(O)_hR^{31}$, $-NR^{31}R^{32}$, $-CONR^{31}R^{32}$, $-CO_2R^{31}$, $-SO_2NR^{31}R^{32}$, or $-NR^{31}SO_2R^{32}$; or alternatively R^{26} and R^{27}, together with the atoms to which they are bonded, form a cycloalkyl, substituted cycloalkyl, heterocycloalkyl, or substituted heterocycloalkyl ring;

Ar is aryl or substituted aryl; and

R^a is -CN, $-C(O)R^b$, $-C(O)OR^b$, $-C(O)N(R^b)_2$;

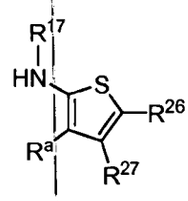
each R^b is independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, or substituted heteroarylalkyl;

h is 0, 1 or 2; and

R^{31} and R^{32} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl; or alternatively R^{31} and R^{32}, together with the atoms to which they are bonded, form a cycloheteroalkyl or substituted cycloheteroalkyl ring.

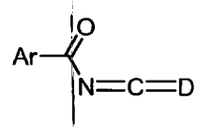
235. The process of claim 234, wherein the base is an inorganic base.

236. The process of claim 234, wherein the compound having structural Formula (b) is prepared by reacting a compound having structural Formula (c):



(c),

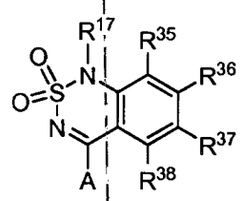
with a compound having structural Formula (d):



(d).

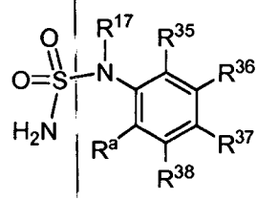
237. The process of claim 234 or 236, wherein Ar is phenyl or substituted phenyl.

238. A process of preparing a compound having structural Formula (e):



(e),

comprising reacting a compound having structural Formula (f)



(f),

with a base,

wherein:

A is $-NH_2$ or $-OR^b$;

R^{17} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, or substituted arylalkyl;

R^{35}, R^{36}, R^{37}, and R^{38} are each independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl, -CN, $-NO_2$, $-OR^{41}$, $-S(O)_kR^{41}$, $-NR^{41}R^{42}$, $-CONR^{41}R^{42}$, $-CO_2R^{41}$, $-SO_2NR^{41}R^{42}$, and $-NR^{41}SO_2R^{42}$; or alternatively, R^{35} and R^{36}, R^{36} and R^{37}, or R^{37} and R^{38}, together with the atoms to which they are bonded, form a cycloalkyl, substituted cycloalkyl, heterocycloalkyl, or substituted heterocycloalkyl ring;

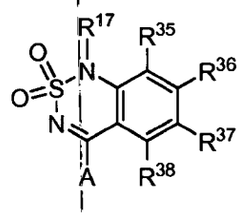
R^a is is -CN, $-C(O)R^b$, $-C(O)OR^b$, $-C(O)N(R^b)_2$;

each R^b is independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, or substituted heteroarylalkyl; and

R^{41} and R^{42} are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, acyl, substituted acyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl; or alternatively R^{41} and R^{42}, together with the atoms to which they are bonded, form a cycloheteroalkyl or substituted cycloheteroalkyl ring.

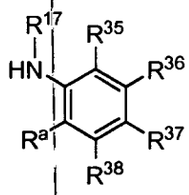
239. The process of claim 238, wherein the base is an inorganic base.

240. A process of preparing a compound having structural Formula (e):



(e),

comprising reacting a compound having structural Formula (g)



(g)

with $NH_2S(O)_2NH_2$ or Cl-$S(O)_2$-NH_2 in the presence of a base to provide directly a compound having structural Formula (e); or alternatively to provide the compound having structural formula (f) of claim 221 which is further reacted with a base to provide a compound having structural Formula (e).

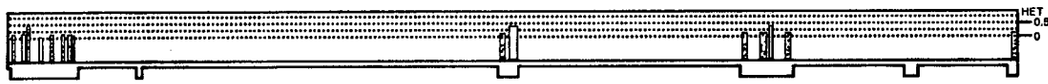
241. The process of claim 240, wherein the base is an organic base.

gene model (contig mRNA transcript):	Contig Label	Contig	mrna	protein	mrna orientation	transcript	snp count
	reference	NT_021937	NM_138697	NP_619642	forward	plus strand 8, coding	

Region	Contig position	mRNA pos	dbSNP rs# cluster id	Hetero-zygosity	Validation	3D	OMIM	Function	dbSNP allele	Protein residue	Codon pos	Amino acid pos
exon_1	1152801	1						start codon				1
exon_1	1152811	11	rs35375392	0.034				nonsynonymous	A	Tyr [Y]	2	4
				0.034				contig reference	G	Cys [C]	2	4
exon_2	1168473	329	rs41278020	N.D.				nonsynonymous	T	Val [V]	2	110
				N.D.				contig reference	C	Ala [A]	2	110
exon_3	1172598	1039	rs10864628	0.128	✓	Yes		nonsynonymous	G	Glu [E]	1	347
				0.128	✓	Yes		contig reference	A	Lys [K]	1	347
	1172626	1067	rs41307749	N.D.				nonsynonymous	G	Cys [C]	2	356
				N.D.				contig reference	C	Ser [S]	2	356
	1172673	1114	rs34160967	0.137	✓			nonsynonymous	A	Thr [T]	1	372
				0.137	✓			contig reference	G	Ala [A]	1	372
exon_5	1174423	1520	rs35118458	0.059	✓			nonsynonymous	A	Gln [Q]	2	507
				0.059	✓			contig reference	G	Arg [R]	2	507
exon_6	1176292	1807	rs41278022	N.D.				nonsynonymous	T	Cys [C]	1	603
				N.D.				contig reference	C	Arg [R]	1	603
	1176759	2274	rs34857011	0.126	✓			synonymous	A	Glu [E]	3	758
				0.126	✓			contig reference	G	Glu [E]	3	758

FIG. 1

gene model (contig mRNA transcript):	Contig Label	Contig	mrna	protein	mrna orientation	transcript	snp count
	reference	NT_004610	NM_152232	NP_689418	reverse	minus strand 17, coding	



Color Legend

Region	Contig position	mRNA pos	dbSNP rs# cluster id	Hetero-zygosity	Validation	3D	OMIM	Function	dbSNP allele	Protein residue	Codon pos	Amino acid pos
exon_6	1990442	2514	rs9988418	0.074	✓			nonsynonymous	A	Lys [K]	2	838
				0.074	✓			contig reference	G	Arg [R]	2	838
	1990585	2731	rs12075191	0.104	✓			synonymous	T	Ile [I]	3	790
				0.104	✓			contig reference	C	Ile [I]	3	790
	1990636	2320	rs12033832	0.457	✓			synonymous	T	Ser [S]	3	773
				0.457	✓			contig reference	C	Ser [S]	3	773
	1990843	2113	rs34542537	0.030	✓			synonymous	T	Pro [P]	3	704
				0.030	✓			contig reference	C	Pro [P]	3	704
	1991007	1949	rs41273165	N.D.				nonsynonymous	A	Met [M]	1	650
				N.D.				contig reference	G	Val [V]	1	650
	1991171	1785	rs41273167	N.D.				nonsynonymous	C	Thr [T]	2	595
				N.D.				contig reference	T	Ile [I]	2	595
	1991235	1721	rs6662276	0.122	✓ H			nonsynonymous	A	Thr [T]	1	574
				0.122	✓ H			contig reference	G	Ala [A]	1	574
	1991236	1720	rs11805253	N.D.	99			synonymous	T	Ala [A]	3	573
				N.D.	99			contig reference	C	Ala [A]	3	573

FIG. 2A

exon_4	2000188	1457	rs28374389	N.D.			nonsynonymous	G	Val [V]	1	486
				N.D.			contig reference	A	Ile [I]	1	486
	2000300	1345	rs9439751	N.D.			synonymous	A	Leu [L]	3	448
				N.D.			contig reference	G	Leu [L]	3	448
	2000315	1330	rs35775756	N.D.			synonymous	T	Asp [D]	3	443
				N.D.			contig reference	C	Asp [D]	3	443
exon_3	2005063	1244	rs35605435	N.D.			nonsynonymous	A	Ile [I]	1	415
				N.D.			contig reference	G	Val [V]	1	415
	2005356	951	rs34545913	N.D.			nonsynonymous	C	Pro [P]	2	317
				N.D.			contig reference	G	Arg [R]	2	317
	2005357	950	rs34447754	N.D.			nonsynonymous	G	Gly [G]	1	317
				N.D.			contig reference	C	Arg [R]	1	317
	2005424	883	rs28470550	N.D.		Yes	synonymous	G	Thr [T]	3	294
				N.D.		Yes	contig reference	T	Thr [T]	3	294
	2005735	572	rs35874116	N.D.			nonsynonymous	G	Val [V]	1	191
				N.D.			contig reference	A	Ile [I]	1	191
exon_1	2010471	27	rs9701796	N.D.	✂		nonsynonymous	G	Cys [C]	2	9
				N.D.	✂		contig reference	C	Ser [S]	2	9
exon_1	2010496	2					start codon				1

FIG. 2B

9 Species
Homo
Pan
Macaca
Mus
Rattus
Canis
Gallus
Takifugu
Danio
Mammals only
Homo
Pan
Macaca
Canis
Rattus
Mus

FIG. 3

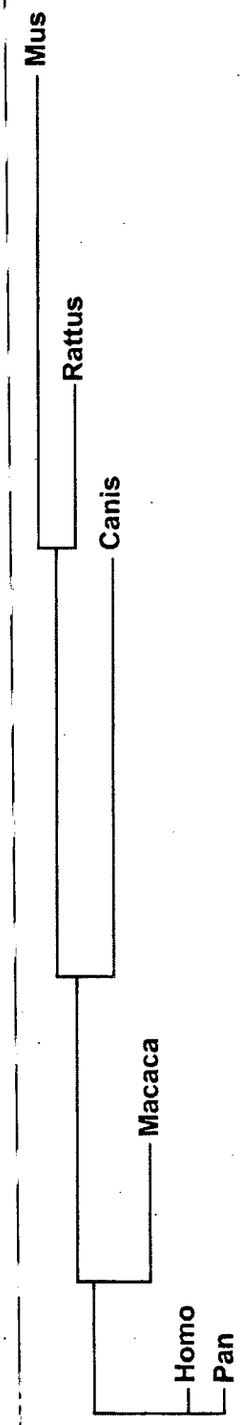


FIG. 4

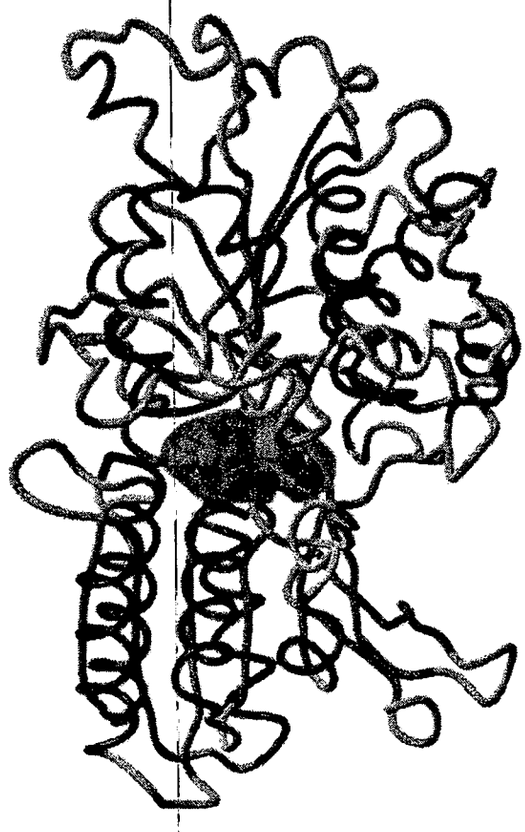


FIG. 5

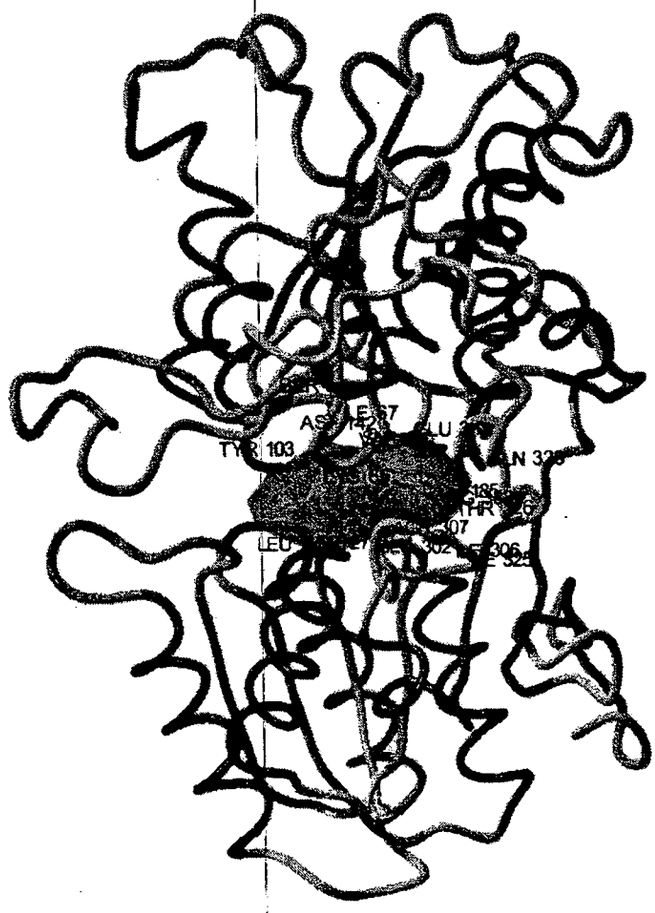


FIG. 6

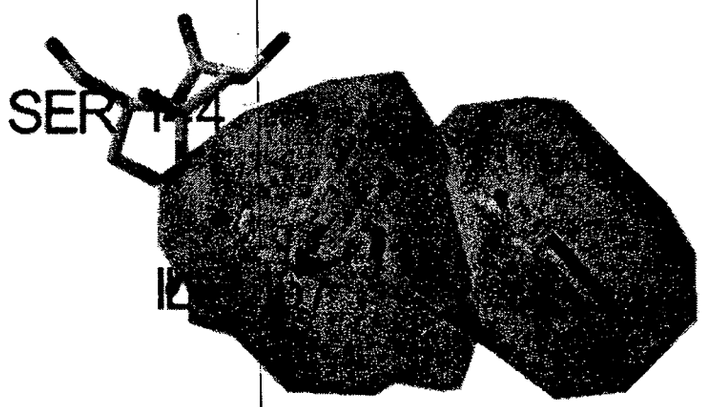


FIG. 7A

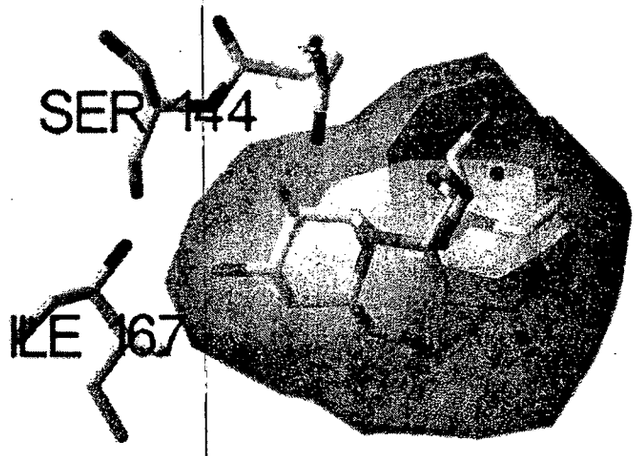


FIG. 7B

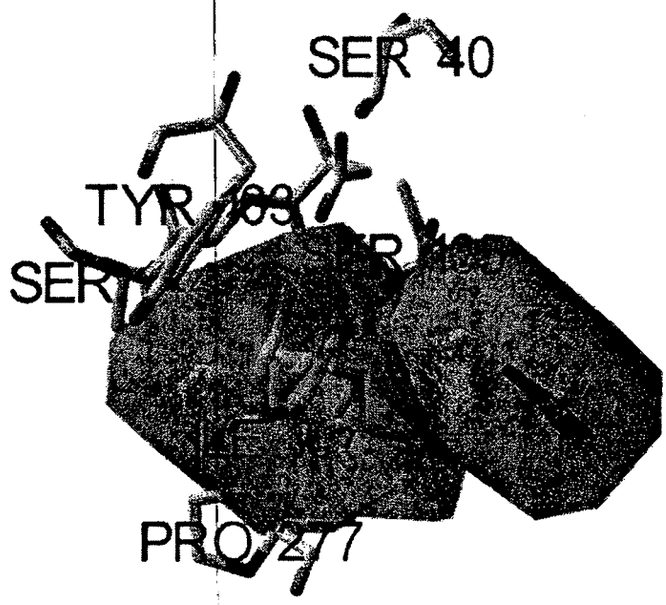


FIG. 8A

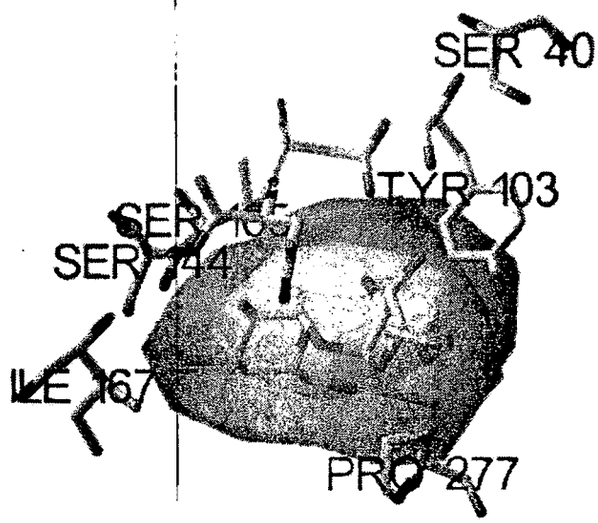


FIG. 8B

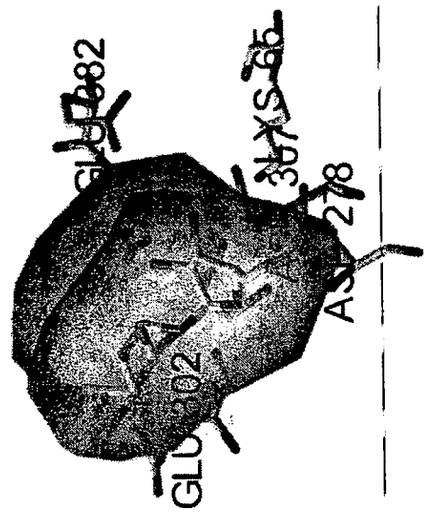


FIG. 9B

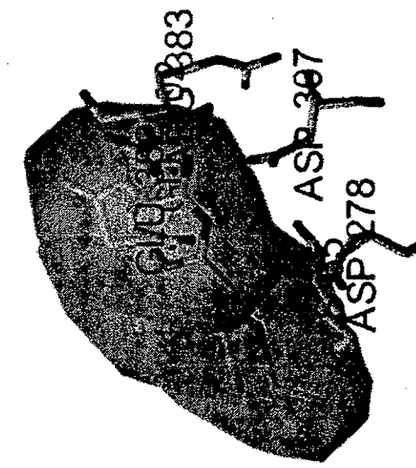


FIG. 9C

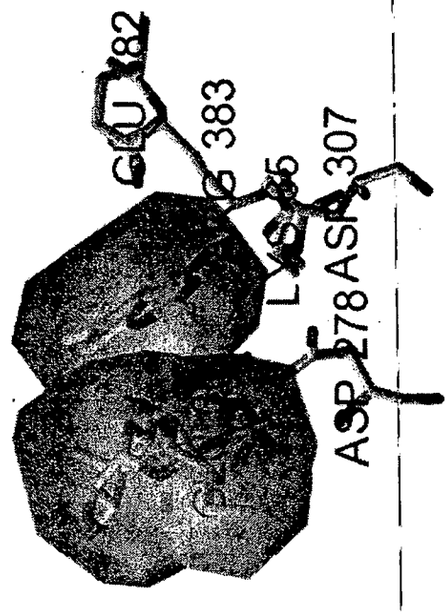


FIG. 9A

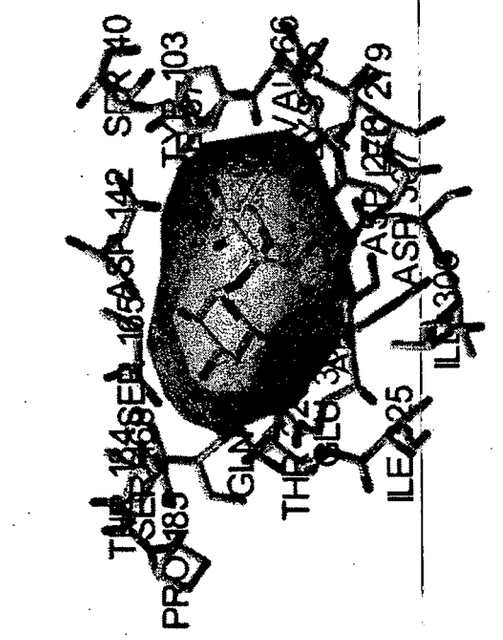


FIG. 10B

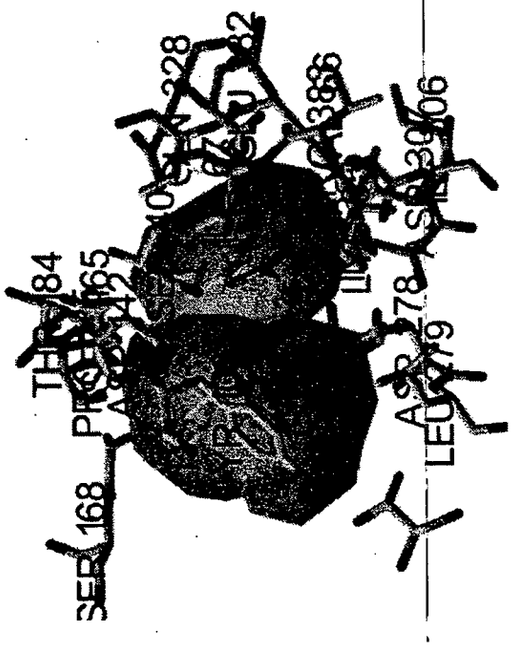


FIG. 10A

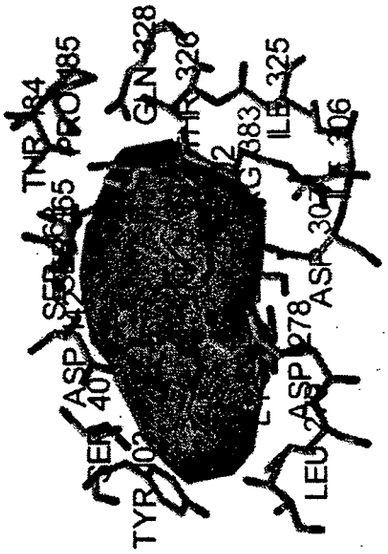


FIG. 10C

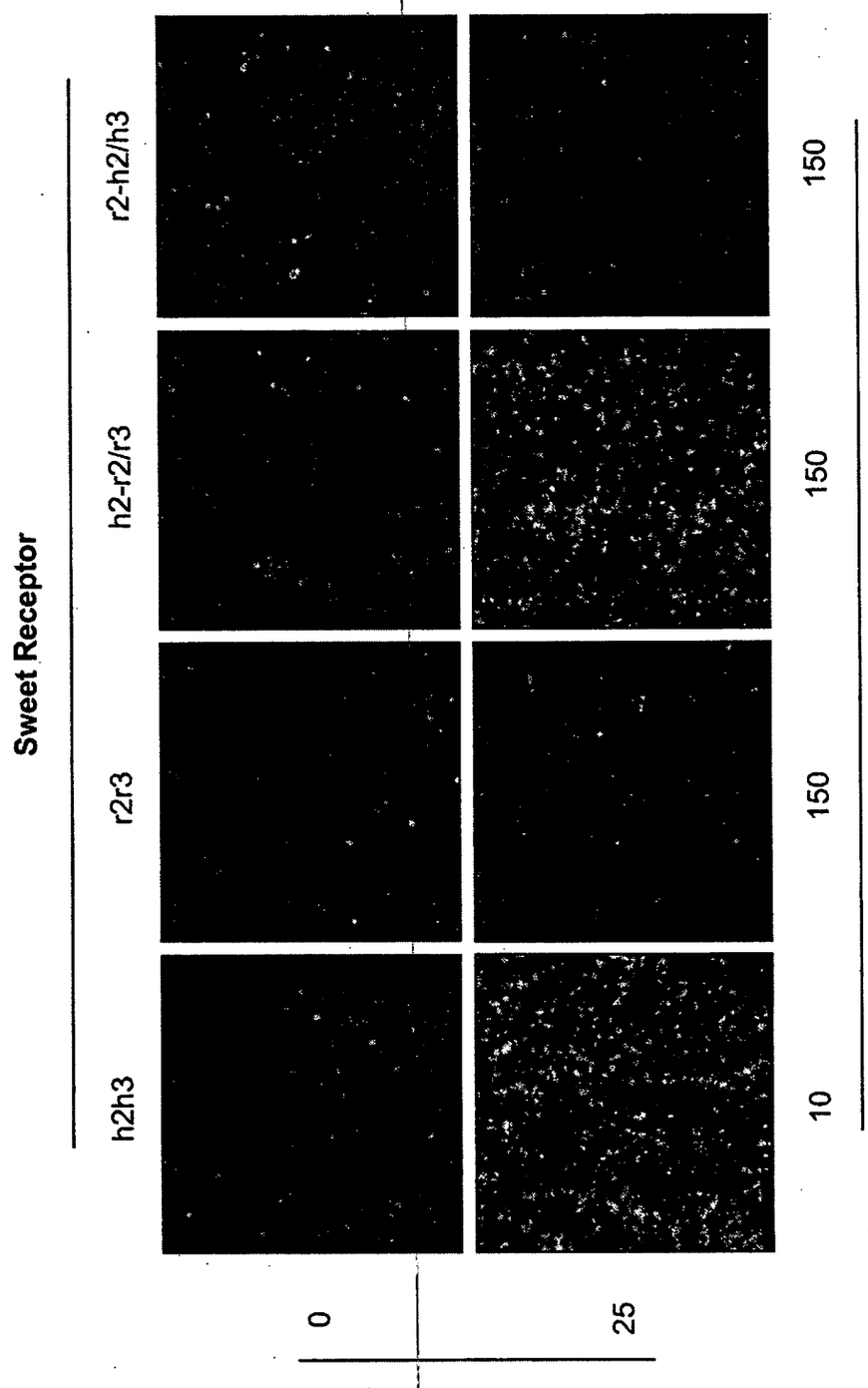

Sweet Receptor
h2h3
r2r3
h2-r2/r3
r2-h2/h3
10
150
150
150
Sucralose (μM)
S2423 (μM)
0
25

FIG. 11

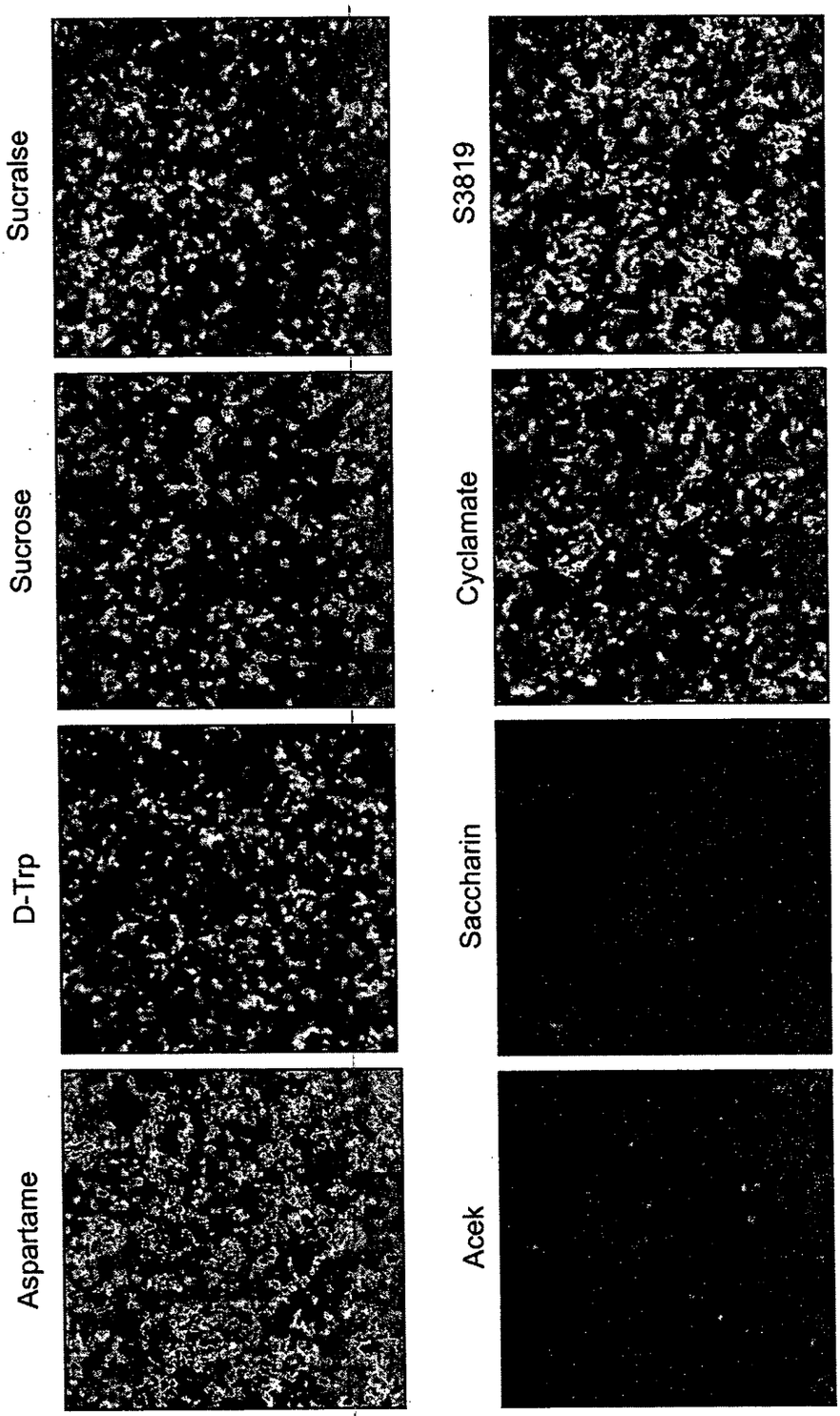

Sucralse
S3819
Sucrose
Cyclamate
D-Trp
Saccharin
Aspartame
Acek

FIG. 12

II PARTE

Industria y Comercio
SUPERINTENDENCIA

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

SOLICITUD DE

PATENTE DE INVENCION
PCT ENTRADA EN FASE NACIONAL
(II PARTE)

09-139683

21. EXPEDIENTE No.

54. TITULO: MODULACION DE RECEPTORES QUIMIOSENSORIALES Y LIGANDOS RELACIONADOS CON LOS MISMOS

51. CLASIFICACION INTERNACIONAL: A61K 31/495, A61P 27/00, C07D 487/08, C12N 5/06, G01N 33/53

71. SOLICITANTE: SENOMYX INC.

DOMICILIO: 4767 Nexus Centre Drive, San Diego, California 92121, ESTADOS UNIDOS DE AMERICA

74. APODERADO: Dra. MARGARITA CASTELLANOS A.

22. BOGOTA, D.C., 07 DIC. 2009

MODULACIÓN DE RECEPTORES QUIMIOSENSORIALES Y LIGANDOS RELACIONADOS CON LOS MISMOS

ANTECEDENTES DE LA INVENCIÓN

El sistema gustativo proporciona información sensorial acerca de la composición química del mundo externo. La transducción gustativa constituye una de las formas más sofisticadas de sensación desencadenada por químicos en los animales. La señalización del gusto se encuentra a través del reino animal, desde simples metazoos hasta el más complejo de los vertebrados. Se cree que las sensaciones asociadas con el gusto involucran distintas vías de señalización mediadas por receptores, *es decir*, receptores metabotrópicos o ionotrópicos. Las células que expresan los receptores gustativos, cuando se exponen a ciertos estímulos químicos, provocan una sensación gustativa mediante despolarización para generar un potencial de acción, el cual se cree que desencadena la sensación. Se cree que este evento desencadena la liberación de neurotransmisores en las sinapsis neuronales de los aferentes gustativos, iniciando por consiguiente la señalización a lo largo de las vías neuronales que median la percepción gustativa.

Como tales, los receptores gustativos específicamente reconocen moléculas que provocan una sensación gustativa específica. En la presente también se efectúa referencia a estas moléculas como "estimulantes del sabor". Muchos receptores gustativos pertenecen a la superfamilia de receptores 7-transmembrana, los cuales también se conocen como receptores acoplados a proteína G (GPCRs, por sus siglas en inglés). Se cree que otros sabores se encuentran mediados por proteínas de canales. Los receptores acoplados a proteína G controlan muchas funciones fisiológicas, tales como la función

endocrina, la función exocrina, la frecuencia cardíaca, la lipólisis, el metabolismo de los carbohidratos, y la señalización transmembrana.

Por ejemplo, la familia C de los receptores acoplados a proteína G (GPCRs) de los humanos comprende ocho receptores de glutamato metabotrópicos (mGlu(1-8)), dos receptores de ácido gamma-aminobutírico(B) (GABA(B)) heterodiméricos, un receptor sensor de calcio (CaR), tres receptores gustativos (T1R), un receptor de L-alfa-amino ácidos (GPRC6A) promiscuo, y cinco receptores huérfanos. La familia C de GPCRs está caracterizada por un gran dominio amino-terminal, el cual se une a los agonistas ortostéricos endógenos. Además, también se han informado moduladores alostéricos los cuales se unen a los siete dominios transmembrana de los receptores.

En general, al unirse el ligando al GPCR, el receptor presumiblemente experimenta un cambio conformacional que conduce a la activación de una proteína G. Las proteínas G están comprendidas de tres subunidades: una subunidad α de unión a guanil nucleótido, una subunidad β, y una subunidad γ. Las proteínas G alternan entre dos formas, dependiendo de si GDP o GTP está unida a la subunidad α. Cuando GDP está unida, la proteína G existe como un heterotrímero: el complejo $G_{\alpha\beta\gamma}$. Cuando GTP está unida, la subunidad α se disocia del heterotrímero, dejando un complejo $G_{\beta\gamma}$. Cuando un complejo $G_{\alpha\beta\gamma}$ se asocia de modo operativo con un receptor acoplado a proteína G activado en una membrana celular, se incrementa la velocidad de intercambio de GTP por GDP unida y se incrementa la velocidad de disociación de la subunidad G_α unida del complejo $G_{\alpha\beta\gamma}$. La subunidad G_α libre y el complejo $G_{\beta\gamma}$ son de este modo capaces de transmitir una señal a elementos secuencia abajo de una variedad de vías de transducción de señales. Estos eventos forman la base para una multiplicidad de diferentes fenómenos de señalización celular, que incluyen por ejemplo los

fenómenos de señalización que se identifican como percepciones sensoriales neurológicas tales como el gusto y/o el olfato.

Se cree que los mamíferos tienen cinco modalidades gustativas básicas: dulce, amarga, agria, salada, y umami (el sabor del glutamato monosódico). Numerosos estudios fisiológicalos en animales han demostrado que las células receptoras del sabor pueden responder de modo selectivo a diferentes estímulos químicos. En los mamíferos, las células receptoras del sabor se encuentran agrupadas en las papilas gustativas que se distribuyen en diferentes papilas en el epitelio de la lengua. La papila circunvalada, que se encuentra en la parte bien trasera de la lengua, contiene cientos a miles de papilas gustativas. Por el contrario, la papila foliada, situada en el borde lateral posterior de la lengua, contiene docenas a cientos de papilas gustativas. Además, la papila fungiforme, situada en el frente de la lengua, contiene solamente una sola papila gustativa o unas pocas papilas gustativas.

Cada papila gustativa, dependiendo de la especie, contiene 50-150 células, que incluyen a las células precursoras, a las células de soporte, y a las células receptoras del sabor. Las células receptoras se encuentran enervadas en su base por terminaciones nerviosas aferentes que transmiten la información a los centros gustativos de la corteza a través de sinapsis en el tronco cerebral y en el tálamo. Es importante dilucidar los mecanismos de la señalización y del procesamiento de la información de las células gustativas para comprender la función, regulación, y percepción del sentido del gusto.

El sistema gustativo se ha seleccionado durante la evolución para detectar compuestos nutritivos y beneficiosos así como también sustancias nocivas o tóxicas. Fuera de la lengua, también se ha localizado la expresión de $G\alpha_{gust}$ en las células gástricas y pancreáticas, lo cual sugiere que también puede existir un mecanismo sensor del sabor en el tracto gastrointestinal (GI). La expresión de los

receptores gustativos también se ha encontrado en el recubrimiento del estómago y del intestino, lo cual sugiere que los receptores gustativos pueden desempeñar un rol en la percepción molecular de entidades y toxinas terapéuticas.

En la actualidad se conocen secuencias completas o parciales de numerosos receptores humanos y otros receptores quimiosensoriales eucarióticos. Dentro de varios de los últimos años, una cantidad de grupos que incluyen al presente cesionario Senomyx, Inc. han informado la identificación y la clonación de genes a partir de dos familias de GPCR que se encuentran involucrados en la modulación del gusto y han obtenido resultados experimentales en relación con la comprensión de la biología del gusto. Estos resultados indican que el sabor amargo, dulce y a aminoácido, al que también se hace referencia como sabor umami, se desencadenan mediante la activación de dos tipos de receptores específicos situados en la superficie de las células receptoras del sabor (TRCs, por sus siglas en inglés) sobre la lengua *es decir*, T2Rs y T1Rs. Actualmente se cree que al menos 26 a 33 genes codifican receptores funcionales (T2Rs) para las sustancias de sabor amargo en humanos y roedores respectivamente.

Por el contrario existen solamente 3 T1Rs, T1R1, T1R2 y T1R3, los cuales se encuentran involucrados en el sabor umami y dulce. Estructuralmente, los receptores T1R y T2R poseen el sello distintivo de los receptores acoplados a proteína G (GPCRs), *es decir*, los 7 dominios transmembrana flanqueados por pequeños términos extracelulares e intracelulares amino- y carboxil- respectivamente.

Se han clonado T2Rs a partir de diferentes mamíferos incluyendo ratas, ratones y humanos. Los T2Rs comprenden una nueva familia de receptores acoplados a proteína G humanos y de roedores que están expresados en subconjuntos de células receptoras del sabor del epitelio de la lengua y del

paladar. Estos receptores gustativos se organizan en grupos en células gustativas y se encuentran genéticamente unidos a loci que ejercen una influencia en el sabor amargo. El hecho de que los T2Rs modulen el sabor amargo se ha demostrado en ensayos basados en células. Por ejemplo, se ha demostrado que mT2R-5, hT2R-4 y mT2R-8 son activados por moléculas amargas en ensayos de gustducina *in vitro*, proporcionando una prueba experimental de que los T2Rs funcionan como receptores del sabor amargo. Véase también los T2Rs descriptos en la Patente Estadounidense No. 7.105.650.

Los miembros de la familia T1R en general incluyen T1R1, T1R2, y T1R3, *por ejemplo*, rT1R3, mT1R3, hT1R3, rT1R2, mT1R2, hT1R2, y rT1R1, mT1R1 y hT1R1. Se sabe que los tres miembros de los génes de T1R T1R1, T1R2 y T1R3 forman heterodímeros funcionales que específicamente reconocen edulcorantes y aminoácidos. Generalmente se cree que la combinación T1R2/T1R3 reconoce edulcorantes naturales y artificiales mientras que la combinación T1R1/T1R3 reconoce diversos L-aminoácidos y glutamato monosódico (MSG, por sus siglas en inglés), respectivamente. Por ejemplo, la co-expresión de T1R1 y T1R3 en células hospedantes recombinantes resulta en un receptor gustativo hetero-oligomérico que responde a estímulos del sabor umami. Los estímulos del sabor umami incluyen a modo de ejemplo al glutamato monosódico y a otras moléculas que provocan una sensación gustativa "sabrosa". Por el contrario, la co-expresión de T1R2 y T1R3 en células hospedantes recombinantes resulta en un receptor del sabor dulce hetero-oligomérico que responde a ambos edulcorantes que ocurren naturalmente y artificiales.

Existe una necesidad en la técnica de desarrollar diversos modos de identificar compuestos u otras entidades adecuados para modificar receptores y sus ligandos asociados con la quimiosensorialidad o con reacciones o sensaciones relacionadas con la quimiosensorialidad. Además, existe una

necesidad en la técnica de compuestos o de otras entidades con dichas características.

BREVE SÍNTESIS DE LA INVENCIÓN

La presente invención se basa, al menos en parte, en el descubrimiento de que un dominio extracelular, *por ejemplo*, el dominio Venus atrapamoscas (Venus flytrap domain) de un receptor quimiosensorial, especialmente uno o más sitios de interacción dentro del dominio Venus atrapamoscas, constituye un objetivo adecuado para que los compuestos u otras entidades modulen el receptor quimiosensorial y/o sus ligandos. En consecuencia, la presente invención proporciona métodos de cribado para identificar modificadores de receptores quimiosensoriales y sus ligandos así como también modificadores capaces de modular receptores quimiosensoriales y sus ligandos.

En una realización, la presente invención proporciona un método de cribado para un candidato a un modificador del ligando del receptor quimiosensorial. El método comprende determinar si una entidad de ensayo es adecuada para interactuar con un receptor quimiosensorial *a través de* un sitio de interacción dentro del dominio Venus atrapamoscas del receptor quimiosensorial.

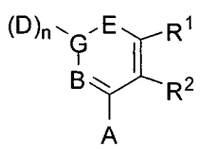
En otra realización, la presente invención proporciona un método de cribado para a un candidato a un modificador del ligando del receptor quimiosensorial. El método comprende determinar si una entidad de ensayo es adecuada para interactuar con un receptor quimiosensorial *a través de* un primer sitio de interacción dentro del dominio Venus atrapamoscas del receptor quimiosensorial, en donde el primer sitio de interacción se identifica a la luz de un segundo sitio de interacción identificado en base a la interacción entre un ligando del receptor quimiosensorial y el receptor quimiosensorial.

Aún en otra realización, la presente invención proporciona un método de cribado para un candidato a un modificador del receptor quimiosensorial. El método comprende determinar si una entidad de ensayo es adecuada para interactuar con un receptor quimiosensorial *a través de* un sitio de interacción dentro del dominio Venus atrapamoscas del receptor quimiosensorial, en donde el sitio de interacción incluye un residuo de interacción seleccionado del grupo integrado por N143, S144, I167, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, P185, T184, T326, E302, V384, A305, I325, I306, D307, E382, I279, I67, V66, V309, S303, T242, F103, Q328, y S168 de T1R2 y una combinación de los mismos, en donde una entidad de ensayo adecuada para interactuar con el sitio de interacción del receptor quimiosensorial es indicativa de un candidato de un modificador del receptor quimiosensorial.

Aún en otra realización, la presente invención proporciona un método de modulación de la actividad de un ligando del receptor quimiosensorial. El método comprende poner en contacto un modificador del ligando del receptor quimiosensorial con una célula que contiene un dominio Venus atrapamoscas T1R2 en presencia de un ligando del receptor quimiosensorial, en donde el modificador del ligando del receptor quimiosensorial interactúa con un sitio de interacción del receptor quimiosensorial.

Todavía en otra realización, la presente invención proporciona un modificador del ligando del receptor quimiosensorial, en donde en presencia de un ligando del receptor quimiosensorial éste interactúa con el dominio Venus atrapamoscas T1R2 *a través de* al menos tres residuos de interacción seleccionados del grupo integrado por N143, S144, I167, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, y S168 de T1R2.

Todavía en otra realización, la presente invención proporciona un modificador del ligando del receptor quimiosensorial que tiene una estructura de la Fórmula (I):



(I)

o un tautómero, sal, solvato, y/o éster del mismo, en donde:

G forma un enlace único o bien con D o E y un enlace doble con el otro de D o E;

R^1 es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, $-NO_2$, $-OR^3$, $-S(O)_aR^3$, $-NR^3R^4$, $-CONR^3R^4$, $-CO_2R^3$, $-NR^3CO_2R^4$, $-NR^3CONR^4R^5$, $-NR^3CSNR^4R^5$, $-NR^3C(=NH)NR^4R^5$, $-SO_2NR^3R^4$, $-NR^4SO_2R^3$, $-NR^3SO_2NR^4R^5$, $-B(OR^3)(OR^4)$, $-P(O)(OR^3)(OR^4)$ o $-P(O)(R^3)(OR^4)$;

R^2 es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, $-NO_2$, $-OR^6$, $-S(O)_bR^6$, $-NR^6R^7$, $-CONR^6R^7$, $-CO_2R^6$, $-NR^6CO_2R^7$, $-NR^6CONR^7R^8$, $-NR^6CSNR^7R^8$, $-NR^6C(=NH)NR^7R^8$, $-SO_2NR^5R^6$, $-NR^5SO_2R^6$, $-NR^5SO_2NR^6R^7$, $-B(OR^5)(OR^6)$, $-P(O)(OR^5)(OR^6)$, o $-P(O)(R^5)(OR^6)$; o alternativamente, R^1 y R^2, conjuntamente con los átomos a los cuales ellos están unidos, forman un anillo arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido en donde el anillo está opcionalmente fusionado con otro anillo arilo, arilo

sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido;

con la condición de que R^1 y R^2 no sean ambos hidrógeno;

A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, halo, -CN, $-NO_2$, $-OR^9$, $-S(O)_cR^9$, $-NR^9COR^{10}$, $-NHOR^9$, $-NR^9R^{10}$, $-NOR^9$, $-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$, $-NR^9C(=NH)NR^{10}R^{11}$, $-B(OR^{10})(OR^{11})$, $-P(O)(OR^{10})(OR^{11})$ o $-P(O)(R^{10})(OR^{11})$;

B es -N- o $-C(R^{12})-$;

R^{12} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, $-NR^{13}R^{14}$, -CN, $-OR^{13}$, $-S(O)_dR^{13}$, $-CO_2R^{13}$ o $-CONR^{13}R^{14}$;

G es -C- o $-S(O)_2-$;

siempre que cuando G sea $-S(O)_2-$, entonces G forme un enlace único con E;

cuando el enlace entre D y G es un enlace único, entonces D es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, $-OR^{15}$, $-NH-OR^{15}$, $-S(O)_eR^{15}$, $-NR^{15}R^{16}$, $-NH-NHR^{15}$, $-CO_2R^{15}$, o $-CONR^{15}R^{16}$;

cuando G forma un enlace doble con D, entonces D es =O, =S , $=N-OR^{15}$, o $=N-NHR^{15}$;

n es 0 cuando G es $-S(O)_2-$, y n es 1 cuando G es -C-;

E es $-NR^{17}-$, -N- o $-C(R^{18})-$;

siempre que E sea $-NR^{17}-$ solamente cuando G forme un enlace único con E;

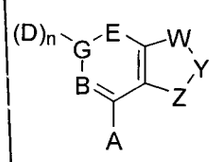
R^{17} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido o $-CO_2R^{19}$;

R^{18} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, $-NR^{20}R^{21}$, -CN, $-OR^{20}$, $-S(O)_fR^{20}$, $-CO_2R^{20}$ o $-CONR^{20}R^{21}$;

a, b, c, d, e y f son independientemente 0, 1 o 2; y

R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{13}, R^{14}, R^{15}, R^{16}, R^{18}, R^{20}, y R^{21} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido; o alternativamente, R^3 y R^4, R^4 y R^5, R^6 y R^7, R^7 y R^8, R^9 y R^{10}, R^{10} y R^{11}, R^{13} y R^{14}, R^{15} y R^{16}, o R^{20} y R^{21}, conjuntamente con los átomos a los cuales ellos están unidos, forman un anillo cicloheteroalquilo o cicloheteroalquilo sustituido.

En una realización de la Fórmula (I), el compuesto de la presente invención tiene la Fórmula estructural (II):



(II)

en donde:

Y forma un enlace único o bien con W o Z y un enlace doble con el otro de W o Z;

W es $-C(R^{24})-$, -S-, -N-, $-N(R^{25})-$, u -O-;

Y es $-C(R^{26})-$ o -N-;

Z es $-C(R^{27})-$, -S-, -N-, $-N(R^{28})-$, u -O-;

R^{24} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, $-NO_2$, $-OR^{29}$, $-S(O)_gR^{29}$, $-NR^{29}R^{30}$, $-CONR^{29}R^{30}$, $-CO_2R^{29}$, $-SO_2NR^{29}R^{30}$, $-NR^{29}SO_2R^{30}$, $-B(OR^{29})(OR^{30})$, $-P(O)(OR^{29})(OR^{30})$ o $-P(O)(R^{29})(OR^{30})$;

R^{26} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, halo, -CN, $-NO_2$, $-OR^{31}$, $-S(O)_hR^{31}$, $-OCOR^{31}$, $-NR^{31}R^{32}$, $-CONR^{31}R^{32}$, $-CO_2R^{31}$, $-SO_2NR^{31}R^{32}$, $-NR^{31}SO_2R^{32}$, $-B(OR^{31})(OR^{32})$, $-P(O)(OR^{31})(OR^{32})$ o $-P(O)(R^{31})(OR^{32})$;

R^{27} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, halo, -CN, $-NO_2$, $-OR^{33}$, $-S(O)_iR^{33}$, $-OCOR^{33}$, $-NR^{33}R^{34}$, $-CONR^{33}R^{34}$, $-COR^{33}$, $-CO_2R^{33}$, $-SO_2NR^{33}R^{34}$, $-NR^{33}SO_2R^{34}$, $-B(OR^{33})(OR^{34})$, $-P(O)(OR^{33})(OR^{34})$ o $-P(O)(R^{33})(OR^{34})$ o alternativamente R^{24} y R^{26} o R^{26} y R^{27} conjuntamente con los átomos a los cuales ellos están unidos forman un anillo cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido;

g, h e i son independientemente 0 o 1;

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R^{25} y R^{28} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido; y

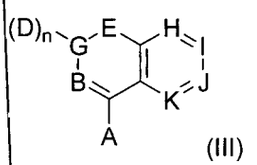
R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, y R^{34} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido; o alternativamente R^{29} y R^{30}, R^{31} y R^{32} o R^{33} y R^{34} conjuntamente con los átomos a los cuales ellos están unidos forman un anillo cicloheteroalquilo o cicloheteroalquilo sustituido; y

con las siguientes condiciones:

(a) cuando W es -O- o -S- o -NR^{25}, entonces Z es –$C(R^{27})$ o -N-; y

(b) cuando Z es -O- o -S- o -NR^{28}, entonces W es -$C(R^{24})$ o -N-.

En una realización de la Fórmula (I), el compuesto de la presente invención tiene la Fórmula estructural (III):



(III)

en donde:

H es -$C(R^{35})$- o -N-;

I es -$C(R^{36})$ o -N-;

J es -$C(R^{37})$- o -N-;

K es -$C(R^{38})$- o -N-;

R^{35} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo

sustituido, -CN, -NO_2, -OR^{39}, -$S(O)_jR^{39}$, -$OCOR^{39}$, -$NR^{39}R^{40}$, -$CONR^{39}R^{40}$, -CO_2R^{39}, -$SO_2NR^{39}R^{40}$, -$NR^{39}SO_2R^{40}$, -$B(OR^{39})(OR^{40})$, -$P(O)(OR^{39})(OR^{40})$ o -$P(O)(R^{39})(OR^{40})$;

R^{36} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, -NO_2, -OR^{41}, -$S(O)_kR^{41}$, -$OCOR^{41}$, -$NR^{41}R^{42}$, -$CONR^{41}R^{42}$, -CO_2R^{41}, -$SO_2NR^{41}R^{42}$, -$NR^{41}SO_2R^{42}$, -$B(OR^{41})(OR^{42})$, -$P(O)(OR^{41})(OR^{42})$ o -$P(O)(R^{41})(OR^{42})$;

R^{37} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, -NO_2, -OR^{43}, -$S(O)_lR^{43}$, -$OCOR^{43}$, -$NR^{43}R^{44}$, -$CONR^{43}R^{44}$, -CO_2R^{43}, -$SO_2NR^{43}R^{44}$, -$NR^{43}SO_2R^{44}$, -$B(OR^{43})(OR^{44})$, -$P(O)(OR^{43})(OR^{44})$ o -$P(O)(R^{43})(OR^{44})$;

R^{38} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, -NO_2, -OR^{45}, -$S(O)_mR^{45}$, -$OCOR^{45}$, -$NR^{45}R^{46}$, -$CONR^{45}R^{46}$, -COR^{45}, -CO_2R^{45}, -$SO_2NR^{45}R^{46}$, -$NR^{45}SO_2R^{46}$, -$B(OR^{45})(OR^{46})$, -$P(O)(OR^{45})(OR^{46})$ o -$P(O)(R^{45})(OR^{46})$; o alternativamente R^{36} y R^{37} o R^{37} y R^{38} tomados conjuntamente con el átomo al cual ellos están unidos, forman un anillo cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo, o cicloheteroalquilo sustituido;

j, k, l y m son independientemente 0, 1 o 2; y

R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, y R^{46} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido,

acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido o alternativamente R^{39} y R^{40}, R^{41} y R^{42}, R^{43} y R^{44} o R^{45} y R^{46} conjuntamente con los átomos a los cuales ellos están unidos forman un anillo cicloheteroalquilo o cicloheteroalquilo sustituido;

con la condición de que a lo sumo, dos de H, I, J y K sean -N-.

En una realización, la presente invención proporciona una composición ingerible que comprende un modificador del ligando del receptor quimiosensorial, en donde en presencia de un ligando del receptor quimiosensorial éste interactúa con el dominio Venus atrapamoscas de T1R2 *a través de* al menos tres residuos de interacción seleccionados del grupo integrado por N143, S144, I167, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, y S168 de un T1R2 humano. En una realización, el modificador del ligando del receptor quimiosensorial es un compuesto que tiene la Fórmula estructural (I), (II), o (III), o un tautómero, sal, solvato, y/o éster del mismo. En otra realización, la composición ingerible comprende además uno o más edulcorantes.

En una realización, la presente invención proporciona un método de mejoramiento del sabor dulce de una composición ingerible que comprende poner en contacto a la composición ingerible o a los precursores de la misma con un modificador del ligando del receptor quimiosensorial para formar una composición ingerible modificada. En una realización, el modificador del ligando del receptor quimiosensorial es un compuesto que tiene la Fórmula estructural (I), (II), o (III), o un tautómero, sal, solvato, y/o éster del mismo.

En una realización, la presente invención proporciona un método para tratar una afección asociada con un receptor quimiosensorial que comprende administrar a un sujeto que necesita dicho tratamiento una cantidad efectiva de

una entidad seleccionada del grupo integrado por un modificador del receptor quimiosensorial, un modificador del ligando del receptor quimiosensorial, y una combinación de los mismos, en donde la entidad interactúa con un sitio de interacción del receptor quimiosensorial. En una realización, el modificador del ligando del receptor quimiosensorial es un compuesto que tiene la Fórmula estructural (I), (II), o (III), o un tautómero, sal, solvato, y/o éster del mismo.

BREVE DESCRIPCIÓN DE LAS FIGURAS

La Figura 1 contiene variaciones polimórficas ejemplificativas de T1R1 humano.

La Figura 2 contiene variaciones polimórficas ejemplificativas de T1R2 humano.

La Figura 3 muestra los dendogramas para los alineamientos de secuencias de T1R1.

La Figura 4 muestra los dendogramas para los alineamientos de secuencias de T1R2.

La Figura 5 muestra espacios de interacción ejemplificativos para la sucralosa y uno de los compuestos de la presente invención. La proteína está representada como un diagrama de cintas.

La Figura 6 muestra espacios de interacción y residuos ejemplificativos para la sucralosa y uno de los compuestos de la presente invención. La proteína está representada como un diagrama de cintas.

La Figura 7 muestra espacios de interacción y residuos ejemplificativos asociados con la región bisagra para la sucralosa y uno de los compuestos de la presente invención.

La Figura 8 muestra superficies de interacción parciales y residuos de interacción ejemplificativos próximos a la región bisagra para la sacarosa y la sucralosa.

La Figura 9 muestra espacios de interacción y residuos ejemplificativos asociados con los lóbulos para a sucralosa y uno de los compuestos de la presente invención.

La Figura 10 muestra espacios de interacción y residuos ejemplificativos asociados con un sitio de interacción para la sucralosa y uno de los compuestos de la presente invención.

La Figura 11 muestra resultados ejemplificativos para estudios de mapeo que utilizan receptores quiméricos de humanos-ratas.

La Figura 12 muestra resultados para los resultados de la mutagénesis ejemplificativos.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Antes de describir específicamente la invención, se proporcionan las siguientes definiciones.

El término familia "T1R" incluye variantes, alelos, mutantes, y homólogos polimórficos que: (1) tienen aproximadamente 30-40% de identidad de secuencia de aminoácidos, más específicamente aproximadamente 40, 50, 60, 70, 75, 80, 85, 90, 95, 96, 97, 98, o 99% de identidad de secuencia de aminoácidos con respecto a los T1Rs conocidos o descriptos, *por ejemplo*, en las Solicitudes de Patentes Estadounidenses Acta No. 10/179.373 presentada el 26 de junio 2002, Acta No. 09/799.629 presentada el 5 de abril de 2001 y Acta No. 10/035.045 presentada el 3 de enero de 2002, sobre una ventana de aproximadamente 25 aminoácidos, de modo óptimo 50-100 aminoácidos; (2) específicamente se unen a anticuerpos formados contra un inmunógeno que comprende una secuencia de

aminoácidos seleccionada del grupo integrado por las secuencias T1R descriptas infra, y las variantes modificadas de forma moderada de las mismas; (3) específicamente se hibridan (con un tamaño de al menos aproximadamente 100, opcionalmente al menos aproximadamente 500-1000 nucleótidos) bajo condiciones de hibridación estrictas a una secuencia seleccionada del grupo integrado por las secuencias de ADN T1R descriptas infra, y las variantes modificadas de forma moderada de las mismas; (4) comprenden una secuencia al menos aproximadamente 40% idéntica a una secuencia de aminoácidos seleccionada del grupo integrado por las secuencias de aminoácidos T1R descriptas infra o (5) se amplifican mediante cebadores que específicamente se hibridan bajo condiciones de hibridación estrictas a las secuencias T1R descriptas.

En particular, estos "T1Rs" incluyen a los receptores gustativos GPCRs a los que se hace referencia como hT1R1, hT1R2, hT1R3, rT1R1, rT1R2, rT1R3, mT1R1, mT1R2, y mT1R3 que poseen las secuencias de ácidos nucleicos y las secuencias de aminoácidos conocidas o descriptas, *por ejemplo*, en las Patentes Estadounidenses Acta No. 10/179.373 presentada el 26 de junio de 2002, Acta No. 09/799.629 presentada el 5 de abril de 2001 y Acta No. 10/035.045 presentada el 3 de enero 2002, y las variantes, alelos, mutantes, ortólogos y quimeras de las mismas que específicamente se unen y/o responden a los ligandos dulce, umami, o a cualquier otro ligando relacionado con la quimiosensorialidad incluyendo activadores, inhibidores y mejoradores. Además los T1Rs incluyen los receptores gustativos GPCRs expresados en humanos o en otros mamíferos, *por ejemplo*, las células asociadas con el gusto y/o parte del sistema gastrointestinal que incluye sin limitación alguna, el esófago, estómago, intestino (delgado y grueso), colon, hígado, tracto biliar, páncreas, vesícula biliar, *etc.* Además, los polipéptidos T1R incluyen secuencias quiméricas derivadas de

porciones de un polipéptido T1R particular tal como T1R1, T1R2 o T1R3 de diferentes especies o mediante la combinación de porciones de diferentes T1Rs en donde dichas secuencias T1R quiméricas se combinan para producir un receptor gustativo dulce o umami funcional. Por ejemplo los T1Rs quiméricos pueden comprender la región extracelular de un T1R, es decir, T1R1 o T1R2 y la región transmembrana de otro T1R, ya sea T1R1 o T1R2.

De manera topológica, ciertos GPCRs quimiosensoriales tienen un "dominio N-terminal"; "dominios extracelulares", un "dominio transmembrana" que comprende siete regiones transmembrana, y los correspondientes lazos citoplasmáticos y extracelulares, "regiones citoplasmáticas", y una "región C-terminal" (véase, *por ejemplo*, Hoon *et al.*, *Cell* 96:541-51 (1999); Buck*et al.*, *Cell* 65:175-87 (1991)). Estas regiones se pueden identificar estructuralmente utilizando métodos conocidos por aquéllos expertos en la técnica, tales como los programas de análisis de secuencias que identifican dominios hidrofóbicos e hidrofílicos (*véase*, *por ejemplo*, Stryer, Biochemistry, (3ra ed. 1988); véase también cualquiera de una cantidad de programas de análisis de secuencias basados en Internet, tales como aquéllos que se encuentran en dot.imgen.bcm.tmc.edu). Estas regiones son útiles para elaborar proteínas quiméricas y para los ensayos *in vitro* de la invención, *por ejemplo*, los ensayos de unión a ligando.

"Dominios extracelulares" por consiguiente se refiere a los dominios de los receptores quimiosensoriales, *por ejemplo*, los polipéptidos T1R que sobresalen de la membrana celular y se encuentran expuestos a la cara extracelular de la célula. Dichas regiones incluirían el "dominio N-terminal" que se encuentra expuesto a la cara extracelular de la célula, así como también los lazos extracelulares del dominio transmembrana que se encuentran expuestos a la cara extracelular de la célula, *es decir*, los lazos extracelulares entre las regiones

transmembrana 2 y 3, las regiones transmembrana 4 y 5, y las regiones transmembrana 6 y 7. El "dominio N-terminal" comienza en el N-término y se extiende a una región cercana al comienzo de la región transmembrana. Estas regiones extracelulares son útiles para los ensayos de unión a ligando *in vitro*, tanto en la fase soluble como sólida. Además, las regiones transmembrana, que se describen a continuación, también se pueden encontrar involucradas en la unión a ligando, ya sea en combinación con la región extracelular o solas, y por consiguiente son también útiles para los ensayos de unión a ligando *in vitro*.

"Dominio transmembrana", el cual comprende las siete "regiones" transmembrana, se refiere a los dominios de los receptores quimiosensoriales, *por ejemplo*, los polipéptidos T1R que se sitúan dentro de la membrana plasmática, y también puede incluir los correspondientes lazos citoplasmáticos (intracelulares) y extracelulares, a los que también se hace referencia como "regiones" transmembrana. Las siete regiones transmembrana y los lazos extracelulares y citoplasmáticos se pueden identificar utilizando métodos standard, según se describe en Kyte *et al.*, *J. Mol. Biol.* 157:105-32 (1982)), o en Stryer, *supra*.

"Dominios citoplasmáticos" se refiere a los dominios de los receptores quimiosensoriales, *por ejemplo*, las proteínas T1R que están orientadas hacia la parte interna de la célula, *por ejemplo*, el "dominio C-terminal" y los lazos intracelulares del dominio transmembrana, *por ejemplo*, los lazos intracelulares entre las regiones transmembrana 1 y 2, las regiones transmembrana 3 y 4, y las regiones transmembrana 5 y 6. "Dominio C-terminal" se refiere a la región que se extiende desde el extremo de la última región transmembrana hacia el C-término de la proteína, y que normalmente se encuentra situada dentro del citoplasma.

El término "receptor 7-transmembrana" denota un polipéptido que pertenece a una superfamilia de proteínas de transmembrana que poseen siete

regiones que abarcan la membrana plasmática siete veces (de este modo, las siete regiones se denominan dominios "transmembrana" o "TM" TM I a TM VII).

La frase "actividad" o "efectos funcionales" en el contexto de los ensayos descriptos para los compuestos de ensayo que modulan un receptor quimiosensorial, *por ejemplo*, que mejoran la transducción de señales mediada por miembros de la familia T1R tales como la actividad o los efectos funcionales del receptor dulce o umami incluye la determinación de cualquier parámetro que se encuentre indirectamente o directamente bajo la influencia del receptor quimiosensorial particular, *por ejemplo*, los efectos funcionales, físicos y químicos. Ésta incluye, sin limitación alguna, unión a ligando, cambios en el flujo iónico, potencial de membrana, flujo de corriente, transcripción, unión a proteína G, fosforilación o desfosforilación de GPCR, transducción de señales, interacciones receptor-ligando, concentraciones de segundo mensajero (*por ejemplo*, cAMP, cGMP, IP3, o Ca^{2+} intracelular), *in vitro*, *in vivo*, y *ex vivo* y también incluye otros efectos fisiológicos que incrementan o disminuyen la liberación de neurotransmisores u hormonas.

El término "determinar el efecto funcional" o "actividad" del receptor denota ensayos para un compuesto que incrementa o disminuye un parámetro que se encuentra indirectamente o directamente bajo la influencia de un receptor quimiosensorial, *por ejemplo*, los efectos funcionales, físicos y químicos. Dichos efectos funcionales se pueden medir a través de cualquier medio conocido por aquéllos expertos en la técnica, *por ejemplo*, cambios en las caractarísticas espectroscópicas (*por ejemplo*, índice de fluorescencia, absorbancia, refractivo), hidrodinámicas (*por ejemplo*, forma), en las propiedades cromatográficas, o de solubilidad, control en parche, colorantes sensibles al voltaje, corrientes de célula completa, eflujo de radioisótopos, marcadores inducibles, receptor quimiosensorial de ovocitos, *por ejemplo,* expresión del gen de T1R; receptor

quimiosensorial de células de cultivo tisular, *por ejemplo*, expresión de T1R; activación transcripcional del receptor quimiosensorial, *por ejemplo*, genes de T1R; ensayos de unión a ligando; cambios en el voltaje, el potencial de membrana y la conductancia; ensayos de flujo iónico; cambios en los segundos mensajeros intracelulares tales como cAMP, cGMP, y trifosfato de inositol (IP3); cambios en los niveles de calcio intracelular; liberación de neurotransmisores, y similares.

"Inhibidores", "activadores", y "modificadores" del receptor quimiosensorial, *por ejemplo*, las proteínas T1R se utilizan de modo indistinto para referirse a moléculas inhibidoras, activadoras, o moduladoras identificadas utilizando ensayos *in vitro* e *in vivo* para la transducción de señales quimiosensoriales, *por ejemplo*, ligandos, agonistas, antagonistas, y sus homólogos y miméticos. Los inhibidores son compuestos que, *por ejemplo*, se unen a, bloquean parcialmente o totalmente la estimulación, disminuyen, evitan, retrasan la activación, inactivan, desensibilizan, o regulan en sentido descendente la transducción del gusto, *por ejemplo*, antagonistas. Los activadores son compuestos que, *por ejemplo*, se unen a, estimulan, incrementan, inician, activan, facilitan, mejoran la activación, sensibilizan, o regulan en sentido ascendente la transducción de señales quimiosensoriales, *por ejemplo*, agonistas. Los modificadores incluyen compuestos que, *por ejemplo*, alteran, directamente o indirectamente, la actividad de un receptor o la interacción de un receptor con sus ligandos, *por ejemplo*, los ligandos del receptor y que opcionalmente se unen a o interactúan con activadores o inhibidores; Proteínas G; quinasas (*por ejemplo*, homólogos de rodopsin quinasa y quinasas de receptores beta adrenérgicos que están involucrados en la desactivación y en la desensibilización de un receptor); y arrestinas, que también desactivan y desensibilizan receptores. Los modificadores incluyen versiones genéticamente modificadas de receptores quimiosensoriales, *por ejemplo*, miembros de la familia TR1, *por ejemplo*, con actividad alterada, así

como también ligandos, antagonistas, agonistas, moléculas químicas pequeñas y similares que ocurren naturalmente y sintéticos. El término "modificador del ligando del receptor quimiosensorial" según se utiliza en la presente incluye un mejorador del ligando del receptor quimiosensorial. En la presente invención ello incluye, sin limitación alguna, ligandos (agonistas o antagonistas) dulces, ligandos (agonistas o antagonistas) umami, mejoradores dulces y mejoradores umami e inhibidores del sabor dulce o del sabor umami.

"Mejorador" en la presente se refiere a un compuesto que modula (incrementa) la activación de un receptor particular, con preferencia el quimiosensorial, *por ejemplo*, el receptor T1R2/T1R3 o el receptor T1R1/T1R3 pero el cual por sí mismo no resulta en la activación sustancial del receptor particular. En la presente dichos mejoradores favorecerán la activación de un receptor quimiosensorial a través de su ligando. Típicamente el "mejorador" será específico para un ligando particular, *es decir*, éste no favorecerá la activación de un receptor quimiosensorial a través de ligandos quimiosensoriales distintos al ligando o a los ligandos quimiosensoriales particulares íntimamente relacionados con el mismo.

"Mejorador putativo" en la presente se refiere a un compuesto identificado, *por ejemplo*, *in silico* (simulación computacional) o no, como un potencial mejorador utilizando ensayos que se described en la presente pero cuya actividad de mejorador no se ha confirmado todavía *in vivo*, *por ejemplo*, en ensayos de sabor adecuados.

Los términos "polipéptido," "péptido" y "proteína" se utilizan de modo indistinto en la presente para referirse a un polímero de residuos de aminoácidos. Los términos se aplican a polímeros de aminoácidos en los cuales uno o más residuos de aminoácidos es un mimético químico artificial de un correspondiente aminoácido que ocurre naturalmente, así como también a polímeros de

aminoácidos que ocurren naturalmente y a polímeros de aminoácidos que ocurren no naturalmente.

El "dominio extracelular" y el receptor quimiosensorial, *por ejemplo*, las composiciones o regiones de receptor T1R descriptas en la presente también incluyen "análogos", o "variantes moderadas" y "miméticos" ("peptidomiméticos") con estructuras y una actividad que sustancialmente corresponden a las secuencias ejemplificativas. De este modo, los términos "variante moderada" o "análogo" o "mimético" se refieren a un polipéptido que posee una secuencia de aminoácidos modificada, de modo tal que el(os) cambio(s) no altere(n) sustancialmente la estructura y/o actividad del polipéptido (de la variante moderada), según se define en la presente. Éstas incluyen variaciones modificadas de forma moderada de una secuencia de aminoácidos, es decir, sustituciones, adiciones o deleciones de aminoácidos de aquellos residuos que no sean decisivos para la actividad de la proteína, o la sustitución de aminoácidos con residuos que posean propiedades similares (*por ejemplo*, acídicos, básicos, cargados positivamente o negativamente, polares o no polares, *etc.*) de modo tal que las sustituciones de los aminoácidos incluso decisivos no altere sustancialmente la estructura y/o actividad.

Más particularmente, "variantes modificadas de forma moderada" se aplica a ambas secuencias de aminoácidos y ácidos nucleicos. Con respecto a las secuencias de ácidos nucleicos particulares, las variantes modificadas de forma moderada se refieren a aquellos ácidos nucleicos que codifican secuencias de aminoácidos idénticas o esencialmente idénticas, o cuando el ácido nucleico no codifica una secuencia de aminoácidos, a secuencias esencialmente idénticas. Debido a la degeneración del código genético, una gran cantidad de ácidos nucleicos funcionalmente idénticos codifican cualquier proteína determinada.

Por ejemplo, los codonos GCA, GCC, GCG y GCU todos codifican el aminoácido alanina. De este modo, en cada posición donde una alanina está especificada por un codón, el codón se puede alterar a cualquiera de los correspondientes codones descriptos sin alterar el polipéptido codificado.

Dichas variaciones de ácidos nucleicos son "variaciones silenciosas", las cuales constituyen una especie de variaciones modificadas de forma moderada. Cada secuencia de ácidos nucleicos en la presente que codifica un polipéptido también describe cada posible variación silenciosa del ácido nucleico. Un experto reconocerá que cada codón en un ácido nucleico (excepto AUG, el cual es normalmente el único codón para la metionina, y TGG, el cual es normalmente el único codón para el triptófano) se puede modificar para producir una molécula funcionalmente idéntica. En consecuencia, cada variación silenciosa de un ácido nucleico que codifica un polipéptido se encuentra implícita en cada secuencia descripta.

Las tablas de sustitución moderada que proporcionan aminoácidos funcionalmente similares son muy conocidas en la técnica. Por ejemplo, un lineamiento ejemplificativo para seleccionar sustituciones moderadas incluye (residuo original seguido por la sustitución ejemplificativa): ala/gly o ser; arg/lys; asn/gln o his; asp/glu; cys/ser; gln/asn; gly/asp; gly/ala o pro; his/asn o gln; ile/leu o val; leu/ile o val; lys/arg o gln o glu; met/leu o tyr o ile; phe/met o leu o tyr; ser/thr; thr/ser; trp/tyr; tyr/trp o phe; val/ile o leu. Un lineamiento ejemplificativo alternativo utiliza los siguientes seis grupos, conteniendo cada uno aminoácidos que son sustituciones moderadas para unos y otros: 1) Alanina (A), Serina (S), Treonina (T); 2) Ácido aspártico (D), Ácido glutámico (E); 3) Asparagina (N), Glutamina (Q); 4) Arginina (R), Lisina (I); 5) Isoleucina (I), Leucina (L), Metionina (M), Valina (V); y 6) Fenilalanina (F), Tirosina (Y), Triptófano (W); (véase también, *por ejemplo*, Creighton, Proteins, W. H. Freeman and Company (1984); Schultz

and Schimer, Principles of Protein Estructura, Springer-Verlag (1979)). Un experto en la técnica apreciará que las sustituciones identificadas precedentemente no constituyen las únicas sustituciones moderadas posibles. Por ejemplo, para algunos propósitos, se pueden considerar todos los aminoácidos cargados como sustituciones moderadas entre sí ya sean positivos o negativos. Además, las sustituciones, deleciones o adiciones individuales que alteran, adicionan o suprimen un aminoácido único o un pequeño porcentaje de aminoácidos en una secuencia codificada también se pueden considerar "variaciones modificadas de forma moderada".

Los términos "mimético" y "peptidomimético" se refieren a un compuesto químico sintético que tiene sustancialmente las mismas características estructurales y/o funcionales de los polipéptidos, *por ejemplo*, un dominio extracelular o cualquier región dentro del mismo de T1R2 o T1R1. El mimético o bien puede estar compuesto por completo de análogos de aminoácidos sintéticos, no naturales, o bien puede consistir en una molécula quimérica de aminoácidos peptídicos parcialmente naturales y de análogos de aminoácidos parcialmente no naturales. El mimético también puede incorporar cualquier cantidad de sustituciones moderadas de aminoácidos naturales siempre que dichas sustituciones también no alteren sustancialmente la estructura y/o actividad del mimético.

Como en el caso de los polipéptidos de la invención los cuales constituyen variantes moderadas, la experimentación de rutina determinará si un mimético se encuentra dentro del alcance de la invención, *es decir*, que su estructura y/o función no esté sustancialmente alterada. Las composiciones de miméticos de polipéptidos pueden contener cualquier combinación de componentes estructurales no naturales, que son típicamente de tres grupos estructurales: a) grupos de unión a residuos además de las uniones de enlace amida naturales

("enlace peptídico"); b) residuos no naturales en lugar de residuos de aminoácidos que ocurren naturalmente; o c) residuos que inducen el mimetismo estructural secundario, *es decir*, que inducen o estabilizan una estructura secundaria, *por ejemplo*, una conformación de hélice alfa, lámina beta, vuelta gamma, vuelta beta, y similares. Un polipéptido se puede caracterizar como un mimético cuando todos o algunos de sus residuos están unidos a través de medios químicos además de enlaces peptídicos naturales. Los residuos peptidomiméticos individuales pueden estar unidos a través de enlaces peptídicos, otros enlaces químicos o medios de acoplamiento, tales como *por ejemplo*, glutaraldehído, ésteres de N-hidroxisuccinimida, maleimidas bifuncionales, N,N'-diciclohexilcarbodiimida (DCC) o N,N'-diisopropilcarbodiimida (DIC). Los grupos de unión que pueden constituir una alternativa para las uniones de enlace amida tradicionales ("enlace peptídico") incluyen, *por ejemplo*, cetometileno (*por ejemplo*, -C(O)-CH_2- para -C(O)-NH-), aminometileno -CH_2(NH)-, etileno, olefina -CH=CH-, éter -CH_2O-, tioéter -CH_2S-, tetrazol (CN_4), tiazol, retroamida, tioamida o éster (véase, *por ejemplo*, Spatola, Chemistry and Biochemistry of Amino Acids, Peptides and Proteins, Vol. 7, 267-357, Marcell Dekker, Peptide Backbone Modifications, NY (1983)). Un polipéptido también se puede caracterizar como un mimético al contener todos o algunos residuos no naturales en lugar de residuos de aminoácidos que ocurren naturalmente; los residuos no naturales están bien descriptos en la literatura científica y de patentes.

"Alquilo", por sí mismo o como parte de otro sustituyente, se refiere a un radical hidrocarburo monovalente de cadena recta, ramificada o cíclico, saturado o no saturado derivado de la remoción de un átomo de hidrógeno de un átomo de carbono único de un alcano, alqueno o alquino principal. El término "alquilo" incluye "cicloalquilo" según se define en la presente a continuación. Los grupos alquilo típicos incluyen, pero no se limitan a, metilo; etilos tales como etanilo,

etenilo, etinilo; propilos tales como propan–1–ilo, propan–2–ilo, ciclopropan–1–ilo, prop–1–en–1–ilo, prop–1–en–2–ilo, prop–2–en–1–ilo (alilo), cicloprop–1–en–1–ilo; cicloprop–2–en–1–ilo, prop–1–in–1–ilo, prop–2–in–1–ilo, *etc.*; butilos tales como butan–1–ilo, butan–2–ilo, 2–metil–propan–1–ilo, 2–metil–propan–2–ilo, ciclobutan–1–ilo, but–1–en–1–ilo, but–1–en–2–ilo, 2–metil–prop–1–en–1–ilo, but–2–en–1–ilo, but–2–en–2–ilo, buta–1,3–dien–1–ilo, buta–1,3–dien–2–ilo, ciclobut–1–en–1–ilo, ciclobut–1–en–3–ilo, ciclobuta–1,3–dien–1–ilo, but–1–in–1–ilo, but–1–in–3–ilo, but–3–in–1–ilo, *etc.*; y similares. El término "alquilo" específicamente pretende incluir grupos que tienen cualquier grado o nivel de saturación, *es decir*, grupos que tienen exclusivamente enlaces carbono-carbono únicos, grupos que tienen uno o más enlaces carbono-carbono dobles, grupos que tienen uno o más enlaces carbono-carbono triples y grupos que tienen mezclas de enlaces carbono-carbono únicos, dobles y triples. Cuando se pretende un nivel de saturación específico, se utilizan las expresiones "alcanilo", "alquenilo", y "alquinilo". En algunas realizaciones, un grupo alquilo comprende desde 1 hasta 20 átomos de carbono (alquilo C_1-C_{20}). En otras realizaciones, un grupo alquilo comprende desde 1 hasta 10 átomos de carbono (alquilo C_1-C_{10}). Todavía en otras realizaciones, un grupo alquilo comprende desde 1 hasta 6 átomos de carbono (alquilo C_1-C_6). Se advierte que cuando un grupo alquilo está conectado además a otro átomo, éste se transforma en un grupo "alquileno". En otros términos, el término "alquileno" se refiere a un alquilo divalente. Por ejemplo, -CH_2CH_3 es un etilo, mientras que -CH_2CH_2- es un etileno. Es decir, "Alquileno", por sí mismo o como parte de otro sustituyente, se refiere a un radical hidrocarburo divalente de cadena recta, ramificada o cíclico, saturado o no saturado derivado de la remoción de dos átomos de hidrógeno de un átomo de carbono único o dos átomos de carbono diferentes de un alcano, alqueno o alquino principal. El término "alquileno" incluye "cicloalquileno" según se define en la presente a

continuación. El término "alquileno" específicamente pretende incluir grupos que tienen cualquier grado o nivel de saturación, *es decir*, grupos que tienen exclusivamente enlaces carbono-carbono únicos, grupos que tienen uno o más enlaces carbono-carbono dobles, grupos que tienen uno o más enlaces carbono-carbono triples y grupos que tienen mezclas de enlaces carbono-carbono únicos, dobles y triples. Cuando se pretende un nivel de saturación específico, se utilizan las expresiones "alcanileno", "alquenileno", y "alquinileno". En algunas realizaciones, un grupo alquileno comprende desde 1 hasta 20 átomos de carbono (alquileno C_1-C_{20}). En otras realizaciones, un grupo alquileno comprende desde 1 hasta 10 átomos de carbono (alquileno C_1-C_{10}). Todavía en otras realizaciones, un grupo alquileno comprende desde 1 hasta 6 átomos de carbono (alquileno C_1-C_6).

"Alcanilo", por sí mismo o como parte de otro sustituyente, se refiere a un radical alquilo de cadena recta, ramificada o cíclico saturado derivado de la remoción de un átomo de hidrógeno de un átomo de carbono único de un alcano principal. El término "alcanilo" incluye "cicloalcanilo" según se define en la presente a continuación. Los grupos alcanilo típicos incluyen, pero no se limitan a, metanilo; etanilo; propanilos tales como propan–1–ilo, propan–2–ilo (isopropilo), ciclopropan–1–ilo, *etc.*; butanilos tales como butan–1–ilo, butan–2–ilo (*sec*–butilo), 2–metil–propan–1–ilo (isobutilo), 2–metil–propan–2–ilo (*t*–butilo), ciclobutan–1–ilo, *etc.*; y similares.

"Alquenilo", por sí mismo o como parte de otro sustituyente, se refiere a un radical alquilo de cadena recta, ramificada o cíclico no saturado que tiene al menos un enlace carbono-carbono doble derivado de la remoción de un átomo de hidrógeno de un átomo de carbono único de un alqueno principal. El término "alquenilo" incluye "cicloalquenilo" según se define en la presente a continuación. El grupo puede encontrarse o bien en la conformación *cis* o *trans* alrededor

del(os) enlace(s) doble(s). Los grupos alquenilo típicos incluyen, pero no se limitan a, etenilo; propenilos tales como prop–1–en–1–ilo, prop–1–en–2–ilo, prop–2–en–1–ilo (alilo), prop–2–en–2–ilo, cicloprop–1–en–1–ilo; cicloprop–2–en–1–ilo; butenilos tales como but–1–en–1–ilo, but–1–en–2–ilo, 2–metil–prop–1–en–1–ilo, but–2–en–1–ilo, but–2–en–1–ilo, but–2–en–2–ilo, buta–1,3–dien–1–ilo, buta–1,3–dien–2–ilo, ciclobut–1–en–1–ilo, ciclobut–1–en–3–ilo, ciclobuta–1,3–dien–1–ilo, *etc.*; y similares.

"Alquinilo", por sí mismo o como parte de otro sustituyente se refiere a un radical alquilo de cadena recta, ramificada o cíclico no saturado que tiene al menos un enlace carbono-carbono triple derivado de la remoción de un átomo de hidrógeno de un átomo de carbono único de un alquino principal. Los grupos alquinilo típicos incluyen, pero no se limitan a, etinilo; propinilos tales como prop–1–in–1–ilo, prop–2–in–1–ilo, *etc.*; butinilos tales como but–1–in–1–ilo, but–1–in–3–ilo, but–3–in–1–ilo, *etc.*; y similares.

"Alcoxi", por sí mismo o como parte de otro sustituyente, se refiere a un radical de la fórmula -O-R^{199}, donde R^{199} es alquilo o alquilo sustituido según se define en la presente.

"Acilo" por sí mismo o como parte de otro sustituyente se refiere a un radical -C(O)R^{200}, donde R^{200} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido según se define en la presente. Los ejemplos representativos incluyen, pero no se limitan a formilo, acetilo, ciclohexilcarbonilo, ciclohexilmetilcarbonilo, benzoilo, bencilcarbonilo y similares.

"Arilo", por sí mismo o como parte de otro sustituyente, se refiere a un grupo hidrocarburo aromático monovalente derivado de la remoción de un átomo de hidrógeno de un átomo de carbono único de un sistema de anillos aromáticos principal, según se define en la presente. Los grupos arilo típicos incluyen, pero

no se limitan a, grupos derivados de aceantrileno, acenaftileno, acefenantrileno, antraceno, azuleno, benceno, criseno, coroneno, fluoranteno, fluoreno, hexaceno, hexafeno, hexaleno, *as*-indaceno, *s*-indaceno, indano, indeno, naftaleno, octaceno, octafeno, octaleno, ovaleno, penta-2,4-dieno, pentaceno, pentaleno, pentafeno, perileno, fenaleno, fenantreno, piceno, pleiadeno, pireno, pirantreno, rubiceno, trifenileno, trinaftaleno y similares. En algunas realizaciones, un grupo arilo comprende desde 6 hasta 20 átomos de carbono (arilo C_6-C_{20}). En otras realizaciones, un grupo arilo comprende desde 6 hasta 15 átomos de carbono (arilo C_6-C_{15}). Todavía en otras realizaciones, un grupo arilo comprende desde 6 hasta 15 átomos de carbono (arilo C_6-C_{10}).

"Arilalquilo", por sí mismo o como parte de otro sustituyente, se refiere a un grupo alquilo acíclico en el cual uno de los átomos de hidrógeno unido a un átomo de carbono, típicamente un átomo de carbono terminal o sp^3, está reemplazado con un grupo arilo, según se define en la presente. Los grupos arilalquilo típicos incluyen, pero no se limitan a, bencilo, 2–feniletan–1–ilo, 2–fenileten–1–ilo, naftilmetilo, 2–naftiletan–1–ilo, 2–naftileten–1–ilo, naftobencilo, 2–naftofeniletan–1–ilo y similares. Cuando se pretenden restos alquilo específicos, se utiliza la nomenclatura arilalcanilo, arilalquenilo y/o arilalquinilo. En algunas realizaciones, un grupo arilalquilo es arilalquilo (C_6-C_{30}), *por ejemplo*, el resto alcanilo, alquenilo o alquinilo del grupo arilalquilo es alquilo (C_1-C_{10}) y el resto arilo es arilo (C_6-C_{20}). En otras realizaciones, un grupo arilalquilo es arilalquilo (C_6-C_{20}), *por ejemplo*, el resto alcanilo, alquenilo o alquinilo del grupo arilalquilo es alquilo (C_1-C_8) y el resto arilo es arilo (C_6-C_{12}). Todavía en otras realizaciones, un grupo arilalquilo es arilalquilo (C_6-C_{15}), *por ejemplo*, el resto alcanilo, alquenilo o alquinilo del grupo arilalquilo es alquilo (C_1-C_5) y el resto arilo es arilo (C_6-C_{10}).

"Cicloalquilo" por sí mismo o como parte de otro sustituyente, se refiere a un radical alquilo cíclico saturado o no saturado, según se define en la presente.

De modo similar, "Cicloalquileno", por sí mismo o como parte de otro sustituyente, se refiere a un radical alquileno cíclico saturado o no saturado, según se define en la presente. Cuando se pretende un nivel de saturación específico, se utiliza la nomenclatura "cicloalcanilo", "cicloalquenilo", o "cicloalquinilo". Los grupos cicloalquilo típicos incluyen, pero no se limitan a, grupos derivados de ciclopropano, ciclobutano, ciclopentano, ciclohexano, y similares. En algunas realizaciones, el grupo cicloalquilo comprende desde 3 hasta 10 átomos en el anillo (cicloalquilo C_3-C_{10}). En otras realizaciones, el grupo cicloalquilo comprende desde 3 hasta 7 átomos en el anillo (cicloalquilo C_3-C_7). El cicloalquilo puede estar además sustituido con uno o más heteroátomos que incluyen, pero no se limitan a, N, P, O, S, y Si, los cuales se unen a los átomos de carbono del cicloalquilo a través de un enlace monovalente o multivalente.

"Heteroalquilo", "Heteroalcanilo", "Heteroalquenilo" y "Heteroalquinilo", por sí mismos o como parte de otros sustituyentes, se refieren a grupos alquilo, alcanilo, alquenilo y alquinilo, respectivamente, en los cuales uno o más de los átomos de carbono (y opcionalmente cualquiera de los átomos de hidrógeno asociados), están cada uno, independientemente entre sí, reemplazados con los mismos o diferentes heteroátomos o grupos heteroatómicos. De modo similar, "Heteroalquileno", "Heteroalcanileno", "Heteroalquenileno" y "Heteroalquinileno", por sí mismos o como parte de otros sustituyentes, se refieren a grupos alquileno, alcanileno, alquenileno y alquinileno, respectivamente, en los cuales uno o más de los átomos de carbono (y opcionalmente cualquiera de los átomos de hidrógeno asociados), están cada uno, independientemente entre sí, reemplazados con los mismos o diferentes heteroátomos o grupos heteroatómicos. Los heteroátomos o grupos heteroatómicos típicos que pueden reemplazar los átomos de carbono incluyen, pero no se limitan a, -O-, -S-, -N-, -Si-, -NH-, -S(O)-, -$S(O)_2$-, -S(O)NH-, -$S(O)_2$NH- y similares y las combinaciones

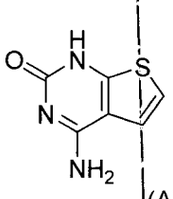
de los mismos. Los heteroátomos o grupos heteroatómicos pueden estar ubicados en cualquier posición interior de los grupos alquilo, alquenilo o alquinilo. Los grupos heteroatómicos típicos que pueden estar incluidos en estos grupos incluyen, pero no se limitan a, -O-, -S-, -O-O-, -S-S-, -O-S-, $-NR^{201}R^{202}-$, =N-N=, -N=N-, $-N=N-NR^{203}R^{204}$, $-PR^{205}-$, $-P(O)_2-$, $-POR^{206}-$, $-O-P(O)_2-$, -SO-, $-SO_2-$, $-SnR^{207}R^{208}-$ y similares, donde R^{201}, R^{202}, R^{203}, R^{204}, R^{205}, R^{206}, R^{207} y R^{208} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo, cicloheteroalquilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido.

"Cicloheteroalquilo," o "Heterociclilo", por sí mismo o como parte de otro sustituyente, se refiere a un radical alquilo cíclico saturado o no saturado en el cual uno o más átomos de carbono (y opcionalmente cualquiera de los átomos de hidrógeno asociados) están independientemente reemplazados con el mismo o diferente heteroátomo. De modo similar, "Cicloheteroalquileno", por sí mismo o como parte de otro sustituyente, se refiere a un radical alquileno cíclico saturado o no saturado en el cual uno o más átomos de carbono (y opcionalmente cualquiera de los átomos de hidrógeno asociados) están independientemente reemplazados con el mismo o diferente heteroátomo. El cicloheteroalquilo puede estar además sustituido con uno o más heteroátomos que incluyen, pero no se limitan a, N, P, O, S, y Si, los cuales se unen a los átomos de carbono del cicloheteroalquilo a través de un enlace monovalente o multivalente. Los heteroátomos típicos para reemplazar el(os) átomo(s) de carbono incluyen, pero no se limitan a, N, P, O, S, Si, *etc.* Cuando se pretende un nivel de saturación específico, se utiliza la nomenclatura "cicloheteroalcanilo" o "cicloheteroalquenilo". Los grupos cicloheteroalquilo típicos incluyen, pero no se limitan a, grupos derivados de

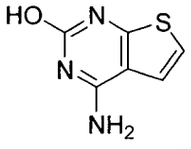
epóxidos, azirinas, tiiranos, imidazolidina, morfolina, piperazina, piperidina, pirazolidina, pirrolidona, quinuclidina, y similares. En algunas realizaciones, el grupo cicloheteroalquilo comprende desde 3 hasta 10 átomos en el anillo (cicloheteroalquilo de 3-10 miembros). En otras realizaciones, el grupo cicloalquilo comprende desde 5 a 7 átomos en el anillo (cicloheteroalquilo de 5-7 miembros). Un grupo cicloheteroalquilo puede estar sustituido en cualquier heteroátomo, por ejemplo, un átomo de nitrógeno, con un grupo alquilo (C_1-C_6). Como ejemplos específicos, se encuentran incluidos dentro de la definición de "cicloheteroalquilo" N-metil-imidazolidinilo, N-metil-morfolinilo, N-metil-piperazinilo, N-metil-piperidinilo, N-metil-pirazolidinilo y N-metil-pirrolidinilo. Un grupo cicloheteroalquilo puede estar unido al resto de la molécula *a través de* un átomo de carbono del anillo o de un heteroátomo del anillo.

"Compuestos" se refiere a los compuestos comprendidos por las fórmulas estructurales descriptas en la presente e incluye cualquiera de los compuestos específicos dentro de estas fórmulas cuya estructura se describe en la presente. Los compuestos se pueden identificar o bien por su estructura química y/o por su nombre químico. Cuando la estructura química y el nombre químico se encuentran en desacuerdo, la estructura química determina la identidad del compuesto. Los compuestos descriptos en la presente pueden contener uno o más centros quirales y/o enlaces dobles y por consiguiente, pueden existir como estereoisómeros, tales como diastereómeros, enantiómeros o isómeros de enlace doble (*es decir*, isómeros geométricos). En consecuencia, las estructuras químicas representadas en la presente comprenden todos los posibles enantiómeros y estereoisómeros de los compuestos ilustrados incluyendo la forma estereoisoméricamente pura (*por ejemplo*, geométricamente pura, enantioméricamente pura o diastereoméricamente pura) y las mezclas enantioméricas y estereoisoméricas. Las mezclas enantioméricas y

estereoisoméricas se pueden resolver dentro de sus enantiómeros o estereoisómeros componentes utilizando técnicas de separación o técnicas de síntesis quiral muy conocidas por el experto. Los compuestos también pueden existir en diversas formas tautoméricas que incluyen la forma enol, la forma ceto y las mezclas de las mismas. En consecuencia, las estructuras químicas representadas en la presente comprenden todas las posibles formas tautoméricas de los compuestos ilustrados. Los compuestos descriptos también incluyen compuestos isotópicamente marcados donde uno o más átomos tienen una masa atómica diferente de la masa atómica que se encuentra convencionalmente en la naturaleza. Los ejemplos de isótopos que se pueden incorporar dentro de los compuestos de la invención incluyen, pero no se limitan a, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, *etc.* Los compuestos pueden existir en formas no solvatadas así como también en formas solvatadas, incluyendo formas hidratadas y como N-óxidos. En general, los compuestos ser hidratados, solvatados o N-óxidos. Ciertos compuestos pueden existir en múltiples formas cristalinas o amorfas. En general, todas las formas físicas son equivalentes para los usos contemplados en la presente y pretenden encontrarse dentro del alcance de la presente invención. Además, debería comprenderse, cuando se ilustran estructuras parciales de los compuestos, que los paréntesis indican el punto de unión de la estructura parcial al resto de la molécula. El término "tautómero" según se utiliza en la presente se refiere a isómeros que cambian entre sí con gran facilidad de modo que ellos puedan existir conjuntamente en equilibrio. Por ejemplo, los siguientes compuestos A y B son tautómeros entre sí:



(A)



(B)

"Halo", por sí mismo o como parte de otro sustituyente se refiere a un radical -F, -Cl, -Br o -I.

"Heteroarilo", por sí mismo o como parte de otro sustituyente, se refiere a un radical heteroaromático monovalente derivado de la remoción de un átomo de hidrógeno de un átomo único de un sistema de anillos heteroaromáticos principal, según se define en la presente. Los grupos heteroarilo típicos incluyen, pero no se limitan a, grupos derivados de acridina, β-carbolina, cromano, cromeno, cinolina, furano, imidazol, indazol, indol, indolina, indolizina, isobenzofurano, isocromeno, isoindol, isoindolina, isoquinolina, isotiazol, isoxazol, naftiridina, oxadiazol, oxazol, perimidina, fenantridina, fenantrolina, fenazina, ftalazina, pteridina, purina, pirano, pirazina, pirazol, piridazina, piridina, pirimidina, pirrol, pirrolizina, quinazolina, quinolina, quinolizina, quinoxalina, tetrazol, tiadiazol, tiazol, tiofeno, triazol, xanteno, y similares. En algunas realizaciones, el grupo heteroarilo comprende desde 5 hasta 20 átomos en el anillo (heteroarilo de 5-20 miembros). En otras realizaciones, el grupo heteroarilo comprende desde 5 hasta 10 átomos en el anillo (heteroarilo de 5-10 miembros). Los grupos heteroarilo ejemplificativos incluyen aquéllos derivados de furano, tiofeno, pirrol, benzotiofeno, benzofurano, benzimidazol, indol, piridina, pirazol, quinolina, imidazol, oxazol, isoxazol y pirazina.

"Heteroarilalquilo" por sí mismo o como parte de otro sustituyente se refiere a un grupo alquilo acíclico en el cual uno de los átomos de hidrógeno unido a un átomo de carbono, típicamente un átomo de carbono terminal o sp^3, está reemplazado con un grupo heteroarilo. Cuando se pretenden restos alquilo específicos, se utiliza la nomenclatura heteroarilalcanilo, heteroarilaquenilo y/o heteroarilalquinilo. En algunas realizaciones, el grupo heteroarilalquilo es un heteroarilalquilo de 6-21 miembros, *por ejemplo*, el resto alcanilo, alquenilo o

alquinilo del heteroarilalquilo es alquilo (C_1-C_6) y el resto heteroarilo es un heteroarilo de 5-15 miembros. En otras realizaciones, el heteroarilalquilo es un heteroarilalquilo de 6-13 miembros, *por ejemplo*, el resto alcanilo, alquenilo o alquinilo es alquilo (C_1-C_3) y el resto heteroarilo es un heteroarilo de 5-10 miembros.

"Sistema de Anillos Aromáticos Principal" se refiere a un sistema de anillos cíclicos o policíclicos no saturados que tienen un sistema de electrones π conjugados. Se encuentran específicamente incluidos dentro de la definición de "sistema de anillos aromáticos principal" los sistemas de anillos fusionados en los cuales uno o más de los anillos son aromáticos y uno o más de los anillos son saturados o no saturados, tales como, por ejemplo, fluoreno, indano, indeno, fenaleno, *etc.* Los sistemas de anillos aromáticos principales típicos incluyen, pero no se limitan a, aceantrileno, acenaftileno, acefenantrileno, antraceno, azuleno, benceno, criseno, coroneno, fluoranteno, fluoreno, hexaceno, hexafeno, hexaleno, *as*-indaceno, *s*-indaceno, indano, indeno, naftaleno, octaceno, octafeno, octaleno, ovaleno, penta-2,4-dieno, pentaceno, pentaleno, pentafeno, perileno, fenaleno, fenantreno, piceno, pleiadeno, pireno, pirantreno, rubiceno, trifenileno, trinaftaleno y similares.

"Sistema de Anillos Heteroaromáticos Principal" se refiere a un sistema de anillos aromáticos principal en el cual uno o más átomos de carbono (y opcionalmente cualquiera de los átomos de hidrógeno asociados) está cada independientemente reemplazado con el mismo o diferente heteroátomo. Los heteroátomos típicos para reemplazar los átomos de carbono incluyen, pero no se limitan a, N, P, O, S, Si, *etc.* Se encuentran específicamente incluidos dentro de la definición de "sistema de anillos heteroaromático principal" los sistemas de anillos fusionados en los cuales uno o más de los anillos son aromáticos y uno o más de los anillos son saturados o no saturados, tales como, por ejemplo, benzodioxano,

benzofurano, cromano, cromeno, indol, indolina, xanteno, *etc.* Los sistemas de anillos heteroaromáticos principales típicos incluyen, pero no se limitan a, arsindol, carbazol, β-carbolina, cromano, cromeno, cinolina, furano, imidazol, indazol, indol, indolina, indolizina, isobenzofurano, isocromeno, isoindol, isoindolina, isoquinolina, isotiazol, isoxazol, naftiridina, oxadiazol, oxazol, perimidina, fenantridina, fenantrolina, fenazina, ftalazina, pteridina, purina, pirano, pirazina, pirazol, piridazina, piridina, pirimidina, pirrol, pirrolizina, quinazolina, quinolina, quinolizina, quinoxalina, tetrazol, tiadiazol, tiazol, tiofeno, triazol, xanteno y similares.

"Paciente" incluye a humanos. Los términos "humano" y "paciente" se utilizan de modo indistinto en la presente.

"Farmacéuticamente aceptable" se refiere a que sea adecuado para utilizar en contacto con los tejidos de humanos y animales sin toxicidad, irritación, respuesta alérgica indebidas, y similares, en proporción con una relación beneficio/riesgo razonable, y efectivo para su uso pretendido dentro del alcance del buen discernimiento médico.

"Prevenir" o "prevención" se refiere a una reducción en el riesgo de contraer una enfermedad o trastorno (*es decir*, provocar que al menos uno de los síntomas clínicos de la enfermedad no se desarrolle en un paciente que puede estar expuesto o predispuesto a la enfermedad pero que aún no experimenta o presenta síntomas de la enfermedad).

"Grupo protector" se refiere a un agrupamiento de átomos que cuando está unido a un grupo funcional reactivo en una molécula enmascara, reduce o evita la reactividad del grupo funcional. Los ejemplos de grupos protectores se pueden encontrar en Green *et al.*, "Protective Groups in Organic Chemistry", (Wiley, 2da ed. 1991) y Harrison *et al.*, "Compendium of Synthetic Organic Methods", Vols. 1-8 (John Wiley and Sons, 1971-1996). Los grupos protectores amino representativos

incluyen, pero no se limitan a, los grupos formilo, acetilo, trifluoracetilo, bencilo, benciloxicarbonilo ("CBZ"), *terc*-butoxicarbonilo ("Boc"), trimetilsililo ("TMS"), 2-trimetilsilil-etansulfonilo ("SES"), tritilo y tritilo sustituido, aliloxicarbonilo, 9-fluorenilmetiloxicarbonilo ("FMOC"), nitro-veratriloxicarbonilo ("NVOC") y similares. Los grupos protectores hidroxi representativos incluyen, pero no se limitan a, aquéllos donde el grupo hidroxi se encuentra o bien acilado o bien alquilado tales como éteres de bencilo, y tritilo así como también éteres de alquilo, éteres de tetrahidropiranilo, éteres de trialquilsililo y éteres de alilo.

"Anillo sacárido" también se conoce como anillo de azúcar e incluye anillos monosacáridos, disacáridos, y polisacáridos. Con preferencia, el anillo sacárido es un anillo monosacárido. Los ejemplos de monosacáridos incluyen glucosa (dextrosa), fructosa, galactosa, xilosa y ribosa. Por "derivado de anillo sacárido", se denota el anillo sacárido no natural o artificial en donde los centros estereoquímicos son parcialmente o completamente diferentes de aquéllos del anillo sacárido natural.

"Sal" se refiere a una sal de un compuesto, que posee la actividad farmacológica deseada del compuesto principal. Dichas sales incluyen: (1) sales de adición de ácidos, formadas con ácidos inorgánicos tales como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido nítrico, ácido fosfórico, y similares; o formadas con ácidos orgánicos tales como ácido acético, ácido propiónico, ácido hexanoico, ácido ciclopentanpropiónico, ácido glicólico, ácido pirúvico, ácido láctico, ácido malónico, ácido succínico, ácido málico, ácido maleico, ácido fumárico, ácido tartárico, ácido cítrico, ácido benzoico, ácido 3-(4-hidroxibenzoil)benzoico, ácido cinámico, ácido mandélico, ácido metansulfónico, ácido etansulfónico, ácido 1,2-etan-disulfónico, ácido 2-hidroxietansulfónico, ácido bencensulfónico, ácido 4-clorobencensulfónico, ácido 2-naftalensulfónico, ácido 4-toluensulfónico, ácido alcanforsulfónico, ácido

4-metilbiciclo[2.2.2]-oct-2-en-1-carboxílico, ácido glucoheptónico, ácido 3-fenilpropiónico, ácido trimetilacético, ácido butilacético terciario, ácido lauril sulfúrico, ácido glucónico, ácido glutámico, ácido hidroxinaftoico, ácido salicílico, ácido esteárico, ácido mucónico, y similares; o (2) sales formadas cuando un protón acídico presente en el compuesto principal reemplazado con un ión metálico, *por ejemplo*, un ión de metal alcalino, un ión alcalinotérreo, o un ión de aluminio; o coordenadas con una base orgánica tales como etanolamina, dietanolamina, trietanolamina, N-metilglucamina y similares.

"Solvato" significa un compuesto formado mediante solvatación (la combinación de moléculas de solvente con moléculas o iones del soluto), o un agregado que consiste en un ión o molécula de soluto, es decir, un compuesto de la presente invención, con una o más moléculas de solvente. Cuando el solvente es agua, el correspondiente solvato es "hidrato".

"N-óxido", también conocido como óxido de amina o amin-N-óxido, significa un compuesto que deriva de un compuesto de la presente invención a través de la oxidación de un grupo amina del compuesto de la presente invención. Un N-óxido típicamente contiene el grupo funcional R_3N^+-O^- (escrito algunas veces como $R_3N{=}O$ o $R_3N{\rightarrow}O$).

"Sustituido", cuando se utiliza para modificar un grupo o radical especificado, significa que uno o más átomos de hidrógeno del grupo o radical especificado están cada uno, independientemente entre sí, reemplazados con el(os) mismo(s) o diferente(s) sustituyente(s). Los grupos sustituyentes útiles para sustituir átomos de carbono saturados en el grupo o radical especificado incluyen, pero no se limitan a $-R^a$, halo, $-O^-$, $=O$, $-OR^b$, $-SR^b$, $-S^-$, $=S$, $-NR^cR^c$, $=NR^b$, $=N-OR^b$, trihalometilo, $-CF_3$, $-CN$, $-OCN$, $-SCN$, $-NO$, $-NO_2$, $=N_2$, $-N_3$, $-S(O)_2R^b$, $-S(O)_2NR^b$, $-S(O)_2O^-$, $-S(O)_2OR^b$, $-OS(O)_2R^b$, $-OS(O)_2O^-$, $-OS(O)_2OR^b$, $-P(O)(O^-)_2$, $-P(O)(OR^b)(O^-)$, $-P(O)(OR^b)(OR^b)$, $-C(O)R^b$, $-C(S)R^b$, $-C(NR^b)R^b$, $-C(O)O^-$,

$-C(O)OR^b$, $-C(S)OR^b$, $-C(O)NR^cR^c$, $-C(NR^b)NR^cR^c$, $-OC(O)R^b$, $-OC(S)R^b$, $-OC(O)O^-$, $-OC(O)OR^b$, $-OC(S)OR^b$, $-NR^bC(O)R^b$, $-NR^bC(S)R^b$, $-NR^bC(O)O^-$, $-NR^bC(O)OR^b$, $-NR^bC(S)OR^b$, $-NR^bC(O)NR^cR^c$, $-NR^bC(NR^b)R^b$ y $-NR^bC(NR^b)NR^cR^c$, donde R^a está seleccionado del grupo integrado por alquilo, cicloalquilo, heteroalquilo, cicloheteroalquilo, arilo, arilalquilo, heteroarilo y heteroarilalquilo; cada R^b es independientemente hidrógeno o R^a; y cada R^c es independientemente R^b o alternativamente, los dos R^cs se pueden tomar conjuntamente con el átomo de nitrógeno al cual ellos están unidos para formar un cicloheteroalquilo de 4, 5, 6 o 7 miembros el cual puede opcionalmente incluir desde 1 hasta 4 de los mismos o diferentes heteroátomos adicionales seleccionados del grupo integrado por O, N y S. Como ejemplos específicos, $-NR^cR^c$ se denota por incluir $-NH_2$, -NH-alquilo, N-pirrolidinilo y N-morfolinilo. Como otro ejemplo específico, un alquilo sustituido se denota por incluir –alquilen–O–alquilo, –alquilen–heteroarilo, –alquilen–cicloheteroalquilo, –alquilen–$C(O)OR^b$, –alquilen–$C(O)NR^bR^b$, y $-CH_2-CH_2-C(O)-CH_3$. El uno o más grupos sustituyentes, tomados conjuntamente con los átomos a los cuales ellos están unidos, pueden formar un anillo cíclico que incluye cicloalquilo y cicloheteroalquilo.

De modo similar, los grupos sustituyentes útiles para sustituir átomos de carbono no saturados en el grupo o radical especificado incluyen, pero no se limitan a, $-R^a$, halo, $-O^-$, $-OR^b$, $-SR^b$, $-S^-$, $-NR^cR^c$, trihalometilo, $-CF_3$, -CN, -OCN, -SCN, -NO, $-NO_2$, $-N_3$, $-S(O)_2R^b$, $-S(O)_2O^-$, $-S(O)_2OR^b$, $-OS(O)_2R^b$, $-OS(O)_2O^-$, $-OS(O)_2OR^b$, $-P(O)(O^-)_2$, $-P(O)(OR^b)(O^-)$, $-P(O)(OR^b)(OR^b)$, $-C(O)R^b$, $-C(S)R^b$, $-C(NR^b)R^b$, $-C(O)O^-$, $-C(O)OR^b$, $-C(S)OR^b$, $-C(O)NR^cR^c$, $-C(NR^b)NR^cR^c$, $-OC(O)R^b$, $-OC(S)R^b$, $-OC(O)O^-$, $-OC(O)OR^b$, $-OC(S)OR^b$, $-NR^bC(O)R^b$, $-NR^bC(S)R^b$, $-NR^bC(O)O^-$, $-NR^bC(O)OR^b$, $-NR^bC(S)OR^b$, $-NR^bC(O)NR^cR^c$, $-NR^bC(NR^b)R^b$ y $-NR^bC(NR^b)NR^cR^c$, donde R^a, R^b y R^c son según se definieron previamente.

Los grupos sustituyentes útiles para sustituir átomos de nitrógeno en grupos heteroalquilo y cicloheteroalquilo incluyen, pero no se limitan a, $-R^a$, $-O^-$, $-OR^b$, $-SR^b$, $-S^-$, $-NR^cR^c$, trihalometilo, $-CF_3$, -CN, -NO, $-NO_2$, $-S(O)_2R^b$, $-S(O)_2O^-$, $-S(O)_2OR^b$, $-OS(O)_2R^b$, $-OS(O)_2O^-$, $-OS(O)_2OR^b$, $-P(O)(O^-)_2$, $-P(O)(OR^b)(O^-)$, $-P(O)(OR^b)(OR^b)$, $-C(O)R^b$, $-C(S)R^b$, $-C(NR^b)R^b$, $-C(O)OR^b$, $-C(S)OR^b$, $-C(O)NR^cR^c$, $-C(NR^b)NR^cR^c$, $-OC(O)R^b$, $-OC(S)R^b$, $-OC(O)OR^b$, $-OC(S)OR^b$, $-NR^bC(O)R^b$, $-NR^bC(S)R^b$, $-NR^bC(O)OR^b$, $-NR^bC(S)OR^b$, $-NR^bC(O)NR^cR^c$, $-NR^bC(NR^b)R^b$ y $-NR^bC(NR^b)NR^cR^c$, donde R^a, R^b y R^c son según se definieron previamente.

Los grupos sustituyentes de las listas precedentes útiles para sustituir otros grupos o átomos especificados serán evidentes para aquéllos expertos en la técnica.

Los sustituyentes utilizados para sustituir un grupo especificado pueden estar además sustituidos, típicamente con uno o más de los mismos o diferentes grupos seleccionados de los diversos grupos especificados precedentemente.

"Tratar" o "tratamiento" de cualquier enfermedad o trastorno se refiere, en algunas realizaciones, a mejorar la enfermedad o trastorno (*es decir*, a detener o reducir el desarrollo de la enfermedad o al menos uno de los síntomas clínicos de la misma). En otras realizaciones "tratar" o "tratamiento" se refiere a mejorar al menos un parámetro físico, el cual puede no ser discernible por el paciente. Aún en otras realizaciones, "tratar" o "tratamiento"se refiere a inhibir la enfermedad o trastorno, ya sea físicamente, (*por ejemplo*, estabilización de un síntoma discernible), fisiológicamente, (*por ejemplo*, estabilización de un parámetro físico) o ambos. Aún en otras realizaciones, ""tratar" o "tratamiento" se refiere a retrasar el comienzo de la enfermedad o trastorno.

"Cantidad terapéuticamente efectiva" significa la cantidad de un compuesto que, cuando se administra a un paciente para tratar una enfermedad, es suficiente

para llevar a cabo dicho tratamiento para la enfermedad. La "cantidad terapéuticamente efectiva" variará dependiendo del compuesto, de la enfermedad y de su gravedad y de la edad, peso, *etc.*, del paciente a ser tratado.

"Vehículo" se refiere a un diluyente, adyuvante, excipiente o portador con el cual se administra un compuesto.

La presente invención se basa, al menos en parte, en el descubrimiento de que un dominio extracelular, *por ejemplo*, el dominio Venus atrapamoscas de un receptor quimiosensorial, especialmente uno o más sitios de interacción dentro del dominio Venus atrapamoscas, es un objetivo adecuado para los compuestos u otras entidades para modular el receptor quimiosensorial y/o sus ligandos. En consecuencia, la presente invención proporciona métodos de cribado para identificar modificadores de receptores quimiosensoriales así como también modificadores de ligandos de receptores quimiosensoriales. Además, la presente invención proporciona compuestos y composiciones capaces de modular receptores quimiosensoriales así como también ligandos de receptores quimiosensoriales.

De acuerdo con un aspecto de la presente invención, ésta proporciona métodos de cribado de modificadores de receptores quimiosensoriales mediante la determinación de si una entidad de ensayo es adecuada para interactuar con un receptor quimiosensorial *a través de* uno o más sitios de interacción dentro del dominio extracelular del receptor quimiosensorial, *por ejemplo,* el dominio Venus atrapamoscas del receptor quimiosensorial. De acuerdo con otro aspecto de la presente invención, ésta proporciona métodos de cribado de modificadores de ligandos de receptores quimiosensoriales mediante la determinación de si una entidad de ensayo es adecuada para interactuar con un receptor quimiosensorial, y opcionalmente su ligando *a través de* uno o más sitios de interacción dentro del dominio extracelular, *por ejemplo,* el dominio Venus atrapamoscas del receptor

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quimiosensorial, opcionalmente en presencia de un ligando del receptor quimiosensorial.

En general, el dominio extracelular de un receptor quimiosensorial se refiere al amino-término extracelular de un receptor quimiosensorial y usualmente incluye un dominio de unión a ligando y un dominio conector rico en cisteína, que conecta el dominio de unión a ligando y el resto de la proteína. En GPCRs de Clase C, generalmente se hace referencia al dominio de unión a ligando como un dominio Venus atrapamoscas, cuya estructura se ha dilucidado, *por ejemplo*, utilizando cristalografía de rayos X.

Un dominio Venus atrapamoscas típicamente consiste en dos lóbulos relativamente rígidos conectados a través de tres hebras que forman una región "bisagra" flexible. En ausencia de un ligando, el dominio Venus atrapamoscas tiende a adoptar conformaciones abiertas con lóbulos bien separados así como también conformaciones cerradas con lóbulos más cercanos conjuntamente. En un ejemplo, el dominio Venus atrapamoscas incluye una región a partir del aminoácido 36 hasta el aminoácido 509 de T1R1 humano, del aminoácido 31 hasta el aminoácido 507 de T1R2 humano, y/o del aminoácido 35 al aminoácido 511 de T1R3 humano.

El dominio Venus atrapamoscas de la presente invención incluye cualquier dominio de unión a ligando o dominio de interacción de ligando dentro del dominio extracelular de un receptor quimiosensorial. En una realización, el dominio Venus atrapamoscas de la presente invención incluye cualquier dominio de unión a ligando de un miembro de la familia T1R. En otra realización, el dominio Venus atrapamoscas de la presente invención incluye cualquier dominio extracelular de un receptor quimiosensorial con una estructura que comprende dos lóbulos conectados a través de una región bisagra. Aún en otra realización, el dominio Venus atrapamoscas de la presente invención incluye cualquier dominio que

corresponde a la estructura y/o función de una region que incluye el aminoácido 36 hasta el aminoácido 509 de T1R1 humano, el aminoácido 31 hasta el aminoácido 507 de T1R2 humano, y/o el aminoácido 35 hasta el aminoácido 511 de T1R3 humano. Todavía en otra realización, el dominio Venus atrapamoscas de la presente invención incluye cualquier dominio de unión a ligando de T1R1, T1R2, y/o T1R3 así como también cualquier variación, alelo, o mutación polimórficos del mismo. En las Figuras 1-4 se muestran ilustraciones ejemplificativas de variaciones polimórficas para T1R1 y T1R2.

De acuerdo con la presente invención, un receptor quimiosensorial puede consistir en cualquier receptor asociado con sensaciones quimiosensoriales o transducción de señales desencadenadas por ligandos quimiosensoriales, *por ejemplo, a través de* los receptores gustativos o de los receptores relacionados con el gusto expresados en las papilas gustativas, en el tracto gastrointestinal, *etc.* En una realización, un receptor quimiosensorial es un receptor que pertenece a la superfamilia de receptor 7-transmembrana o a los receptores acoplados a proteína G (GPCRs). En otra realización, un receptor quimiosensorial es un receptor que lleva a cabo la transducción de señales *a través de* una o más proteínas G. Aún en otra realización, un receptor quimiosensorial es un receptor que pertenece a la familia C o clase C de GPCRs. Aún en otra realización, un receptor quimiosensorial es un receptor que pertenece a la familia T1R. Aún en otra realización, un receptor quimiosensorial es un receptor de T1R1, T1R2, T1R3, o sus equivalencias o variaciones o una combinación de los mismos. Todavía en otra realización, un receptor quimiosensorial es un heterodímero de T1R2 y T1R3, o sus equivalencias o variaciones.

De acuerdo con la presente invención, un sitio de interacción dentro del dominio Venus atrapamoscas de un receptor quimiosensorial puede ser uno o más residuos de interacción o un espacio de interacción tridimensional o una

combinación de los mismos. En una realización, el sitio de interacción de la presente invención se encuentra dentro del dominio Venus atrapamoscas de T1R2. En otra realización, el sitio de interacción de la presente invención se encuentra dentro del dominio Venus atrapamoscas de T1R3. Aún en otra realización, el sitio de interacción de la presente invención se encuentra dentro del dominio Venus atrapamoscas de ambos T1R2 y T1R3.

Usualmente dicho sitio de interacción se puede determinar a través de cualquier medio conocido adecuado o descubierto posteriormente en la técnica. Por ejemplo, dicho sitio de interacción se puede determinar en base a modelización computacional, *por ejemplo*, utilizando software tal como Homology o Modeller (de Accelrys Corporation) para construir modelos de homología tridimensionales de dominio Venus atrapamoscas de un receptor quimiosensorial, *por ejemplo*, los dominios Venus atrapamoscas de T1R2 y/o T1R3 basados en estructuras cristalinas de dominios Venus atrapamoscas homólogos.

Dicho sitio de interacción también se puede determinar, *por ejemplo*, en base a cristalografía de rayos X y la estructura tridimensional de un receptor quimiosensorial determinada a partir del mismo, *por ejemplo*, el heterodímero de T1R2, T1R3, o T1R2/T1R3. Alternativamente, por ejemplo, dicho sitio de interacción se puede determinar en base a técnicas de mecánica molecular, *por ejemplo*, análisis en modo normal, técnicas de generación de lazos, simulaciones de Monte Carlo y/o de dinámica molecular para explorar movimientos y conformaciones alternativas de los dominios Venus atrapamoscas, simulaciones de docking para ensamblar ligandos de receptores candidatos y modificadores de ligandos de receptores candidatos dentro de estos modelos o dentro de estructuras de receptores quimiosensoriales, *por ejemplo*, T1R1 y T1R2 determinadas por vía experimental.

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Además, por ejemplo, dicho sitio de interacción se puede determinar en base a mutagénesis, *por ejemplo*, mutagénesis dirigida a un sitio o una combinación de dos o más métodos conocidos adecuados o descubiertos posteriormente, *por ejemplo*, los métodos descriptos en la presente.

En un ejemplo, dicho sitio de interacción se sitúa en parte de un receptor quimiosensorial, *por ejemplo*, T1R2 y se puede determinar en presencia o ausencia de la otra parte del receptor quimiosensorial, *por ejemplo*, T1R3. En otro ejemplo, dicho sitio de interacción se puede determinar en presencia o ausencia de un modificador del receptor quimiosensorial y/o modificador del ligando del receptor quimiosensorial.

En una realización, el sitio de interacción dentro del dominio Venus atrapamoscas de un receptor quimiosensorial incluye uno o más residuos de interacción del dominio Venus atrapamoscas de un receptor quimiosensorial. De acuerdo con la presente invención, el residuo de interacción del dominio Venus atrapamoscas de un receptor quimiosensorial es un residuo asociado con cualquier interacción directa o indirecta entre un receptor quimiosensorial y un modificador del receptor quimiosensorial o un modificador del ligando del receptor quimiosensorial o ambos.

En un ejemplo, el residuo de interacción de la presente invención incluye cualquier residuo de un receptor quimiosensorial asociado con una interacción entre un modificador del receptor quimiosensorial y un receptor quimiosensorial. En otro ejemplo, el residuo de interacción de la presente invención incluye cualquier residuo de un receptor quimiosensorial asociado con una interacción entre un modificador del ligando del receptor quimiosensorial y un receptor quimiosensorial. Aún en otro ejemplo, el residuo de interacción de la presente invención incluye cualquier residuo de un receptor quimiosensorial asociado con

una interacción entre un receptor quimiosensorial, un modificador del receptor quimiosensorial y un modificador del ligando del receptor quimiosensorial.

Todavía en otro ejemplo, el residuo de interacción de la presente invención incluye cualquier residuo de un receptor quimiosensorial asociado con una interacción entre un receptor quimiosensorial y una entidad gustativa dulce, *por ejemplo* cualquier compuesto de sabor dulce natural o sintetizado que incluye, sin limitación alguna, compuestos de sabor dulce no calóricos, compuestos de sabor dulce reducidos en calorías, compuestos de sabor dulce calóricos no objetivo, *etc.* Los compuestos de sabor dulce ejemplificativos incluyen, sin limitación alguna, ácido ciclámico, mogrosida, tagatosa, maltosa, galactosa, manosa, sacarosa, fructosa, lactosa, aspartame, neotame y otros derivados de aspartame, sacarina, sucralosa, acesulfame K, glucosa, eritritol, D-triptófano, glicina, manitol, sorbitol, maltitol, lactitol, isomalt, jarabe de glucosa hidrogenado (HGS, por sus siglas en inglés), hidrolizado de almidón hidrogenado (HSH, por sus siglas en inglés), esteviosida, rebaudiosida A y otros glucósidos dulces basados en Ste*via*, alitame, carrelame y otros edulcorantes basados en guanidina, tagatosa, xilitol, jarabe de maíz de alta fructosa, *etc.*

Todavía en otro ejemplo, el residuo de interacción de la presente invención incluye cualquier residuo de un receptor quimiosensorial asociado con una interacción entre un receptor quimiosensorial y un mejorador de la entidad gustativa dulce. Todavía en otro ejemplo, el residuo de interacción de la presente invención incluye cualquier residuo de un receptor quimiosensorial asociado con una interacción entre un receptor quimiosensorial, una entidad gustativa dulce, y un mejorador de la entidad gustativa dulce.

En otro caso, el residuo de interacción de la presente invención es un residuo dentro del dominio Venus atrapamoscas de un receptor quimiosensorial, en donde cualquier mutación del mismo podría resultar en un cambio de la

actividad del receptor quimiosensorial o del impacto de un ligando del receptor quimiosensorial al receptor quimiosensorial o ambos. Por ejemplo, el residuo de interacción de la presente invención puede incluir cualquier residuo dentro del dominio Venus atrapamoscas de un receptor quimiosensorial, en donde la mutación del mismo resulta en un cambio detectable, *por ejemplo*, un cambio cualitativo o cuantitativo de la actividad del receptor quimiosensorial en respuesta a un modificador del receptor quimiosensorial y/o modificador del ligando del receptor quimiosensorial.

Aún en otro caso, el residuo de interacción de la presente invención es un residuo dentro del dominio Venus atrapamoscas de un receptor quimiosensorial que interactúa o forma interaccion(es) productiva(s), *por ejemplo*, van der Waals, ocultamiento de grupos atómicos o átomos hidrofóbicos, enlaces hidrógeno, interacciones de agrupamientos de anillos, o interacciones electrostáticas de unión en puente de sales con un modificador del receptor quimiosensorial o modificador del ligando del receptor quimiosensorial, o ambos.

Todavía en otro caso, el residuo de interacción del dominio Venus atrapamoscas de un receptor quimiosensorial puede consistir en cualquier residuo que constituye uno o más componentes estructurales de interacción del dominio Venus atrapamoscas, los cuales se encuentran asociados, directamente o indirectamente, con la interacción entre un receptor quimiosensorial y un modificador del receptor quimiosensorial o un modificador del ligando del receptor quimiosensorial o ambos. Por ejemplo, la estructura del dominio Venus atrapamoscas de un receptor quimiosensorial generalmente incluye dos lóbulos unidos a través de una región bisagra. Los residuos que constituyen un componente estructural de interacción del dominio Venus atrapamoscas pueden ser, *por ejemplo*, residuos que constituyen la región bisagra, el costado interno de cada lóbulo, o los residuos en cada lóbulo que se llevan hacia una proximidad

cercana durante el cambio conformacional o de la activación del dominio Venus atrapamoscas, incluyendo sin limitación alguna, los residuos sobre las superficies internas de los lóbulos que se dirigen unos hacia otros o sobre las puntas de los lóbulos donde los residuos se encuentran parcialmente expuestos a solvente pero aún se cierran a los residuos sobre el lóbulo opuesto, *etc.*

Los residuos de interacción ejemplificativos del dominio Venus atrapamoscas de un receptor quimiosensorial incluyen cualquiera de uno o más residuos de 1) N143, S144, e I167 de un T1R2 humano, 2) S40, S144, S165, Y103, D142, y P277 de un T1R2 humano, 3) K65, R383, D307, E302, y D278 de un T1R2 humano, 4) I167, P185, T184, T326, E302, V384, A305, I325, I306, R383, D307, E382, D278, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, y S168 de un T1R2 humano, 5) N143, S144, I167, K65, R383, D307, E302, D278, P185, T184, T326, E302, V384, A305, I325, I306, D307, E382, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, y S168 de un T1R2 humano, y 6) N143, I167, K65, R383, D307, E302, D278, P185, T184, T326, V384, A305, I325, I306, D307, E382, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, y S168 de un T1R2 humano.

Los residuos de interacción ejemplificativos del dominio Venus atrapamoscas de un receptor quimiosensorial con respecto a un modificador del receptor quimiosensorial incluyen uno o más residuos de 1) N143, S144, e I167 de un T1R2 humano, 2) S40, S144, S165, Y103, D142, y P277 de un T1R2 humano, 3) I167, P185, T184, T326, E302, V384, A305, I325, I306, R383, D307, E382, D278, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, y S168 de un T1R2 humano, 4) N143 e I167 de un T1R2 humano, 5) S40, S165, Y103, D142, y P277 de un T1R2 humano, y 8) I167, P185, T184, T326, V384, A305, I325, I306, R383, D307, E382, D278, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, y S168 de un T1R2 humano.

Los residuos de interacción ejemplificativos del dominio Venus atrapamoscas de un receptor quimiosensorial con respecto a una entidad gustativa dulce tal como sacarosa y sucralosa incluyen uno o más residuos de S40, S144, Y103, D142, P277 de un T1R2 humano Los residuos de interacción ejemplificativos del dominio Venus atrapamoscas de un receptor quimiosensorial con respecto a una entidad gustativa dulce tal como sacarina o acesulfame K incluyen uno o más residuos de K65, R383, D307, E302, y D278 de un T1R2 humano.

Los residuos de interacción ejemplificativos del dominio Venus atrapamoscas de un receptor quimiosensorial con respecto a un modificador del ligando del receptor quimiosensorial, *por ejemplo*, un mejorador del ligando del receptor quimiosensorial incluyen uno o más residuos de 1) K65, R383, D307, E302, y D278 de un T1R2 humano, 2) S40, S144, S165, Y103, D142, y P277 de un T1R2 humano, y 3) I167, P185, T184, T326, E302, V384, A305, I325, I306, R383, D307, E382, D278, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, y S168 de un T1R2 humano.

En el contexto de la presente invención, cualquier referencia a un residuo de interacción particular, *por ejemplo*, N143 de un receptor T1R2 humano, incluye todos sus correspondientes residuos, *por ejemplo*, 1) cualquier residuo de un T1R2 humano o no humano que corresponda a la misma posición en cualquier método de alineación de secuencias, 2) cualquier residuo de un T1R2 humano o no humano que corresponda a la misma posición en cualquier método de modelización computacional en presencia o ausencia de un ligando o modificador de ligando, 3) cualquier residuo de un T1R2 humano o no humano que corresponda al rol estructural o funcional del residuo de interacción particular, 4) cualquier residuo de un T1R2 humano o no humano que constituya una variación, alelos, mutación, *etc.* polimórficos del residuo particular, 5) cualquier residuo de

un T1R2 humano o no humano que constituya una sustitución moderada o una variante del residuo particular modificada en forma moderada, y 6) cualquier correspondiente residuo de un T1R2 humano o no humano en su forma modificada, *por ejemplo*, un mimético químico artificial del residuo de interacción particular o forma no modificada, *por ejemplo*, una forma que ocurre naturalmente.

En otra realización, el sitio de interacción dentro del dominio Venus atrapamoscas de un receptor quimiosensorial consiste en un espacio de interacción tridimensional dentro del dominio Venus atrapamoscas delineado o definido, parcialmente o por completo, por los residuos de interacción o una o más interfases, *por ejemplo*, puntos, líneas o superficies de interacción entre un receptor quimiosensorial y uno o más modificadores de receptores quimiosensoriales o modificadores de ligandos de receptores quimiosensoriales o una combinación de los mismos. De acuerdo con la presente invención, un residuo que delinea o cubre un espacio incluye cualquier residuo que tenga una o más estructuras principales y/o átomos de cadena lateral que se encuentran ubicados de modo que ellos puedan potencialmente interactuar con átomos de un ligando del receptor quimiosensorial o modificador del ligando del receptor quimiosensorial o ambos.

Por ejemplo, el espacio de interacción de la presente invención puede consistir en cualquier espacio parcial o total dentro del dominio Venus atrapamoscas que se encuentra usualmente ocupado por uno o más modificadores de receptores quimiosensoriales o modificadores de ligandos de receptores quimiosensoriales cuando ellos interactúan con un receptor quimiosensorial en forma individual o conjunta. En un ejemplo, el espacio de interacción de la presente invención consiste en un espacio dentro del dominio Venus atrapamoscas usualmente ocupado por un modificador del receptor quimiosensorial, *por ejemplo*, una entidad gustativa dulce. En otro ejemplo, el

espacio de interacción de la presente invención consiste en un espacio dentro del dominio Venus atrapamoscas usualmente ocupado por un modificador del ligando del receptor quimiosensorial, *por ejemplo*, un mejorador gustativo dulce en presencia de un ligando del receptor quimiosensorial. Aún en otro ejemplo, el espacio de interacción de la presente invención consiste en un espacio dentro del dominio Venus atrapamoscas usualmente ocupado por un modificador del receptor quimiosensorial, *por ejemplo*, una entidad gustativa dulce y un modificador del ligando del receptor quimiosensorial, *por ejemplo*, un mejorador de la entidad gustativa dulce. Todavía en otro ejemplo, el espacio de interacción de la presente invención consiste en un espacio dentro del dominio Venus atrapamoscas que se encuentra definido, conformado, o transformado en base a una interacción entre un receptor quimiosensorial y su ligando o su modificador de ligando que tuvo lugar parcialmente o por completo fuera del espacio.

De acuerdo con la presente invención, el dominio Venus atrapamoscas de un receptor quimiosensorial generalmente se puede visualizar como dos lóbulos unidos a través de una región bisagra. Un espacio de interacción ejemplificativo dentro del dominio Venus atrapamoscas de un receptor quimiosensorial incluye cualquier espacio asociado con la región bisagra, el costado interno de uno o dos lóbulos, la punta de uno o dos lóbulos o una combinación de los mismos de un receptor quimiosensorial.

Un espacio de interacción ejemplificativo dentro del dominio Venus atrapamoscas de un receptor quimiosensorial con respecto a un modificador del receptor quimiosensorial incluye cualquier espacio dentro del dominio Venus atrapamoscas delineado o al menos parcialmente definido por la región bisagra. De acuerdo con la presente invención, la región bisagra usualmente comprende residuos que se encuentran próximos a las tres hebras que conectan los dos lóbulos. En un ejemplo, la región bisagra comprende residuos que son homólogos

a los residuos observados que coordinan agonistas y antagonistas en estructuras cristalinas de uno o más dominios Venus atrapamoscas tales como aquéllos del receptor mGluR. En otro ejemplo, la región bisagra de T1R2 incluye a los residuos N143, S144, e I167 de T1R2.

Los sitios de interacción ejemplificativos dentro del dominio Venus atrapamoscas de un receptor quimiosensorial con respecto a un modificador del ligando del receptor quimiosensorial incluyen cualquier espacio delineado o al menos parcialmente definido por el costado interno de uno o dos lóbulos lejanos a la región bisagra, así como también residuos sobre las puntas de los lóbulos que se introducen en cercana proximidad a los residuos sobre el otro lóbulo.

Aún en otra realización, el sitio de interacción dentro del dominio Venus atrapamoscas de un receptor quimiosensorial consiste en una combinación de uno o más residuos de interacción con un espacio de interacción del receptor quimiosensorial. Por ejemplo, el sitio de interacción de un receptor quimiosensorial puede consistir en residuos de interacción asociados con un componente estructural de interacción de un receptor quimiosensorial en combinación con un espacio tridimensional adyacente, *por ejemplo*, no inferior a 1 Angstrom y no mayor a 30 Angstroms, a ese componente estructural de interacción. Otro ejemplo del sitio de interacción de un receptor quimiosensorial incluye residuos de interacción asociados con un componente estructural de interacción de un receptor quimiosensorial en combinación con un espacio tridimensional además del componente estructural de interacción.

En general, los métodos de cribado proporcionados por la presente invención se pueden llevar a cabo a través de cualquier medio conocido adecuado o descubierto posteriormente. En una realización, los métodos de cribado proporcionados por la presente invención se llevan a cabo *in silico*, *por ejemplo*, *a través de* "cribado por virtud" utilizando cualquier sistema de

modelización computacional adecuado o *a través de* un diseño específico racional de un compuesto utilizando cualquier sistema de diseño computacional adecuado.

En otra realización, los métodos de cribado proporcionados por la presente invención se llevan a cabo *a través de* ensayos biológicos, *por ejemplo*, cribado de productividad elevada de las interacciones entre los compuestos y un receptor quimiosensorial o sus fragmentos, *por ejemplo*, receptores quimiosensoriales genéticamente modificados o fragmentos de los mismos tales como dominios Venus atrapamoscas mutados de receptores quimiosensoriales. Aún en otra realización, los métodos de cribado proporcionados por la presente invención se llevan a cabo *a través de* una combinación de ensayo(s) biológico(s) y diseño y/o modelación computacional. Por ejemplo, los métodos de cribado proporcionados por la presente invención pueden consistir en una combinación de un cribado de productividad elevada de las interacciones entre compuestos y dominios Venus atrapamoscas mutados de receptores quimiosensoriales precribados o diseñados por computadora.

En un ejemplo, el método de cribado proporcionado por la presente invención para modificadores de receptores quimiosensoriales incluye la determinación de un sitio de interacción utilizando un modificador del receptor quimiosensorial conocido, *por ejemplo*, estructuralmente similar a un modificador del receptor quimiosensorial de interés y luego la determinación de si una entidad de ensayo es adecuada para interactuar con el receptor quimiosensorial *a través del* sitio de interacción así determinado.

En otro ejemplo, el método de cribado proporcionado por la presente invención para modificadores de receptores quimiosensoriales incluye la determinación de si una entidad de ensayo es adecuada para interactuar con un receptor quimiosensorial *a través de* un sitio de interacción predeterminado, *por ejemplo*, un sitio de interacción seleccionado o determinado antes del cribado,

que incluye sin limitación alguna, seleccionado o determinado en base a características deseadas de modificadores de receptores quimiosensoriales o a modificadores de receptores quimiosensoriales conocidos.

Aún en otro ejemplo, el método de cribado proporcionado por la presente invención para modificadores de ligandos de receptores quimiosensoriales incluye la determinación de un sitio de docking para un ligando del receptor quimiosensorial y subsiguientemente la determinación de si una entidad de ensayo es adecuada para interactuar con el ligando del receptor quimiosensorial *a través de* un sitio de interacción seleccionado a la luz del ensamble del ligando del receptor quimiosensorial. De acuerdo con la presente invención, el proceso de docking puede incluir cualquiera de los métodos conocidos o descubiertos posteriormente. Por ejemplo, el docking puede consistir en un proceso en el cual el centro de masa, orientaciones, y grados internos de libertad de una molécula son modificados para adaptarlos dentro de un espacio predeterminado en un modelo estructural. En un ejemplo, el docking puede consistir en un proceso que incluye la traducción y rotación de un ligando del receptor quimiosensorial en relación con el modelo estructural de receptor quimiosensorial, *por ejemplo*, el dominio Venus atrapamoscas de un modelo de receptor quimiosensorial mientras se regulan simultáneamente los ángulos torsionales internos del ligando del receptor quimiosensorial para adaptarlos dentro del sitio de interacción del receptor quimiosensorial. Un ejemplo de un programa de docking ampliamente utilizado es GLIDE de Schroedinger, Inc.

Aún en otro ejemplo, el método de cribado proporcionado por la presente invención para modificadores de ligandos de receptores quimiosensoriales incluye la determinación de un sitio de docking para un ligando del receptor quimiosensorial y subsiguientemente la determinación de un sitio de interacción que utiliza un modificador del ligando del receptor quimiosensorial conocido y

luego la determinación de si una entidad de ensayo es adecuada para interactuar con el ligando del receptor quimiosensorial *a través del* sitio de interacción así determinado.

Aún en otro ejemplo, el método de cribado proporcionado por la presente invención para modificadores de ligandos de receptores quimiosensoriales incluye la determinación de si una entidad de ensayo es adecuada para interactuar con un receptor quimiosensorial *a través de* un sitio de interacción predeterminado para modificadores de ligandos de receptores quimiosensoriales.

Todavía en otro ejemplo, el método de cribado proporcionado por la presente invención para modificadores de ligandos de receptores quimiosensoriales incluye la determinación de si una entidad de ensayo es adecuada para interactuar con un receptor quimiosensorial mediante la determinación, *por ejemplo*, de modo concurrente de si un ligando del receptor quimiosensorial y la entidad de ensayo son adecuados para interactuar con el receptor quimiosensorial en un sitio de interacción predeterminado del receptor quimiosensorial o un sitio de interacción determinado utilizando ligandos de receptores quimiosensoriales conocidos y su modificador de interés.

Todavía en otro ejemplo, el método de cribado proporcionado por la presente invención para modificadores de ligandos de receptores quimiosensoriales incluye la determinación de si una entidad de ensayo es adecuada para interactuar con un receptor quimiosensorial *a través de* un sitio de interacción, ya sea predeterminado o no, así como también de si una entidad de ensayo es adecuada para interactuar con un ligando del receptor quimiosensorial.

Todavía en otro ejemplo, el método de cribado proporcionado por la presente invención para modificadores de ligandos de receptores quimiosensoriales incluye la determinación de si una entidad de ensayo es adecuada para interactuar con un receptor quimiosensorial *a través de* un sitio de

interacción, ya sea predeterminado o no, así como también de si dicha interacción puede estabilizar una conformación, *por ejemplo*, una conformación semicerrada o cerrada dentro del dominio Venus atrapamoscas formada por la interacción entre un ligando del receptor quimiosensorial y un receptor quimiosensorial, *por ejemplo*, mediante la formación de interacciones adicionales productivas dentro de la región bisagra, lóbulos del dominio Venus atrapamoscas, o puntas del dominio atrapamoscas *a través de* van der Waals, ocultamiento de grupos atómicos o átomos hidrofóbicos, enlaces hidrógeno, interacciones de agrupamientos de anillos, o interacciones electrostáticas de unión en puente de sales, *etc.*

En general, se puede utilizar cualquier medio adecuado conocido o descubierto posteriormente para determinar si una entidad de ensayo es adecuada para interactuar con sitio de interacción de la presente invención. Por ejemplo, se podría determinar la idoneidad de una entidad de ensayo en base a si parte o toda una entidad de ensayo se adapta dentro de un espacio particular vinculado con un sitio de interacción, *por ejemplo*, si una entidad de ensayo se adapta dentro de un espacio particular vinculado con un sitio de interacción sustancialmente del mismo modo que lo hace un modificador del receptor quimiosensorial o modificador del ligando del receptor quimiosensorial conocido.

Alternativamente se podría determinar la idoneidad de una entidad de ensayo con respecto a un sitio de interacción en base a si forma interacciones con un receptor quimiosensorial similares a las interacciones formadas por un modificador del receptor quimiosensorial o modificador del ligando del receptor quimiosensorial conocido cuando ellos interactuán con el sitio de interacción.

Además, se podría determinar la idoneidad de una entidad de ensayo en base a si forma interacciones productivas con un sitio de interacción, *por ejemplo*, van der Waals, ocultamiento de grupos atómicos o átomos hidrofóbicos, enlaces

hidrógeno, interacciones de agrupamientos de anillos, o interacciones electrostáticas de unión en puente de sales, *etc.* En una realización, se podría determinar la idoneidad de una entidad de ensayo que consiste en un modificador del ligando del receptor quimiosensorial en base a si forma interacciones productivas con un sitio de interacción sin formar superposición de van der Waals con uno o más átomos de un receptor quimiosensorial o del ligando del receptor quimiosensorial, *por ejemplo*, en el contexto de una o más conformaciones del dominio Venus atrapamoscas a la luz de la posible flexibilidad del dominio Venus atrapamoscas.

De acuerdo con la presente invención, una entidad de ensayo adecuada para interactuar con uno o más sitios de interacción dentro del dominio Venus atrapamoscas de un receptor quimiosensorial es indicativa de un candidato para un modificador del receptor quimiosensorial o modificador del ligando del receptor quimiosensorial. En una realización, una entidad de ensayo adecuada para interactuar con uno o más sitios de interacción dentro del dominio Venus atrapamoscas de T1R2 es indicativa de un candidato para un modificador del receptor T1R2 o para un modificador del ligando del receptor T1R2. En otra realización, una entidad de ensayo adecuada para interactuar con uno o más sitios de interacción dentro del dominio Venus atrapamoscas de T1R2 es indicativa de un candidato para un modificador del receptor T1R o modificador del ligando del receptor T1R. Aún en otra realización, una entidad de ensayo adecuada para interactuar con uno o más sitios de interacción dentro del dominio Venus atrapamoscas de T1R2 es indicativa de un candidato para un modificador del receptor o modificador del ligando del receptor para un receptor de la superfamilia GPCR. Todavía en otra realización, una entidad de ensayo adecuada para interactuar con uno o más sitios de interacción dentro del dominio Venus atrapamoscas de un receptor quimiosensorial es indicativa de un candidato para

un modificador del receptor o modificador del ligando del receptor de un receptor que corresponde al receptor quimiosensorial o que pertenece a la misma familia o clase que la del receptor quimiosensorial.

De acuerdo con la presente invención, una entidad de ensayo adecuada para interactuar con uno o más sitios de interacción dentro del dominio Venus atrapamoscas de un receptor quimiosensorial es indicativa de un candidato para un modificador del receptor quimiosensorial o modificador del ligando del receptor quimiosensorial. En una realización, una entidad de ensayo adecuada para interactuar con uno o más sitios de interacción dentro del dominio Venus atrapamoscas de T1R2 es indicativa de un candidato para un modificador del receptor T1R2 o modificador del ligando del receptor T1R2.

En un ejemplo, una entidad de ensayo adecuada para interactuar con uno o más sitios de interacción que contienen uno o más residuos de interacción de K65, D278, L279, D307, R383, y V384 de T1R2 humano es indicativa de un candidato para un mejorador del ligando del receptor T1R2.

En otro ejemplo, una entidad de ensayo adecuada para interactuar con uno o más sitios de interacción que contienen uno o más residuos de interacción de S40, S144, Y103, D142, y P277 de T1R2 humano es indicativa de un candidato para un mejorador del ligando del receptor T1R2 con respecto a la sacarosa o a la sucralosa o a cualquier ligando con una estructura similar a la sacarosa o a la sucralosa o a cualquier ligando que interactúa con T1R2 en una manera similar a aquélla de la sacarosa o de la sucralosa, *por ejemplo, a través de* uno o más residuos y/o espacios de interacción utilizados pos la sacarosa o la sucralosa.

En el contexto de la presente solicitud, cualquier referencia a un modificador, *por ejemplo* mejorador o inhibidor de un receptor T1R2 o de un ligando del receptor T1R2 incluye un modificador para cualquier receptor T1R, cualquier receptor de la super-familia GPCR, o cualquier receptor que

corresponde a un receptor T1R2, *por ejemplo*, cualquier receptor con una estructura, función, o patrón de expresión que se superpone o similar a aquél de T1R2. En la presente invención, una entidad de ensayo puede consistir en cualquier compuesto o molécula, *por ejemplo*, cualquier compuesto o entidad que potencialmente podría ser una fuente para un modificador del receptor quimiosensorial o modificador del ligando del receptor quimiosensorial deseado. Por ejemplo, una entidad de ensayo puede consistir en un miembro de una biblioteca combinatoria, en un miembro de una biblioteca de un compuesto natural, en un compuesto "designado específicamente" es decir designado en base a diversas características o fundamentos deseables, *etc.*

En general, un ligando o modificador del receptor quimiosensorial incluye cualquier compuesto o entidad capaz de interactuar con, *por ejemplo*, de unirse a un receptor quimiosensorial o de modular la estructura o función de un receptor quimiosensorial, *por ejemplo*, de activar, desactivar, incrementar, o disminuir la actividad de transducción de señales de un receptor quimiosensorial, especialmente *a través de* la vía de transducción de señales de la proteína G.

En una realización, un ligando o modificador del receptor quimiosensorial es un compuesto o entidad gustativa dulce que incluye sin limitación alguna cualquier compuesto de sabor dulce natural o sintetizado, *por ejemplo*, compuestos de sabor dulce no calóricos, compuestos de sabor dulce reducidos en calorías, compuestos de sabor dulce calóricos no objetivo, *etc.* Los compuestos de sabor dulce ejemplificativos incluyen, sin limitación alguna, ácido ciclámico, mogrosida, tagatosa, maltosa, galactosa, manosa, sacarosa, fructosa, lactosa, aspartame, neotame y otros derivados de aspartame, sacarina, sucralosa, acesulfame K, glucosa, eritritol, D-triptófano, glicina, manitol, sorbitol, maltitol, lactitol, isomalt, jarabe de glucosa hidrogenado (HGS), hidrolizado de almidón hidrogenado (HSH), esteviosida, rebaudiosida A y otros glucósidos

dulces basados en Ste*via*, alitame, carrelame y otros edulcorantes basados en guanidina, tagatosa, xilitol, jarabe de maíz de alta fructosa, *etc.*

En otra realización, un ligando o modificador del receptor quimiosensorial (utilizado de modo indistinto en la presente invención) es un compuesto o entidad capaz de activar un receptor quimiosensorial, *por ejemplo*, de activar la vía de transducción de señales de la proteína G asociada con el receptor quimiosensorial. Aún en otra realización, un ligando o modificador del receptor quimiosensorial es un compuesto o entidad capaz de bloquear o de disminuir la activación de un receptor quimiosensorial. Todavía en otra realización, un ligando o modificador del receptor quimiosensorial es un compuesto o entidad capaz de modular la actividad de un receptor quimiosensorial y de inducir una transducción de señales o reacción terapéuticamente deseable. Todavía en otra realización, un ligando o modificador del receptor quimiosensorial es un modificador del ligando del receptor quimiosensorial.

De acuerdo con la presente invención, un modificador del ligando del receptor quimiosensorial incluye cualquier compuesto o entidad capaz de interactuar o de modular la actividad de un modificador del receptor quimiosensorial o la actividad de un receptor quimiosensorial en presencia de un modificador del receptor quimiosensorial. En una realización, un modificador del ligando del receptor quimiosensorial es un mejorador de un modificador del receptor quimiosensorial. En otra realización, un modificador del ligando del receptor quimiosensorial es un antagonista de un modificador del receptor quimiosensorial. Aún en otra realización, un modificador del ligando del receptor quimiosensorial es un mejorador de un modificador del receptor quimiosensorial que no tiene la actividad sustancial del modificador del receptor quimiosensorial. Todavía en otra realización, un modificador del ligando del receptor quimiosensorial es un mejorador de un compuesto de sabor dulce que no tiene

por sí mismo un sabor dulce sustancial, *por ejemplo*, según lo consideren los animales o los humanos tales como la mayoría de un panel de al menos ocho degustadores humanos, *a través de* procedimientos normalmente conocidos en el área. Aún todavía en otra realización, un modificador del ligando del receptor quimiosensorial es un mejorador o inhibidor de un modificador del receptor quimiosensorial y es capaz de inducir una transducción de señales o reacción terapéutica deseable.

De acuerdo con otro aspecto de la presente invención, ésta proporciona modificadores de ligandos de receptores quimiosensoriales. En una realización, ésta proporciona modificadores de ligandos de receptores quimiosensoriales identificados a través de los métodos de cribado de la presente invención. En otra realización, ésta proporciona modificadores de ligandos de receptores quimiosensoriales capaces de interactuar con un receptor quimiosensorial *a través de* un sitio de interacción de la presente invención. Aún en otra realización, ésta proporciona modificadores de ligandos de receptores quimiosensoriales capaces de interactuar con un receptor quimiosensorial *a través de* uno o más residuos de interacción del receptor quimiosensorial. Todavía en otra realización, ésta proporciona modificadores de ligandos de receptores quimiosensoriales capaces de interactuar con un receptor quimiosensorial *a través de* un espacio de interacción dentro del dominio Venus atrapamoscas que se encuentra delineado, definido, o conformado, parcialmente o por completo, por residuos de interacción del receptor quimiosensorial. Aún todavía en otra realización, ésta proporciona modificadores de ligandos de receptores quimiosensoriales que excluyen, *por ejemplo*, mejoradores dulces naturales o sintetizados conocidos anteriormente a la presente invención.

En el contexto de la presente invención, "capaz de interactuar con" o "que interactúa con" significa que un compuesto o molécula se une a o forma una o

más interacciones moleculares, *por ejemplo*, interacciones productivas con otra molécula, *por ejemplo*, un receptor quimiosensorial. Las interacciones moleculares ejemplificativas, *por ejemplo*, las interacciones productivas incluyen van der Waals, ocultamiento de grupos atómicos o átomos hidrofóbicos, enlaces hidrógeno, interacciones de agrupamientos de anillos, o interacciones electrostáticas de unión en puente de sales, o una combinación de los mismos.

En una realización, la presente invención proporciona modificadores de ligandos de receptores quimiosensoriales capaces de interactuar con un receptor quimiosensorial *a través de* un grupo de residuos de interacción o de un espacio de interacción dentro del dominio Venus atrapamoscas que se encuentra delineado, conformado, o definido, parcialmente o por completo, por el grupo o cualquier subgrupo de residuos de interacción, opcionalmente en presencia de un ligando del receptor quimiosensorial, *por ejemplo*, 1) S40, S144, S165, Y103, D142, P277 de un T1R2 humano, 2) K65, R383, D307, E302, y D278 de un T1R2 humano, 3) I167, P185, T184, T326, E302, V384, A305, I325, I306, R383, D307, E382, D278, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, y S168 de un T1R2 humano, 4) S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, y D278 de un T1R2 humano, 5) S40, S144, S165, Y103, D142, P277, I167, P185, T184, T326, E302, V384, A305, I325, I306, R383, D307, E382, D278, I279, I67, V66, V309, S303, T242, F103, Q328, y S168 de un T1R2 humano, 6) K65, R383, D307, E302, D278, I167, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, y S168 de un T1R2 humano, 7) S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, I167, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, y S168 de un T1R2 humano, 8) N143, S144, e I167 de un T1R2 humano, o 9) N143, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, I167, P185, T184, T326,

E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, y S168 de un T1R2 humano.

En otra realización, la presente invención proporciona mejoradores de ligandos de receptores quimiosensoriales capaces de interactuar con un receptor quimiosensorial en presencia de un ligando del receptor quimiosensorial *a través de* uno o más residuos de interacción de K65, D278, L279, D307, R383, V384 de un T1R2 humano.

Aún en otra realización, la presente invención proporciona mejoradores de sacarosa o sucralosa capaces de interactuar con un receptor quimiosensorial en presencia de sacarosa o sucralosa *a través de* uno o más residuos de interacción de S40, S144, Y103, D142, P277 de un T1R2 humano.

Todavía en otra realización, la presente invención proporciona modificadores de ligandos de receptores quimiosensoriales capaces de interactuar con un receptor quimiosensorial, opcionalmente en presencia de un ligando del receptor quimiosensorial *a través de* al menos 1, 2, 3, 4, 5, 6, 7, 8, 9, o 10 residuos de interacción seleccionados del grupo de N143, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, I167, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, y S168 de un T1R2 humano.

Todavía en otra realización, la presente invención proporciona modificadores de ligandos de receptores quimiosensoriales capaces de interactuar con un receptor quimiosensorial para estabilizar una conformación, *por ejemplo*, una conformación semicerrada o cerrada formada por la interacción entre un receptor quimiosensorial y un ligando del receptor quimiosensorial.

Aún todavía en otra realización, la presente invención proporciona modificadores de ligandos de receptores quimiosensoriales, *por ejemplo*, sacarina, análogos de sacarina, acesulfame K, análogos de acesulfame K, o

cualquier compuesto capaz de interactuar con un receptor quimiosensorial *a través de* un sitio de interacción que es similar a o que se superpone con un sitio de interacción utilizado por sacarina o acesulfame K. En un ejemplo, la presente invención proporciona mejoradores de ligandos de receptores quimiosensoriales, *por ejemplo*, sacarina, análogos de sacarina, acesulfame K, o análogos de acesulfame K que interactúan con un receptor quimiosensorial a través de un sitio de interacción que incluye uno o más residuos de interacción de K65, R383, D307, E302 y D278 de un T1R2 humano.

De acuerdo con aún otro aspecto de la presente invención, ésta proporciona modificadores de receptores quimiosensoriales. En una realización, ésta proporciona modificadores de receptores quimiosensoriales identificados a través de los métodos de cribado de la presente invención. En otra realización, ésta proporciona modificadores de receptores quimiosensoriales capaces de interactuar con un receptor quimiosensorial *a través de* un sitio de interacción de la presente invención. Aún en otra realización, ésta proporciona modificadores de receptores quimiosensoriales capaces de interactuar con un receptor quimiosensorial *a través de* uno o más residuos de interacción del receptor quimiosensorial. Todavía en otra realización, ésta proporciona modificadores de receptores quimiosensoriales capaces de interactuar con un receptor quimiosensorial *a través de* un espacio de interacción dentro del dominio Venus atrapamoscas que se encuentra delineado, definido, o conformado, parcialmente o por completo, por residuos de interacción del receptor quimiosensorial. Aún todavía en otra realización, ésta proporciona modificadores de receptores quimiosensoriales que excluyen, *por ejemplo*, entidades gustativas dulces naturales o sintetizadas conocidas anteriormente a la presente invención.

En una realización, la presente invención proporciona modificadores de receptores quimiosensoriales capaces de interactuar con un receptor

quimiosensorial *a través de* un grupo de residuos de interacción o de un espacio de interacción dentro del dominio Venus atrapamoscas que se encuentra delineado, conformado, o definido, parcialmente o por completo por el grupo o cualquier subgrupo de residuos de interacción, *por ejemplo*, 1) S40, S144, S165, Y103, D142, P277 de un T1R2 humano, 2) K65, R383, D307, E302, y D278 de un T1R2 humano, 3) I167, P185, T184, T326, E302, V384, A305, I325, I306, R383, D307, E382, D278, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, y S168 de un T1R2 humano, 4) S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, y D278 de un T1R2 humano, 5) S40, S144, S165, Y103, D142, P277, I167, P185, T184, T326, E302, V384, A305, I325, I306, R383, D307, E382, D278, I279, I67, V66, V309, S303, T242, F103, Q328, y S168 de un T1R2 humano, 6) K65, R383, D307, E302, D278, I167, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, y S168 de un T1R2 humano, 7) S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, I167, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, y S168 de un T1R2 humano, 8) N143, S144, e I167 de un T1R2 humano, o 9) N143, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, I167, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, y S168 de un T1R2 humano.

Todavía en otra realización, la presente invención proporciona modificadores de receptores quimiosensoriales capaces de interactuar con un receptor quimiosensorial *a través de* al menos 1, 2, 3, 4, 5, 6, 7, 8, 9, o 10 residuos de interacción seleccionados del grupo de N143, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, I167, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, y S168 de un T1R2 humano.

De acuerdo con todavía otro aspecto de la presente invención, ésta proporciona métodos para modular un receptor quimiosensorial y/o su ligando mediante la modulación de uno o más sitios de interacción del receptor quimiosensorial. Por ejemplo, se puede modular un receptor quimiosensorial poniendo en contacto, *in vivo* o *in vitro*, un modificador del receptor quimiosensorial o un modificador del ligando del receptor quimiosensorial o ambos, (*por ejemplo*, excluyendo opcionalmente entidades gustativas dulces o mejoradores dulces naturales conocidos anteriormente a la presente invención) con células que contienen el receptor quimiosensorial, en donde el modificador del receptor quimiosensorial o ligando del receptor quimiosensorial es capaz de interactuar con o de dirigirse a uno o más sitios de interacción del receptor quimiosensorial.

En una realización, el método de modulación de un receptor quimiosensorial y/o de su ligando consiste en modular uno o más residuos de interacción o espacios de interacción o una combinación de los mismos. En otra realización, el método de modulación de un receptor quimiosensorial y/o de su ligando consiste en interactuar con uno o más residuos de interacción en presencia de un ligando del receptor quimiosensorial. Aún en otra realización, el método de modulación de un receptor quimiosensorial o de su ligando incluye modular el impacto de un ligando del receptor quimiosensorial sobre el receptor quimiosensorial interactuando con el receptor quimiosensorial *a través de* uno o más residuos de interacción en presencia del ligando del receptor quimiosensorial.

Aún en otra realización, el método de modulación de un receptor quimiosensorial y/o de su ligando consiste en interactuar con el receptor quimiosensorial *a través de* un grupo de residuos de interacción o de un espacio de interacción delineado, conformado, o definido, parcialmente o por completo,

por el grupo o subgrupo de residuos de interacción, opcionalmente en presencia de un ligando del receptor quimiosensorial, *por ejemplo*, 1) S40, S144, S165, Y103, D142, P277 de un T1R2 humano, 2) K65, R383, D307, E302, y D278 de un T1R2 humano, 3) I167, P185, T184, T326, E302, V384, A305, I325, I306, R383, D307, E382, D278, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, y S168 de un T1R2 humano, 4) S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, y D278 de un T1R2 humano, 5) S40, S144, S165, Y103, D142, P277, I167, P185, T184, T326, E302, V384, A305, I325, I306, R383, D307, E382, D278, I279, I67, V66, V309, S303, T242, F103, Q328, y S168 de un T1R2 humano, 6) K65, R383, D307, E302, D278, I167, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, y S168 de un T1R2 humano, 7) S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, I167, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, y S168 de un T1R2 humano, 8) N143, S144, e I167 de un T1R2 humano, o 9) N143, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, I167, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, y S168 de un T1R2 humano.

Aún en otra realización, el método de modulación de un receptor quimiosensorial y/o de su ligando consiste en interactuar con el receptor quimiosensorial *a través de* uno o más residuos de interacción de N143, S144, e I167 de un T1R2 humano.

Aún en otra realización, el método de modulación de un receptor quimiosensorial y/o de su ligando consiste en interactuar con el receptor quimiosensorial, opcionalmente en presencia de un ligando del receptor quimiosensorial *a través* de uno o más residuos de interacción de K65, D278, L279, D307, R383, V384 de un T1R2 humano.

Todavía en otra realización, el método de modulación de un receptor quimiosensorial y/o de su ligando consiste en interactuar con el receptor quimiosensorial, opcionalmente en presencia de sacarosa o sucralosa *a través de* uno o más residuos de interacción de S40, S144, Y103, D142, P277 de un T1R2 humano.

Todavía en otra realización, el método de mejoramiento de un receptor quimiosensorial y/o de su ligando consiste en interactuar con el receptor quimiosensorial, opcionalmente en presencia de un ligando del receptor quimiosensorial *a través de* uno o más residuos de interacción de K65, D278, L279, D307, R383, V384, S40, S144, Y103, D142, P277 de un T1R2 humano.

Todavía en otra realización, el método de modulación de un receptor quimiosensorial y/o de su ligando consiste en interactuar con el receptor quimiosensorial, opcionalmente en presencia de un ligando del receptor quimiosensorial *a través de* al menos 1, 2, 3, 4, 5, 6, 7, 8, 9, o 10 residuos de interacción seleccionados del grupo de N143, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, I167, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, y S168 de un T1R2 humano.

Todavía en otra realización, el método de modulación de un receptor quimiosensorial y/o de su ligando consiste en interactuar con el receptor quimiosensorial, opcionalmente en presencia de un ligando del receptor quimiosensorial *a través de* al menos 1, 2, 3, 4, 5, 6, 7, 8, 9, o 10 residuos de interacción seleccionados del grupo de N143, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, I167, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, y S168 de un T1R2 humano.

De acuerdo con la presente invención, un método de modulación de un receptor quimiosensorial y/o de su ligando incluye modular la actividad, estructura, función, expresión, y/o modificación de un receptor quimiosensorial así como también modular, tratar, o medir profilácticamente una afección, *por ejemplo*, una afección fisiológica o patológica, asociada con un receptor quimiosensorial.

En general, una afección fisiológica o patológica asociada con un receptor quimiosensorial incluye una afección asociada con un sabor, *por ejemplo*, dulce, umami, amargo, agrio, salado, o una combinación de los mismos o una afección asociada con, *por ejemplo*, el sistema gastrointestinal, trastornos metabólicos, trastornos gastrointestinales funcionales, *etc.*

En una realización, el método de la presente invención, *por ejemplo*, la modulación de un receptor quimiosensorial y/o de su ligando incluye modular, incrementar o disminuir un sabor dulce o umami o una reacción de un sujeto, fisiológica o de otro tipo, a un sabor dulce o umami. En otra realización, el método de la presente invención, *por ejemplo*, la modulación de un receptor quimiosensorial y/o de su ligando incluye el mejoramiento de un sabor dulce o umami o de una reacción de un sujeto, fisiológica o de otro tipo, a un sabor dulce o umami.

Aún en otra realización, el método de la presente invención, *por ejemplo*, la modulación de un receptor quimiosensorial y/o de su ligando incluye la modulación, el tratamiento, y/o la medición profiláctica de una afección asociada con el sistema gastrointestinal que incluye sin limitación alguna afecciones asociadas con la motilidad esofágica (*por ejemplo*, acalasia cricofaríngea, globo histérico, acalasia, espasmo esofágico difuso y trastornos motores relacionados, esclerodermia que involucra el esófago, *etc.*), trastornos inflamatorios (*por ejemplo*, reflujo gastroesofágico y esofagitis, esofagitis infecciosa, *etc.*), úlcera péptica, úlcera duodenal, úlcera gástrica, gastrinoma, erosiones y úlceras por

estrés, erosiones y úlceras asociadas con drogas, gastritis, cáncer esofágico, tumores del estómago, trastornos de la absorción (*por ejemplo*, de la absorción de nutrientes específicos tales como carbohidratos, proteínas, aminoácidos, grasas, colesterol y vitaminas solubles en grasas, agua y sodio, calcio, hierro, vitaminas solubles en agua, *etc.*), trastornos de malabsorción, defectos en la funciones de las mucosas (*por ejemplo*, trastornos inflamatorios o infiltrativos, anormalidades bioquímicas o genéticas, trastornos endocrinos y metabólicos, enteropatía perdedora de proteínas, *etc.*), enfermedades autoinmunes del tracto digestivo (*por ejemplo*, enfermedad celíaca, enfermedad de Crohn, colitis ulcerativa, *etc.*), síndrome de intestino irritable, enfermedad inflamatoria intestinal, complicaciones de la enfermedad inflamatoria intestinal, manifestaciones extraintestinales de la enfermedad inflamatoria intestinal, trastornos de la motilidad intestinal, trastornos vasculares del intestino, trastornos anorectales (*por ejemplo*, hemorroides, inflamación anal, *etc.*), cáncer colorectal, tumores del intestino delgado, cánceres del ano, trastornos del metabolismo hepático, hiperbilirubinemia, hepatitis, enfermedad hepática alcohólica y cirrosis, cirrosis biliar, neoplasmas del hígado, enfermedades infiltrativas y metabólicas que afectan el hígado (*por ejemplo*, hígado graso, síndrome de reye, glucogenosis diabética, enfermedad por almacenamiento de glucógeno, enfermedad de Wilson, hemocromatosis), enfermedades de la vesícula biliar y de los conductos biliares, trastornos del páncreas (*por ejemplo*, pancreatitis, insuficiencia pancreática exocrina, cáncer pancreático, *etc.*), tumores endocrinos del tracto gastrointestinal y del páncreas, *etc.*

Todavía en otra realización, el método de la presente invención, *por ejemplo,* la modulación de un receptor quimiosensorial y/o de su ligando incluye la modulación, tratamiento, y/o la medición profiláctica de una afección asociada con trastornos metabólicos, *por ejemplo*, del apetito, peso corporal, ingesta de

alimentos o de líquidos o la reacción de un sujeto a la ingesta de alimentos o de líquidos, o el estado de saciedad o la percepción de un sujeto de un estado de saciedad, la regulación e ingesta nutricionales, (*por ejemplo*, la malnutrición proteico-energética, deterioros fisiológicos asociados con la malnutrición proteico-energética, *etc.*), obesidad, obesidad secundaria (*por ejemplo*, hipotiroidismo, enfermedad de Cushing, insulinoma, trastornos hipotalámicos, *etc.*), trastornos de la alimentación (*por ejemplo*, anorexia nerviosa, bulimia, *etc.*), deficiencia y exceso vitamínicos, metabolismo de la insulina, diabetes (tipo I y tipo II) y complicaciones de la misma (*por ejemplo*, anomalías circulatorias, retinopatía, neuropatía diabética, neuropatía diabética, úlceras del pie diabético, *etc.*), metabolismo de la glucosa, metabolismo de las grasas, hipoglucemia, hiperglucemia, hiperlipoproteinemias, *etc.*

Aún todavía en otra realización, el método de la presente invención, *por ejemplo*, la modulación de un receptor quimiosensorial y/o de su ligando incluye la modulación, tratamiento, y/o la medición profiláctica de una afección asociada con trastornos gastrointestinales funcionales, *por ejemplo*, en ausencia de cualquier afección patológica particular tal como úlcera péptica y cáncer, un sujeto tiene dispepsia abdominal, *por ejemplo*, una sensación de distensión abdominal, náuseas, vómitos, dolor abdominal, anorexia, reflujo de ácidos gástricos, o movimiento intestinal anormal (constipación, diarrea y similares), opcionalmente en base a la retención de los contenidos en el tracto gastrointestinal, especialmente en el estómago. En un ejemplo, los trastornos gastrointestinales funcionales incluyen una afección sin cualquier enfermedad orgánica del tracto gastrointestinal, pero con uno o más síntomas gastrointestinales reproducibles que afectan la calidad de vida de un sujeto, *por ejemplo*, un humano.

Los trastornos gastrointestinales funcionales ejemplificativos incluyen, sin limitación alguna, dispepsia funcional, afección por reflujo gastroesofágico,

gastroparesis diabética, esofagitis por reflujo, disfunción gastrointestinal postoperatoria y similares, náuseas, vómitos, sensación enfermiza, acidez estomacal, sensación de distención, pesadez estomacal, eructos, retortijones en el pecho, dolores en el pecho, disconfort gástrico, anorexia, disfagia, reflujo de ácidos gástricos, dolores abdominales, constipación, diarrea, falta de aire, sensación de sofocación, bajo incentivo o nivel de energía, obstrucción faríngea, sensación de sustancia extraña, fácil fatigabilidad, tortícolis, espasmo muscular, sequedad bucal (boca seca, sed, *etc.*), taquipnea, sensación de ardor en el tracto gástrico intestinal, sensación de frío en las extremidades, dificultad en la concentración, impaciencia, trastornos del sueño, dolor de cabeza, malestar general, palpitaciones, sudor nocturno, ansiedad, mareos, vértigo, sofocación, sudor excesivo, depresión, *etc.*

Aún todavía en otra realización, el método de la presente invención, *por ejemplo*, la modulación de un receptor quimiosensorial y/o de su ligando incluye el incremento o la estimulación de la digestión, absorción, nivel de nutrientes en sangre, y/o motilidad del tracto gastrointestinal en un sujeto, *por ejemplo*, la estimulación del vaciamiento gástrico (*por ejemplo*, la depuración de los contenidos estomacales), reducción de la distensión abdominal en el período postprandial temprano, mejoramiento de la anorexia, *etc.* En general, dicha estimulación se puede lograr ya sea directamente o *a través del* incremento de la secreción de una entidad de regulación, *por ejemplo*, hormonas, *etc.*

Aún todavía en otra realización, el método de la presente invención, *por ejemplo*, la modulación de un receptor quimiosensorial y/o de su ligando incluye el incremento de una o más funciones gastrointestinales de un sujeto, *por ejemplo*, para mejorar la calidad de vida o el estado de salud de un sujeto.

Aún todavía en otra realización, el método de la presente invención, *por ejemplo*, la modulación de un receptor quimiosensorial y/o de su ligando incluye la

modulación de la actividad de las células que expresan T1R (*por ejemplo*, T1R1, T1R2, o T1R3), *por ejemplo*, las células hepáticas (*por ejemplo*, hepatocitos, células endoteliales, células de Kupffer, células estrelladas, células epiteliales de los conductos biliares, *etc.*), las células cardíacas (*por ejemplo*, las células endoteliales, cardíacas, y del músculo liso, *etc.*), las células pancreáticas (*por ejemplo*, célula alfa, célula beta, célula delta, célula neurosecretora PP, célula D1, *etc.*), células en la tetilla (*por ejemplo*, células epiteliales ductales, *etc.*), células del estómago (*por ejemplo*, células mucosas, células parietales, células principales, células G, células P/D1), células intestinales (*por ejemplo*, células enteroendocrinas, células de cepillo, *etc.*), células de las glándulas salivales (*por ejemplo*, células seromucosas, células mucosas, células mioepiteliales, células de conductos intercalados, células de conductos estriados, *etc.*), células L (*por ejemplo*, que expresan GLP-1, *etc.*), células enterocromafines (*por ejemplo*, que expresan serotonina), células tipo enterocromafines, células G (*por ejemplo*, que expresan gastrina), células D (células delta, *por ejemplo*, que expresan somatostatina), células I (*por ejemplo*, que expresan colecistoquinina (CCK), células K (*por ejemplo*, que expresan polipéptidos inhibidores gástricos), células P/D1 (*por ejemplo*, que expresan ghrelin), células principales (*por ejemplo*, que expresan pepsina), y células S (*por ejemplo*, que expresan secretina). En un ejemplo, el método de la presente invención incluye el incremento del nivel de expresión de T1R en células que expresan T1R. En otro ejemplo, el método de la presente invención incluye el incremento del nivel de secreción de células que expresan T1R.

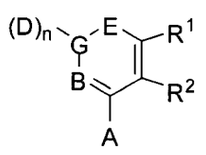
Aún todavía en otra realización, el método de la presente invención, *por ejemplo*, la modulación de un receptor quimiosensorial y/o de su ligando incluye la modulación de la expresión, secreción, y/o nivel funcional de las células que expresan T1R asociadas con hormonas, péptidos, producción de enzimas. En un

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ejemplo, el método de la presente invención incluye la modulación del nivel de glucosa, *por ejemplo*, se pueden utilizar inhibidores de un receptor quimiosensorial tal como T1R2 para disminuir el nivel de glucosa (*por ejemplo*, la absorción de glucosa) en un sujeto. En otro ejemplo, el método de la presente invención incluye la modulación del nivel de incretinas, *por ejemplo*, se pueden utilizar agonistas de un receptor quimiosensorial tal como T1R2 para incrementar el péptido tipo glucagon 1 (GLP-1) y de este modo incrementar la producción de insulina. Aún en otro ejemplo, el método de la presente invención incluye la modulación de la expresión, secreción, y/o nivel de actividad de hormonas o péptidos producidos por células que expresan T1R o células que producen hormonas gastrointestinales, *por ejemplo*, ligandos para los receptores 5HT (*por ejemplo,* serotonina), incretinas (*por ejemplo*, GLP-1 y polipéptido insulinotrópico dependiente de glucosa (GIP)), gastrina, secretina, pepsina, colecistoquinina, amilasa, ghrelin, leptina, somatostatina, *etc.* Todavía en otro ejemplo, el método de la presente invención incluye la modulación de vías asociadas con hormonas, péptidos, y/o enzimas segregados por células que expresan T1R.

Los modificadores de ligandos de receptores quimiosensoriales ejemplificativos proporcionados por la presente invención y/o adecuados para utilizarse para los métodos de la presente invención incluyen los compuestos de las siguientes fórmulas.

En una realizaciónde la presente invención, el modificador del ligando del receptor quimiosensorial es un compuesto que tiene una Fórmula estructural (I):



(I)

o un tautómero, sal, solvato, y/o éster del mismo, en donde:

G forma un enlace único o bien con D o E y un enlace doble con el otro de D o E;

R^1 es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, $-NO_2$, $-OR^3$, $-S(O)_aR^3$, $-NR^3R^4$, $-CONR^3R^4$, $-CO_2R^3$, $-NR^3CO_2R^4$, $-NR^3CONR^4R^5$, $-NR^3CSNR^4R^5$, $-NR^3C(=NH)NR^4R^5$, $-SO_2NR^3R^4$, $-NR^4SO_2R^3$, $-NR^3SO_2NR^4R^5$, $-B(OR^3)(OR^4)$, $-P(O)(OR^3)(OR^4)$ o $-P(O)(R^3)(OR^4)$;

R^2 es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, $-NO_2$, $-OR^6$, $-S(O)_bR^6$, $-NR^6R^7$, $-CONR^6R^7$, $-CO_2R^6$, $-NR^6CO_2R^7$, $-NR^6CONR^7R^8$, $-NR^6CSNR^7R^8$, $-NR^6C(=NH)NR^7R^8$, $-SO_2NR^5R^6$, $-NR^5SO_2R^6$, $-NR^5SO_2NR^6R^7$, $-B(OR^5)(OR^6)$, $-P(O)(OR^5)(OR^6)$, o $-P(O)(R^5)(OR^6)$; o alternativamente, R^1 y R^2, conjuntamente con los átomos a los cuales ellos están unidos, forman un anillo arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido en donde el anillo está opcionalmente fusionado con otro anillo arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido;

con la condición de que R^1 y R^2 no sean ambos hidrógeno;

A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, halo, -CN, $-NO_2$, $-OR^9$, $-S(O)_cR^9$, $-NR^9COR^{10}$, $-NHOR^9$, $-NR^9R^{10}$, $-NOR^9$,

$-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$, $-NR^9C(=NH)NR^{10}R^{11}$, $-B(OR^{10})(OR^{11})$, $-P(O)(OR^{10})(OR^{11})$ o $-P(O)(R^{10})(OR^{11})$;

B es -N- o $-C(R^{12})-$;

R^{12} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, $-NR^{13}R^{14}$, -CN, $-OR^{13}$, $-S(O)_dR^{13}$, $-CO_2R^{13}$ o $-CONR^{13}R^{14}$;

G es -C- o $-S(O)_2-$;

siempre que cuando G sea $-S(O)_2-$, entonces G forme un enlace único con E;

cuando el enlace entre D y G es un enlace único, entonces D es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, $-OR^{15}$, $-NH-OR^{15}$, $-S(O)_eR^{15}$, $-NR^{15}R^{16}$, $-NH-NHR^{15}$, $-CO_2R^{15}$, o $-CONR^{15}R^{16}$;

cuando G forma un enlace doble con D, entonces D es =O, =S , $=N-OR^{15}$, o $=N-NHR^{15}$;

n es 0 cuando G es $-S(O)_2-$, y n es 1 cuando G es -C-;

E es $-NR^{17}-$, -N- o $-C(R^{18})-$;

siempre que E sea $-NR^{17}-$ solamente cuando G forme un enlace único con E; R^{17} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido o $-CO_2R^{19}$;

R^{18} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido,

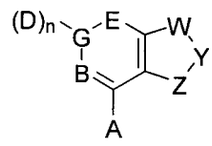
heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, $-NR^{20}R^{21}$, -CN, $-OR^{20}$, $-S(O)_fR^{20}$, $-CO_2R^{20}$ o $-CONR^{20}R^{21}$;

a, b, c, d, e y f son independientemente 0, 1 o 2; y

R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{13}, R^{14}, R^{15}, R^{16}, R^{18}, R^{20}, y R^{21} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido; o alternativamente, R^3 y R^4, R^4 y R^5, R^6 y R^7, R^7 y R^8, R^9 y R^{10}, R^{10} y R^{11}, R^{13} y R^{14}, R^{15} y R^{16}, o R^{20} y R^{21}, conjuntamente con los átomos a los cuales ellos están unidos, forman un anillo cicloheteroalquilo o cicloheteroalquilo sustituido.

En una realización de la Fórmula (I), R^1 y R^2, conjuntamente con los átomos a los cuales ellos están unidos, forman un anillo arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido en donde el anillo está opcionalmente fusionado a otro anillo arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido.

En una realización de la Fórmula (I), el modificador del ligando del receptor quimiosensorial es un compuesto que tiene una Fórmula estructural (II),



(II)

en donde:

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Y forma un enlace único o bien con W o Z y un enlace doble con el otro de W o Z;

W es $-C(R^{24})-$, -S-, -N-, $-N(R^{25})-$, o -O-;

Y es $-C(R^{26})-$ o -N-;

Z es $-C(R^{27})-$, -S-, -N-, $-N(R^{28})-$, u -O-;

R^{24} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido -CN, $-NO_2$, $-OR^{29}$, $-S(O)_gR^{29}$, $-NR^{29}R^{30}$, $-CONR^{29}R^{30}$, $-CO_2R^{29}$, $-SO_2NR^{29}R^{30}$, $-NR^{29}SO_2R^{30}$, $-B(OR^{29})(OR^{30})$, $-P(O)(OR^{29})(OR^{30})$ o $-P(O)(R^{29})(OR^{30})$;

R^{26} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido -CN, $-NO_2$, $-OR^{31}$, $-S(O)_hR^{31}$, $-NR^{31}R^{32}$, $-CONR^{31}R^{32}$, $-CO_2R^{31}$, $-OCOR^{31}$, $-SO_2NR^{31}R^{32}$, $-NR^{31}SO_2R^{32}$, $-B(OR^{31})(OR^{32})$, $-P(O)(OR^{31})(OR^{32})$ o $-P(O)(R^{31})(OR^{32})$;

R^{27} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido -CN, $-NO_2$, $-OR^{33}$, $-S(O)_iR^{33}$, $-NR^{33}R^{34}$, $-CONR^{33}R^{34}$, $-COR^{33}$, $-CO_2R^{33}$, $-OCOR^{33}$, $-SO_2NR^{33}R^{34}$, $-NR^{33}SO_2R^{34}$, $-B(OR^{33})(OR^{34})$, $-P(O)(OR^{33})(OR^{34})$ o $-P(O)(R^{33})(OR^{34})$; o alternativamente R^{24} y R^{26} o R^{26} y R^{27} conjuntamente con los átomos a los cuales ellos están unidos forman un anillo cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido;

g, h e i son independientemente 0 o 1;

R^{25} y R^{28} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido,

heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido; y

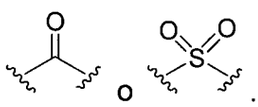
R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, y R^{34} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido; o alternativamente R^{29} y R^{30}, R^{31} y R^{32} o R^{33} y R^{34} conjuntamente con los átomos a los cuales ellos están unidos forman un anillo cicloheteroalquilo o cicloheteroalquilo sustituido; y

con las siguientes condiciones:

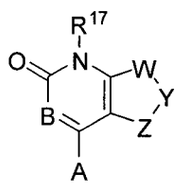
(a) cuando W es -O- o -S- o -NR^{25}, entonces Z es –$C(R^{27})$ o -N-; y

(b) cuando Z es -O- o -S- o -NR^{28}, entonces W es -$C(R^{24})$ o -N-.

En una realización de la Fórmula (II), $(D)_n$-G es



En una realización de la Fórmula (II), el compuesto de la presente invención tiene la Fórmula estructural (IIa):



(IIa)

con las siguientes condiciones:

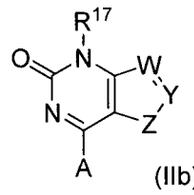
(a) cuando W es -O- o -S- o -NR^{25}, entonces Z es –$C(R^{27})$ o -N-;

(b) cuando Z es -O- o -S- o -NR^{28}, entonces W es -$C(R^{24})$ o -N-; y

(c) cuando B es -N-, entonces A no es halo.

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En una realización de la Fórmula (IIa), el compuesto de la presente invención tiene la Fórmula estructural (IIb):



(IIb)

en donde, W es -C(R^{24})- o -N-; Y es -C(R^{26})- o -N-; y Z es -S-, -N(R^{28})- u -O-.

En una realización de la Fórmula (IIb), W es -C(R24)-, e Y es -C(R26)-.

En una realización de la Fórmula (IIb), W es -C(R^{24})-; Y es -C(R^{26})-; R^{24} es hidrógeno, alquilo, alquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, -CN, -NO_2, -OR^{29}, -$S(O)_gR^{29}$, -$OCOR^{29}$, -$NR^{29}R^{30}$, -$CONR^{29}R^{30}$ o -CO_2R^{29}; y R^{26} es hidrógeno, alquilo, alquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, -CN, -NO_2, -OR^{31}, -$OCOR^{31}$, -$S(O)_hR^{31}$, -$NR^{31}R^{32}$, -$CONR^{31}R^{32}$ o -CO_2R^{31}. En una realización preferida, R^{24} es hidrógeno, -CF_3, alquilo o alquilo sustituido; y R^{26} es hidrógeno, -CF_3, alquilo o alquilo sustituido.

En una realización de la Fórmula (IIb), W es -C(R^{24})-; e Y es -C(R^{26})-; A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, -CN, -NO_2, -$S(O)_cR^9$, -NR^9R^{10}, -$CONR^9R^{10}$, -CO_2R^9 o -$NR^9CO_2R^{10}$; R^{17} es hidrógeno, alquilo, alquilo sustituido, arilalquilo, o arilalquilo sustituido; R^{24} es hidrógeno, alquilo, alquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, -CN, -NO_2, -OR^{29}, -$S(O)_gR^{29}$, -$OCOR^{29}$, -$NR^{29}R^{30}$, -$CONR^{29}R^{30}$ o -CO_2R^{29}; y R^{26} es hidrógeno, alquilo, alquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, -CN, -NO_2, -OR^{31}, -$S(O)_hR^{31}$, -$OCOR^{31}$, -$NR^{31}R^{32}$, -$CONR^{31}R^{32}$ o -CO_2R^{31}.

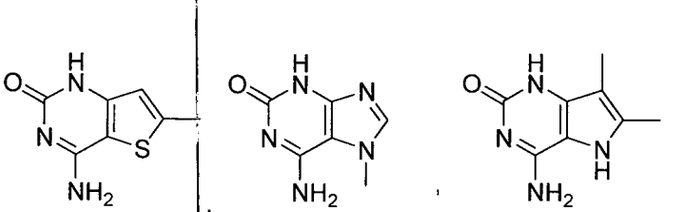
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En una realización de la Fórmula (IIb), W es -C(R^{24})-; e Y es -C(R^{26})-; A es -NR^9COR^{10}, -$NHOR^9$, -NR^9R^{10}, -NOR^9, -$CONR^9R^{10}$, -CO_2R^9, -$NR^9CO_2R^{10}$, -OR^9, -$NR^9CONR^{10}R^{11}$, -$NR^9CSNR^{10}R^{11}$ o -$NR^9C(=NH)NR^{10}R^{11}$; R^{17} es hidrógeno, alquilo, alquilo sustituido, arilalquilo, o arilalquilo sustituido; R^{24} es hidrógeno, alquilo, alquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, -CN, -NO_2, -OR^{29}, -$S(O)_gR^{29}$, -$OCOR^{29}$, -$NR^{29}R^{30}$, -$CONR^{29}R^{30}$ o -CO_2R^{29}; y R^{26} es hidrógeno, alquilo, alquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, -CN, -NO_2, -OR^{31}, -$S(O)_hR^{31}$, -$OCOR^{31}$, -$NR^{31}R^{32}$, -$CONR^{31}R^{32}$ o -CO_2R^{31}. En una realización preferida, A es -OH, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -$NHOCH_3$, -$NOCH_3$, -$NHC(O)CH_3$, -$NHC(O)OCH_3$, -$NHC(O)NH_2$, -$NHC(S)NH_2$, -$NHC(NH)NH_2$, -CN, -CH_2OH, -CH_2NH_2, -CH_2NHCH_3, -$CH_2N(CH_3)_2$, -CO_2H, -$CONH_2$, -$CONHCH_3$ o -$CH_2NHC(O)CH_3$; R^{17} es hidrógeno, metilo, etilo, propilo, *iso*-propilo, *n*-butilo, *iso*-butilo, *sec*-butilo, *t*-butilo, fenilo o bencilo; y R^{24} es hidrógeno, -CF_3, metilo, etilo, propilo, *iso*-propilo, *n*-butilo, *iso*-butilo, *sec*-butilo o *t*-butilo; y R^{26} es hidrógeno, -CF_3, metilo, etilo, propilo, *iso*-propilo, *n*-butilo, *iso*-butilo, *sec*-butilo o *t*-butilo. En una realización más preferida, A es -NH_2, R^{17} es hidrógeno o metilo, R^{24} es hidrógeno, -CF_3, metilo o etilo, y R^{26} es hidrógeno, -CF_3, metilo o etilo.

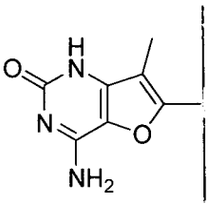
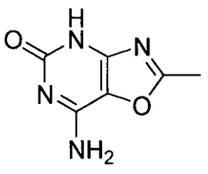
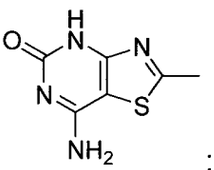
En algunas realizaciones de la Fórmula (IIb), R^{28} es hidrógeno, alquilo o arilalquilo.

En algunas realizaciones de la Fórmula (IIb), R^{28} es hidrógeno, metilo o bencilo.

En algunas realizaciones específicas de la Fórmula (IIb), los compuestos tienen la fórmula estructural seleccionada del grupo integrado por:

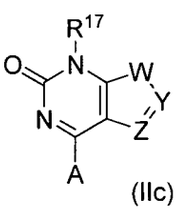


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o un tautómero, sal, solvato, y/o éster del mismo. En algunas realizaciones preferidas, la sal de estos compuestos es la sal clorhidrato o trifluoracetato.

En una realización de la Fórmula (IIa), el compuesto de la presente invención tiene la Fórmula estructural (IIc):


(IIc)

en donde, W es -S-, -N(R^{25})-, u -O-; Y es -C(R^{26})- o -N-; y Z es -C(R^{27})- o -N-. En una realización preferida, Y es -C(R^{26})-, y Z es -C(R^{27})-.

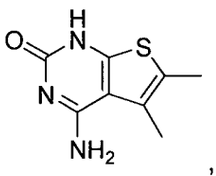
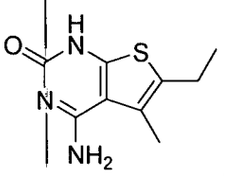
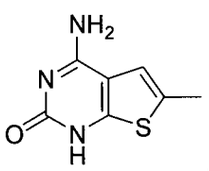
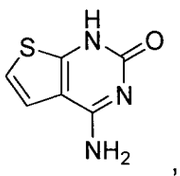
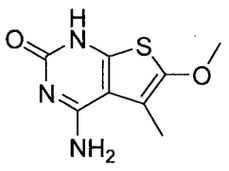
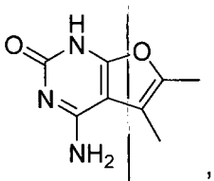
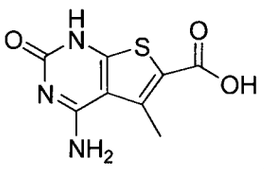
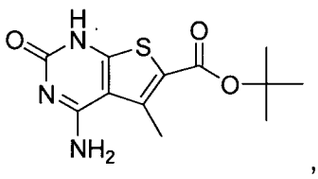
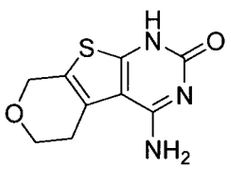
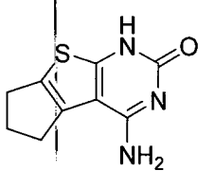
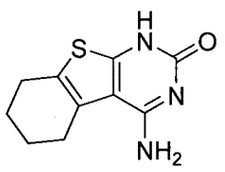
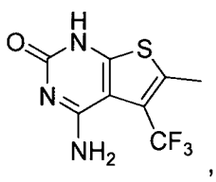
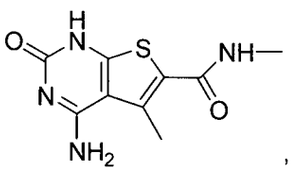
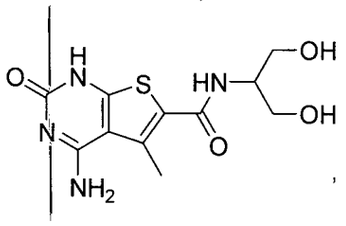
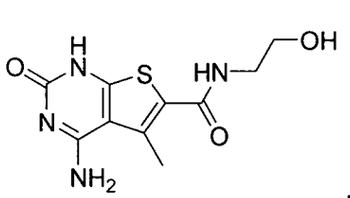
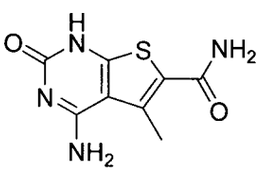
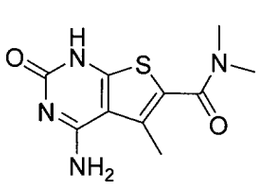
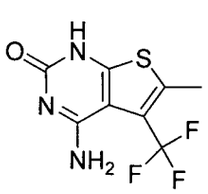
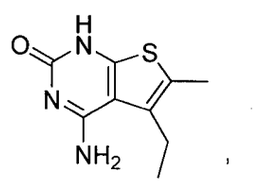
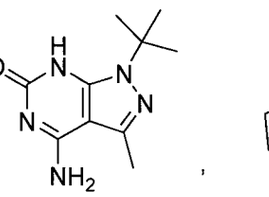
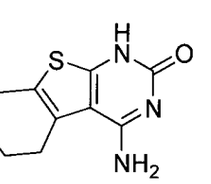
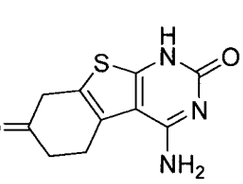
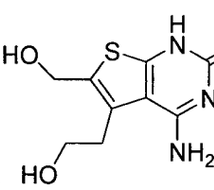
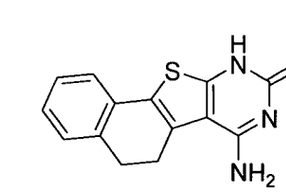
En una realización de la Fórmula (IIa), W es -S-, -N(R^{25})-, u -O-; Y es -C(R^{26})- o -N-; Z es -C(R^{27})- o -N-; R^{27} es hidrógeno, alquilo, alquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, -CN, -NO_2, -OR^{33}, -$S(O)_iR^{33}$, -$OCOR^{33}$, -$NR^{33}R^{34}$, -$CONR^{33}R^{34}$ o -CO_2R^{33}; y R^{26} es hidrógeno, alquilo, alquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, -CN, -NO_2, -OR^{31}, -$S(O)_hR^{31}$, -$OCOR^{31}$, -$NR^{31}R^{32}$, -$CONR^{31}R^{32}$ o -CO_2R^{31}.

En una realización de la Fórmula (IIa), W es -S-, -N(R^{25})-, u -O-; Y es -C(R^{26})- o -N-; Z es -C(R^{27})- o -N-; R^{26} y R^{27} conjuntamente con el átomo al cual ellos están unidos forman un anillo cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido.

En una realización de la Fórmula (IIa), W es -S-, -N(R^{25})-, u -O-; Y es -C(R^{26})- o -N-; Z es -C(R^{27})- o -N-; A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, -NR^9COR^{10}, -$NHOR^9$, -NOR^9, -OR^9, -$NR^9CONR^{10}R^{11}$, -$NR^9CSNR^{10}R^{11}$ o -$NR^9C(=NH)NR^{10}R^{11}$, -CN, -NO_2, -$S(O)_cR^9$, -NR^9R^{10}, -$C(O)NR^9R^{10}$, -CO_2R^9 o -$NR^9CO_2R^{10}$; y R^{17} es hidrógeno, alquilo, alquilo sustituido, arilalquilo, o arilalquilo sustituido.

En una realización de la Fórmula (IIa), W es -S-, -N(R^{25})-, u -O-; Y es -C(R^{26})- o -N-; Z es -C(R^{27})- o -N-; A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, -NR^9COR^{10}, -$NHOR^9$, -NOR^9, -OR^9, -$NR^9CONR^{10}R^{11}$, -$NR^9CSNR^{10}R^{11}$ o -$NR^9C(=NH)NR^{10}R^{11}$, -CN, -NO_2, -$S(O)_cR^9$, -NR^9R^{10}, -$NR^9C(O)R^{10}$, -$C(O)NR^9R^{10}$, -CO_2R^9 o -$NR^9CO_2R^{10}$; R^{17} es hidrógeno, alquilo, alquilo sustituido, arilalquilo, o arilalquilo sustituido; R^{27} es hidrógeno, alquilo, alquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, -CN, -NO_2, -OR^{33}, -$S(O)_iR^{33}$, -$OCOR^{33}$, -$NR^{33}R^{34}$, -$C(O)NR^{33}R^{34}$ o -CO_2R^{33}; y R^{26} es hidrógeno, alquilo, alquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, -CN, -NO_2, -OR^{31}, -$S(O)_hR^{31}$, -$OC(O)R^{31}$, -$NR^{31}R^{32}$, -$C(O)NR^{31}R^{32}$ o -CO_2R^{31}, o alternativamente R^{26} y R^{27} conjuntamente con el(os) átomo(s) al(os) cual(es) ellos están unidos forman un anillo cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido. En una realización más preferida, A es -NH_2; R^{17} es hidrógeno, metilo, etilo, propilo, *iso*-propilo, *n*-butilo, *iso*-butilo, *sec*-butilo, *t*-butilo, fenilo o bencilo; R^{26} y R^{27} son independientemente hidrógeno, alcanilo, alcanilo sustituido, alcoxi, ácido carboxílico, amida de ácido carboxílico, o éster de ácido carboxílico; o alternativamente, R^{26} y R^{27} conjuntamente con el(os) átomo(s) al(os) cual(es) ellos están unidos forman un anillo cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido.

En algunas realizaciones específicas de la Fórmula (IIa), los compuestos tienen la fórmula estructural seleccionada del grupo integrado por:


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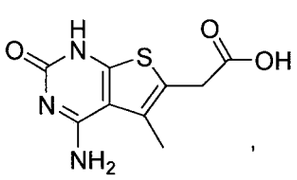
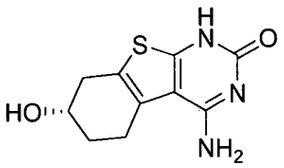
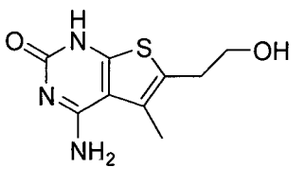
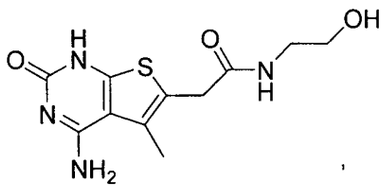
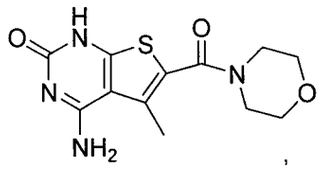
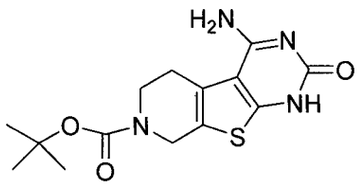
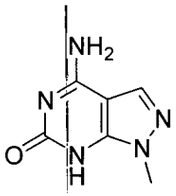
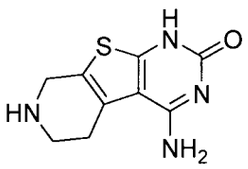
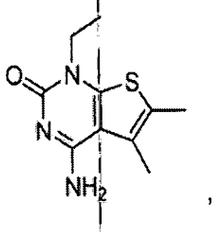
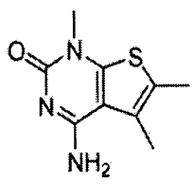
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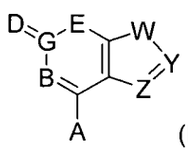
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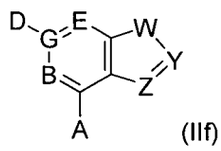
o un tautómero, sal, solvato, y/o éster del mismo. En algunas realizaciones preferidas, la sal de estos compuestos es la sal clorhidrato o trifluoracetato.

En una realización de la Fórmula (II), el compuesto de la presente invención tiene la Fórmula estructural (IIe):


(IIe)

en donde, G forma un enlace único con E y un enlace doble con D; B es -N-; E es $-NR^{17}-$; D es =S , $=N-OR^{15}$, o $=N-NHR^{15}$; W es -S-, $-N(R^{25})-$ u -O-; Y es $-C(R^{26})-$; y Z es $-C(R^{27})-$.

En una realización de la Fórmula (II), el compuesto de la presente invención tiene la Fórmula estructural (IIf):



(IIf)

en donde,

G forma un enlace doble con E y un enlace único con D;

B es -N-;

E es -N-;

D es $-OR^{15}$, $-NH-OR^{15}$, $-NH-NHR^{15}$, $-S(O)_eR^{15}$, o $-NR^{15}R^{16}$;

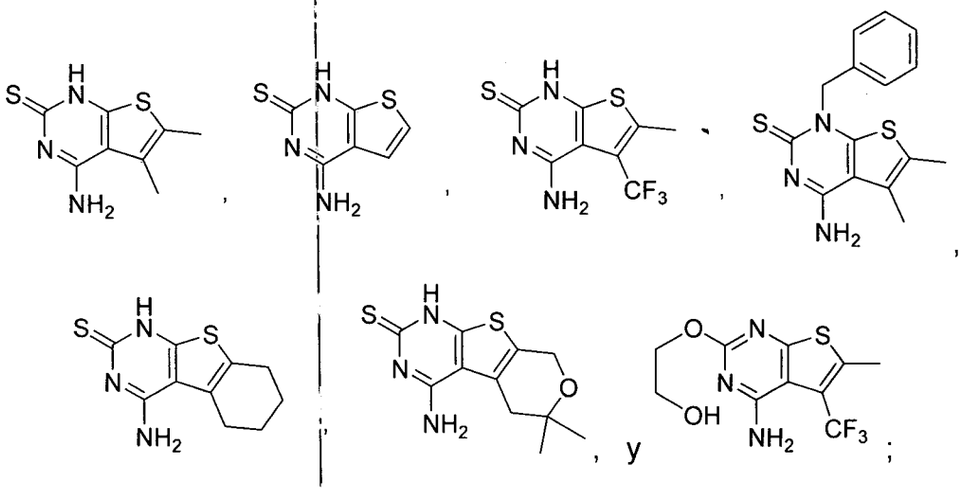
W es -S-, $-N(R^{25})-$ u -O-;

Y es $-C(R^{26})-$; y

Z es $-C(R^{27})-$.

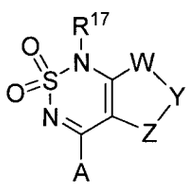
En una realización de la Fórmula (IIe) o (IIf), A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, $-OR^9$, $-SR^9$, -CN, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$ o $-NR^9C(=NH)NR^{10}R^{11}$. Con más preferencia, R^{17} es hidrógeno, alquilo, alquilo sustituido, arilalquilo, o arilalquilo sustituido; R^{26} y R^{27} son independientemente hidrógeno, alcanilo, alcanilo sustituido, alcoxi; o alternativamente, R^{26} y R^{27} conjuntamente con el(os) átomo(s) al(os) cual(es) ellos están unidos forman un anillo cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido.

En algunas realizaciones específicas de la Fórmula (IIe) o (IIf), el compuesto de la presente invención tiene la Fórmula estructural seleccionada del grupo integrado por



o un tautómero, sal, solvato, y/o éster del mismo. En algunas realizaciones preferidas, la sal de estos compuestos es la sal clorhidrato o trifluoracetato.

En una realización de la Fórmula (II), el compuesto de la presente invención tiene la Fórmula estructural (IId):



(IId)

con las siguientes condiciones:

(a) cuando W es -O- o -S- o -NR^{25}, entonces Z es –$C(R^{27})$ o -N-; y

(b) cuando Z es -O- o -S- o -NR^{28}, entonces W es -$C(R^{24})$ o -N-.

En una realización de la Fórmula (IId), W es -S-, NR^{25}, -O-; Y es -CR^{26}-; Z es -$C(R^{27})$-; y W e Y forma un enlace único e Y y Z forma un enlace doble.

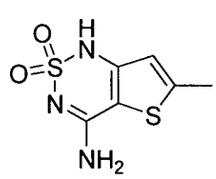
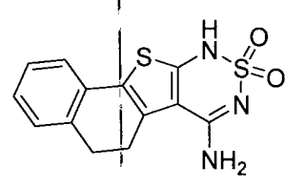
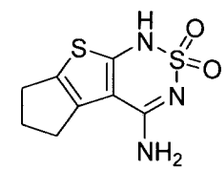
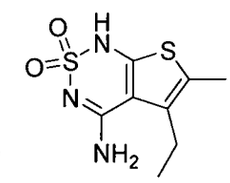
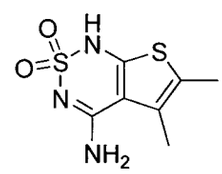
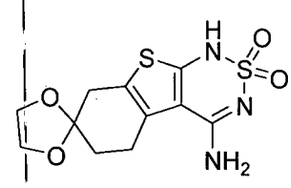
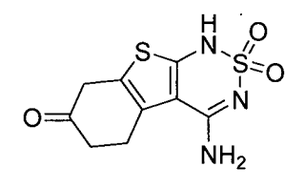
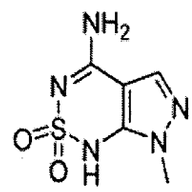
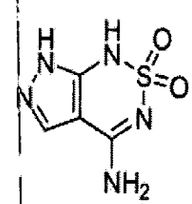
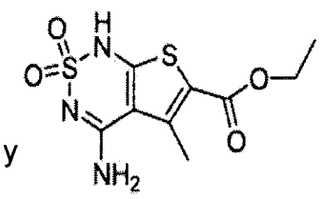
En una realización de la Fórmula (IId), W es -$C(R^{24})$-; Y es -CR^{26}-; Z es -S-, -NR^{28}-, -O-; y W e Y forma un enlace doble e Y y Z forma un enlace único.

En una realización de la Fórmula (IId), W es -S-, NR^{25}, -O-; Y es -N-; Z es -$C(R^{27})$-; y W e Y forma un enlace único e Y y Z forma un enlace doble.

En una realización de la Fórmula (IId), W es - NR^{25}; Y es -N-; y Z es -$C(R^{27})$-; e Y forma un enlace único con cada uno de W y un enlace doble con Z.

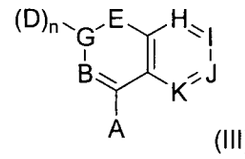
En algunas realizaciones de la Fórmula (IId), A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, -OR^9, -SR^9, -CN, -NR^9R^{10}, -$CONR^9R^{10}$, -CO_2R^9, -$NR^9CO_2R^{10}$, -$NR^9CONR^{10}R^{11}$, -$NR^9CSNR^{10}R^{11}$ o -$NR^9C(=NH)NR^{10}R^{11}$. Con preferencia, R^{17} es hidrógeno. Con más preferencia, R^{26} y R^{27} son independientemente hidrógeno, alcanilo, alcanilo sustituido, alcoxi, ácido carboxílico, éster de ácido carboxílico; o alternativamente, R^{26} y R^{27} conjuntamente con el(os) átomo(s) al(os) cual(es) ellos están unidos forman un anillo ciclialquilo o cicloalquilo sustituido.

En algunas realizaciones específicas de la Fórmula (IId), el compuesto de la presente invención tiene la Fórmula estructural seleccionada del grupo integrado por:


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o un tautómero, sal, solvato, y/o éster del mismo. En algunas realizaciones preferidas, la sal de estos compuestos el la sal clorhidrato o la sal trifluoracetato.

En una realización de la Fórmula (I), el modificador del ligando del receptor quimiosensorial es un compuesto que tiene una Fórmula estructural (III):



(III)

en donde:

H es -C(R^{35})- o -N-;

I es -C(R^{36}) o -N-;

J es -C(R^{37})- o -N-;

K es -C(R^{38})- o -N-;

R^{35} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido, -CN, -NO_2, -OR^{39}, -$S(O)_jR^{39}$, -$NR^{39}R^{40}$, -$CONR^{39}R^{40}$, -CO_2R^{39}, -$SO_2NR^{39}R^{40}$, -$NR^{39}SO_2R^{40}$, -$B(OR^{39})(OR^{40})$, -$P(O)(OR^{39})(OR^{40})$ o -$P(O)(R^{39})(OR^{40})$;

R^{36} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido, -CN, -NO_2, -OR^{41}, -$S(O)_kR^{41}$, -$NR^{41}R^{42}$, -$CONR^{41}R^{42}$, -CO_2R^{41}, -$OCOR^{41}$, -$SO_2NR^{41}R^{42}$, -$NR^{41}SO_2R^{42}$, -$B(OR^{41})(OR^{42})$, -$P(O)(OR^{41})(OR^{42})$ o -$P(O)(R^{41})(OR^{42})$;

R^{37} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido, -CN, -NO_2, -OR^{43}, -$S(O)_lR^{43}$, -$NR^{43}R^{44}$, -$CONR^{43}R^{44}$, -CO_2R^{43},

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$-OCOR^{43}$, $-SO_2NR^{43}R^{44}$, $-NR^{43}SO_2R^{44}$, $-B(OR^{43})(OR^{44})$, $-P(O)(OR^{43})(OR^{44})$ o $-P(O)(R^{43})(OR^{44})$; o alternativamente R36 y R37, tomados conjuntamente con el átomo al cual ellos están unidos, forman un anillo cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo, o cicloheteroalquilo sustituido;

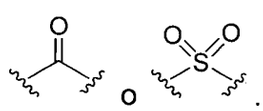
R^{38} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido, -CN, $-NO_2$, $-OR^{45}$, $-S(O)_mR^{45}$, $-NR^{45}R^{46}$, $-CONR^{45}R^{46}$, $-COR^{45}$, $-CO_2R^{45}$, $-OCOR^{45}$, $-SO_2NR^{45}R^{46}$, $-NR^{45}SO_2R^{46}$, $-B(OR^{45})(OR^{46})$, $-P(O)(OR^{45})(OR^{46})$ o $-P(O)(R^{45})(OR^{46})$;

j, k, l y m son independientemente 0, 1 o 2; y

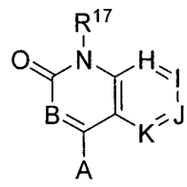
R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, y R^{46} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido o alternativamente R^{39} y R^{40}, R^{41} y R^{42}, R^{43} y R^{44} o R^{45} y R^{46} conjuntamente con los átomos a los cuales ellos están unidos forman un anillo cicloheteroalquilo o cicloheteroalquilo sustituido;

con la condición de que a lo sumo, dos de H, I, J y K sean -N-. Con "a lo sumo dos de H, I, J y K sean –N-", se denota que hay cero átomos de nitrógeno, un átomo de nitrógeno, o dos átomos de nitrógeno entre H, I, J y K.

En una realización de la Fórmula (III), $(D)_n$-G es



En una realización de la Fórmula (III), el compuesto de la presente invención tiene la Fórmula estructural (IIIa):



(IIIa)

En una realización de la Fórmula (IIIa), A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, $-OR^9$, $-NO_2$, $-S(O)_cR^9$, $-NHOR^9$, $-NR^9COR^{10}$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$, o $-NR^9C(=NH)NR^{10}R^{11}$. Con preferencia, A es -OH, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHOCH_3$, $-NOCH_3$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$ o $-CH_2NHC(O)CH_3$.

En una realización de la Fórmula (IIIa), R^{17} es hidrógeno, alquilo, alquilo sustituido, arilalquilo, o arilalquilo sustituido. Con preferencia, R^{17} es hidrógeno, metilo, etilo, propilo, *iso*-propilo, *n*-butilo, *iso*-butilo, *sec*-butilo, *t*-butilo, fenilo o bencilo.

En una realización de la Fórmula (IIIa), H es $-C(R^{35})-$; I es $-C(R^{36})$; J es $-C(R^{37})-$; y K es $-C(R^{38})-$.

En una realización de la Fórmula (IIIa), A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, -CN, $-OR^9$, $-NO_2$, $-S(O)_cR^9$, $-NHOR^9$, $-NR^9COR^{10}$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$ o $-NR^9CO_2R^{10}$; y R^{17} es hidrógeno, alquilo, alquilo sustituido, arilalquilo, o arilalquilo sustituido.

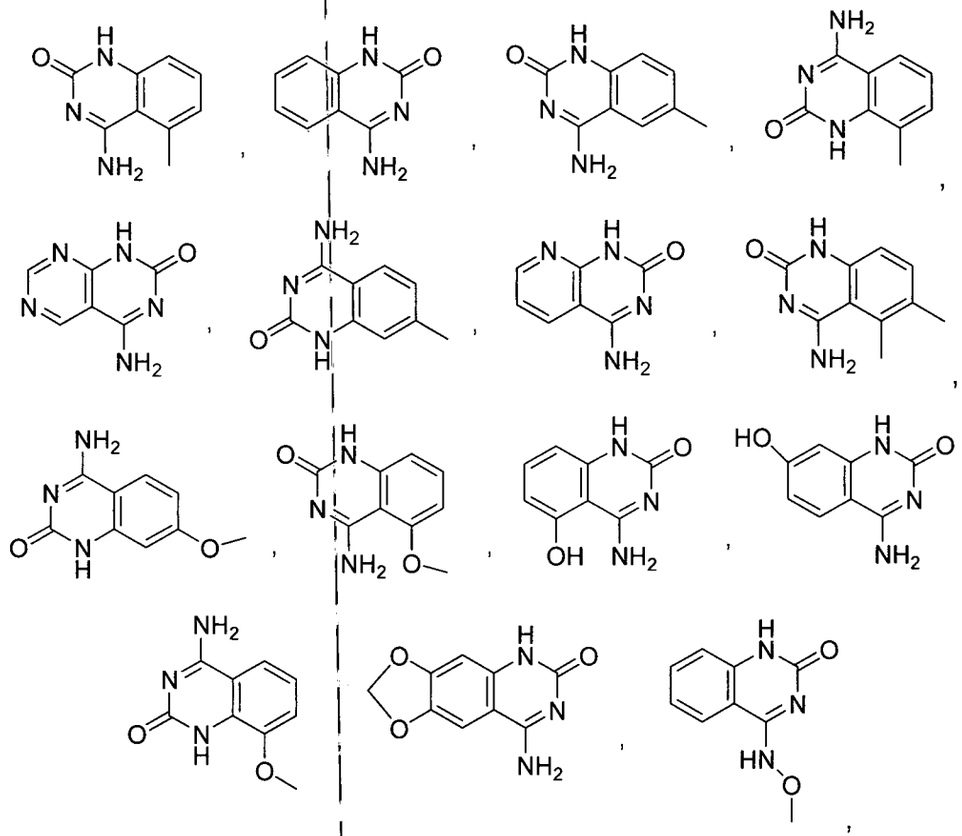
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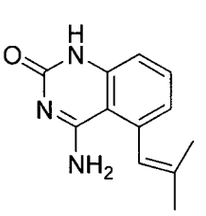
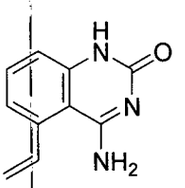
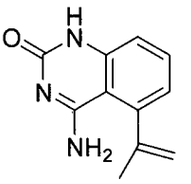
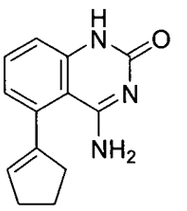
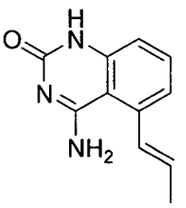
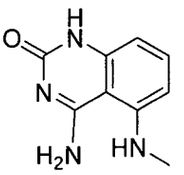
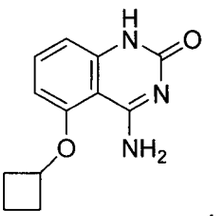
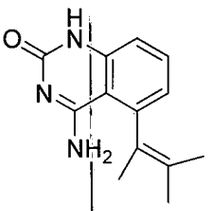
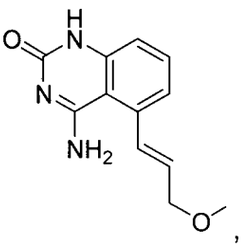
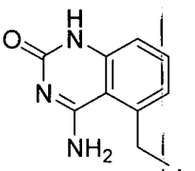
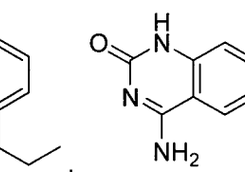
En una realización de la Fórmula (IIIa), A es -OH, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -$NHOCH_3$, -$NOCH_3$, -$NHC(O)CH_3$, -$NHC(O)OCH_3$, -$NHC(O)NH_2$, -$NHC(S)NH_2$, -$NHC(NH)NH_2$, -CN, -CH_2OH, -CH_2NH_2, -CH_2NHCH_3, -$CH_2N(CH_3)_2$, -CO_2H, -$CONH_2$, -$CONHCH_3$ o -$CH_2NHC(O)CH_3$; y R^{17} es hidrógeno, metilo, etilo, propilo, *iso*-propilo, *n*-butilo, *iso*-butilo, *sec*-butilo, *t*-butilo, fenilo o bencilo.

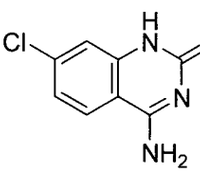
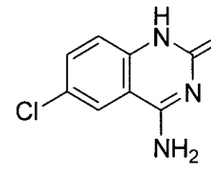
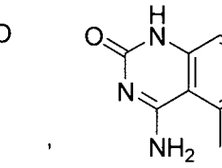
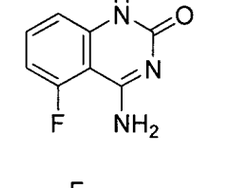
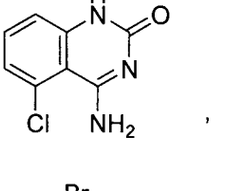
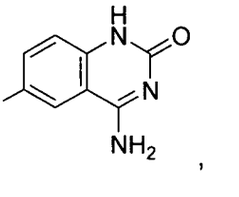
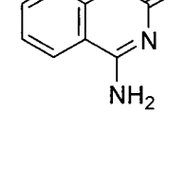
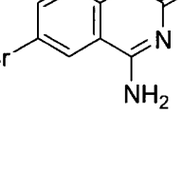
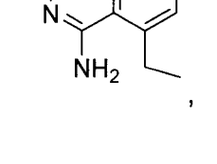
En una realización de la Fórmula (IIIa), R^{35} es hidrógeno, alquilo, alquilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, -CN, -NO_2, -OR^{39}, -$S(O)_jR^{39}$, -$OCOR^{39}$, -$NR^{39}COR^{40}$, -$CONR^{39}R^{40}$, -CO_2R^{39}, $NR^{39}R^{40}$, -$SO_2NR^{39}R^{40}$, or-$NR^{39}SO_2R^{40}$; R^{36} es hidrógeno, alquilo, alquilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, -CN, -NO_2, -OR^{41}, -$S(O)_jR^{41}$, -$OCOR^{41}$, $NR^{41}R^{42}$, -$NR^{41}COR^{42}$, -$CONR^{41}R^{42}$, -CO_2R^{41}, -$SO_2NR^{41}R^{42}$, o -$NR^{41}SO_2R^{42}$; R^{37} es hidrógeno, alquilo, alquilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, -CN, -NO_2, -OR^{43}, -$S(O)_jR^{43}$, -$OCOR^{43}$, $NR^{43}R^{44}$, -$NR^{43}COR^{44}$, -$CONR^{43}R^{44}$, -CO_2R^{43}, -$SO_2NR^{43}R^{44}$, o -$NR^{43}SO_2R^{44}$; o alternativamente R^{36} y R^{37}, conjuntamente con los átomos a los cuales ellos están unidos, forman un anillo cicloheteroalquilo o cicloheteroalquilo sustituido; y R^{38} es hidrógeno, alquilo, alquilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, -CN, -NO_2, -OR^{45}, -$S(O)_jR^{45}$, -$OCOR^{45}$, $NR^{45}R^{46}$, -$NR^{45}COR^{46}$, -$CONR^{45}R^{46}$, -CO_2R^{45}, -$SO_2NR^{45}R^{46}$, -$NR^{45}SO_2R^{46}$. Se prefiere que R^{38} sea hidrógeno, alcanilo, alcanilo sustituido, alquenilo, alquenilo sustituido, cicloalcanilo, cicloalcanilo sustituido, cicloalquenilo, cicloalquenilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, -CN, -NO_2, -OR^{45}, -$S(O)_jR^{45}$, -$OCOR^{45}$, $NR^{45}R^{46}$, -$NR^{45}COR^{46}$, -$CONR^{45}R^{46}$, -CO_2R^{45}, -$SO_2NR^{45}R^{46}$, -$NR^{45}SO_2R^{46}$. También se prefiere que A sea -NH_2, que R^{17} sea hidrógeno, metilo, etilo o bencilo; y que R^{35}, R^{36}, R^{37} y R^{38} sean independientemente hidrógeno, flúor, cloro, bromo, metilo, trifluormetilo, etilo, isopropilo, ciclopropilo, propenilo, metilpropenilo, butenilo, metilbutenilo, propenilo sustituido, metilpropenilo sustituido, butenilo sustituido, metilbutenilo sustituido,

-NH-alcanilo, -NH-(alcanilo sustituido), -OH, -OCH_3, -O-cicloalcanilo, –O-bencilo, -CO_2H.

En algunas realizaciones específicas de la Fórmula (IIIa), el compuesto tiene la fórmula estructural seleccionada del grupo integrado por




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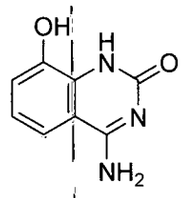
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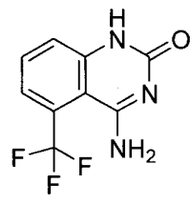
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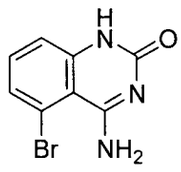
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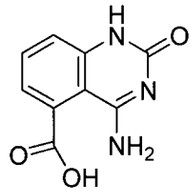
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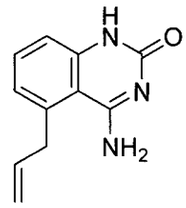
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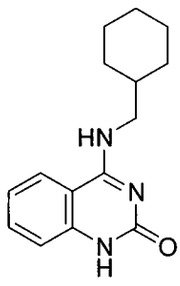


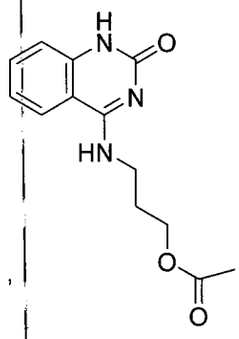


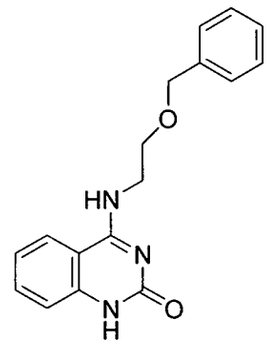


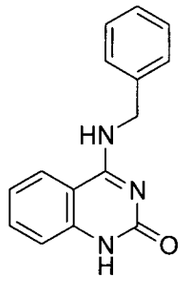


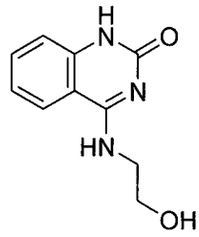


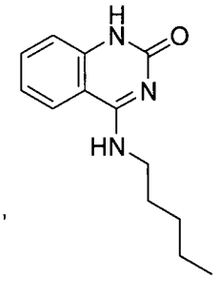


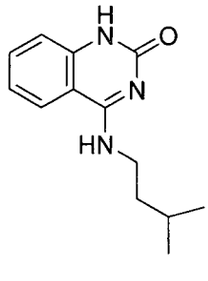


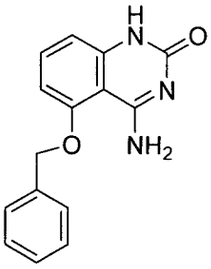


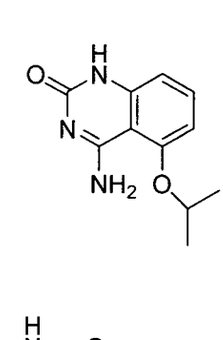


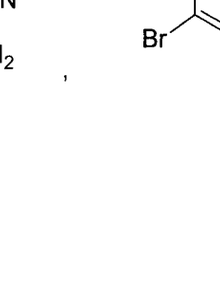


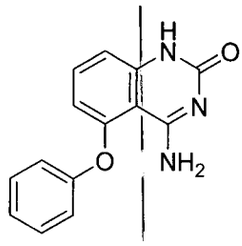


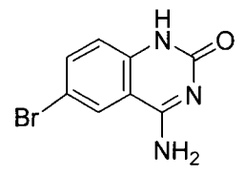


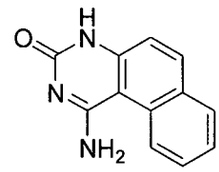


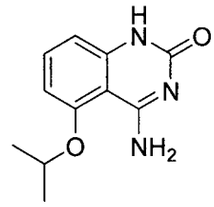


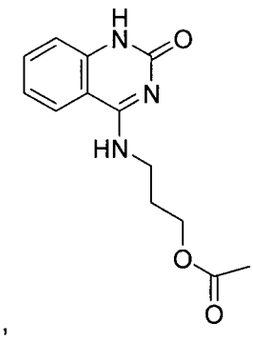


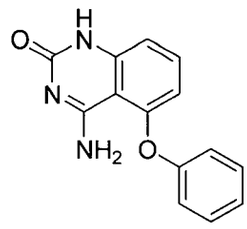


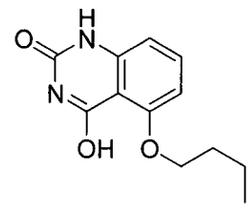


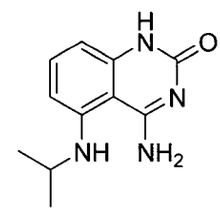


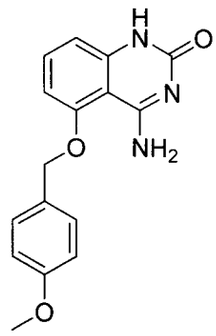


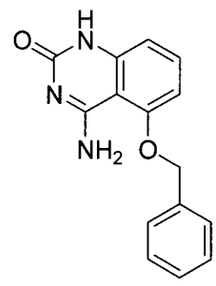


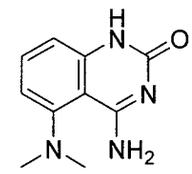


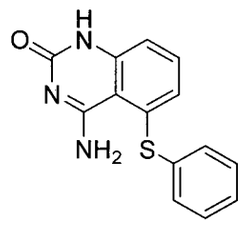


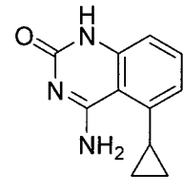


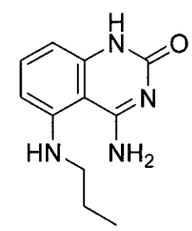


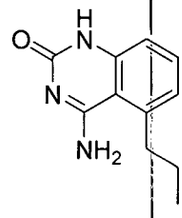


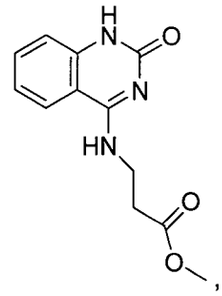


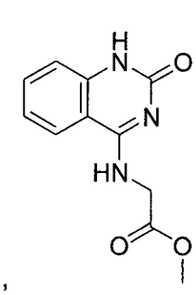


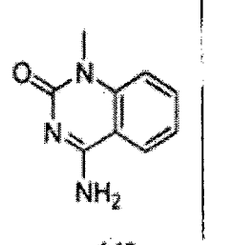


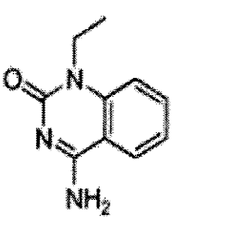


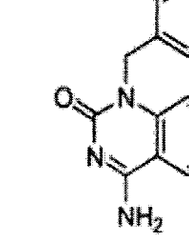












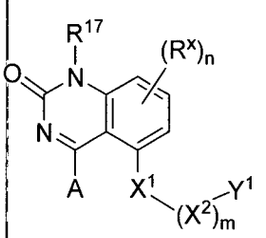
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o un tautómero, sal, solvato, y/o éster del mismo. En algunas realizaciones preferidas, la sal de estos compuestos es la sal clorhidrato o trifluoracetato.

En una realización de la Fórmula (IIIa), el compuesto de la presente invención tiene la Fórmula estructural (IIIa1):



(IIIa1)

en donde,

A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, $-OR^9$, $-NO_2$, $-S(O)_cR^9$, $-NOR^9$, $-NHOR^9$, $-NR^9COR^{10}$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$ o $-NR^9CO_2R^{10}$;

R^{17} es hidrógeno, alquilo, alquilo sustituido, arilalquilo, o arilalquilo sustituido;

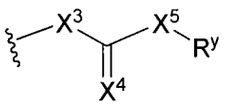
X^1 es $-CH_2-$, $-O-$, $-NR^9-$, $-S-$, $-S(O)-$, o $-S(O)_2-$;

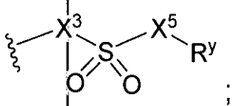
X^2 es alquileno, alquileno sustituido, heteroalquileno, o heteroalquileno sustituido;

m es 0 o 1;

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Y^1 es cicloheteroalquilo, cicloheteroalquilo sustituido, o



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;

X^3 y X^5 son independientemente un enlace covalente, –O– o $–NR^9–$;

X^4 es O, NR^9, N-OR^9, o S;

R^x es halo, -NO_2, -CN, -OH, -NH_2, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido;

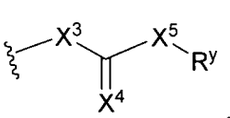
n es 0, 1, 2, o 3;

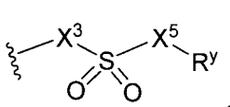
R^Y es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido, $-NR^9R^{10}$; y

cada R^9 y R^{10} es independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido;

con la condición de que cuando X^1 sea –O– o –S–, y m sea cero; entonces X^3 no sea –O–.

En una realización de la Fórmula (IIIa1), X^1 es $–CH_2-$; e Y^1 es



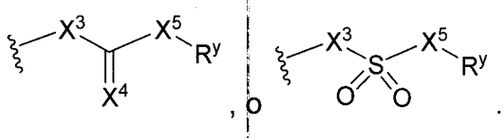
, o


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En una realización de la Fórmula (IIIa1), X^1 es –O–, $–NR^9–$, o –S–; m es 0 o 1, e Y^1 es cicloheteroalquilo o cicloheteroalquilo sustituido.

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En una realización de la Fórmula (IIIa1), X^1 es –O–, $–NR^9–$, o –S–; m es 1, e Y^1 es



En algunas realizaciones de la Fórmula (IIIa1), X^2 es metileno, etileno, propileno, dimetiletileno, metilciclopropileno, o ciclopropilmetileno.

En algunas realizaciones de la Fórmula (IIIa1), A es hidrógeno, alquilo, alquilo sustituido, -CN, $-OR^9$, $-NO_2$, $-S(O)_cR^9$, $-NOR^9$, $-NHOR^9$, $-NR^9COR^{10}$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$ o $-NR^9CO_2R^{10}$.

En algunas realizaciones de la Fórmula (IIIa1), R^{17} es hidrógeno, alquilo, alquilo sustituido.

En algunas realizaciones de la Fórmula (IIIa1), Y^1 es cicloheteroalquilo o cicloheteroalquilo sustituido. Se prefiere que Y^1 sea piperidinilo, piperidinilo sustituido, tetrahidrofuranilo, tetrahidrofuranilo sustituido, tetrahidropiranilo, tetrahidropiranilo sustituido, dihidrofuranilo, dihidrofuranilo sustituido, pirrolidinilo, pirrolidinilo sustituido, oxetanilo, u oxetanilo sustituido. También se prefiere que el cicloheteroalquilo sustituido comprenda uno o más sustituyentes seleccionados del grupo integrado por alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, $-OR^9$, $-NO_2$, $-S(O)_cR^9$, $-NOR^9$, $-NHOR^9$, $-NR^9COR^{10}$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$, y $-NR^9CO_2R^{10}$.

En algunas realizaciones de la Fórmula (IIIa1), X^4 es O.

En algunas realizaciones de la Fórmula (IIIa1), $-X^3-C(X^4)-X^5-$ es –C(O)-,

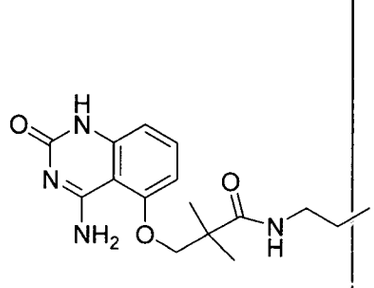
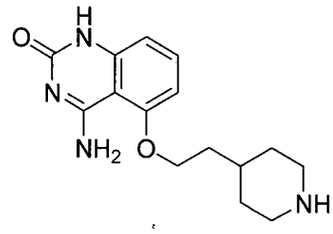
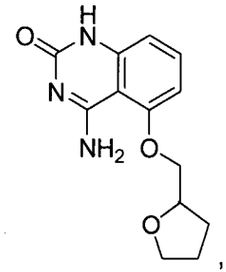
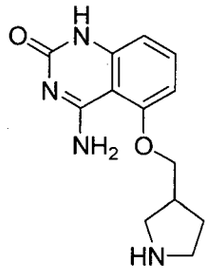
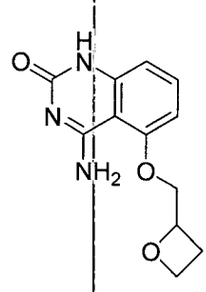
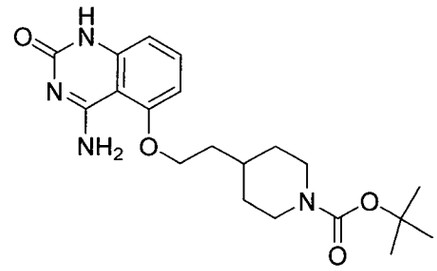
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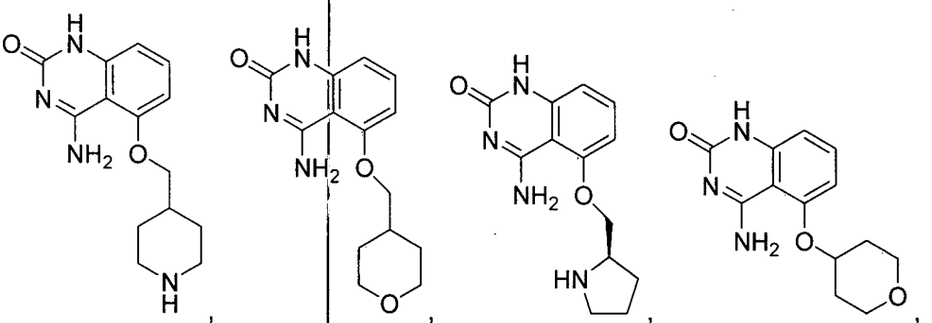
-C(O)-NH-, -NH-C(O)-, -NH-C(O)-NH-, -C(O)-O-, -O-C(O)-, -O-C(O)-O-, -NH-C(O)-O-, -O-C(O)-NH-, –C(NH)-, -C(NH)-NH-, -NH-C(NH)-, -NH-C(NH)-NH-, -C(NH)-O-, -O-C(NH)-, -O-C(NH)-O-, -NH-C(NH)-O-, -O-C(NH)-NH-, -C(N-OH)-, o -C(S)-.

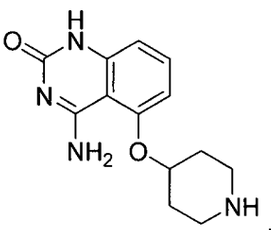
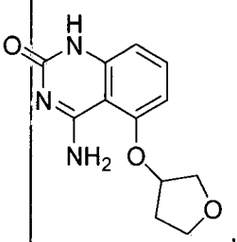
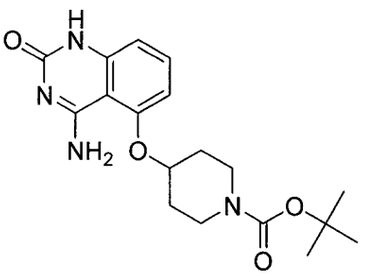
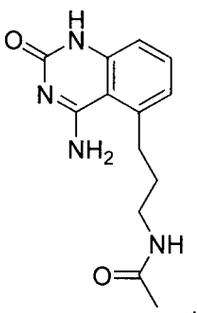
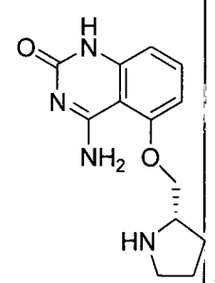
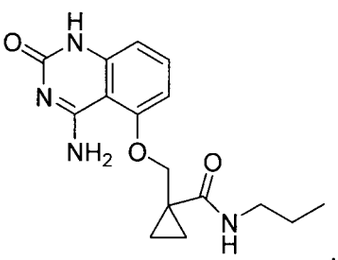
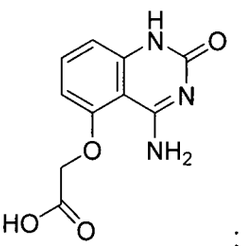
En algunas realizaciones de la Fórmula (IIIa1), A es hidrógeno, alquilo, alquilo sustituido, o $-NR^9R^{10}$; R^{17} es hidrógeno; e Y^1 es piperidinilo, piperidinilo sustituido, tetrahidrofuranilo, tetrahidrofuranilo sustituido, tetrahidropiranilo, tetrahidropiranilo sustituido, dihidrofuranilo, dihidrofuranilo sustituido, pirrolidinilo, pirrolidinilo sustituido, oxetanilo, u oxetanilo sustituido.

En algunas realizaciones de la Fórmula (IIIa1), A es hidrógeno, alquilo, alquilo sustituido, o $-NR^9R^{10}$; R^{17} es hidrógeno; Y^1 es $-X^3-C(X^4)-X^5-$; y $-X^3-C(X^4)-X^5-$ es –C(O)-, -C(O)-NH-, -NH-C(O)-, -NH-C(O)-NH-, -C(O)-O-, -O-C(O)-, -O-C(O)-O-, -NH-C(O)-O-, -O-C(O)-NH-, –C(NH)-, -C(NH)-NH-, -NH-C(NH)-, -NH-C(NH)-NH-, -C(NH)-O-, -O-C(NH)-, -O-C(NH)-O-, -NH-C(NH)-O-, -O-C(NH)-NH-, -C(N-OH)-, o -C(S)-.

En algunas realizaciones específicas de la Fórmula (IIIa1), el compuesto tiene la fórmula estructural seleccionada del grupo integrado por

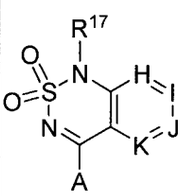

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o un tautómero, sal, solvato, y/o éster del mismo. En algunas realizaciones preferidas, la sal de estos compuestos es la sal clorhidrato o trifluoracetato.

En una realización de la Fórmula (III), el compuesto de la presente invención tiene la Fórmula estructural (IIIb):



(IIIb).

En una realización de la Fórmula (IIIb), A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, -CN, -NO_2, -OR^9, -$S(O)_cR^9$, -NR^9COR^{10}, -$NHOR^9$,

$-NR^9R^{10}$, $-NOR^9$, $-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$, o $-NR^9C(=NH)NR^{10}R^{11}$.

En una realización de la Fórmula (IIIb), R^{17} es hidrógeno, alquilo, o alquilo sustituido.

En una realización de la Fórmula (IIIb), A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, $-OR^1$, $-SR^1$, -CN, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$ o $-NR^9C(=NH)NR^{10}R^{11}$; y R^{17} es hidrógeno, alquilo, o alquilo sustituido.

En una realización de la Fórmula (IIIb), H es $-C(R^{35})-$ o -N-; I es $-C(R^{36})-$; J es $-C(R^{37})-$; y K es $-C(R^{38})-$ o -N-.

En una realización de la Fórmula (IIIb), H es $-C(R^{35})-$; I es $-C(R^{36})-$; J es $-C(R^{37})-$; y K es $-C(R^{38})-$.

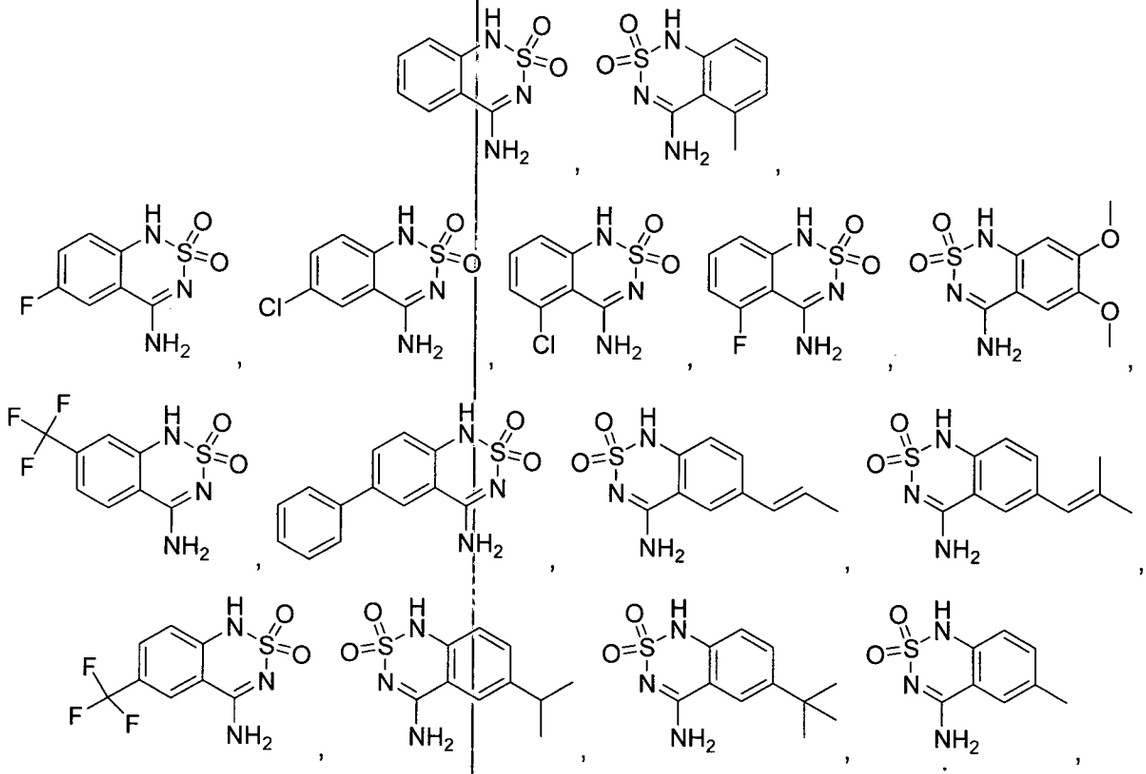
En una realización de la Fórmula (IIIb), R^{35} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido, -CN, $-NO_2$, $-OR^{39}$, $-S(O)_jR^{39}$, $-OCOR^{39}$, $-NR^{39}R^{40}$, $-CONR^{39}R^{40}$, $-CO_2R^{39}$, $-SO_2NR^{39}R^{40}$, $-NR^{39}SO_2R^{40}$; R^{36} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido, -CN, $-NO_2$, $-OR^{41}$, $-S(O)_kR^{41}$, $-OCOR^{41}$, $-NR^{41}R^{42}$, $-CONR^{41}R^{42}$, $-CO_2R^{41}$, $-SO_2NR^{41}R^{42}$, $-NR^{41}SO_2R^{42}$; R^{37} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido, -CN, $-NO_2$, $-OR^{43}$, $-S(O)_lR^{43}$, $-OCOR^{43}$, $-NR^{43}R^{44}$, $-CONR^{43}R^{44}$, $-CO_2R^{43}$, $-SO_2NR^{43}R^{44}$, $-NR^{43}SO_2R^{44}$; R^{38} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo

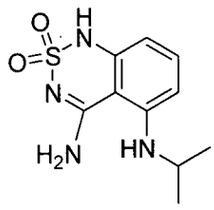
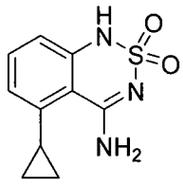
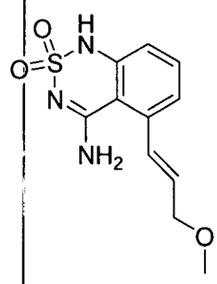
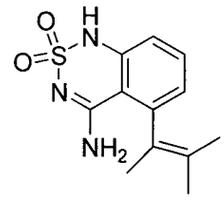
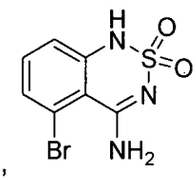
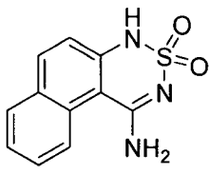
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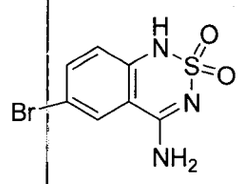
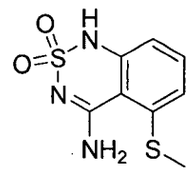
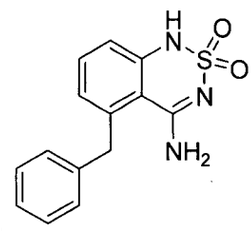
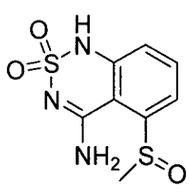
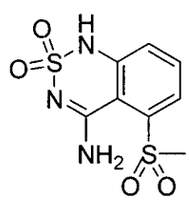
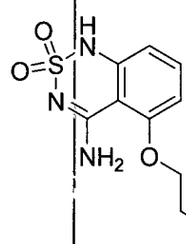
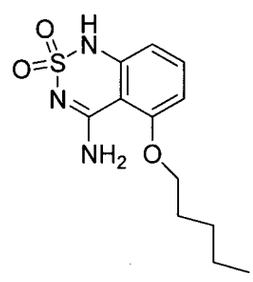
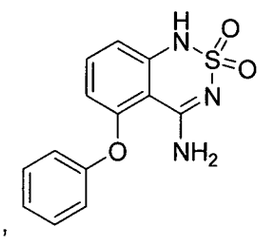
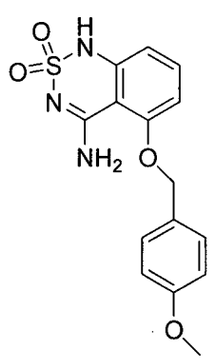
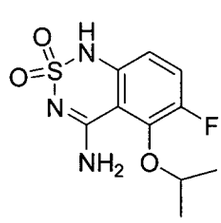
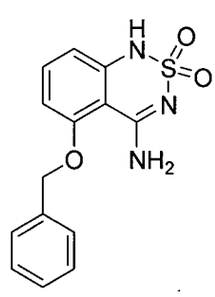
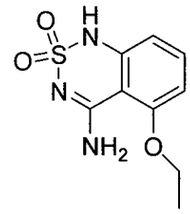
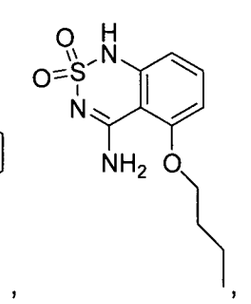
sustituido, acilo, acilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido, -CN, $-NO_2$, $-OR^{45}$, $-S(O)_mR^{45}$, $-OCOR^{45}$, $-NR^{45}R^{46}$, $-CONR^{45}R^{46}$, $-COR^{45}$, $-CO_2R^{45}$, $-SO_2NR^{45}R^{46}$, $-NR^{45}SO_2R^{46}$.

En una realización de la Fórmula (IIIb), A es $-NH_2$, R^{17} es hidrógeno, metilo, etilo o bencilo; y R^{35}, R^{36}, R^{37} y R^{38} son independientemente hidrógeno, flúor, cloro, bromo, -CN, alcanilo, alcanilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, cicloalcanilo, cicloalcanilo sustituido, cicloalquenilo, cicloalquenilo sustituido, heteroalcanilo, heteroalcanilo sustituido, cicloheteroalquilo, cicloheteroalquilo sustituido, -O-alcanilo, -O-(alcanilo sustituido), -O-alquenilo, -O-(alquenilo sustituido), -NH-alcanilo, -NH-(alcanilo sustituido), -NH-alquenilo, -NH-(alquenilo sustituido), -S-alcanilo, -S-(alcanilo sustituido), -S-alquenilo, o -S-(alquenilo sustituido).

En algunas realizaciones específicas de la Fórmula (IIIb), el compuesto tiene la fórmula estructural seleccionada del grupo integrado por:




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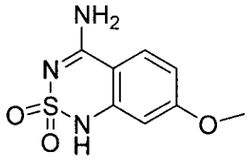
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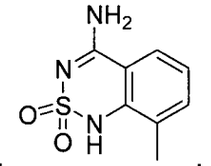
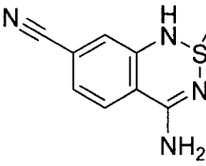
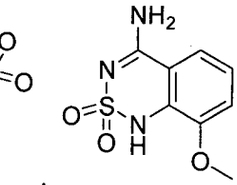
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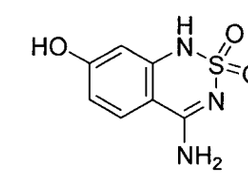
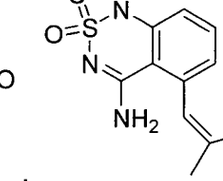
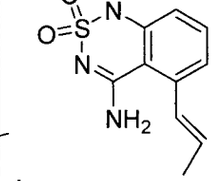
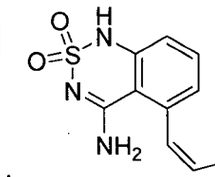
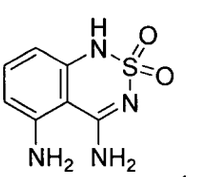
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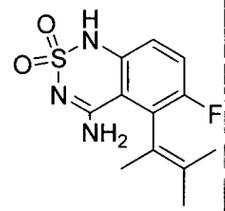
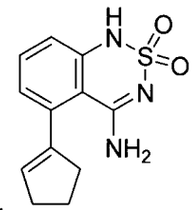
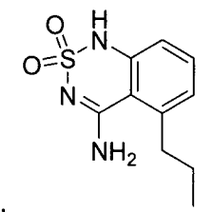
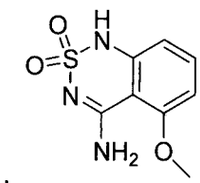
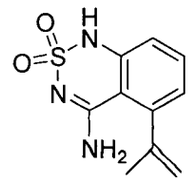
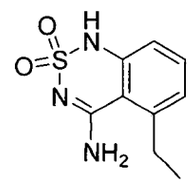
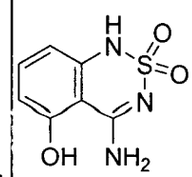
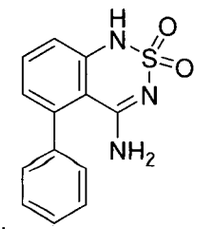
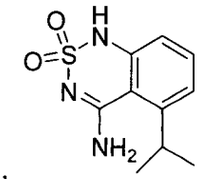
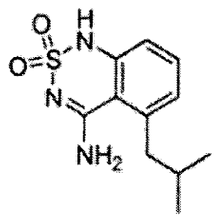
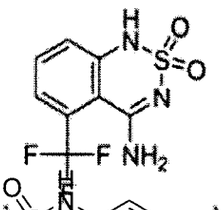
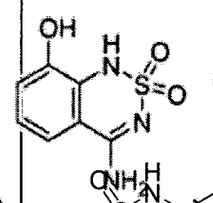
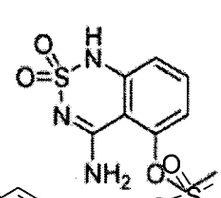
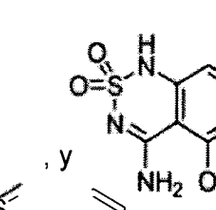
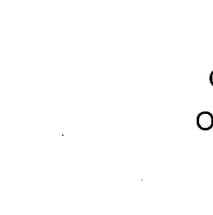
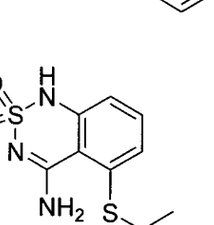
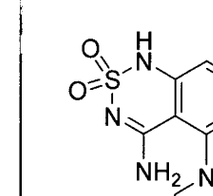
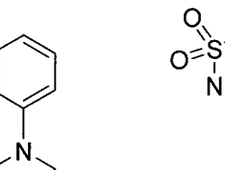
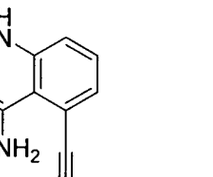
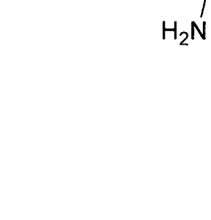
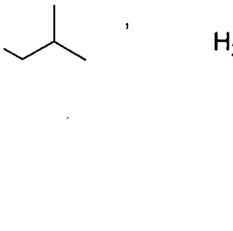
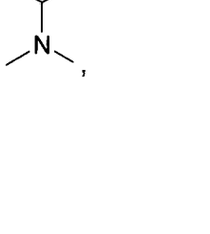
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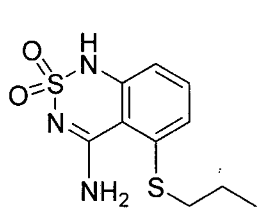
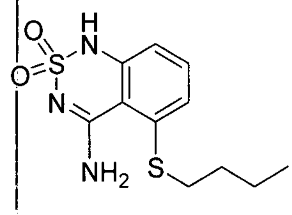
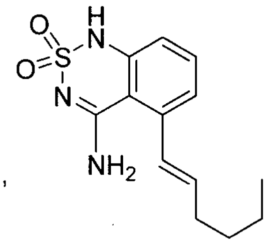
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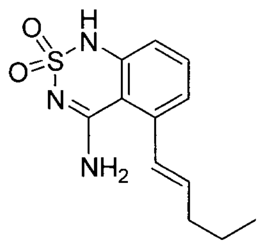
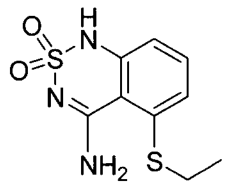
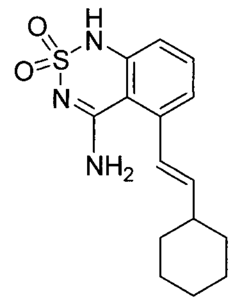
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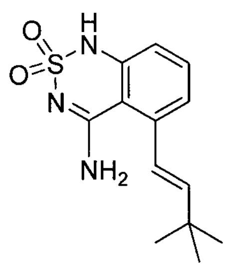
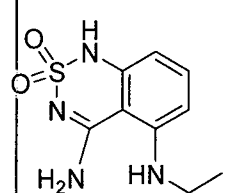
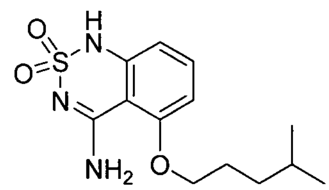
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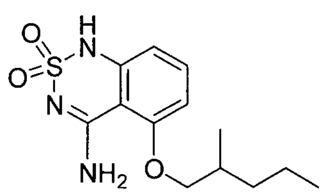
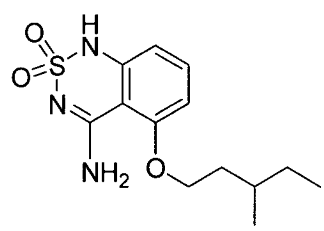
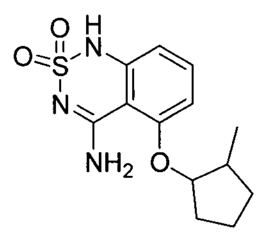
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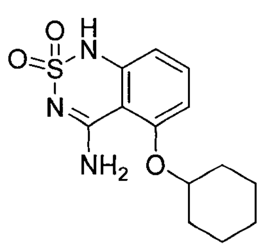
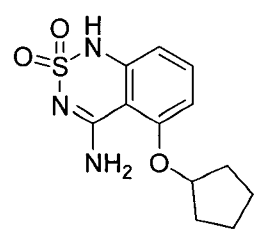
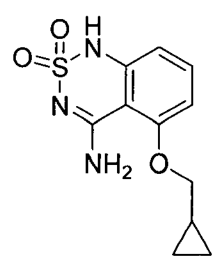
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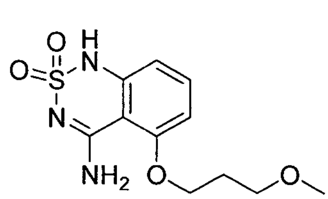
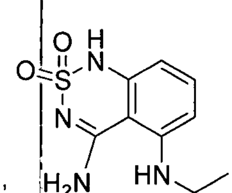
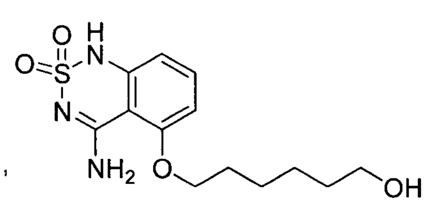
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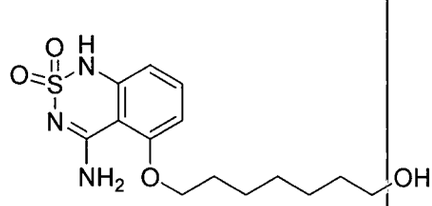
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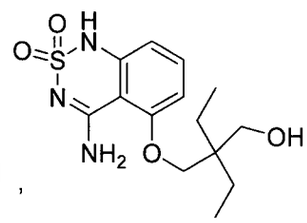
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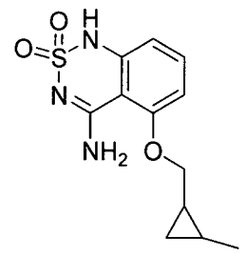
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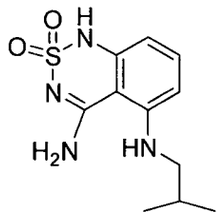
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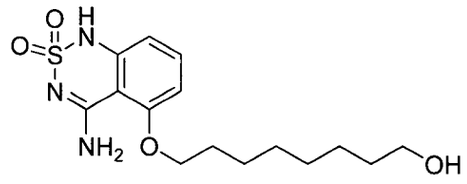
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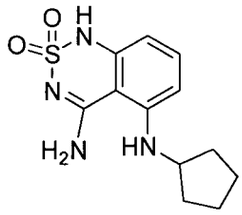


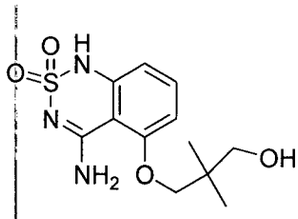


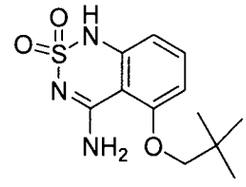


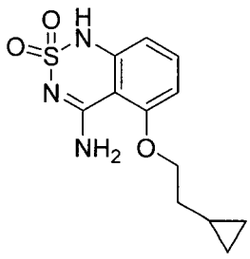


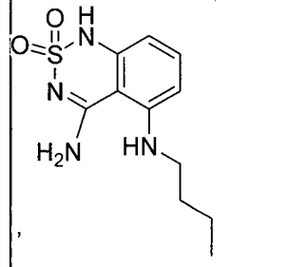


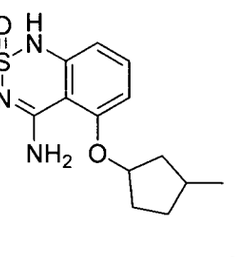


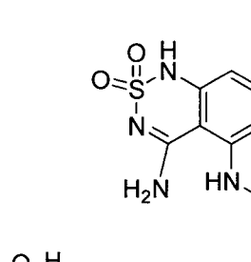


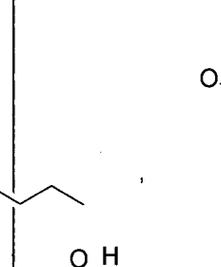


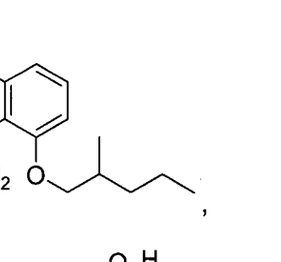


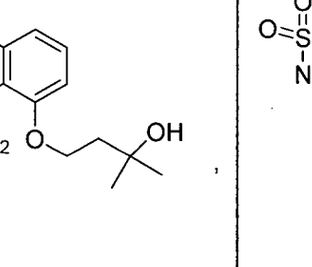


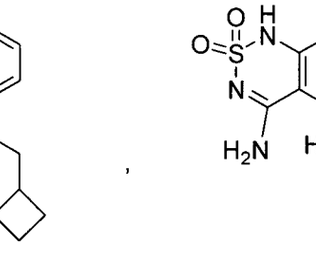




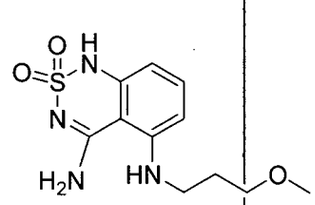


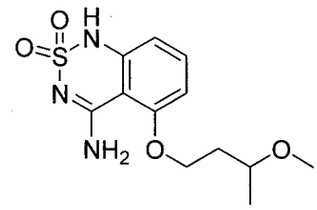


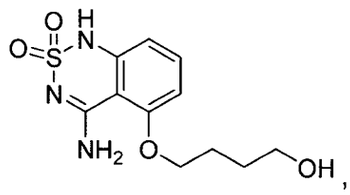


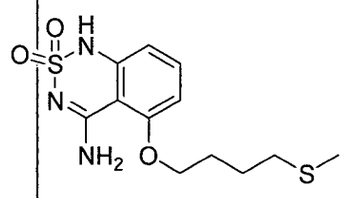


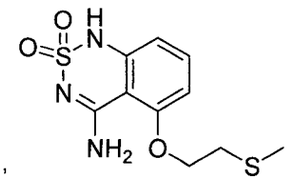
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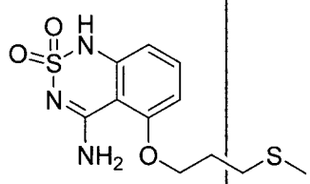


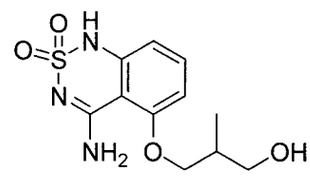


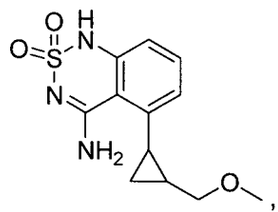


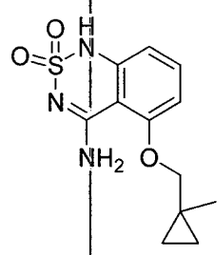


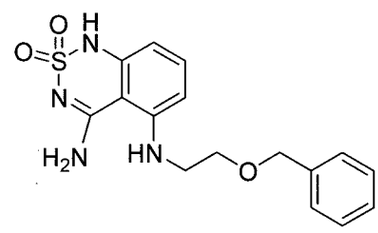


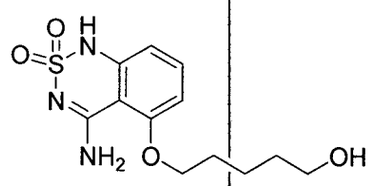


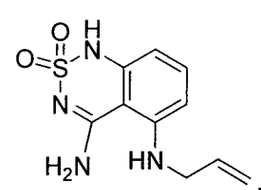


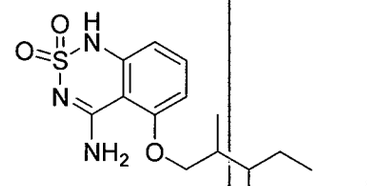


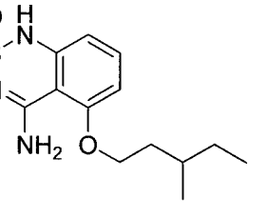


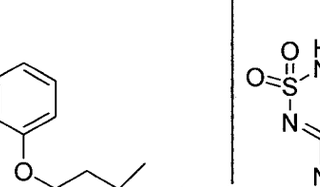


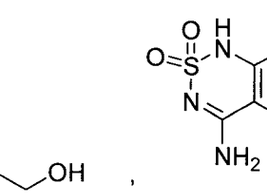




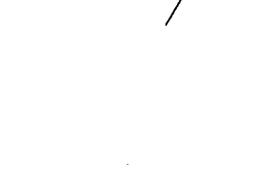




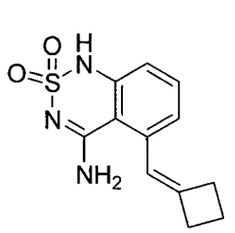


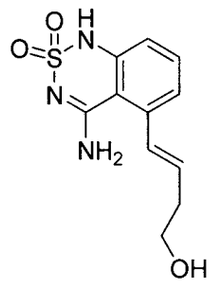


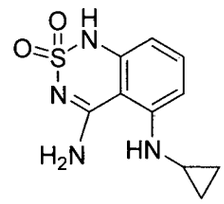


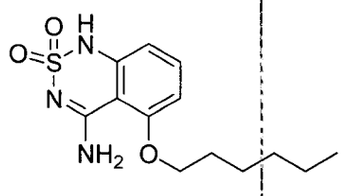


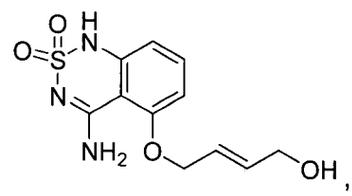
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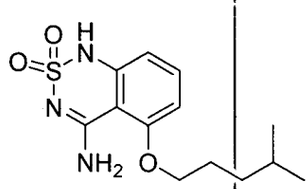


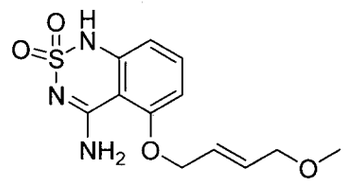


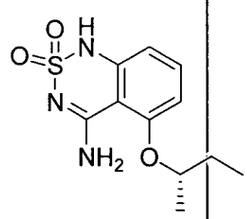


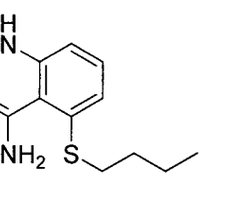


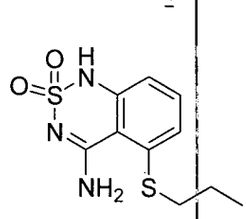


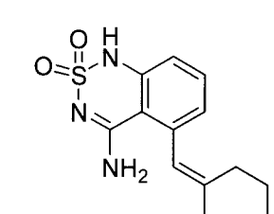


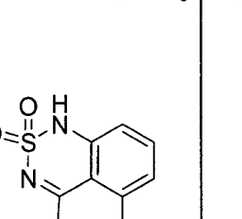


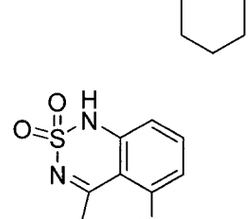


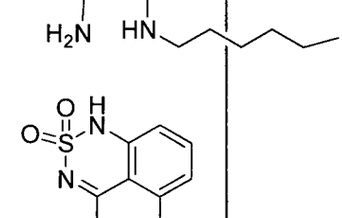


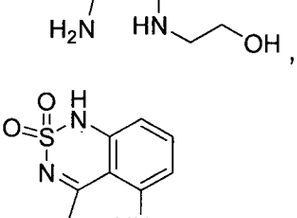


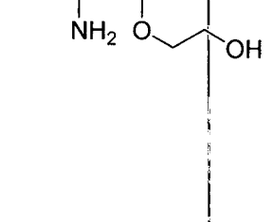


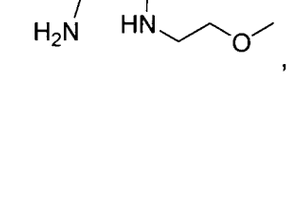


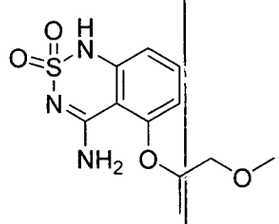


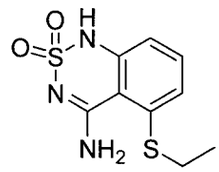


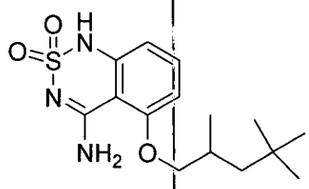


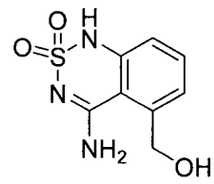


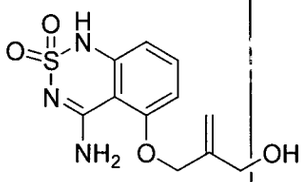


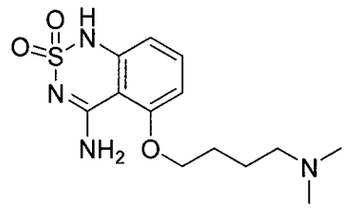


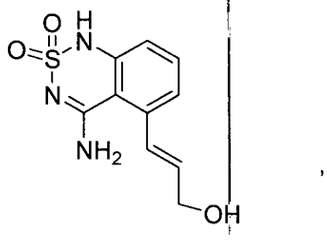


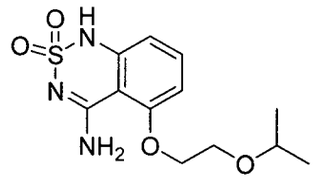


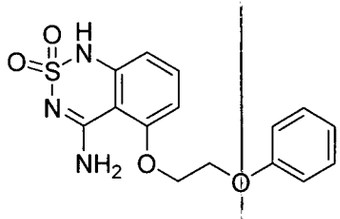


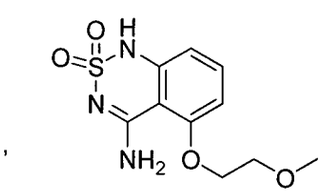


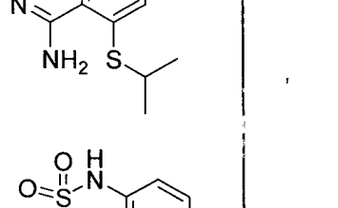


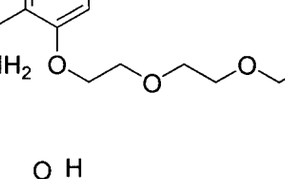


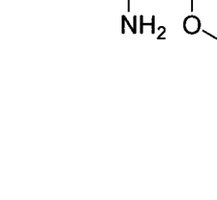


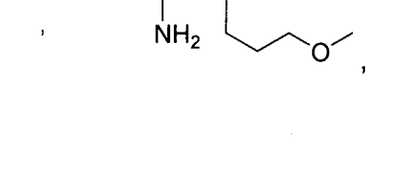


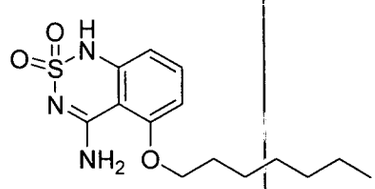


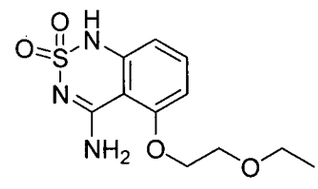


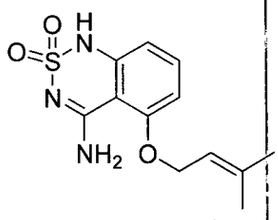


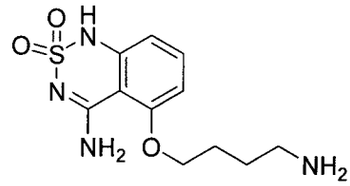


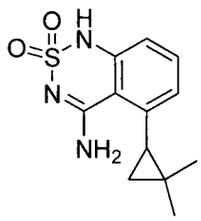


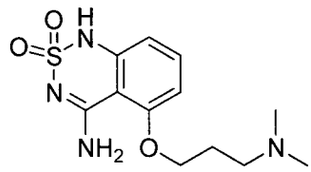


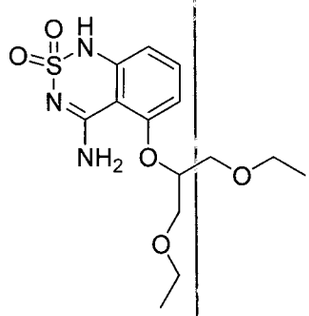


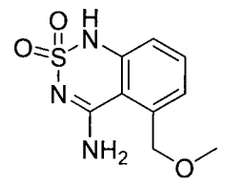


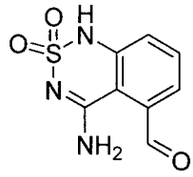


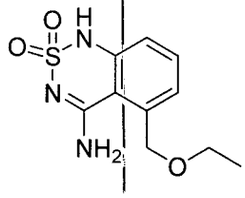


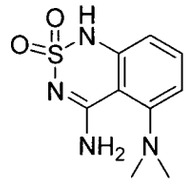


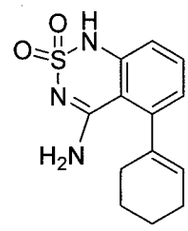


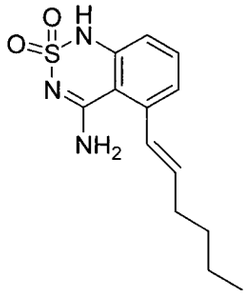


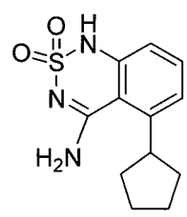


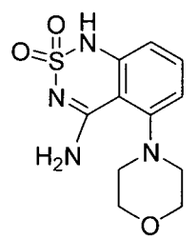




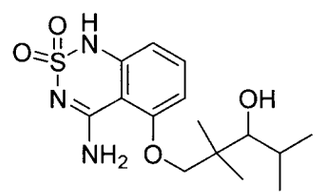
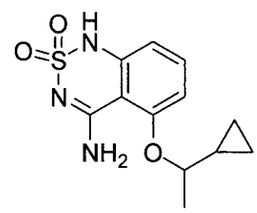
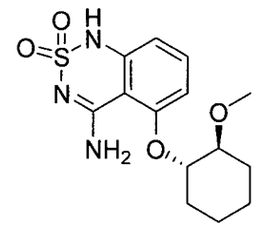
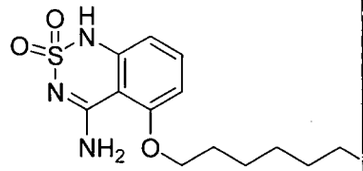
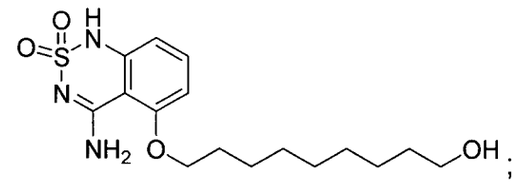






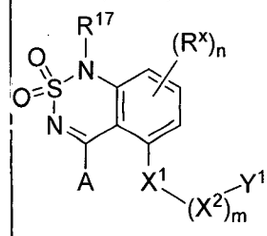


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o un tautómero, sal, solvato, y/o éster del mismo. En algunas realizaciones preferidas, la sal de estos compuestos es la sal clorhidrato o trifluoracetato.

En una realización de la Fórmula (IIIb), el compuesto de la presente invención tiene la Fórmula estructural (IIIb1):



(IIIb1)

en donde,

A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, $-OR^9$, $-NO_2$, $-S(O)_cR^9$, $-NOR^9$, $-NHOR^9$, $-NR^9COR^{10}$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$ o $-NR^9CO_2R^{10}$;

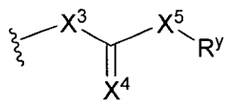
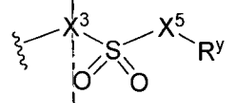
R^{17} es hidrógeno, alquilo, alquilo sustituido, arilalquilo, o arilalquilo sustituido;

X^1 es $-CH_2-$, $-O-$, $-NR^9-$, $-S-$, $-S(O)-$, o $-S(O)_2-$;

X^2 es alquileno, alquileno sustituido, heteroalquileno, o heteroalquileno sustituido;

m es 0 o 1;

Y^1 es heteroarilo, heteroarilo sustituido, cicloheteroalquilo, cicloheteroalquilo sustituido, o


, o

;

X^3 y X^5 son independientemente un enlace covalente, –O– o –NR^9–;

X^4 es O, NR^9, N-OR^9, o S;

R^x es halo, -NO_2, -CN, -OH, -NH_2, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido;

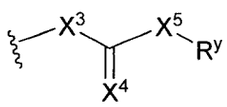
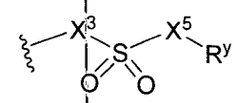
n es 0, 1, 2, o 3;

R^Y es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido, -NR^9R^{10}; y

cada R^9 y R^{10} es independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido;

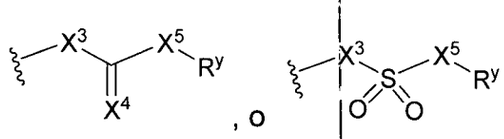
con la condición de que cuando X^1 sea –O– o –S–, y m sea cero; entonces X^3 no sea –O–.

En una realización de la Fórmula (IIIb1), X^1 es –CH_2-; e Y^1 es


, o

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En una realización de la Fórmula (IIIb1), X^1 es –O–, –NR^9–, o –S–; m es 0 o 1, e Y^1 es cicloheteroalquilo o cicloheteroalquilo sustituido.

En una realización de la Fórmula (IIIb1), X^1 es –O–, –NR^9–, o –S–; m es 1, e Y^1 es



En algunas realizaciones de la Fórmula (IIIb1), X^2 es alcanileno, alcanileno sustituido, heteroalcanileno, heteroalcanileno sustituido, alquenileno, alquenileno sustituido, heteroalquenileno, o heteroalquenileno sustituido.

En algunas realizaciones de la Fórmula (IIIb1), X^2 es metileno, etileno, propileno, *iso*-propileno, butileno, *iso*-butileno, *sec*-butileno, pentileno, hexileno, heptileno, dimetiletileno, metilciclopropileno, ciclopropilmetileno, etenileno, propenileno, o butenileno.

En una realización de la Fórmula (IIIb1), A es hidrógeno, alquilo, alquilo sustituido, -CN, -NO_2, -OR^9, -$S(O)_cR^9$, -NR^9COR^{10}, -$NHOR^9$, -NR^9R^{10}, -NOR^9, -$CONR^9R^{10}$, -CO_2R^9, -$NR^9CO_2R^{10}$, -$NR^9CONR^{10}R^{11}$, -$NR^9CSNR^{10}R^{11}$, -$NR^9C(=NH)NR^{10}R^{11}$.

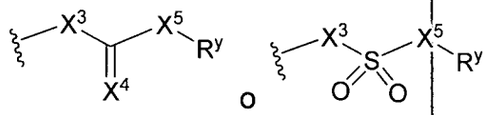
En una realización de la Fórmula (IIIb1), R^{17} es hidrógeno, alquilo, o alquilo sustituido.

En una realización de la Fórmula (IIIb1), Y^1 es cicloheteroalcanilo, cicloheteroalcanilo sustituido, cicloheteroalquenilo, o cicloheteroalquenilo sustituido. Se prefiere que Y^1 sea piperidinilo, piperidinilo sustituido, tetrahidrofuranilo, tetrahidrofuranilo sustituido, tetrahidropiranilo, tetrahidropiranilo sustituido, dihidrofuranilo, dihidrofuranilo sustituido, pirrolidinilo, pirrolidinilo

sustituido, oxetanilo, oxetanilo sustituido, un anillo sacárido o su derivado, un anillo sacárido sustituido o su derivado.

En una realización de la Fórmula (IIIb1), Y^1 es heteroarilo o heteroarilo sustituido. Se prefiere que Y^1 sea piridinilo, piridinilo sustituido, pirrolilo, pirrolilo sustituido, furanilo, furanilo sustituido, pirazolilo, pirazolilo sustituido, isoxazolilo, isoxazolilo sustituido, oxazolilo, y oxazolilo sustituido. También se prefiere que el cicloheteroalcanilo sustituido o que el cicloheteroalquenilo sustituido comprenda uno o más sustituyentes seleccionados del grupo integrado por alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, $-OR^9$, $-NO_2$, $-S(O)_cR^9$, $-NOR^9$, $-NHOR^9$, $-NR^9COR^{10}$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$, y $-NR^9CO_2R^{10}$.

En una realización de la Fórmula (IIIb1), Y es



o

. Se prefiere que X^4 sea O.

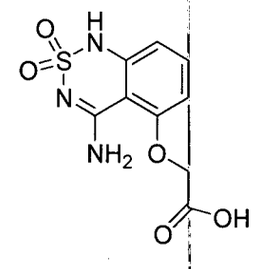
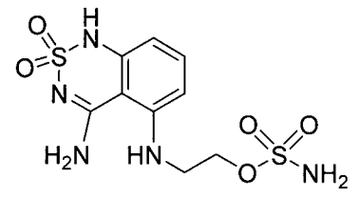
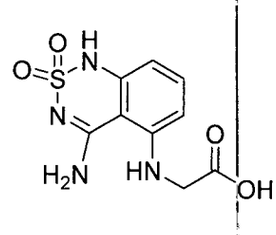
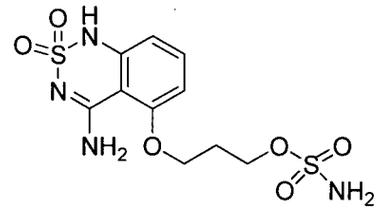
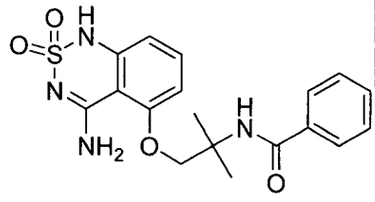
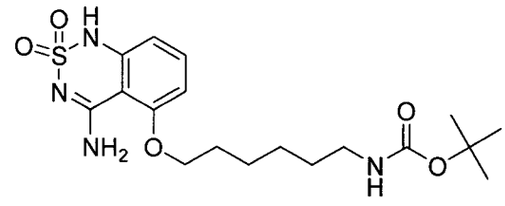
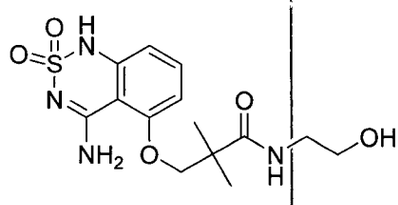
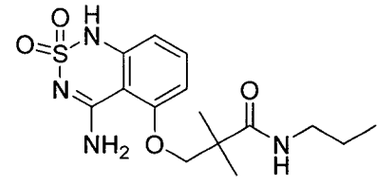
En una realización de la Fórmula (IIIb1), $-X^3-C(X^4)-X^5-$ es –C(O)-, -C(O)-NH-, -NH-C(O)-, -NH-C(O)-NH-, -C(O)-O-, -O-C(O)-, -O-C(O)-O-, -NH-C(O)-O-, -O-C(O)-NH-, –C(NH)-, -C(NH)-NH-, -NH-C(NH)-, -NH-C(NH)-NH-, -C(NH)-O-, -O-C(NH)-, -O-C(NH)-O-, -NH-C(NH)-O-, -O-C(NH)-NH-, -C(N-OH)-, o -C(S)-.

En una realización de la Fórmula (IIIb1), A es hidrógeno, alquilo, alquilo sustituido, o $-NR^9R^{10}$; R^{17} es hidrógeno; e Y^1 es piperidinilo, piperidinilo sustituido, tetrahidrofuranilo, tetrahidrofuranilo sustituido, tetrahidropiranilo, tetrahidropiranilo sustituido, dihidrofuranilo, dihidrofuranilo sustituido, pirrolidinilo, pirrolidinilo sustituido, oxetanilo, oxetanilo sustituido, un anillo monosacárido, un anillo monosacárido sustituido, piridinilo, piridinilo sustituido, pirrolilo, pirrolilo sustituido,

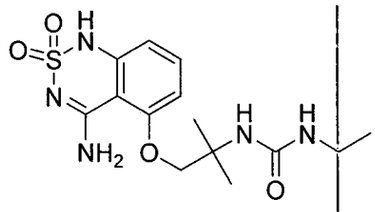
furanilo, furanilo sustituido, pirazolilo, pirazolilo sustituido, isoxazolilo, isoxazolilo sustituido, oxazolilo, u oxazolilo sustituido.

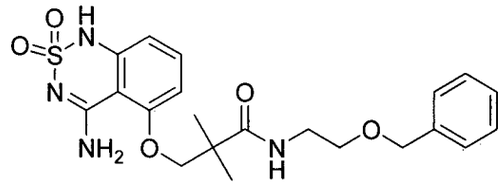
En una realización de la Fórmula (IIIb1), A es hidrógeno, alquilo, alquilo sustituido, o $-NR^9R^{10}$; R^{17} es hidrógeno; Y^1 es $-X^3-C(X^4)-X^5-$; y $-X^3-C(X^4)-X^5-$ es –C(O)-, -C(O)-NH-, -NH-C(O)-, -NH-C(O)-NH-, -C(O)-O-, -O-C(O)-, -O-C(O)-O-, -NH-C(O)-O-, -O-C(O)-NH-, –C(NH)-, -C(NH)-NH-, -NH-C(NH)-, -NH-C(NH)-NH-, -C(NH)-O-, -O-C(NH)-, -O-C(NH)-O-, -NH-C(NH)-O-, -O-C(NH)-NH-, $-S(O)_2-$, $-NH-S(O)_2-$, $-S(O)_2-NH-$, $-O-S(O)_2-$, $-S(O)_2-O-$, -C(N-OH)-, o -C(S)-.

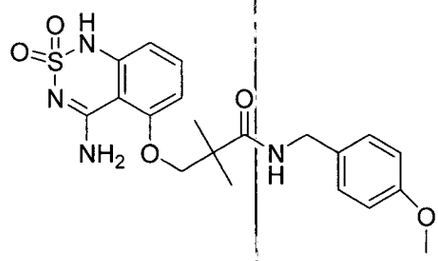
En algunas realizaciones específicas de la Fórmula (IIIb1), el compuesto tiene la fórmula estructural seleccionada del grupo integrado por

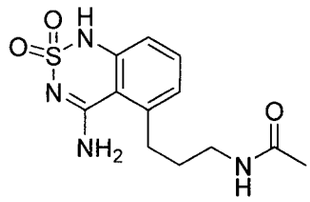

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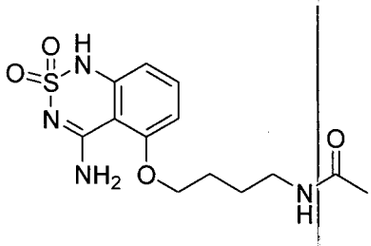
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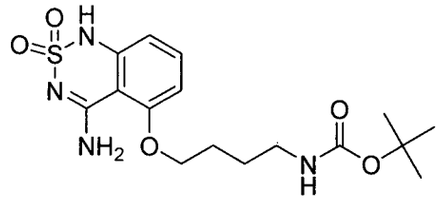


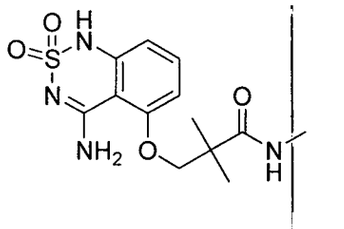


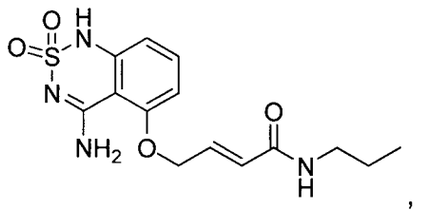


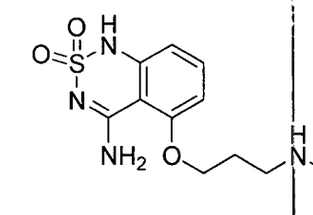


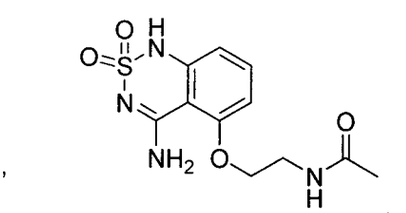


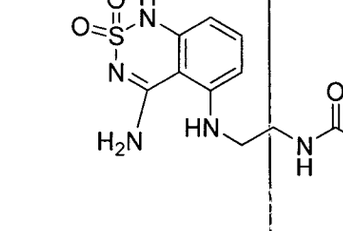


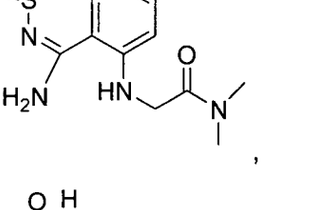


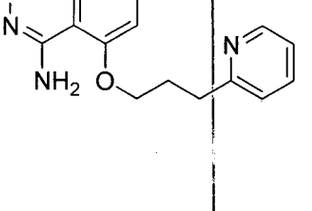


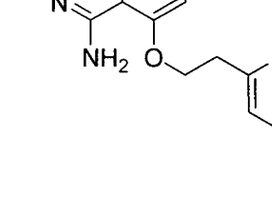




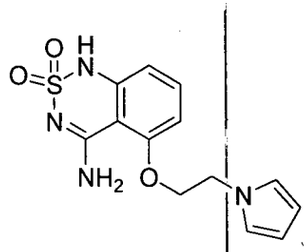


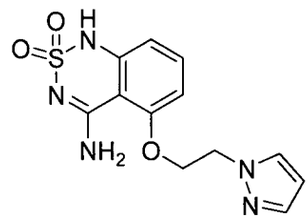


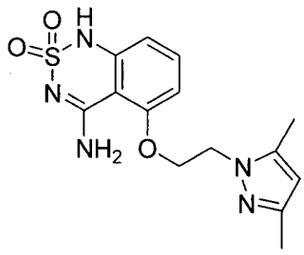


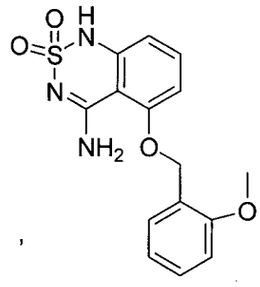


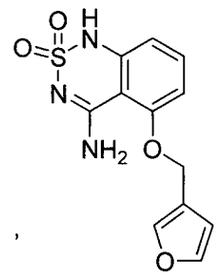
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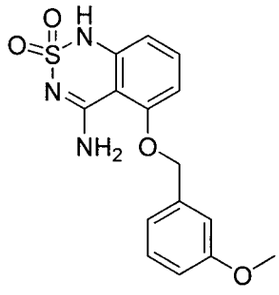


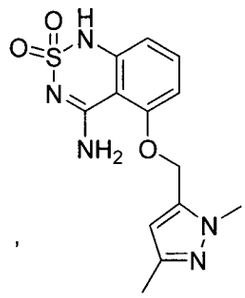


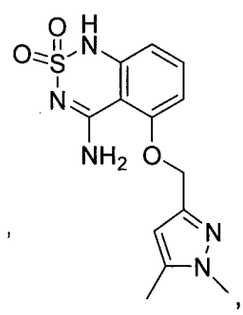


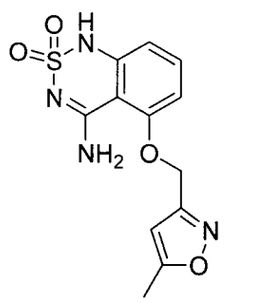


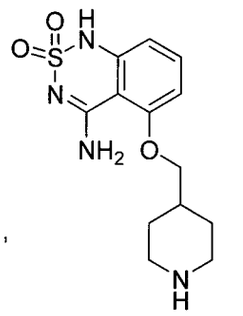


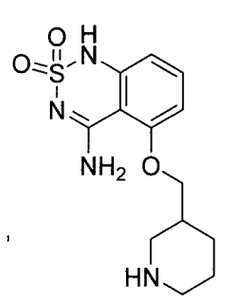


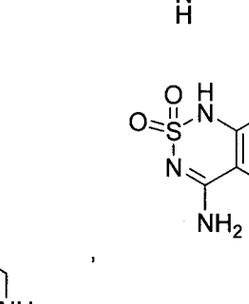


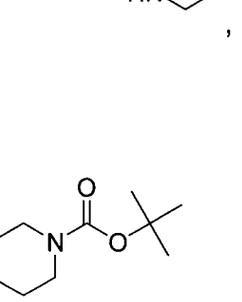


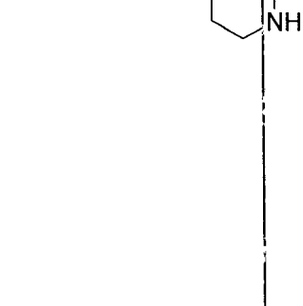


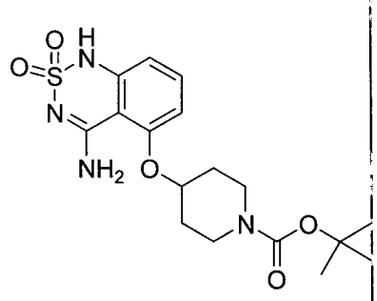


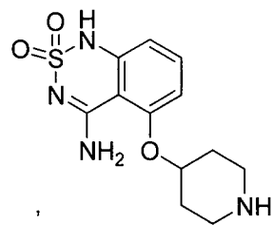


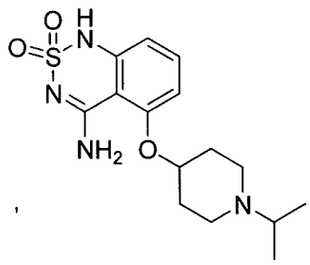


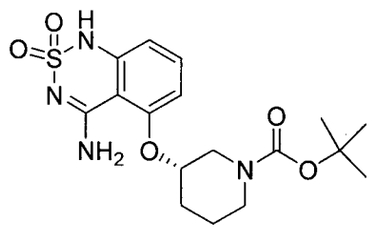


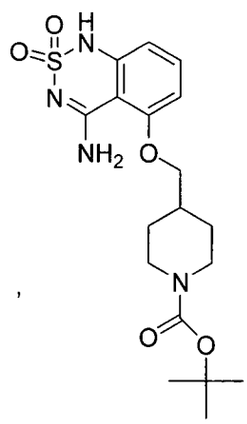


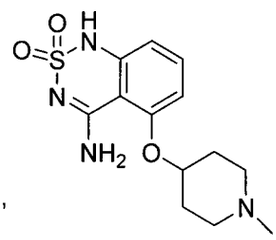


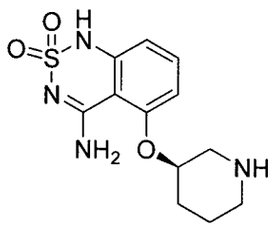


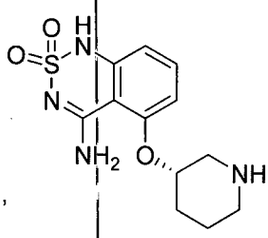


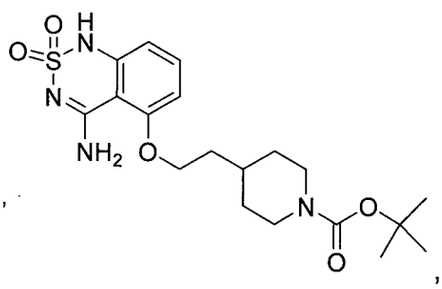


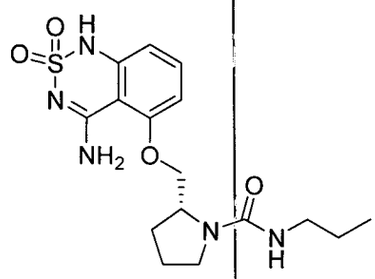


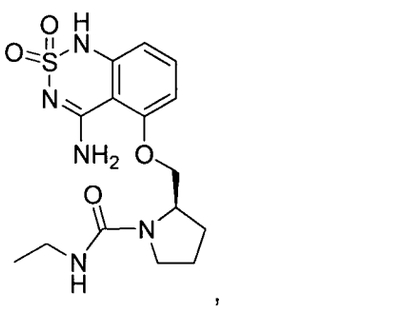


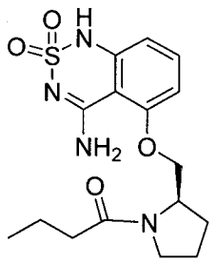


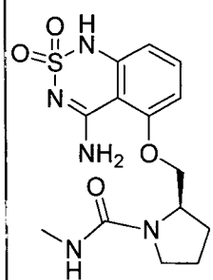


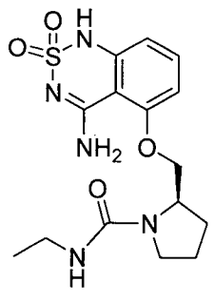


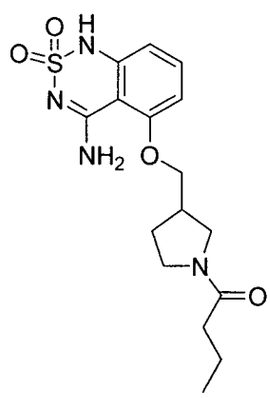


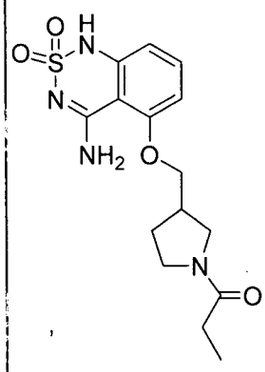


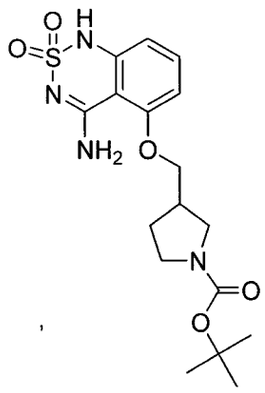


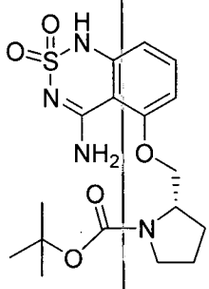


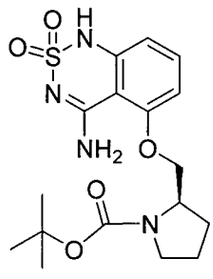


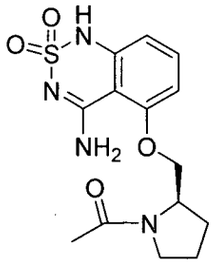


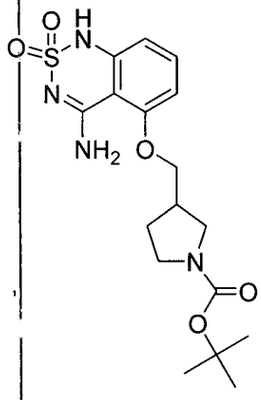


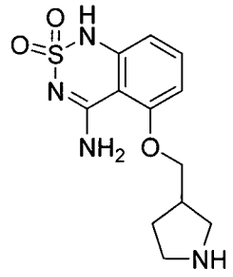


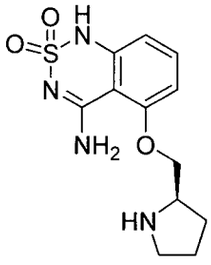


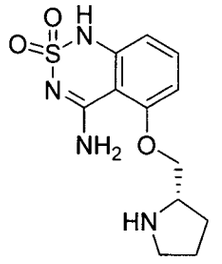


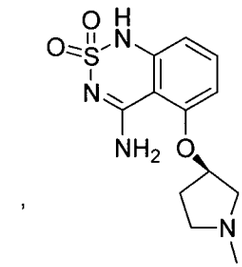




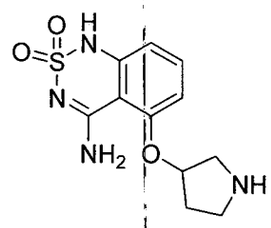


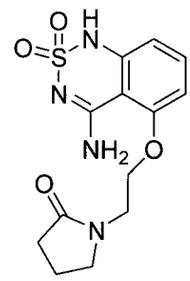


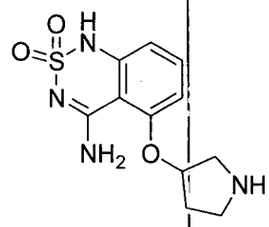


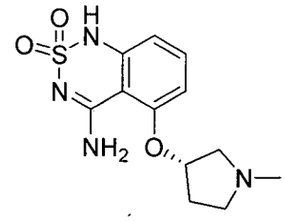


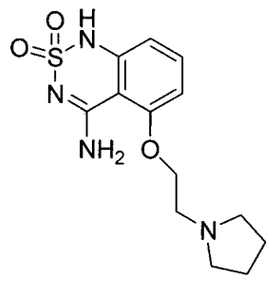
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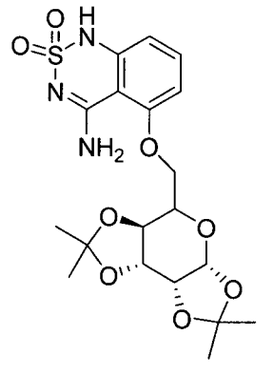


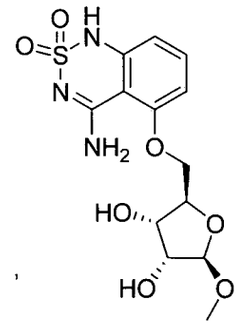


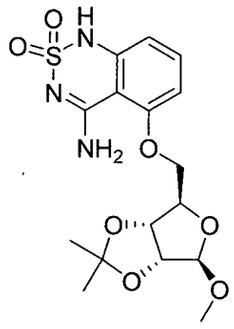


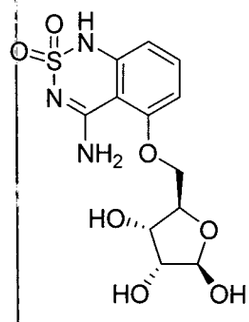


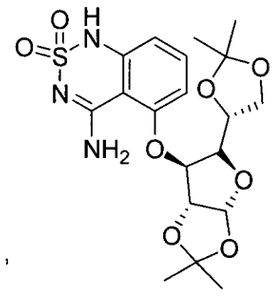


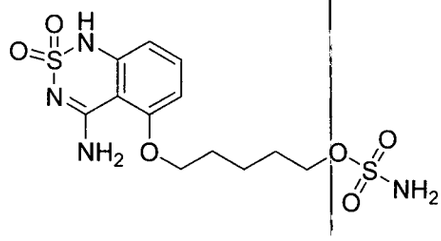


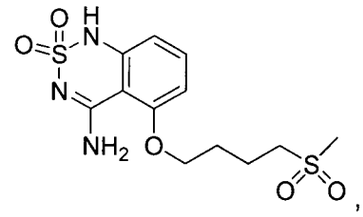


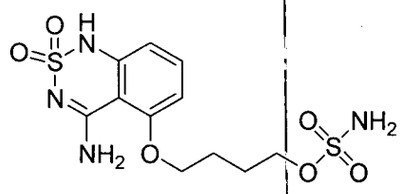


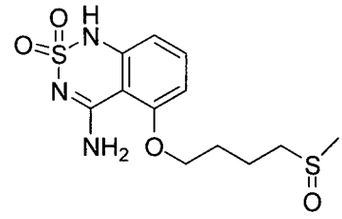


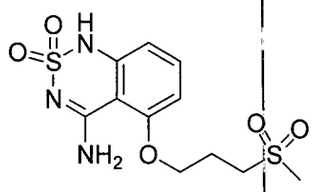


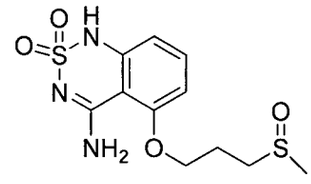


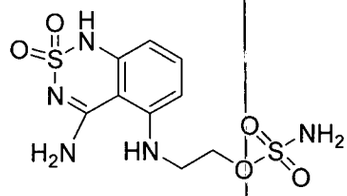


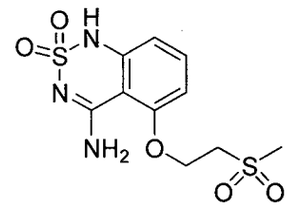


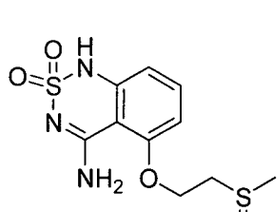


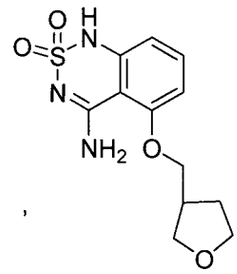


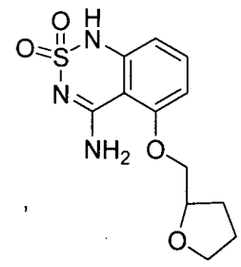


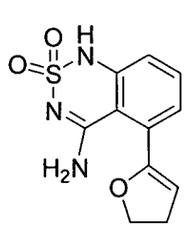


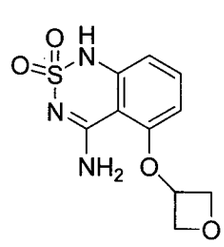


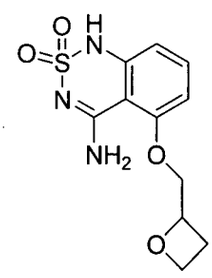


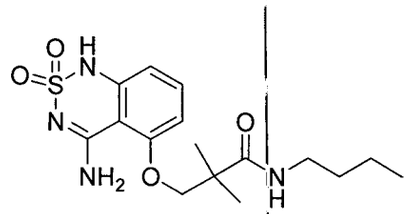


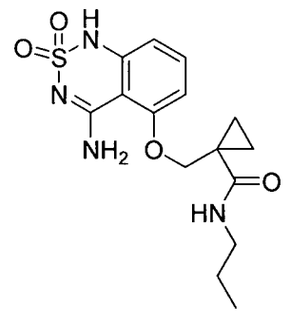


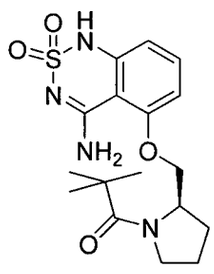


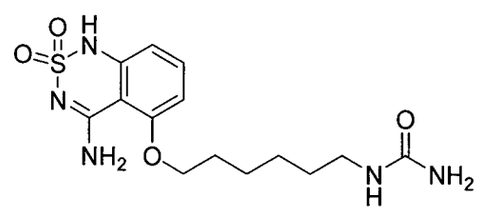


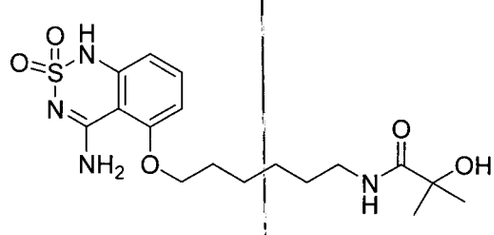


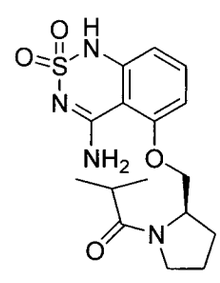


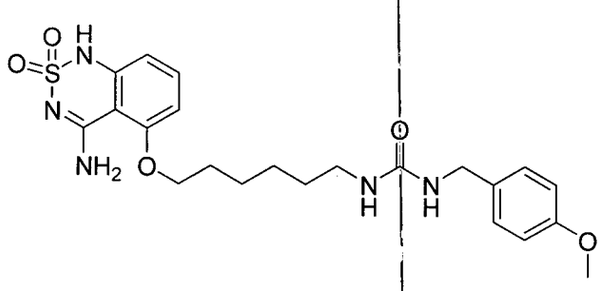


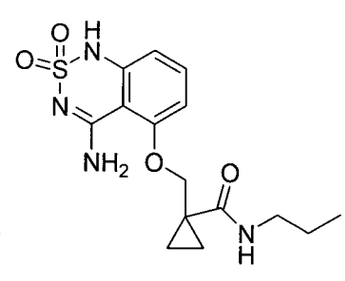


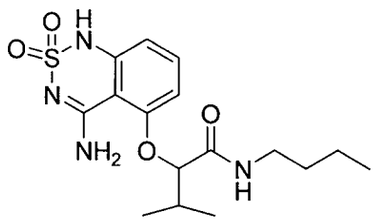


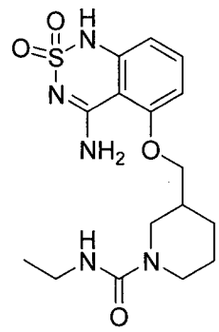


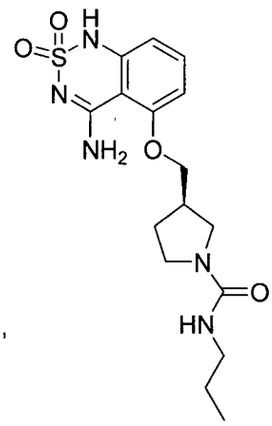


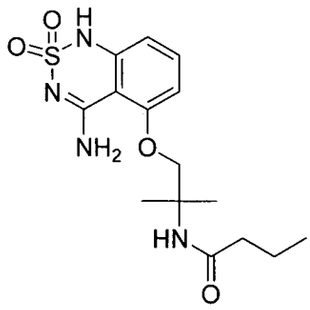


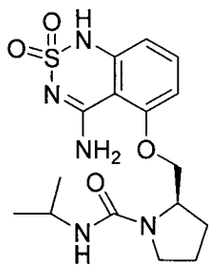


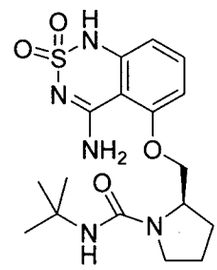


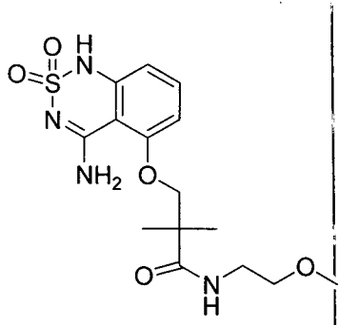


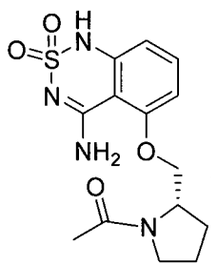


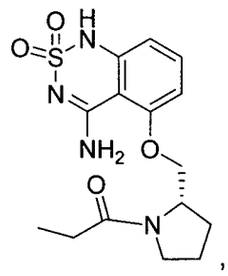


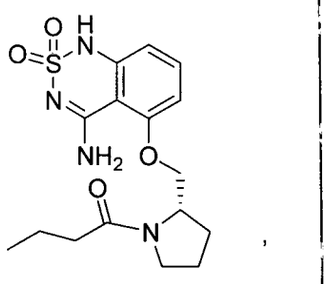


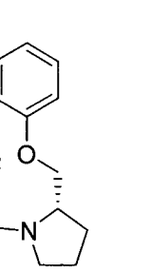


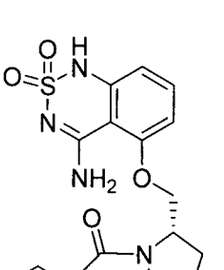


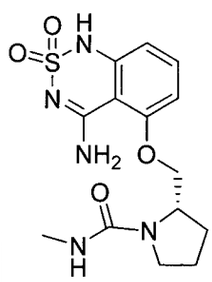


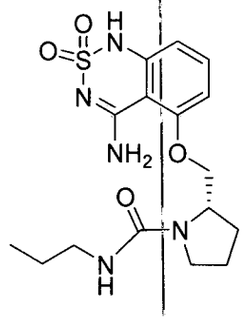




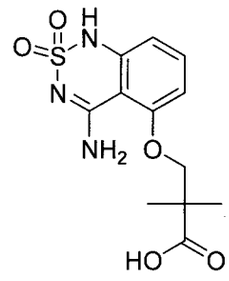




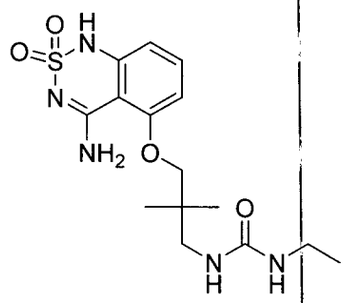




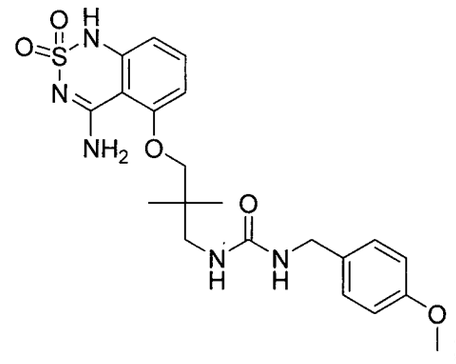
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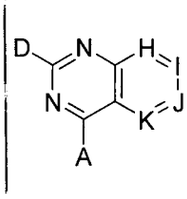
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o un tautómero, sal, solvato, y/o éster del mismo. En algunas realizaciones preferidas, la sal de estos compuestos es una sal clorhidrato o trifluoracetato.

En una realización de la Fórmula (III), el compuesto de la presente invención tiene la Fórmula estructural (IIIc)

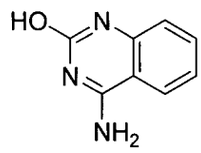
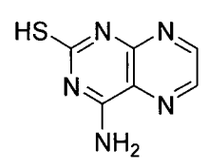
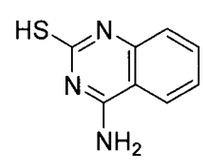
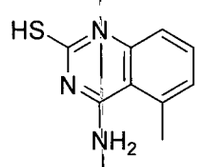
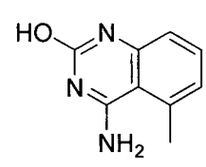
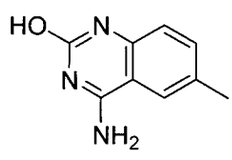
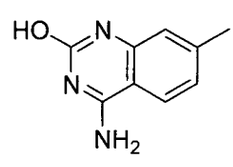
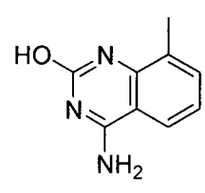
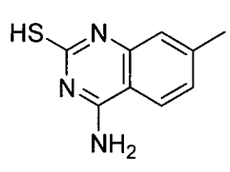
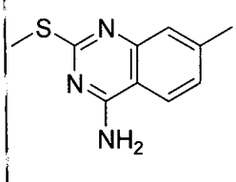
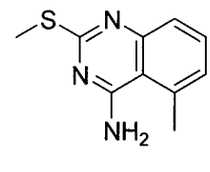
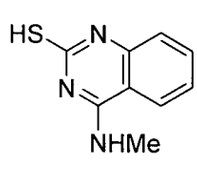


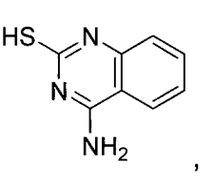
(IIIc)

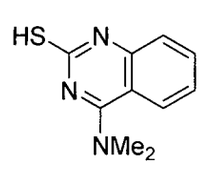
en donde D es halo, $-OR^{15}$, $-NH-OR^{15}$, $-NH-NHR^{15}$, $-S(O)_eR^{15}$, o $-NR^{15}R^{16}$.

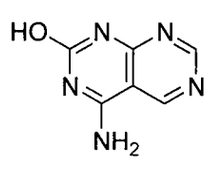
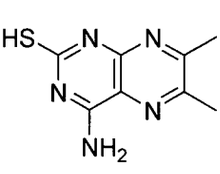
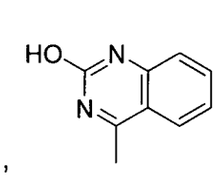
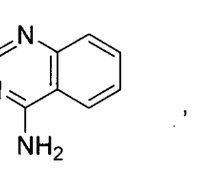
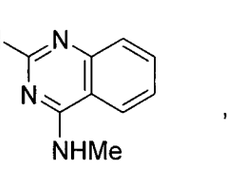
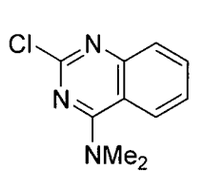
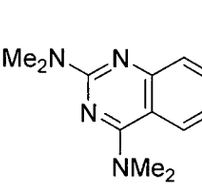
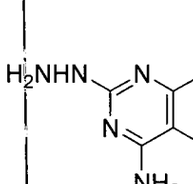
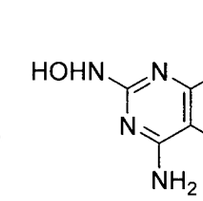
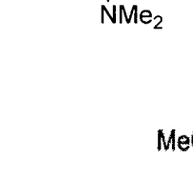
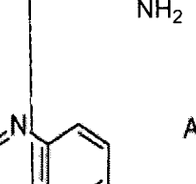
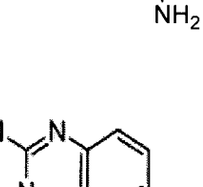
En una realización de la Fórmula (IIIc), R^{35}, R^{36}, R^{37}, y R^{38} son independientemente hidrógeno, alquilo, o alquilo sustituido. Se prefiere que H sea $-C(R^{35})-$; que I sea $-C(R^{36})$; que J sea $-C(R^{37})-$; y que K sea $-C(R^{38})-$.

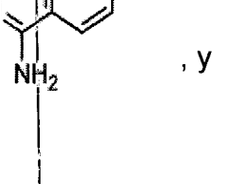
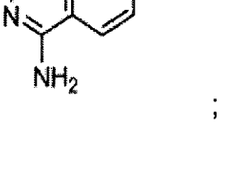
En algunas realizaciones específicas de la Fórmula (IIIc), el compuesto tiene la fórmula estructural seleccionada del grupo integrado por


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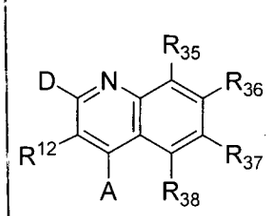
, y

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o un tautómero, sal, solvato y/o éster del mismo. En algunas realizaciones preferidas, la sal de estos compuestos es la sal clorhidrato o trifluoracetato.

En una realización de la Fórmula (III), el compuesto de la presente invención tiene la Fórmula estructural (XI):



(XI)

en donde,

R^{12} es hidrógeno, -OH, -SH, -CN, $-CH_2OH$ o $-CO_2H$;

D es -OH o -SH; y

A es -OH, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, o $-CH_2NHC(O)CH_3$;

siempre que cuando R^{12} sea hidrógeno, entonces R^{35}, R^{36}, R^{37}, y R^{38} no sean hidrógeno.

En una realización de la Fórmula (XI), R^{12} es -OH, -SH, -CN, $-CH_2OH$ o $-CO_2H$; y A es $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, o $-CH_2NHC(O)CH_3$.

En algunas realizaciones de la Fórmula (XI),

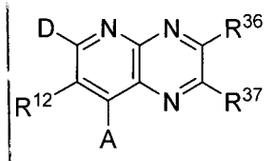
cuando R^{36}, R^{37}, R^{38} y R^{35} son hidrógeno, D es –OH, y A es $-CO_2H$; entonces R^{12} no es $-CO_2H$ u -OH;

cuando R^{36}, R^{37}, R^{38} y R^{35} son hidrógeno, D es –OH, y A es $–NH_2$; entonces R^{12} no es $-CO_2H$ o CN;

cuando R^{36}, R^{38} y R^{35} son hidrógeno, R^{37} es -OMe, D es –OH, y A es $-CH_2OH$; entonces R^{12} no es $-CH_2OH$; y

cuando R^{36}, R^{38} y R^{35} son hidrógeno, R^{37} es hidrógeno o metilo, D es –OH, y A es $–CO_2H$; entonces R^{12} no es -SH.

En una realización de la Fórmula (III), el compuesto de la presente invención tiene la Fórmula estructural (XII):



(XII)

en donde

R^{12} es hidrógeno, -OH, -SH, -CN, $-CH_2OH$ o $-CO_2H$;

D es -SH u –OH;

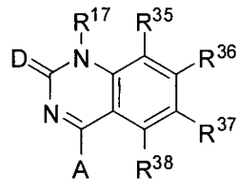
A es -OH, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, o $-CH_2NHC(O)CH_3$;

R^{36} es hidrógeno, $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, $-CH_3$, $-C_2H_5$, $-CH(CH_3)_2$, $-CH_2OH$, $-CH_2OCH_3$, -CN, $-C(O)NR^{41}R^{42}$, $-CO_2R^{41}$, $-SO_2NR^{39}R^{40}$, $-NR^{39}SO_2R^{40}$, $-B(OR^{39})(OR^{40})$, $-P(O)(OR^{39})(OR^{40})$ o $-P(O)(R^{39})(OR^{40})$;y

R^{37} es hidrógeno, $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, $-CH_3$, $-C_2H_5$, $-CH(CH_3)_2$, $-CH_2OH$, $-CH_2OCH_3$, -CN, $-C(O)NR^{43}R^{44}$, $-CO_2R^{43}$, $-SO_2NR^{43}R^{44}$, $-NR^{43}SO_2R^{44}$, $-B(OR^{43})(OR^{44})$, $-P(O)(OR^{43})(OR^{44})$ o $-P(O)(R^{43})(OR^{44})$.

En una realización de la Fórmula (XII), R^{12} es -OH, -SH, -CN, $-CH_2OH$ o $-CO_2H$.

En una realización de la Fórmula (III), el compuesto de la presente invención tiene la Fórmula estructural (XIII):



(XIII)

en donde:

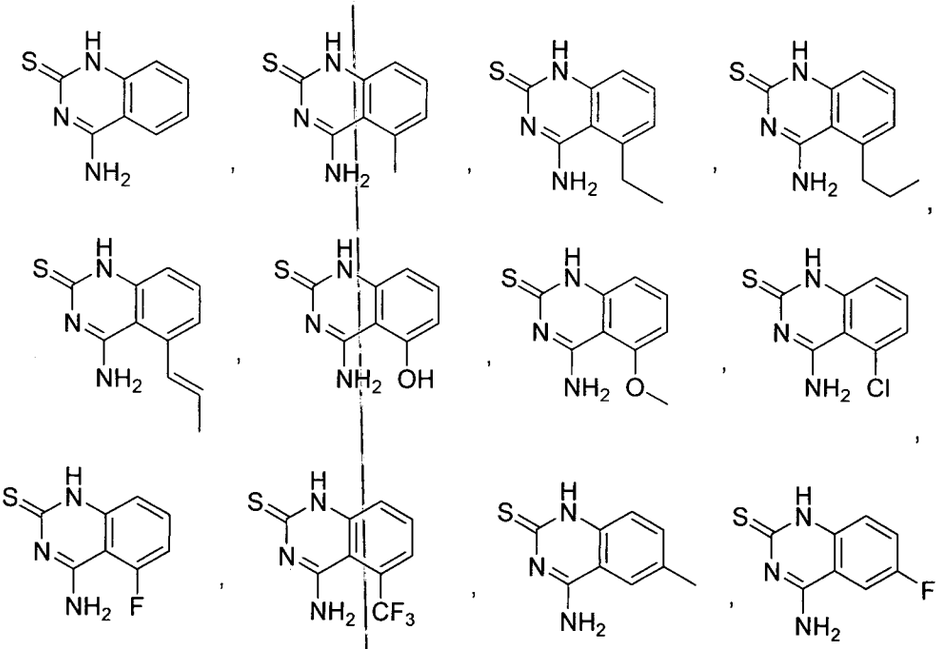
D es =O o =S;

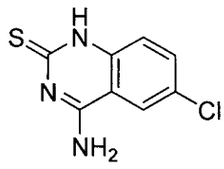
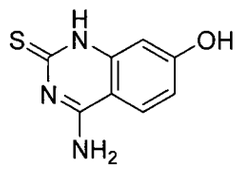
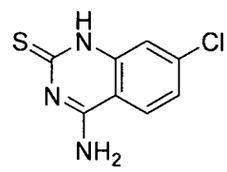
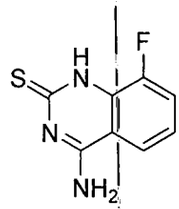
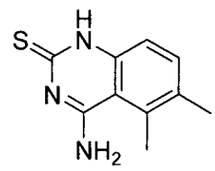
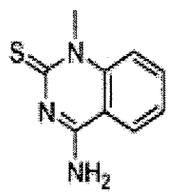
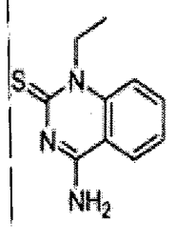
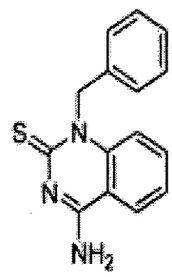
A es -OH, NH_2, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, o $-CH_2NHC(O)CH_3$;

R^{17} es hidrógeno, alquilo, arilo, arilalquilo.

En una realización de la Fórmula (XIII), cuando A es $-NH_2$, y R^{35}, R^{36}, R^{37} y R^{38} son hidrógeno; entonces R^{17} no es metilo, etilo o fenilo.

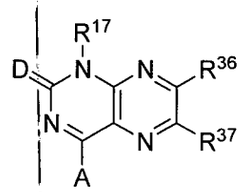
En algunas realizaciones específicas de la Fórmula (XIII), el compuesto tiene la fórmula estructural seleccionada del grupo integrado por




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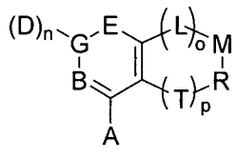
o un tautómero, sal, solvato, y/o éster del mismo. En algunas realizaciones preferidas, la sal de estos compuestos es la sal clorhidrato o trifluoracetato.

En una realización de la Fórmula (III), el compuesto de la presente invención tiene la Fórmula estructural (XIV):


(XIV),

en donde A es -OH, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, o $-CH_2NHC(O)CH_3$; y R^{17} es alquilo, arilo, o arilalquilo.

En una realización de la Fórmula (I), el modificador del ligando del receptor quimiosensorial es un compuesto que tiene una Fórmula estructural (IV):



(IV)

en donde:

L es $-CHR^{60}-$, $-NR^{47}$, -O- o -S-;

M es $-CHR^{61}-$, $-NR^{48}$, -O- o -S-;

R es $-CHR^{62}-$, $-NR^{49}$, -O- o -S-;

T es $-CHR^{63}-$, $-NR^{50}$, -O- o -S-;

o y p son independientemente 0, 1, o 2;

R^{60} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido, -CN, $-NO_2$, $-OR^{64}$, $-S(O)_tR^{64}$, $-OCOR^{64}$, $-NR^{64}COR^{65}$, $-NR^{64}R^{65}$, $-CONR^{64}R^{65}$, $-CO_2R^{64}$, $-SO_2NR^{64}R^{65}$, $-NR^{64}SO_2R^{65}$, $-B(OR^{64})(OR^{65})$, $-P(O)(OR^{64})(OR^{65})$ o $-P(O)(R^{64})(OR^{65})$;

R^{61} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido, -CN, $-NO_2$, $-OR^{66}$, $-S(O)_uR^{66}$, $-OCOR^{66}$, $-NR^{66}COR^{67}$, $-NR^{66}R^{67}$, $-CONR^{66}R^{67}$, $-CO_2R^{66}$, $-SO_2NR^{66}R^{67}$, $-NR^{66}SO_2R^{67}$, $-B(OR^{66})(OR^{67})$, $-P(O)(OR^{66})(OR^{67})$ o $-P(O)(R^{66})(OR^{67})$;

R^{62} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido,

heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido, -CN, $-NO_2$, $-OR^{68}$, $-S(O)_vR^{68}$, $-OCOR^{68}$, $-NR^{68}COR^{69}$, $-NR^{68}R^{69}$, $-CONR^{68}R^{69}$, $-CO_2R^{68}$, $-SO_2NR^{68}R^{69}$, $-NR^{68}SO_2R^{69}$, $-B(OR^{68})(OR^{69})$, $-P(O)(OR^{68})(OR^{69})$ o $-P(O)(R^{68})(OR^{69})$;

R^{63} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido, -CN, $-NO_2$, $-OR^{70}$, $-S(O)_xR^{70}$, $-OCOR^{70}$, $-NR^{70}COR^{71}$, $-NR^{70}R^{71}$, $-CONR^{70}R^{71}$, $-CO_2R^{70}$, $-SO_2NR^{70}R^{71}$, $-NR^{70}SO_2R^{71}$, $-B(OR^{70})(OR^{71})$, $-P(O)(OR^{70})(OR^{71})$ o $-P(O)(R^{70})(OR^{71})$; o alternativamente R^{60} y R^{61}, R^{61} y R^{62}, o R^{62} y R^{63} conjuntamente con los átomos a los cuales ellos están unidos forman un anillo arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido;

t, u, v y x son independientemente 0, 1 o 2;

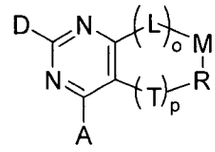
R^{64} a R^{71} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido o alternativamente R^{64} y R^{65}, R^{66} y R^{67}, R^{68} y R^{69}, o R^{70} y R^{71} conjuntamente con los átomos a los cuales ellos están unidos forman un anillo cicloheteroalquilo o cicloheteroalquilo sustituido; y

R^{47} a R^{50} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido;

con la condición de que a lo sumo solamente uno de L, M, R y T sea un heteroátomo.

En una realización de la Fórmula (IV), B es -N-, y E es $-NR^{17}-$ o -N-. Se prefiere que G sea -C-.

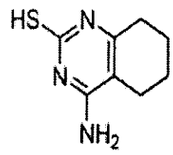
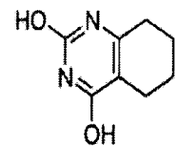
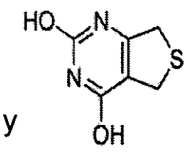
En una realización de la Fórmula (IV), el compuesto de la presente invención tiene la Fórmula estructural (XV):



XV

en donde D es -SH u –OH; y A es -OH, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, o $-CH_2NHC(O)CH_3$.

En algunas realizaciones específicas de la Fórmula (XV), el compuesto tiene la fórmula estructural seleccionada del grupo integrado por

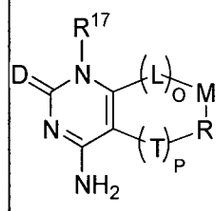

,

, y

;

o un tautómero, sal, solvato, y/o éster del mismo. En algunas realizaciones preferidas, la sal de estos compuestos es la sal clorhidrato o trifluoracetato.

En una realización de la Fórmula (IV), B es -N-; E es $-NR^{17}-$ o -N-; A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, $-OR^9$, $-SR^9$, -CN, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$ o $-NR^9C(=NH)NR^{10}R^{11}$; y D s =O, =S , $=N-OR^{15}$.

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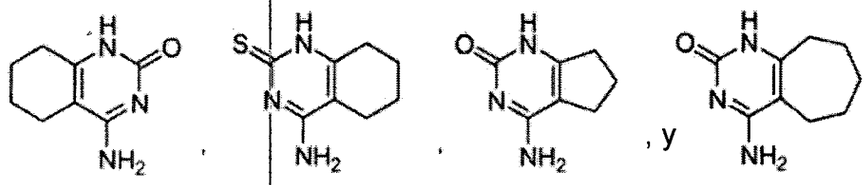
En una realización de la Fórmula (IV), el compuesto de la presente invención tiene la Fórmula estructural (IVb):



(IVb),

en donde L es -CHR^{60}-; M es -CHR^{61}-; R es -CHR^{62}-; T es -CHR^{63}-.

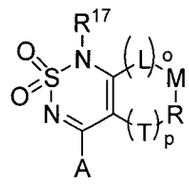
En algunas realizaciones específicas de la Fórmula (IV), el compuesto tiene la fórmula estructural seleccionada del grupo integrado por:



;

o un tautómero, sal, solvato, y/o éster del mismo. En algunas realizaciones preferidas, la sal de estos compuestos es la sal clorhidrato o trifluoracetato.

En una realización de la Fórmula (IV), el compuesto de la presente invención tiene la Fórmula estructural (IVa):



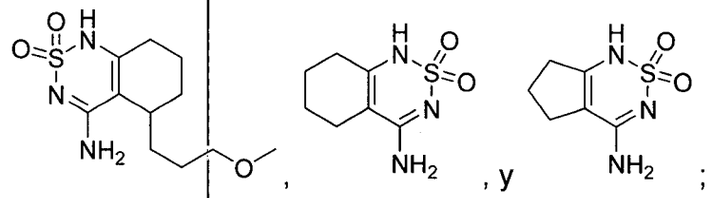
(IVa).

En una realización de la Fórmula (IVa), L es -CHR^{60}-; M es -CHR^{61}-; R es -CHR^{62}-; y T es -CHR^{63}-. Se prefiere que A sea hidrógeno, alquilo, alquilo

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sustituido, arilo, arilo sustituido, -OR^9, -SR^9, -CN, -NR^9R^{10}, -$CONR^9R^{10}$, -CO_2R^9, -$NR^9CO_2R^{10}$, -$NR^9CONR^{10}R^{11}$, -$NR^9CSNR^{10}R^{11}$ o -$NR^9C(=NH)NR^{10}R^{11}$.

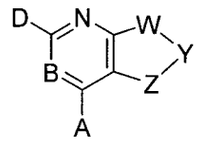
En algunas realizaciones específicas de la Fórmula (IVa), el compuesto tiene la fórmula estructural seleccionada del grupo integrado por:



, y ;

o un tautómero, sal, solvato, y/o éster del mismo. En algunas realizaciones preferidas, la sal de estos compuestos es la sal clorhidrato o trifluoracetato.

En una realización de la Fórmula (II), el compuesto de la presente invención tiene la Fórmula estructural (Va):



(Va)

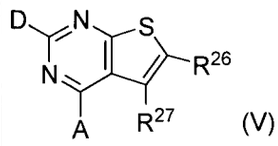
en donde D es hidrógeno, alquilo, arilo, halo, -OH, -NH_2, -SR^{15}, -CH_3, -CO_2H o -$CONH_2$; A es -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -$NHC(O)CH_3$, -$NHC(O)OCH_3$, -$NHC(O)NH_2$, -$NHC(S)NH_2$, -$NHC(NH)NH_2$, -CN, -CH_2OH, -CH_2NH_2, -CH_2NHCH_3, -$CH_2N(CH_3)_2$, -CO_2H, -$CONH_2$, -$CONHCH_3$, o -$CH_2NHC(O)CH_3$; y R^{15} es hidrógeno, alquilo, alquilo sustituido, arilalquilo.

En una realización de la Fórmula (Va), Y forma un enlace único con W y un enlace doble con Z; W es -$C(R^{24})$- o –N-; Y es –$C(R^{26})$- o –N-; y Z es –S-, -$N(R^{28})$, u –O-.

En una realización de la Fórmula (Va), Y forma un enlace doble con W y un enlace único con Z; W es –S-, -N(R^{25}), u –O-; Y es –C(R^{26})- o –N-; y Z es -C(R^{27})- o –N-.

En algunas realizaciones de la Fórmula (Va), en donde B es –C(R^{12})-.

En una realización de la Fórmula (Va), el compuesto de la presente invención tiene la Fórmula estructural (V):



(V)

en donde:

R^{26} es hidrógeno, alquilo, halo, -CO_2R^{54}, -$CONR^{54}R^{55}$, -$SO_2NR^{54}R^{55}$, -$NR^{54}SO_2R^{55}$, -$B(OR^{54})(OR^{55})$, -$P(O)(OR^{54})(OR^{55})$ o -$P(O)(R^{54})(OR^{55})$;

R^{27} es hidrógeno, alcoxi, alquilo, alquilo sustituido, halo, -CN, -$C(O)NR^{56}R^{57}$, -CO_2R^{56}, -$SO_2NR^{56}R^{57}$, -$NR^{56}SO_2R^{57}$, -$B(OR^{56})(OR^{57})$, -$P(O)(OR^{56})(OR^{57})$ o -$P(O)(R^{56})(OR^{57})$; o alternativamente R^{52} y R^{53} conjuntamente con los átomos a los cuales ellos están unidos forman un anillo cicloheteroalquilo o cicloheteroalquilo sustituido y

R^{54}, R^{55}, R^{56}, y R^{57} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido; o alternativamente R^{54} y R^{55} o R^{56} y R^{57} conjuntamente con los átomos a los cuales ellos están unidos forman un anillo cicloheteroalquilo o cicloheteroalquilo sustituido;

siempre que cuando R^{26} y R^{27} sean hidrógeno, y D sea –SH; entonces A sea -NH_2.

En una realización de la Fórmula (V),

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cuando D es metilo, A es dimetilamino, y R^{53} es hidrógeno; entonces R^{52} no es metilo, etilo o carboxilo;

cuando D es metilo, A es dimetilamino, y R^{53} es metilo; entonces R^{52} no es metilo;

cuando D es $-SCH_3$, A es dimetilamino, y R^{53} es hidrógeno; entonces R^{52} no es carboetoxi;

cuando D es hidrógeno, A es dimetilamino, y R^{53} es hidrógeno; entonces R^{52} no es carboxilo o carboetoxi;

cuando D es hidrógeno, A es dimetilamino y R^{53} es metilo; entonces R^{52} no es metilo;

cuando D es hidrógeno, A es metilamino y R^{53} es hidrógeno; entonces R^{52} no es metilo, etilo o carboetoxi;

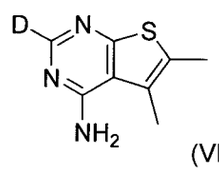
cuando D es hidrógeno, A es metilamino y R^{53} es metilo; entonces R^{52} no es metilo o carboetoxi;

cuando D es hidrógeno, A es metilamino y R^{53} es $-CH_2NMe$; entonces R^{52} no es metilo o carboetoxi;

cuando D es fenilo, A es metilamino y R^{53} es hidrógeno entonces R^{52} no es metilo; y

cuando D es fenilo, A es $-NH(CO)CH_3$ y R^{53} es metilo entonces R^{52} no es carbometoxi.

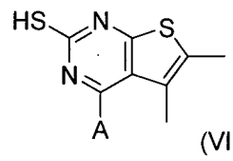
En una realización de la Fórmula (V), el compuesto de la presente invención tiene la Fórmula estructural (VI):



(VI),

en donde D es hidrógeno, $-CH_3$, $-C_2H_5$, fenilo o bencilo.

En una realización de la Fórmula (V), el compuesto de la presente invención tiene la Fórmula estructural (VII):



(VII),

en donde A es hidrógeno, $-CH_3$, $-C_2H_5$, fenilo o bencilo.

En una realización de la Fórmula (V), el compuesto de la presente invención tiene la Fórmula estructural (VIII):

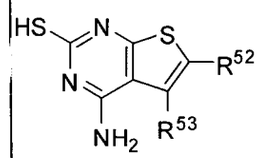


(VIII)

en donde

R^9 y R^{10} son independientemente hidrógeno, $-CH_3$, $-C_2H_5$, fenilo o bencilo; y siempre que ambos R^9 y R^{10} no sean hidrógeno.

En una realización de la Fórmula (V), el compuesto de la presente invención tiene la Fórmula estructural (IX):



(IX)

en donde

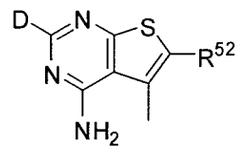
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R^{52} es alquilo, alquilo sustituido, -CN, $-C(O)NR^{54}R^{55}$, $-CO_2R^{54}$, $-SO_2NR^{54}R^{55}$, $-NR^{54}SO_2R^{55}$, $-B(OR^{54})(OR^{55})$, $-P(O)(OR^{54})(OR^{55})$, o $-P(O)(R^{54})(OR^{55})$;

R^{53} es alquilo, CO_2R^{56} o $-CONR^{56}R^{57}$, $-SO_2NR^{56}R^{57}$, $-NR^{56}SO_2R^{57}$, $-B(OR^{56})(OR^{57})$, $-P(O)(OR^{56})(OR^{57})$ o $-P(O)(R^{56})(OR^{57})$;

R^{54} a R^{57} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido; o alternativamente R^{52} y R^{53} conjuntamente con los átomos a los cuales ellos están unidos forman un anillo cicloheteroalquilo o cicloheteroalquilo sustituido.

En una realización de la Fórmula (V), el compuesto de la presente invención tiene la Fórmula estructural (X):



(X)

en donde,

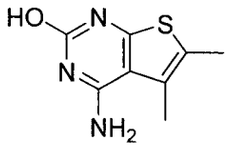
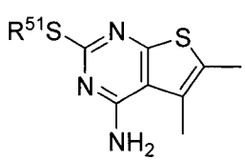
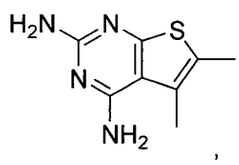
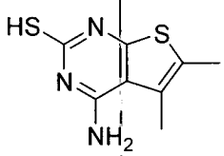
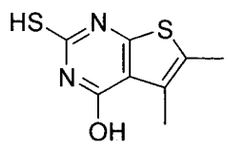
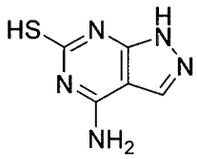
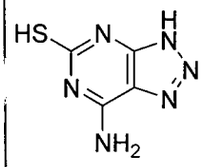
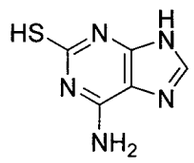
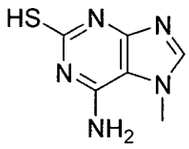
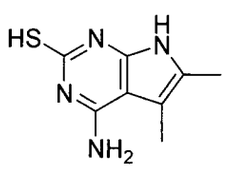
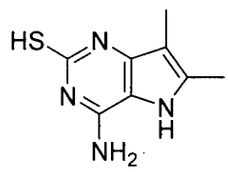
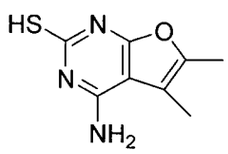
D es -OH, -SH o $-NH_2$,

R^{52} es alquilo, alquilo sustituido, alcoxi, -CN, $-C(O)NR^{54}R^{55}$, $-CO_2R^{54}$, $-SO_2NR^{54}R^{55}$, $-NR^{54}SO_2R^{55}$, $-B(OR^{54})(OR^{55})$, $-P(O)(OR^{54})(OR^{55})$, $-P(O)(R^{54})(OR^{55})$,

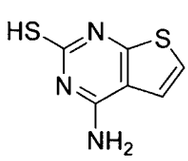
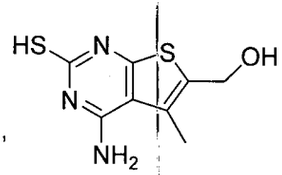
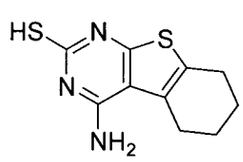
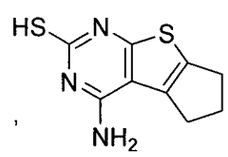
R^{54} y R^{55} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido; o alternativamente R^{54} y R^{55}

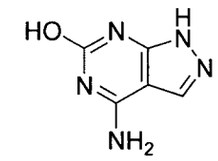
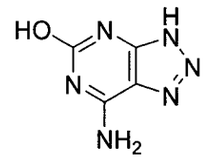
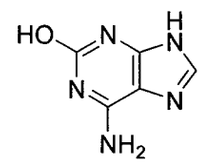
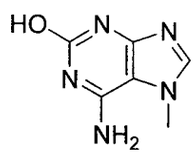
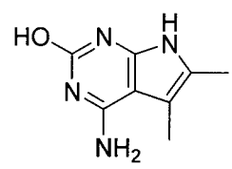
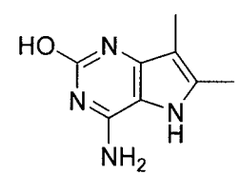
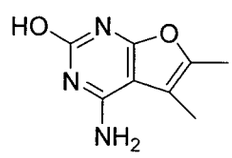
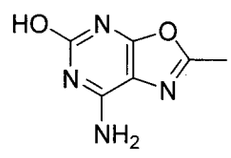
conjuntamente con los átomos a los cuales ellos están unidos forman un anillo cicloheteroalquilo o cicloheteroalquilo sustituido.

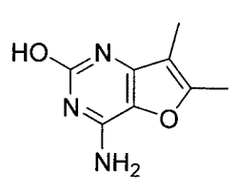
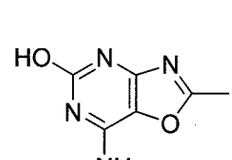
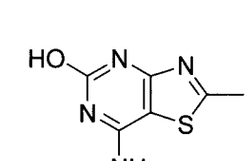
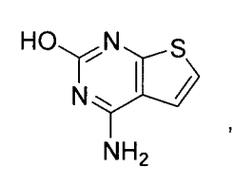
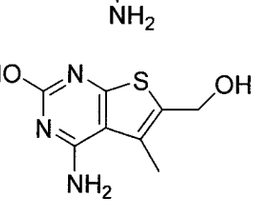
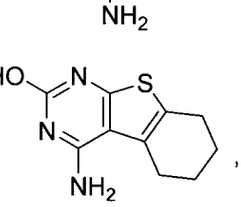
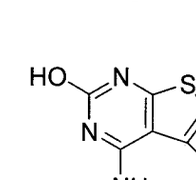
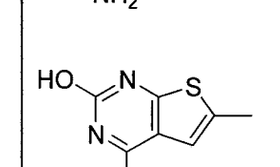
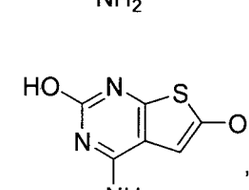
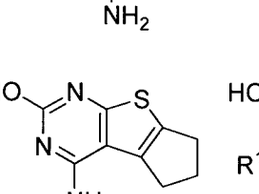
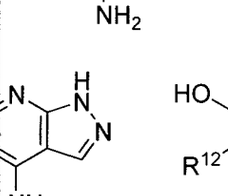
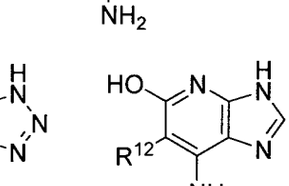
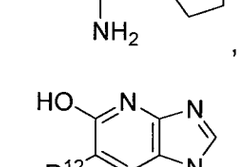
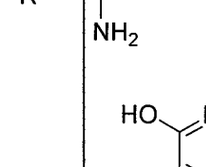
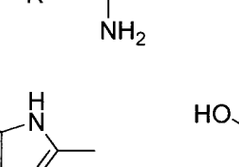
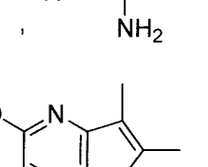
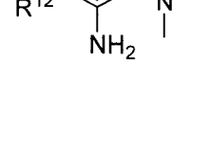
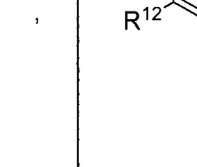
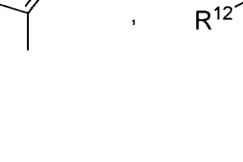
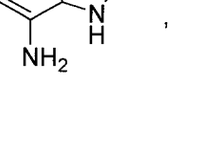
En algunas realizaciones específicas de la Fórmula (Va), el compuesto tiene la fórmula estructural seleccionada del grupo integrado por

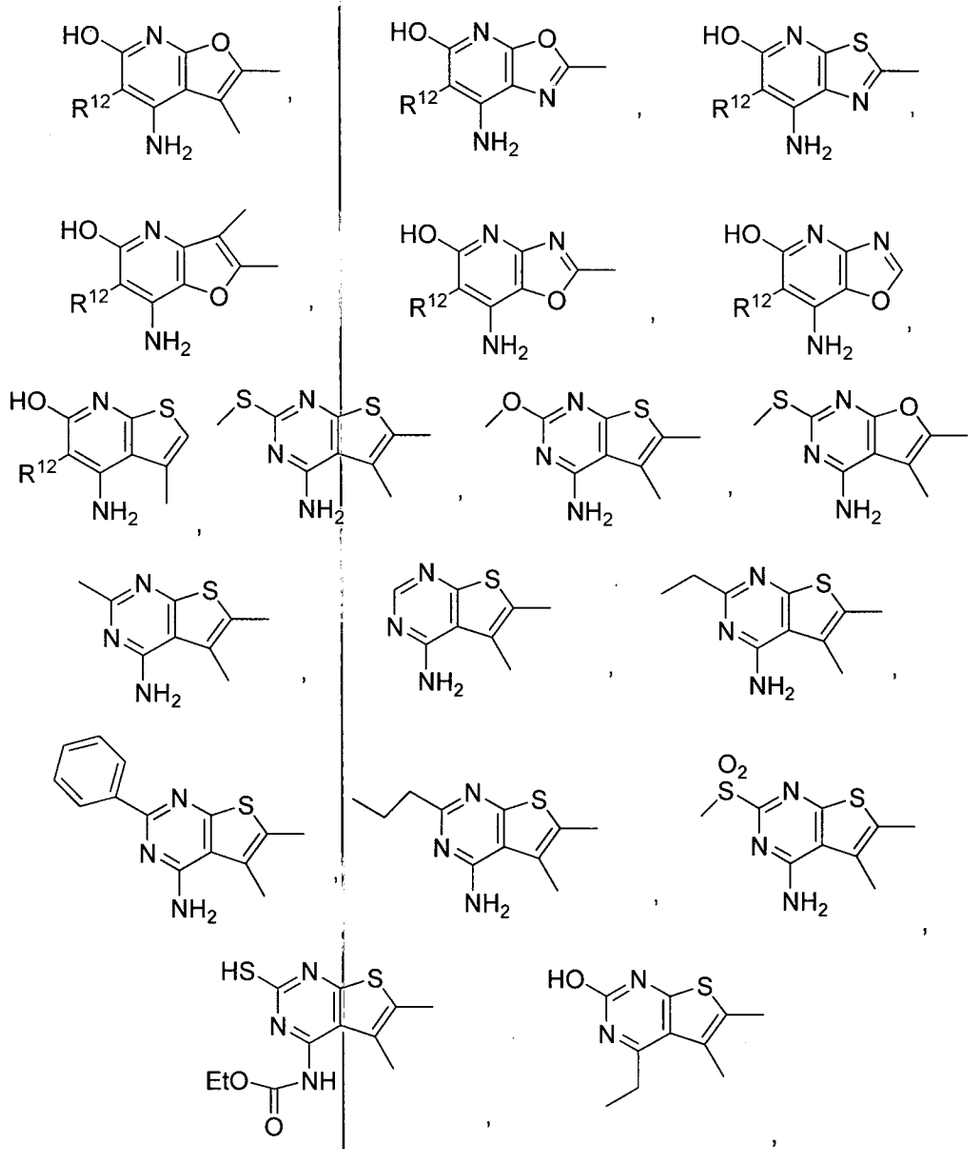

















en donde,

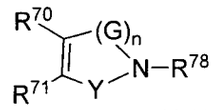
R^{12} es –OH, -SH, -CN, $-CH_2OH$, o $–CO_2H$; y

R^{51} es $–CH_3$, $-CH_2CH_3$, bencilo, o $–CH_2CO_2CH_2CH_3$;

o un tautómero, sal, solvato, y/o éster del mismo. En algunas realizaciones preferidas, la sal de estos compuestos es la sal clorhidrato o trifluoracetato.

En otra realización de la presente invención, el modificador del ligando del receptor quimiosensorial es un compuesto que tiene una Fórmula de estructura (XVI):

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(XVI)

o un tautómero, sal, solvato, y/o éster del mismo en donde:

n es 1, 2 o 3;

cada G es independientemente $-C(R^{77})(R^{79})-$, $-C(O)-$, $-NR^{77}-$ o $-S(O)_2-$; siempre que cuando n sea mayor a uno entonces solamente un G es $-C(O)-$, $-C(S)$, $-S(O)_2-$ o $-NR^{77}-$;

Y es $-C(O)-$, $-C(S)$ o $-S(O)_2-$;

R^{70} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, $-CN$, $-NO_2$, $-OR^{72}$, $-S(O)_aR^{72}$, $-NR^{72}R^{73}$, $-CONR^{72}R^{73}$, $-CO_2R^{72}$, $-NR^{72}CO_2R^{73}$, $-NR^{72}CONR^{73}R^{74}$, $-NR^{72}CSNR^{73}R^{74}$ or $-NR^{72}C(=NH)NR^{73}R^{74}$, $-SO_2NR^{72}R^{73}$, $-NR^{72}SO_2R^{73}$, $-NR^{72}SO_2NR^{73}R^{74}$, $-B(OR^{72})(OR^{73})$, $-P(O)(OR^{72})(OR^{73})$ o $-P(O)(R^{72})(OR^{73})$;

a y b son independientemente 0, 1 o 2;

R^{71} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, $-CN$, $-NO_2$, $-OR^{74}$, $-S(O)_bR^{74}$, $-NR^{74}R^{75}$, $-CONR^{74}R^{75}$, $-CO_2R^{74}$, $-NR^{74}CO_2R^{75}$, $-NR^{74}CONR^{75}R^{76}$, $-NR^{74}CSNR^{75}R^{76}$ o $-NR^{74}C(=NH)NR^{75}R^{76}$, $-SO_2NR^{74}R^{75}$, $-NR^{74}SO_2R^{75}$, $-NR^{74}SO_2NR^{75}R^{76}$, $-B(OR^{74})(OR^{75})$, $-P(O)(OR^{74})(OR^{75})$, $-P(O)(R^{74})(OR^{75})$ o alternativamente, R^{71} y R^{72} conjuntamente con los átomos a los cuales ellos están unidos forman un anillo arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o

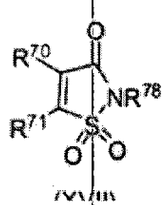
cicloheteroalquilo sustituido donde el anillo está opcionalmente fusionado con otro anillo arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido;

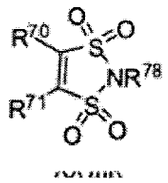
R^{72} a R^{76} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido o alternativamente, R^{72} y R^{73}, R^{73} y R^{74}, R^{74} y R^{75} y R^{75} y R^{76} conjuntamente con los átomos a los cuales ellos están unidos forman un anillo cicloheteroalquilo o cicloheteroalquilo sustituido; y

R^{77} a R^{79} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido o alternativamente, R^{77} y R^{79}, conjuntamente con los átomos a los cuales ellos están unidos forman un anillo cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido.

En algunas realizaciones de la Fórmula (XVI), cuando G es -C(O)- y R^{78} es hidrógeno, R^{71} y R^{72} no forman un anillo fenilo. En otras realizaciones, R^{70} y R^{71} conjuntamente con los átomos a los cuales ellos están unidos forman un anillo arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido donde el anillo está opcionalmente fusionado con otro arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido.

Todavía en otras realizaciones de la Fórmula (XVI), se proporciona un compuesto de la fórmula estructural (XVII), (XVIII), (XIX) o (XX):

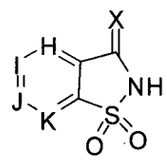




donde o es 1 o 2.

En algunas realizaciones, R^{70} y R^{71} conjuntamente con los átomos a los cuales ellos están unidos forman un anillo arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido donde el anillo está opcionalmente fusionado con otro anillo arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido.

En otra realización de la Fórmula (XVI), el modificador del ligando del receptor quimiosensorial es un compuesto que tiene una Fórmula de estructura (XXI):



(XXI)

en donde:

X es O o S;

H es -N- o -CR^{81}-;

I es -N- o -CR^{82}-;

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J es -N- o -CR^{83}-;

K es -N- o -CR^{84}-;

con la condición de que no más de 2 de H, I, J o K sean -N-;

R^{81} es hidrógeno, alcoxi, -OCH_3, -OC_2H_5, -OC_3H_7, alquilo, -CH_3, -C_2H_5, -$CH(CH_3)_2$, -CH_2OH, halo, cloro, flúor, -CH_2OCH_3, -CN, -$C(O)NR^{85}R^{86}$, -CO_2R^{85}, -$SO_2NR^{85}R^{86}$, -$NR^{85}SO_2R^{86}$, -$B(OR^{85})(OR^{86})$, -$P(O)(OR^{85})(OR^{86})$ o -$P(O)(R^{85})(OR^{86})$;

R^{82} es hidrógeno, alcoxi, -OCH_3, -OC_2H_5, -OC_3H_7, alquilo, -CH_3, -C_2H_5, -$CH(CH_3)_2$, -CH_2OH, halo, cloro, flúor, -CH_2OCH_3, -CN, -$C(O)NR^{88}R^{87}$, -CO_2R^{88}, -$SO_2NR^{88}R^{87}$, -$NR^{88}SO_2R^{87}$, -$B(OR^{88})(OR^{87})$, -$P(O)(OR^{88})(OR^{87})$ o -$P(O)(R^{88})(OR^{87})$;

R^{83} es hidrógeno, alcoxi, -OCH_3, -OC_2H_5, -OC_3H_7, alquilo, -CH_3, -C_2H_5, -$CH(CH_3)_2$, -CH_2OH, halo, cloro, flúor, -CH_2OCH_3, -CN, -$C(O)NR^{90}R^{89}$, -CO_2R^{90}, -$SO_2NR^{90}R^{89}$, -$NR^{90}SO_2R^{89}$, -$B(OR^{90})(OR^{89})$, -$P(O)(OR^{90})(OR^{89})$ o -$P(O)(R^{90})(OR^{89})$;

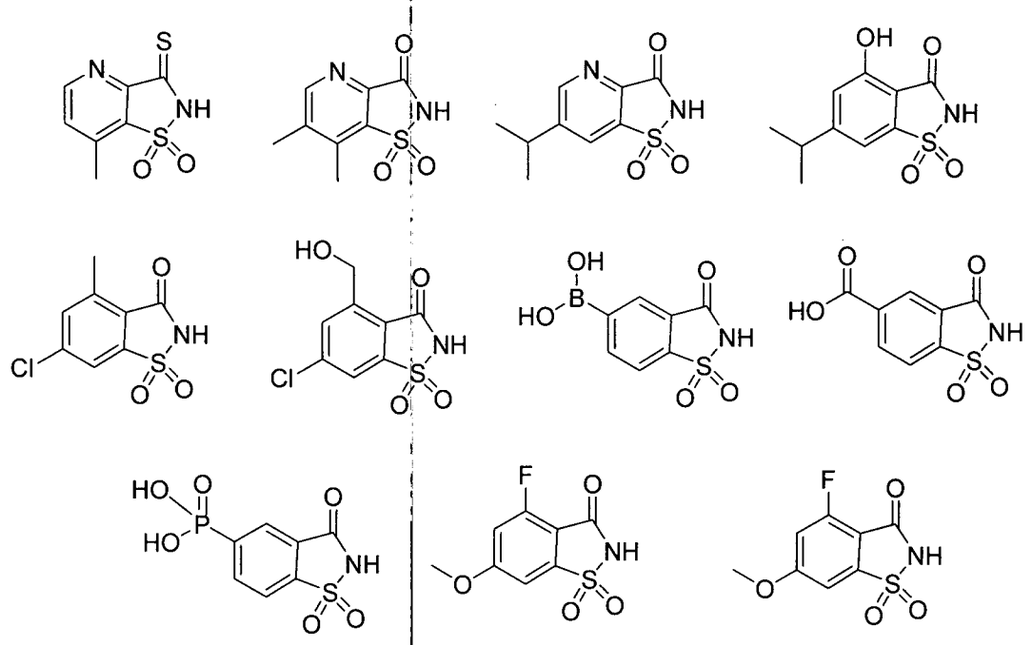
R^{84} es hidrógeno, alcoxi, -OCH_3, -OC_2H_5, -OC_3H_7, alquilo, -CH_3, -C_2H_5, -$CH(CH_3)_2$, -CH_2OH, halo, cloro, flúor, -CH_2OCH_3, -CN, -$C(O)NR^{92}R^{91}$, -CO_2R^{90}, -$SO_2NR^{92}R^{91}$, -$NR^{92}SO_2R^{91}$, -$B(OR^{92})(OR^{91})$, -$P(O)(OR^{92})(OR^{91})$ o -$P(O)(R^{92})(OR^{91})$;y

R^{85} a R^{91} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido o alternativamente R^{85} y R^{86}, R^{87} y R^{88}, R^{89} y R^{90}, o R^{91} y R^{92} conjuntamente con los átomos a los cuales ellos están unidos forman un anillo cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido;

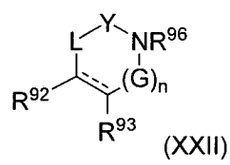
siempre que R^{81}, R^{82}, R^{83} y R^{84} no sean todos hidrógeno.

En algunas realizaciones de la Fórmula (XXII), R^{81}, R^{82}, R^{83} y R^{84} son independientemente hidrógeno, alcoxi, $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, alquilo, $-CH_3$, $-C_2H_5$, $-CH(CH_3)_2$, $-CH_2OH$, halo, cloro, flúor, $-CH_2OCH_3$, -CN, -C(O)NHMe, $-CO_2H$, $-CO_2CH_3$, $-SO_2N(CH_3)_2$, $-NHSO_2CH_3$, $-B(OH)_2$ o $-P(O)(OH)_2$.

Todavía en otras realizaciones de la Fórmula (XXII), se proporcionan compuestos que tienen las estructuras a continuación:



En otra realización de la presente invención, el modificador del ligando del receptor quimiosensorial es un compuesto que tiene una Fórmula de estructura (XXII):



(XXII)

o un tautómero, sal, solvato, y/o éster del mismo, en donde:

cada G es independientemente $-C(R^{94})(R^{95})-$, $-C(O)-$, $-NR^{94}-$ o $-S(O)_2-$;

n es 1, 2 o 3;

siempre que cuando n sea mayor a uno entonces solamente un G es $-C(O)-$, $-S(O)_2-$ o $-NR^{94}-$;

Y es $-C(O)-$, $-C(S)-$ o $-S(O)_2-$;

L es $-C(R^{104})(R^{105})-$, $-O-$, o $-NR^{104}-$;

R^{92} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, $-NO_2$, $-OR^{98}$, $-S(O)_yR^{98}$, $-NR^{98}R^{99}$, $-CONR^{98}R^{99}$, $-CO_2R^{98}$, $-NR^{98}CO_2R^{99}$, $-NR^{98}CONR^{99}R^{100}$, $-NR^{98}CSNR^{99}R^{100}$ o $-NR^{98}C(=NH)NR^{99}R^{100}$, $-SO_2NR^{98}R^{99}$, $-NR^{98}SO_2R^{99}$, $-NR^{98}SO_2NR^{99}R^{100}$, $-B(OR^{98})(OR^{99})$, $-P(O)(OR^{98})(OR^{99})$ o $-P(O)(R^{98})(OR^{99})$;

R^{93} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, $-NO_2$, $-OR^{100}$, $-S(O)_zR^{101}$, $-NR^{101}R^{102}$, $-CONR^{101}R^{102}$, $-CO_2R^{101}$, $-NR^{101}CO_2R^{102}$, $-NR^{101}CONR^{102}R^{103}$, $-NR^{101}CSNR^{102}R^{103}$ o $-NR^{101}C(=NH)NR^{102}R^{103}$, $-SO_2NR^{101}R^{102}$, $-NR^{101}SO_2R^{102}$, $-NR^{101}SO_2NR^{102}R^{103}$, $-B(OR^{101})(OR^{102})$, $-P(O)(OR^{101})(OR^{102})$, $-P(O)(R^{101})(OR^{102})$ o alternativamente, R^{92} y R^{93} conjuntamente con los átomos a los cuales ellos están unidos forman un anillo arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido donde el anillo está opcionalmente fusionado con otro anillo arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido;

y y z son independientemente 0, 1 o 2;

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R^{98} a R^{103} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido o alternativamente, R^{98} y R^{99}, R^{99} y R^{100}, R^{101} y R^{102}, o R^{102} y R^{103} conjuntamente con los átomos a los cuales ellos están unidos forman un anillo cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido;

R^{94} a R^{95} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido o alternativamente, R^{94} y R^{95}, conjuntamente con los átomos a los cuales ellos están unidos forman un anillo cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido;

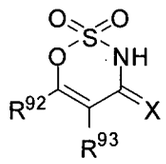
R^{96} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido; y

R^{104} a R^{105} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido o alternativamente, R^{104} y R^{105}, conjuntamente con los átomos a los cuales ellos están unidos forman un anillo cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido.

En algunas realizaciones, cuando L es O, R^{95} es hidrógeno, R^{92} es metilo y el enlace que conecta los átomos de carbono unidos a R^{92} y R^{93} es un enlace doble entonces R^{93} no es hidrógeno.

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En algunas realizaciones de la Fórmula (XXII), se proporciona un compuesto de la fórmula estructural (XXIII):

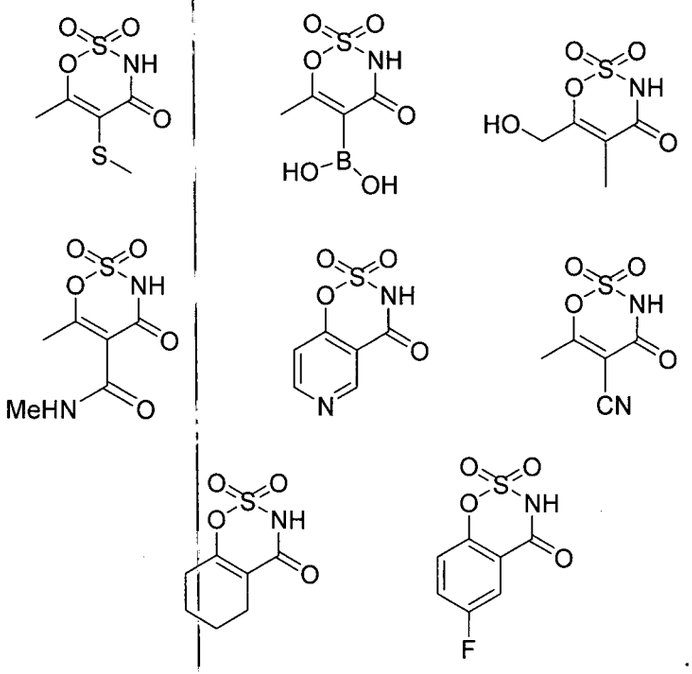


(XXIII)

donde cuando R^{92} es $-CH_3$ entonces R^{93} no es hidrógeno y que ambos R^{92} y R^{93} no son hidrógeno.

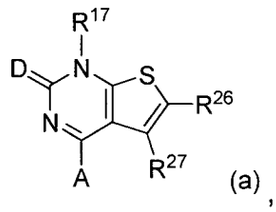
En algunas realizaciones de la Fórmula (XXII), R^{92} y R^{93} son independientemente hidrógeno, $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, alquilo, $-CH_3$, $-C_2H_5$, $-CH(CH_3)_2$, $-CH_2OH$, halo, cloro, flúor, $-CH_2OCH_3$, -CN, $-SCH_3$, -C(O)NHMe, $-CO_2H$, $-CO_2CH_3$, $-SO_2N(CH_3)_2$, $-NHSO_2CH_3$, $-B(OH)_2$ o $-P(O)(OH)_2$. En otras realizaciones, R^{92} y R^{93} conjuntamente con los átomos a los cuales ellos están unidos forman un anillo cicloalquilo, cicloheteroalquilo, arilo o heteroarilo.

En otras realizaciones de la Fórmula (XXII), se proveen compuestos que tienen las estructuras a continuación:

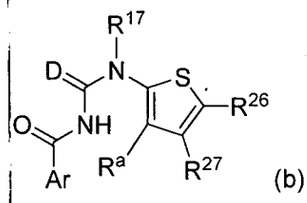


Anteriormente se han descripto en detalle las definiciones y sustituyentes para diversos géneros y subgéneros de los compuestos have presentes. Un experto en la técnica debería comprender que cualquier combinación de las definiciones y sustituyentes descriptos precedentemente no debería resultar en una especie o compuesto inoperable. Por "especie o compuesto inoperable", se denota una estructura de compuesto que viola el principio científico relevante (tal como, por ejemplo, un átomo de carbono que se conecta a más de cuatro enlaces covalentes) o que es tan inestable que la separación del compuesto a partir de una reacción es imposible (tal como, por ejemplo, más de tres grupos carbonilo que se conectan continuamente entre sí).

En una realización, la presente invención proporciona un proceso para preparar un compuesto que tiene la Fórmula estructural (a):


(a),

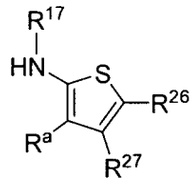
que comprende hacer reaccionar un compuesto que tiene la Fórmula estructural (b)


(b)

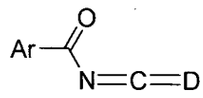
con una base, en donde D es oxígeno o azufre; A es $-NH_2$ u $-OR^b$; R^{17} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, o arilalquilo sustituido; R^{26} y R^{27} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, $-NO_2$, $-OR^{31}$, $-S(O)_hR^{31}$, $-NR^{31}R^{32}$, $-CONR^{31}R^{32}$, $-CO_2R^{31}$, $-SO_2NR^{31}R^{32}$, o $-NR^{31}SO_2R^{32}$; o alternativamente R^{26} y R^{27}, conjuntamente con los átomos a los cuales ellos están unidos, forman un anillo cicloalquilo, cicloalquilo sustituido, heterocicloalquilo, o heterocicloalquilo sustituido; Ar es arilo o arilo sustituido; y R^a es -CN, $-C(O)R^b$, $-C(O)OR^b$, $-C(O)N(R^b)_2$; cada R^b es independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, o heteroarilalquilo sustituido; h es 0, 1 o 2; y R^{31} y R^{32} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido,

arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido; o alternativamente R^{31} y R^{32}, conjuntamente con los átomos a los cuales ellos están unidos, forman un anillo cicloheteroalquilo o cicloheteroalquilo sustituido. Se prefiere que la base sea una base inorgánica, tal como NaOH.

En una realización, el compuesto que tiene la Fórmula estructural (b) se prepara haciendo reaccionar un compuesto que tiene la Fórmula estructural (c):

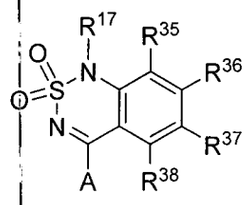


(c), con un compuesto que tiene la Fórmula estructural (d):



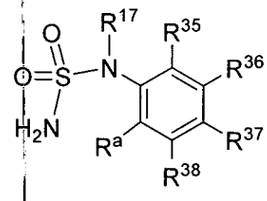
(d). Con preferencia, el grupo Ar precedente es fenilo o fenilo sustituido.

En otra realización, la presente invención proporciona un proceso de preparación de un compuesto que tiene la Fórmula estructural (e):



(e),

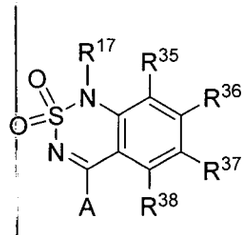
que comprende hacer reaccionar un compuesto que tiene la Fórmula estructural (f)



(f),

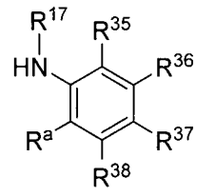
con una base, en donde A es $-NH_2$ u $-OR^b$; R^{17} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, o arilalquilo sustituido; R^{35}, R^{36}, R^{37}, y R^{38} son cada uno independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido, -CN, $-NO_2$, $-OR^{41}$, $-S(O)_kR^{41}$, $-NR^{41}R^{42}$, $-CONR^{41}R^{42}$, $-CO_2R^{41}$, $-SO_2NR^{41}R^{42}$, y $-NR^{41}SO_2R^{42}$; o alternativamente, R^{35} y R^{36}, R^{36} y R^{37}, o R^{37} y R^{38}, conjuntamente con los átomos a los cuales ellos están unidos, forman un anillo cicloalquilo, cicloalquilo sustituido, heterocicloalquilo, o heterocicloalquilo sustituido; R^a es -CN, $-C(O)R^b$, $-C(O)OR^b$, $-C(O)N(R^b)_2$; cada R^b es independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, o heteroarilalquilo sustituido; y R^{41} y R^{42} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido; o alternativamente R^{41} y R^{42}, conjuntamente con los átomos a los cuales ellos están unidos, forman un anillo cicloheteroalquilo o cicloheteroalquilo sustituido. Se prefiere que la base sea una base inorgánica, tal como NaOH.

En otra realización, la presente invención proporciona un proceso de preparación de un compuesto que tiene la Fórmula estructural (e):



(e),

que comprende hacer reaccionar un compuesto que tiene la Fórmula estructural (g)



(g)

con $NH_2S(O)_2NH_2$ o Cl-$S(O)_2$-NH_2 en presencia de una base para proporcionar directamente un compuesto que tiene la Fórmula estructural (e); o alternativamente para proporcionar el compuesto que tiene la Fórmula estructural (f) de la reivindicación 221 el cual se hace reaccionar además con una base para proporcionar un compuesto que tiene la Fórmula estructural (e). Se prefiere que la base sea una base orgánica, tal como DBU.

En general, los compuestos de la presente invención, *por ejemplo*, los compuestos con las fórmulas descriptas en la presente se pueden sintetizar de acuerdo con los procesos descriptos precedentemente y con los siguientes procedimientos y/o esquemas ejemplificativos.

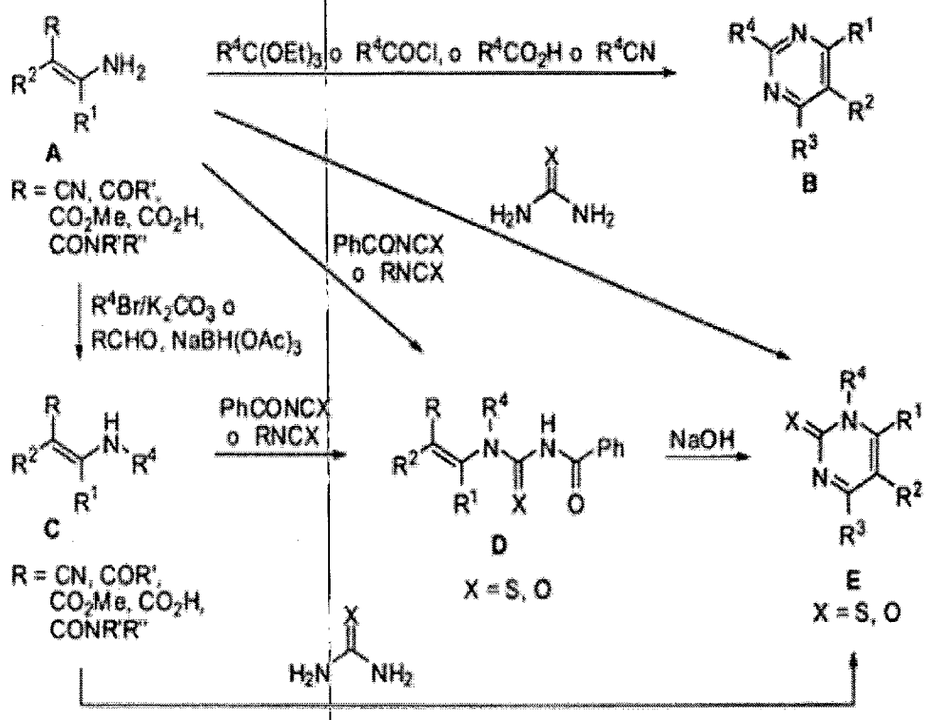
Según se planteó en la presente precedentemente, generalmente se puede formar una sal del compuesto de la presente invención haciendo reaccionar el compuesto con un ácido o base. En una realización, la presente invención proporciona además un método de síntesis para preparar una sal del compuesto que tiene cualquiera de las fórmulas estructurales mencionadas precedentemente a gran escala. El método de síntesis permite la preparación de una gran cantidad de una sal del presente compuesto de modo rápido y económico. El método de síntesis se puede aplicar ya sea en una disposición de laboratorio como en una disposición industrial. Un ejemplo del método de síntesis se describe en detalle como Ejemplo 165 en la presente a continuación.

GSB

En general, los compuestos de la presente invención, *por ejemplo*, los compuestos con las fórmulas descriptas en la presente se pueden sintetizar de acuerdo con los siguientes procedimientos y/o esquemas ejemplificativos.

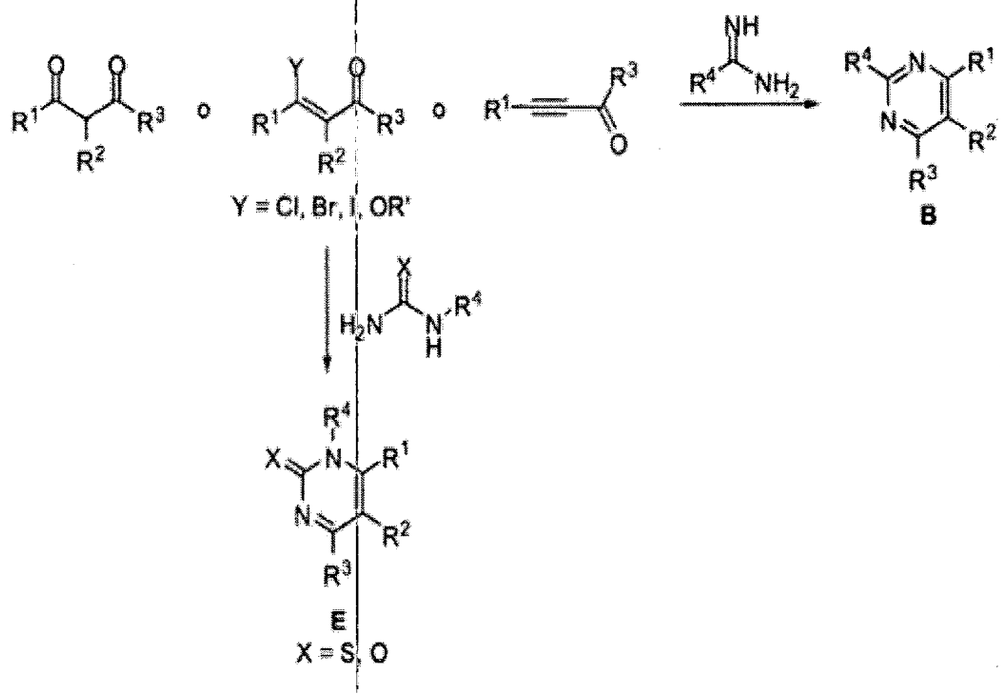
Las pirimidinas **B** que incluyen derivados de pirimidina fusionada tales como quinazolinas y pirido[2,3-d]pirimidinas se sintetizan a partir de los derivados de 2-amino carboxilo, 2-amino cetonas, o 2-amino nitrilos **A** a través de la reacción con los correspondientes derivados de carboxilo según se ilustra en el Esquema 1 (Rad-Moghadam *et al.*, *J. of Heterocyclic Chem.* **2006**, *43*, 913; Roy *et al.*, *J. Org. Chem.* **2006**, *71*, 382; Jung *et al.*, *J. Med. Chem.* **2006**, *49*, 955; Khabnadideh *et al.*, *Bioorg. Med. Chem.* **2005**, *13*, 2637). El grupo amino en el material de partida **A** se puede funcionalizar además a través de la alquilación (Brown *et al.*, *J. Med. Chem.* **1990**, *33*, 1771) o de la aminación reductiva (Uehling *et al.*, *J. Med. Chem.* **2006**, *49*, 2758, *etc.*) para proporcionar los correspondientes derivados de 2-amino carboxilo, 2-amino cetonas o 2-amino nitrilos *N*-monosustituidos **C**. La reacción de acoplamiento de **A** o **C** con iso(tio)cianatos tales como, por ejemplo, benzoiliso(tio)cianatos y la subsiguiente ciclación a través del tratamiento con NaOH proporcionan los derivados de pirimidin-2(1H)-(ti)ona **E** que incluyen, pero no se limitan a, pirimidin-2(1H)-(ti)onas fusionadas tales como los derivados de quinazolin-2(1H)-(ti)ona y pirido[2,3-d]pirimidin-2(1H)-(ti)ona (El-Sherbeny *et al.*, *Med. Chem. Rev.* **2000**, *10*, 122 y las referencias citadas en el mismo; Reddy *et al.*, *Synthetic Commun.* **1988**, *18*, 525; Wilson, *Org. Lett.* **2001**, *3*, 585, y las referencias citadas en el mismo). La cicliación directa de **A** o **C** con (tio)ureas en presencia de NaOH también resulta en la formación de los derivados de pirimidin-2(1H)-(ti)ona **E** (Esquema 1) (Naganawa *et al.*, *Bioorg. Med. Chem.* **2006**, *14*, 7121 y las referencias citadas en el mismo).

Esquema 1



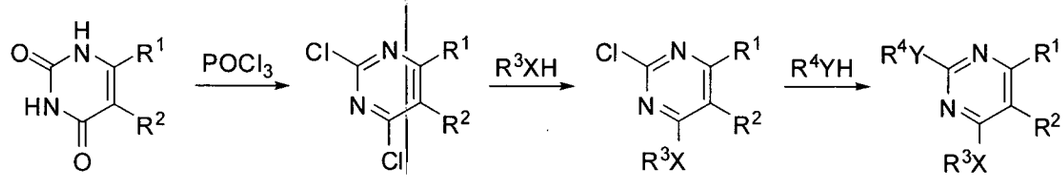
Las pirimidinas **B** y las pirimidin-2(1H)-(ti)onas **E** también se pueden preparar a partir de los correspondientes derivados de 1,3-dicarbonilo y derivados de carbonilo α,β-no saturado a través de la condensación con derivados de (tio)urea, amidinas, o guanidinas según se muestra en el Esquema 2 (Sharma *et al.*, *Eur. J. Med. Chem.* **2006**, *41*, 83, y las referencias citadas en el mismo; Bellur *et al.*, *Tetrahedron* **2006**, *62*, 5426 y las referencias citadas en el mismo; Hauser *et al.*, *J. Org. Chem.* **1953**, *18*, 588).

Esquema 2



Varias pirimidinas y pirimidin-2(1H)-(ti)onas así como también sus derivados de pirimidina y pirimidin-2(1H)-(ti)ona fusionada tales como quinazolinas y quinazolin-2(1H)-onas se pueden sintetizar a partir de los derivados de pirimidin-2,4(1H,3H)-diona así como también de pirimidin-2,4(1H,3H)-dionas fusionadas tales como los derivados de quinazolin-2,4(1H,3H)-diona y pirido[2,3-d]pirimidin-2,4(1H,3H)-diona (Esquema 3). La reacción de los derivados de pirimidin-2,4(1H,3H)-diona con fosgeno o $POCl_3$ proporciona las correspondientes 2,4-dicloropirimidinas (Lee *et al.*, *Synlett.* **2006**, 65 y las referencias citadas en el mismo). Los subsiguientes desplazamientos de los dos cloruros con diversos nucleófilos resultó en la formación de pirimidinas y pirimidin-2(1H)-(ti)onas así como también de derivados de pirimidina y pirimidin-2(1H)-(ti)ona fusionada (Kanuma *et al.*, *Bioorg. & Med. Chem. Lett.* **2005**, *15*, 3853 y las referencias citadas en el mismo; Liu *et al.*, *Bioorg. & Med. Chem. Lett.* **2007**, *17*, 668; Wilson *et al.*, *Bioorg. & Med. Chem.* **2007**, *15*, 77; Boarland *et al.*, *J. Chem. Soc.* **1951**, 1218).

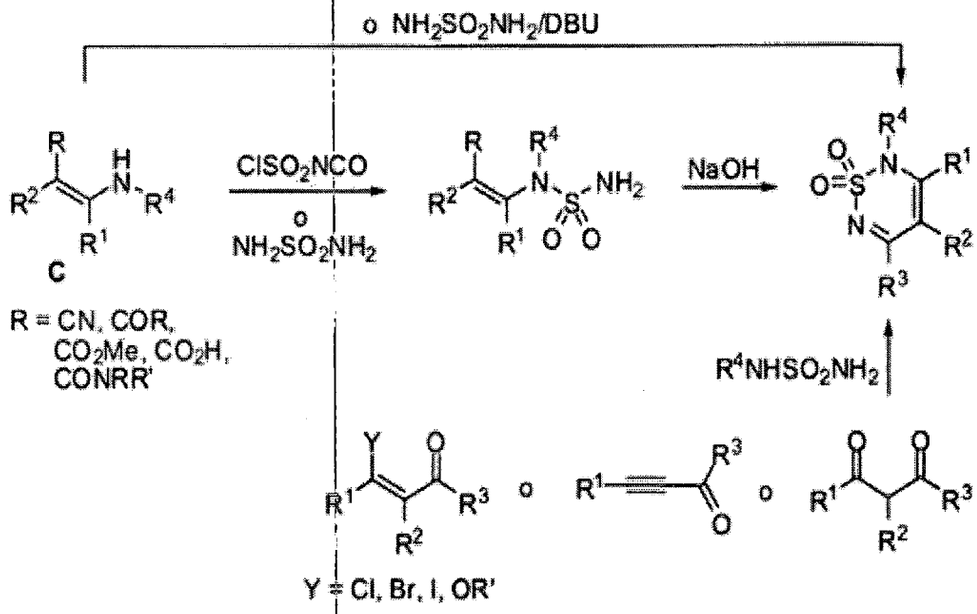
Esquema 3



De modo similar, los [1,2,6]tiadiazin-2,2-dióxidos y los derivados de [1,2,6]tiadiazin-2,2-dióxido fusionado tales como, por ejemplo, 1H-benzo[c][1,2,6]tiadiazin-2,2-dióxidos también se sintetizan a partir de los derivados de 2-amino carboxilo, 2-amino cetonas, o 2-amino nitrilos **A** o **C** (Esquema 4), a través de la reacción con NH_2SO_2Cl (Hirayama *et al.*, *Bioorg. & Med. Chem.* **2002**, *10*, 1509; Kanbe *et al.*, *Bioorg. & Med. Chem. Lett.* **2006**, *16*, 4090 y las referencias citadas en los mismos) o $NH_2SO_2NH_2$ (Maryanoff *et al.*, *J. Med. Chem.* **2006**, *49*, 3496, y las referencias citadas en el mismo) y seguida por ciclación en presencia de NaOH (Goya *et al.*, *Heterocycles*, **1986**, *24*, 3451; Albrecht *et al.*, *J. Org. Chem.* **1979**, *44*, 4191; Goya *et al.*, *Arch. Pharm. (Weinheim)* **1984**, *317*, 777). La condensación de los correspondientes derivados de 1,3-dicarbonilo, derivados de carbonilo α,β-no saturado con los derivados de sulfamida (Esquema 4) también resulta en la formación de los derivados de [1,2,6]tiadiazin-2,2-dióxido (Wright, *J. Org. Chem.* **1964**, *29*, 1905).

Esquema 4

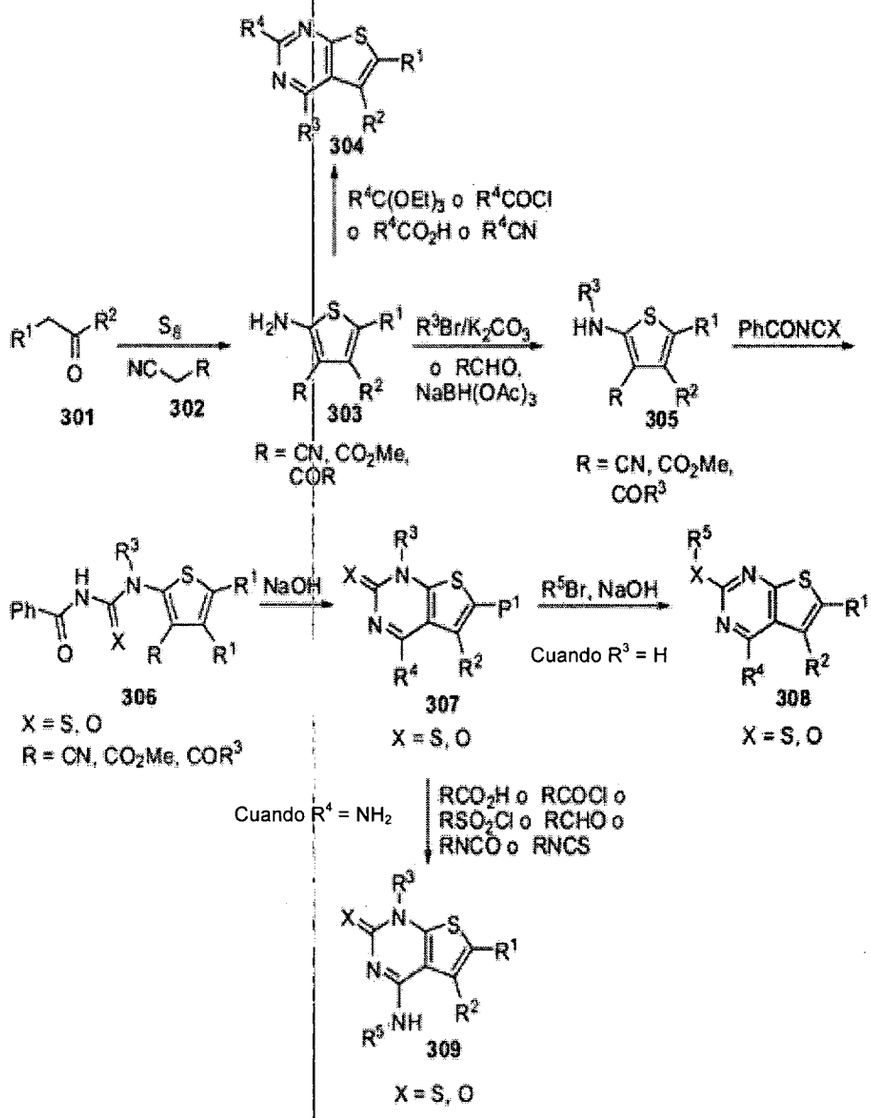
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Los métodos para la síntesis de los derivados de tieno[2,3-d]pirimidina se describen en el Esquema 5. Los derivados de 2-amino tiofeno **303** se sintetizan *a través* de la reacción de Gewald (Chen *et al.*, *Synthetic Communication* **2004**, *34*, 3801 y las referencias citadas en el mismo; Elmegeed *et al.*, *Eur. J. Med. Chem.* **2005**, *40*, 1283 y las referencias citadas en el mismo). El compuesto **303** se puede ciclar con los correspondientes derivados de carboxilo para proporcionar los derivados de tieno[2,3-d]pirimidina **304** (Rad-Moghadam, *J. Heterocyclic Chem.* **2006**, *43*, 913; Seijas *et al.*, *Tetrahedron Lett.* **2000**, *41*, 2215, y las referencias citadas en los mismos; Jung *et al.*, *J. Med. Chem.* **2006**, *49*, 955.).

Esquema 5

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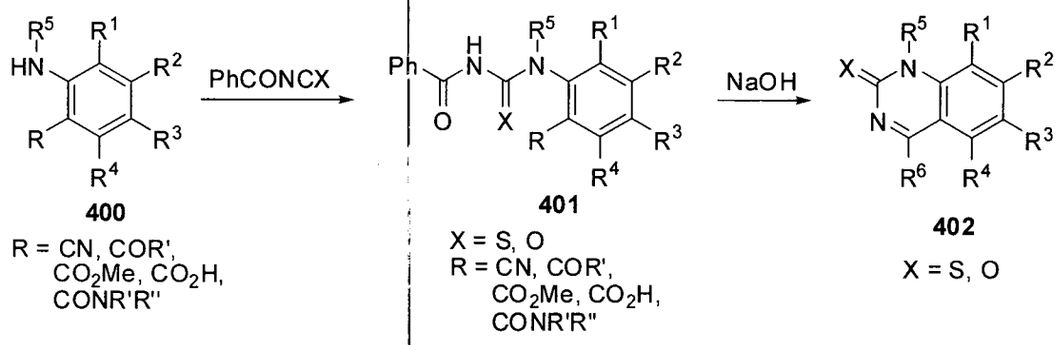


Los derivados de 2-amino tiofeno **303** se pueden alquilar además ya sea a través del tratamiento con R_3Br/K_2CO_3 o con $RCHO/NaBH(OAc)_3$ para proporcionar los derivados de 2-amino tiofeno *N*-alquilados **305** (Brown *et al.*, *J. Med. Chem.* **1990**, *33*, 1771; Uehling *et al.*, *J. Med. Chem.* **2006**, *49*, 2758 y las referencias citadas en los mismos), los cuales luego se hacen reaccionar, por ejemplo, con benzoiliso(tio)cianato para proporcionar los correspondientes derivados de benzoil (tio)urea **306**. Los compuestos **306** se pueden ciclar a través del tratamiento con NaOH para proporcionar los derivados de tieno[2,3-d]pirimidina **7** (El-Sherbeny *et al.*, *Med. Chem. Rev.* **2000**, *10*, 122, y las

referencias citadas en el mismo; Reddy *et al.*, *Synthetic Commun.* **1988**, *18*, 525; Wilson, *Org. Lett.* **2001**, *3*, 585 y las referencias citadas en los mismos). Cuando R^3 = H, los compuestos **307** se pueden hacer reaccionar con R_5Br/NaOH para proporcionar los productos alquilados **8** (Hirota *et al.*, *Bioorg. Med. Chem.* **2003**, *11*, 2715.). Cuando $R^4 = NH_2$, el grupo amino se puede funcionalizar además para proporcionar los productos **309**.

De modo similar, los derivados de quinazolin-2(1H)-ona y quinazolin-2(1H)-tionas **402** se sintetizaron a partir de diversos derivados de ácido 2-aminobenzoico, derivados de 2-aminobenzonitrilo, derivados de 2-aminoacetofenona y derivados de 2-aminobenzamida **400** según se muestra en el Esquema 6. La reacción de acoplamiento de los compuestos **400** con benzoil iso(tio)cianatos conduce a la formación de los correspondientes derivados de benzoil (tio)urea **401**. Su ciclación en presencia de NaOH proporciona los derivados de quinazolin-2(1H)-(ti)ona **402** (El-Sherbeny, *Med. Chem. Rev.* **2000**, *10*, 122 y las referencias citadas en el mismo; Reddy *et al.*, *Synthetic Commun.* **1988**, *18*, 525; Wilson, *Org. Lett.* **2001**, *3*, 585 y las referencias citadas en los mismos).

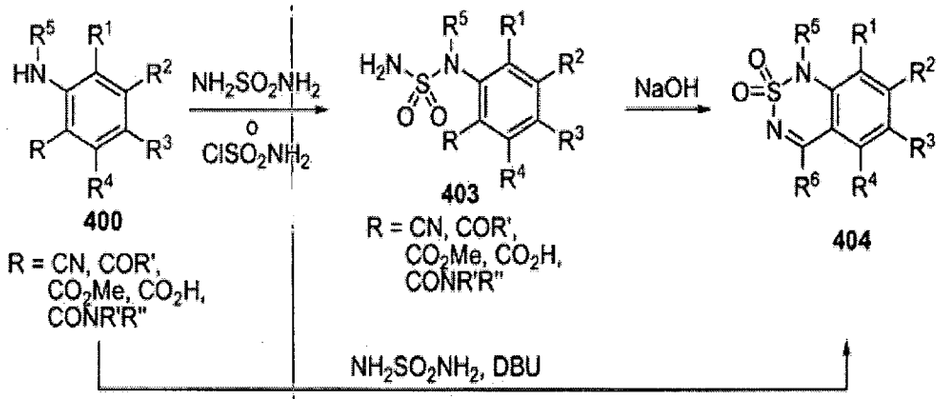
Esquema 6



Los derivados de 1H-benzo[c][1,2,6]tiadiazin-2,2-dióxido **404** se sintetizan a partir de los mismos materiales de partida **400** (Esquema 7) *a través* de sus reacciones con sulfamida o cloruro de sulfamoilo, seguido por la ciclación con

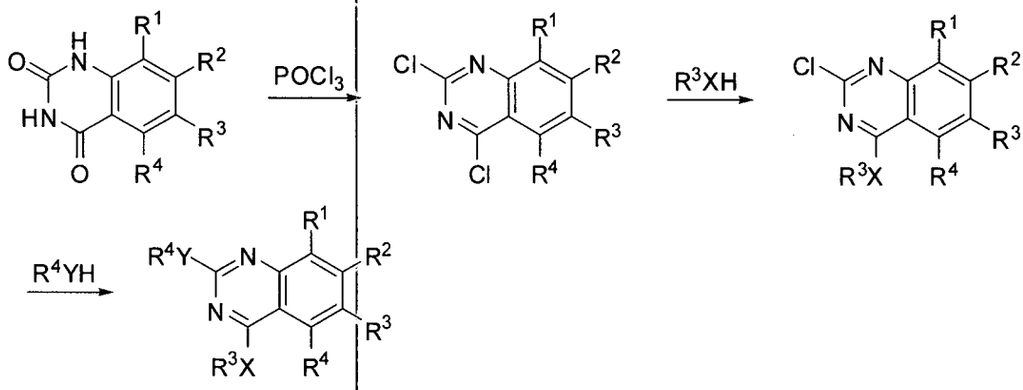
NaOH. La reacción directa de los compuestos **400** con sulfamida en presencia de DBU a temperatura elevada también resultó en la formación de los derivados de 1H-benzo[c][1,2,6]tiadiazin-2,2-dióxido **404** (Maryanoff *et al.*, *J. Med. Chem.* **2006**, *49*, 3496, y las referencias citadas en el mismo).

Esquema 7



Los derivados de quinazolina también se sintetizan a partir de quinazolin-2,4(1H,3H)-dionas (Esquema 8). La reacción de quinazolin-2,4(1H,3H)-dionas con $POCl_3$ proporcionó las correspondientes dicloroquinazolinas (Zunszain *et al.*, *Bioorg. & Med. Chem.* **2005**, *13*, 3681 y las referencias citadas en el mismo). Los subsiguientes desplazamientos de los dos cloruros con diversos nucleófilos resultó en la formación de los derivados de quinazolina (Esquema 8) (Kanuma *et al.*, *Bioorg. & Med. Chem. Lett.* **2005**, *15*, 3853 y las referencias citadas en el mismo; Blackburn, *Bioorg. & Med. Chem. Lett.* **2006**, *16*, 2621).

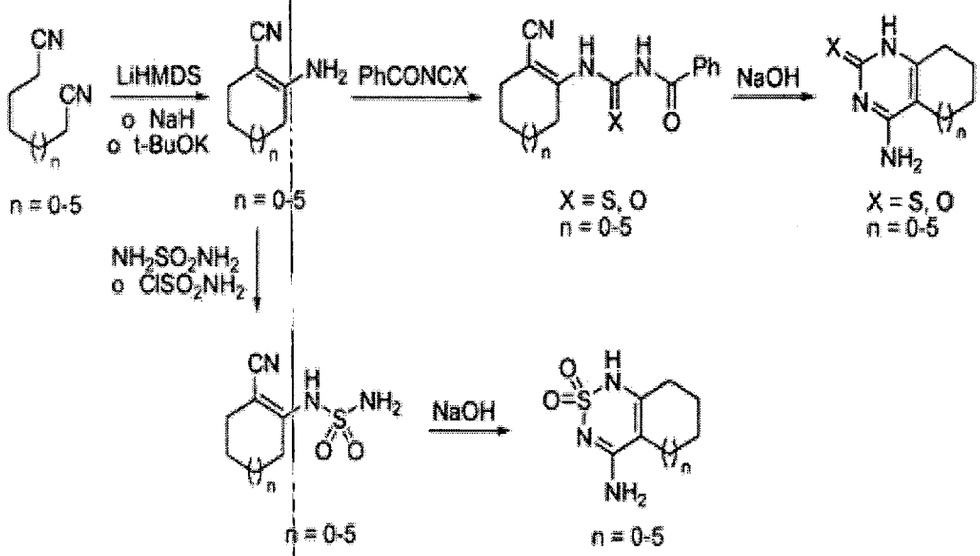
Esquema 8



Los derivados de 4-amino-5,6,7,8-tetrahidroquinazolin-2(1H)-(ti)ona y 4-amino-5,6,7,8-tetrahidro-1H-benzo[c][1,2,6]tiadiazin-2,2-dióxido, así como también los análogos estructurales con diferentes tamaños de anillo, según se muestra en el Esquema 9, generalmente se sintetizan de acuerdo con los métodos descriptos en la presente. La ciclación de Thorpe-Ziegler de dinitrilos en presencia de una base proporciona los derivados de nitrilo β-amino-α,β-no saturado (Winkler *et al.*, *Tetrahedron* **2005**, *61*, 4249; Yoshizawa *et al.*, *Green Chem.* **2002**, *4*, 68, y las referencias citadas en los mismos; Rodriguez-Hahn *et al.*, *Synthetic Commun.* **1984**, *14*, 967, y las referencias citadas en el mismo; Francis *et al.*, *J. Med. Chem.* **1991**, *34*, 2899). Los nitrilos β-amino-α,β-no saturados se pueden hacer reaccionar, por ejemplo, con benzoiliso(tio)cianato y subsiguientemente ciclar a través del tratamiento con NaOH para proporcionar los derivados de 4-amino-5,6,7,8-tetrahidroquinazolin-2(1H)-(ti)ona (El-Sherbeny *et al.*, *Med. Chem. Rev.* **2000**, *10*, 122, y las referencias citadas en el mismo; Reddy *et al.*, *Synthetic Commun.* **1988**, *18*, 525) así como también sus análogos estructurales con diferentes tamaños de anillo (Esquema 9). De modo similar la reacción de los derivados de nitrilo β-amino-α,β-no saturado con cloruro de sulfamoilo, seguida por el tratamiento con NaOH proporciona los derivados de 4-amino-5,6,7,8-tetrahidro-1H-benzo[c][1,2,6]tiadiazin-2,2-dióxido, así como también análogos estructurales con diferentes tamaños de anillo (Esquema 9)

(Hirayama *et al.*, *Bioorg. & Med. Chem.* **2002**, *10*, 1509; Kanbe *et al.*, *Bioorg. & Med. Chem. Lett.* **2006**, *16*, 4090 y las referencias citadas en los mismos).

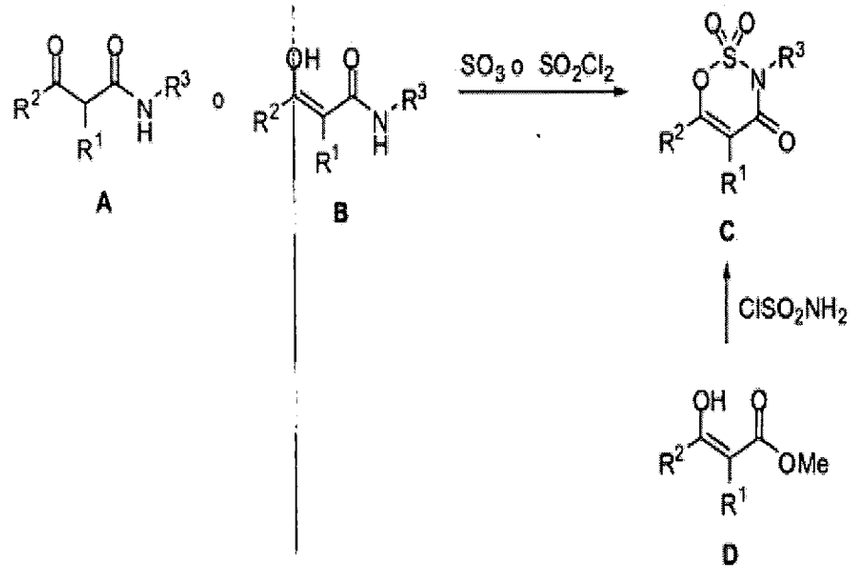
Esquema 9



Los derivados de acesulfame y de acesulfame fusionado **C** tales como los benzo[e][1,2,3]oxatiazin-4(3H)-ona-2,2-dióxidos se pueden sintetizar *a través* de la reacción de los derivados de 1,3-dicarbonilo **A** o de los derivados de 2-hidroxi carboxilo **B** y **D** con SO_3 o $ClSO_2NH_2$, según se describe en el Esquema 10 (Linkies *et al*, *Synthesis* **1990**, 405 y las referencias citadas en el mismo; Ahmed *et al.*, *J. Org. Chem.* **1988**, *53*, 4112; Ahmed *et al.*, *Heterocycles* **1989**, *29*, 1391).

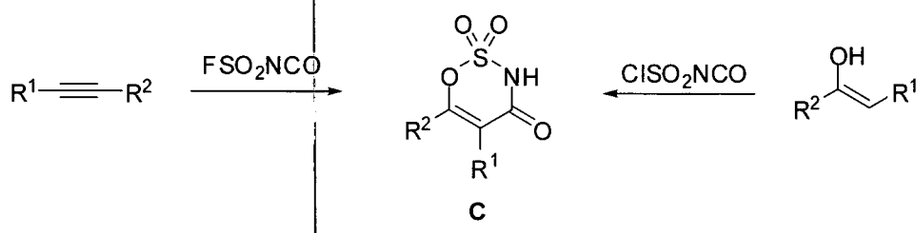
Esquema 10

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Los derivados de acesulfame **C** también se pueden sintetizat *a través de* de la ciclación de alquinos o enoles con FSO_2NCO (Clauss *et al.*, *Tetrahedron Lett.* **1970**, *2*, 119) o $ClSO_2NCO$ (Rasmussen *et al.*, *J. Org. Chem.* **1973**, *38*, 2114; Etter *et al.*, *J. Org. Chem.* **1986**, *51*, 5405; Tripathi *et al.*, *Indian J. Chem. Sect. B* **1987**, *26B*, 1082.) según se muestra en el Esquema 11.

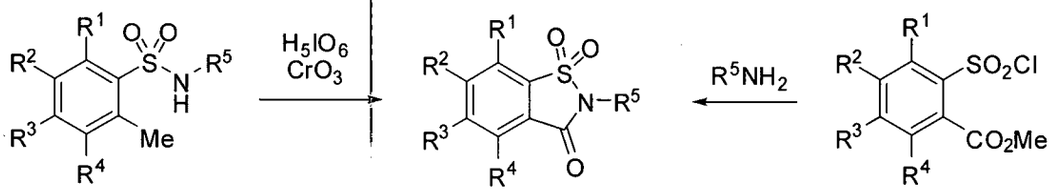
Esquema 11



Los derivados de sacarina se pueden sintetizar a través de la ciclación oxidativa directa de N-alquil-o-metil-arenosulfonamidas según se muestra en el Esquema 12 (Xu *et al.*, *Tetrahedron* **2006**, *62*, 7902 y las referencias citadas en el mismo; Pal *et al.*, *Letters in Drug Design & Discdurantey* **2005**, *2*, 329). La ciclación de los derivados de cloruro de o-carboxil-arenosulfonilo con aminas primarias también puede proporcionar derivados de sacarina (Robinson *et al.*, *Eur. J. Org. Chem.* **2006**, *19*, 4483 y las referencias citadas en el mismo; Yamada

et al., *J. Med. Chem.* **2005**, *48*, 7457 y las referencias citadas en el mismo; Da Settimo *et al.*, *J. Med. Chem.* **2005**, *48*, 6897). Otros derivados de isotiazol-3(2H)-ona-1,1-dióxido fusionado heteroaromáticos también se pueden sintetizar de modo similar.

Esquema 12



De acuerdo con la presente invención, los modificadores de receptores quimiosensoriales o los modificadores de ligandos de receptores quimiosensoriales de la presente invención se pueden utilizar para uno o más métodos de la presente invención, *por ejemplo*, para la modulación de un receptor quimiosensorial y/o de sus ligandos. En general, los modificadores de receptores quimiosensoriales y los modificadores de ligandos de receptores quimiosensoriales de la presente invención se proporcionan en una composición, tal como, *por ejemplo*, una composición ingerible. Según se utiliza en la presente, una "composición ingerible" incluye cualquier sustancia destinada al consumo oral ya sea sola o conjuntamente con otra sustancia. La composición ingerible incluye tanto a "productos alimenticios o de bebidas" como a "productos no comestibles". Por "Productos alimenticios o de bebidas", se denota cualquier producto comestible destinado al consumo por parte de humanos o animales, incluyendo sólidos, semisólidos, o líquidos (por ejemplo, bebidas). El término "productos no comestibles" o "composición no comestible" incluye suplementos, nutracéuticos, productos alimenticios funcionales (por ejemplo, cualquier alimento fresco o procesado del que se afirma que posee propiedades de estimulación de la salud

y/o de prevención de enfermedades más allá de la función nutricional básica de suministro de nutrientes), medicaciones farmacéuticas y sin receta médica, productos de cuidado oral tales como dentífricos y enjuagues bucales, productos cosméticos tales como ungüentos para los labios edulcorados y otros productos de cuidado personal que utilizan sucralosa y/u otros edulcorantes.

La composición ingerible también incluye una composicióm farmacéutica, medicinal o comestible, o alternativamente en una formulación, *por ejemplo*, una formulación farmacéutica o medicinal o una formulación o producto alimenticio o de bebida.

En una realización, los modificadores de receptores quimiosensoriales o los modificadores de ligandos de receptores quimiosensoriales proporcionados por la presente invención se pueden utilizar en concentraciones muy bajas en el orden de unas pocas partes por millón, en combinación con uno o más edulcorantes conocidos, naturales o artificiales, de modo de reducir la concentración del edulcorante conocido requerido para preparar una composición ingerible que tenga el grado de dulzor deseado.

Los edulcorantes artificiales o conocidos normalmente utilizados de uso en dichas combinaciones de edulcorantes incluyen pero no se limitan a los edulcorantes sacáridos comunes, *por ejemplo*, sacarosa, fructosa, glucosa, y las composiciones edulcorantes que comprenden azúcares naturales, tales como jarabe de maíz (que incluye jarabe de maíz de alta fructosa) u otros jarabes o concentrados edulcorantes derivados de fuentes vegetales y frutales naturales, edulcorantes de "alcohol de azúcar" semisintéticos tales como eritritol, isomalt, lactitol, manitol, sorbitol, xilitol, maltodextrina, y similares, y edulcorantes artificiales tales como aspartame, sacarina, acesulfame-K, ciclamato, sucralosa, y alitame. Los edulcorantes también incluyen ácido ciclámico, mogrosida, tagatosa, maltosa, galactosa, manosa, sacarosa, fructosa, lactosa, neotame y otros

derivados de aspartame, glucosa, D-triptófano, glicina, maltitol, lactitol, isomalt, jarabe de glucosa hidrogenado (HGS), hidrolizado de almidón hidrogenado (HSH), esteviosida, rebaudiosida A y otros glucósidos dulces basados en Ste*via*, carrelame y otros edulcorantes basados en guanidina, etc. El término "edulcorantes" también incluye combinaciones de edulcorantes según se describe en la presente.

Los modificadores de receptores quimiosensoriales y modificadores de ligandos de receptores quimiosensoriales de la presente invención también se pueden proporcionar, individualmente o en combinación, con cualquier composición ingerible conocida o descubierta posteriormente. Por ejemplo, la composición ingerible puede consistir en una composición comestible o en una composición no comestible. Por "composición comestible", se denota cualquier composición que se pueda consumir como alimento por parte de humanos o de animales, incluyendo sólidos, gel, pasta, material espumoso, semisólidos, líquidos, o las mezclas de los mismos. Por "composición no comestible", se denota cualquier composición que se encuentre destinada a ser consumida o utilizada por humanos o animales no como alimento, incluyendo sólidos, gel, pasta, material espumoso, semisólidos, líquidos, o las mezclas de los mismos. La composición no comestible incluye, pero no se limita a una composición madicinal, la cual se refiere a una composición no comestible destinada a ser utilizada por humanos o animales para propósitos terapéuticos. Por "animal", se incluye cualquier animal no humano, tal como, por ejemplo, animales de granja y mascotas.

En una realización, los modificadores de receptores quimiosensoriales y los modificadores de ligandos de receptores quimiosensoriales se adicionan a una composición no comestible o producto no comestible, tal como suplementos, nutracéuticos, productos alimenticios funcionales (por ejemplo, cualquier alimento

fresco o procesado del que se afirma que posee propiedades de estimulación de la salud y/o de prevención de enfermedades más allá de la función nutricional básica de suministro de nutrientes), medicaciones farmacéuticas y sin receta médica, productos de cuidado oral tales como dentífricos y enjuagues bucales, productos cosméticos tales como ungüentos para los labios edulcorados y otros productos de cuidado personal que utilizan sucralosa y/u otros edulcorantes.

En general, los productos sin receta médica (OTC, por sus siglas en inglés) y los productos de higiene oral generalmente se refieren a productos para el uso doméstico y/o personal los cuales se pueden vender sin una receta y/o sin una visita a un profesional médico. Los ejemplos de productos OTC incluyen, pero no se limitan a Vitaminas y suplementos dietarios; Analgésicos y/o anestésicos tópicos; Remedios para la tos, el resfrío y las alergias; Remedios antihistamínicos y/o para la alergia; y las combinaciones de los mismos. Las vitaminas y los suplementos dietarios incluyen, pero no se limitan a vitaminas, suplementos dietarios, tónicos/bebidas nutritivas embotelladas, vitaminas específicas para los niños, suplementos dietarios, cualquier otro producto de o que se relaciona con o proporciona nutrición, y las combinaciones de los mismos. Los analgésicos y/o anestésicos tópicos incluyen cualquier crema/ungüento/gel tópico que se utiliza para aliviar molestias y dolores superficiales o profundos, por ejemplo dolor muscular; geles para la dentición; parches con ingredientes analgésicos; y las combinaciones de los mismos. Los remedios para la tos, el resfrío y las alergias incluyen, pero no se limitan a descongestivos, remedios para la tos, preparaciones faríngeas, golosinas medicadas, remedios antihistamínicos y para la tos, el resfrío y la alergia específicos para los niños; y productos de combinación. Los remedios antihistamínicos y/o para la alergia incluyen, pero no se limitan a cualquier cualquier tratamiento sistémico para la fiebre del heno, alergias nasales, picaduras y mordeduras de insectos. Los ejemplos de productos

de higiene oral incluyen, pero no se limitan a bandas de limpieza bucal, pastas dentales, cepillos de dientes, enjuagues bucales/enjuagues dentales, cuidado de la dentadura postiza, refrescantes bucales, blanqueadores dentales domésticos e hilo dental.

En otra realización, los modificadores de receptores quimiosensoriales y los modificadores de ligandos de receptores quimiosensoriales se adicionan a formulaciones o productos alimenticios o de bebidas. Los ejemplos de formulaciones o productos alimenticios o de bebidas incluyen, pero no se limitan a recubrimientos, garrapiñados, o glaseados dulces para cualquier entidad o producto comestible incluidos en la categoría Sopas, en la categoría Alimentos Procesados Secos, en la categoría Bebidas, en la categoría Comidas Preparadas, en la categoría Alimentos Enlatados o Conservados, en la categoría Alimentos Procesados Congelados, en la categoría Alimentos Procesados Enfriados, en la categoría Alimentos "Snack", en la categoría Productos Horneados, en la categoría Golosinas, en la categoría Productos Lácteos, en la categoría Helados, en la categoría Reemplazo de Comidas, en la categoría Pastas y Fideos, y en la categoría Salsas, Aderezos, Condimentos, en la categoría Alimentos para Bebés, y/o en la categoría Alimentos para Untar.

En general, la categoría Sopas se refiere a sopa enlatada/conservada, deshidratada, instantánea, enfriada, UHT y congelada. Para el propósito de esta definición sopa(s) denota un alimento preparado a partir de carne, aves de corral, pescado, vegetales, granos, frutas y otros ingredientes, cocinados en un líquido el cual puede incluir trozos visibles de algunos o de todos estos ingredientes. Éstas pueden ser claras (como un caldo) o espesas (como una sopa "crema"), livianas, en puré o no condensadas y con gran cantidad de vegetales (chunky), listas para servir, semicondensadas o condensadas y se pueden servir calientes o frías, como el primer plato o el plato principal de una comida o como un snack entre

comidas (sorbidas como una bebida). Las sopa puede utilizarse como ingrediente para preparar otros componentes de comidas y puede tener un rango desde caldos (consomé) hasta salsas (sopas en base a crema o queso).

La categoría "Alimentos Culinarios y Deshidratados" usualmente denota: (i) Productos auxiliares para la cocción tales como: polvos, gránulos, pastas, productos líquidos concentrados, que incluyen caldo concentrado, caldo y productos tipo caldo en polvo, tabletas o cubitos comprimidos o en forma granulada, los cuales se venden en forma separada como un producto final o como un ingrediente dentro de un producto, salsas y mezclas para recetas (independientemente de la tecnología); (ii) Productos que brindan soluciones para comidas tales como: sopas deshidratadas y liofilizadas, que incluyen mezclas de sopas deshidratadas, sopas instantáneas deshidratadas, sopas listas para cocinar deshidratadas, preparaciones deshidratadas o ambientales de platos elaborados, comidas y platos de entrada que se sirven una vez que incluyen platos con pastas, papas y arroz; y (iii) Productos de ornamento de comidas tales como: condimentos, marinados, aderezos para ensaladas, glasés para ensaladas, salsas para mojar, apanados, mezclas de pastas para rebozar, alimentos para untar de conservación estable, salsas de barbacoa, mezclas para recetas líquidas, concentrados, salsas o mezclas de salsas, que incluyen mezclas para recetas para ensaladas, que se venden como producto final o como un ingrediente dentro de un producto, ya sea deshidratados, líquidos o congelados.

La categoría Bebidas usualmente denota bebidas, concentrados y mezclas de bebidas, que incluyen pero no se limitan a, bebidas carbonatadas y no carbonatadas, bebidas alcohólicas y no alcohólicas, bebidas listas para consumir, formulaciones concentradas líquidas para preparar bebidas tales como sodas, y mezclas precursoras de bebidas en polvo seco. La categoría Bebidas también incluye a las bebidas alcohólicas, a las bebidas suaves, a las bebidas deportivas,

a las bebidas isotónicas, y a las bebidas calientes. Las bebidas alcohólicas incluyen, pero no se limitan a cerveza, sidra/sidra de pera, FABs, vino, y licores. Las bebidas suaves incluyen, pero no se limitan a carbonatadas, tales como colas y carbonatadas sin cola; jugos de frutas, tales como jugo, néctares, bebidas en jugo y bebidas con sabor a frutas; agua embotellada, que incluye agua carbonatada, agua mineral y agua purificada/de mesa; bebidas funcionales, las cuales pueden ser carbonatadas o destiladas e incluyen bebidas deportivas, energizantes o elíxires; concentrados, tales como concentrados líquidos y en polvo en una medida lista para beber. Las bebidas calientes incluyen, pero no se limitan a café, tal como café recién hecho, instantáneo, y combinado; té, tal como té negro, verde, blanco, oolong, y saborizado; y otras bebidas calientes que incluyen polvos, gránulos, bloques o tabletas en base a sabores, malta o plantas mezclados con leche o agua.

La categoría Alimentos "Snack" generalmente se refiere a cualquier alimento que puede consistir en una comida informal liviana que incluye, pero no se limitan a Snacks y barras de snack dulces y salados. Los ejemplos alimentos "snack" incluyen, pero no se limitan a snacks de frutas, chips/papas fritas, snacks extruidos, chips de tortilla/maíz, rosetas de maíz, rosquillas, nueces y otros snacks dulces y salados. Los ejemplos de barras de snack incluyen, pero no se limitan a barras de granola/muesli, barras del desayuno, barras energizantes, barras frutales y otras barras de snack.

La categoría Productos Horneados generalmente se refiere a cualquier producto comestible cuyo proceso de preparación involucra la exposición al calor o a excesiva luz solar. Los ejemplos de productos horneados incluyen, pero no se limitan a pan, arrollados, galletitas, magdalenas, cereales, masas tostadas, masas, barquillos, tortillas, biscochos, pasteles, rosquillas de pan, tartas, quiches, tortas, cualquier alimento horneado, y cualquier combinación de los mismos.

La categoría Helados generalmente se refiere a postres helados que contienen crema y azúcar y saborizantes. Los ejemplos de helados incluyen, pero no se limitan a: helados de impulso; helados para llevar; yogur congelado y helado artesanal; helados de soja, avena, frijol (por ejemplo, frijol rojo y frijol mungo), y a base de arroz.

La categoría Golosinas generalmente se refiere a productos comestibles que son dulces para el gusto. Los ejemplos de golosinas incluyen, pero no se limitan a caramelos, gelatinas, golosinas de chocolate, golosinas de azúcar, gomas, y similares y cualquier producto de combinación.

La categoría Reemplazo de Comidas generalmente se refiere a cualquier alimento destinado a reemplazar a las comidas normales, particularmente para personas preocupadas por la salud o el estado físico. Los ejemplos de reemplazo de comidas incluyen, pero no se limitan a productos para el control del peso y para la convalecencia.

La categoría Comidas Preparadas generalmente se refiere a cualquier alimento que se pueda servir como comida sin un procesamiento o preparación extensos. La comida preparada incluye productos que han tenido "conocimientos prácticos" culinarios adicionados a ellos por parte del fabricante, resultando en un alto grado de prontitud, terminación y conveniencia. Los ejemplos de comida preparada incluyen, pero no se limitan a comidas preparadas enlatadas/conservadas, congeladas, secas, enfriadas; precocinadas; pizza congelada; pizza enfriada; y ensaladas preparadas y comidas instantáneas.

La categoría Pasta y Fideos incluye cualquier pasta y/o fideos incluyendo, pero sin limitarse a pastas enlatadas, secas y enfriadas/frescas; y fideos naturales, instantáneos, enfriados, congelados y snack.

La categoría Alimentos Enlatados/Conservados incluye, pero no se limita a carne y productos de la carne, pescado/mariscos, vegetales, tomates, frijoles,

frutas, comidas preparadas, sopa, pastas enlatados/conservados, y a otros alimentos enlatados/conservados.

La categoría Alimentos Procesados Congelados incluye, pero no se limita a carne roja procesada, de ave de corral procesada, de pescado/mariscos procesada, sustitutos de la carne, vegetales procesados, papas, productos de panadería, postres, comidas preparadas, pizza, sopa, fideos procesados congelados, y a otros alimentos congelados.

La categoría Alimentos Procesados Secos incluye, pero no se limita a arroz, mezclas para postres, comidas preparadas secas, sopa deshidratada, sopa instantánea, pastas secas, fideos naturales, y fideos instantáneos.

La categoría Alimentos Procesados Enfriados incluye, pero no se limita a carnes procesadas, productos de pescado/mariscos procesados, kits para almuerzos, frutas recién recogidas, comidas preparadas, pizza, ensaladas preparadas, sopa, pastas y fideos frescos.

La categoría Salsas, Aderezos y Condimentos incluye, pero no se limita a purés y pastas de tomate, cubitos de caldo, hierbas y especias, glutamato monosódico (MSG), salsas de mesa, salsas en base a soja, salsas en pasta, salsas húmedas/para cocción, salsas secas/mezclas en polvo, ketchup, mayonesa, mostaza, aderezos para ensaladas, vinagretas, salsas para mojar, productos en salmuera, y otras salsas, aderezos y condimentos.

La categoría Alimentos para Bebés incluye, pero no se limita a fórmulas en base a leche o soja; y alimentos para bebés preparados, secos y otros.

La categoría Aimentos para Untar incluye, pero no se limita a mermeladas y jaleas, miel, alimentos para untar de chocolate, alimentos para untar en base a nuez, y alimentos para untar en base a levadura.

La categoría Productos Lácteos generalmente se refiere a productos comestibles producidos a partir de la leche de un mamífero. Los ejemplos de

productos lácteos incluyen, pero no se limitan a productos de leche bebible, queso, yogur y bebidas de leche amarga, y otros productos lácteos.

A continuación se proporcionan ejemplos adicionales de composiciones comestibles, particularmente de formulaciones o productos alimenticios y de bebidas. Las composiciones comestibles ejemplificativas incluyen una o más golosinas, golosinas de chocolate, tabletas, barritas, líneas uniformes/líneas blandas en bolsas, surtidos en cajas, surtidos en cajas standard, miniaturas envueltas, chocolate de estación, chocolate con juguetes, alfajores, otras golosinas de chocolate, mentas, mentas standard, mentas en polvo, caramelos hervidos, pastillas, gomas, jaleas y chicles, toffees, caramelos y turrones, golosinas medicadas, chupetines, regaliz, otras golosinas de azúcar, goma, goma de mascar, goma azucarada, goma sin azúcar, goma funcional, chicle globo, pan, pan envasado/industrial, pan no envasado/artesanal, masas, tortas, tortas envasadas/industriales, tortas no envasadas/artesanales, galletitas, bizcochos recubiertos con chocolate, bizcochos de sandwich, bizcochos rellenos, galletas y bizcochos sabrosos, sustitutos del pan, cereales para el desayuno, cereales de centeno, cereales familiares para el desayuno, copos, muesli, otros cereales, cereales para el desayuno de los niños, cereales calientes, helado, helado de impulso, helado lácteo de porción única, helado de agua de porción única, helado lácteo en envase múltiple, helado de agua en envase múltiple, helado para llevar, helado lácteo para llevar, postres helados, helado a granel, helado de agua para llevar, yogur congelado, helado artesanal, productos lácteos, leche, leche fresca/pasteurizada, leche fresca/pasteurizada completamente grasa, leche fresca/pasteurizada semidescremada, leche larga vida/uht, lecha larga vida/uht completamente grasa, leche larga vida/uht semidescremada, leche larga vida/uht libre de grasa, leche de cabra, leche condensada/evaporada, leche condensada/evaporada natural, leche saborizada, funcional y otra condensada,

bebidas de leche saborizadas, bebidas de leche saborizadas solamente lácteas, bebidas de leche saborizadas con jugo de frutas, leche de soja, bebidas de leche agria, bebidas lácteas fermentadas, blanqueadores de café, leche en polvo, bebidas de leche en polvo saborizadas, crema, queso, queso procesado, queso procesado untable, queso procesado no untable, queso no procesado, queso no procesado untable, queso duro, queso duro envasado, queso duro no envasado, yogur, yogur natural, yogur saborizado, yogur con frutas, yogur probiótico, yogur bebible, yogur bebible regular, yogur bebible probiótico, postres enfriados y de almacenamiento estable, postres en base a lácteos, postres en base a soja, snacks enfriados, queso blanco y requesón, queso blanco y requesón naturales, queso blanco y requesón saborizados, queso blanco y requesón sabrosos, snacks dulces y sabrosos, snacks de frutas, chips/papas fritas, snacks extruidos, chips de tortilla/maíz, rosetas de maíz, rosquillas, nueces, otros snacks dulces y salados, barras de snack, barras del desayuno, barras energizantes, barras frutales, otras barras de snack, productos de reemplazo de comidas, productos para el control del peso, bebidas para la convalescencia, comidas preparadas, comidas preparadas enlatadas, comidas preparadas congeladas, comidas preparadas secas, comidas preparadas enfriadas, precocinadas, pizza congelada, pizza enfriada, sopa, sopa enlatada, sopa deshidratada, sopa instantánea, sopa enfriada, sopa caliente, sopa congelada, pastas, pastas enlatadas, pastas secas, pastas enfriadas/frescas, fideos, fideos naturales, fideos instantáneos, fideos instantáneos para taza/recipiente, fideos instantáneos en saquitos, fideos enfriados, fideos para comidas instantáneas, alimentos enlatados, productos de carne y carne enlatados, pescado/mariscos enlatados, vegetales enlatados, tomates enlatados, frijoles enlatados, fruta enlatada, comidas preparadas enlatadas, sopa enlatada, pastas enlatadas, otros alimentos enlatados, alimentos congelados, carne roja procesada congelada, de aves de corral procesada

congelada, pescado/mariscos procesados congelados, vegetales procesados congelados, sustitutos de la carne congelados, papas congeladas, papas fritas cocidas en horno, otros productos con papas cocidos en horno, papas congeladas no para horno, productos de panadería congelados, postres congelados, comidas preparadas congeladas, pizza congelada, sopa congelada, fideos congelados, otros alimentos congelados, alimentos secos, mezclas para postres, comidas preparadas secas, sopa deshidratada, sopa instantánea, pastas secas, fideos naturales, fideos instantáneos, fideos instantáneos para taza/recipiente, fideos instantáneos en saquitos, alimentos enfriados, carnes procesadas enfriadas, productos de pescado/mariscos enfriados, pescado procesado enfriado, pescado recubierto enfriado, pescado ahumado enfriado, kit para el almuerzo enfriado, comidas preparadas enfriadas, pizza enfriada, sopa enfriada, pastas enfriadas/frescas, fideos enfriados, aceites y grasas, aceite de oliva, aceite vegetal y de semillas, grasas para cocción, manteca, margarina, aceites y grasas untables, aceites y grasas untables funcionales, salsas, aderezos y condimentos, pastas y purés de tomate, cubitos de consomé, cubitos de caldo, gránulos de caldillo, fondos y mercadería líquidos, hierbas y especias, salsas fermentadas, salsas en base a soja, salsas para pastas, salsas húmedas, salsas secas/mezclas en polvo, ketchup, mayonesa, mayonesa regular, mostaza, aderezos para ensaladas, aderezos para ensaladas regulares, aderezos para ensaladas con bajas grasas, vinagretas, salsas para mojar, productos en salmuera, otras salsas, aderezos y condimentos, álimentos para bebés, fórmula láctea, fórmula láctea standard, fórmula láctea posterior, fórmula láctea para niños pequeños, fórmula láctea hipoalergénica, alimentos para bebés preparados, alimentos para bebés secos, otros alimentos para bebés, alimentos para untar, jaleas y mermeladas, miel, alimentos para untar de chocolate, alimentos para untar en base a nueces, y alimentos para untar en base a levadura. Las composiciones comestibles

ejemplificativas también incluyen golosinas, productos de panadería, helados, productos lácteos, snacks dulces y salados, barras de snack, productos de reemplazo de comidas, comidas preparadas, sopas, pastas, fideos, alimentos enlatados, alimentos congelados, alimentos secos, alimentos enfriados, aceites y grasas, alimentos para bebés, o alimentos para unatr o una mezcla de los mismos. Las composiciones comestibles ejemplificativas también incluyen cereales para el desayuno, bebidas dulces o composiciones concentradas sólidas o líquidas para preparar bebidas, idealmente de modo de permitir la reducción en la concentración de edulcorantes artificiales, o edulcorantes sacáridos conocidos previamente.

Típicamente se adicionará al producto comestible o medicinal al menos una cantidad de modulador del receptor quimiosensorial, una cantidad de modulador del ligando del receptor quimiosensorial, una cantidad de modulador del sabor dulce, una cantidad de agente saborizante dulce, o una cantidad de mejorador del sabor dulce de uno o más de los modificadores de receptores quimiosensoriales o modificadores de ligandos de receptores quimiosensoriales de la presente invención, opcionalmente en presencia de edulcorantes conocidos, *por ejemplo*, de modo que el producto comestible o medicinal de sabor dulce modificado tenga un mayor sabor dulce en comparación con el producto comestible o medicinal preparado sin los modificadores de la presente invención, según lo determinen los seres humanos o los animales en general, o en el caso del ensayo de las formulaciones, según lo determinen una mayoría de un panel de al menos ocho degustadores humanos, a través de procedimientos normalmente conocidos en el área.

Por supuesto que la concentración de agente saborizante dulce necesaria para modular o mejorar el sabor de la composición o producto comestible o medicinal dependerá de muchas variables, que incluyen el tipo específico de

composición comestible y sus diversos otros ingredientes, especialmente la presencia de otros agentes saborizantes dulces conocidos y las concentraciones de los mismos, la variabilidad genética natural y las preferencias individuales y las condiciones de salud de los diversos seres humanos que prueben las composiciones, y el efecto subjetivo del compuesto particular en el sabor de dichos compuestos quimiosensoriales.

Una aplicación de los modificadores de receptores quimiosensoriales y/o modificadores de ligandos de receptores quimiosensoriales consiste en modular (induciendo, mejorando o inhibiendo) las propiedades del sabor dulce o de otro sabor de otros estimulantes del sabor dulce naturales o sintéticos, y las composiciones comestibles elaboradas a partir de ellos. Típicamente se requerirá un rango amplio pero también un rango bajo de concentraciones de los compuestos o entidades de la presente invención, *es decir*, desde aproximadamente 0,001 ppm hasta 100 ppm, o rangos alternativos más estrechos desde aproximadamente 0,1 ppm hasta aproximadamente 10 ppm, desde aproximadamente 0,01 ppm hasta aproximadamente 30 ppm, desde aproximadamente 0,05 ppm hasta aproximadamente 10 ppm, desde aproximadamente 0,01 ppm hasta aproximadamente 5 ppm, o desde aproximadamente 0,02 ppm hasta aproximadamente 2 ppm, o desde aproximadamente 0,01 ppm hasta aproximadamente 1 ppm.

Aún en otra realización, el modificador del receptor quimiosensorial y el modificador del ligando del receptor quimiosensorial de la presente invención se pueden proporcionar en composiciones farmacéuticas que contienen una cantidad terapéuticamente efectiva de uno o más compuestos de la presente invención, con preferencia en forma purificada, conjuntamente con una cantidad adecuada de un vehículo farmacéuticamente aceptable, de modo de proporcionar la forma para la apropiada administración a un paciente.

Cuando se administran a un paciente, los compuestos de la presente invención y los vehículos farmacéuticamente aceptables son con preferencia estériles. Cuando un compuesto de la presente invención se administra por vía intravenosa, el vehículo preferido el el agua. También se pueden emplear soluciones salinas y soluciones de glicerol y dextrosa acuosas como vehículos líquidos, particularmente para las soluciones inyectables. Los vehículos farmacéuticos adecuados también incluyen excipientes tales como almidón, glucosa, lactosa, sacarosa, gelatina, malta, arroz, harina, tiza, gel de sílice, estearato de sodio, monoestearato de glicerol, talco, cloruro de sodio, leche descremada en polvo, glicerol, propileno, glicol, agua, etanol y similares. Si se desea, las composiciones farmacéuticas presentes, también pueden contener pequeñas cantidades de agentes humectantes o emulsionantes, o agentes que regulan el pH. Además, se puede utilizar agentes auxiliares, estabilizantes, espesantes, lubricantes y colorantes.

Las composiciones farmacéuticas que comprenden un compuesto de la presente invención se pueden elaborar a través de procesos de mezclado, disolución, granulación, elaboración de grageas, reducción de sustancias a polvo, emulsión, encapsulación, atrapamiento o liofilización convencionales. Las composiciones farmacéuticas se pueden formular de manera convencional utilizando uno o más portadores, diluyentes, excipientes o auxiliares fisiológicamente aceptables, los cuales facilitan el procesamiento de los compuestos de la presente invención en preparaciones que s epueden utilizar farmacéuticamente. La formulación apropiada depende de la vía de administración seleccionada.

Las composiciones farmacéuticas presentes pueden tomar la forma de soluciones, suspensiones, emulsiones, comprimidos, píldoras, pelets, cápsulas, líquidos que contienen cápsulas, polvos, formulaciones de liberación sostenida,

supositorios, emulsiones, aerosoles, sprays, suspensiones, o cualquier otra forma adecuada para el uso. En algunas realizaciones, el vehículo farmacéuticamente aceptable es una cápsula (véase *por ejemplo*, Grosswald *et al.*, Patente Estadounidense No. 5.698.155). Otros ejemplos de vehículos farmacéuticos adecuados se han descripto en la técnica (véase Remington: The Science and Practice of Pharmacy, Philadelphia College of Pharmacy and Science, 20ma Edición, 2000).

Para la administración tópica un compuesto de la presente invención se puede formular como soluciones, geles, ungüentos, cremas, suspensiones, *etc.* según se conoce bien en la técnica.

Las formulaciones sistémicas incluyen aquéllas diseñadas para la administración a través de inyección, *por ejemplo*, de inyección subcutánea, intravenosa, intramuscular, intratecal o intraperitoneal, así como también aquéllas diseñadas para la administración transdérmica, transmucosal, oral o pulmonar. Las formulaciones sistémicas se pueden elaborar en combinación con un agente activo adicional que mejore la depuración mucociliar de la mucosidad de las vías respiratorias o que reduzca la viscosidad de la mucosidad. Estos agentes activos incluyen, pero no se limitan a, bloqueadores del canal de sodio, antibióticos, N-acetil cisteína, homocisteína y fosfolípidos.

En algunas realizaciones, los compuestos de la presente invención se formulan de acuerdo con procedimientos de rutina como una composición farmacéutica adaptada para la administración intravenosa a seres humanos. Típicamente, los compuestos de la presente invención para la administración intravenosa consisten en soluciones en buffer acuoso isotónico estéril. Para inyección, un compuesto de la presente invención se puede formular en soluciones acuosas, con preferencia en buffers fisiológicamente compatibles tales como solución de Hank, solución de Ringer, o buffer salino fisiológico. La solución

puede contener agentes de formulación tales como agentes de suspensión, estabilizantes y/o dispersantes. Cuando sea necesario, las composiciones farmacéuticas también pueden incluir un agente solubilizante.

Las composiciones farmacéuticas para la administración intravenosa opcionalmente pueden incluir un anestésico local tal como lignocaína para aliviar el dolor en el sitio de la inyección. Generalmente, los ingredientes se suministran ya sea en forma separada o mezclados conjuntamente en forma de dosificación unitaria, por ejemplo, como un polvo liofilizado o un concentrado libre de agua en un recipiente herméticamente sellado tal como una ampolla o sachet que indica la cantidad de agente activo. Cuando el compuesto de la presente invención se administra a través de infusión, éste puede dispensarse, por ejemplo, con una botella para infusión que contiene salina o agua de grado farmacéutico estéril. Cuando el compuesto de la presente invención se administra a través de inyección, se puede proporcionar una ampolla de agua estéril para inyección o salina de modo que los ingredientes se puedan mezclar antes de la administración.

Para la administración transmucosal, se utilizan en la formulación penetrantes apropiados para la barrera a ser permeada. Dichos penetrantes son generalmente conocidos en la técnica.

Las composiciones farmacéuticas para el suministro oral se pueden encontrar en forma de comprimidos, grageas, suspensiones acuosas u oleosas, gránulos, polvos, emulsiones, cápsulas, jarabes, o elíxires, por ejemplo. Las composiciones farmacéuticas que se administran por vía oral pueden contener uno o más agentes opcionales, por ejemplo, agentes edulcorantes tales como fructosa, aspartame o sacarina; agentes saborizantes tales como menta, aceite de gaulteria, o agentes colorantes de cereza y agentes conservantes, para proporcionar una preparación farmacéuticamente sabrosa.

Más aún, cuando se encuentran en forma de comprimidos o píldoras, las composiciones farmacéuticas pueden estar recubiertas para retrasar la desintegración y la absorción en el tracto gastrointestinal, proporcionando por lo tanto una acción sostenida durante un período de tiempo extenso. Las membranas permeables de modo selectivo que rodean un compuesto conductor osmóticamente activo también son adecuadas para los compuestos de la presente invención que se administran por vía oral. En estas últimas plataformas, el fluido del ambiente que rodea a la cápsula es absorbido por el compuesto conductor, el cual se hincha para desplazar al agente o composición de agente a través de una abertura. Estas plataformas de suministro pueden proporcionar un perfil de suministro de orden esencialmente cero en oposición a los mayores perfiles de las formulaciones de liberación inmediata. También se puede utilizar un material de retraso del tiempo tal como monoestearato de glicerol o estearato de glicerol. Las composiciones orales pueden incluir vehículos standard tales como manitol, lactosa, almidón, estearato de magnesio, sacarina sódica, celulosa, carbonato de magnesio, *etc.* Dichos vehículos son con preferencia de grado farmacéutico.

Para las preparaciones líquidas orales tales como, por ejemplo, suspensiones, elíxires y soluciones, los portadores, excipientes o diluyentes adecuados incluyen agua, salina, alquilenglicoles (*por ejemplo*, propilen glicol), polialquilen glicoles (*por ejemplo*, polietilen glicol) aceites, alcoholes, buffers ligeramente acídicos entre pH 4 y pH 6 (*por ejemplo*, acetato, citrato, ascorbato a entre aproximadamente 5,0 mM hasta aproximadamente 50,0 mM) *etc.* Además, se pueden adicionar agentes saborizantes, conservantes, agentes colrantes, sales biliares, acilcarnitinas y similares.

Para la administración bucal, las composiciones farmacéuticas pueden tomar la forma de comprimidos, grageas, *etc.* formulados de manera convencional.

Las formulaciones de drogas líquidas adecuadas para utilizar con nebulizadores y dispositivos de spray líquido y dispositivos de aerosol EHD típicamente incluirán un compuesto de la presente invención con un vehículo farmacéuticamente aceptable. Con preferencia, el vehículo farmacéuticamente aceptable es un líquido tal como alcohol, agua, polietilen glicol o un perfluorcarbono. Opcionalmente, se puede adicionar otro material para alterar las propiedades del aerosol de la solución o suspensión de los compuestos de la invención. Con preferencia, este material es líquido tal como un alcohol, glicol, poliglicol o un ácido graso. Otros métodos de formulación de suspensiones o soluciones de drogas líquidas adecuadas para utilizar en dispositivos de aerosol son conocidos por aquéllos expertos en la técnica (véase, *por ejemplo*, Biesalski, Patente Estadounidense No. 5.112.598; Biesalski, Patente Estadounidense No. 5.556.611).

Un compuesto de la presente invención también se puede formular en composiciones farmacéuticas rectales o vaginales tales como supositorios o enemas de retención, *por ejemplo*, que contienen bases de supositorios convencionales tales como manteca de cacao u otros glicéridos.

Además de las formulaciones descriptas previamente, un compuesto de la presente invención también se puede formular como una preparación de depósito. Dichas formulaciones de acción prolongada se pueden administrar mediante implantación (por ejemplo, por vía subcutánea o intramuscular) o mediante inyección intramuscula. De este modo, por ejemplo, un compuesto de la presente invención se puede formular con materiales poliméricos o hidrofóbicos (por ejemplo, como una emulsión en un aceite aceptable) o resinas de intercambio

iónico adecuados, o como derivados moderadamente solubles, por ejemplo, como una sal moderadamente soluble.

Cuando un compuesto de la presente invención es acídico, éste puede estar incluido en cualquiera de las formulaciones descriptas precedentemente como el ácido libre, una sal farmacéuticamente aceptable, un solvato o hidrato. Las sales farmacéuticamente aceptables sustancialmente mantienen la actividad del ácido libre, se pueden preparar a través de la reacción con bases y tienden a ser más solubles en solventes acuosos y en otros solventes próticos que la correspondiente forma de ácido libre.

Un compuesto de la presente invención, y/o una composición farmacéutica del mismo, generalmente se utilizarán en una cantidad efectiva para lograr el propósito pretendido. Para el uso para tratar o prevenir enfermedades o trastornos los compuestos de la presente invención y/o las composiciones farmacéuticas de los mismos, se administran o aplican en una cantidad terapéuticamente efectiva.

La cantidad de un compuesto de la presente invención que será efectiva en el tratamiento de un trastorno o afección particular descriptos en la presente dependerá de la naturaleza del trastorno o afección y se puede determinar mediante métodos clínicos standard conocidos en la técnica. Además, opcionalmente pueden emplearse ensayos *in vitro* o *in vivo* para auxiliar a identificar rangos de dosificación óptimos. Por supuesto que la cantidad de un compuesto de la presente invención administrada dependerá, entre otros factores, del sujeto que se está tratando, del peso del sujeto, de la gravedad de la aflicción, de la manera de administración y del criterio del médico a cargo.

Por ejemplo, la dosificación se puede suministrar en una composición farmacéutica mediante una administración única, mediante aplicaciones múltiples o liberación controlada. En algunas realizaciones, los compuestos de la presente invención se suministran mediante administración de liberación sostenida oral. La

dosificación se puede repetir de modo intermitente, se puede proporcionar sola o en combinación con otras drogas y puede continuar siempre que sea requerida para el tratamiento efectivo del trastorno o estado de enfermedad.

Los rangos de dosificación adecuados para la administración oral dependen de la potencia, pero generalmente se encuentran entre aproximadamente 0,001 mg hasta aproximadamente 200 mg de un compuesto de la presente invención por kilogramo de peso corporal. Los rangos de dosificación se pueden determinar fácilmente a través de métodos conocidos por el experto de pericia corriente en la técnica.

Los rangos de dosificación adecuados para la administración intravenosa (i.v.) son de aproximadamente 0,01 mg hasta aproximadamente 100 mg por kilogramo de peso corporal. Los rangos de dosificación adecuados para la administración intranasal son generalmente de aproximadamente 0,01 mg/kg de peso corporal hasta aproximadamente 1 mg/kg de peso corporal. Los supositorios generalmente contienen aproximadamente 0,01 miligramo hasta aproximadamente 50 miligramos de un compuesto de la presente invención por kilogramo de peso corporal y comprenden el ingrediente activo en el rango de aproximadamente 0,5% hasta aproximadamente 10% en peso. Las dosificaciones recomendadas para la administración intradérmica, intramuscular, intraperitoneal, subcutánea, epidural, sublingual o intracerebral se encuentran en el rango de aproximadamente 0,001 mg hasta aproximadamente 200 mg por kilogramo de peso corporal. Las dosis efectivas se pueden extrapolar a partir de curvas de respuesta a la dosis derivadas de sistemas de ensayo de modelos animales o *in vitro*. Dichos sistemas y modelos animales son muy conocidos en la técnica.

Con preferencia, una dosis terapéuticamente efectiva de un compuesto de la presente invención descripto en la presente proporcionará un beneficio terapéutico sin provocar una toxicidad sustancial. La toxicidad de los compuestos

de la presente invención se puede determinar utilizando procedimientos farmacéuticos standard y puede ser determinada fácilmente por la pericia del experto. La relación de dosis entre el efecto tóxico y el terapéutico es el índice terapéutico. Un compuesto de la presente invención con preferencia presentará índices terapéuticos particularmente altos en el tratamiento de enfermedades y trastornos. La dosificación de un compuesto de la presente invención descripto en la presente con preferencia se encontrará dentro de un rango de concentraciones en circulación que incluyen una dosis efectiva con poca toxicidad o sin toxicidad.

En ciertas realizaciones de la presente invención, los compuestos de la presente invención y/o las composiciones farmacéuticas de los mismos se pueden utilizar en terapia de combinación con al menos uno de otros agentes. El compuesto de la presente invención y/o la composición farmacéutica del mismo y el otro agente pueden actuar de modo aditivo o, con más preferencia, sinérgico. En algunas realizaciones, un compuesto de la presente invención y/o una composición farmacéutica del mismo se administran en forma concurrente con la administración de otro agente, el cual puede ser parte de la misma composición farmacéutica como el compuesto de la presente invención o una composición farmacéutica diferente. En otras realizaciones, una composición farmacéutica de la presente invención se administra antes de o luego de la administración de otro agente.

Todavía en otra realización, los modificadores de receptores quimiosensoriales y los modificadores de ligandos de receptores quimiosensoriales de la presente invención y/o las composiciones farmacéuticas de los mismos se pueden utilizar de modo ventajoso en medicina humana.

Cuando se utilizan para tratar y/o prevenir enfermedades o trastornos, los compuestos y/o las composiciones farmacéuticas descriptos en la presente se pueden administrar o aplicar en forma individual, o en combinación con otros

agentes. Los compuestos y/o composiciones farmacéuticas de los mismos también se pueden administrar o aplicar en forma individual, en combinación con otros agentes activos.

En la presente se proporcionan métodos de tratamiento y profilaxis a través de la administración a un paciente de una cantidad terapéuticamente efectiva de un compuesto descripto en la presente y/o de una composición farmacéutica del mismo. El paciente puede ser un animal, con más preferencia, un mamífero y aún con más con preferencia, un humano.

En un ejemplo, los compuestos descriptos en la presente y/o las composiciones farmacéuticas de los mismos, se administran por vía oral. Los compuestos de la presente invención y/o las composiciones farmacéuticas de los mismos también se pueden administrar a través de cualquier otra vía conveniente, por ejemplo, mediante infusión o inyección de bolo, mediante absorción a través de los recubrimientos epiteliales o mucocutáneos (*por ejemplo*, mucosas orales, mucosas rectales e intestinales, *etc.*). La administración puede ser sistémica o local. Se conocen diversos sistemas de suministro, (*por ejemplo*, encapsulación en liposomas, micropartículas, microcápsulas, cápsulas, *etc.*) que se pueden utilizar para administrar un compuesto descripto en la presente y/o una composición farmacéutica del mismo. Los métodos de administración incluyen, pero no se limitan a, intradérmica, intramuscular, intraperitoneal, intravenosa, subcutánea, intranasal, epidural, oral, sublingual, intranasal, intracerebral, intravaginal, transdérmica, rectal, mediante inhalación, o por vía tópica, particularmente a los oídos, nariz, ojos, o piel. El modo de administración preferido se deja a criterio del médico y dependerá en parte del sitio de la afección médica. En la mayoría de los casos, la administración resultará en la libración de los compuestos y/o composiciones farmacéuticas de los mismos hacia la corriente sanguínea.

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En otro ejemplo, puede ser deseable administrar uno o más compuestos de la presente invención y/o composiciones farmacéuticas de los mismos localmente al área que necesita tratamiento. Ello se puede lograr, por ejemplo, y no a modo de limitación, a través de una infusión local durante la cirugía, aplicación tópica, *por ejemplo*, en conjunción con un recubrimiento para heridas luego de la cirugía, mediante inyección, por medio de un catéter, por medio de un supositorio, o por medio de un implante, siendo dicho implante de un material poroso, no poroso, o gelatinoso, incluyendo membranas, tales como fibras, o membranas silásticas. En una realización, la administración puede ser a través de la inyección directa en el sitio (o sitio originario) de la afección.

Aún en otro ejemplo, puede ser deseable introducir uno o más compuestos de la presente invención y/o composiciones farmacéuticas de los mismos dentro del sistema nervioso central a través de cualquier vía adecuada, que incluye la inyección intraventricular, intratecal y epidural. La inyección intraventricular puede ser facilitada por un catéter intraventricular, por ejemplo, adosado a un reservorio, tal como un reservorio Ommaya.

Un compuesto de la presente invención y/o una composición farmacéutica del mismo también se pueden administrar directamente al púlmon mediante inhalación. Para la administración mediante inhalación, un compuesto de la presente invención y/o una composición farmacéutica del mismo se pueden suministrar de modo conveniente al pulmón a través de una cantidad de dispositivos diferentes. Por ejemplo, un Inhalador de Dosis Medida ("MDI", por sus siglas en inglés), el cual utiliza envases que contienen un propelente de baja ebullición adecuado, (*por ejemplo*, diclorodifluormetano, triclorofluormetano, diclorotetrafluoretano, dióxido de carbono o cualquier otro gas adecuado) se puede usar para suministrar los compuestos de la presente invención y/o las composiciones farmacéuticas de los mismos directamente al pulmón.

Alternativamente, se puede usar un dispositivo de Inhalador de Polvo Seco ("DPI", por sus siglas en inglés) para administrar un compuesto de la invención y/o una composición farmacéutica del mismo al pulmón. Los dispositivos de DPI típicamente utilizan un mecanismo tal como una ráfaga de gas para crear una nube de polvo seco dentro de un recipiente, que luego puede ser inhalada por el paciente. Los dispositivos de DPI también son muy conocidos en la técnica. Una variación popular consiste en el sistema de DPI de dosis múltiple ("MDDPI", por sus siglas en inglés), el cual permite el suministro de más de una dosis terapáutica. Por ejemplo, las cápsulas y cartuchos de gelatina para utilizar en un inhalador o insuflador se pueden formular conteniendo una mezcla en polvo de un compuesto de la presente invención y una base en polvo adecuada tal como lactosa o almidón para estos sistemas.

Otro tipo de dispositivo que se puede utilizar para suministrar un compuesto de la presente invención y/o una composición farmacéutica del mismo al pulmón consiste en un dispositivo de spray líquido suministrado, por ejemplo, por Aradigm Corporation, Hayward, CA. Los sistemas de spray líquido utilizan orificios de boquilla extremadamente pequeños para dispersar como aerosol formulaciones de drogas líquidas que luego pueden ser inhaladas directamente hacia el pulmón.

Aún en otro ejemplo, se utiliza un nebulizador para suministrar un compuesto de la presente invención y/o una composición farmacéutica del mismo al pulmón. Los nebulizadores crean aerosoles a partir de formulaciones de drogas líquidas utilizando, por ejemplo, energía ultrasónica para formar partículas finas que pueden ser fácilmente inhaladas (véase *por ejemplo*, Verschoyle *et al.*, *British J. Cancer*, **1999**, 80, Suppl. 2, 96). Los ejemplos de nebulizadores incluyen los dispositivos suministrados por Sheffield Pharmaceuticals, Inc (Véase, Armer *et al.*, Patente Estadounidense No. 5.954.047; van der Linden *et al.*, Patente

Estadounidense No. 5.950.619; van der Linden *et al.*, Patente Estadounidense No. 5.970.974), y Batelle Pulmonary Therapeutics, Columbus, OH.

Aún en otro ejemplo, se utiliza un dispositivo de aerosol electrohidrodinámico ("EHD", por sus siglas en inglés) para suministrar un compuesto de la presente invención y/o una composición farmacéutica del mismo al pulmón. Los dispositivos de aerosol EHD usan energía eléctrica para dispersar como aerosol soluciones o suspensiones de drogas líquidas (véase *por ejemplo*, Noakes *et al.*, Patente Estadounidense No. 4.765.539). Las propiedades electroquímicas de la formulación pueden ser parámetros importantes de optimización cuando se suministra un compuesto de la presente invención y/o una composición farmacéutica del mismo al pulmón con un dispositivo de aerosol EHD y dicha optimización habitualmente se lleva a cabo por un experto en la técnica. Los dispositivos de aerosol EHD pueden suministrar los compuestos al pulmón de modo más eficiente que las otras tecnologías de suministro pulmonar.

Aún en otro ejemplo, los compuestos de la presente invención y/o las composiciones farmacéuticas de los mismos se pueden suministrar en una vesícula, en particular un liposoma (Langer, **1990**, *Science* 249:1527-1533; Treat *et al.*, in "Liposomes in the Therapy of Infectious Disease and Cancer," Lopez-Berestein and Fidler (eds.), Liss, Nueva York, págs. 353-365 (1989); *véase* generalmente "Liposomes in the Therapy of Infectious Disease and Cancer," Lopez-Berestein and Fidler (eds.), Liss, Nueva York, págs. 353-365 (1989)).

Aún en otro ejemplo, los compuestos de la presente invención y/o las composiciones farmacéuticas de los mismos se pueden suministrar a través de sistemas de liberación sostenida, con preferencia sistemas de liberación sostenida oral. En una realización, se puede utilizar una bomba (véase, Langer, *supra*, Sefton, **1987**, *CRC Crit. Ref. Biomed Eng.* 14:201; Saudek *et al.*, **1989**, *N. Engl. J Med.* 321:574).

Aún en otro ejemplo, se pueden utilizar materiales poliméricos (*véase* "Medical Applications of Controlled Release," Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); "Controlled Drug Bioavailability," Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, Nueva York (1984); Langer *et al.*, **1983**, *J Macromol. Sci. Rev. Macromol Chem.* 23:61; *véase también* Levy *et al.*, **1985**, *Science* 228: 190; During *et al.*, **1989**, *Ann. Neurol.* 25:351; Howard *et al.*, **1989**, *J. Neurosurg.* 71:105).

Todavía en otras realizaciones, se utilizan materiales poliméricos para el suministro de liberación sostenida oral. Los polímeros preferidos incluyen carboximetilcelulosa, hidroxipropilcelulosa, hidroxipropilmetilcelulosa e hidroxietilcelulosa de sodio (con más preferencia, hidroxipropil metilcelulosa). Se han descripto otros éteres de celulosa preferidos (Alderman, *Int. J. Pharm. Tech. & Prod. Mfr.*, **1984**, 5(3) 1-9). Los factores que afectan la liberación de drogas son muy conocidos por el experto y se han descripto en la técnica (Bamba *et al.*, *Int. J. Pharm.*, **1979**, 2, 307).

Aún en otro ejemplo, se pueden utilizar preparaciones recubiertas entéricas para la administración de liberación sostenida oral. Los materiales de recubrimiento preferidos incluyen polímeros con una solubilidad que depende del pH (*es decir*, liberación controlada por el pH), polímeros con una velocidad de hinchamiento, disolución o erosión baja o que depende del pH, (*es decir*, liberación de tiempo controlado), polímeros que son degradados por enzimas (*es decir*, liberación controlada por enzimas) y polímeros que forman capas firmes que se destruyen mediante un aumento en la presión (*es decir*, liberación controlada por la presión).

Todavía en otro ejemplo, se utilizan sistemas de suministro osmótico para la administración de liberación sostenida oral (Verma *et al.*, *Drug Dev. Ind. Pharm.*, **2000**, 26:695-708). Aún en otras realizaciones, se utilizan dispositivos

osmóticos OROS™ para los dispositivos de suministro de liberación sostenida oral (Theeuwes *et al.*, Patente Estadounidense No. 3.845.770; Theeuwes *et al.*, Patente Estadounidense No. 3.916.899).

Todavía en otro ejemplo, un sistema de liberación controlada se puede colocar cercano al objetivo de los compuestos y/o composiciones farmacéuticas de la invención, requiriendo solamente de este modo una fracción de la dosis sistémica (Véase, *por ejemplo*, Goodson, en "Medical Applications of Controlled Release," *supra,* vol. 2, págs. 115-138 (1984). También se pueden utilizar otros sistemas de liberación controlada planteados en Langer, **1990**, *Science* 249:1527-1533.

Habiendo ahora generalmente descripto la invención, la misma se comprenderá más fácilmente mediante la referencia a los siguientes ejemplos, los cuales se proporcionan a modo de ilustración y no están destinados a ser limitativos. Se comprende se pueden efectuar diversas modificaciones y cambios a las realizaciones ejemplificativas descriptas en la presente sin apartarse del espíritu y alcance de la invención.

EJEMPLOS

EXPERIMENTO 1: Modelación e Identificación de Potenciales Mejoradotes de Ligandos de Receptores Quimiosensoriales

Procedimiento general

Los procedimientos generales para identificar un potencial mejorador del ligando del receptor quimiosensorial se sintetizan como sigue.

1. Se construye un modelo de la estructura del dominio Venus atrapamoscas de T1R2

2. Se ensambla un ligando del receptor quimiosensorial, *por ejemplo*, un edulcorante dentro del sitio activo de la estructura del dominio Venus atrapamoscas de T1R2, con o sin T1R3 presente

3. Se ensambla un mejorador del ligando del receptor quimiosensorial, *por ejemplo*, un mejorador dulce dentro del sitio activo en presencia del ligando del receptor quimiosensorial, *por ejemplo*, el edulcorante

4. Se selecciona un mejorador del ligando del receptor quimiosensorial, *por ejemplo*, un candidato de mejorador dulce en base a dos criterios: a) éste se adapta al sitio activo en el modelo, y b) éste forma interacciones productivas con el dominio Venus atrapamoscas de T1R2 y con el ligando del receptor quimiosensorial, *por ejemplo*, el edulcorante. Las interacciones pueden ser van der Waals, ocultamiento de grupos atómicos o átomos hidrofóbicos, enlaces hidrógeno, interacciones de agrupamientos de anillos, o interacciones electrostáticas de unión en puente de sales. Los residuos clave para dichas interacciones incluyen los residuos bisagra, los residuos "pinza" (pincer"), de sitio activo cercano, *por ejemplo*, los residuos de interacción descriptos en la presente invención. Los candidatos no se encuentran limitados a adaptarse por completo dentro del sitio activo, puesto que éste está abierto y los candidatos a mejorador del ligando del receptor quimiosensorial se pueden extender más allá del sitio activo siempre que ellos se extiendan parcialmente hacia él.

Modelo de la estructura

Un modelo de la estructura del dominio Venus atrapamoscas de T1R2 puede provenir de las estructuras cristalinas de T1R2 o de T1R2 en complejo con T1R3. Los dominios se pueden encontrar en forma abierta o cerrada, y pueden o pueden no ser APO o contener un ligando. Alternativamente se puede construir un modelo de la estructura del dominio Venus atrapamoscas de T1R2 utilizando métodos de modelación por homología standard que usan estructuras cristalinas de dominios Venus atrapamoscas disponibles tales como los dominios Venus atrapamoscas del receptor mGluR como plantillas para construir el modelo.

Un ejemplo de un procedimiento para construir dicho modelo consiste en utilizar el software comercial Homology o Modeller de Accelrys Corporation que se encuentra bien documentado en la literatura y disponible en el comercio. Además se pueden explorar conformaciones alternativas del modelo utilizando técnicas de mecánica molecular adicionales que pueden incluir pero no limitarse a análisis en modo normal para explorar el movimiento relativo de los lóbulos del modelo, técnicas de generación de lazos para generar conformaciones alternativas de lazos en el modelo, o simulaciones de Monte Carlo y/o de dinámica molecular.

Ensamble

Un ligando del receptor quimiosensorial, *por ejemplo*, *un edulcorante se ensambló* primero dentro del sitio activo de T1R2. Su postura modelada dentro del sitio activo se seleccionó por su capacidad para formar productivas interacciones de van der Waals, de agrupamientos de anillos, enlaces hidrógeno, y/o unión en puente de sales con los residuos de interacción dentro del sitio activo del dominio Venus atrapamoscas de T1R2.

Un candidato a modificador del ligando del receptor quimiosensorial, *por ejemplo*, un mejorador dulce luego se *ensambló* dentro del sitio activo en presencia del ligando, *por ejemplo*, el edulcorante descripto en el párrafo previo. Su postura activa y su calidad de candidato a potencial modificador del ligando del receptor quimiosensorial, *por ejemplo*, mejorador dulce se basaron en su capacidad para formar interacciones productivas en forma de interacciones de van der Waals, de agrupamientos de anillos, enlaces hidrógeno, y/o unión en puente de sales con los residuos de interacción descriptos en la presente invención, con los residuos adicionales del dominio T1R2, y opcionalmente con el ligando del receptor quimiosensorial, *por ejemplo*, el edulcorante colocado en el sitio activo según se describió precedentemente.

Candidatos a Modificadores de Ligandos de Receptores Quimiosensoriales

Una molécula se consideró un candidato si ésta se pudo ensamblar dentro del sitio activo en presencia de un ligando del receptor quimiosensorial, *por ejemplo*, un edulcorante, formando interacciones productivas con los residuos de interacción descriptos en la presente invención. Definimos dos espacios dentro del sitio activo: un primer espacio ocupado por un ligando del receptor quimiosensorial, *por ejemplo*, un edulcorante, y un segundo espacio ocupado por un modificador del ligando del receptor quimiosensorial, *por ejemplo*, un mejorador. Los resultados de modelación y mutagénesis establecieron residuos clave que se consideraron probables para cubrir estos espacios para el ligando del receptor quimiosensorial, *por ejemplo*, edulcorantes y modificadores de ligandos de receptores quimiosensoriales, *por ejemplo*, mejoradores dulces. En el contexto del estudio, "residuo que cubre el espacio" significó que el residuo tenía átomos de cadena lateral y/o de estructura principal que se ubicaron de modo que ellos pudieran interactuar potencialmente con átomos del ligando del receptor quimiosensorial, *por ejemplo*, un edulcorante (espacio #1) y/o modificador del ligando del receptor quimiosensorial, *por ejemplo*, mejorador dulce (espacio #2). Mientras que el ligando del receptor quimiosensorial, *por ejemplo*, un edulcorante y el modificador del ligando del receptor quimiosensorial, *por ejemplo*, un mejorador dulce por sí mismos no pueden ocupar el mismo espacio, sus correspondientes espacios se pueden superponer debido a la capacidad de los residuos para ponerse en contacto tanto con el ligando del receptor quimiosensorial, *por ejemplo*, un edulcorante como con el modificador del ligando del receptor quimiosensorial, *por ejemplo*, un mejorador dulce, debido a la flexibilidad de la proteína, debido a la flexibilidad del ligando, y debido al potencial para múltiples modos de unión para un ligando del receptor quimiosensorial, *por ejemplo*, un edulcorante o un modificador del ligando del receptor quimiosensorial,

por ejemplo, un mejorador dulce. La información acerca de los residuos importantes que cubren el espacio #1 y el espacio #2 provino de modelación y docking y de mutagénesis dirigida a un sitio.

Se considera que los residuos bisagra se encuentran asociados con el primer espacio (espacio #1). Hemos descubierto que uno de los espacios ocupados por un ligando del receptor quimiosensorial, *por ejemplo*, un edulcorante se encuentra parcialmente cubierto por residuos denominados residuos bisagra en la presente. Muchos dominios Venus atrapamoscas se han cristalizado con agonistas incluyendo mGluR1, mGluR2, y mGluR3 que muestran interacciones que forman agonistas con residuos homólogos a aquéllos identificados en la presente para T1R2. Muchos ligandos de receptores quimiosensoriales, *por ejemplo*, edulcorantes ensamblados al modelo de T1R2 se pueden ensamblar a esta región. Nuestra mutagénesis dirigida a un sitio también proporciona una fuerte evidencia para respaldar el descubrimiento de que los *residuos bisagra* o residuos espacialmente adyacentes al mismo constituyen residuos clave para la activación de un receptor quimiosensorial, *por ejemplo*, un receptor relacionado con T1R2. Dado que los ligandos de receptores quimiosensoriales, *por ejemplo*, los edulcorantes varían de tamaño, existen residuos adicionales que cubren este primer espacio para los residuos más grandes donde la lista de estos residuos adicionales depende, parcialmente del tamaño del ligando del receptor quimiosensorial, *por ejemplo*, del edulcorante.

Se considera que los residuos pinza se encuentran asociados con el segundo espacio (espacio #2). Los dominios Venus atrapamoscas se conocen por efectuar la transición de un estado "abierto" a un estado "cerrado" en la unión a agonistas. El dominio atrapamoscas está compuesto por dos lóbulos a los que normalmente se hace referencia en la literatura como el lóbulo superior y el lóbulo inferior. En el estado "abierto" los lóbulos se encuentran separados, mientras que

en el estado "cerrado" los lóbulos experimentan un movimiento relativo que une al lóbulo superior e inferior. Además de la estabilización directa del estado cerrado de T1R2 por el agonista, nuestro estudio de modelación ha demostrado que existe una estabilización adicional del estado cerrado a través de las interacciones de los residuos en el lóbulo superior con los correspondientes residuos en el lóbulo inferior que en la presente se denominan "residuos pinza". Hemos descubierto que un sitio de interacción, *por ejemplo*, un espacio de interacción para un modificador del ligando del receptor quimiosensorial, *por ejemplo*, un mejorador dulce es el espacio que se encuentra parcialmente cubierto por estos residuos pinza, puesto que las interacciones adicionales en esta región pueden estabilizar además la forma cerrada, forma agonizada del dominio Venus atrapamoscas. Nuestro estudio de mutagénesis dirigida a un sitio también proporciona evidencia que respalda el descubrimiento de que los residuos pinza y los residuos espacialmente adyacentes a ellos constituyen residuos clave asociados con la modulación del ligando del receptor quimiosensorial, *por ejemplo*, la actividad de mejoramiento del ligando.

El primer y el segundo espacio se pueden intercambiar. En el planteo precedente el modificador del receptor quimiosensorial, *por ejemplo*, un edulcorante se une a la bisagra mientras que el modificador del ligando del receptor quimiosensorial, *por ejemplo*, un mejorador dulce se une a la región pinza. Ello es sólo un ejemplo y no debería interpretarse en forma restrictiva. Por ejemplo, nuestro estudio de modelación y docking también ha demostrado que un probable modo de unión para la sacarina como un agonista (edulcorante) involucra la unión a la región pinza. Dicho resultado fue además respaldado por nuestra mutagénesis dirigida a un sitio. Con un modificador del receptor quimiosensorial, *por ejemplo*, un edulcorante unido a la región pinza existe la oportunidad de la estabilización adicional de la forma cerrada del dominio Venus

atrapamoscas a través de la unión de un modificador del ligando del receptor quimiosensorial, *por ejemplo*, un mejorador dulce a la región bisagra.

Definiciones Procedimentales.

1. Ensamble.

El ensamble generalmente se considera como el proceso de traducción y rotación de la molécula candidata relativa a un receptor quimiosensorial, *por ejemplo*, el modelo estructural T1R2 mientras se regulan simultáneamente los ángulos torsionales internos de la molécula candidata para que adaptar la molécula candidata dentro del sitio activo del receptor quimiosensorial, *por ejemplo*, el modelo estructural T1R2. Las posturas de la molécula candidata molécula (posiciones, orientaciones relativas, y torsiones internas) se seleccionan en base a si la molécula se adapta al sitio activo, y a si la molécula puede formar productivas interacciones de van der Waals, enlaces hidrógeno, interacciones de agrupamientos de anillos, e interacciones de unión en puente de sales con los residuos del sitio activo y con el ligando del receptor quimiosensorial, *por ejemplo*, un edulcorante. Se pueden identificar los residuos clave. Un candidato se considera más probable si éste interactúa con grupos de residuos en el sitio activo como la región bisagra, el sitio activo cercano, los residuos pinza, y la totalidad del sitio activo. Éste también se considera más probable si forma interacciones directas con un ligando del receptor quimiosensorial, *por ejemplo*, un edulcorante.

2. Modelación por Homología

La Modelación por Homología generalmente se considera como el proceso de construcción de un modelo del dominio Venus atrapamoscas de un receptor quimiosensorial, *por ejemplo*, T1R2 a partir de su secuencia de aminoácidos y a partir de las coordenadas tridimensionales de una o más proteínas del dominio Venus atrapamoscas homólogas. La Modelación por Homología se puede llevar a cabo utilizando métodos standard bien descriptos en the literatura y disponibles

en software comercial tal como el programa Homology o Modeler de Accelrys Corporation. Se utilizaron modelos en base a estructuras de formas abiertas y cerradas determinadas experimentalmente, así como también la animación de modelos utilizando análisis en modo normal, para definir los residuos pinza planteados precedentemente.

Ilustraciones Ejemplificativas de Estudios de Modelación

Las Figuras 5 a 10 ilustran espacios de interacción y residuos asociados con uno de nuestros estudios de modelación molecular.

EXPERIMENTO 2: Estudio de Mutagénesis para la Identificación del Modificador del Ligando del Receptor Quimiosensorial: Mejorador

En nuestras solicitudes de patentes previas (Publicación Internacional No. WO07047988 y Publicación Internacional No. WO070104709), describimos un método que utiliza receptores quiméricos del sabor umami quiméricos de humano-rata para efectuar un mapeo de los sitios de unión de los estimulantes del sabor dulce y umami. Nuestros datos demostraron que una cantidad de edulcorantes, incluyendo sacarosa, fructosa, arspartame, neotame, D-triptófano (D-Trp), Acesulfame K, sacarina y dulcina, todos interactúan con el dominio Venus atrapamoscas (VFT) de T1R2, mientras que los estimulantes del sabor umami, incluyendo L-glutamato, inosin-5'-monofosfato (IMP), y, guanosin-5'-monofosfato (GMP), todos interactúan con el dominio Venus atrapamoscas de T1R1.

Bajo la guía de la modelación molecular, llevamos a cabo la mutagénesis dirigida a un sitio en el VFT de T1R2 humano. La mutagénesis se realizó utilizando el método basado en PCR de rutina. Se transfectaron temporalmente mutantes de T1R2 humano en células HEK293 conjuntamente con el ADNc de tipo salvaje de T1R3 humano, y las células transfectadas se caracterizaron utilizando una máquina FLIPR automatizada o un sistema de captación de imágenes de calcio según se describe en nuestras solicitudes de patentes

previas. Con el objeto de controlar la expresión de la membrana plasmática, el plegamiento de proteínas y otros factores que podrían contribuir a los cambios en la del actividad receptor, utilizamos 2 edulcorantes que interactúan con otros dominios del receptor dulce humano como controles positivos. Los 2 edulcorantes de control fueron el ciclamato y el compuesto X (Senomyx). Se sabe a partir de nuestros datos previos que el ciclamato interactúa con el dominio transmembrana de T1R3 humano, mientras que el compuesto X interactúa con el dominio transmembrana de T1R2 humano.

Los datos de la mutagénesis para una cantidad de edulcorantes se sintetizan en las siguientes tablas. En base a los datos, concluimos en que 6 residuos (S40, S144, S165, Y103, D142, P277) son decisivos para la interacción con esos edulcorantes.

Datos de mutagénesis en FLIPR

	Aspartame (15 Mm)	D-Trp (20 mM)	Fructosa (200 mM)	Sacarosa (200 mM)	Sucralosa (3,2 mM)	Ciclamato (80 mM)	S3819 (25 µM)
WT	+++	+++	+++	+++	+++	+++	+++
V384F	++	++	++	++	++	+++	+++
V384A	++	++	++	++	++	+++	+++
E382A	+	++	+	+	++	++	++
S165I	-	-	+	+	++	++	++
D278A	++	++	++	+	-	+++	+++
K65A	++	++	+	+	+	++	++
S165A	+++	++	++	++	++	++	+++
I67A	+++	+++	+++	+++	+++	+++	+++
N143A	+++	++	++	++	+++	+++	+++
S303A	+++	+++	++	++	++	+++	+++
Q328A	+++	+++	+++	+++	+++	+++	+++
T184A	+++	++	+++	+++	+++	+++	+++
T242A	+++	++	++	++	++	+++	+++
L279A	+++	+++	++	++	++	++	+++
T326A	++	++	++	++	++	++	++

Datos de mutagénesis en captación de imágenes de calcio

	Aspartame (15 mM)	D-Trp (20 mM)	Fructosa (20 mM)	Sacarosa (200 mM)	Sucralosa (3,2 mM)	Ciclamato (80 mM)	S3819 (25 µM)
WT	++	++	++	++	++	++	++
I167A	+	+	+	+	+	+	+
Y103A	-	+	+	+	-	+	+

D278A	+	+	+	+	-	++	++
D307A	+	+	-	-	+	+	+
E302A	-	+	+	+	+	+	+
S165I	-	-	+	+	+	+	+
S40A	-	-	-	-	-	+	+
D142A	-	-	-	-	-	+	+
R383A	-	-	-	-	-	-	+
A305F	-	-	-	-	-	-	+
Y215A	-	-	-	-	-	-	-
D142I	-	-	-	-	-	-	-

Mutaciones adicionales en R383

	Aspartame (15 mM)	Neotame (80 µM)	Sacarosa (200 mM)	Sucralosa (3,2 mM)	D-Trp (20 mM)	Ciclamato (80 mM)	S3819 (25 µM)
WT	++	+++	++	+++	+++	+++	+++
R383H	+	++	+	++	++	++	++
R383Q	-	+	-	+	+	+	+
R383I	-	-	-	-	-	-	-
R383F	-	++	-	-	+	+	+
R383K	-	+	-	+	+	+	+
R383N	-	+	-	+	+	+	+
R383S	-	+	-	+	+	+	+
R383A	-	-	-	-	-	-	+

El mejorador dulce, el compuesto A, es selectivo para el receptor del sabor humano, e inactivo en el receptor del sabor de la rata. Utilizando los receptores

quiméricos de humano-rata descriptos previamente, efectuamos un mapeo del sitio de unión del compuesto A a VFT de hT1R2. Según se muestra en la Figura 11, el compuesto A mejoró la actividad de la sucralosa en el receptor dulce humano (h2/h3) pero no en el receptor dulce de la rata (r2/r3). Cuando reemplazamos el VFT del receptor T1R2 de la rata con su contrapartida humano (h2-r2/r3), el receptor se puede mejorar a través del compuesto A. Por otra parte, cuando reemplazamos el VFT del receptor T1R2 humano con su contrapartida en la rata (r2-h2/h3), el receptor ya no puede ser mejorado a través del compuesto A. Concluimos en que el compuesto A interactúa con el VFT de T1R2 humano. Debido a la diferente sensibilidad de los receptores humano y de rata a la sucralosa, se utilizaron diferentes concentraciones de sucralosa para lograr ~EC20 de los diferentes receptores.

Siguiendo al compuesto A, se han identificado 8 análogos más por mejorar la actividad de la sucralosa del receptor dulce humano. Los mismos experimentos de mapeo se llevaron a cabo en estos 8 análogos, y observamos el mismo patrón de actividad al del compuesto A según se sintetiza en la siguiente tabla. Concluimos en que todos los 8 análogos del compuesto A interactúan con VFT de T1R2 humano.

Luego de efectuar un mapeo de los mejoradores para el VFT de T1R2 humano, llevamos a cabo el análisis de mutagénesis para definir más aún el sitio de interacción. Según se sintetiza en la siguiente tabla, se identificaron seis residuos (K65, D278, L279, D307, R383, V384) como decisivos para las actividades del compuesto A y de sus análogos. Estos compuestos, a saber, los compuestos A y A1 a A8, constituyen compuestos representativos de la presente invención que incluyen los compuestos de Fórmula estructural (I) y sus fórmulas subgenéricas. De un modo interesante, V384 también es importante para las actividades de 2 edulcorantes relacionados estructuralmente (según se muestra

en la Figura 12), sacarina y acesulfame K (AceK), lo cual indica que estos edulcorantes podrían ocupar un espacio similar en el VFT de T1R2 humano. Las concentraciones para los edulcorantes son Aspartame (15 mM), D-Trp (20 mM), Sacarosa (200 mM), Sucralosa (3,2 mM), AceK (8 mM), Sacarina (3,2 mM), Ciclamato (80 mM), S3819 (25 µM).

	h2/h3		r2/r3	h2-r2/r3	r2-h2/h3
Compuesto A (25 µM)	+		-	+	-
Compuesto A1 (25 µM)	+		-	+	-
Compuesto A2 (25 µM)	+		-	+	-
Compuesto A3 (25 µM)	+		-	+	-
Compuesto A4 (25 µM)	+		-	+	-
Compuesto A5 (25 µM)	+		-	+	-
Compuesto A6 (25 µM)	+		-	+	-
Compuesto A7 (25 µM)	+		-	+	-
Compuesto A8 (100 µM)	+		-	+	-

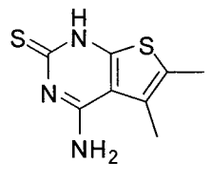
		Actividad de Mejoramiento (a 25 μM) para el Compuesto A y sus análogos								
hT1R2	Sucralosa	A	A4	A1	A5	A2	A6	A3	A8	A7
WT	++	++	++	+++	++	+++	++	+	++	+++
V384A	++	++	++	+++	++	+++	++	+	++	+++
E382A	++	++	++	+++	++	+++	++	+	++	+++
Y103A	-	+	+	++	+	++	+	+	++	++
P277A	+	++	+	+++	+	+++	+	+	++	+++
D278A*	-	++	+	+++	+	+++	+	+	+	++
K65A	+	-	-	-	-	-	-	-	-	-
L279A	++	-	-	-	-	-	-	-	-	-
V384F	++	+	+	+	+	+	+	-	-	+
S165I	++	++	++	+++	++	+++	++	+	++	+++
I67A	++	++	++	+++	++	+++	++	+	++	+++
S165A	++	+	++	+++	++	+++	++	+	++	+++
N143A	++	++	++	+++	++	+++	++	+	++	+++
T326A	++	++	++	+++	++	+++	++	+	++	+++
T242A	++	++	++	+++	++	+++	++	+	++	+++
S303A	++	++	++	+++	++	+++	++	+	++	+++
Q328A	++	++	++	+++	++	+++	++	+	++	+++
T184V	++	++	++	+++	++	+++	++	+	++	+++
T184A	++	++	++	+++	++	+++	++	+	++	+++
V64M	++	++	++	+++	++	+++	++	+	++	+++
S168T	++	++	++	+++	++	+++	++	+	++	+++
R383H	++	++	++	+++	++	+++	++	+	++	+++
S40T	+	++	++	+++	++	+++	++	+	++	+++
I167A	+	+	+	++	+	++	+	+	+	++

E302A	+	+	+	++	+	++	+	+	+	++
R383F	+	-	-	-	-	-	-	-	-	-
D307A	+	-	-	-	-	-	-	-	-	-
D142A	-	+	+	++	+	++	+	+	+	++
S40A	-	+	+	++	+	++	+	+	+	++
R383A	-	+	+	++	+	++	+	+	+	++
A305F	-	-	-	-	-	-	-	-	-	-

* D278 es un residuo decisivo para los mejoradores, debido a que todos los mejoradores en la tabla precedente presentan actividad agonista sobre el mutante D278A, es decir, ellos activan el receptor mutante en ausencia de sucralosa.

EXPERIMENTO 3: Síntesis Química de los Compuestos de la Presente Invención

Ejemplo 1: 4–amino–5,6–dimetiltieno[2,3–d]pirimidin–2(1H)–tiona



7

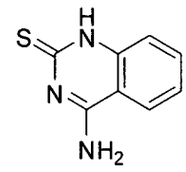
Una solución de N–(3–ciano–4,5–dimetiltiofen–2–ilcarbamotioil)benzamida (ejemplo 1a) (1,90 g, 6,03 mmol) y NaOH (2 N, 8,3 mL) en EtOH (25 mL) se agitó a 100ºC bajo nitrógeno durante media hora. Luego de enfriarse hasta temperatura ambiente, la solución de reacción clara se filtró y el filtrado se neutralizó cuidadosamente con 10% AcOH con agitación enérgica a 0ºC. El precipitado resultante se recogió mediante filtración, se lavó con agua tibia y luego 20% EtOH en agua para proporcionar el producto final 4–amino–5,6–dimetiltieno[2,3–

d]pirimidin–2(1H)–tiona (1,11 g, 87%) como un sólido blancuzco. P.f.: > 260ºC. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,25 (s, 3H), 2,26 (s, 3H). MS 212 (MH^+).

Ejemplo 1a: N–(3–ciano–4,5–dimetiltiofen–2–ilcarbamotioil)benzamida

A una solución de 2–amino–4,5–dimetiltiofen–3–carbonitrilo (1,52 g, 10,0 mmol) en 1,4-dioxano (20 mL) se le adicionó isotiocianato de benzoilo (1,63 g, 10,0 mmol). Luego la mezcla de reacción se agitó a temperatura ambiente bajo nitrógeno durante la noche. La precipitación se recogió mediante filtración, se lavó con EtOAc/Hexanos (1:4), y se secó bajo vacío durante la noche para proporcionar N–(3–ciano–4,5–dimetiltiofen–2–ilcarbamotioil)benzamida como un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 2,23 (s, 3H), 2,31 (s, 3H), 7,58-7,54 (m, 2H), 7,68-7,66 (m, 1H), 7,94 (d, J = 7,2 Hz, 2H), 9,13 (bs, 1H). MS 316 (MH^+).

Ejemplo 2: 4–aminoquinazolin–2(1H)–tiona



153

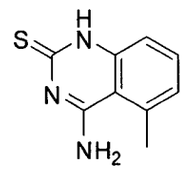
Preparada como en el Ejemplo 1 a partir de N–(2–cianofenilcarbamotioil)benzamida (Ejemplo 2a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,25 (dt, J = 1,0, 8,2 Hz, 1H), 7,35 (d, J = 8,2 Hz, 1H), 7,65 (dt, J = 1,0, 8,2 Hz, 1H), 8,05 (dd, J = 1,0, 8,1 Hz, 1H), 8,30 (s, 1H), 8,35 (s, 1H), 12,34 (s, 1H). MS 178 (MH^+).

Ejemplo 2a: N–(2–cianofenilcarbamotioil)benzamida:

Preparada como en el Ejemplo 1a a partir de 2–aminobenzonitrilo e isotiocianato de benzoilo como un sólido amarillo pálido. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,35-7,56 (m, 3H), 7,67 (t, 1H), 7,75-7,76 (d, J = 5,2 Hz, 2H), 7,89-

7,91 (d, *J* = 7,2 Hz, 2H), 7,98-8,01 (dd, *J*1= 1,6 Hz, *J*2= 8,2 Hz, 2H), 11,90 (s, 1H), 12,54 (s, 1H). MS 282 (MH^+).

Ejemplo 3: 4–amino–5–metilquinazolin–2(1H)–tiona



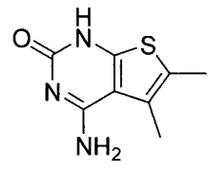
155

Preparada como en el Ejemplo 1 a partir de N–(2–ciano–3–metilfenilcarbamotioil)benzamida (Ejemplo 3a) como un sólido blancuzco. P.f.: > 250ºC. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,68 (s, 3H), 7,03 (d, *J* = 6,8 Hz, 1H), 7,13 (b, 1H), 7,22 (d, *J* = 6,8 Hz, 1H), 7,48 (t, *J* = 6,8 Hz, 1H), 8,50 (b, 1H), 12,26 (s, 1H). ^{13}C RMN (DMSO-d_6) δ 23,26, 109,86, 114,37, 127,16, 134,31, 136,97, 143,57, 160,58, 179,67. MS 192 (MH^+).

Ejemplo 3a: N–(2–Cianofenilcarbamotioil)benzamida

Preparada como en el Ejemplo 1a a partir de 2–amino–6–metilbenzonitrilo e isotiocianato de benzoilo como un sólido amarillo pálido. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,40 (m, 1H), 7,52-7,69 (m, 5H), 7,98-8,01 (m, 2H), 11,99 (s, 1H), 12,54 (s, 1H). MS 296 (MH^+).

Ejemplo 4: 4–amino–5,6–dimetiltieno[2,3–d]pirimidin–2(1H)–ona



1

Una solución de N–(3–ciano–4,5–dimetiltiofen–2–ilcarbamoil)benzamida (ejemplo 4a) (44,35 g, 148,1 mmol) y NaOH (2 N, 204 mL) en EtOH (400 mL) se agitó a 100ºC bajo nitrógeno durante cuatro horas. La solución de reacción clara se filtró y el filtrado se enfrió hasta temperatura ambiente, y luego se neutralizó cuidadosamente con 10% AcOH (~ 120 mL) con agitación enérgica a 0ºC. Luego de agitarse durante la noche desde 0ºC hasta temperatura ambiente, el precipitado resultante se recogió mediante filtración, se lavó con agua tibia (60–70ºC, 150 mL x 4) y 20% EtOH en agua (200 mL x 2), y luego se secó a 50ºC bajo vacío durante la noche para proporcionar el producto final 4–amino–5,6–dimetiltieno[2,3–d]pirimidin–2(1H)–ona (27,7 g, 96%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,98 (brs, 1H), 2,24 (s, 3H), 2,19 (s, 3H). MS 196 (MH^+).

Ejemplo 4a: N–(3–ciano–4,5–dimetiltiofen–2–ilcarbamoil)benzamida

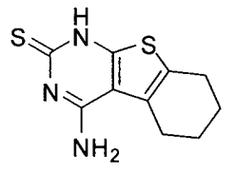
A una solución de 2–amino–4,5–dimetiltiofen–3–carbonitrilo (ejemplo 4b) (25 g, 164,5 mmol) en 1,4-dioxano (600 mL) se le adicionó isocianato de benzoilo (24,2 g, 164,5 mmol). Luego la mezcla de reacción se agitó a temperatura ambiente bajo nitrógeno durante la noche. El precipitado se recogió mediante filtración, se lavó con 1,4-dioxano (20 mL x 3), y se secó bajo vacío a 40ºC durante 3 horas para proporcionar N–(3–ciano–4,5–dimetiltiofen–2–ilcarbamoil)benzamida (44,35 g, 90%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,10 (s, 3H), 2,24 (s, 3H), 7,52-7,56 (m, 2H), 7,64-7,69 (m, 1H), 8,01-8,03 (m, 2H), 11,57 (brs, 1H), 12,05 (brs, 1H). MS 300 (MH^+).

Ejemplo 4b: 2–amino–4,5–dimetiltiofen–3–carbonitrilo

A una solución de butanona (162,0 mL, 1,8 mol), azufre (57,99 g, 1,8 mol), y malononitrilo (119,49 g, 1,8 mol) en Etanol anhidro (1,2 L) se le adicionó a 0ºC trietilamina (251,4 mL, 1,8 mol). La reacción se agitó a 0ºC durante 15 minutos luego se calentó a 80ºC durante 70 minutos. Luego de enfriarse hasta

temperatura ambiente, el etanol (920 mL) se removió bajo presión reducida y se adicionó NaCl acuoso (30%, 750 mL). La mezcla resultante se agitó durante 10 minutos y se extrajo con dietil éter (1 L). La capa acuosa se extrajo además con dietil éter (500 mL) y los sólidos insolubles se removieron mediante filtración luego de lo cual la capa orgánica se separó y se combinó con el primer extracto de dietil éter. El extracto orgánico combinado se secó sobre $MgSO_4$, se filtró y se concentró bajo presión reducida. El residuo se agitó durante 2 horas en diclorometano (300 mL) y se recogió un sólido. Se aisló más sólido de la solución de diclorometano enfriada hasta -78°C. El producto sólido combinado se reflujó en diclorometano (600 mL) durante 10 minutos luego se agitó a temperatura ambiente durante 30 minutos y se enfrió hasta -78°C. El precipitado resultante se recogió mediante filtración para proporcionar el producto crudo (115 g). El filtrado se concentró y el residuo se cromatografió sobre gel de sílice (eluyente: diclorometano) para proporcionar un sólido que se combinó con el producto crudo previo. El residuo resultante se purificó mediante cromatografía flash sobre gel de sílice (diclorometano) para producir 2–amino–4,5–dimetiltiofen–3–carbonitrilo (105 g, 38%) como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,93 (d, J = 1,2 Hz, 3H), 2,07 (d, J = 1,2 Hz, 3H), 3,33 (s, 2H). MS 153 (MH^+).

Ejemplo 5: 4–amino–5,6–butilentieno[2,3–d]pirimidin–2(1H)–tiona



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Preparada como en el Ejemplo 1 a partir de N–(3–ciano–4,5,6,7–tetrahidrobenzo[b]tiofen–2–ilcarbamotioil)benzamida (Ejemplo 5a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,75 (m, 4H), 2,62 (m, 2H), 2,74 (m, 2H). MS 238 (MH^+).

713

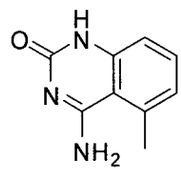
Ejemplo 5a: N–(3–ciano–4,5,6,7–tetrahidrobenzo[b]tiofen–2–ilcarbamotioil)–benzamida.

Preparada como en el Ejemplo 1a a partir de 2–amino–4,5,6,7–tetrahidrobenzo[b]tiofen–3–carbonitrilo (ejemplo 5b) e isotiocianato de benzoilo como un sólido amarillo pálido. MS 342 (MH^+).

Ejemplo 5b: 2–amino–4,5,6,7–tetrahidrobenzo[b]tiofen–3–carbonitrilo

Una solución de ciclohexanona (1,96 g, 20,0 mmol), malononitrilo (1,32 g, 20,0 mmol), azufre (640 mg, 20,0 mmol), y trietilamina (2,03 g, 20 mmol) en EtOH (50 mL) se reflujó durante 6 h bajo nitrógeno. El solvente se removió bajo presión reducida y el residuo se particionó entre EtOAc y agua. La capa orgánica se separó, se lavó con salmuera, y se secó sobre Na_2SO_4. Luego de la evaporación del solvente, el residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con EtOAc/Hexanos (2:3) para proporcionar el producto del título como un sólido amarillo. ^1H RMN (400 MHz, $CDCl_3$) δ 1,79 (m, 4H), 2,50 (m, 4H), 4,59 (s, 2H). MS 179 (MH^+).

Ejemplo 6: 4–amino–5–metilquinazolin–2(1H)–ona



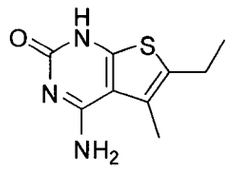
157

Preparada como en el Ejemplo 1 a partir de N–(2–ciano–3–metilfenilcarbamoil)benzamida (ejemplo 6a). ^1H RMN (400 MHz, DMSO-d_6) δ 3,04 (s, 3H), 7,43 (d, J = 7,2 Hz, 1H), 7,51 (d, J = 7,2 Hz, 1H), 7,97 (t, J = 7,2 Hz, 1H). MS 176 (MH^+).

Ejemplo 6a: N–(2–ciano–3–metilfenilcarbamoil)benzamida

Preparada como en el Ejemplo 1a a partir de 2–amino–6–metilbenzonitrilo e isocianato de benzoilo como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,19 (d, J = 7,6 Hz, 1H), 7,52-7,68 (m, 5H), 8,02-8,08 (m, 2H), 11,32 (s, 1H), 11,46 (s, 1H). MS 280 (MH^+).

Ejemplo 7: 4–amino–6–etil–5–metiltieno[2,3–d]pirimidin–2(1H)–ona



75

Preparada como en el Ejemplo 1 a partir de N–(3–ciano–5–etil–4–metiltiofen–2–ilcarbamoil)benzamida (Ejemplo 7a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,11 (t, J = 7,6 Hz, 3H), 2,26 (s, 3H), 2,60-2,67 (q, J = 7,6 Hz, 2H). MS 210 (MH^+).

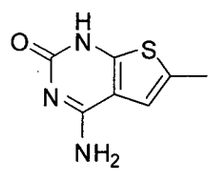
Ejemplo 7a: N–(3–ciano–5–etil–4–metiltiofen–2–ilcarbamoil)benzamida

Preparada como en el Ejemplo 1a a partir de 2–amino–5–etil–4–metiltiofen–3–carbonitrilo (ejemplo 7b) e isocianato de benzoilo como un sólido amarillo pálido. MS 314 (MH^+).

Ejemplo 7b: 2–amino–5–etil–4–metiltiofen–3–carbonitrilo

Preparado como en el Ejemplo 5b a partir de 2–pentanona, malononitrilo, y azufre como un sólido amarillo. MS 167 (MH^+).

Ejemplo 8: 4–amino–6–metiltieno[2,3–d]pirimidin–2(1H)–ona



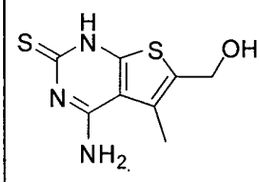
77

Preparada como en el Ejemplo 1 a partir de N–(3–ciano–5–metiltiofen–2–ilcarbamoil)benzamida (Ejemplo 8a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,34 (s, 3H), 6,97 (s, 1H), 7,50 (s, 1H). MS 182 (MH^+).

Ejemplo 8a: N–(3–ciano–5–metiltiofen–2–ilcarbamoil)benzamida

Preparada como en el Ejemplo 1a a partir de 2–amino–5–metiltiofen–3–carbonitrilo e isocianato de benzoilo como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,36 (d, J = 1,2 Hz, 3H), 6,89 (d, J = 1,2 Hz, 1H), 7,55 (t, J = 8,0 Hz, 2H), 7,66 (d, J = 7,2 Hz, 1H), 8,03-8,01 (m, 2H), 11,60 (brs, 1H), 12,08 (bs, 1H). MS 286 (MH^+).

Ejemplo 9: 4–amino–6–(hidroximetil)–5–metiltieno[2,3–d]pirimidin–2(1H)–tiona



37

Preparada como en el Ejemplo 1 a partir de N–(3–ciano–5–(hidroximetil)–4–metiltiofen–2–ilcarbamotioil)benzamida (Ejemplo 9a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,30 (s, 3H), 4,54-4,55 (d, J = 5,2 Hz, 2H), 5,54 (t, 1H). MS 228 (MH^+).

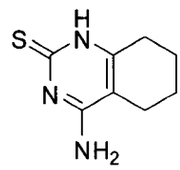
Ejemplo 9a: N–(3–ciano–5–(hidroximetil)–4–metiltiofen–2–ilcarbamotioil)–benzamida

Preparada como en el Ejemplo 1a a partir de 2–amino–5–(hidroximetil)–4–metiltiofen–3–carbonitrilo (Ejemplo 9b) e isotiocianato de benzoilo como un sólido amarillo. MS 332 (MH^+).

Ejemplo 9b: 2–amino–5–(hidroximetil)–4–metiltiofen–3–carbonitrilo

Preparado como en el Ejemplo 5b a partir de 4–hidroxibutan–2–ona , malononitrilo, y azufre como un sólido amarillo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,97 (s, 3H), 4,30-4,31 (d, J = 5,6 Hz, 2H), 5,10 (t, 1H), 7,00 (s, 2H).

Ejemplo 10: 4–amino–5,6,7,8–tetrahidroquinazolin–2(1H)–tiona



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Preparada como en el Ejemplo 1 a partir de N–(2–cianociclohex–1–enilcarbamotioil)benzamida (Ejemplo 10a) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,60-1,65 (m, 4H), 2,13 (m, 2H), 2,38 (m, 2H), 6,93 (s, 1H), 7,56 (s, 1H), 11,84 (s, 1H). MS 182 (MH^+).

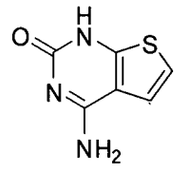
Ejemplo 10a: N–(2–cianociclohex–1–enilcarbamotioil)benzamida

Preparada como en el Ejemplo 1a a partir de 2–aminociclohex–1–enocarbonitrilo (Ejemplo 10b) e isotiocianato de benzoilo como un sólido blanco. MS 286 (MH^+).

Ejemplo 10b: 2–aminociclohex–1–enocarbonitrilo

Una mezcla agitada de 1,7–heptanodinitrilo (24,44 g, 0,2 mol) y *t*–BuOK (22,44 g, 0,2 mol) se calentó a 80ºC durante 3 h bajo nitrógeno. Luego la mezcla se enfrió hasta temperatura ambiente y se almacenó a esa temperatura durante la noche. El residuo se trató con agua, y se extrajo con éter (2X). Las capas orgánicas combinadas se lavaran con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo se purificó mediante recristalización a partir de MeOH para proporcionar el compuesto del título como un sólido blanco (18,2 g, 75%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,58-1,71 (m, 4H), 2,12-2,20 (m, 4H), 4,23 (bs, 2H). MS 123 (MH^+).

Ejemplo 11: 4–amino–6–metiltieno[2,3–d]pirimidin–2(1H)–ona



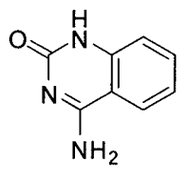
69

Preparada como en el Ejemplo 1 a partir de N–(3–cianotiofen–2–ilcarbamoil)benzamida (Ejemplo 11a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 6,97 (s, J = 5,2 Hz, 1H), 7,31 (d, J = 6,0 Hz, 1H), 7,60 (s, 2H), 11,38 (bs, 1H). MS 168 (MH^+).

Ejemplo 11a: N–(3–cianotiofen–2–ilcarbamoil)benzamida

Preparada como en el Ejemplo 1a a partir de 2–aminotiofen–3–carbonitrilo e isocianato de benzoilo como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,23-7,19 (m, 2H), 7,55 (t, J = 8,0 Hz, 2H), 7,70-7,66 (m, 1H), 8,04-8,02 (m, 2H), 11,62 (bs, 1H), 12,18 (bs, 1H). MS 272 (MH^+).

Ejemplo 12: 4–aminoquinazolin–2(1H)–ona



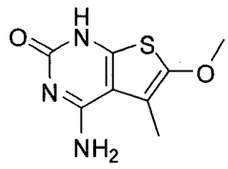
149

Preparada como en el Ejemplo 1 a partir de N–(2–cianofenilcarbamoil)benzamida (Ejemplo 12a) como un sólido blanco (156 mg, 41%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,12-7,20 (m, 2H), 7,59-7,63 (m, 1H), 8,08-8,10 (d, 1H), 8,60 (b, 2H), 11,2 (b, 1H). ^{13}C RMN (DMSO-d_6) δ 108,72, 115,98, 122,32, 125,51, 135,38, 142,96, 154,96, 163,51. MS 162 (MH^+).

Ejemplo 12a: N–(2–cianofenilcarbamoil)benzamida

Preparada como en el Ejemplo 1a a partir de 2–aminobenzonitrilo e isocianato de benzoilo como un polvo blanco (661 mg, 59%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,27-7,29 (t, 1H), 7,52-7,56 (t, 1H), 7,64-7,74 (m, 2H), 7,82-7,85 (dd, 1H), 8,02-8,04 (m, 2H), 8,22-8,24 (d, 1H). MS 266 (MH^+).

Ejemplo 13: 4–amino–6–metoxi–5–metiltieno[2,3–d]pirimidin–2(1H)–ona



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Preparada como en el Ejemplo 1 a partir de N–(3–ciano–5–metoxi–4–metiltiofen–2–ilcarbamoil)benzamida (Ejemplo 13a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,19 (s, 3H), 3,78 (s, 3H), 2,74 (s, 2H). MS 212 (MH^+).

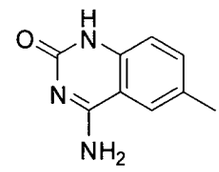
Ejemplo 13a: N–(3–ciano–5–metoxi–4–metiltiofen–2–ilcarbamoil)benzamida.

Preparada como en el Ejemplo 1a a partir de 2–amino–5–metoxi–4–metiltiofen–3–carbonitrilo (Ejemplo 13b) e isocianato de benzoilo como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,03 (s, 3H), 3,86 (s, 3H), 7,54 (t, J = 7,2 Hz, 2H), 7,67 (t, J = 7,6 Hz, 1H), 8,01-8,03 (d, J = 8,4 Hz, 2H), 11,60 (s, 1H), 12,03 (s, 1H). MS 316 (MH^+).

Ejemplo 13b: 2–amino–5–metoxi–4–metiltiofen–3–carbonitrilo

Preparado como en el Ejemplo 5b a partir de 1–metoxipropan–2–ona, malononitrilo, y azufre como un sólido marrón. MS 169 (MH^+).

Ejemplo 14: 4–amino–6–metilquinazolin–2(1H)–ona



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Preparada como en el Ejemplo 1 a partir de N–(2–ciano–4–metilfenilcarbamoil)benzamida (Ejemplo 14a) como un sólido blanco (259 mg, 57%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,29 (s, 3H), 6,99-7,05 (m, 1H), 7,35-7,37 (d, 1H), 7,72 (b, 2H), 7,79 (s, 1H) 10,55 (bs, 1H). MS 176 (MH^+).

Ejemplo 14a: N–(2–ciano–4–metilfenilcarbamoil)benzamida

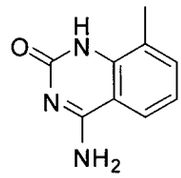
Preparada como en el Ejemplo 1a a partir de 2–amino–5–metilbenzonitrilo (Ejemplo 14b) como un polvo blanco (724 mg, 46%). MS 280 (MH^+).

Ejemplo 14b: 2–amino–5–metilbenzonitrilo

Se adicionó en porciones 5–metil–2–nitrobenzonitrilo (1,92 g, 11,84 mmol) a una solución agitada de $SnCl_2$ (11,22 g, 59,2 mmol) en HCl conc. (12 mL) y EtOH (12 mL). La temperatura de la reacción se mantuvo a 20–30°C utilizando un baño de hielo. Luego la mezcla de reacción se agitó a temperatura ambiente durante 1 h y se virtió en una solución acuosa de NaOH enfriada con hielo (6 N, app. 30 mL) para neutralizar hasta pH7. El producto se extrajo en EtOAc, se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró para proporcionar el producto del título (1,56 g, 99%) como un sólido amarillo-marrón. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,21 (s, 3H), 5,79 (bs, 2H), 6,68-6,71 (d, 1H), 7,10-7,13 (dd, 1H), 7,15 (s, 1H). ^{13}C RMN (DMSO-d_6) δ 20,13, 93,99, 116,12, 118,94, 125,38, 132,32, 135,76, 150,21. MS 133 (MH^+).

720

Ejemplo 15: 4–amino–8–metilquinazolin–2(1H)–ona



165

Preparada como en el Ejemplo 1 a partir de N–(2–ciano–6–metilfenilcarbamoil)benzamida (Ejemplo 15a) como un sólido blanco (60 mg, 56%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,29 (s, 3H), 6,96-7,00 (t, 1H), 7,37-7,38 (d, 1H), 7,70-7,72 (b, 2H), 7,80-7,82 (d, 1H), 9,87 (bs, 1H). MS 176 (MH^+).

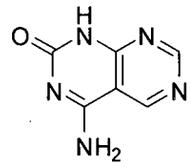
Ejemplo15a: N–(2–ciano–6–metilfenilcarbamoil)benzamida

Preparada como en el Ejemplo 1a a partir de 2–amino–3–metilbenzonitrilo (Ejemplo 15b) e isocianato de benzoilo como un polvo blanco (186 mg, 67%). MS 280 (MH^+).

Ejemplo 15b: 2–amino–3–metilbenzonitrilo

A una solución de 2–bromo–6–metilanilina (126 µL, 1 mmol) en NMP seca (3 mL) se le adicionó CuCN (197 mg, 2,2 mmol). La mezcla se irradió en un microondas a 220ºC durante 40 minutos, se enfrió hasta temperatura ambiente y se virtió en una mezcla de amoníaco (50% p/v, 10 mL) y hielo. La mezcla se agitó durante 30 min y el producto se extrajo con diclorometano (3 x 20 mL). Las capas orgánicas se combinaron, se lavaron con agua y salmuera, se secaron sobre $MgSO_4$ y se concentraron. El material crudo se purificó sobre gel de sílice (50% EtOAc/hexanos) para producir un aceite marrón que se cristalizó en reposo (128 mg, 96%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,08 (s, 3H), 5,68 (bs, 2H), 6,51-6,55 (t, 1H), 7,17-7,19 (d, 1H), 7,22-7,24 (dd, 1H). MS 133 (MH^+).

Ejemplo 16: 4–aminopirimido[4,5–d]pirimidin–2(1H)–ona



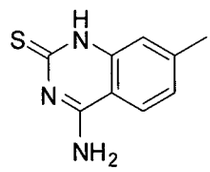
181

Preparada como en el Ejemplo 1 a partir de N–(2–ciano–4,5–dimetilfuran–3–ilcarbamoil)benzamida (Ejemplo 16a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,91 (s, 1H), 8,92 (s, 1H), 9,24 (s, 2H), 11,50 (b, 1H). MS 164 (MH^+).

Ejemplo 16a: N–(2–ciano–4,5–dimetilfuran–3–ilcarbamoil)benzamida

Preparada como en el Ejemplo 1a a partir de 4–aminopirimidin–5–carbonitrilo e isocianato de benzoilo como un polvo blancuzco. MS 268 (MH^+).

Ejemplo 17: 4–amino–7–metilquinazolin–2(1H)–tiona



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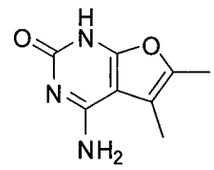
Preparada como en el Ejemplo 1 a partir de N–(2–ciano–5–metilfenilcarbamotioil)benzamida (Ejemplo 17a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,35 (s, 3H), 7,08 (d, J = 8,0 Hz, 1H), 7,13 (s, 1H), 7,93 (d, J = 8,0 Hz, 1H), 8,21 (s, 1H), 8,24 (s, 1H), 12,26 (s, 1H). MS 192 (MH^+).

Ejemplo 17a: N–(2–ciano–5–metilfenilcarbamotioil)benzamida

Preparada como en el Ejemplo 1a a partir de 2–amino–4–metilbenzonitrilo e isotiocianato de benzoilo como un polvo amarillo pálido. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,32 (d, J = 8,0 Hz, 1H), 7,51-7,58 (m, 3H), 7,67 (t, J = 7,8 Hz, 1H),

7,78 (d, J = 8,0 Hz, 1H), 7,98-8,01 (m, 2H), 11,88 (s, 1H), 12,49 (s, 1H). MS 296 (MH^+).

Ejemplo 18: 4–amino–5,6–dimetilfuro[2,3–d]pirimidin–2(1H)–ona



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Preparada como en el Ejemplo 1 a partir de N–(2–ciano–4,5–dimetilfuran–3–ilcarbamoil)benzamida (Ejemplo 18a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,11 (s, 3H), 2,20 (s, 3H). MS 180 (MH^+).

Ejemplo 18a: N–(2–ciano–4,5–dimetilfuran–3–ilcarbamoil)benzamida

Preparada en una manera similar al Ejemplo 1a a partir de 2–amino–4,5–dimetilfuran–3–carbonitrilo e isocianato de benzoilo como un sólido blancuzco. MS 284 (MH^+).

Ejemplo 19: 4–amino–7–metilquinazolin–2(1H)–ona



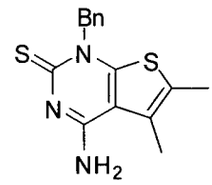
163

Preparada como en el Ejemplo 1 a partir de N–(2–ciano–5–metilfenilcarbamoil)benzamida (Ejemplo 19a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,59 (s, 3H), 7,37 (s, 1H), 7,49 (d, J = 7,2 Hz, 1H), 8,21 (d, J = 7,2 Hz, 1H). MS 176 (MH^+).

Ejemplo 19a: N–(2–ciano–5–metilfenilcarbamoil)benzamida

Preparada como en el Ejemplo 1a a partir de 2–amino–4–metilbenzonitrilo e isocianato de benzoilo como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,10-7,13 (m, 1H), 7,54 (t, J = 7,8 Hz, 2H), 7,66 (t, J = 7,8 Hz, 1H), 7,71 (d, J = 8,0 Hz, 1H), 8,02-8,04 (m, 2H), 8,07 (s, 1H), 11,32 (s, 1H), 11,44 (s, 1H). MS 280 (MH^+).

Ejemplo 20: 4–amino–1–bencil–5,6–dimetiltieno[2,3–d]pirimidin–2(1H)–tiona



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Preparada como en el Ejemplo 1 a partir de N–(bencil(3–ciano–4,5–dimetiltiofen–2–il)carbamotioil)benzamida (Ejemplo 20a). MS 302 (MH^+).

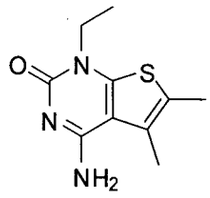
Ejemplo 20a: N–(bencil(3–ciano–4,5–dimetiltiofen–2–il)carbamotioil)–benzamida.

Preparada como en el Ejemplo 1a a partir de 2–(bencilamino)–4,5–dimetiltiofen–3–carbonitrilo (Ejemplo 20b) e isotiocianato de benzoilo. MS 406 (MH^+).

Ejemplo 20b: 2–(bencilamino)–4,5–dimetiltiofen–3–carbonitrilo

A una solución de 2–amino–4,5–dimetiltiofen–3–carbonitrilo (151 mg, 1,0 mmol) y benzaldehído (106 mg, 1mmol) en 15 mL de 4% ácido acético en dicloroetano se le adicionó cianoborohidruro soportado con sílice (2,0 g, 2,0 mmol). La reacción se colocó en un reactor de microondas durante 5 minutos a 135°C. El cianoborohidruro soportado con sílice se removió mediante filtración, y el producto se purificó mediante HPLC prep utilizando acetonitrilo/agua como solvente. MS 243 (MH^+).

Ejemplo 21: 4–amino–1–etil–5,6–dimetiltieno[2,3–d]pirimidin–2(1H)–ona



129

Preparada como en el Ejemplo 1 a partir de N–((3–ciano–4,5–dimetiltiofen–2–il)(etil)carbamoil)benzamida (Ejemplo 21a). MS 224 (MH^+).

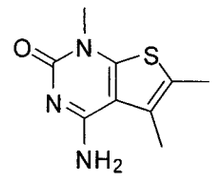
Ejemplo 21a: N–((3–ciano–4,5–dimetiltiofen–2–il)(etil)carbamoil)benzamida.

Preparada en una manera similar al Ejemplo 1a a partir de 2–(etilamino)–4,5–dimetiltiofen–3–carbonitrilo (Ejemplo 21b) e isocianato de benzoilo. MS 328 (MH^+).

Ejemplo 21b: 2–(etilamino)–4,5–dimetiltiofen–3–carbonitrilo

A una mezcla de 2–(bencilamino)–4,5–dimetiltiofen–3–carbonitrilo (302 mg, 2,0 mmol), carbonato de potasio (276 mg, 2,0 mmol), y una cantidad catalítica de yoduro de potasio en acetonitrilo (1 mL) en un vial para microondas de 20 mL se le adicionó yoduro de etilo (310 mg, 2,0 mmol). El vial de reacción se colocó en un reactor de microondas durante 15 minutos a 165°C. La mezcla de reacción se disolvió en acetato de etilo y se lavó con agua y salmuera. La porción de acetato de etilo se secó sobre sulfato de sodio y el solvente se evaporó bajo presión reducida, y el producto se purificó mediante HPLC prep utilizando acetonitrilo/agua como solvente. MS 181 (MH^+).

Ejemplo 22: 4–Amino–1,5,6–trimetiltieno[2,3–d]pirimidin–2(1H)–ona



131

Preparada como en el Ejemplo 1 a partir de N–((3–ciano–4,5–dimetiltiofen–2–il)(metil)carbamoil)benzamida (Ejemplo 22a). MS 210 (MH^+).

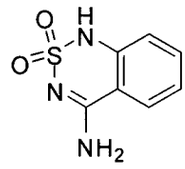
Ejemplo 22a: N–((3–ciano–4,5–dimetiltiofen–2–il)(metil)carbamoil)–benzamida.

Preparada como en el Ejemplo 1a a partir de 4,5–dimetil–2–(metilamino)tiofen–3–carbonitrilo (Ejemplo 22b) e isocianato de benzoilo. MS 314 (MH^+).

Ejemplo 22b: 4,5–dimetil–2–(metilamino)tiofen–3–carbonitrilo

Preparado como en el Ejemplo 21b a partir de 2–amino–4,5–dimetiltiofen–3–carbonitrilo y yoduro de metilo.

Ejemplo 23: 1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido

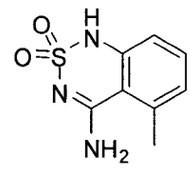


159

Una mezcla agitada de 2–cianoanilina (236 mg, 2,0 mmol), sulfamida (192 mg, 2,0 mmol) y DBU (304 mg, 2,0 mmol) se calentó a 160ºC bajo nitrógeno durante 3 días. Luego de enfriarse hasta temperatura ambiente, la mezcla de reacción se diluyó con agua y se extrajo tres veces con EtOAc. La capa acuosa se removió bajo vacío y el residuo se purificó mediante cromatografía sobre gel de

sílice eluyendo con 10% MeOH en diclorometano para proporcionar el compuesto del título como un sólido amarillo pálido. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,03 (dd, J = 0,8, 8,0 Hz, 1H), 7,12 (dt, J = 0,8, 8,0 Hz, 1H), 7,56 (dt, J = 0,8, 8,0 Hz, 1H), 7,85 (dd, J = 0,8, 8,0 Hz, 1H). MS 198 (MH^+).

Ejemplo 24: 5–metil–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



169

Una solución de N–(2–ciano–3–metilfenil)sulfamida (Ejemplo 24a) (211 mg, 1,0 mmol) en EtOH se trató con NaOH (2,0 N, 1,0 mL, 2,0 mmol) y la solución resultante se calentó hasta 100ºC y se agitó a esa temperatura durante 0,5 h. Luego de enfriarse hasta temperatura ambiente, la solución de reacción clara se filtró y la filtración se neutralizó cuidadosamente con 10% AcOH mientras se agitaba enérgicamente a 0ºC. El precipitado resultante se recogió mediante filtración, se lavó con agua tibia y 20% EtOH en agua para proporcionar el producto del título 5–metil–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,59 (s, 3H), 6,85-6,87 (d, J = 8,4 Hz, 1H), 6,92-6,94 (d, J = 7,2 Hz, 1H), 7,24 (s, 1H), 7,37 (t, J = 7,6 Hz, 1H), 8,24 (s, 1H), 10,76 (s, 1H). MS 212 (MH^+).

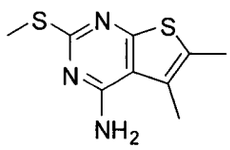
Ejemplo 24a: N–(2–ciano–3–metilfenil)sulfamida

Una solución de 2–amino–6–metilbenzonitrilo (1,32 g, 10 mmol) y sulfamida (4,81 g, 50 mmol) en 1,4-dioxano seco (50 mL) se reflujó bajo nitrógeno durante 3 días. Luego de que la mezcla de reacción se enfriara hasta temperatura ambiente, el precipitado se filtró y se lavó con dioxano. El filtrado se concentró bajo presión reducida, y el residuo se purificó mediante cromatografía sobre gel de sílice

727

eluyendo con EtOAc/hexanos (3:7) para proporcionar el compuesto del título como un sólido blanco pálido. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,44 (s, 3H), 7,19-7,21 (m, 3H), 7,39-7,41 (d, J = 8,4 Hz, 1H), 7,53 (t, J = 8,0 Hz, 1H), 9,41 (s, 1H).

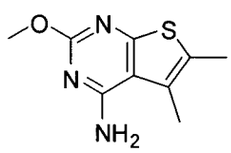
Ejemplo 25: 5,6–dimetil–2–(metiltio)tieno[2,3–d]pirimidin–4–amina



109

A una suspensión de N–(3–ciano–4,5–dimetiltiofen–2–ilcarbamotioil)–benzamida (Ejemplo 1a) (1,33 g, 4,22 mmol) en etanol (25 mL) se le adicionó NaOH (2,0 N, 5,8 mL) a temperatura ambiente bajo nitrógeno. Luego de agitar a 100ºC bajo nitrógeno durante 0,5 h, la mezcla de reacción se enfrió en un baño de hielo y se adicionó gota a gota MeI (0,8 mL). Luego de agitar durante otra 0,5 h, el precipitado resultante se recogió mediante filtración, se enjuagó con agua, 20% EtOH/H_2O, y se secó bajo vacío para proporcionar el compuesto del título (840 mg, 89%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,32 (s, 3H), 2,34 (s, 3H), 2,42 (s, 3H), 6,93 (bs, 2H). MS 226 (MH^+).

Ejemplo 26: 2–metoxi–5,6–dimetiltieno[2,3–d]pirimidin–4–amina

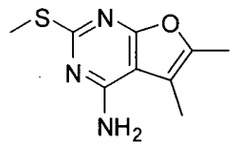


111

Preparada en una manera similar al Ejemplo 25 a partir de N–(3–ciano–4,5–dimetiltiofen–2–ilcarbamoil)benzamida (Ejemplo 4a) y yoduro de metilo en

86% de rendimiento. ^{1}H RMN (400 MHz, $CDCl_3$) δ 2,35 (s, 3H), 2,36 (s, 3H), 3,53 (s, 3H), 6,0 (bs, 2H). MS 210 (MH^+).

Ejemplo 27: 5,6–dimetil–2–(metiltio)furo[2,3–d]pirimidin–4–amina



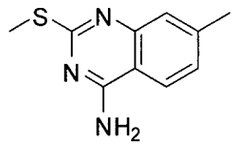
113

Preparada como en el Ejemplo 25 a partir de N–(2–ciano–4,5–dimetilfuran–3–ilcarbamotioil)benzamida (Ejemplo 27a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,16 (s, 3H), 2,23 (s, 3H), 2,41 (s, 3H), 6,92 (s, 2H). MS 210 (MH^+).

Ejemplo 27a: N–(2–ciano–4,5–dimetilfuran–3–ilcarbamotioil)benzamida

Preparada como en el Ejemplo 1a a partir de 2–amino–4,5–dimetilfuran–3–carbonitrilo e isotiocianato de benzoilo. MS 300 (MH^+).

Ejemplo 28: 7–metil–2–(metiltio)quinazolin–4–amina

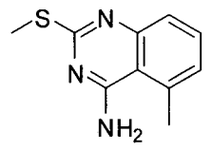


171

Preparada como en el Ejemplo 25 a partir de N–(2–ciano–5–metilfenilcarbamotioil)benzamida (Ejemplo 17a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,40 (s, 3H), 2,45 (s, 3H), 7,17 (dd, J = 2,0, 8,8 Hz, 1H), 7,32 (s, 1H), 7,71 (b, 2H), 8,01 (d, J = 8,4 Hz, 1H). MS 206 (MH^+).

724

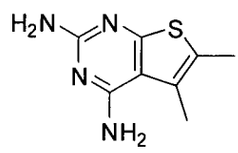
Ejemplo 29: 5–metil–2–(metiltio)quinazolin–4–amina



173

Preparada como en el Ejemplo 25 a partir de N–(2–ciano–3–metilfenilcarbamotioil)benzamida (Ejemplo 3a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,46 (s, 3H), 2,75 (s, 3H), 7,11 (d, J = 7,2 Hz, 1H), 7,33 (d, J = 7,2 Hz, 1H), 7,51 (dd, J = 0,8, 7,2 Hz, 1H). MS 206 (MH^+).

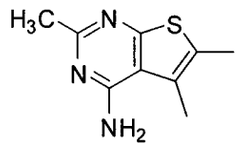
Ejemplo 30: 5,6–dimetiltieno[2,3–d]pirimidin–2,4–diamina



5

Una mezcla de 2–amino–4,5–dimetiltiofen–3–carbonitrilo (500 mg, 3,29 mmol), cianoguanidina (276,6 mg, 3,29 mmol) y HCl (2 N, 1,5 mL) en agua (10 mL) se reflujó bajo nitrógeno durante 2 h. La mezcla de reacción se enfrió hasta temperatura ambiente, y se basificó con solución acuosa de NaOH diluida hasta un pH 7~8. Luego de la evaporación del agua, el residuo se purificó mediante HPLC preparativa eluyendo con acetonitrilo y agua para proporcionar el compuesto del título (33 mg, 5%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,22 (s, 3H), 2,27 (s, 3H), 5,85 (bs, 2H), 6,29 (bs, 2H). MS 195 (MH^+).

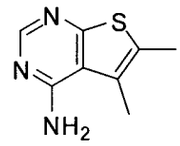
Ejemplo 31: 2,5,6–trimetiltieno[2,3–d]pirimidin–4–amina



115

Una mezcla de 2–amino–4,5–dimetiltiofen–3–carbonitrilo (200 mg, 1,32 mmol), acetato de amoníaco (204 mg, 2,64 mmol), y ortoacetato de trietilo (2,0 mL) se agitó en un tubo sellado a 120ºC durante la noche. Luego de que la mezcla de reacción se enfriara hasta temperatura ambiente, el precipitado se recogió mediante filtración, se enjuagó con EtOAc y se secó al aire para proporcionar el compuesto del título (52 mg, 60%) como un sólido amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 2,41 (s, 3H), 2,45 (s, 3H), 2,56 (s, 3H), 5,28 (bs, 2H). MS 194 (MH^+).

Ejemplo 32: 5,6–dimetiltieno[2,3–d]pirimidin–4–amina

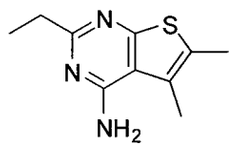


117

Preparada como en el Ejemplo 31 a partir de 2–amino–4,5–dimetiltiofen–3–carbonitrilo y ortoformiato de trietilo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,36 (s, 3H), 2,39 (s, 3H), 6,85 (bs, 2H), 8,14 (s, 1H). MS 180 (MH^+).

731

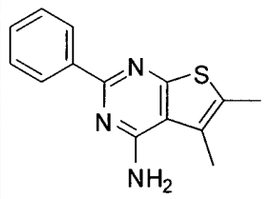
Ejemplo 33: 2–etil–5,6–dimetiltieno[2,3–d]pirimidin–4–amina



119

Preparada como en el Ejemplo 31 a partir de 2–amino–4,5–dimetiltiofen–3–carbonitrilo y ortopropanato de trietilo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,19 (t, J = 7,6 Hz, 3H), 2,33(s,3H), 2,36 (s, 3H), 2,61 (q, J = 7,6 Hz, 2H), 6,74 (bs, 2H). MS 208 (MH^+).

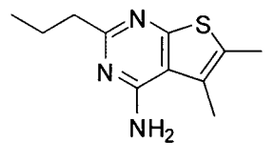
Ejemplo 34: 5,6–dimetil–2–feniltieno[2,3–d]pirimidin–4–amina



121

Una mezcla de 2–amino–4,5–dimetiltiofen–3–carbonitrilo (152 mg, 1,0 mmol), acetato de amoníaco (308,3 mg, 4,0 mmol) y ortobenzoato de trietilo (2,0 mL) en un tubo sellado se colocó en un microondas a 200ºC durante 20 min. Luego de que la mezcla de reacción se enfriara hasta temperatura ambiente, ésta se diluyó con EtOAc, se lavó con $NaHCO_3$ saturado y H_2O. El solvente se removió mediante vacío y el residuo se purificó mediante HPLC preparativa eluyendo con acetonitrilo y agua para proporcionar el compuesto del título (80 mg, 31%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 2,45 (s, 3H), 2,48 (s, 3H), 5,34 (bs, 2H), 7,46-7,43 (m, 3H), 8,4-8,38 (m, 2H). MS 256 (MH^+).

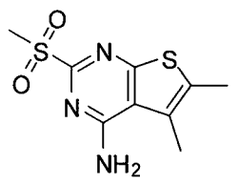
Ejemplo 35: 5,6–dimetil–2–propiltieno[2,3–d]pirimidin–4–amina



123

Preparada como en el Ejemplo 34 a partir de 2–amino–4,5–dimetiltiofen–3–carbonitrilo y ortobutanato de trietilo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,87 (t, J = 7,6 Hz, 3H), 1,72-1,67 (m, 2H), 2,33(s, 3H), 2,36 (s, 3H), 2,57 (t, J = 7,2 Hz, 2H), 6,73 (bs, 2H). MS 222 (MH^+).

Ejemplo 36: 5,6–dimetil–2–(metilsulfonil)tieno[2,3–d]pirimidin–4–amina

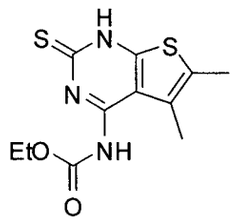


125

A una suspensión de 5,6–dimetil–2–(metiltio)tieno[2,3–d]pirimidin–4–amina (Ejemplo 1) (200 mg, 0,89 mmol) en DCM (25 mL) se le adicionó ácido *m*-cloroperoxibenzoico (767 mg, 4,44 mmol). Luego de agitar a temperatura ambiente durante la noche, la mezcla de reacción se diluyó con EtOAc, se lavó con agua y salmuera, se secó sobre Na_2SO_4, se filtró y se evaporó. El residuo se purificó mediante HPLC preparativa eluyendo con acetonitrilo y agua para proporcionar el compuesto del título (45 mg, 20%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,42 (s, 6H), 3,27 (s, 3H). MS 258 (MH^+).

733

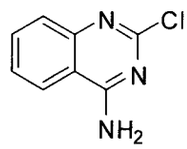
Ejemplo 37: 5,6–dimetil–2–tioxo–1,2–dihidrotieno[2,3–d]pirimidin–4–ilcarbamato de etilo



133

A una suspensión de 4–amino–5,6–dimetiltieno[2,3–d]pirimidin–2(1H)–tiona (211 mg, 1 mmol) en DMF (5 mL) se le adicionó Et_3N (0,21 mL, 1,5 mmol) y cloroformiato de etilo (0,143 mL, 1,5 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche, luego se diluyó con EtOAc, se lavó con agua y salmuera, se secó sobre Na_2SO_4, se filtró y se evaporó. El residuo se purificó sobre Biotage SP-1 eluyendo con EtOAc/hexano para proporcionar el compuesto del título (154 mg, 54%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,22 (t, J = 7,2 Hz, 3H), 2,38 (s, 3H), 2,39 (s, 3H), 4,25 (q, J = 7,2 Hz, 2H), 7,25–7,21 (m, 2H). MS 284 (MH^+)

Ejemplo 38: 2–cloroquinazolin–4–amina

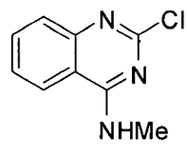


185

A una solución de 2,4-dicloroquinazolina (2,0 g, 10 mmol) en THF (10 mL), se le adicionó amoníaco (28-30% en agua, 18 mL). La mezcla de reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con EtOAc, se lavó con $NaHCO_3$ saturado, agua y salmuera, se secó sobre

Na_2SO_4, se filtró y se evaporó. El sólido resultante se lavó con EtOAc para proporcionar el compuesto del título (1,3 g, 72%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,52-7,48 (m, 1H), 7,6-7,58 (m, 1H), 7,8-7,76 (m, 1H), 8,22-8,20 (m, 1H), 8,32 (bs, 2H).

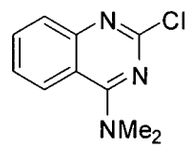
Ejemplo 39: 2–cloro–N–metilquinazolin–4–amina



187

Preparada como en el Ejemplo 38 a partir de 2,4–dicloroquinazolina y metilamina. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,98 (d, J = 4,4 Hz, 3H), 7,53-7,49 (m, 1H), 7,61-7,58 (m, 1H), 7,79-7,75 (m, 1H), 88,19-8,17 (m, 1H),,78 (bs, 1H).

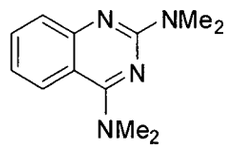
Ejemplo 40: 2–cloro–N,N–dimetilquinazolin–4–amina



189

Preparada como en el Ejemplo 38 a partir de 2,4–dicloroquinazolina y dimetilamina. ^{1}H RMN (400 MHz, $CDCl_3$) δ 3,42 (s, 6H), 7,42-7,39 (m, 1H), 7,72-7,70 (m, 1H), 7,79-7,77 (m, 1H), 8,03-8,01 (m, 1H). MS 208 (MH^+).

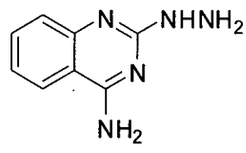
Ejemplo 41: N2,N2,N4,N4–tetrametilquinazolin–2,4–diamina



191

Preparada como en el Ejemplo 38 a partir de 2,4–dicloroquinazolina y dimetilamina. ^{1}H RMN (400 MHz, $CDCl_3$) δ 3,27-3,23 (m, 12H), 7,01-6,97 (m, 1H), 7,51-7,47 (m, 2H), 7,80-7,78 (m,1H). MS 217 (MH^+).

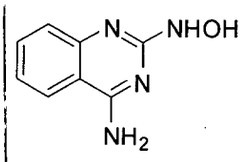
Ejemplo 42: 2–hidrazinilquinazolin–4–amina



193

Una mezcla de 2–cloroquinazolin–4–amina (Ejemplo 38) (100 mg, 0,56 mmol) e hidrazina (0,09 mL, 2,79 mmol) en etanol (5 mL) se calentó en un tubo sellado a 80ºC durante la noche. Luego de que la mezcla de reacción se enfriara, el precipitado resultante se recogió mediante filtración, se enjuagó con etanol y se secó al aire para proporcionar el compuesto del título (84 mg, 86%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 4,2 (bs, 2H), 4,6 (bs, 2H), 7,0 (t, J = 7,2 Hz, 1H), 7,27 (d, J = 8,0 Hz, 1H), 7,43 (s, 1H), 7,61 (s, 1H), 7,87 (d, J = 7,6 Hz, 1H).

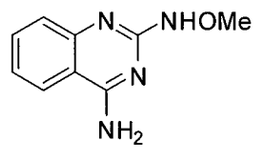
Ejemplo 43: 2–(hidroxiamino)quinazolin–4–amina



195

Preparada como en el Ejemplo 42 a partir de 2–cloroquinazolin–4–amina (Ejemplo 38) e hidroxilamina. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,44-7,35 (m, 2H), 7,78-7,74 (m, 2H), 8,24-8,22 (m, 1H), 8,95-8,76 (m, 2H). MS 177 (MH^+).

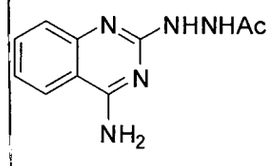
Ejemplo 44: 2–(metoxiamino)quinazolin–4–amina



197

Preparada como en el Ejemplo 42 a partir de 2–cloroquinazolin–4–amina (Ejemplo 38) y metoxilamina. ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,79 (s, 3H), 7,48-7,44 (m, 1H), 7,86-7,80 (m, 2H), 8,27 (d, J = 8,0 Hz, 1H), 8,99 (s, 1H), 9,16 (s, 1H), 12,39-12,08 (m, 1H). MS 191 (MH^+).

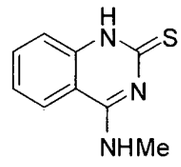
Ejemplo 45: N'–(4–aminoquinazolin–2–il)acetohidrazida



199

Preparada como en el Ejemplo 42 a partir de 2–cloroquinazolin–4–amina (Ejemplo 38) y metoxilamina. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,86 (s, 3H), 7,09 (t, J = 7,2 Hz,1H), 7,27 (d, J = 8,4 Hz,1H), 7,54-7,44 (m, 3H), 8,04-7,99 (m, 2H), 9,63 (s, 1H). MS 218 (MH^+).

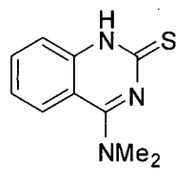
Ejemplo 46: 4–(metilamino)quinazolin–2(1H)–tiona



175

Una mezcla de 2–cloro–N–metilquinazolin–4–amina (Ejemplo 39) (100 mg, 0,52 mmol), tiourea (47,5 mg, 0,62 mmol) y ácido fórmico (0,02 mL, 0,52 mmol) en etanol (5 mL) se reflujó durante 1,5 h. Luego de enfriarse hasta temperatura ambiente, la mezcla de reacción se neutralizó con solución acuosa de NaOH diluida. El solvente se removió bajo vacío y el residuo se purificó mediante HPLC preparativa eluyendo con acetonitrilo y agua para proporcionar el compuesto del título (18 mg, 18%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,99 (d, J = 4,8 Hz, 3H), 7,25 (t, J = 7,6 Hz, 1H), 7,35 (d, J = 8,0 Hz, 1H), 7,65-7,61 (m, 1H), 8,0 (d, J = 8,0 Hz, 1H), 8,70 (d, J = 4,4 Hz, 1H), 12,32 (s, 1H). MS 192 (MH^+).

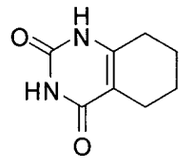
Ejemplo 47: 4–(dimetilamino)quinazolin–2(1H)–tiona



177

Preparada como en el Ejemplo 46 a partir de 2–cloro–N,N–dimetilquinazolin–4–amina (Ejemplo 40) y tiourea. ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,31 (s, 6H), 7,24-7,19 (m, 1H), 7,40-7,38 (m, 1H), 7,65-7,61 (m, 1H), 8,00 (d, J = 8,0 Hz, 1H), 12,35(s, 1H). MS 206 (MH^+).

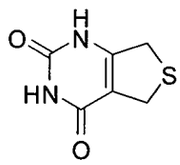
Ejemplo 48: 5,6,7,8–tetrahidroquinazolin–2,4(1H,3H)–diona



203

Una solución de 2–oxociclohexanocarbonitrilo (615 mg, 5,0 mmol) y urea (600 mg, 10,0 mmol) en HCl 1,25 N en EtOH (20 mL) se reflujó durante la noche. Luego de que ésta se enfriara hasta 0ºC, la precipitación se recogió mediante filtración, se lavó con EtOH/H_2O, y se secó bajo vacío durante la noche para proporcionar el producto como un sólido blanco. ^{1}H RMN (400 MHz, CD_3OD) δ 1,67-1,80 (m, 4H), 2,25-2,29 (m, 2H), 2,38-2,42 (m, 2H). MS 167 (MH^+).

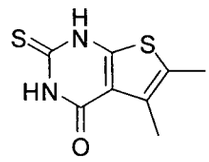
Ejemplo 49: 5,7–dihidrotieno[3,4–d]pirimidin–2,4(1H,3H)–diona



205

Preparada como en el Ejemplo 48 a partir de 4–oxotetrahidrotiofen–3–carbonitrilo como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,74 (t, J = 3,6 Hz, 2H), 3,96 (t, J = 3,6 Hz, 2H), 11,06(s, 1H), 11,21 (s, 1H). MS 171 (MH^+).

Ejemplo 50: 5,6–dimetil–2–tioxo–2,3–dihidrotieno[2,3–d]pirimidin–4(1H)–ona



9

A una suspensión de 4,5–dimetil–2–tioureidotiofen–3–carboxilato de etilo (Ejemplo 50a) (37 mg, 0,17 mmol) en EtOH seco (10 mL) se le adicionó hidróxido de sodio (21 mg, 0,52 mmol). Luego la mezcla de reacción se agitó a temperatura ambiente durante 5 minutos y se reflujó durante 10 minutos. La mezcla de reacción se enfrió hasta temperatura ambiente, se neutralizó con 10% AcOH y luego se concentró hasta sequedad. El residuo se purificó mediante cromatografía sobre gel de sílice (Gradiente 0–50% EtOAc en Hexanos) para proporcionar el compuesto del título (8 mg) en 24% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,25 (s, 6H), 12,24 (s, 1H), 13,27 (s, 1H). MS 202 (MH^+).

Ejemplo 50a: 4,5–dimetil–2–tioureidotiofen–3–carboxilato de etilo

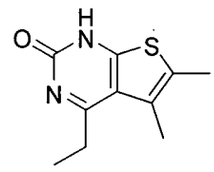
A una solución de 2–isotiocianato–4,5–dimetiltiofen–3–carboxilato de etilo (Ejemplo 50b) (1,21 g, 5,27 mmol) en diclorometano (10 mL) se le adicionó a 0°C amoníaco (7 M en MeOH, 1,12 mL, 7,91 mmol). Luego la mezcla de reacción se agitó a temperatura ambiente durante 3 h, se inactivó con agua y se extrajo con diclorometano (3 X). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$, se filtraron y se concentraron. El residuo anaranjado oscuro se purificó mediante cromatografía sobre gel de sílice (Gradiente 0–50% EtOAc en Hexanos) para proporcionar el compuesto del título (37,1 mg, 3%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,32 (t, 3H, J = 7,1 Hz), 2,18 (s, 3H), 2,19 (s, 3H), 4,30 (q, 2H, J = 7,1 Hz), 8,43 (s, 2H), 11,38 (s, 1H). MS 259 (MH^+).

Ejemplo 50b: 2–isotiocianato–4,5–dimetiltiofen–3–carboxilato de etilo

A una mezcla de tiofosgeno (5,10 mL, 7,64 mmol) y carbonato de calcio (1,05 g, 10,54 mmol) en $CHCl_3/H_2O$ (1/2 en volumen, 6 mL) se le adicionó gota a

gota una solución de 2–amino–4,5–dimetiltiofen–3–carboxilato de etilo (1,05 g, 5,27 mmol) en $CHCl_3$ (7 mL) a 0ºC durante un período de 1 h. Luego la mezcla de reacción se agitó durante 2,5 h a 0ºC, se lavó con agua (3 X). La capa orgánica se secó sobre $MgSO_4$, se filtró y se concentró para proporcionar el compuesto del título (1,21 g, 100%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,32 (t, 3H, J = 7,1 Hz), 2,19 (s, 3H), 2,30 (s, 3H), 4,28 (q, 2H, J = 7,1 Hz).

Ejemplo 51: 4–etil–5,6–dimetiltieno[2,3–d]pirimidin–2(1H)–ona



135

A una solución de 1–(4,5–dimetil–3–propioniltiofen–2–il)urea (Ejemplo 51a) (15,4 mg, 0,068 mmol) en EtOH seco (10 mL) se le adicionó hidróxido de sodio (8,4 mg, 0,20 mmol). Luego la mezcla de reacción se agitó a ta durante 30 minutos bajo nitrógeno. La mezcla de reacción se neutralizó con 10% AcOH y luego se concentró hasta sequedad. El residuo se purificó mediante cromatografía sobre gel de sílice (Gradiente 0–10% MeOH en diclorometano) para proporcionar el compuesto del título (2,7 mg, 19%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,42 (t, J = 7,6 Hz, 3H), 2,31 (s, 3H), 2,33 (s, 3H), 3,06 (q, J = 7,6 Hz, 2H). MS 209 (MH^+).

Ejemplo 51a: 1–(4,5–dimetil–3–propioniltiofen–2–il)urea

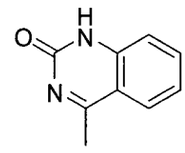
A una solución de trifosgeno (68 mg, 0,224 mmol) en diclorometano seco (2 mL) se le adicionó gota a gota una mezcla de 1–(2–amino–4,5–dimetiltiofen–3–il)propan–1–ona (Ejemplo 51b) (111 mg, 0,605 mmol) y DIEA (0,24 mL, 1,344 mmol) en diclorometano seco (3,5 mL) durante un período de 20 minutos. Luego de que la mezcla de reacción se agitara durante 5 minutos, se adicionó en una porción una mezcla de amoníaco (7 M en MeOH, 0,086 mL, 0,605 mmol) y DIEA

(0,24 mL, 1,344 mmol) en diclorometano seco (2mL). Luego la mezcla de reacción se agitó a temperatura ambiente durante 1 h bajo nitrógeno. La mezcla de reacción se concentró hasta sequedad. El residuo se disolvió en EtOAc (50 mL) y luego se lavó con 10% $NaHSO_4$, 5% $NaHCO_3$, y salmuera. La capa orgánica se secó sobre $MgSO_4$, se filtró y se concentró. El residuo amarillo se purificó mediante cromatografía sobre gel de sílice (Gradiente 0–50% EtOAc en Hexanos) para proporcionar el compuesto del título (15,4 mg, 30%). ^1H RMN (400 MHz, $CDCl_3$) δ 1,18 (t, 3H, J = 7,2 Hz), 2,25 (s, 3H), 2,30 (s, 3H), 2,87 (q, 2H, J = 7,2 Hz), 4,77 (s, 2H), 11,99 (s, 1H). MS 227 (MH^+).

Ejemplo 51b: 1–(2–amino–4,5–dimetiltiofen–3–il)propan–1–ona

A una solución de 3–oxopentanonitrilo (971 mg, 10 mmol) en EtOH seco (100 mL) se le adicionó a temperatura ambiente bajo nitrógeno azufre (2,57 g, 10 mmol), butanona (0,91 mL, 10 mmol) y morfolina (0,88 mL, 10 mmol). Luego la mezcla de reacción se reflujó a 90°C durante 6 h, y después se agitó durante la noche a temperatura ambiente bajo nitrógeno. La mezcla de reacción anaranjado marrón se concentró. El residuo se diluyó con agua, y se extrajo con EtOAc (2 X). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$, se filtraron y se concentraron. El residuo se purificó dos veces: primero mediante cromatografía sobre gel de sílice (Gradiente 0–25% EtOAc en Hexanos), y luego mediante HPLC Prep (0–90% acetonitrilo en agua) para proporcionar el compuesto del título (123 mg, 7%). ^1H RMN (400 MHz, $CDCl_3$) δ 1,17 (t, 3H, J = 7,2 Hz), 2,17 (s, 3H), 2,24 (s, 3H), 2,78 (q, 2H, J = 7,2 Hz), 6,81 (s, 2H). MS 184 (MH^+).

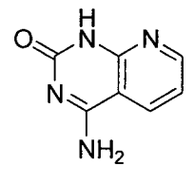
Ejemplo 52: 4–etil–5,6–dimetiltieno[2,3–d]pirimidin–2(1H)–ona



183

A una solución de bromuro de metilmagnesio (3,0 M en éter, 4,0 mL, 12,0 mmol) en éter seco (5 mL) se le adicionó gota a gota una solución de 2–aminobenzonitrilo (723 mg, 6,0 mmol) en éter seco (5 mL) a ta bajo nitrógeno. Luego de que se reflujara durante 2 h bajo nitrógeno, la mezcla de reacción se enfrió hasta 0ºC y se le adicionó gota a gota cloroformiato de metilo (0,7 mL, 9,0 mmol). Se adicionó THF seco (5 mL) para disolver el precipitado resultante. Luego la mezcla de reacción se reflujó durante la noche bajo nitrógeno. La mezcla de reacción se acidificó con HCl 1 N y luego se neutralizó con solución acuosa de 5% $NaHCO_3$. La mezcla acuosa se lavó con EtOAc y la capa acuosa se concentró. El residuo se purificó mediante HPLC Prep ((0–90% acetonitrilo en agua) para proporcionar el compuesto del título (15,2 mg). ^{1}H RMN (400 MHz, CD_3OD) δ 2,79 (s, 3H), 7,33 (d, J = 7,1 Hz, 1H), 7,34 (t, J = 7,1 Hz, 1H), 7,75 (td, J = 1,2, 7,8 Hz, 1H), 8,03 (dd, J = 1,2 8,4 Hz, 1H). MS 161 (MH^+).

Ejemplo 53: 4–aminopirido[2,3–*d*]pirimidin–2(1*H*)–ona



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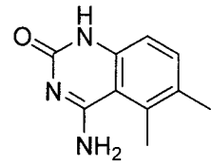
Una solución de *N*–(3–cianopiridin–2–ilcarbamoil)benzamida (ejemplo 53a) (360 mg, 1,35 mmol) y NaOH (2 N, 1,85mL) en EtOH (5mL) se agitó a 100ºC bajo nitrógeno durante media hora. Luego de enfriarse hasta temperatura ambiente, la

solución de reacción clara se filtró y el filtrado se neutralizó cuidadosamente con 10% AcOH con agitación enérgica a 0ºC. El precipitado resultante se recogió mediante filtración, y se lavó con 20% EtOH tibio en agua para proporcionar el producto final 4–aminopirido[2,3–d]pirimidin–2(1 H)–ona (120 mg, 55%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,22 (dd, J = 4,4 Hz, 4,8 Hz, 1H), 7,29 (dd, J = 4,8 Hz, 1H), 8,24 (dd, J = 2 Hz, 1,6 Hz, 1H), 8,59 (dd, J = 2 Hz, 1,6 Hz, 1H), 8,66-8,71 (m, 2H), 8,70 (d, J = 1,2 Hz, 1H). MS 162 (MH^+).

Ejemplo 53a: *N*–(3–cianopiridin–2–ilcarbamoil)benzamida

A una solución de 2–amino–3–cianopiridina (300 mg, 2,5 mmol) en 1,4-dioxano (5 mL) se le adicionó isocianato de benzoilo (370 mg, 2,5 mmol). Luego la mezcla de reacción se agitó a temperatura ambiente bajo nitrógeno durante la noche. La precipitación se recogió mediante filtración, se lavó con EtOAc/Hexanos (1:4), y se secó bajo vacío para proporcionar N–(3–cianopiridin–2–ilcarbamoil)benzamida como un sólido blanco (360 mg, 54%). MS 266 (MH^+).

Ejemplo 54: 5,6–dimetilquinazolin–2,4(1*H*,3*H*)–diona



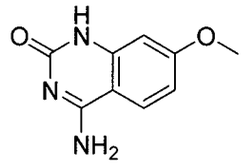
172

Preparada como en el Ejemplo 53 a partir de *N*–(2–ciano–3,4–dimetilfenilcarbamoil)benzamida (Ejemplo 54a) como un sólido blanco (90 mg, 66%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,24 (s, 3H), 2,54 (s, 3H), 6,87 (d, J = 8,4 Hz, 1H), 7,32 (d, J = 8,4 Hz, 1H), 10,51 (s, 1H). MS 189 (MH^+).

Ejemplo 54a: *N*–(2–ciano–3,4–dimetilfenilcarbamoil)benzamida:

Preparada como en el Ejemplo 53a a partir de 6–amino–2,3–dimetilbenzonitrilo e isocianato de benzoilo como un sólido blancuzco (210 mg, 72%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,27 (s, 3H), 2,43 (s, 3H), 7,48 (d, J = 6,4 Hz, 2H), 7,53 (t, J = 8 Hz, 7,6 Hz, 2H), 7,65 (t, J = 7,2 Hz, 1H), 7,94 (d, J = 8 Hz, 1H), 8,03 (d, J = 7,6 Hz, 2H), 11,29 (s, 1H), 11,37 (s, 1H). MS 293 (MH^+).

Ejemplo 55: 4–amino–7–metoxiquinazolin–2(1*H*)–ona



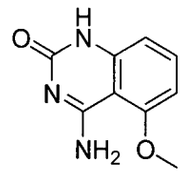
204

Preparada como en el Ejemplo 53 a partir de *N*–(2–ciano–5–metoxifenilcarbamoil)benzamida (Ejemplo 55a) como un sólido blanco (24 mg, 37%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,79 (s, 3H), 6,63 (d, J = 4 Hz, 1H), 6,67 (dd, J = 2,4 Hz, 2,8 Hz, 1H), 7,67 (br, 2H), 7,89 (d, J = 8,8 Hz, 1H), 10,61 (s, 1H). MS 191 (MH^+).

Ejemplo 55a: *N*–(2–ciano–5–metoxifenilcarbamoil)benzamida:

Preparada como en el Ejemplo 53a a partir de 2–amino–4–metoxibenzonitrilo e isocianato de benzoilo como un sólido blanco (99 mg, 45%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,86 (s, 3H), 6,87 (dd, J = 2,5 Hz, 2,4 Hz, 1H), 7,54 (t, J = 8 Hz, 2H), 7,66 (t, J = 1,2 Hz, 1H), 7,77 (d, J = 7,2 Hz, 1H), 7,89 (d, J = 8,4 Hz, 1H), 8,03 (d, J = 2,8 Hz, 2H), 11,35 (s, 1H), 11,52 (s, 1H). MS 295 (MH^+).

Ejemplo 56: 4–amino–5–metoxiquinazolin–2(1*H*)–ona



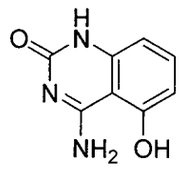
170

Preparada como en el Ejemplo 53 a partir de *N*–(2–ciano–3–metoxifenilcarbamoil)benzamida (Ejemplo 56a) como un sólido amarillo claro (35 mg, 51%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,93 (s, 3H), 6,67 (dd, J = 7,6 Hz, 8,4 Hz, 2H), 7,45 (t, J = 8 Hz, 1H), 7,75 (s, 1H), 7,93-7,97 (br, 1H), 10,69 (s, 1H). MS 191 (MH^+).

Ejemplo 56a: *N*–(2–ciano–3–metoxifenilcarbamoil)benzamida:

Preparada como en el Ejemplo 53a a partir de 2–amino–6–metoxibenzonitrilo e isocianato de benzoilo como un sólido anaranjado claro (118 mg, 41%). ^{1}H RMN (400 MHz, DMSO–d_6) δ 3,94 (s, 3H), 6,98 (d, J = 8 Hz, 1H), 7,54 (t, J = 8 hz, 2H), 7,64 (t, J = 8,4 Hz, 2H), 7,88 (d, J = 8,4 Hz, 1H), 8,04 (d, J = 5,6 Hz, 2H), 11,35 (s, 1H), 11,51 (s, 1H). MS 295 (MH^+).

Ejemplo 57: 4–amino–5–hidroxiquinazolin–2(1*H*)–ona



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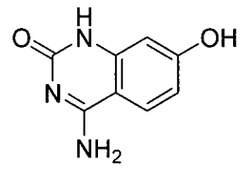
Preparada como en el Ejemplo 53 a partir de *N*–(2–ciano–3–hidroxifenilcarbamoil)benzamida (Ejemplo 57a) como un sólido verde (50 mg, 53%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 6,66 (d, J = 8,4 Hz, 1H), 6,73 (d, J = 7,6

Hz, 1H), 7,57 (t, J = 8,8 Hz, 1H), 9,47 (s, 1H), 9,68 (s, 1H), 11,84 (s, 1H). MS 177 (MH^+).

Ejemplo 57a: *N*–(2–ciano–3–hidroxifenilcarbamoil)benzamida:

Preparada como en el Ejemplo 53a a partir de 2–amino–6–hidroxibenzonitrilo e isocianato de benzoilo como un sólido blancuzco (166 mg, 46%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 6,76 (d, J = 8,4 Hz, 1H), 7,46 (t, J = 8 Hz, 1H), 7,54 (t, J = 8 Hz, 2H), 7,66-7,73 (m, 2H), 8,04-8,06 (d, J = 8 Hz, 2H), 11,24 (s, 1H), 11,30 (s, 1H), 11,42 (s, 1H). MS 281 (MH^+).

Ejemplo 58: 4–amino–7–hidroxiquinazolin–2(1*H*)–ona



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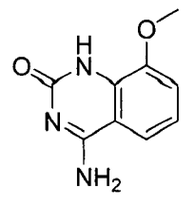
Preparada como en el Ejemplo 53 a partir de *N*–(2–ciano–5–hidroxifenilcarbamoil)benzamida (Ejemplo 58a) como un sólido gris claro (104 mg, 41%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 6,51 (s, 2H), 6,52 (d, J = 2,4 Hz, 1H), 7,69-7,72 (br, 1H), 7,82 (d, J = 9,2 Hz, 2H), 10,57 (br, 1H). MS 177 (MH^+).

Ejemplo 58a: *N*–(2–ciano–5–hidroxifenilcarbamoil)benzamida:

Preparada como en el Ejemplo 53a, pero se reflujó en acetona en lugar de 1,4-dioxano, a partir de 2–amino–4–hidroxibenzonitrilo e isocianato de benzoilo como un sólido amarillo (399 mg, 94%). MS 281 (MH^+).

Ejemplo 59: 4–amino–8–metoxiquinazolin–2(1*H*)–ona

747



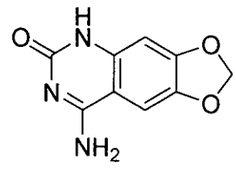
182

Preparada como en el Ejemplo 53 a partir de *N*–(2–ciano–6–metoxifenilcarbamoil)benzamida (Ejemplo 59a) como un sólido blanco oscuro (75mg, 39%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,86 (s, 3H), 7,02 (t, J = 8,4 Hz, 1H), 7,17 (d, J = 7,2 Hz, 1H), 7,56 (d, J = 7,6 Hz, 1H), 7,85 (br, 2H), 9,73(s, 1H). MS 191 (MH^+).

Ejemplo 59a: *N*–(2–ciano–6–metoxifenilcarbamoil)benzamida:

Preparada como en el Ejemplo 53a a partir de 2–amino–3–metoxibenzonitrilo e isocianato de benzoilo como un sólido anaranjado claro (280 mg, 95%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,89 (s, 3H), 7,42 (t, J = 3,2 Hz, 2H), 7,46 (d, J = 3,6 Hz, 1H), 7,54 (t, J = 8 Hz, 2H), 7,66 (t, J = 7,6 Hz, 1H), 8,05 (d, J = 8,6 Hz, 2H), 10,55 (s, 1H), 11,32 (s, 1H). MS 295 (MH^+).

Ejemplo 60: 8–amino–[1,3]dioxolo[4,5–*g*]quinazolin–6(5*H*)–ona



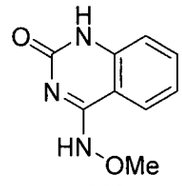
184

Preparada como en el Ejemplo 53 a partir de *N*–(6–cianobenzo[*d*][1,3]dioxol–5–ilcarbamoil)benzamida (Ejemplo 60a) como un sólido amarillo claro (80 mg, 77%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 6,24 (s, 2H), 6,74 (s, 1H), 7,75 (s, 1H), 9,36 (d, J = 10,4 Hz, 1H), 9,80 (d, J = 7,2 Hz, 1H), 12,01(s, 1H). MS 205 (MH^+).

Ejemplo 60a: *N*–(6–cianobenzo[*d*][1,3]dioxol–5–ilcarbamoil)benzamida:

Preparada como en el Ejemplo 53a a partir de 6–aminobenzo[*d*][1,3]dioxol–5–carbonitrilo e isocianato de benzoilo como un sólido amarillo (157 mg, 82%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 6,19 (s, 2H), 7,42 (s, 1H), 7,54 (t, J = 8 Hz, 2H), 7,66 (t, J = 7,6 Hz, 1H), 7,74 (s, 1H), 8,03 (d, J =9,2 Hz, 2H), 11,32 (d, J = 12,8 Hz, 2H). MS 309 (MH^+).

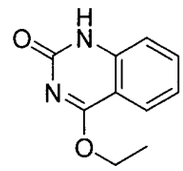
Ejemplo 61: 4–(metoxiamino)quinazolin–2(1*H*)–ona



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A una suspensión de 2,4–dicloroquinazolina (995 mg, 5,0 mmol) en EtOH seco (100 mL), se le adicionaron en una porción a 0°C clorhidrato de metoxiamina (569 mg, 5,5 mmol) y NaOH (227 mg, 5,5 mmol). La mezcla de reacción se agitó a 0°C durante 1 hora, luego se colocó en un refrigerador a 4°C durante 72 h. Una vez completa, la reacción se concentró, y el residuo se disolvió en EtOAc y se lavó con $NaHCO_3$ saturado (1x) y salmuera (1x). La fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró. El producto crudo se purificó mediante HPLC preparativa (10–90% CH_3CN en H_2O) para proporcionar 4–(metoxiamino)quinazolin–2(1*H*)–ona (556 mg, 36%) como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,68 (s, 3H), 7,02 (t, *J* = 7,4 Hz, 1H), 7,35 (d, *J* = 7,9 Hz, 1H), 7,52 (ddd, *J* = 8,1, 7,0, 1,5 Hz, 1H), 7,77 (dd, *J* = 7,8, 1,4 Hz, 1H), 10,13 (br s, 1H), 10,89 (br s, 1H). MS 192,2 (MH^+).

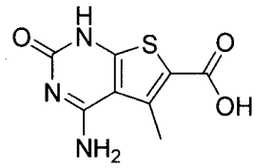
Ejemplo 62: 4–Etoxiquinazolin–2(1*H*)–ona



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La purificación mediante HPLC preparativa (10–90% CH_3CN en H_2O) de la reacción cruda del ejemplo 61 también proporcionó 4–etoxiquinazolin–2(1*H*)–ona (90 mg, 9%) como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,35 (t, J = 7,0 Hz, 3H), 4,44 (q, J = 7,0 Hz, 2H), 7,34 (ddd, J = 8,1, 7,0, 1,2 Hz, 1H), 7,46 (dd, J = 8,2, 1,0 Hz, 1H), 7,71 (ddd, J = 8,5, 7,0, 1,2 Hz, 1H), 8,01 (dd, J = 8,2, 1,5 Hz, 1H), 12,25 (br s, 1H). MS 191,1 (MH^+).

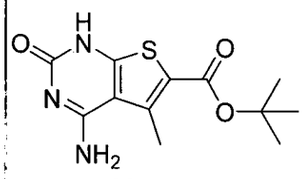
Ejemplo 63: Ácido 4–amino–5–metil–2–oxo–1,2–dihidrotieno[2,3–*d*]pirimidin–6–carboxílico



84

A una solución de 4–amino–5–metil–2–oxo–1,2–dihidrotieno[2,3–*d*]pirimidin–6–carboxilato de *terc*–butilo (Ejemplo 64a) (10,7 g, 38,03 mmol) en CH_2Cl_2 (25 mL), se le adicionó ácido trifluoracético (25 mL, 324,5 mmol). La mezcla de reacción se agitó a ta durante la noche. El sólido precipitado se recogió mediante filtración, y se lavó con CH_2Cl_2 para producir ácido 4–amino–5–metil–2–oxo–1,2–dihidrotieno[2,3–*d*]pirimidin–6–carboxílico (6,98 g, 82%) como un sólido marrón claro. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,78 (s, 3H). MS 226,0 (MH^+).

Ejemplo 64: 4–amino–5–metil–2–oxo–1,2–dihidrotieno[2,3–*d*]pirimidin–6–carboxilato de *terc*–butilo



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A una suspensión de 5–(3–benzoilureido)–4–ciano–3–metiltiofen–2–carboxilato de *terc*–butilo (ejemplo 64a) (18 g, 60,52 mmol) en EtOH (200 mL) se le adicionó NaOH (75 mL, 2 N). La suspensión se tornó clara, y la mezcla se calentó hasta reflujo durante 30 min. Luego de enfriarse hasta ta, la reacción se filtró, y el filtrado se enfrió hasta 0ºC en un baño de hielo/agua. La solución se neutralizó con 10% ácido acético. El sólido precipitado se recogió mediante filtración, y se calentó en EtOH a 80ºC bajo N_2 durante 20 min. Luego de enfriarse hasta ta, el producto se recogió mediante filtración y se lavó con 10% EtOH en H_2O para producir 4–amino–5–metil–2–oxo–1,2–dihidrotieno[2,3–*d*]pirimidin–6–carboxilato de *terc*–butilo (10,73 g, 63%) como un sólido marrón. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,51 (s, 9H), 2,73 (s, 3H), 3,18 (s, 2H). MS 282,2 (MH^+).

Ejemplo 64a: 5–(3–benzoilureido)–4–ciano–3–metiltiofen–2–carboxilato de *terc*–butilo

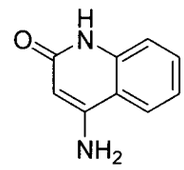
A una solución de 5–amino–4–ciano–3–metiltiofen–2–carboxilato de *terc*–butilo (ejemplo 64b) (16 g, 67,14 mmol) en dioxano (200 mL), se le adicionó isocianato de benzoilo (10 g, 67,14 mmol). La mezcla de reacción se agitó a ta durante la noche, y una vez completa se diluyó con EtOAc, se lavó con $NaHCO_3$, agua, salmuera, se secó sobre $MgSO_4$, se filtró y se concentró para producir 5–(3–benzoilureido)–4–ciano–3–metiltiofen–2–carboxilato de *terc*–butilo (21,78 g, 84%) como un sólido marrón. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,54 (s, 9H), 3,58

(s, 3H), 7,58 (t, *J* = 7,5 Hz, 2H), 7,71 (t, *J* = 7,5 Hz, 1H), 7,88 (d, *J* = 7,5 Hz, 1H), 8,05 (d, *J* = 7,5 Hz, 2H), 12,25 (br s, 1H).

Ejemplo 64b: 5–amino–4–ciano–3–metiltiofen–2–carboxilato de *terc*–butilo

A una solución de 3–oxobutanoato de terc–butilo (30 mL, 183,94 mmol) en EtOH seco (360 mL), se le adicionaron azufre elemental (5,90 g, 183,94 mmol), malononitrilo (12,16 g, 183,94 mmol) y trietilamina (25,6 mL, 183,94 mmol). La mezcla de reacción se calentó hasta 80°C, y se agitó durante 2 h. Luego de enfriarse hasta ta, la mezcla se concentró bajo presión reducida. El residuo resultante se disolvió en EtOAc, se lavó con $NaHCO_3$, agua, salmuera, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo crudo se purificó mediante cromatografía flash sobre gel de sílice (20% EtOAc en hexano) para producir 5–amino–4–ciano–3–metiltiofen–2–carboxilato de *terc*–butilo (31,2 g, 73%) como un sólido marrón.

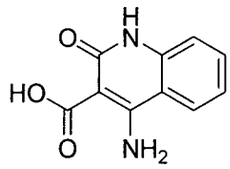
Ejemplo 65: 4–aminoquinolin–2(1H)–ona



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Se calentó ácido 4–amino–2–*oxo*–1,2–dihidroquinolin–3–carboxílico (Ejemplo 64) (0,030 g, 0,15 mmol) puro a 295°C durante 10 minutos, luego se enfrió hasta temperatura ambiente para proporcionar 4–aminoquinolin–2(1H)–ona (0,023 g, 99%) como un sólido amarillo claro. P.f.: > 250°C. ^{1}H RMN (400 MHz, DMSO-d_6) δ 5,42 (s, 1H), 6,55 (s, 2H), 7,07 (t, *J* = 7,6 Hz, 1H), 7,19 (d, *J* = 8,0 Hz, 1H), 7,42 (t, *J* = 7,2 Hz, 1H), 7,86 (d, *J* = 7,6 Hz, 1H), 10,71 (s, 1H). MS 161 (MH^+).

Ejemplo 66: Ácido 4–amino–2–oxo–1,2–dihidroquinolin–3–carboxílico



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Se disolvió 4–amino–2–oxo–1,2–dihidroquinolin–3–carboxilato de bencilo (Ejemplo 66a) (0,6 g, 2,04 mmol) en DMF (8 mL) y se calentó a 70ºC bajo un balón de hidrógeno en presencia de 10% Pd/C (0,15g) durante 1 hora. El Pd/C se separó mediante filtración y se lavó con diclorometano y los solventes se removieron bajo vacío. El residuo se disolvió/suspendió en NaOH (2 M, 40 mL), se agitó a temperatura ambiente durante 30 minutos y la solución se lavó con diclorometano. La capa acuosa se enfrió hasta 0ºC y se acidificó hasta un pH 1 con HCl 2 M. El precipitado resultante se recogió y se lavó con diclorometano para proporcionar ácido 4–amino–2–oxo–1,2–dihidroquinolin–3–carboxílico (0,050 g, 12%) como un sólido amarillo claro. P.f.: > 250ºC. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,32 (m, 1H), 7,39 (d, J = 7,6 Hz, 1H), 7,69 (m, 1H), 8,27 (d, J = 8,4 Hz, 1H), 8,86 (s, 1H), 9,87 (s, 1H), 11,95 (s, 1H). MS 205 (MH^+).

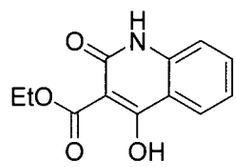
Ejemplo 66a: 4–amino–2–oxo–1,2–dihidroquinolin–3–carboxilato de bencilo

Se disolvió 4–cloro–2–oxo–1,2–dihidroquinolin–3–carboxilato de bencilo (Ejemplo 66b) (0,55 g, 1,75 mmol) en DMF (8 mL) y se adicionó 4–metoxibencilamina (0,56 mL, 4,31 mmol). La reacción se calentó a 115ºC durante 30 minutos, luego se enfrió hasta temperatura ambiente y se virtió en hielo agua. El precipitado resultante se disolvió en 10 mL de TFA y se agitó a temperatura ambiente durante 15 minutos, luego la mezcla se virtió en hielo agua. El precipitado resultante se recogió, se disolvió en diclorometano, se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar el 4–amino–2–oxo–1,2–dihidroquinolin–3–carboxilato de bencilo crudo (600 mg) el cual se utilizó como tal sin purificación adicional. MS 295 (MH^+).

Ejemplo 66b: 4–cloro–2–oxo–1,2–dihidroquinolin–3–carboxilato de bencilo

Se adicionó lentamente malonato de dibencilo (7,75 mL, 31,6 mmol) a una suspensión de 60% hidruro de sodio en aceite mineral (1,41 g, 35,3 mmol) en DMF anhidra (100 mL) a -20°C bajo nitrógeno. Luego de agitar a temperatura ambiente durante 30 minutos, se adicionó anhídrido isatoico (5,0 g, 30,7 mmol), y la reacción se calentó a 120°C durante 1 hora. Luego la reacción se enfrió hasta -50°C y se adicionó lentamente cloruro de oxalilo (10,7 mL, 123 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 horas luego se virtió en NaCl acuoso (10%, 750 mL) a 0°C, y el precipitado resultante se separó mediante filtración. El precipitado se disolvió en diclorometano, se secó sobre $MgSO_4$, se filtró y se evaporó bajo presión reducida. Se adicionó dietil éter al residuo, y el sólido resultante se recogió para proporcionar 4–cloro–2–oxo–1,2–dihidroquinolin–3–carboxilato de bencilo (3,56 g, 37% de rendimiento) el cual se utilizó sin purificación adicional. MS 314 (MH^+).

Ejemplo 67: 4–hidroxi–2–oxo–1,2–dihidroquinolin–3–carboxilato de etilo

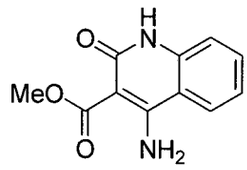


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Se adicionó lentamente malonato de dietilo (11,4 mL, 75,1 mmol) a una suspensión de 60% hidruro de sodio en aceite mineral (3,09 g, 77,3 mmol) en DMF anhidra (100 mL) a -10°C bajo nitrógeno. Luego de agitar a temperatura ambiente durante 30 minutos, se adicionó anhídrido isatoico (12,0 g, 73,6 mmol), y la reacción se calentó a 115°C durante 2,5 horas. La reacción se enfrió hasta temperatura ambiente, luego se virtió en hielo agua (1,4 L) y se acidificó hasta un pH 4 con HCl 2 M. El precipitado resultante se recogió, luego se disolvió/suspendió en diclorometano (450 mL). La solución de diclorometano se

separó mediante filtración luego se evaporó para proporcionar un residuo que se trituró enérgicamente con dietil éter (150 mL) durante 1 hora. El sólido se recogió para proporcionar 4–hidroxi–2–oxo–1,2–dihidroquinolin–3–carboxilato de etilo (3,63 g, 21%) como un sólido blanco. P.f.: 190ºC. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,31 (t, J = 7,2 Hz, 3H), 4,35 (q, J = 7,2 Hz, 2H), 7,21 (m, 1H), 7,27 (d, J = 8,0 Hz, 1H), 7,63 (m, 1H), 7,93 (dd, J = 0,8, 8,4 Hz, 1H), 11,51 (s, 1H), 13,40 (s, 1H). MS 234 (MH^+).

Ejemplo 68: 4–amino–2–oxo–1,2–dihidroquinolin–3–carboxilato de metilo



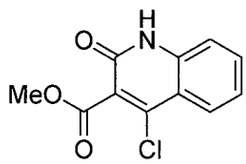
210

Se disolvió 4–(4–metoxibencilamino)–2–oxo–1,2–dihidroquinolin–3–carboxilato de metilo (Ejemplo 68a) (0,841 g, 2,49 mmol) en TFA (5 mL) y se agitó a temperatura ambiente durante 30 minutos. El TFA se removió bajo presión reducida, y el residuo se disolvió en diclorometano, luego se separó mediante precipitación adicionando dietil éter en exceso. El sólido resultante se recogió mediante filtración, se suspendió en diclorometano, y se lavó con bicarbonato de sodio concentrado. El sólido se recogió para proporcionar 4–amino–2–oxo–1,2–dihidroquinolin–3–carboxilato de metilo (0,230 g, 42%) como un sólido blanco. P.f.: 236ºC. ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,73 (s, 3H), 7,12 (t, J = 8,0 Hz, 1H), 7,17 (d, J = 8,0 Hz, 1H), 7,52 (t, J = 8,0 Hz, 1H), 8,08 (d, J = 8,0 Hz, 1H), 8,38 (bs, 2H), 10,88 (bs, 1H). MS 219 (MH^+).

Ejemplo 68a: 4–(4–metoxibencilamino)–2–oxo–1,2–dihidroquinolin–3–carboxilato de metilo

Se disolvió 4–cloro–2–oxo–1,2–dihidroquinolin–3–carboxilato de metilo (Ejemplo 69) (0,928 g, 3,91 mmol) en DMF (6 mL), y se adicionó 4–metoxibencilamina (1,14 mL, 8,78 mmol). La reacción se calentó a 90ºC durante 30 minutos, luego se enfrió hasta temperatura ambiente y se virtió en una mezcla agitada de 50 mL de hexanos y 100 mL de hielo agua. El precipitado resultante se recogió mediante filtración y se cromatografió además sobre gel de sílice (0% a 20% MeOH en diclorometano) para proporcionar 4–(4–metoxibencilamino)–2–oxo–1,2–dihidroquinolin–3–carboxilato de metilo como un sólido blancuzco (0,841 g, 64%). MS 339 (MH^+).

Ejemplo 69: 4–cloro–2–oxo–1,2–dihidroquinolin–3–carboxilato de metilo

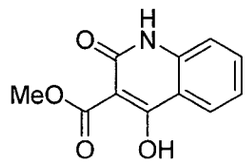


190

Se adicionó lentamente malonato de dimetilo (2,2 mL, 19,2 mmol) a una suspensión de 60% hidruro de sodio en aceite mineral (0,81 g, 20,3 mmol) en DMF anhidra (100 mL) a -10ºC bajo nitrógeno. Luego de agitar a temperatura ambiente durante 30 minutos, se adicionó anhídrido isatoico (3,0 g, 18,4 mmol), y la mezcla de reacción se calentó a 115ºC durante 2,5 horas. Luego la reacción se enfrió hasta -40ºC y se adicionó lentamente cloruro de oxalilo (6 mL, 68,8 mmol). La reacción se agitó a temperatura ambiente durante 20 minutos, y luego se virtió en 1200 mL de 10% NaCl a 0ºC. El precipitado resultante se recogió mediante filtración para proporcionar 4–cloro–2–oxo–1,2–dihidroquinolin–3–carboxilato de metilo crudo (1,40 g, 32%), el cual se utilizó sin purificación adicional. ^1H RMN

(400 MHz, DMSO-d_6) δ 3,87 (s, 3H), 7,39 (m, 2H), 7,70 (m, 1H), 7,92 (d, J = 8,4 Hz, 1H), 12,49 (s, 1H). MS 238 (MH^+).

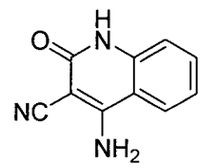
Ejemplo 70: 4–hidroxi–2–oxo–1,2–dihidroquinolin–3–carboxilato de metilo



192

Se adicionó lentamente malonato de dimetilo (2,2 mL, 19,2 mmol) a una suspensión de 60% hidruro de sodio en aceite mineral (0,81 g, 20,3 mmol) en DMF anhidra (50 mL) a -10°C bajo nitrógeno. Luego de agitar a temperatura ambiente durante 30 minutos, se adicionó anhídrido isatoico (3,0 g, 18,4 mmol), y la reacción se calentó a 115°C durante 2,5 horas. La reacción se enfrió hasta temperatura ambiente, luego se virtió en hielo agua (500 mL) y se acidificó hasta un pH 2 con HCl 2 M. El precipitado resultante se recogió mediante filtración para proporcionar 4–hidroxi–2–oxo–1,2–dihidroquinolin–3–carboxilato de metilo (2,89 g, 72%), el cual se utilizó sin purificación adicional. ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,86 (s, 3H), 7,23 (m, 2H), 7,63 (m, 1H), 7,94 (dd, J = 0,8, 8,0 Hz, 1H), 11,55 (s, 1H), 13,33 (s, 1H). MS 220 (MH^+).

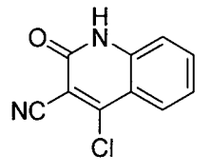
Ejemplo 71: 4–amino–2–oxo–1,2–dihidroquinolin–3–carbonitrilo



200

Se suspendió 4–cloro–2–oxo–1,2–dihidroquinolin–3–carbonitrilo (ejemplo 72) (0,66 g, 3,23 mmol) en DMF (7 mL), y se adicionó 4–metoxibencilamina (0,94 mL, 7,26 mmol). La reacción se calentó a 100ºC durante 1 hora y la DMF se removió bajo vacío. El residuo se disolvió en TFA (6 mL) y se agitó a temperatura ambiente durante 30 minutos y se adicionó diclorometano (10 mL). El producto sólido que se formó se recogió, se suspendió en agua y la solución se agitó durante la noche. El sólido se recogió mediante filtración para proporcionar 4–amino–2–oxo–1,2–dihidroquinolin–3–carbonitrilo (0,150 g, 25%) como un sólido blanco. P.f.: > 250ºC. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,19 (m, 2H), 7,57 (m, 1H), 7,88 (bs, 2H), 8,12 (d, J = 7,6 Hz, 1H), 11,23 (s, 1H). MS 186 (MH^+).

Ejemplo 72: 4–cloro–2–oxo–1,2–dihidroquinolin–3–carbonitrilo



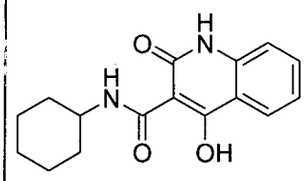
198

Se calentaron 2,4–dicloroquinolin–3–carbonitrilo (Ejemplo 72a) (0,95 g, 4,26 mmol) y acetato de amonio (0,36 g, 4,67 mmol) en ácido acético (20 mL) a 140ºC durante 4 horas, luego se enfriaron hasta temperatura ambiente. La reacción se virtió en hielo agua (400 mL), y el precipitado resultante se recogió mediante filtración para proporcionar 4–cloro–2–oxo–1,2–dihidroquinolin–3–carbonitrilo (0,668 g, 77%) como un sólido amarillo claro. P.f.: > 250ºC. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,42 (m, 2H), 7,79 (m, 1H), 7,96 (d, J = 8,4 Hz, 1H), 12,72 (s, 1H). MS 205 (MH^+).

Ejemplo 72a: 2,4–dicloroquinolin–3–carbonitrilo

Se disolvió N–ciclohexil–4–hidroxi–2–oxo–1,2–dihidroquinolin–3–carboxamida (Ejemplo 73) (1,18 g, 4,12 mmol) en oxicloruro de fósforo (15 mL) y se adicionó lentamente trietilamina (1,72 mL, 12,4 mmol). La reacción se calentó a 120ºC durante 7 horas, luego se enfrió hasta temperatura ambiente y se virtió cuidadosamente en hielo agua (300 mL). El precipitado resultante se recogió mediante filtración para proporcionar 2,4–dicloroquinolin–3–carbonitrilo (0,848 g, 92%), el cual se utilizó sin purificación adicional. MS 223 (MH^+).

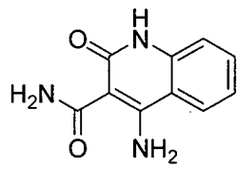
Ejemplo 73: N–ciclohexil–4–hidroxi–2–oxo–1,2–dihidroquinolin–3–carboxamida



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Se suspendió 4–hidroxi–2–oxo–1,2–dihidroquinolin–3–carboxilato de metilo (Ejemplo 70) (2,70 g, 12,3 mmol) en tolueno (27 mL), y se adicionó ciclohexilamina (1,40 g, 14,1 mmol). La reacción se calentó a 115ºC durante 5 horas, luego se enfrió hasta temperatura ambiente. Se adicionó dietil éter (50 mL), y el precipitado resultante se recogió mediante filtración para proporcionar N–ciclohexil–4–hidroxi–2–oxo–1,2–dihidroquinolin–3–carboxamida (1,22 g, 35%) como un sólido blancuzco. P.f.: 221ºC. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,37 (m, 4H), 1,55 (m, 1H), 1,68 (m, 2H), 1,88 (m, 2H), 3,86 (m, 1H), 7,28 (t, J = 8,0 Hz, 1H), 7,36 (d, J = 8,0 Hz, 1H), 7,68 (t, J = 7,6 Hz, 1H), 7,95 (d, J = 8,0 Hz, 1H), 10,35 (d, J = 7,6 Hz, 1H), 11,83 (bs, 1H). MS 287 (MH^+).

Ejemplo 74: 4–amino–2–oxo–1,2–dihidroquinolin–3–carboxamida



202

Se disolvió *N,N*–bis(4–metoxibencil)–4–(4–metoxibencilamino)–2–oxo–1,2–dihidroquinolin–3–carboxamida (Ejemplo 74a) (2,0 g, 3,55 mmol) en TFA (15 mL) y la solución se agitó a temperatura ambiente durante 6 horas. El TFA se removió bajo vacío, y el sólido resultante se agitó en agua durante la noche, luego se recogió mediante filtración para proporcionar 1,8 gramos de producto final crudo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,18 (m, 2H), 7,25 (d, J = 7,2 Hz, 1H), 7,56 (t, J = 8,0 Hz, 1H), 8,09 (d, J = 7,6 Hz, 2H), 9,83 (d, J = 4,8 Hz, 1H), 10,85 (bs, 1H), 11,12 (s, 1H). MS 204 (MH^+).

Ejemplo 74a: *N,N*–bis(4–metoxibencil)–4–(4–metoxibencilamino)–2–oxo–1,2–dihidroquinolin–3–carboxamida

Se disolvió 4–cloro–*N,N*–bis(4–metoxibencil)–2–oxo–1,2–dihidroquinolin–3–carboxamida (Ejemplo 74b) (4,25 g, 9,18 mmol) en DMF (20 mL), y se adicionó 4–metoxibencilamina (2,68 mL, 20,6 mmol). La reacción se calentó a 100ºC durante 1,5 horas, luego se enfrió hasta temperatura ambiente y se virtió en hielo agua (300 mL). El precipitado resultante se recogió mediante filtración y se cromatografió además sobre gel de sílice (0% a 20% MeOH en diclorometano) para proporcionar *N,N*–bis(4–metoxibencil)–4–(4–metoxibencilamino)–2–oxo–1,2–dihidroquinolin–3–carboxamida cruda (3,65 g, 71%), la cual se utilizó sin purificación adicional. MS 564 (MH^+).

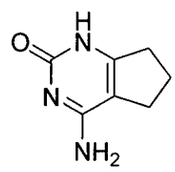
Ejemplo 74b: 4–cloro–*N,N*–bis(4–metoxibencil)–2–oxo–1,2–dihidroquinolin–3–carboxamida

Se adicionó trietilamina (5,73 mL, 41,2 mmol) a oxicloruro de fósforo (60 mL), seguida por 4–hidroxi–*N,N*–bis(4–metoxibencil)–2–oxo–1,2–dihidroquinolin–3–carboxamida (Ejemplo 74c) (6,11 g, 13,7 mmol). La reacción se calentó a 65°C durante 4 horas, luego se enfrió hasta temperatura ambiente y se virtió cuidadosamente en hielo agua (1200 mL). La solución se extrajo con diclorometano (2x200 mL). Las capas orgánicas se combinaron y se lavaron con agua, se secaron sobre $MgSO_4$, se filtraron y se evaporaron. El residuo se disolvió en diclorometano (18 mL) y se virtió en 200 mL de 30% hexanos en dietil éter. El precipitado resultante se recogió mediante filtración para proporcionar 4–cloro–*N,N*–bis(4–metoxibencil)–2–oxo–1,2–dihidroquinolin–3–carboxamida cruda (4,25 g, 67%) la cual se utilizó sin purificación adicional. MS 463 (MH^+).

Ejemplo 74c: 4–hidroxi–*N,N*–bis(4–metoxibencil)–2–oxo–1,2–dihidroquinolin–3–carboxamida

Se suspendieron 4–hidroxi–2–oxo–1,2–dihidroquinolin–3–carboxilato de etilo (Ejemplo 67) (3,58 g, 15,4 mmol) y bis(4–metoxibencil)amina (4,54 g, 17,6 mmol) en tolueno (36 mL) y se calentaron a 115°C durante 5 horas, luego se enfriaron hasta temperatura ambiente. Se adicionó dietil éter (50 mL), y el precipitado resultante se recogió mediante filtración para proporcionar 4–hidroxi–*N,N*–bis(4–metoxibencil)–2–oxo–1,2–dihidroquinolin–3–carboxamida cruda (6,45 g, 95%) la cual se utilizó sin purificación adicional.

Ejemplo 75: 4–amino–6,7–dihidro–1H–ciclopenta[d]pirimidin–2(5H)–ona



206

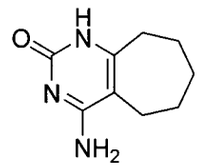
Una solución de N–(2–cianociclopent–1–enilcarbamoil) benzamida (ejemplo 75a) (500 mg, 1,96 mmol) y NaOH (2 N, 2,7 mL) en EtOH (20 mL) se

agitó a 100ºC bajo nitrógeno durante 2 horas. Luego de enfriarse hasta temperatura ambiente, la solución de reacción clara se filtró y el filtrado se neutralizó cuidadosamente con 10% AcOH con agitación enérgica a 0ºC. El precipitado resultante se recogió mediante filtración, se lavó con agua tibia y luego 20% EtOH en agua para proporcionar el producto final 4–amino–6,7–dihidro–1H–ciclopenta[d]pirimidin–2(5H)–ona (200 mg, 68%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 10,57 (brs, 1H), 6,93 (brs, 1H), 6,65 (brs, 1H), 2,56 (t, J = 7,2 Hz, 2H), 2,43 (t, J = 7,6 Hz, 2H) 1,96–1,89 (m, 2H). MS 152 (MH^+).

Ejemplo 75a: N–(2–cianociclopent–1–enilcarbamoil)benzamida

A una solución de 2–aminociclopent–1–enocarbonitrilo (400 mg, 3,7 mmol) en 1,4-dioxano (20 mL) se le adicionó isocianato de benzoilo (545 g, 3,7 mmol). Luego la mezcla de reacción se agitó a temperatura ambiente bajo nitrógeno durante la noche. El precipitado se recogió mediante filtración, se lavó con 1,4-dioxano, y se secó para proporcionar N–(2–cianociclopent–1–enilcarbamoil) benzamida (720 mg, 76%) como un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 11,33 (s, 1H), 11,22 (brs, 1H), 7,99-7,97 (m, 2H), 7,67-7,63 (m, 1H), 7,54-7,51 (m, 2H), 3,04-3,0 (m, 2H), 2,51-2,47 (m, 2H) 1,95-1,90 (m, 2H). MS 256 (MH^+).

Ejemplo 76: 4–amino–6,7,8,9–tetrahidro–1H–ciclohepta[d]pirimidin–2(5H)–ona



208

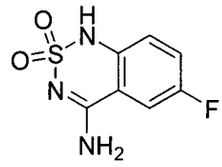
Preparada como en el Ejemplo 75 a partir de (Z)–N–(2–cianociclohept–1–enilcarbamoil) benzamida (Ejemplo 76a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 10,29

(brs, 1H), 6,72 (brs, 2H), 2,49-2,46 (m, 2H), 2,38-2,36 (m, 2H) 1,72-1,66 (m, 2H), 1,52-1,48 (m, 2H) 1,41-1,36 (m, 2H). MS 180 (MH^+).

Ejemplo 76a: (Z)–N–(2–cianociclohept–1–enilcarbamoil)benzamida:

Preparada como en el Ejemplo 75a a partir de (Z)–2–aminociclohept–1–enocarbonitrilo e isocianato de benzoilo como un sólido blanco. MS 284 (MH^+).

Ejemplo 77: 6–fluor–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



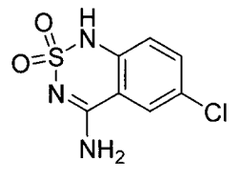
500

Una solución de N–(2–ciano–4–fluorfenil)sulfamida (Ejemplo 77a) (211 mg, 1,0 mmol) en EtOH (1 mL) se trató con NaOH (2,0 N, 1,0 mL, 2,0 mmol), y la solución resultante se calentó hasta 100ºC durante 0,5 h. Luego de que se enfriara hasta temperatura ambiente la solución se neutralizó con 10% AcOH. El precipitado resultante se recogió mediante filtración, se lavó con agua para proporcionar 6–fluor–1H–benzo[c][1,2,6]tiadiazin–4–amin4–2,2–dióxido como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,01-7,05 (dd, J = 8,8Hz, 5,2Hz, 1H), 7,45-7,5 (m, 1H), 7,80-7,83 (dd, J = 9,6Hz, 2,4Hz, 1H), 8,24 (s, 1H), 11,03 (s, 1H).

Ejemplo 77a: N–(2–ciano–4–fluorfenil)sulfamida

Una solución de 2–amino–5–fluorbenzonitrilo (136 mg, 1 mmol) y cloruro de sulfamoilo (114 mg, 1 mmol) en DMA (2 mL) se agitó a temperatura ambiente durante 2 horas. La reacción se purificó mediante Varian HPLC (10% Acetonitrilo/agua) para proporcionar N–(2–ciano–4–fluorfenil)sulfamida como un sólido blanco pálido. ^{1}H RMN (400 MHz, DMSO-d_6) 7,18 (m, 2H), 7,56-7,60 (dd J = 8,8 Hz, 2,8Hz 2H), 9,44 (s, 1H).

Ejemplo 78: 6–cloro–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



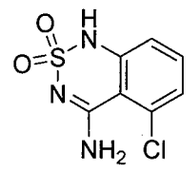
501

Preparada como en el Ejemplo 77 a partir de N–(2–ciano–4–clorofenil)sulfamida (Ejemplo 78a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,00-7,03 (d, J = 8,8Hz, 1H), 7,59-7,62 (dd, J = 8,8Hz, 4Hz, 1H), 8,05-8,06 (d, J = 2,4Hz, 1H), 8,27-8,33 (d, J = 25Hz,1H), 11,19 (s, 1H).

Ejemplo 78a: N–(2–ciano–4–clorofenil)sulfamida

Preparada como en el Ejemplo 77a a partir de 2–amino–5–clorobenzonitrilo y cloruro de sulfamoilo. ^{1}H RMN (400 MHz, DMSO-d_6) 7,3 (S, 2H), 7,54-7,56 (d J = 9,2 Hz, 1H), 7,74-7,77 (dd J = 8,4Hz, 2 Hz, 1H), 9,67 (s, 1H).

Ejemplo 79: 5–cloro–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



502

Preparado como en el Ejemplo 77 a partir de 5–cloro–(2–ciano–3–clorofenil)sulfamida (Ejemplo 79a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,00-7,03 (m,1H), 7,20-7,23 (dd, J = 8,4Hz, 1,2Hz, 1H), 7,48-7,52 (m, 1H), 7,75 (s,1H), 8,61 (s,1H), 11,22 (s, 1H).

Ejemplo 79a: N–(2–ciano–3–clorofenil)sulfamida

Preparada como en el Ejemplo 77a a partir de 2–amino–6–clorobenzonitrilo y cloruro de sulfamoilo.

Ejemplo 80: 5–fluor–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



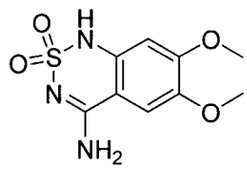
503

Preparado como en el Ejemplo 77 a partir de N–(2–ciano–3–fluorfenil)sulfamida (Ejemplo 80a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 6,84-6,97 (m, 2H), 7,53-7,57 (m, 1H), 7,59 (s, 1H), 8,42 (s,1H), 11,29 (s, 1H).

Ejemplo 80a: N–(2–ciano–3–fluorfenil)sulfamida

Preparada como en el Ejemplo 77a a partir de 2–amino–6–fluorbenzonitrilo y cloruro de sulfamoilo

Ejemplo 81: 6,7–dimetoxi–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



504

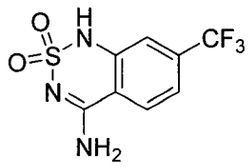
Preparado como en el Ejemplo 77 a partir de N–(2–ciano–4,5–dimetoxifenil)sulfamida (Ejemplo 81a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,75-3,79 (d, J = 14,4, 6H), 6,48 (s, 1H), 7,38 (s, 1H), 7,89 (b,1H), 8,04 (b,1H), 0,64 (s, 1H).

Ejemplo 81a: N–(2–ciano–4,5–dimetoxifenil)sulfamida

765

Preparada como en el Ejemplo 77a a partir de 2–amino–4,5–dimetoxibenzonitrilo y cloruro de sulfamoilo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,77-3,80 (d, J = 14,8, 6H), 7,05 (s, 1H), 7,06 (s, 1H), 7,29 (s,1H), 9,15 (s, 1H).

Ejemplo 82: 7–trifluormetil–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



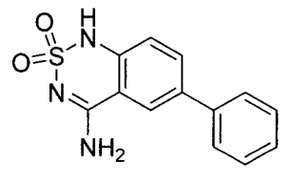
505

Preparado como en el Ejemplo 77 a partir de N–(2–ciano–5–trifluormetilfenil)sulfamida (Ejemplo 82a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,28 (s, 1H), 7,43-7,45 (dd, J = 8,8Hz, 1,6Hz, 1H), 8,14-8,16 (d, J = 7,6Hz, 1H), 8,41-8,52 (b, 2H), 11,40 (s, 1H).

Ejemplo 82a: N–(2–ciano–5–trifluormetilfenil)sulfamida

Preparada como en el Ejemplo 77a a partir de 2–amino–4–trifluormetilbenzonitrilo y cloruro de sulfamoilo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,53(s, 1H), 7,74-7,76 (d, J = 8,4Hz, 1H), 8,01-8,03 (dd, J = 8,4Hz, 1,6Hz, 1H), 8,23 (s,1H), 10,16 (b, 1H).

Ejemplo 83: 6–fenil–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



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Preparado como en el Ejemplo 77 a partir de N–(2–ciano–4–fenilfenil)sulfamida (Ejemplo 83a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 6,72-6,70(d, J

= 8Hz1H), 6,97-7,0 (m, 1H), 7,08-7,12 (m, 2H), 7,34-7,36 (m,2H), 7,50-7,53 (dd, *J* = 8,4Hz, 1,6Hz, 1H), 7,83 (b, 1H), 7,87 (s, 1H), 8,07(b, 1H) 10,75 (s, 1H).

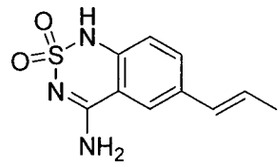
Ejemplo 83a: N–(2–ciano–4–fenilfenil)sulfamida

En un vial para microondas de 2 mL, se disolvieron ácido fenil borónico (75 mg, 0,6 mmol), N–(2–ciano–4–bromofenil)sulfamida (Ejemplo 83b) (137 mg, 0,5 mmol), y carbonato de potasio (400 mg, 1,5 mmol) en mezcla de DME/Agua (1,5 mL, DME/Agua 4:1). La solución se desgasificó mediante el burbujeo de gas N_2 hacia la solución de reacción durante 5 minutos y se adicionó Tetrakis trifenilfosfin paladio (25 mg, 0,025 mmol). La reacción se colocó en un reactor de microondas durante 5 minutos a 150°C. La reacción cruda se disolvió en agua y se lavó con acetato de etilo. La solución acuosa se evaporó bajo vacío para proporcionar N–(2–ciano–4–fenilfenil)sulfamida.

Ejemplo 83b: N–(2–ciano–4–bromolfenil)sulfamida

Preparada como en el Ejemplo 77a a partir de 2–amino–5–bromobenzonitrilo y cloruro de sulfamoilo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,31(s, 2H), 7,48-7,50 (d, *J* = 8 Hz, 1H), 7,85-7,88 (dd, *J* = 9,3Hz, 1,2Hz, 1H), 8,05-8,06 (d, *J* = 2,4Hz, 1H), 9,67 (s, 1H).

Ejemplo 84: 6–(E)–prop–1–enil–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



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Preparado como en el Ejemplo 77 a partir de N–(2–ciano–4–(E)–prop–1–enilfenil)sulfamida (Ejemplo 84a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,83-1,82(d, *J* =

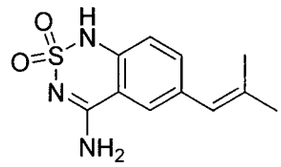
767

5,6Hz 3H), 6,29-6,25 (m, 2H), 6,85-6,87 (d, *J* = 8,4Hz, 1H), 7,5-7,53 (dd, *J* = 8,4Hz, 1,6Hz, 1H), 7,86 (s, 1H), 7,96 (b, 2H), 10,95 (b, 1H).

Ejemplo 84a: N–(2–ciano–4–(E)–prop–1–enilfenil)sulfamida

Preparada como en el Ejemplo 77a a partir de N–(2–ciano–4–bromolfenil)sulfamida (Ejemplo 83b) y ácido (*E*)–prop–1–enilborónico.

Ejemplo 85: 6–(2–metilprop–1–enil)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



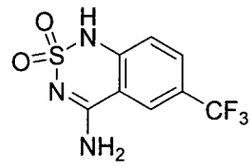
508

Preparado como en el Ejemplo 77 a partir de N–(2–ciano–4–(2–metilprop–1–enil) fenil)sulfamida (Ejemplo 85a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,8-1,85(dd, *J* = 22,4Hz, 1,2Hz, 6H), 6,18 (s, 1H), 6,84-6,86 (d, *J* = 8,4Hz, 1H), 7,31-7,33 (d, *J* = 8,4Hz, 1H), 7,66 (s, 1H), 7,78 (b, 2H), 10,91 (b, 1H).

Ejemplo 85a: N–(2–ciano–4–(2–metilprop–1–enil) fenil)sulfamida

Preparada como en el Ejemplo 77a a partir de N–(2–ciano–4–bromolfenil)sulfamida (Ejemplo 83b) y ácido 2–metilprop–1–enilborónico.

Ejemplo 86: 6–trifluormetil–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



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Preparado como en el Ejemplo 77 a partir de N–(2–ciano–4–trifluorfenil)sulfamida (Ejemplo 86a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,14-7,16 (d, J = 8,8Hz, 1H), 7,85-7,88 (dd, J = 8,8Hz, 1,6Hz, 1H), 8,37-8,39 (d, J = 9,6Hz, 1H), 8,52 (b, 2H), 11,56 (s, 1H).

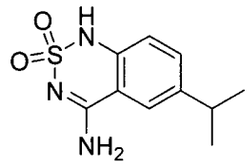
Ejemplo 86a: N–(2–ciano–4–trifluormetilfenil)sulfamida

Preparada como en el Ejemplo 77a a partir de 2–amino–5–(trifluormetil)benzonitrilo (Ejemplo 86b) y cloruro de sulfamoilo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,53(s, 2H), 7,74-7,76 (d, J = 8,4 Hz, 1H), 8,01-8,03 (dd, J = 8,4Hz, 1,6Hz, 1H), 8,23-8,233 (d, J = 1,2Hz, 1H), 10,16 (b, 1H).

Ejemplo 86b: 2–amino–5–(trifluormetil)benzonitrilo

En un vial para microondas de 20 mL, 2–bromo–4–(trifluormetil)anilina (238 mg, 1 mmol) y cianuro de cobre (90 mg, 1 mmol) se disolvieron en N–metilpirrolidona (NMP) (10 mL). La reacción se colocó en un reactor de microondas durante 5 minutos a 200°C. El crudo se disolvió en acetato de etilo y el precipitado se removió mediante filtración. La solución clara se lavó con agua. La capa orgánica se recogió, se secó sobre sulfato de sodio, y se evaporó bajo vacío. El residuo se purificó mediante Varia HPLC (10% acetonitrilo/agua) para proporcionar el compuesto del título.

Ejemplo 87: 6–isopropil–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



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Preparado como en el ejemplo 77 a partir de N–(2–ciano–4–isopropilfenil)sulfamida (Ejemplo 87a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,18-1,2(d,

J = 6,4Hz, 6H), 2,85 (m, 1H), 6,91-6,93 (d, *J* = 8,8Hz, 1H), 7,42-7,45 (dd, *J* = 8,8Hz, 2Hz 1H), 7,768-7,773 (d, *J* = 2Hz, 1H), 8,13 (b, 2H), 10,8 (s, 1H).

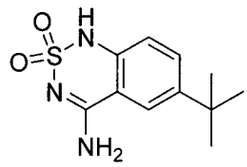
Ejemplo 87a: N–(2–ciano–4–isopropilfenil)sulfamida

Preparada como en el Ejemplo 77a a partir de 2–amino–5–isopropilbenzonitrilo (Ejemplo 87b) y cloruro de sulfamoilo.

Ejemplo 87b: 2–amino–5–isopropilbenzonitrilo

Preparado como en el Ejemplo 86b a partir de 2–bromo–4–isopropilanilina.

Ejemplo 88: 6–isobutil–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



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Preparado como en el Ejemplo 77 a partir de N–(2–ciano–4–isobutilfenil)sulfamida (Ejemplo 88a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,27(s, 9H), 6,92-6,94 (d, *J* = 8,4Hz, 1H), 7,58-7,61 (dd, *J* = 8,8Hz, 2,4Hz 1H), 7,84-7,85 (d, *J* = 2,4Hz, 1H), 8,06 (b, 1H), 8,33 (b, 1H), 10,8 (s, 1H).

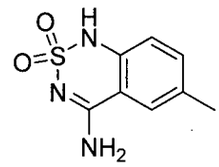
Ejemplo 88a: N–(2–ciano–4–isobutilfenil)sulfamida

Preparada como en el Ejemplo 77a a partir de 2–amino–5–isobutilbenzonitrilo (Ejemplo 88b) y cloruro de sulfamoilo.

Ejemplo 88b: 2–amino–5–isobutilbenzonitrilo

Preparado como en el Ejemplo 86b a partir de 2–bromo–4–isobutilanilina.

Ejemplo 89: 6–metil–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



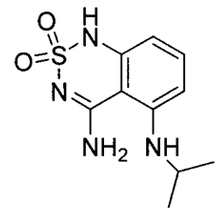
512

Preparado como en el Ejemplo 77 a partir de N–(2–ciano–4–metilfenil)sulfamida (Ejemplo 89a). MS 212 (MH^+).

Ejemplo 89a: N–(2–ciano–4–metilfenil)sulfamida

Preparada como en el Ejemplo 77a a partir de 2–amino–5–metilbenzonitrilo (Ejemplo 14b) y cloruro de sulfamoilo.

Ejemplo 90: N^5–isopropil–1H–benzo[c][1,2,6]tiadiazin–4,5–diamin–2,2–dióxido



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Una solución de 2–amino–6–(isopropilamino)benzonitril sulfamida (Ejemplo 90a) (0,14 g, 0,54 mmol) y NaOH (2 N, 0,54 mL) en EtOH (3 mL) se agitó a 90°C bajo nitrógeno durante 0,5 hora. La mezcla de reacción se enfrió hasta temperatura ambiente, y se concentró bajo vacío. Se adicionó H_2O (1 mL) y la mezcla de reacción se neutralizó hasta un pH ~ 3 con 10% AcOH. El precipitado resultante se extrajo con EtOAc, y luego de la evaporación de los solventes el residuo se purificó mediante cromatografía preparativa de capa delgada utilizando una solución de DCM/EtOAc (4:1) como eluyente, para proporcionar N^5–isopropil–1H–benzo[c][1,2,6]tiadiazin–4,5–diamin–2,2–dióxido (0,02 g). ^1H RMN (400 MHz,

DMSO-d_6) δ 1,11 (d, J = 6,4 Hz, 6H), 1,84 (bs, 1H), 5,24 (bs, NH), 6,22-6,19 (m, 2H, NH), 7,09 (t, J = 8,0 Hz, 1H), 7,48 (bs, 2H). MS 255 (MH^+).

Ejemplo 90a: 2–amino–6–(isopropilamino)benzonitril sulfamida

A una solución de 2–amino–6–(isopropilamino)benzonitrilo (Ejemplo 90b) (0,09 g, 0,54 mmol) en DMA (3 mL) se le adicionó cloruro de sulfamoilo (0,19 g, 1,62 mmol). La mezcla de reacción se agitó a temperatura ambiente bajo nitrógeno durante 2 horas, se diluyó con H_2O (5 mL) y se extrajo con EtOAc. Los solventes de las fases orgánicas combinadas se evaporaron y el residuo se purificó mediante cromatografía preparativa de capa delgada utilizando una solución de Hexano/EtOAc (3:2) como eluyente, para proporcionar 2–amino–6–(isopropilamino)benzonitril sulfamida (0,14 g). MS 255 (MH^+).

Ejemplo 90b: 2–amino–6–(isopropilamino)benzonitrilo

A una solución de 2–(isopropilamino)–6–nitrobenzonitrilo (Ejemplo 90c) (0,21 g, 1,02 mmol) en MeOH (9 mL) se le adicionó HCl concentrado (2 mL). Luego se adicionó a modo de porción Fe (0,17 g, 3,07 mmol), y la mezcla de reacción se reflujó a 90°C duranta 15 minutos. Luego de enfriarse hasta temperatura ambiente, de la dilución con H_2O (50 mL) y de la extracción con DCM (3x 50 mL), las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ y los solventes se evaporaron para proporcionar 2–amino–6–(isopropilamino)benzonitrilo (0,19 g, 100%) como un aceite marrón el cual se utilizó en la etapa siguiente sin purificación adicional alguna. MS 176 (MH^+).

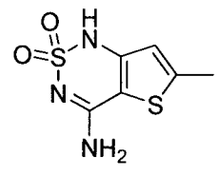
Ejemplo 90c: 2–(isopropilamino)–6–nitrobenzonitrilo

A una solución de 2,6–dinitrobenzonitrilo (0,58 g, 3,00 mmol) en DMF (6 mL) se le adicionó isopropilamina (0,71 g, 12,00 mmol) y la mezcla de reacción se agitó a 50°C bajo nitrógeno durante diez minutos. Luego de enfriarse hasta temperatura ambiente, de la dilución con H_2O y de la extracción con EtOAc, los solventes de las fases orgánicas combinadas se evaporaron y el residuo se

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purificó mediante cromatografía flash (sistema Biotage, 80 g de columna de gel de sílice) utilizando una solución de Hexano/EtOAc (3:2) como eluyente, para proporcionar 2–(isopropilamino)–6–nitrobenzonitrilo (0,22 g, 35%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,20 (d, J = 6,4 Hz, 6H), 3,85-3,80 (m, 1H), 5,94 (d, J = 8,0 Hz, NH), 7,26 (d, J = 9,0 Hz, 1H), 7,42 (d, J = 9,0 Hz, 1H), 7,60 (t, J = 8,8 Hz, 1H).

Ejemplo 91: 6–metil–1H–tieno[3,2–c][1,2,6]tiadiazin–4–amin–2,2–dióxido

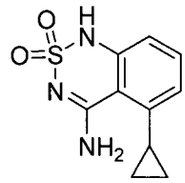


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Una solución de 3–amino–5–metiltiofen–2–carbonitrilo (250 mg, 1,0 eq., 1,81 mmol) y cloruro de sulfamoilo (2,71 mmol, 1,5 eq., 314 mg) en DMA (5 mL) se agitó a temperatura ambiente durante la noche. Se adicionaron agua (30 mL) y NaOH (1,5 eq., 10 N, 2,71 mmol, 271 uL) y la mezcla se congeló en un baño de acetona/hielo seco y los volátiles se removieron sobre el liofilizador. El sólido resultante se lavó con agua y luego se suspendió en EtOH (25 mL, 200 proof). A esta suspensión se le adicionó NaOH (1 N, 2,5 eq., 4,52 mmol, 4,52 mL) y la mezcla se calentó hasta reflujo durante 45 minutos. La mezcla de reacción se enfrió hasta temperatura ambiente y se inactivó con HCl (1 N, 2,5 eq., 4,52 mmol, 4,52 mL). El pH se reguló hasta ~ 1-2 con HCl 1 N y los volátiles se removieron sobre un evaporador rotatorio. El sóido resultante se suspendió en agua (10 mL), se agitó, se separó mediante filtración, y se lavó con agua. El producto crudo se secó en un horno de vacío para proporcionar 6–metil–1H–tieno[3,2–c][1,2,6]tiadiazin–4–amin–2,2–dióxido (257 mg) como un polvo blancuzco ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,46 (d, J = 0,8 Hz, 3H), 6,53 (q, J = 0,8 Hz, 1H), 7,75 (br.

s, 2H), 11,34 (s, 1H). ^{1}H RMN (400 MHz, CD_3OD) δ 2,52 (d, J = 0,8 Hz, 3H), 6,55 (q, J = 0,8 Hz, 1H). MS 218 (MH^+).

Ejemplo 92: 5–ciclopropil–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



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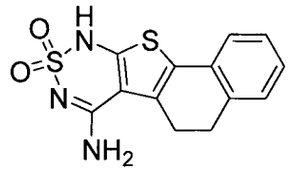
Una solución de 2–amino–6–ciclopropilbenzonitrilo (Ejemplo 92a) (1,0 eq., 626 μmol, 99 mg) y cloruro de sulfamoilo (1,5 eq., 939 μmol, 109 mg) en DMA (1 mL) se agitó en un vial de centelleo a temperatura ambiente. Luego de 2 horas, se adicionaron NaOH (1,5 eq., 939 μmol, 1 N, 939 μL) y agua (18 mL) y el producto precipitado resultante se agitó durante la noche a temperatura ambiente. El precipitado se separó mediante filtración y se lavó con agua (3 X 5 mL). El precipitado húmedo se disolvió en EtOH (5 mL, 200 proof) y se adicionó NaOH (2,5 eq., 1565 μmol, 1 N, 1565 μL). La reacción se calentó hasta 80° C con agitación durante la noche. La mezcla de reacción se enfrió hasta temperatura ambiente y se adicionó HCl (2,5 eq., 1565 μmol, 1 N, 1565 μL) al vial de reacción. El etanol y la mayoría del agua se removieron sobre el evaporador rotatorio. El precipitado resultante se suspendió en agua (5 mL), se agitó, se separó mediante filtración, y se lavó con agua (20 mL). El producto se secó en un horno de vacío para proporcionar 5–ciclopropil–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido (41 mg, 28%) como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,71 (m, 2H), 1,04 (m, 2H), 2,401 (m, 1H), 6,85 (d, J = 8 Hz, 2H), 7,37 (t + br. s, J = 8 Hz, 2H), 8,40 (br. s, 1H), 10,80 (s, 1H). ^{1}H RMN (400 MHz, CD_3OD) δ 0,89 (m, 2H),

1,15 (m,2H), 2,36 (m, 1H), 6,90 (d, *J* = 8 Hz, 1H), 6,97 (d, *J* = 8 Hz, 1H), 7,41 (t, *J* = 8 Hz, 1H). MS 238 (MH^+).

Ejemplo 92a: 2–amino–6–ciclopropilbenzonitrilo

Un vial para microondas de 2-5 mL que contenía 2–amino–6–bromobenzonitrilo (1,0 eq., 1,0 mmol, 197 mg), ácido ciclopropilborónico (1,3 eq., 1,3 mmol, 112 mg), y K_3PO_4 (3,5 eq., 3,5 mmol, 743 mg) se enjuagó con nitrógeno. A este vial se le adicionó tolueno (4 mL, Sure–Seal), agua (200 μL), triciclohexilfosfina (0,018 eq., 18,1 μmol, 88% pura, 20% en Hexanos, 32 μL), y acetato de paladio (II) (0,05 eq. "Pd," trímero, 0,0167 mmol, 12 mg), todos bajo nitrógeno. El vial de reacción se enjuagó con nitrógeno, se tapó con un septo con tapa a presión, y se sometió a microondas durante 30 minutos a 130°C. La mezcla de reacción se enfrió hasta temperatura ambiente, se particionó entre EtOAc (3 mL) y agua (1 mL). Las capas se separaron, la capa acuosa se extrajo con EtOAc (2 X 3 mL), las capas orgánicas combinadas se secaron sobre sulfato de sodio. El EtOAc se filtró a través de una frita PTFE de 0,45 μm para remdurante los sólidos finamente divididos y se concentró sobre un evaporador rotatorio. El producto crudo se purificó sobre gel de sílice (cartucho SiliaPrep de 80 g, elución gradiente desde 10% EtOAc/hexanos hasta 40% EtOAc/hexanos, cargado en solución en hexanos:DCM 1:1). Las fracciones que contenían el producto se concentraron sobre un evaporador rotatorio para proporcionar 2–amino–6–ciclopropilbenzonitrilo (99 mg, 62,7%) como un sólido ceroso amarillo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,668 (m, 2H), 0,979 (m, 2H), 1,978 (m, 1H), 5,882 (br. s, 2H), 6,128 (d, *J* = 8 Hz, 1H), 6,546 (d, *J* = 8 Hz, 1H), 7,129 (t, *J* = 8 Hz, 1H).

Ejemplo 93: 5,6–[4',5'–dihidronafto[1',2'–b]]–1H–tieno[2,3–c][1,2,6]tiadiazin–4–amin–2,2–dióxido



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Una solución de 2–sulfamoilamino–4,5–dihidronafto[1,2–b]tiofen–3–carbonitrilo (Ejemplo 93a) (336 mg, 1,11 mmol) en EtOH (5 mL) se trató con NaOH (2,0 N, 1,1 mL, 2,22 mmol), y la solución resultante se calentó hasta 100ºC y se agitó a esa temperatura durante 1,5 h. Luego de que se enfriara hasta temperatura ambiente, la solución clara se filtró, y el filtrado se neutralizó cuidadosamente con 10% AcOH mientras se agitaba enérgicamente a 0ºC. El precipitado resultante se recogió mediante filtración, se lavó con agua tibia, y 20% EtOH en agua para proporcionar 105 mg del producto del título como un sólido blancuzco en 31% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,48 (m, 4H), 5,70 (s, 2H), 6,87-6,89 (d, J = 7,6 Hz, 1H), 6,96 (t, 1H), 7,06-7,10 (m, 2H). MS 306 (MH^+).

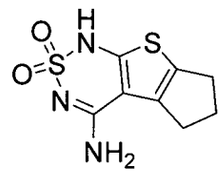
Ejemplo 93a: 2–sulfamoilamino–4,5–dihidronafto[1,2–b]tiofen–3–carbonitrilo

A una solución de 2–amino–4,5–dihidronafto[1,2–b]tiofen–3–carbonitrilo (Ejemplo 93b) (250 mg, 1,11 mmol) en dimetilacetamida (5 mL) se le adicionó cloruro de sulfamoilo (385 mg, 3,33 mmol). La mezcla de reacción se agitó a temperatura ambiente bajo nitrógeno durante aproximadamente 1 h, luego ésta se diluyó con agua y se extrajo con EtOAc, la capa orgánica se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se evaporó para proporcionar el producto crudo el cual se llevó a la etapa siguiente.

Ejemplo 93b: 2–amino–4,5–dihidronafto[1,2–b]tiofen–3–carbonitrilo

Una solución de 3,4–dihidronaftalen–2(1H)–ona (2,2 g, 15,05 mmol), malononitrilo (994 mg, 15,05 mmol), azufre (482 mg, 15,05 mmol), y trietilamina (1,52 g, 15,05 mmol) en EtOH (100 mL) se reflujó durante 2 h bajo nitrógeno. Luego el solvente se removió bajo presión reducida y el residuo se cristalizó a partir de EtOAc/Hexanos para proporcionar 2,91 g del producto del título como un sólido marrón en 86% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,59 (t, 2H), 2,86 (t, 2H), 6,94 (d, 1H), 7,03 (t, 1H), 7,11–7,16 (m, 2H), 7,48 (s, 2H).

Ejemplo 94: 5,6–(dihidro–4'H–ciclopenta–1'H)tieno[2,3–c][1,2,6]tiadiazin–4–amin–2,2–dióxido



517

Preparado como en el Ejemplo 93 a partir de 2–sulfamoilamino–5,6–dihidro–4H–ciclopenta[b]tiofen–3–carbonitrilo (Ejemplo 94a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,15 (m, 2H), 2,53 (m, 2H), 2,68 (m, 2H), 5,39 (s, 2H). MS 244 (MH^+).

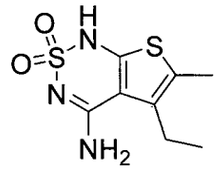
Ejemplo 94a: 2–sulfamoilamino–5,6–dihidro–4H–ciclopenta[b]tiofen–3–carbonitrilo

Preparado como en el Ejemplo 93a a partir de 2–amino–5,6–dihidro–4H–ciclopenta[b]tiofen–3–carbonitrilo (Ejemplo 94b). ^{1}H RMN (400 MHz, $CDCl_3$) δ 2,41 (m, 2H), 2,82 (m, 2H), 2,89 (m, 2H), 5,46 (s, 1H).

Ejemplo 94b: 2–amino–5,6–dihidro–4H–ciclopenta[b]tiofen–3–carbonitrilo

Preparado como en el Ejemplo 93b a partir de ciclopentanona. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,23 (m, 2H), 2,53 (m, 2H), 2,63 (m, 2H), 7,00 (s, 2H).

Ejemplo 95: 5–etil–6–metil–1H–tieno[2,3–c][1,2,6]tiadiazin–4–amin–2,2–dióxido



518

Preparado como en el Ejemplo 93 a partir de 2–sulfamoilamino–4–etil–5–metiltiofen–3–carbonitrilo (Ejemplo 95a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,01 (t, 3H), 2,06 (s, 3H), 2,53 (q, 2H), 5,50 (s, 2H). MS 246 (MH^+).

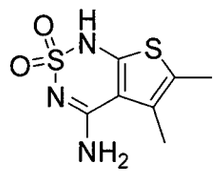
Ejemplo 95a: 2–sulfamoilamino–4–etil–5–metiltiofen–3–carbonitrilo

Preparado como en el Ejemplo 93a a partir de 2–amino–4–etil–5–metiltiofen–3–carbonitrilo (Ejemplo 95b). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,17 (t, 3H), 2,31 (s, 3H), 2,59 (q, 2H), 5,45 (s, 2H).

Ejemplo 95b: 2–amino–4–etil–5–metiltiofen–3–carbonitrilo

Preparado como en el Ejemplo 93b a partir de pentan–3–ona. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,01 (t, 3H), 2,06 (s, 3H), 2,33 (q, 2H), 6,84 (s, 2H). MS 167 (MH^+).

Ejemplo 96: 5,6–dimetil–1H–tieno[2,3–c][1,2,6]tiadiazin–4–amin–2,2–dióxido



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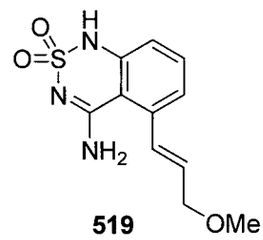
Preparado como en el Ejemplo 93 a partir de 2–sulfamoilamino–4,5–dimetiltiofen–3–carbonitrilo (Ejemplo 96a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,04 (s, 3H), 2,10 (s, 3H), 5,48 (s, 2H). MS 232 (MH^+).

Ejemplo 96a: 2–sulfamoilamino–4,5–dimetiltiofen–3–carbonitrilo

778

A una solución de 2–amino–4,5–dimetiltiofen–3–carbonitrilo (Ejemplo 4b) (1,0 g, 6,57 mmol) en 1,4-dioxano (50 mL) se le adicionó sulfamida (3,87 g, 40,30 mmol). La mezcla de reacción se calentó hasta reflujo durante 24 h, luego se enfrió hasta temperatura ambiente, el solvente se removió bajo presión reducida y el residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con EtOAc/Hexanos (2:3) para proporcionar 300 mg de producto como un aceite rojo oscuro. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,09 (3, 3H), 2,26 (s, 3H), 7,32 (s, 2H), 10,17 (s, 1H).

Ejemplo 97: (*E*)–5–(3–metoxiprop–1–enil)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



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Una solución de (*E*)–2–sulfamoilamino–6–(3–metoxiprop–1–enil)benzonitrilo (Ejemplo 97a) (139 mg, 0,5 mmol) en EtOH se trató con NaOH (2,0 N, 0,5 mL, 1,0 mmol), y la solución resultante se calentó hasta 100°C, y se agitó a esa temperatura durante 4 h. Luego de que se enfriara hasta temperatura ambiente, la solución de reacción clara se filtró, y el filtrado se neutralizó cuidadosamente con 10% AcOH mientras se agitaba enérgicamente a 0°C. El precipitado resultante se recogió mediante filtración, se lavó con agua tibia, y 20% EtOH en agua para proporcionar el producto del título (*E*)–5–(3–metoxiprop–1–enil)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido (108 mg, 78%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,29 (s, 3H), 4,06 (dd, J = 4,8, 1,2 Hz, 2H), 6,26 (dt, J = 16,2, 5,0 Hz, 1H), 6,91-6,95 (m, 2H), 6,97 (bs, 1H), 7,16 (d, J

= 7,2 Hz, 1H), 7,46 (t, *J* = 8,0 Hz, 1H), 8,31 (s, 1H), 10,93 (s, 1H). ^{13}C RMN (DMSO-d_6) δ 58,4, 72,5, 111,6, 117,0, 122,4, 129,0, 132,5, 134,0, 138,1, 143,7, 162,9. MS 268 (MH^+).

Ejemplo 97a: (*E*)–2–sulfamoilamino–6–(3–metoxiprop–1–enil)benzonitrilo

A una solución de (*E*)–2–amino–6–(3–metoxiprop–1–enil)benzonitrilo (Ejemplo 97b) (188 mg, 1,0 mmol) en DMA se le adicionó NH_2SO_2Cl (347 mg, 3,0 mmol) a 0ºC bajo nitrógeno. Luego la mezcla de reacción se agitó a temperatura ambiente durante 6 hs, se diluyó con EtOAc, se lavó con salmuera (5X), y se secó sobre Na_2SO_4. El solvente se evaporó bajo presión reducida para proporcionar (*E*)–2–sulfamoilamino–6–(3–metoxiprop–1–enil)benzonitrilo como un sólido amarillo pálido, el cual se utilizó en la etapa siguiente sin purificación adicional.

Ejemplo 97b: (*E*)–2–amino–6–(3–metoxiprop–1–enil)benzonitrilo

A una solución de 2–amino–6–bromobenzonitrilo (1,0 g, 5,0 mmol), (*E*)–2–(3–metoxipropenil)–4,4,5,5–tetrametil–(1,3,2)–dioxaboroano (1,2 g, 6,0 mmol), y K_2CO_3 (1,38 g, 10,0 mmol) en DME/H_2O (4:1, 20 mL) se le adicionó $Pd(PPh_3)_4$ (289 mg) a temperatura ambiente bajo nitrógeno. La mezcla de reacción se entibió hasta 85ºC y se agitó a esa temperatura bajo nitrógeno durante la noche. Luego de que se enfriara hasta temperatura ambiente, la solución de reacción se diluyó con EtOAc, se lavó con salmuera (2X), y se secó sobre Na_2SO_4. Luego de la remoción del el solvente, el residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con 30% EtOAc en hexanos para proporcionar el compuesto del título como un sólido amarillo pálido. ^{1}H RMN (400 MHz, $CDCl_3$) δ 3,40 (s, 3H), 4,12 (dd, *J* = 6,0, 1,8 Hz, 2H), 4,42 (s, 2H), 6,42 (dt, *J* = 16,0, 5,8 Hz, 1H), 6,63 (d, *J* = 8,0 Hz, 1H), 6,85 (d, *J* = 16,0 Hz, 1H), 6,93 (d, *J* = 8,0 Hz, 1H), 7,26 (t, *J* = 8,0 Hz, 1H). ^{13}C RMN ($CDCl_3$) δ 58,2, 72,7, 95,4, 113,6, 115,0, 116,6, 128,5, 130,9, 133,4, 140,3, 150,1. MS 189 (MH^+).

780

Ejemplo 98: 5–(3–metilbut–2–en–2–il)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



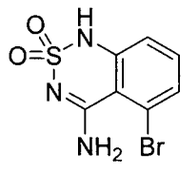
520

Preparado como en el Ejemplo 97 a partir de 2–amino–6–(3–metilbut–2–en–2–il)benzonitrilo (Ejemplo 98a) como un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,53 (s, 3H), 1,80 (s, 3H), 1,86 (s, 3H), 6,70 (dd, J = 7,2, 1,0 Hz, 1H), 6,82 (s, 1H), 6,93 (dd, J = 7,2, 1,0 Hz, 1H), 7,46 (t, J = 7,2 Hz, 1H), 8,28 (s, 1H), 10,98 (s, 1H). ^{13}C RMN (DMSO-d_6) δ 20,8, 21,4, 22,6, 109,4, 116,8, 124,4, 129,7, 132,0, 134,3, 144,1, 144,6, 162,1. MS 266 (MH^+).

Ejemplo 98a: 2–amino–6–(3–metilbut–2–en–2–il)benzonitrilo

Preparado como en el Ejemplo 1a a partir de 2–amino–6–bromobenzonitrilo y ácido 3–metil–2–buten–2–ilborónico como un aceite anaranjado. MS 187 (MH^+).

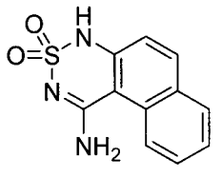
Ejemplo 99: 5–bromo–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



521

Preparado como en el Ejemplo 97 a partir de 2–amino–6–bromobenzonitrilo como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,03-7,07 (m, 1H), 7,37-7,42 (m, 2H), 7,65 (s, 1H), 8,60 (s, 1H), 11,19 (s, 1H). ^{13}C RMN (DMSO-d_6) δ 113,3, 118,0, 121,0, 129,0, 135,0, 145,5, 161,3. MS 275, 277 (MH^+).

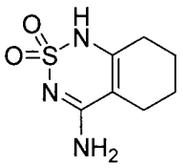
Ejemplo 100: 4H–nafto[2,1–c][1,2,6]tiadiazin–1–amin–2,2–dióxido



522

Preparado como en el Ejemplo 97 a partir de 2–amino–1–naftonitrilo como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,17 (d, J = 8,0 Hz, 1H), 7,48 (dt, J = 1,2, 8,0 Hz, 1H), 7,63 (dt, J = 1,2, 8,0 Hz, 1H), 7,90 (s, 1H), 7,93 (dd, J = 1,2, 8,0 Hz, 1H), 8,24 (s, 1H), 8,39 (d, J = 8,0 Hz, 1H), 11,42 (s, 1H). ^{13}C RMN (DMSO–d_6) δ 106,3, 118,2, 124,9, 125,4, 129,2, 129,8, 130,0, 130,2, 135,9, 143,7, 163,2. MS 248 (MH^+).

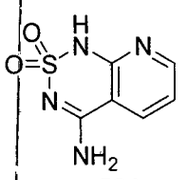
Ejemplo 101: 5,6,7,8–tetrahidro–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



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Preparado como en el Ejemplo 97 a partir de 2–aminociclohex–1–enocarbonitrilo (Ejemplo 10b) como un sólido amarillo pálido. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,54-1,62 (m, 4H), 2,08 (t, J = 5,4 Hz, 2H), 2,20 (t, J = 5,4 Hz, 2H), 6,94 (s, 1H), 7,41 (s, 1H), 10,53 (s, 1H). ^{13}C RMN (DMSO–d_6) δ 21,6, 22,5, 28,3, 97,6, 150,3, 163,4. MS 202 (MH^+).

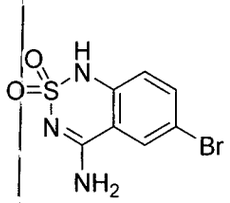
Ejemplo 102: 1H–pirido[2,3–c][1,2,6]tiadiazin–4–amin–2,2–dióxido



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Una mezcla agitada de 2–aminonicotinonitrilo (238 mg, 2,0 mmol), sulfamida (192 mg, 2,0 mmol), y 1 mL de DBU se calentó a 160ºC bajo nitrógeno durante la noche. Luego de que se enfriara hasta temperatura ambiente, la mezcla de reacción se diluyó con agua, y se extrajo tres veces con EtOAc. La capa acuosa se secó bajo vacío, y el residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con 15% MeOH en diclorometano para proporcionar el compuesto del título como un sólido amarillo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 6,87 (t, J = 5,6 Hz, 1H), 7,95 (brs, 2H), 8,22 (d, J = 5,2 Hz, 1H), 8,39-8,37 (m, 1H), 12,58 (brs, 1H). MS 199 (MH^+).

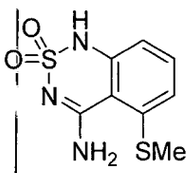
Ejemplo 103: 6–bromo–1H–benzo[c][1,2,6]tiadiazin–4–amina



525

Preparada como en el Ejemplo 97 a partir de 2–amino–5–bromobenzonitrilo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 6,95 (d, J = 8,8 Hz, 1H). 7,73-7,70 (m, 1H), 8,17 (d, J = 1,6 Hz, 1H), 8,28 (brs, 2H), 11,9 (s, 1H). MS 275, 277 (MH^+).

Ejemplo 104: 5–(metiltio)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



526

Preparado como en el Ejemplo 97 a partir de 2–sulfamoilamino–6–(metiltio)benzonitrilo (Ejemplo 104a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,39 (s, 3H), 6,38-6,36 (m, 1H), 6,47-6,45 (m, 1H), 6,59 (brs, 2H), 6,97-6,93 (m, 1H). MS 244 (MH^+).

Ejemplo 104a: 2–sulfamoilamino–6–(metiltio)benzonitrilo

Preparado como en el Ejemplo 1 a partir de 2–amino–6–(metiltio)benzonitrilo (Ejemplo 8b) y cloruro de sulfamoilo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,56 (s, 3H), 7,18 (d, J = 8,4 Hz, 1H), 7,26 (s, 2H), 7,33 (d, J = 8,0 Hz, 1H), 7,59 (t, J = 8,40 Hz, 1H), 9,51 (s, 1H).

Ejemplo 104b: 2–amino–6–(metiltio)benzonitrilo

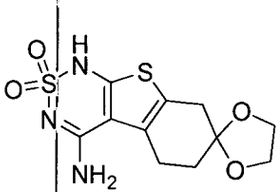
A una solución de 2–(metiltio)–6–nitrobenzonitrilo (Ejemplo 104c) (1,5 g, 7,73 mmol) en EtOH (150 ml)/THF (50 ml)/EtOAc (50 ml) se le adicionaron 200 mg de 10% Pd/C. La mezcla de reacción se hidrogenó en parte en un agitador durante la noche. Luego de la filtración, la solución filtrada se secó bajo vacío, y el residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con EtOAc/Hexano para proporcionar el compuesto del título (79%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 2,51 (s, 3H), 4,47 (s, 2H), 6,53-6,51 (m, 1H), 6,58 (d, J = 8,0 Hz, 1H), 7,27–7,21 (m, 1H).

Ejemplo 104c: 2–(metiltio)–6–nitrobenzonitrilo

A una suspensión de 2,6–dinitrobenzonitrilo (5,0 g, 25,89 mmol) en 100 mL de MeOH anhidro se le adicionó gota a gota NaSMe (2,0 g en 100 mL de MeOH) a través de un embudo de adición bajo nitrógeno a 0ºC. Luego de completar la adición, la mezcla de reacción se agitó a 0ºC durante 1 h. Luego se adicionaron a

la mezcla de reacción 250 mL de agua, el precipitado resultante se recogió mediante filtración y se secó al aire para proporcionar el producto del título como un sólido amarillo (93%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 2,64 (s, 3H), 7,60-7,57 (m, 1H), 7,70 (t, J = 8,4 Hz, 1H), 8,01-7,99 (m, 1H).

Ejemplo 105: 5,6–(1',2',3',4'–tetrahidro–2',2'–etilendioxido–benzo)–1H–tieno-[2,3–c][1,2,6] tiadiazin–4–amin–2,2–dióxido



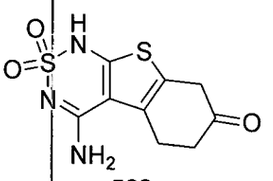
527

Preparado como en el Ejemplo 97 a partir de 2–amino–5,7–dihidro–4H–spiro[benzo[b]tiofen–6,2'–[1,3]dioxolan]–3–carbonitrilo (Ejemplo 105a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,80 (t, J = 6,0 Hz, 2H), 2,65 (s, 2H), 2,79 (t, J = 6,0 Hz, 2H), 3,94-3,91 (m, 4H), 5,99 (brs, 2H). MS 316 (MH^+).

Ejemplo 105a: 2–amino–5,7–dihidro–4H–spiro[benzo[b]tiofen–6,2'–[1,3] dioxolan]–3–carbonitrilo

Una solución de 1,4–dioxaspiro[4,5]decan–8–ona (5,0 g, 32,0 mmol), malononitrilo (2,11 g, 32,01 mmol), azufre (1,03 g, 32,0 mmol), y trietilamina (4,5 mL, 32,0 mmol) en EtOH (100 mL) se agitó a temperatura ambiente durante 1 h bajo nitrógeno. Luego el solvente se removió bajo presión reducida y el residuo se trató con EtOAc. El filtrado resultante se recogió mediante filtración y se secó al aire para proporcionar el producto del título como un sólido verde claro (44%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,77 (t, J = 6,8 Hz, 2H), 2,43 ((t, J = 6,4 Hz, 2H), 2,57 (s, 2H), 3,88 (s, 4H), 6,99 (s, 2H). MS 237 (MH^+).

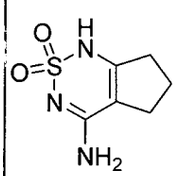
Ejemplo 106: 5,6–(1',2',3',4'–tetrahidro–2'–oxido–benzo)–1H–tieno[2,3–c] [1,2, 6]tiadiazin–4–amin–2,2–dióxido



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Una mezcla agitada de 5,6–(1',2',3',4'–tetrahidro–2',2'–etilenedioxido–benzo)–1H–tieno[2,3–c][1,2,6] tiadiazin–4–amin–2,2–dióxido (Ejemplo 105) (130 mg, 0,41 mmol), 5 mL de THF y 1 mL de HCl 2 N se reflujó bajo nitrógeno durante 2 hs. Luego de que se enfriara hasta temperatura ambiente, el precipitado resultante se recogió mediante filtración y se secó al aire para proporcionar el producto del título como un sólido rosado. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,57 (t, J = 6,8 Hz, 2H), 3,10 (t, J = 6,4 Hz, 2H), 3,50 (s, 2H), 6,91 (brs, 1H), 7,88 (brs, 1H), 11,81 (brs, 1H). MS 272 (MH^+).

Ejemplo 107: 1,5,6,7–tetrahidrociclopenta[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



529

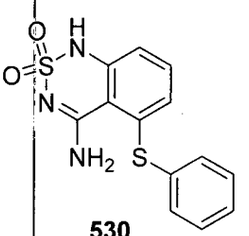
Una solución de 2–sulfamoilaminociclopent–1–enocarbonitrilo (Ejemplo 107a) (108 mg, 0,57 mmol) en EtOH se trató con NaOH (2,0 N, 0,5 mL), y la solución resultante se calentó hasta 100ºC y se agitó a esa temperatura durante 4 h. Luego de que se enfriara hasta temperatura ambiente, la solución de reacción se neutralizó cuidadosamente con HCl 2 N mientras se agitaba enérgicamente a 0ºC. La solución de reacción se secó bajo vacío, y el residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con 10% MeOH en diclorometano para

proporcionar el compuesto del título. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,69-1,63 (m, 2H), 2,2 (t, J = 7,6 Hz, 2H), 2,3 (t, J = 6,8 Hz, 2H), 5,12 (s, 2H). MS 188 (MH^+).

Ejemplo 107a: 2–sulfamoilaminociclopent–1–enocarbonitrilo

A una solución de 2–aminociclopent–1–enocarbonitrilo (440 mg, 4,07 mmol) en 10 mL de DMA se le adicionó cloruro de sulfamoilo (941,3 mg, 8,15 mmol), y la mezcla resultante se agitó a temperatura ambiente bajo nitrógeno durante 2 h. Luego ésta se diluyó con EtOAc, la capa orgánica se lavó con salmuera y se secó bajo vacío, y el residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con EtOAc/Hexano para proporcionar el compuesto del título. ^{1}H RMN (400 MHz, $CDCl_3$) δ 2,04-1,97 (m, 2H), 2,61-2,57(m, 2H), 2,9-2,86 (m, 2H), 5,66 (s, 2H), 8,04 (s, 1H).

Ejemplo 108: 5–(feniltio)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



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Preparado como en el Ejemplo 97 a partir de 2–sulfamoilamino–6–(feniltio)benzonitrilo (Ejemplo 108a) ^{1}H RMN (400 MHz, DMSO-d_6) δ 6,43-6,40 (m, 1H), 6,64-6,62 (m, 1H), 6,75 (brs, 2H), 7,01-6,97 (m, 1H), 7,22-7,15 (m, 3H), 7,3-7,26 (m, 2H). MS 306 (MH^+)

Ejemplo 108a: 2–sulfamoilamino–6–(feniltio)benzonitrilo

Preparado como en el Ejemplo 104a a partir de 2–amino–6–(feniltio)benzonitrilo (Ejemplo 108b). ^{1}H RMN (400 MHz, DMSO-d_6) δ 6,85-6,82 (m, 1H), 7,32 (s, 2H), 7,47-7,42 (m, 6H), 7,53 (t, J = 8,0 Hz, 1H), 9,63 (s, 1H).

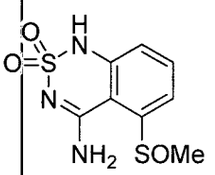
Ejemplo 108b: 2–amino–6–(feniltio)benzonitrilo

Preparado como en el Ejemplo 104b a partir de 2–nitro–6–(feniltio)benzonitrilo (Ejemplo 108c). ^{1}H RMN (400 MHz, DMSO-d_6) δ 6,20 (brs, 2H), 6,32-6,30 (m, 1H), 6,69-6,67 (m, 1H), 7,19 (t, J = 8,0 Hz, 1H), 7,4-7,34 (m, 5H).

Ejemplo 108c: 2–nitro–6–(feniltio)benzonitrilo

A una mezcla de 2, 6–dinitrobenzonitrilo (2,0 g, 10,36 mmol) y K_2CO_3 (1,43 g, 10,36 mmol) en 5 mL de DMF anhidra se le adicionó gota a gota PhSH (1,14 ml en 5 mL de DMF) bajo nitrógeno a 0ºC. Luego de completar la adición, la mezcla de reacción se agitó a 0ºC durante 0,5 h. Luego la mezcla de reacción se virtió en 50 mL de agua, la precipitación resultante se recogió mediante filtración, se lavó con agua y se secó al aire para proporcionar el producto del título.

Ejemplo 109: 5–(metilsulfinil)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



531

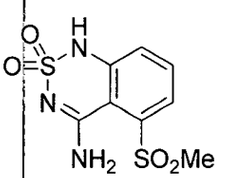
Preparado como en el Ejemplo 107 a partir de 2–sulfamoilamino–6–(metilsulfinil)benzonitrilo (Ejemplo 109a) ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,58 (s, 3H), 6,51 (brs, 2H), 6,78-6,76 (m, 1H), 6,94-6,92 (m, 1H), 7,23-7,19 (m, 1H). MS 260 (MH^+)

Ejemplo 109a: 2–sulfamoilamino–6–(metilsulfinil)benzonitrilo

La mezcla de 2–sulfamoilamino–6–(metiltio)benzonitrilo (Ejemplo 104a) (48 mg, 0,2 mmol) y MCPBA (69 mg, 0,4 mmol) en diclorometano (16 mL) se calentó en reflujo durante la noche. Luego de enfriarse, la precipitación se recogió mediante filtración, se enjuagó con diclorometano, se secó al aire para

proporcionar el compuesto del título. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,83 (s, 3H), 7,35 (brs, 2H), 7,72-6,69 (m, 2H), 7,92 (t, J = 8,0 Hz, 1H), 9,87 (brs, 1H).

Ejemplo 110: 5–(metilsulfonil)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



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Preparado como en el Ejemplo 107 a partir de 2–sulfamoilamino–6–(metilsulfonil)benzonitrilo (Ejemplo 110a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,30 (s, 3H), 6,95–6,93 (m, 1H), 7,01 (bs, 2H), 7,17-7,17 (m, 1H), 7,24-7,21 (m, 1H). MS 276 (MH^+)

Ejemplo 110a: 2–sulfamoilamino–6–(metilsulfonil)benzonitrilo

Preparado como en el Ejemplo 107a a partir de 2–amino–6–(metilsulfonil)benzonitrilo (Ejemplo 109b) ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,37 (s, 3H), 7,46 (s, 2H), 7,85-7,83 (m, 1H), 7,93-7,91 (m, 2H), 9,92 (s, 1H).

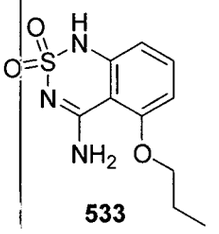
Ejemplo 110b: 2–amino–6–(metilsulfonil)benzonitrilo

Preparado como en el Ejemplo 107b a partir de 2–(metilsulfonil)–6–nitrobenzonitrilo (Ejemplo 110c). ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,26 (s, 3H), 6,63 (brs, 2H), 7,15-7,09 (m, 2H), 7,51-7,47 (m, 1H).

Ejemplo 110c: 2–(metilsulfonil)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 109a a partir de 2–(metiltio)–6–nitrobenzonitrilo (Ejemplo 104c) ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,48 (s, 3H), 8,21 (d, J = 7,6 Hz, 1H), 8,49-8,47 (m, 1H), 8,66-8,64 (m, 1H).

Ejemplo 111: 4–amino–5–(propiloxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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A una suspensión de 2–sulfamoilamino–6–propoxibenzonitrilo (Ejemplo 111a) (4,73 g, 18,53 mmol) en etanol (65 mL), se le adicionó NaOH acuoso (2 N, 18,6 ml, 37,06 mmol). La solución clara resultante se reflujó durante 3 horas bajo nitrógeno. Luego de enfriarse hasta temperatura ambiente, la solución resultante se filtró, el filtrado se enfrió hasta 0°C y se neutralizó con 10% ácido acético. El precipitado resultante se recogió mediante filtración, se suspendió en 50 ml de etanol/agua (1:1) y se entibió hasta 40°C durante 20 min. El sólido se recogió mediante filtración para proporcionar 4–amino–5–(propiloxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido (4 g, 85%) como un polvo amarillo pálido. P.f.: 229–230°C. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,96 (t, J = 7,3 Hz, 3H), 1,81 (sext, J = 7,3 Hz, 2H), 4,10 (t, J = 6,7 Hz, 2H), 6,60 (d, J = 8,6 Hz, 1H), 6,73 (d, J = 8,6 Hz, 1H), 7,44 (t, J = 8,6 Hz, 1H), 7,81 (br s, 1H), 8,35 (br s, 1H), 10,93 (br s, 1H). ^{13}C RMN (400 MHz, DMSO-d_6) δ 11,07, 22,18, 71,41, 100,93, 105,64, 110,21, 135,53, 145,16, 158,47, 161,10. MS 256 (MH^+).

Ejemplo 111a: 2–sulfamoilamino–6–propoxibenzonitrilo

A una solución de 2–amino–6–propoxibenzonitrilo (Ejemplo 111b) (4,23 g, 24,01 mmol) en dimetilacetamida (20 mL) bajo N_2 se le adicionó cloruro de sulfamoilo (5,56 g, 48,02 mmol). Luego la mezcla de reacción se agitó a temperatura ambiente bajo nitrógeno durante 4 horas. Una vez completa, la reacción se inactivó mediante la adición de hielo/agua (250 mL). El precipitado resultante se recogió mediante filtración, se enjuagó con agua y se secó para producir 2–sulfamoilamino–6–propoxibenzonitrilo (4,73 g, 77%) como un sólido amarillo pálido. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,01 (d, J = 7,2 Hz, 3H), 1,76

(sext, *J* = 7,2 Hz, 2H), 4,08 (t, *J* = 6,8 Hz, 2H), 6,96 (d, *J* = 8,5 Hz, 1H), 7,15 (t, *J* = 8,5 Hz, 1H), 7,28 (br s, 2H), 7,57 (d, *J* = 8,5 Hz, 1H), 9,46 (s, 1H). MS 256 (MH^+).

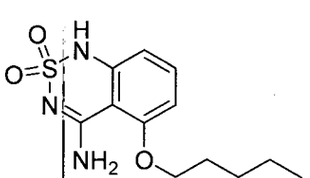
Ejemplo 111b: 2–amino–6–propoxibenzonitrilo

Se disolvió 2–nitro–6–propoxibenzonitrilo (Ejemplo 111c) (4,95 g, 24,01 mmol) en EtOH (50 mL) y THF (15 mL). Se adicionó 10% Pd/C (255 mg, 2,4 mmol), y la reacción se hidrogenó utilizando un aparato Parr durante 12 horas a 2,72 atm (40 psi). Una vez completa, la reacción se filtró a través de celite y el filtrado se concentró para proporcionar 2–nitro–6–propoxibenzonitrilo (4,3 g, 100%) como un gel marrón claro. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,05 (d, *J* = 7,4 Hz, 3H), 1,83 (sext, *J* = 7,0 Hz, 2H), 3,96 (t, *J* = 7,0 Hz, 2H), 4,38 (br s, 2 H), 6,20 (d, *J* = 8,5 Hz, 1H), 6,28 (t, *J* = 8,5 Hz, 1H), 7,19 (d, *J* = 8,5 Hz, 1H).

Ejemplo 111c: 2–nitro–6–propoxibenzonitrilo

A una solución de 2,6–dinitrobenzonitrilo (6 g, 31,07 mmol) en DMF seca (45 mL) a 0°C, se le adicionó gota a gota una solución de sodio (815 mg, 35,42 mmol) en n–propanol (23,5 mL) durante 30 minutos. Luego de la adición completa, la mezcla de reacción se entibió hasta temperatura ambiente y se agitó durante 2,5 horas. La reacción se virtió en una mezcla de hielo/agua (250 mL), y el precipitado se recogió mediante filtración y se secó para producir 2–nitro–6–propoxibenzonitrilo (4,95 g, 77%) como un sólido marrón claro. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,11 (d, *J* = 7,5 Hz, 3H), 1,93 (sext, *J* = 7,5 Hz, 2H), 4,14 (t, *J* = 7,0 Hz, 2H), 7,31 (d, *J* = 8,6 Hz, 1H), 7,69 (t, *J* = 8,6 Hz, 1H), 7,82 (d, *J* = 8,6 Hz, 1H).

Ejemplo 112: 4–amino–5–(pentoxi)–1*H*–benzo[c][1,2,6]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–pentoxibenzonitrilo (Ejemplo 112a) para proporcionar 4–amino–5–(pentoxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido (59 mg, 43%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,88 (t, J = 7,3 Hz, 3H), 1,35 (m, 4H), 1,80 (quint, J = 6,8 Hz, 2H), 4,14 (t, J = 6,4 Hz, 2H), 6,59 (d, J = 8,2 Hz, 1H), 6,73 (d, J = 8,56 Hz, 1H), 7,44 (t, J = 8,5 Hz, 1H), 7,81 (br s, 1H), 8,34 (br s, 1H), 10,92 (br s, 1H). MS 284 (MH^+).

Ejemplo 112a: 2–sulfamoilamino–6–pentoxibenzonitrilo

Preparado como en el Ejemplo 1a a partir de 2–amino–6–pentoxibenzonitrilo para proporcionar 2–sulfamoilamino–6–pentoxibenzonitrilo.

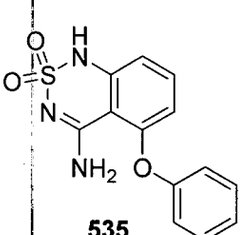
Ejemplo 112b: 2–amino–6–(pentiloxi)benzonitrilo

Preparado como en el Ejemplo 111b a partir de 2–nitro–6–(pentiloxi)benzonitrilo para proporcionar 2–amino–6–(pentiloxi)benzonitrilo. MS 205 (MH^+).

Ejemplo 112c: 2–nitro–6–(pentiloxi)benzonitrilo

Preparado como en el Ejemplo 111c a partir de 2,6–dinitrobenzonitrilo y pentanol para proporcionar 2–nitro–6–(pentiloxi)benzonitrilo.

Ejemplo 113: 4–amino–5–(fenoxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–fenoxibenzonitrilo (Ejemplo 113a) para proporcionar 4–amino–5–(fenoxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido (29 mg, 50%). ^{1}H RMN (400 MHz, MeOD) δ

6,39 (dd, *J* = 8,3, 0,8 Hz, 1H), 6,75 (dd, *J* = 8,2, 1,1 Hz, 1H), 7,18 (m, 2H), 7,30 (m, 1H), 7,40 (t, *J* = 8,5 Hz, 1H), 7,48 (m, 2H). MS 290 (MH^+).

Ejemplo 113a: 2–sulfamoilamino–6–fenoxibenzonitrilo

Preparado como en el Ejemplo 111a a partir de 2–amino–6–fenoxibenzonitrilo (Ejemplo 113b) para proporcionar 2–sulfamoilamino–6–fenoxibenzonitrilo (250 mg, 100%). ^1H RMN (400 MHz, MeOD) δ 6,60 (d, *J* = 8,6 Hz, 1H), 7,11 (d, *J* = 8,0 Hz, 1H), 7,26 (t, *J* = 7,5 Hz, 1H), 7,39 (d, *J* = 8,3 Hz, 1H), 7,45 (m, 2H), 7,50 (t, *J* = 8,6 Hz, 1H). MS 290 (MH^+).

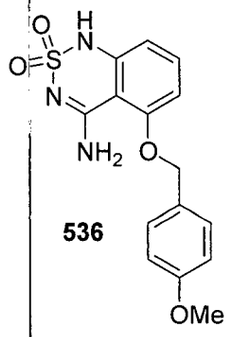
Ejemplo 113b: 2–amino–6–fenoxibenzonitrilo

A una solución de 2–nitro–6–(fenoxi)benzonitrilo (Ejemplo 113c) (1,94 g, 8,08 mmol) en MeOH (164 mL) se le adicionó lentamente HCl concentrado (7,23 mL) seguido por polvo de hierro (1,58 g, 28,3 mmol). La reacción se reflujó durante 30 min y se concentró al vacío. El residuo se disolvió en EtOAc y se lavó con NaOH 1 N, agua y salmuera. La capa orgánica se secó sobre $MgSO_4$, se filtró, se concentró y se purificó mediante cromatografía flash Hexano:EtOAc 1:1 para producir 2–amino–6–fenoxibenzonitrilo (384 mg, 22,6%). ^1H RMN (400 MHz, MeOD) δ 5,97 (d, *J* = 8,3 Hz, 1H), 6,50 (d, *J* = 8,6 Hz, 1H), 7,06 (m, 2H), 7,18 (m, 2H), 7,40 (m, 2H). MS 210 (MH^+).

Ejemplo 113c: 2–nitro–6–fenoxibenzonitrilo

Una solución de 2,6–dinitrobenzonitrilo (2,0 g, 10,5 mmol), fenol (1,42 g, 15,1 mmol) y K_2CO_3 (1,45 g, 10,5 mmol) en DMF (20 mL) se agitó a ta bajo N_2 durante 4,5 horas. Una vez completa, la reacción se diluyó con EtOAc (100 mL), se lavó con H_2O, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo se recristalizó a partir de Hexano/EtOAc para proporcionar 2–nitro–6–fenoxibenzonitrilo (1,94 g, 77%). ^1H RMN (400 MHz, MeOD) δ 7,20 (m, 2H), 7,28 (dd, *J* = 8,6, 1,1 Hz, 1H), 7,34 (m, 1H), 7,51 (m, 2H), 7,78 (t, *J* = 8,7 Hz, 1H), 8,05 (dd, *J* = 8,2, 0,8 Hz, 1H).

Ejemplo 114: 4–amino–5–(4–metoxibenciloxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–(4–metoxibenciloxi) benzonitrilo (Ejemplo 114a) para proporcionar 4–amino–5–(4–metoxi benciloxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido (12 mg, 10%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,76 (s, 3H), 6,72 (d, J = 8,4, 1H), 6,80 (d, J = 8,1, 1H), 6,95 (m, 2H), 7,48 (m, 3H), 10,89 (br s, 1H), 11,0 (br s, 1H). MS 334 (MH^+).

Ejemplo 114a: 2–sulfamoilamino–6–(4–metoxibenciloxi) benzonitrilo

A una solución de isocianato de clorosulfonilo (212 mg, 1,50 mmol) en CH_2Cl_2 (0,55 mL) a 0°C, se le adicionó ácido fórmico (0,575 mL) bajo N_2. La reacción se agitó durante 30 min, y se adicionó a 0°C una solución de 2–amino–6–(4–metoxibenciloxi) benzonitrilo (Ejemplo 114b) (191 mg, 0,75 mmol) en CH_2Cl_2 (4 mL), seguida por Et_3N (0,627 mL, 4,50 mmol). Luego de 30 min, la reacción se concentró al vacío y se diluyó con agua. El pH se reguló hasta 7 con HCl concentrado, y se purificó mediante HPLC de fase inversa (10–90% acetonitrilo en agua) para proporcionar 2–sulfamoilamino–6–(4–metoxibenciloxi) benzonitrilo (130 mg, 52%). ^{1}H RMN (400 MHz, MeOD) δ 3,80 (s, 3H), 5,15 (s, 2H), 6,88 (d, J = 8,1 Hz 1H), 6,94 (m, 2H), 7,40 (m, 2H), 7,48 (t, J = 8,7 Hz, 1H), 7,75 (dd, J = 8,6, 0,8 Hz, 1H).

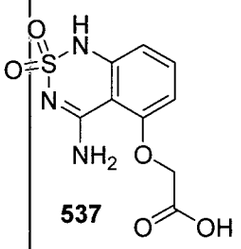
Ejemplo 114b: 2–amino–6–(4–metoxibenciloxi) benzonitrilo

Preparado como en el Ejemplo 113b a partir de 2–nitro–6–(4–metoxibenciloxi) benzonitrilo (Ejemplo 114c) para proporcionar 2–amino–6–(4–metoxibenciloxi) benzonitrilo (451 mg, 22%). ^{1}H RMN (400 MHz, MeOD) δ 3,80 (s, 3H), 5,06 (s, 2H), 6,33 (dd, J = 8,3, 0,8 Hz, 1H), 6,38 (m, 1H), 6,93 (m, 2H), 7,19 (t, J = 8,2 Hz, 1H), 7,38 (m, 2H).

Ejemplo 114c: 2–nitro–6–(4–metoxibenciloxi) benzonitrilo

Preparado como en el Ejemplo 112c a partir de 2,6–dinitrobenzonitrilo y 4–metoxibencil alcohol para proporcionar 2–nitro–6–(4–metoxibenciloxi) benzonitrilo (2,40 g, 81%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 3,82 (s, 3H), 5,26 (s, 2H), 6,93 (m, 2H), 7,35 (dd, J = 8,6, 0,7 Hz, 1H), 7,38 (m, 2H), 7,65 (t, J = 8,6 Hz, 1H), 7,83 (dd, J = 8,2, 0,8 Hz, 1H).

Ejemplo 115: Ácido 4–amino–5–oxiacético–1*H*–benzo[*c*][1,2,3]tiadiazin–2,2–dióxido



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Preparado en una manera similar al Ejemplo 111 a partir de 2–(2–ciano–3–(sulfamoilamino)fenoxi)acetato de etilo (Ejemplo 115a) para proporcionar ácido 4–amino–5–oxiacético–1*H*–benzo[*c*][1,2,3]tiadiazin–2,2–dióxido (74,9 mg, 15%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 4,88 (s, 2H), 6,65 (dd, J = 8,3, 0,8 Hz, 1H), 6,69 (dd, J = 8,5, 0,7 Hz, 1H), 7,46 (t, J = 8,3 Hz, 1H), 8,42 (br s, 1H), 8,53 (br s, 1H) 11,02 (br s, 1H), 13,49 (br s, 1H). MS 272 (MH^+).

Ejemplo 115a: 2–(2–ciano–3–(sulfamoilamino)fenoxi)acetato de etilo

Preparado en una manera similar al Ejemplo 111a a partir de 2–(3–amino–2–cianofenoxi)acetato de etilo (Ejemplo 5b) para proporcionar 2–(2–ciano–3–(sulfamoilamino)fenoxi)acetato de etilo (567 mg, 79%) como un sólido amarillo claro. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,22 (t, J =7,0 Hz, 3H), 4,19 (q, J = 7,0 Hz, 2H), 5,01 (s, 2H), 6,87 (d, J = 8,6 Hz, 1H), 7,20 (d, J = 8,3 Hz, 1H), 7,32 (s, 2H), 7,56 (t, J = 8,6 Hz, 1H), 9,53 (br s, 1H).

Ejemplo 115b: 2–(3–amino–2–cianofenoxi)acetato de etilo

Preparado en una manera similar al Ejemplo 111b a partir de 2–(3–amino–2–nitrofenoxi)acetato de etilo (Ejemplo 115c) para proporcionar 2–(3–amino–2–cianofenoxi)acetato de etilo (539 mg, 56%) como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,21 (t, J =7,6 Hz, 3H), 4,17 (q, J = 7,6 Hz, 2H), 4,85 (s, 2H), 6,06 (br s, 2H), 6,10 (d, J = 8,0 Hz, 1H), 6,38 (dd, J = 8,6, 0,8 Hz, 1H), 7,17 (t, J = 8,4 Hz, 1H).

Ejemplo 115c: 2–(3–amino–2–nitrofenoxi)acetato de etilo

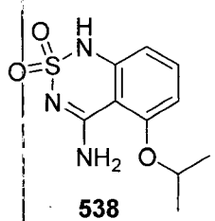
A una solución de 2–hidroxi–6–nitrobenzonitrilo (Ejemplo 115d) (616 mg, 4,33 mmol) y K_2CO_3 (718 mg, 5,20 mmol) en acetona (8 mL), se le adicionó bromoacetato de etilo (0,576 mL, 5,20 mmol). La reacción se reflujó bajo N_2 durante 4,5 horas. Una vez completa, la reacción se filtró, y el filtrado se concentró y se secó para producir 2–(3–amino–2–nitrofenoxi) etilo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,23 (t, J =7,0 Hz, 3H), 4,20 (q, J = 7,1 Hz, 2H), 5,19 (s, 2H), 7,69 (dd, J = 8,6, 0,8 Hz, 1H), 7,89 (t, J = 8,4 Hz, 1H), 7,97 (dd, J = 8,3, 0,8 Hz, 1H).

Ejemplo 115d: 2–hidroxi–6–nitrobenzonitrilo

A una solución de 2,6–dinitrobenzonitrilo (10,0 g, 52,3 mmol) en MeOH (215 mL), se le adicionó una solución de Na (1,32 g, 57,5 mmol) en MeOH (23,3 mL). La reacción se reflujó bajo N_2 durante 2,5 horas, se enfrió hasta ta y el precipitado se recogió mediante filtración. El residuo resultante se combinó con

clorhidrato de piridina (15,1 g, 130 mmol), y los sólidos se fundieron a 200ºC durante 18 horas. Una vez completa, la reacción se enfrió hasta rt, se lavó con salmuera (1 x 300 mL) y se extrajo con EtOAc (2 x 500 mL). Las capas orgánicas se combinaron, se secaron sobre $MgSO_4$, se filtraron y se concentraron para proporcionar 2–hidroxi–6–nitrobenzonitrilo (6,70 g, 87%). ^{1}H RMN (400 MHz, MeOD) δ 7,35 (dd, J = 8,3, 0,8 Hz, 1H), 7,67 (t, J = 8,2 Hz, 1H), 7,77 (dd, J = 8,2, 1,1 Hz, 1H).

Ejemplo 116: 4–amino–5–(isopropoxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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Preparado en una manera similar al Ejemplo 111 a partir de 2–sulfamoilamino–6–isopropoxibenzonitrilo (Ejemplo 116a) para proporcionar 4–amino–5–(isopropoxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido (50 mg, 171%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,38 (d, J = 5,8 Hz, 6H), 4,84 (sept, J = 5,9 Hz, 1H), 6,59 (d, J = 8,7 Hz, 1H), 6,77 (d, J = 8,7 Hz, 1H), 7,45 (d, J = 8,7 Hz, 1H), 7,81 (br s, 1H), 8,32 (br s, 1H), 10,94 (br s, 1H). MS 256 (MH^+).

Ejemplo 116a: 2–sulfamoilamino–6–isopropoxibenzonitrilo

Preparado en una manera similar al Ejemplo 111a a partir de 2–amino–6–isopropoxibenzonitrilo (Ejemplo 6b) para proporcionar 2–sulfamoilamino–6–isopropoxibenzonitrilo (21 mg, 8%). ^{1}H RMN (400 MHz, MeOD) δ 1,37 (d, J = 5,6 Hz, 6H), 4,67 (sept, J = 6,0 Hz, 1H), 6,29 (d, J = 8,2 Hz, 1H), 6,36 (dd, J = 8,1, 0,8 Hz, 1H), 7,07 (t, J = 8,2 Hz, 1H).

Ejemplo 116b: 2–amino–6–isopropoxibenzonitrilo

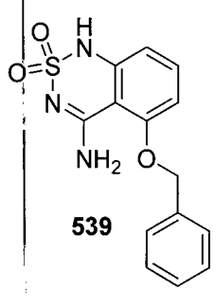
797

Preparado en una manera similar al Ejemplo 113b a partir de 2–nitro–6–isopropoxibenzonitrilo (Ejemplo 116c) para proporcionar 2–amino–6–isopropoxibenzonitrilo (201 mg, 76%) como un aceite amarillo. ^{1}H RMN (400 MHz, MeOD) δ 1,34 (d, J = 6,0 Hz, 6H), 4,64 (sept, J = 6,1 Hz, 1H), 6,25 (d, J = 8,1 Hz, 1H), 6,34 (dd, J = 8,2, 0,8 Hz, 1H), 7,18 (t, J = 8,3 Hz, 1H).

Ejemplo 116c: 2–nitro–6–isopropoxibenzonitrilo

Preparado en una manera similar al Ejemplo 115c a partir de 2–hidroxi–6–nitrobenzonitrilo (Ejemplo 115d) y bromuro de isopropilo para proporcionar 2–nitro–6–isopropoxibenzonitrilo (324 mg, 64%). ^{1}H RMN (400 MHz, MeOD) δ 1,43 (d, J = 6,2 Hz, 6H), 4,89 (sept, J = 6,2 Hz, 1H), 7,61 (dd, J = 8,0, 1,0 Hz, 1H), 7,80 (t, J = 8,2 Hz, 1H), 7,85 (dd, J = 8,2, 1,2 Hz, 1H).

Ejemplo 117: 4–amino–5–(benciloxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–(benciloxi)benzonitrilo (Ejemplo 117a) para proporcionar 4–amino–5–(benciloxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido (42 mg, 61%). ^{1}H RMN (400 MHz, MeOD) δ 5,32 (s, 2H), 6,65 (dd, J = 8,3, 1,2 Hz, 1H), 6,85 (dd, J = 8,6, 1,0 Hz, 1H), 7,36-7,52 (m, 6H). MS 304 (MH^+).

Ejemplo 117a: 2–sulfamoilamino–6–(benciloxi)benzonitrilo

Preparado como en el Ejemplo 111a a partir de 2–amino–6–(benciloxi)benzonitrilo (Ejemplo 117b) para proporcionar 2–sulfamoilamino–6–

(benciloxi)benzonitrilo (74 mg, 30%). ^{1}H RMN (400 MHz, MeOD) δ 5,22 (s, 2H), 6,94 (d, J = 8,5 Hz, 1H), 7,26 (d, J = 8,2 Hz, 1H), 7,32 (m, 1H), 7,38 (t, J = 7,2 Hz, 2H), 7,47 (d, J = 7,4 Hz, 2H), 7,51 (t, J = 8,2 Hz, 1H).

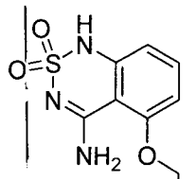
Ejemplo 117b: 2–amino–6–(benciloxi)benzonitrilo

Preparado como en el Ejemplo 113b a partir de 2–nitro–6–(benciloxi)benzonitrilo (Ejemplo 117c) para proporcionar 2–amino–6–(benciloxi)benzonitrilo (215 mg, 63%). ^{1}H RMN (400 MHz, MeOD) δ 5,15 (s, 2H), 6,32 (d, J = 8,2 Hz, 1H), 6,39 (d, J = 8,2 Hz, 1H), 7,20 (t, J = 8,4 Hz, 1H), 7,38 (t, J = 7,6 Hz, 2H), 7,46 (d, J = 7,4 Hz, 2H). MS 225 (MH^+).

Ejemplo 117c: 2–nitro–6–(benciloxi)benzonitrilo

A una solución de 2–hidroxi–6–nitrobenzonitrilo (Ejemplo 115) (1,0 g, 6,09 mmol) y Cs_2CO_3 (2,16 g, 6,64 mmol) en acetona (14 mL) se le adicionó bromuro de bencilo (1,16 g, 6,76 mmol). La reacción se reflujó bajo N_2 durante 1,5 horas, luego se filtró y el filtrado se concentró. El residuo se purificó mediante cromatografía flash Hexano:EtOAc 3:2 para proporcionar 2–nitro–6–(benciloxi)benzonitrilo (500 mg, 32%). ^{1}H RMN (400 MHz, MeOD) δ 5,40 (s, 2H), 7,34-7,45 (m, 3H), 7,53 (m, 2H), 7,69 (dd, J = 8,6, 0,8 Hz, 1H), 7,82 (t, J = 8,4 Hz, 1H), 7,91 (t, J = 8,2, 0,8 Hz, 1H).

Ejemplo 118: 4–amino–5–(etoxi)–1*H*–benzo[c][1,2,6]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–etoxibenzonitrilo (Ejemplo 118a) para proporcionar 4–amino–5–etoxi–1*H*–

benzo[*c*][1,2,6]tiadiazin–2,2–dióxido (120 mg, 50%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,37 (t, J = 6,9 Hz, 3H), 4,18 (q, J = 6,9 Hz, 2H), 6,96 (d, J = 8,8 Hz, 1H), 7,16 (d, J = 8,8 Hz, 1H), 7,27 (br s, 2H), 7,57 (t, J = 8,4 Hz, 1H), 9,44 (br s, 1H). MS 242 (MH^+).

Ejemplo118a: 2–sulfamoilamino–6–etoxibenzonitrilo

Preparado en una manera similar al Ejemplo 111a a partir de 2–amino–6–etoxibenzonitrilo (Ejemplo 8b) para proporcionar 2–sulfamoilamino–6–etoxibenzonitrilo (161 mg, 67%). MS 242 (MH^+).

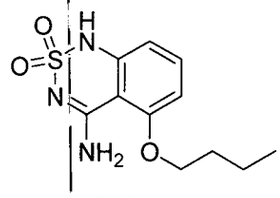
Ejemplo 118b: 2–amino–6–etoxibenzonitrilo

Preparado en una manera similar al Ejemplo 111b a partir de 2–nitro–6–etoxibenzonitrilo (Ejemplo 8c) para proporcionar 2–amino–6–etoxibenzonitrilo (162 mg, 100%). MS 163 (MH^+).

Ejemplo 118c: 2–nitro–6–etoxibenzonitrilo

Preparado en una manera similar al Ejemplo 115c a partir de 2–hidroxi–6–nitrobenzonitrilo (Ejemplo 115d) y bromuro de etilo para proporcionar 2–nitro–6–etoxibenzonitrilo (192 mg, 50%).

Ejemplo 119: 4–amino–5–(butoxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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Preparado en una manera similar al Ejemplo 111 a partir de 2–sulfamoilamino–6–butoxibenzonitrilo (Ejemplo 119a) para proporcionar 4–amino–5–butoxi–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido (67 mg, 50%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,95 (t, J = 7,4 Hz, 3H), 1,44 (sext, J = 7,4 Hz, 2H), 1,81 (quint, J = 7,9 Hz, 2H), 4,17 (t, J = 6,7 Hz, 2H), 6,61 (d, J = 8,2 Hz, 1H), 6,76 (d, J = 8,2

Hz, 1H), 7,46 (t, *J* = 8,2 Hz, 1H), 7,82 (br s, 1H), 8,35 (br s, 1H), 10,96 (br s, 1H). MS 270 (MH^+).

Ejemplo 119a: 2–sulfamoilamino–6–butoxibenzonitrilo

Preparado en una manera similar al Ejemplo 111a a partir de 2–amino–6–butoxibenzonitrilo (Ejemplo 9b) para proporcionar 2–sulfamoilamino–6–butoxibenzonitrilo. MS 270 (MH^+).

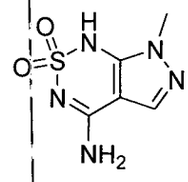
Ejemplo 119b: 2–amino–6–butoxibenzonitrilo

Preparado en una manera similar al Ejemplo 111b a partir de 2–nitro–6–butoxibenzonitrilo (Ejemplo 9c) para proporcionar 2–amino–6–butoxibenzonitrilo (190 mg, 71%). MS 191 (MH^+).

Ejemplo 119c: 2–nitro–6–butoxibenzonitrilo

Preparado en una manera similar al Ejemplo 115c a partir de 2–hidroxi–6–nitrobenzonitrilo (Ejemplo 115d) y bromuro de butilo para proporcionar 2–nitro–6–butoxibenzonitrilo.

Ejemplo 120: 4–amino–1–metil–*1H*–pirazolo[*c*][1,2,6]tiadiazin–2,2–dióxido



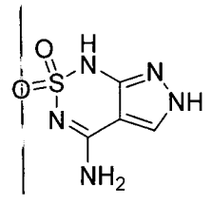
542

Preparado en una manera similar al Ejemplo 111 a partir de 5–sulfamoilamino–1–metil–*1H*–pirazol–4–carbonitrilo (Ejemplo 120a) para proporcionar 4–amino–1–metil–*1H*–pirazolo[c][1,2,6]tiadiazin–2,2–dióxido (100 mg, 50%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,76 (s, 3H), 7,43 (s, 2H), 7,98 (s, 1H), 9,84 (s, 1H).

Ejemplo 120a: 5–sulfamoilamino–1–metil–*1H*–pirazol–4–carbonitrilo

Preparado en una manera similar al Ejemplo 111a a partir de 5–amino–1–metil–*1H*–pirazol–4–carbonitrilo para proporcionar 5–sulfamoilamino–1–metil–*1H*–pirazol–4–carbonitrilo.

Ejemplo 121: 4–amino–*2H*–pirazolo[*c*][1,2,6]tiadiazin–2,2–dióxido



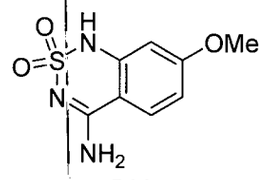
543

Preparado en una manera similar al Ejemplo 111 a partir de 3–sulfamoilamino–*1H*–pirazol–4–carbonitrilo (Ejemplo 11a) para proporcionar 4–amino–*2H*–pirazolo[*c*][1,2,6]tiadiazin–2,2–dióxido (90 mg, 48%).^{1}H RMN (400 MHz, DMSO-d_6) δ 6,97 (s, 2H), 8,47 (s, 1H), 9,71 (s, 1H), 13,36 (s, 1H).

Ejemplo 121a: 3–sulfamoilamino–*1H*–pirazol–4–carbonitrilo

Preparado en una manera similar al Ejemplo 111a a partir de 3–amino–*1H*–pirazol–4–carbonitrilo para proporcionar 3–sulfamoilamino–*1H*–pirazol–4–carbonitrilo.

Ejemplo 122: 4–amino–7–metoxi–*1H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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Preparado en una manera similar al Ejemplo 111 a partir de 2–sulfamoilamino–4–metoxibenzonitrilo (Ejemplo 122a) para proporcionar 4–amino–7–metoxi–*1H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido (49 mg, 65%). ^{1}H RMN (400

MHz, DMSO-d_6) δ 3,81 (s, 3H), 6,58 (d, J = 2,3 Hz, 1H), 6,75 (dd, J = 9,1, 2,7 Hz, 1H), 7,82 (d, J = 8,8 Hz, 1H), 10,85 (br s, 1H), 10,99 (br s, 1H). MS 228 (MH^+).

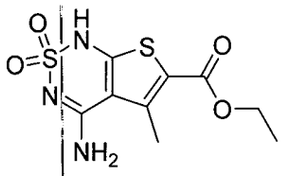
Ejemplo 122a: 2–sulfamoilamino–4–metoxibenzonitrilo

Preparado en una manera similar al Ejemplo 114a a partir de 2–amino–4–metoxibenzonitrilo (Ejemplo 122b) para proporcionar 2–sulfamoilamino–4–metoxibenzonitrilo como cristales blancos (111 mg, 44%). ^{1}H RMN (400 MHz, MeOD) δ 3,85 (s, 3H), 6,73 (dd, J = 9,0, 2,8 Hz, 1H), 7,54 (d, J = 9,0 Hz, 1H), 7,84 (d, J = 2,4 Hz, 1H). MS 228 (MH^+).

Ejemplo 122b: 2–amino–4–metoxibenzonitrilo

Preparado en una manera similar al Ejemplo 111b a partir de 2–nitro–4–metoxibenzonitrilo para proporcionar 2–amino–4–metoxibenzonitrilo (910 mg, 78%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 3,79 (s, 3H), 4,73 (br s, 2H), 6,20 (m, 1H), 6,31 (m, 1H), 7,30 (d, J = 8,7 Hz, 1H).

Ejemplo 123: 4–amino–5–metil–2–oxo–1,2–dihidrotieno[*c*][1,3,6]tiadiazin–2,2–dioxido–6–carboxilato de etilo



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Preparado en una manera similar al Ejemplo 111 a partir de 5–sulfamoilamino–4–ciano–3–metiltiofen–2–carboxilato de etilo (Ejemplo 123a) para proporcionar 4–amino–5–metil–2–oxo–1,2–dihidrotieno[*c*][1,3,6]tiadiazin–2,2–dióxido–6–carboxilato de etilo (1,22 g, 72%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,26 (t, J = 6,9 Hz, 3H), 2,73 (s, 3H), 4,17 (q, J = 7,0 Hz, 2H). MS 290 (MH^+).

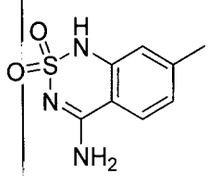
Ejemplo 123a: 5–sulfamoilamino–4–ciano–3–metiltiofen–2–carboxilato de etilo

Preparado en una manera similar al Ejemplo 114a a partir de 5–amino–4–ciano–3–metiltiofen–2–carboxilato de etilo (Ejemplo 123b) para proporcionar 5–sulfamoilamino–4–ciano–3–metiltiofen–2–carboxilato de etilo (1,73 g, 80%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,28 (t, J = 7,0 Hz, 3H), 2,36 (s, 3H), 4,24 (q, J = 7,1 Hz, 2H).

Ejemplo 123b: 5–amino–4–ciano–3–metiltiofen–2–carboxilato de etilo

A una solución de 3–oxobutanoato de etilo (3,0 mL, 23,5 mmol), malononitrilo (1,55 g, 23,5 mmol) y azufre (753 mg, 23,5 mmol) en EtOH (39 mL), se le adicionó Et_3N (3,28 mL, 23,5 mmol). La reacción se reflujó bajo N_2 durante 3 horas, luego se purificó directamente mediante cromatografía flash (CH_2Cl_2:EtOAc 99:1) para proporcionar 5–amino–4–ciano–3–metiltiofen–2–carboxilato de etilo (2,18 g, 44%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,21 (t, J = 7,0 Hz, 3H), 2,36 (s, 3H), 4,15 (q, J = 7,2 Hz, 2H).

Ejemplo 124: 4–amino–7–metil–1H–benzo[c][1,2,6]tiadiazin–2,2–dióxido



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Preparado en una manera similar al Ejemplo 111 a partir de 2–sulfamoilamino–4–metilbenzonitrilo (Ejemplo 124a) para proporcionar 4–amino–7–metil–*1H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido (50 mg, 50%). ^{1}H RMN (400 MHz, MeOD) δ 2,40 (s, 3H), 6,92 (s, 1H), 7,03 (m, 1H), 7,70 (d, J = 8,2 Hz, 1H). MS 212 (MH^+).

Ejemplo 124a: 2–sulfamoilamino–4–metilbenzonitrilo

Preparado en una manera similar al Ejemplo 114a a partir de 2–amino–4–metilbenzonitrilo (Ejemplo 14b) para proporcionar 2–sulfamoilamino–4–

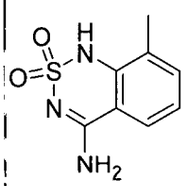
804

metilbenzonitrilo (205 mg, 82%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 2,35 (s, 3H), 6,88 (m, 1H), 7,38 (d, J = 7,7 Hz, 1H), 7,72 (br s, 1H), 7,97 (s, 1H), 9,37 (s, 1H),. MS 212 (MH^+).

Ejemplo 124b: 2–amino–4–metilbenzonitrilo

Una solución de 2–bromo–4–metilbenzonitrilo (2,0 g, 10,7 mmol) y CuCN (1,92 g, 21,4 mmol) en NMP (10 mL) se hizo reaccionar en un microondas durante 20 min a 200ºC. Una vez completa la reacción se enfrió hasta 0ºC, y se adicionó lentamente 15% NH_4OH acuoso (215 mL). La mezcla se agitó a ta durante 30 min, luego se extrajo con CH_2Cl_2. La capa orgánica se lavó con H_2O, salmuera, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo se purificó mediante cromatografía flash (Hexano:EtOAc 3:1) para proporcionar 2–amino–4–metilbenzonitrilo (1,24 g, 88%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,45 (s, 3H), 5,70 (m, 1H), 5,84 (m, 1H), 6,41 (d, J = 8,0 Hz, 1H).

Ejemplo 125: 4–amino–8–metil–*1H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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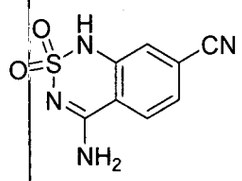
Preparado en una manera similar al Ejemplo 111 a partir de 2–sulfamoilamino–3–metilbenzonitrilo (Ejemplo 125a) para proporcionar 4–amino–8–metil–*1H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido (9 mg, 8%). ^{1}H RMN (400 MHz, MeOD) δ 2,37 (s, 3H), 7,09 (t, J = 7,7 Hz, 1H), 7,45 (d, J = 7,3 Hz, 1H), 8,04 (d, J = 7,7 Hz, 1H). MS 212 (MH^+).

Ejemplo 125a: 2–sulfamoilamino–3–metilbenzonitrilo

Preparado en una manera similar al Ejemplo 114a a partir de 2–amino–3–metilbenzonitrilo (Ejemplo 15b) para proporcionar 2–sulfamoilamino–3–

metilbenzonitrilo (115 mg, 46%). ^{1}H RMN (400 MHz, MeOD) δ 2,34 (s, 3H), 7,31 (t, J = 7,5 Hz, 1H), 7,57 (m, 2H). MS 212 (MH^+).

Ejemplo 126: 4–amino–7–ciano–*1H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



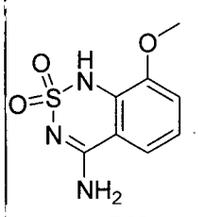
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Preparado en una manera similar al Ejemplo 114a a partir de 2–aminotereftalonitrilo (Ejemplo 126a) para proporcionar 4–amino–7–ciano–*1H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido (40 mg, 16%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,37 (d, J = 1,5 Hz, 1H), 7,57 (dd, J = 8,2, 1,6 Hz, 1H), 8,12 (d, J = 8,5 Hz, 1H), 8,51 (br s, 2H), 11,51 (s, 1H). MS 223 (MH^+).

Ejemplo 126a: 2–aminotereftalonitrilo

Preparado en una manera similar al Ejemplo 124b a partir de 2,5–dibromoanilina para proporcionar 2–aminotereftalonitrilo (1,14 g, 100%). ^{1}H RMN (400 MHz, MeOD) δ 6,91 (dd, J = 8,2, 1,6 Hz, 1H), 7,12 (d, J = 1,6 Hz, 1H), 7,51 (d, J = 8,0 Hz, 1H).

Ejemplo 127: 4–amino–8–metoxi–*1H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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Preparado en una manera similar al Ejemplo 111 a partir de 2–sulfamoilamino–3–metoxibenzonitrilo (Ejemplo 127a) para proporcionar 4–amino–

8–metoxi–*1H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido (11 mg, 15%). ^{1}H RMN (400 MHz, MeOD) δ 3,97 (s, 3H), 7,14 (t, J = 7,9 Hz, 1H), 7,22 (dd, J = 7,8, 1,2 Hz, 1H), 7,72 (d, J = 8,2, 1,2 Hz, 1H). MS 228 (MH^+).

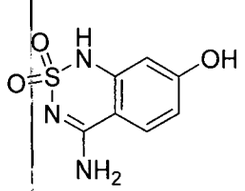
Ejemplo 127a: 2–sulfamoilamino–3–metoxibenzonitrilo

Preparado en una manera similar al Ejemplo 114a a partir de 2–amino–3–metoxibenzonitrilo (Ejemplo 127b) para proporcionar 2–sulfamoilamino–3–metoxibenzonitrilo (113 mg, 45%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,85 (s, 3H), 7,27 (m, 1H), 7,30 (dd, J = 7,7, 1,7 Hz, 1H), 7,35 (dd, J = 7,9, 1,7 Hz, 1H), 8,87 (s, 1H), 9,09 (br s, 1H). MS 228 (MH^+).

Ejemplo 127b: 2–amino–3–metoxibenzonitrilo

Preparado en una manera similar al Ejemplo 111b a partir de 3–metoxi–2–nitrobenzonitrilo para proporcionar 2–amino–3–metoxibenzonitrilo (346 mg, 60%). ^{1}H RMN (400 MHz, MeOD) δ 3,87 (s, 3H), 6,65 (t, J = 7,7 Hz, 1H), 6,95 (dd, J = 7,7, 1,2 Hz, 1H), 7,00 (dd, J = 8,2, 1,2 Hz, 1H). MS 149 (MH^+).

Ejemplo 128: 4–amino–7–hidroxi–*1H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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Preparado en una manera similar al Ejemplo 111 a partir de 2–sulfamoilamino–4–hidroxibenzonitrilo (Ejemplo 128a) para proporcionar 4–amino–7–hidroxi–*1H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido (7 mg, 14%). ^{1}H RMN (400 MHz, MeOD) δ 6,50 (d, J = 2,0 Hz, 1H), 6,65 (dd, J = 9,0, 2,4 Hz, 1H), 7,82 (d, J = 8,8 Hz, 1H). MS 214 (MH^+).

Ejemplo 128a: 2–sulfamoilamino–4–hidroxibenzonitrilo

Preparado en una manera similar al Ejemplo 114a a partir de 2–amino–4–hidroxibenzonitrilo (Ejemplo 18b) para proporcionar 2–sulfamoilamino–4–hidroxibenzonitrilo (51 mg, 22%). ^{1}H RMN (400 MHz, MeOD) δ 6,56 (dd, J = 8,6, 2,4 Hz, 1H), 7,43 (d, J = 8,6 Hz, 1H), 7,68 (d, J = 2,2 Hz, 1H). MS 214 (MH^+).

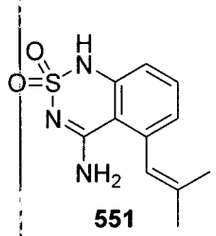
Ejemplo 128b: 2–amino–4–hidroxibenzonitrilo

Preparado en una manera similar al Ejemplo 111b a partir de 4–hidroxi–2–nitrobenzonitrilo (Ejemplo 128c) para proporcionar 2–amino–4–hidroxibenzonitrilo (286 mg, 100%). ^{1}H RMN (400 MHz, MeOD) δ 6,15 (dd, J = 8,5, 2,3 Hz, 1H), 6,20 (d, J = 1,9 Hz, 1H), 7,18 (d, J = 8,6 Hz, 1H).

Ejemplo 128c: 4–hidroxi–2–nitrobenzonitrilo

Una mezcla de 4–metoxi–2–nitrobenzonitrilo (820 mg, 4,6 mmol) y clorhidrato de piridina (755 mg, 4,6 mmol) se calentó a 200°C bajo N_2 durante 18 horas. Una vez completa, la reacción se enfrió hasta temperatura ambiente, se lavó con salmuera y se extrajo con EtOAc (2 x 100 mL). Las capas orgánicas se combinaron, se secaron sobre $MgSO_4$, se filtraron y se concentraron. El residuo se purificó mediante cromatografía flash (Hexano:EtOAc 1:1) para proporcionar 4–hidroxi–2–nitrobenzonitrilo (200 mg, 26%). ^{1}H RMN (400 MHz, MeOD) δ 7,24 (dd, J = 8,6, 2,4 Hz, 1H), 7,70 (d, J = 2,4 Hz, 1H), 7,83 (d, J = 8,6 Hz, 1H).

Ejemplo 129: 4–amino–5–(2–metilprop–1–enil)–1H–benzo[c] [1,2,3] tiadiazin–2,2–dióxido



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A una solución agitada de 2–sulfamoilamino–6–(2–metilprop–1–enil)benzonitrilo (Ejemplo 129a) (1,69 g, 6,73 mmol) en EtOH (29,0 mL), bajo una

atmósfera de nitrógeno, se le adicionó a temperatura ambiente una solución acuosa de NaOH (2,0 M, 6,73 mL, 13,45 mmol). La mezcla obtenida se calentó a reflujo durante 4 h, se enfrió hasta temperatura ambiente y se neutralizó con 10% AcOH (pH ~ 6). La mezcla neutralizada se mantuvo en un baño de hielo durante 30 min. El precipitado obtenido se filtró, se lavó con agua fría y se secó, para proporcionar 1,49 g (88%) del compuesto del título como un sólido blanco. El producto se purificó mediante cristalización a partir de etanol. P.f.: > 260ºC. ^{1}H-RMN (400 MHz, DMSO-d_6) δ 10,91 (s amplio, 1H), 8,30 (s amplio, 1H), 7,46 (t, J = 8,00 Hz, 1H), 6,96 (s amplio, 1H), 6,92 (d, J = 8,4 Hz, 1H), 6,83 (d, J = 7,2 Hz, 1H), 6,46 (s amplio, 1H), 1,89-1,87 (m, 3H), 1,65–1,63 (m, 3H). ^{13}C-RMN (100MHz, DMSO–d_6) δ 162,1, 143,1, 138,8, 137,6, 132,9, 124,4, 123,3, 115,7, 110,7, 25,8 y 19,2. MS 252 (MH^+).

Ejemplo 129a: 2–sulfamoilamino–6–(2–metilprop–1–enil)benzonitrilo

Una solución de 2–amino–6–(2–metilprop–1–enil)benzonitrilo (Ejemplo 129b) (1,24 g; 7,23 mmol) en N,N–dimetilacetamida (DMA) (20,0 mL), bajo una atmósfera de nitrógeno, se trató con cloruro de sulfamoilo (1,67 g; 14,45 mmol) a temperatura ambiente. La mezcla obtenida se agitó a temperatura ambiente durante 2 h y la reacción se inactivó con agua (40 mL). La mezcla se extrajo con EtOAc (4 x 80 mL), el extracto combinado se lavó con agua (2 x 20 mL) y salmuera, y se secó con $MgSO_4$. El filtrado se evaporó y el residuo se purificó mediante cromatografía sobre gel de sílice utilizando gradiente (Hexanos/EtOAc 1:0 a 1:1), para proporcionar 1,69 g (93%) del compuesto del título como un sólido blanco. ^{1}H-RMN (400 MHz, DMSO-d_6) δ 9,42 (s amplio, 1H), 7,61 (t, J = 8,0 Hz, 1H), 7,44 (d, J = 8,0 Hz, 1H), 7,24 (s amplio, 2H), 7,19 (d, J = 8,0 Hz, 1H), 6,35 (s amplio, 1H), 1,92–1,95 (m, 3H), 1,76–1,79 (m, 3H).

Ejemplo 129b: 2–amino–6–(2–metilprop–1–enil)benzonitrilo

Se adicionó lentamente HCl concentrado (65,5 mL) a una solución de 2–nitro–6–(2–metilprop–1–enil)benzonitrilo (Ejemplo 129c) (2,00 g; 9,89 mmol) en EtOH (120,2 mL) a temperatura ambiente. Luego, la mezcla obtenida se trató con polvo de hierro (5,52 g; 98,91 mmol), adicionado en pequeñas porciones a la misma temperatura. La mezcla se agitó a temperatura ambiente durante 15 min, y luego se calentó a reflujo durante 30 min. La mezcla se enfrió hasta temperatura ambiente, el EtOH se evaporó y el pH se reguló hasta un pH~10 con NaOH acuoso (2,0 M). La mezcla basificada se extrajo con EtOAc (4x100 mL) y el extracto combinado se secó con $MgSO_4$ anhidro. El filtrado se evaporó y el residuo se purificó mediante cromatografía sobre gel de sílice utilizando gradiente hexanos a hexanos/EtOAc (8:2), para proporcionar 1,32 g (77%) del compuesto del título como un aceite amarillo. ^{1}H-RMN (400 MHz, DMSO-d_6) δ 7,19-7,25 (m, 1H), 6,62 (d, J = 8,4 Hz, 1H), 6,46 (d, J = 7,2 Hz, 1H), 6,23 (s amplio, 1H), 5,91 (s amplio, 2H), 1,86-1,88 (m, 3H), 1,72-1,74 (m, 3H).

Ejemplo 129c: 2–nitro–6–(2–metilprop–1–enil)benzonitrilo

Una suspensión de trifluormetansulfonato de 2–ciano–3–nitrofenilo (Ejemplo 129d) (4,80 g; 16,21 mmol), ácido 2–metil–1–propenilborónico (2,43 g; 24,32 mmol), tetrakis(trifenilfosfin)paladio (0) (1,87 g; 1,62 mmol), carbonato de sodio (1,89 g; 17,83 mmol) y agua (33,0 mL) en dimetoxietano (DME) (132,0 mL) se calentó a reflujo durante 4 h, bajo una atmósfera de nitrógeno. La mezcla de reacción se enfrió hasta temperatura ambiente y se diluyó con agua (100 mL) y EtOAc (250 mL). La fase orgánica se separó y la fase acuosa se extrajo con EtOAc (3 x 100 mL). El extracto combinado se lavó con salmuera y se secó con $MgSO_4$ anhidro. El filtrado se evaporó y el residuo se purificó mediante cromatografía sobre gel de sílice utilizando gradiente hexanos a hexanos/EtOAc (7:3), para proporcionar 2,01 g (61%) del compuesto del título como un sólido

amarillo. ^{1}H-RMN (400 MHz, DMSO-d_6) δ 8,19-8,23 (m, 1H), 7,83-7,93 (m, 2H), 6,45 (s amplio, 1H), 1,95-1,98 (m, 3H), 1,75-1,79 (m, 3H).

Ejemplo 129d: Trifluormetansulfonato de 2–ciano–3–nitrofenilo

A una solución de 2–hidroxi–6–nitrobenzonitrilo (Ejemplo 129e) (2,90 g, 17,67 mmol) en CH_2Cl_2 (90,0 mL), a 0°C y bajo una atmósfera de nitrógeno, se le adicionó trietilamina (3,58 g, 4,93 mL, 35,34 mmol), seguida por la adición gota a gota de anhídrido trifluormetansulfónico (7,48 g, 4,46 mL, 26,51 mmol). La mezcla de reacción se agitó a 0°C durante 30 min y la reacción se inactivó con solución de Na_2CO_3 acuosa saturada (100 mL). La capa orgánica se separó y la fase acuosa se extrajo con CH_2Cl_2 (3 x 100 mL). El extracto combinado se secó con $MgSO_4$ anhidro, se filtró y se evaporó. El residuo se purificó mediante cromatografía sobre gel de sílice utilizando gradiente hexanos a hexanos/EtOAc (6:4), para proporcionar 5,23 g (100%) del compuesto del título como un sólido marrón. ^{1}H-RMN (400 MHz, DMSO-d_6) δ 8,49-8,53 (m, 1H), 8,23-8,27 (m, 1H), 8,13-8,19 (m, 1H).

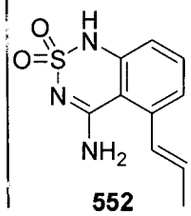
Ejemplo 129e: 2–hidroxi–6–nitrobenzonitrilo

Se mezclaron conjuntamente como sólidos bajo nitrógeno 2–metoxi–6–nitrobenzonitrilo (Ejemplo 129f) (10,73 g, 60,2 mmol) y clorhidrato de piridina (16,0 g, 138 mmol), y luego se calentaron en un baño de aceite precalentado a 200°C durante 40 min. Luego de enfriarse hasta temperatura ambiente, se adicionaron agua (200 mL) y CH_2Cl_2 (200 mL) y se agitó enérgicamente durante 1 hora. Luego, el producto precipitado se recogió mediante filtración y se recristalizó a partir de agua, para proporcionar 8,2 g, (83%) de 2–hidroxi–6–nitrobenzonitrilo como un sólido marrón. ^{1}H-RMN (400 MHz, DMSO–d_6) δ 12,13 (s amplio, 1H), 7,68–7,79 (m, 2H), 7,39–7,44 (m, 1H).

Ejemplo 129f: 2–metoxi–6–nitrobenzonitrilo

Una solución de metóxido de sodio, obtenida mediante la adición de sodio (1,68 g, 73,1 mmol) a MeOH anhidro (73 mL), se adicionó a 2,6–dinitrobenzonitrilo (13,20 g, 68,4 mmol) en MeOH seco (284 mL) bajo nitrógeno a temperatura ambiente durante 10 min. La reacción se reflujó durante 1 hora, y luego el MeOH se removió bajo vacío. Se adicionó diclorometano (400 mL), y los sólidos insolubles se separaron mediante filtración. La capa orgánica se lavó con salmuera (100 mL), se secó con $MgSO_4$, y se removió bajo vacío para proporcionar 11,45 g (94%) de 2–metoxi–6–nitrobenzonitrilo, el cual se utilizó sin purificación adicional. ^{1}H-RMN (400 MHz, DMSO-d_6) δ 7,87-7,94 (m, 2H), 7,68-7,75 (m, 1H), 4,01 (s, 3H).

Ejemplo 130: 4–amino–5–((*E*)–prop–1–enil)–1H–benzo[c][1,2,3]tiadiazin–2,2–dióxido



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A una solución agitada de (*E*)–2–sulfamoilamino–6–(prop–1–enil)benzonitrilo (Ejemplo 130a) (0,82 g, 3,45 mmol) en EtOH (15,0 mL), bajo una atmósfera de nitrógeno, se le adicionó a temperatura ambiente una solución acuosa de NaOH (2,0 M, 3,45 mL, 6,90 mmol). La mezcla obtenida se calentó a reflujo durante 4 h. La mezcla se enfrió hasta temperatura ambiente y se neutralizó (pH ~ 6) con 10% AcOH. La mezcla neutralizada se mantuvo en un baño de hielo durante 30 min. El precipitado obtenido se filtró, se lavó con agua y se secó para proporcionar 0,70 g (86%) del compuesto del título. El producto se purificó mediante cristalización a partir de etanol. P.f.: > 260°C. ^{1}H-RMN (400 MHz, DMSO-d_6) δ 10,90 (s amplio, 1H), 8,32 (s amplio, 1H), 7,45 (t, J = 7,6 Hz, 1H), 7,11 (d, J = 7,6 Hz, 1H), 6,95 (s amplio, 1H), 6,91 (d, J = 7,2 Hz, 1H), 6,75

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(dd, J = 15,6 Hz, J = 1,2 Hz, 1H), 6,23 (dq, J = 15,6 Hz, J = 6,8 Hz, 1H), 1,88 (dd, J = 6,8 Hz, J = 1,6 Hz, 3H). ^{13}C-RMN (100MHz, DMSO-d_6) δ 162,2, 142,9, 138,3, 133,2, 131,2, 128,8, 121,7, 115,8, 110,4, and 18,7. MS 238 (MH^+).

Ejemplo 130a: (*E*)–2–sulfamoilamino–6–(prop–1–enil)benzonitrilo

Una solución de (*E*)–2–amino–6–(prop–1–enil)benzonitrilo (Ejemplo 130b) (0,60 g, 3,82 mmol) en N,N–dimetilacetamida (DMA) (15,5 mL), bajo una atmósfera de nitrógeno, se trató con cloruro de sulfamoilo (0,88 g, 7,63 mmol) a temperatura ambiente. La mezcla obtenida se agitó a temperatura ambiente durante 2 h y la reacción se inactivó con agua (20 mL). La mezcla se extrajo con EtOAc (4 x 80 mL), el extracto combinado se lavó con agua (2 x 20 mL) y salmuera, y se secó con $MgSO_4$. El filtrado se evaporó y el residuo se purificó mediante cromatografía sobre gel de sílice utilizando gradiente hexanos a hexanos/EtOAc (1:1) para proporcionar 0,83 g (92%) del compuesto del título como un sólido blanco. ^{1}H-RMN (400 MHz, DMSO-d_6) δ 9,39 (s amplio, 1H), 7,48-7,60 (m, 2H), 7,38-7,43 (m, 1H), 7,21 (s amplio, 2H), 6,51-6,65 (m, 2H), 1,88-1,94 (m, 3H).

Ejemplo 130b: (*E*)–2–amino–6–(prop–1–enil)benzonitrilo

Se adicionó lentamente HCl concentrado (34,5 mL) a una solución de (*E*)–2–nitro–6–(prop–1–enil)benzonitrilo (Ejemplo 2c) (0,98 g, 5,21 mmol) en EtOH (63,5 mL) a temperatura ambiente. Luego, la mezcla obtenida se trató con polvo de hierro (2,91 g, 52,08 mmol), adicionado en pequeñas porciones a la misma temperatura. La mezcla se agitó a temperatura ambiente durante 15 min. y luego se calentó a reflujo durante 30 min. La mezcla se enfrió hasta temperatura ambiente, el EtOH se evaporó y el pH se reguló hasta un pH~10 con solución acuosa de NaOH (2,0 M). La mezcla basificada se extrajo con EtOAc (4x100 mL) y el extracto combinado se secó con $MgSO_4$ anhidro. El filtrado se evaporó y el residuo se purificó mediante cromatografía sobre gel de sílice utilizando gradiente

hexanos a hexanos/EtOAc (8:2), para proporcionar 0,67 g (81%) del compuesto del título como un sólido blanco. ^{1}H-RMN (400 MHz, DMSO-d_6) δ 7,16-7,23 (m, 1H), 6,78 (d, J = 7,2 Hz, 1H), 6,59-6,64 (m, 1H), 6,35-6,53 (m, 2H), 5,92 (s amplio, 2H), 1,83-1,89 (m, 3H).

Ejemplo 130c: (*E*)–2–nitro–6–(prop–1–enil)benzonitrilo

Una suspensión de 2–yodo–6–nitrobenzonitrilo (Ejemplo 130d) (1,52 g, 5,53 mmol), tetrakis(tifenilfosfin)paladio(0) (0,64 g, 0,55 mmol), ácido *trans*–1–propen–1–ilborónico (0,95 g, 11,06 mmol), carbonato de sodio (0,65 g, 6,08 mmol) y agua (10,0 mL) en dimetoxietano (DME) (40,0 mL) se calentó a reflujo durante 15 h, bajo una atmósfera de nitrógeno. La mezcla de reacción se enfrió hasta temperatura ambiente y se diluyó con agua (20 mL) y EtOAc (100 mL). La fase orgánica se separó y la fase acuosa se extrajo con EtOAc (3 x 50 mL). El extracto combinado se lavó con salmuera y se secó con $MgSO_4$ anhidro. El filtrado se evaporó y el residuo se purificó mediante cromatografía sobre gel de sílice utilizando gradiente hexanos a hexanos/EtOAc (7:3), para proporcionar 0,98 g (94%) del compuesto del título como un sólido blanco. ^{1}H-RMN (400 MHz, DMSO-d_6) δ 8,16-8,24 (m, 2H), 7,83-7,89 (m, 1H), 6,71-6,84 (m, 2H), 1,90-2,02 (m, 3H).

Ejemplo 130d: 2–yodo–6–nitrobenzonitrilo

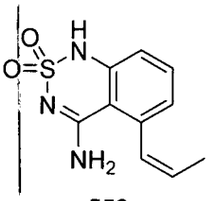
Se adicionó en pequeñas porciones 2–amino–6–nitrobenzonitrilo (Ejemplo 130e) (4,32 g, 26,5 mmol) a una suspensión de nitrito de sodio (2,19 g, 31,7 mmol) en H_2SO_4 concentrado (43 mL) y ácido acético (43 mL) a 45°C. La reacción se calentó a 45°C durante 1 h y luego se adicionó en pequeñas porciones a una solución de yoduro de potasio (7,47 g, 45,0 mmol) en H_2SO_4 (1 M, 43 mL). Luego de agitar a temperatura ambiente durante 1,5 h, se adicionó a la reacción agua helada y el producto precipitado se recogió mediante filtración. El producto se purificó mediante cromatografía sobre gel de sílice eluyendo con CH_2Cl_2, para proporcionar 2–yodo–6–nitrobenzonitrilo (3,86 g, 53%) como un sólido amarillo.

^{1}H-RMN (400 MHz, DMSO-d_6) δ 8,46-8,52 (m, 1H), 8,34-8,38 (m, 1H), 7,66-7,71 (m, 1H).

Ejemplo 130e: 2–amino–6–nitrobenzonitrilo

Se adicionó HCl concentrado (39 mL) a una solución de 2,6–dinitrobenzonitrilo (11,3 g, 58,5 mmol) en MeOH (235 mL) y 1,4-dioxano (145 mL) a 70°C. Se retiró el calentamiento externo, y se adicionó lentamente en porciones polvo de hierro (11,44 g, 205 mmol) a una velocidad que mantuvo una temperatura de 70°C. Luego de que se completó la adición de hierro, la reacción se calentó a reflujo durante 30 min adicionales, luego se enfrió hasta temperatura ambiente y se virtió en EtOAc (400 mL) y agua (400 mL). Los sólidos se separaron mediante filtración y se extrajeron dos veces con EtOAc en ebullición (300 mL). El extracto orgánico combinado se secó con $MgSO_4$, se filtró y se evaporó para proporcionar 2–amino–6–nitrobenzonitrilo (6,5 g, 68%) como un sólido rojo, el cual se utilizó sin purificación adicional. ^{1}H-RMN (400 MHz, DMSO-d_6) δ 7,48-7,54 (m, 1H), 7,41-7,45 (m, 1H), 7,18-7,22 (m, 1H), 6,74 (s amplio, 2H).

Ejemplo 131: 4–amino–5–((*Z*)–prop–1–enil)–1H–benzo[c][1,2,3]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 129 a partir de (*Z*)–2–sulfamoilamino–6–(prop–1–enil)benzonitrilo (Ejemplo 131a) para proporcionar 4–amino–5–((*Z*)–prop–1–enil)–1H–benzo[c][1,2,3]tiadiazin–2,2–dióxido (28,2 mg, 91%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 10,92 (s amplio, 1H), 8,30 (s

amplio, 1H), 7,44-7,51 (m, 1H), 6,90-7,00 (m, 2H), 6,83-6,89 (m, 1H), 6,65-6,73 (m, 1H), 5,88-5,99 (m, 1H), 1,60-1,66 (m, 3H).

Ejemplo 131a: (*Z*)–2–sulfamoilamino–6–(prop–1–enil)benzonitrilo

Preparado como en el Ejemplo 129a a partir de (*Z*)–2–amino–6–(prop–1–enil)benzonitrilo (Ejemplo 3b) en una cantidad de 32,7 mg (92%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,45 (s amplio, 1H), 7,59-7,65 (m, 1H), 7,47 (d, J = 7,6 Hz, 1H), 7,18-7,28 (m, 3H), 6,50-6,57 (m, 1H), 5,99-6,09 (m, 1H), 1,74-1,79 (m, 3H).

Ejemplo 131b: (*Z*)–2–amino–6–(prop–1–enil)benzonitrilo

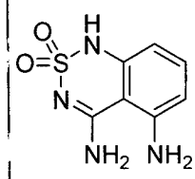
Se adicionó HCl concentrado (1,54 mL) a una suspensión de (Z)–2–nitro–6–(prop–1–enil)benzonitrilo (Ejemplo 3c) (0,35 g, 1,86 mmol) en MeOH (30 mL) y 1,4-dioxano (15 mL) a temperatura ambiente, seguido por la adición a modo de porción de polvo de hierro (0,73 g, 13,0 mmol). La mezcla obtenida se calentó a reflujo durante 2,5 h, se enfrió hasta 0ºC y el pH se reguló hasta un pH~10 con solución acuosa de 50% NaOH. La mezcla se extrajo con EtOAc (3 x 50 mL), el extracto combinado se secó con $MgSO_4$, se filtró y se concentró. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con gradiente 0% a 100% DCM en hexanos, para proporcionar 0,24 g (80%) de (Z)–2–amino–6–(prop–1–enil)benzonitrilo como un aceite amarillo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,24-7,30 (m, 1H), 6,68 (d, J = 8,4 Hz, 1H), 6,55 (d, J = 7,2 Hz, 1H), 6,42-6,48 (m, 1H), 5,98 (s amplio, 2H), 5,89-5,97 (m, 1H), 1,74-1,78 (m, 3H). MS 159 (MH^+).

Ejemplo 131c: (*Z*)–2–nitro–6–(prop–1–enil)benzonitrilo

Preparado como en el Ejemplo 129c partir de trifluormetansulfonato de 2–ciano–3–nitrofenilo (Ejemplo 129d) y ácido *cis*–1–propen–1–ilborónico. El producto crudo se purificó mediante cromatografía sobre gel de sílice eluyendo con gradiente solvente 0% a 100% DCM en hexanos, para proporcionar 0,80 g (97%) de (Z)–2–nitro–6–(prop–1–enil)benzonitrilo (97%) como un sólido amarillo.

^{1}H RMN (400 MHz, DMSO-d_6) δ 8,25-8,30 (m, 1H), 7,90-7,98 (m, 2H), 6,25-6,70 (m, 1H), 6,17-6,28 (m, 1H), 1,78-1,82 (m, 3H).

Ejemplo 132: 4,5–diamino–1H–benzo[c][1,2,3]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 129 a partir de 2–sulfamoilamino–6–aminobenzonitrilo (Ejemplo 132a) en una cantidad de 95,3 mg (84%) como un sólido marrón. ^{1}H RMN (400 MHz, DMSO-d_6) δ 10,55 (s amplio, 1H), 7,80 (s amplio, 2H), 7,09-7,16 (t, J = 8,0 Hz, 1H), 6,42 (d, J = 8,4 Hz, 1H), 6,22 (d, J = 8,4 Hz, 1H), 5,79 (s amplio, 2H).

Ejemplo 132a: 2–sulfamoilamino–6–aminobenzonitrilo

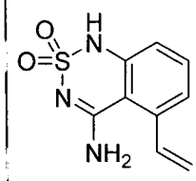
Preparado como en el Ejemplo 129a a partir de 2,6–diaminobenzonitrilo (Ejemplo 132b) en una cantidad de 129,4 mg (60%) como un sólido marrón. ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,00 (s amplio, 1H), 7,18 (t, J = 8,0 Hz, 1H), 7,08 (s amplio, 2H), 6,62-6,67 (m, 1H), 6,49-6,54 (m, 1H), 5,95 (s amplio, 2H).

Ejemplo 132b: 2,6–diamonobenzonitrilo

Se adicionó HCl concentrado (44,3 mL) a una solución de 2,6–dinitrobenzonitrilo (12,9 g, 67,1 mmol) en MeOH (269 mL) y 1,4-dioxano (166 mL) a 70°C. Se retiró el calentamiento externo, y se adicionó lentamente en porciones polvo de hierro (13,1 g, 235 mmol) a una velocidad que mantuvo una temperatura de 70°C. Luego de que se completó la adición de hierro, la reacción se calentó a reflujo durante 30 min adicionales, luego se enfrió hasta temperatura ambiente y se virtió en EtOAc (400 mL) y agua (400 mL). Los sólidos se separaron mediante filtración y se extrajeron dos veces con EtOAc en ebullición (300 mL). Las capas

orgánicas se combinaron, se secaron con $MgSO_4$, se filtraron y se concentraron. El producto crudo se purificó mediante cromatografía de fase inversa (0–100% CH_3CN en H_2O) para proporcionar el compuesto del título (1,0 g, 11%), el cual se utilizó sin purificación adicional. MS 134 (MH^+).

Ejemplo 133: 4–amino–5–vinil–1H–benzo[c][1,2,3]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 129 a partir de 2–sulfamoilamino–6–vinilbenzonitrilo (Ejemplo 133a) en una cantidad de 30,0 mg (48%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 10,95 (s amplio, 1H), 8,33 (s amplio, 1H), 7,48 (t, J = 8,0 Hz, 1H), 7,18 (d, J = 7,6 Hz, 1H), 7,09 (dd, J = 17,6, 10,8 Hz, 1H), 6,90-6,99 (m, 2H), 5,78 (dd, J = 17,6, 1,6 Hz, 1H), 5,47 (dd, J = 11,2, 1,2 Hz, 1H).

Ejemplo 133a: 2–sulfamoilamino–6–vinilbenzonitrilo

Preparado como en el Ejemplo 129a a partir de 2–amino–6–vinilbenzonitrilo (Ejemplo 133b) en una cantidad de 63,0 mg (81%), como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,46 (s amplio, 1H), 7,59-7,67 (m, 2H), 7,46-7,52 (m, 1H), 7,23 (s amplio, 2H), 6,93 (dd, J = 17,2, 10,8 Hz, 1H), 6,08 (d, J = 17,2 Hz, 1H), 5,59 (d, J = 11,2 Hz, 1H).

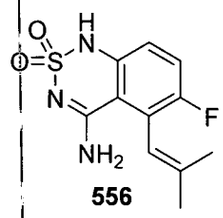
Ejemplo 133b: 2–amino–6–vinilbenzonitrilo

Preparado como en el Ejemplo 129b a partir de 2–nitro–6–vinilbenzonitrilo (Ejemplo 133c) en una cantidad de 123,9 mg (71%), como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,25 (t, J = 8,0 Hz, 1H), 6,87 (d, J = 7,2 Hz, 1H), 6,80 (dd, J = 17,2, 11,6 Hz, 1H), 6,69 (d, J = 8,4 Hz, 1H), 6,00 (s amplio, 2H), 5,92 (d, J = 17,2 Hz, 1H), 5,44 (d, J = 10,8 Hz, 1H).

Ejemplo 133c: 2–nitro–6–vinilbenzonitrilo

Preparado como en el Ejemplo 129c partir de trifluormetansulfonato de 2–ciano–3–nitrofenilo (Ejemplo 129d) en una cantidad de 0,61 g (86%) como un sólido amarillo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,26-8,34 (m, 2H), 7,90-7,98 (m, 1H), 7,09 (dd, J = 17,6, 11,2 Hz, 1H), 6,26 (d, J = 17,6 Hz, 1H), 5,80 (d, J = 11,6 Hz, 1H).

Ejemplo 134: 4–amino–6–fluor–5–(2–metilprop–1–enil)–1H–benzo[c][1,2,3] tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 129 a partir de 3–fluor–2–(2–metilprop–1–enil)–6–sulfamoilaminobenzonitrilo (Ejemplo 134a) en una cantidad de 125,0 mg (86%) como un sólido blanco. P.f.: >250ºC. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,51 (s, 3H), 1,90 (s, 3H), 6,27 (s, 1H), 7,00 (m, 1H), 7,10 (s amplio, 1H), 7,45 (m, 1H), 8,35 (s amplio, 1H), 10,95 (s amplio, 1H). MS 270 (MH^+).

Ejemplo 134a: 3–fluor–2–(2–metilprop–1–enil)–6–sulfamoilaminobenzonitrilo

Preparado como en el Ejemplo 129a a partir de 6–amino–3–fluor–2–(2–metilprop–1–enil)benzonitrilo (Ejemplo 134b) en una cantidad de 156,0 mg (88%), como un sólido blanco. MS 270 (MH^+).

Ejemplo 134b: 6–amino–3–fluor–2–(2–metilprop–1–enil)benzonitrilo

Preparado como en el Ejemplo 129b a partir de 3–fluor–2–(2–metilprop–1–enil)–6–nitrobenzonitrilo (Ejemplo 134c) en una cantidad de 0,38 g, (84%) como un sólido blanco. MS 191 (MH^+).

Ejemplo 134c: 3–fluor–2–(2–metilprop–1–enil)–6–nitrobenzonitrilo

Se suspendieron 2–bromo–3–fluor–6–nitrobenzonitrilo (Ejemplo 134d) (0,62 g, 2,53 mmol), ácido 2–metilprop–1–enilborónico (0,50 g, 5,05 mmol), acetato de paladio (II) (0,023 g, 0,102 mmol), K_3PO_4 (1,61 g, 7,58 mmol), y diciclohexil(2',6'–dimetoxibifenil–2–il)fosfina (0,083 g, 0,202 mmol) en THF anhidro (16 mL) bajo nitrógeno y se calentaron a 70ºC durante 4,5 h. El solvente se removió bajo vacío, y el producto se purificó mediante cromatografía sobre gel de sílice eluyendo con gradiente 0% a 100% acetato de etilo en hexanos, para proporcionar 3–fluor–2–(2–metilprop–1–enil)–6–nitrobenzonitrilo 0,44 g (78%) como un sólido amarillo. MS 221 (MH^+).

Ejemplo 134d: 2–bromo–3–fluor–6–nitrobenzonitrilo

Se adicionó trietilamina (2,53 mL, 18,2 mmol) a una suspensión de 2–bromo–3–fluor–6–nitrobenzamida (Ejemplo 6e) (1,60 g, 6,08 mmol) en $POCl_3$ (32 mL), y la mezcla se calentó a 75ºC durante 1,5 h. La mezcla se virtió cuidadosamente en una mezcla de hielo y agua (400 mL) y se extrajo dos veces con CH_2Cl_2. El extracto combinado se secó con $MgSO_4$, se filtró y se concentró bajo vacío. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con gradiente solvente 0% a 100% EtOAc en hexanos, para proporcionar 2–bromo–3–fluor–6–nitrobenzonitrilo 0,95 g, (64%) como un sólido amarillo.

Ejemplo 134e: 2–bromo–3–fluor–6–nitrobenzamida

Se disolvió ácido 2–bromo–3–fluor–6–nitrobenzoico (Ejemplo 134f) (24,83 g, 94,0) mmol, (mezcla de dos regioisómeros) en THF anhidro (200 mL) bajo una atmósfera de nitrógeno a temperatura ambiente. Se adicionó DMF anhidra (0,75 mL) y la mezcla obtenida se enfrió hasta 0ºC. Se adicionó lentamente cloruro de oxalilo (12,3 mL, 141 mmol) y la mezcla de reacción se agitó a 0ºC durante 10 min, y a temperatura ambiente durante 2 h adicionales. La reacción se evaporó

hasta sequedad, se suspendió en THF anhidro (100 mL) y se adicionó lentamente a hidróxido de amonio concentrado (350 mL) a 0ºC. Luego de agitar durante 45 minutos a 0ºC la mezcla se extrajo con CH_2Cl_2 (5 x 100 mL), y luego se descartaron las extracciones orgánicas. En este punto el regioisómero deseado existía como un precipitado insoluble en la capa acuosa, que se recogió mediante filtración para proporcionar 10,3 g (42%) de 2–bromo–3–fluor–6–nitrobenzamida la cual se utilizó sin purificación adicional. ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,27 (dd, J = 8,8, 4,4 Hz, 1H), 8,10 (s amplio, 1H), 7,95 (s amplio, 1H), 7,66 (dd, J = 9,6, 7,6 Hz, 1H).

Ejemplo 134f: Ácido 2–bromo–3–fluor–6–nitrobenzoico

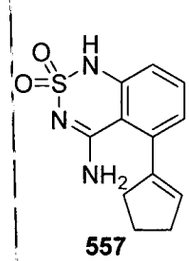
En un frasco de tres bocas de 1 L adaptado con un embudo de decantación y un termómetro se cargaron ácido 2–bromo–3–fluorbenzoico (Ejemplo 134g) (28,23 g, 0,13 mol) y H_2SO_4 concentrado (200 mL). Luego de enfriarse hasta 0ºC, se adicionó gota a gota HNO_3 (70%, 16,0 mL) durante 30 min, manteniendo la temperatura entre 0 a 10ºC. Luego de 1 h, la mezcla de reacción se virtió en el hielo triturado manteniendo la temperatura por debajo de 20 °C. La mezcla se extrajo con EtOAc (2 x 200 mL), el extracto combinado se lavó con salmuera y se secó con $MgSO_4$. El filtrado se evaporó para proporcionar 27,27 g (77%) de una mezcla de ácido 2–bromo–3–fluor–6–nitrobenzoico y ácido 2–bromo–3–fluor–5–nitrobenzoico (1:0,4) como un sólido marrón. ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,33 (dd, J = 9,6, 4,8 Hz, 1H), 7,21 (dd, J = 10,0, 8,0 Hz, 1H).

Ejemplo 134g: Ácido 2–bromo–3–fluorbenzoico

En un frasco de tres bocas de 1 L adaptado con un embudo de decantación y un termómetro, se cargaron ácido 2–amino–3–fluorbenzoico (20,0 g, 0,13 mol) y acetonitrilo (160 mL). Luego de enfriarse hasta 0ºC, se adicionó gota a gota HBr (47%, 160 mL) durante 10 min. A la solución resultante se le adicionó gota a gota una solución de $NaNO_2$ (10,0 g, 0,14 mol) en agua (20,0 mL) durante 1 h. Luego

de la adición, la mezcla de reacción se agitó a 0°C durante 5 min, y se adicionó a modo de porción bromuro de cobre (I) (22,0 g, 0,15 mol) durante 30 min. La agitación se continuó a 70°C en un baño de aceite durante 1 h. Luego de enfriarse hasta 0°C, se adicionaron 700 mL de agua y el precipitado se filtró, se lavó con agua fría y se secó bajo vacío para proporcionar 28,23 g (100%) del compuesto del título como un sólido blanco. El producto crudo se utilizó en la etapa siguiente sin purificación.

Ejemplo 135: 4–amino–5–(ciclopenten–1–il)–1H–benzo[c][1,2,3]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 129 a partir de 2–sulfamoilamino–6–(ciclopenten–1–il)benzonitrilo (Ejemplo 135a) en una cantidad de 36,0 mg (33%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,97 (m, 2H), 2,48 (m, 2H), 2,58 (m, 2H), 5,94 (m, 1H), 6,83 (s amplio, 1H), 6,92 (m, 2H), 7,46 (m, 1H), 8,25 (s amplio, 1H), 11,02 (s amplio, 1H). MS 264 (MH^+).

Ejemplo 135a: 2–sulfamoilamino–6–(ciclopenten–1–il)benzonitrilo

Preparado como en el Ejemplo 129a a partir de 2–amino–6–(ciclopenten–1–il)benzonitrilo (Ejemplo 135b) en una cantidad de 156,0 mg (88%), como un sólido blanco.

Ejemplo 135b: 2–amino–6–(ciclopenten–1–il)benzonitrilo

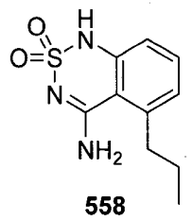
Preparado como en el Ejemplo 129b a partir de 2–(ciclopenten–1–il)–6–nitrobenzonitrilo (Ejemplo 135c) en una cantidad de 0,44 g, (84%) como un sólido blanco. MS 185 (MH^+).

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Ejemplo 135c: 2–(ciclopenten–1–il)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 129c partir de trifluormetansulfonato de 2–ciano–3–nitrofenilo (Ejemplo 129d) en una cantidad de 0,62 g (84%) como un sólido blanco.

Ejemplo 136: 4–amino–5–*n*–propil–1H–benzo[c][1,2,3]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 129 a partir de 2–sulfamoilamino–6–*n*–propilbenzonitrilo (Ejemplo 136a) en una cantidad de 144,3 mg (66%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 10,73 (s amplio, 1H), 8,14 (s amplio, 1H), 7,44 (s amplio, 1H), 7,38 (t, J = 8,0 Hz, 1H), 6,97 (d, J = 6,8 Hz, 1H), 6,86 (d, J = 8,0 Hz, 1H), 2,97 (t, J = 7,6 Hz, 2H), 1,51 (hex, J = 7,6 Hz, 2H), 0,81 (t, J = 7,6 Hz, 3H).

Ejemplo 136a: 2–sulfamoilamino–6–*n*–propilbenzonitrilo

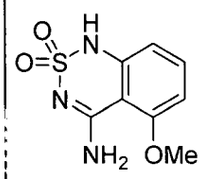
Preparado como en el Ejemplo 129a a partir de 2–amino–6–*n*–propilbenzonitrilo (Ejemplo 136b) en una cantidad de 238,4 mg (91%), como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,37 (s amplio, 1H), 7,55 (t, J = 8,4 Hz, 1H), 7,39- 7,44 (m, 1H), 7,17-7,23 (m, 3H), 2,71 (t, J = 8,0 Hz, 2H), 1,60 (hex, J = 7,6 Hz, 2H), 0,90 (t, J = 7,6 Hz, 3H).

Ejemplo 136b: 2–amino–6–*n*–propilbenzonitrilo

Se agitaron (Z)–2–amino–6–(prop–1–enil)benzonitrilo (Ejemplo 131b) (0,45 g, 2,82 mmol) y 10% Pd/C (0,17 g) en EtOH (15 mL) bajo una atmósfera de hidrógeno durante 4 h. El catalizador se separó mediante filtración, y la capa orgánica se concentró bajo vacío para proporcionar 0,43 g (96%) de 2–amino–6–

n–propilbenzonitrilo como un aceite amarillo, el cual se utilizó sin purificación adicional. MS 161 (MH^+).

Ejemplo 137: 4–amino–5–metoxi–1H–benzo[c][1,2,3]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 129 a partir de 2–sulfamoilamino–6–metoxibenzonitrilo (Ejemplo 137a) en una cantidad de 138,9 mg (93%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 10,09 (s amplio, 1H), 8,28 (s amplio, 1H), 8,03 (s amplio, 1H), 7,44 (t, J = 8,0 Hz, 1H), 6,70 (d, J = 8,4 Hz, 1H), 6,58 (d, J = 8,0 Hz, 1H), 3,89 (s, 3H).

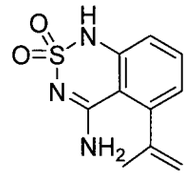
Ejemplo 137a: 2–sulfamoilamino–6–metoxibenzonitrilo

Preparado como en el Ejemplo 129a a partir de 2–amino–6–metoxibenzonitrilo (Ejemplo 137b) en una cantidad de 175,9 mg (84%), como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,44 (s amplio, 1H), 7,56 (t, J = 8,4 Hz, 1H), 7,25 (s amplio, 2H), 7,14 (d, J = 8,0 Hz, 1H), 6,93 (d, J = 8,8 Hz, 1H), 3,87 (s, 3H).

Ejemplo 137b: 2–amino–6–metoxibenzonitrilo

Una solución de 2–metoxi–6–nitrobenzonitrilo (1,01 g, 5,69 mmol), ciclohexeno (2,84 g, 3,51 mL, 34,58 mmol) y 10% Pd/C (0,58 g) en EtOH (25 mL) se reflujó durante 1,5 h. La mezcla se enfrió hasta temperatura ambiente, se filtró y se evaporó, para proporcionar 0,83 g (98%) del compuesto del título. El producto crudo se utilizó en la etapa siguiente sin purificación adicional. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,17 (t, J = 8,0 Hz, 1H), 6,31- 6,35 (m, 1H), 6,17-6,21 (m, 1H), 5,97 (s amplio, 2H), 3,76 (s, 3H).

Ejemplo 138: 4–amino–5–(prop–1–en–2–il)–1H–benzo[c][1,2,3]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 129 a partir de 2–sulfamoilamino–6–(prop–1–en–2–il)benzonitrilo (Ejemplo 138a) en una cantidad de 63,8 mg (82%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 11,05 (s amplio, 1H), 8,32 (s amplio, 1H), 7,44- 7,52 (m, 1H), 6,94-7,00 (m, 1H), 6,84-6,89 (m, 1H), 6,82 (s amplio, 1H), 5,16-5,19 (m, 1H), 5,31-5,35 (m, 1H), 2,00 (s, 3H).

Ejemplo 138a: 2–sulfamoilamino–6–(prop–1–en–2–il)benzonitrilo

Preparado como en el Ejemplo 129a a partir de 2–amino–6–(prop–1–en–2–il)benzonitrilo (Ejemplo 138b) en una cantidad de 80,5 mg (100%), como un sólido amarillo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,40 (s amplio, 1H), 7,58-7,64 (m, 1H), 7,48-7,52 (m, 1H), 7,25 (s amplio, 2H), 7,18-7,24 (m, 1H), 5,34-5,40 (m, 1H), 5,10-5,14 (m, 1H), 2,10 (s, 3H).

Ejemplo 138b: 2–amino–6–(prop–1–en–2–il)benzonitrilo

Preparado como en el Ejemplo 129b a partir de 2–nitro–6–(prop–1–en–2–il)benzonitrilo (Ejemplo 138c) en una cantidad de 303,4 mg (83%), como un sólido amarillo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,18-7,25 (m, 1H), 6,67-6,72 (m, 1H), 6,47-6,51 (m, 1H), 5,97 (s amplio, 2H), 5,24-5,27 (m, 1H), 5,07-5,10 (m, 1H), 2,03-2,06 (m, 3H)

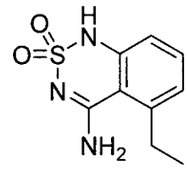
Ejemplo 138c: 2–nitro–6–(prop–1–en–2–il)benzonitrilo

Una suspensión de trifluormetansulfonato de 2–ciano–3–nitrofenilo (Ejemplo 129d) (0,93 g, 3,15 mmol), trifluor(prop–1–en–2–il)borato de potasio

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(0,70 g, 4,73 mmol), dicloro 1,1'–bis(difenilfosfin)ferrocen paladio (II) (0,26 g, 0,32 mmol), carbonato de cesio (3,08 g, 9,45 mmol) y agua (5,6 mL) en THF (56 mL) se calentó a reflujo durante 25 min, bajo una atmósfera de nitrógeno. La mezcla de reacción se enfrió hasta temperatura ambiente y se diluyó con agua (100 mL) y EtOAc (100 mL). La fase orgánica se separó y la fase acuosa se extrajo con EtOAc (3 x 100 mL). El extracto combinado se lavó con HCl diluido (1,5 M), salmuera y se secó con $MgSO_4$ anhidro. El filtrado se evaporó y el residuo se purificó mediante cromatografía sobre gel de sílice utilizando gradiente hexanos a hexanos/EtOAc (7:3), para proporcionar 0,30 g (49%) del compuesto del título como un sólido amarillo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,24-8,29 (m, 1H), 7,86-7,95 (m, 2H), 5,47-5,52 (m, 1H), 5,20-5,23 (m, 1H), 2,12-2,15 (m, 3H).

Ejemplo 139: 4–amino–5–etil–1H–benzo[c][1,2,3]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 129 a partir de 2–sulfamoilamino–6–vinilbenzonitrilo (Ejemplo 139a) en una cantidad de 84,2 mg (80%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 10,74 (s amplio, 1H), 8,16 (s amplio, 1H), 7,24-7,52 (m, 2H), 6,99 (d, J = 7,2 Hz, 1H), 6,84-6,88 (m, 1H), 3,00 (q, J = 7,6 Hz, 2H), 1,12 (t, J = 7,6 Hz, 3H).

Ejemplo 139a: 2–sulfamoilamino–6–vinilbenzonitrilo

Preparado como en el Ejemplo 129a a partir de 2–amino–6–etilbenzonitrilo (Ejemplo 139b) en una cantidad de 280,3 mg (98%), como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,36 (s amplio, 1H), 7,52-7,60 (t, J = 8,4 Hz, 1H),

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7,38-7,43 (m, 1H), 7,19 7,24 (m, 1H), 7,19 (s amplio, 2H), 2,75 (q, J = 8,0, 2H), 1,18 (t, J = 7,6 Hz, 3H).

Ejemplo 139b: 2–amino–6–etilbenzonitrilo

Preparado como en el Ejemplo 129b a partir de 2–etil–6–nitrobenzonitrilo (Ejemplo 139c) en una cantidad de 0,46 g (74%), como un sólido anaranjado. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,18 (t, J = 8,0 Hz, 1H), 6,59 (d, J = 8,0 Hz, 1H), 6,47 (d, J = 7,2 Hz, 1H), 5,89 (s amplio, 2H), 2,60 (q, J = 7,6 Hz, 2H), 1,15 (t, J = 7,6 Hz, 3H).

Ejemplo 139c: 2–etil–6–nitrobenzonitrilo

Una suspensión de 2 etil–6–nitroanilina (Ejemplo 139d) (1,96 g, 11,80 mmol) en una solución de HCl (3,0 M, 24,5 mL) se agitó a temperatura ambiente durante 20 min. Luego de enfriarse hasta 0-5°C, se adicionó una solución de $NaNO_2$ (1,63 g, 23,6 mmol) en agua (12,25 mL) durante un período de 10 min. La mezcla obtenida se agitó a 0-5°C durante 30 min, y la solución homogénea obtenida se transfirió a una solución de CuCN (2,63 g, 29,5 mmol) y KCN (5,06 g, 77,8 mmol) en agua (60 mL) y EtOH (31,0 mL). La mezcla resultante se agitó enérgicamente a temperatura ambiente durante 30 min, y luego se calentó a 70°C durante otros 30 min para completar la reacción. La mezcla fría se filtró y se extrajo con EtOAc (3 x 100 mL). El extracto combinado se lavó con NaOH (0,5 M) y salmuera, y se secó con $MgSO_4$ anhidro. El filtrado se evaporó y el residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con 30% EtOAc en hexanos, para proporcionar 0,66 g (33%) del compuesto del título como un sólido anaranjado. ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,18-8,24 (m, 1H), 7,85-7,97 (m, 2H), 2,93 (q, J = 7,2 Hz, 2H), 1,24 (t, J = 7,2 Hz, 3H).

Ejemplo 139d: 2-etil–6–nitroanilina

Una solución de N–(2–etil–6–nitrofenil)actamida (Ejemplo 139e) (0,62 g, 2,98 mmol) en EtOH (21 mL) y HCl concentrado (13 mL) se reflujó durante 24 h.

El EtOH se evaporó, el residuo se diluyó con agua (10 mL) y el pH se reguló hasta un pH~8 with NaOH (2,0 M solución acuosa). La solución neutralizada se extrajo con EtOAc (3 x 50 mL), el extracto combinado se lavó con agua y salmuera, y se secó con $MgSO_4$ anhidro. El filtrado se evaporó y el residuo se purificó sobre HPLC para proporcionar 0,32 g (64%) de 2–etil–6–nitroanilina como un sólido anaranjado. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,82-7,87 (m, 1H), 7,27-7,32 (m, 1H), 7,16 (s amplio, 2H), 6,55-6,62 (m, 1H), 2,55 (q, J = 7,2 Hz, 2H), 1,13 (t, J = 7,2 Hz, 3H).

Ejemplo 139e: N–(2–etil–6–nitrofenil)acetamida

Una solución de ácido nítrico (4,2 mL) en ácido acético glacial (5,2 mL) se adicionó gota a gota a una solución de N–(2–etilfenil)acetamida (Ejemplo 139f) (1,00 g, 6,13 mmol) en AcOH (22 mL) y anhídrido acético (18 mL) a 0ºC. La reacción se agitó a 0ºC durante 1 h, se diluyó con agua (50 mL) y se neutralizó con Na_2CO_3 (pH~8). La mezcla neutralizada se extrajo con EtOAc (3 x 50 mL), el extracto combinado se lavó con agua y salmuera, y se secó con $MgSO_4$ anhidro. El filtrado se evaporó y el residuo se purificó sobre HPLC para proporcionar 0,62 g (48%) del compuesto del título como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,81 (s amplio, 1H), 7,68-7,73 (m, 1H), 7,57-7,62 (m, 1H), 7,39 (t, J = 8,0 Hz, 1H), 2,64 (q, J = 8,0 Hz, 2H), 2,00 (s, 3H), 1,10 (t, J = 8,0 Hz, 3H).

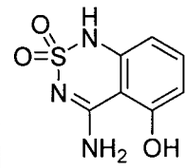
Ejemplo 139f: N–(2–etilfenil)acetamida

Se adicionó 2–etilanilina (9,70 g, 80,0 mmol) a una mezcla de AcOH glacial (30 mL) y anhídrido acético (20 mL), y la mezcla resultante se reflujó a 120ºC durante 3 h. Luego la mezcla de reacción se enfrió hasta temperatura ambiente y se virtió en una mezcla en ebullición de agua y EtOH (20 mL cada uno). La mezcla se agitó a ta durante 1 h y luego se enfrió (0-5ºC) durante la noche. El EtOH se evaporó y el resto de la mezcla se diluyó con agua (100 mL). La mezcla obtenida se neutralizó con Na_2CO_3 y se extrajo con EtOAc. El extracto combinado

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se lavó con salmuera, se secó con $MgSO_4$ anhidro, se filtró y se evaporó. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con 5% MeOH en CH_2Cl_2, para proporcionar 5,50 g (42%) del compuesto del título como un sólido rosado. ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,25 (s amplio, 1H), 7,05-7,40 (m, 4H), 2,55 (q, J = 7,6 Hz, 2H), 2,02 (s, 3H), 1,09 (t, J = 7,6 Hz, 3H).

Ejemplo 140: 4–amino–5–hidroxi–1H–benzo[c][1,2,3]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 129 a partir de 2–sulfamoilamino–6–hidroxibenzonitrilo (Ejemplo 140a) en una cantidad de 50,6 mg (20%) como un sólido marrón. ^{1}H RMN (400 MHz, DMSO-d_6) δ 11,00 (s amplio, 1H), 9,24 (s amplio, 1H), 7,37 (t, J = 8,0 Hz, 1H), 7,18 (s amplio, 2H), 6,97 (d, J = 8,4 Hz, 1H), 6,71 (d, J = 8,4 Hz, 1H).

Ejemplo 140a: 2–sulfamoilamino–6–hidroxibenzonitrilo

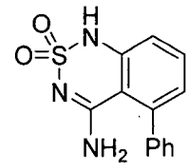
Preparado como en el Ejemplo 129a a partir de 2–amino–6–hidroxibenzonitrilo (Ejemplo 140b) en una cantidad de 0,25 g (99%), como un sólido marrón. ^{1}H RMN (400 MHz, DMSO-d_6) δ 11,01 (s amplio, 1H), 9,25 (s amplio, 1H), 7,37 (t, J = 8,0 Hz, 1H), 7,18 (s amplio, 2H), 6,95-6,99 (m, 1H), 6,69-6,74 (m, 1H).

Ejemplo 140b: 2–amino–6–hidroxibenzonitrilo

Una solución de 2–metoxi–6–nitrobenzonitrilo (Ejemplo 129f) (1,11 g, 6,76 mmol) en EtOH (120 mL) se hidrogenó sobre una cantidad catalítica de 10% Pd/C (0,15 g) a temperatura ambiente bajo hidrógeno (1 atm). Luego de 2 h, la mezcla se filtró y el catalizador se lavó con EtOAc (150 mL). El extracto

combinado se evaporó, para proporcionar 1,11 g (100%) del compuesto del título como un sólido marrón. El producto crudo se utilizó en la etapa siguiente sin purificación adicional. ^{1}H RMN (400 MHz, DMSO-d_6) δ 10,39 (s amplio, 1H), 7,00 (t, J = 8,0 Hz, 1H), 6,12-6,17 (m, 1H), 6,01-6,05 (m, 1H), 5,77 (s amplio, 2H).

Ejemplo 141: 4–amino–5–fenil–1H–benzo[c][1,2,3]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 129 a partir de 2–sulfamoilamino–6–fenilbenzonitrilo (Ejemplo 141a) en una cantidad de 114,7 mg (90%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 11,12 (s amplio, 1H), 8,04 (s amplio, 1H), 7,52-7,58 (m, 1H), 7,39-7,50 (m, 3H), 7,32-7,38 (m, 2H), 7,02-7,07 (m, 1H), 6,97-7,01 (m, 1H), 5,61 (s amplio, 1H).

Ejemplo 141a: 2–sulfamoilamino–6–fenilbenzonitrilo

Preparado como en el Ejemplo 129a a partir de 3–aminobifenil–2–carbonitrilo (Ejemplo 141b) en una cantidad de 142,3 mg (94%), como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,49 (s amplio, 1H), 7,68-7,74 (m, 1H), 7,58-7,62 (m, 1H), 7,44-7,53 (m, 5H), 7,30-7,34 (m, 1H), 7,29 (s amplio, 2H).

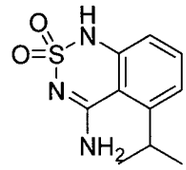
Ejemplo 141b: 3–aminobifenil–2–carbonitrilo

Preparado como en el Ejemplo 129b a partir de 3–nitrobifenil–2–carbonitrilo (Ejemplo 141c) en una cantidad de 117,0 mg (80%), como un sólido blanco. MS 195 (MH^+).

Ejemplo 141c: 3–nitrobifenil–2–carbonitrilo

Preparado como en el Ejemplo 129c partir de trifluormetansulfonato de 2–ciano–3–nitrofenilo (Ejemplo 129d) y ácido fenilborónico .

Ejemplo 142: 4–amino–5–isopropil–1H–benzo[c][1,2,3]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 129 a partir de 2–sulfamoilamino–6–isopropilbenzonitrilo (Ejemplo 142a) en una cantidad de 53,7 mg (49%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 10,74 (s amplio, 1H), 8,19 (s amplio, 1H), 7,42 (t, J = 8,0 Hz, 1H), 7,15 (s amplio, 1H), 7,07-7,13 (m, 1H), 6,83-6,88 (m, 1H), 3,71 (hep, J = 6,4 Hz, 1H), 1,18 (d, J = 6,8 Hz, 6H).

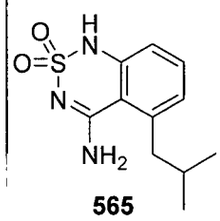
Ejemplo 142a: 2–sulfamoilamino–6–isopropilbenzonitrilo

Preparado como en el Ejemplo 129a a partir de 2–amino–6–isopropilbenzonitrilo (Ejemplo 142b) en una cantidad de 112,0 mg (97%), como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,35 (s amplio, 1H), 7,60 (t, J = 8,4 Hz, 1H), 7,41 (d, J = 8,0 Hz, 1H), 7,27 (d, J = 7,6 Hz, 1H), 7,20 (s amplio, 2H), 3,20 (hep, J = 6,8 Hz, 1H), 1,23 (d, J = 6,8 Hz, 6H).

Ejemplo 142b: 2–amino–6–isopropilbenzonitrilo

Preparado como en el Ejemplo 136b a partir de 2–amino–6–(prop–1–en–2–il)benzonitrilo (Ejemplo 138b) en una cantidad de 112,0 mg (97%), como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,21 (t, J = 8,0 Hz, 1H), 6,60 (d, J = 8,4 Hz, 1H), 6,52 (d, J = 7,2 Hz, 1H), 5,87 (s amplio, 2H), 3,03 (hep, J = 6,8 Hz, 1H), 1,18 (d, J = 6,8 Hz, 6H).

Ejemplo 143: 4–amino–5–isobutil–1H–benzo[c][1,2,3]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 129 a partir de 2–sulfamoilamino–6–isobutilbenzonitrilo (Ejemplo 143a) en una cantidad de 32,5 mg (63%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 10,70 (s amplio, 1H), 8,08 (s amplio, 1H), 7,55 (s amplio, 1H), 7,36 (t, J = 8,0 Hz, 1H), 6,89-6,94 (m, 1H), 6,84-6,88 (m, 1H), 2,87 (d, J = 6,8 Hz, 2H), 1,69-1,81 (m, 1H), 0,72 (d, J = 6,8 Hz, 6H).

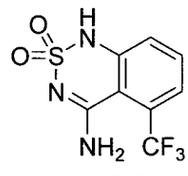
Ejemplo 143a: 2–sulfamoilamino–6–isobutilbenzonitrilo

Preparado como en el Ejemplo 129a a partir de 2–amino–6–isobutilbenzonitrilo (Ejemplo 143b) en una cantidad de 52,0 mg (91%), como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,36 (s amplio, 1H), 7,55 (t, J = 8,0 Hz, 1H), 7,41 (d, J = 8,0 Hz, 1H), 7,21 (s amplio, 2H), 7,16 (d, J = 6,8 Hz, 1H), 2,62 (d, J = 7,6 Hz, 2H), 1,82-1,96 (m, 1H), 0,88 (d, J = 6,4 Hz, 6H).

Ejemplo 143b: 2–amino–6–isobutilbenzonitrilo

Preparado como en el Ejemplo 136b a partir de 2–amino–6–(2–metilprop–1–enil)benzonitrilo (Ejemplo 129b) en una cantidad de 76,4 mg (98%), como un aceite amarillo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,17 (t, J = 8,0 Hz, 1H), 6,60 (d, J = 8,4 Hz, 1H), 6,42 (d, J = 7,6 Hz, 1H), 5,88 (s amplio, 2H), 2,47 (d, J = 7,6 Hz, 2H), 1,78-1,92 (m, 1H), 0,86 (d, J = 6,4 Hz, 6H).

Ejemplo 144: 4–amino–5–trifluormetil–1H–benzo[c][1,2,3]tiadiazin–2,2–dióxido



566

Preparado como en el Ejemplo 129 a partir de 2–sulfamoilamino–6–trifluormetilbenzonitrilo (Ejemplo 144a) en una cantidad de 114,8 mg (96%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 11,41 (s amplio, 1H), 7,64-7,72 (m, 1H), 7,50 (d, J = 7,2 Hz, 1H), 7,38-7,68 (s amplio, 1H), 7,31 (d, J = 8,4 Hz, 1H), 3,10-3,60 (s amplio, 1H).

Ejemplo 144a: 2–sulfamoilamino–6–trifluormetilbenzonitrilo

Preparado como en el Ejemplo 129a a partir de 2–amino–6–trifluormetilbenzonitrilo (Ejemplo 144b) en una cantidad de 138,5 mg (82%), como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,91 (s amplio, 1H), 7,84-7,92 (m, 2H), 7,69-7,76 (m, 1H), 7,42 (s amplio, 2H).

Ejemplo 144b: 2–amino–6–trifluorbenzonitrilo

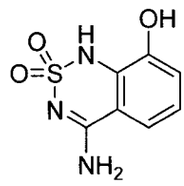
Se trató 2–(4–metoxibencilamino)–6–(trifluormetil)benzonitrilo (Ejemplo 144c) (3,49 g, 11,4 mmol) con ácido trifluoracético (TFA) (35 mL) a 0ºC, y luego se agitó a temperatura ambiente durante 20 min. El TFA se removió bajo vacío, y el residuo se disolvió en CH_2Cl_2 (150 mL) y se lavó con NaOH 1 M. La capa orgánica se secó con $MgSO_4$, se filtró y se removió bajo vacío. El producto crudo se purificó mediante cromatografía sobre gel de sílice eluyendo con CH_2Cl_2 para proporcionar 2,12 g (99%) de 2–amino–6–(trifluormetil)benzonitrilo como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,45 (m, 1H), 7,07 (m, 1H), 6,96 (m, 1H), 6,60 (br s, 2H).

Ejemplo 144c: 2–(4–metoxibencilamino)–6–(trifluormetil)benzonitrilo

Se suspendieron 2–fluor–6–(trifluormetil)benzonitrilo (2,44 g, 12,9 mmol) y 4–metoxibencilamina (7,09 g, 51,7 mmol) en 1,4-dioxano (10 mL) y se calentaron en un microondas a 180ºC durante 30 min. El 1,4-dioxano se removió bajo vacío, y el material crudo se purificó mediante cromatografía sobre gel de sílice eluyendo con CH_2Cl_2 para proporcionar 3,71 g de 2–(4–metoxibencilamino)–6–

(trifluormetil)benzonitrilo (94%) como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,71 (s, 3H), 4,42 (d, J = 5,6 Hz, 2H), 6,89 (m, 2H), 6,97 (m, 2H), 7,29 (m, 3H), 7,48 (m, 1H).

Ejemplo 145: 4–amino–8–hidroxi–1H–benzo[c][1,2,3]tiadiazin–2,2–dióxido



567

Preparado como en el Ejemplo 129 a partir de 2–sulfamoilamino–3–hidroxibenzonitrilo (Ejemplo 145a) en una cantidad de 53,9 mg (66%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 10,14 (s amplio, 2H), 8,04 (s amplio, 2H), 7,31-7,39 (m, 1H), 6,97-7,03 (m, 1H), 6,88 (t, J = 7,6 Hz, 1H).

Ejemplo 145a: 2–sulfamoilamino–3–hidroxibenzonitrilo

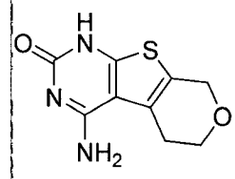
Preparado como en el Ejemplo 129a a partir de 2–amino–3–hidroxibenzonitrilo (Ejemplo 145b) en una cantidad de 83,5 mg (39%), como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 10,23 (s amplio, 1H), 8,66 (s amplio, 1H), 7,14-7,27 (m, 3H), 6,71 (s amplio, 2H).

Ejemplo 145b: 2–amino–3–hidroxibenzonitrilo

A una solución de 2–amino–3–metoxibenzonitrilo (Ejemplo 127b) (0,98 g, 6,59 mmol) en CH_2Cl_2 (25,0 mL), se le adicionó gota a gota a -78ºC una solución de BBr_3 en CH_2Cl_2 (1,0 M, 19,8 mL, 19,77 mmol) bajo una atmósfera de nitrógeno. La mezcla obtenida se agitó a -78ºC durante 30 min, y luego a temperatura ambiente durante la noche. La reacción se inactivó con agua, se basificó con $NaHCO_3$ acuoso saturado (pH~8) y se extrajo con CH_2Cl_2. El extracto combinado se secó con $MgSO_4$, se filtró y se evaporó. El compuesto del título se obtuvo en una cantidad de 0,80 g (91%) como un sólido anaranjado y se utilizó en la etapa

siguiente sin purificación adicional. ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,86 (s amplio, 1H), 6,82-6,87 (m, 2H), 6,46 (t, J = 8,0 Hz, 1H), 5,34 (s amplio, 2H).

Ejemplo 146: 4–amino–5,6–(5',7'–dihidro–4'H–[2',3'–c]pirano)tieno[2,3–d]–pirimidin–2(1H)–ona



568

Una solución de N–(3–ciano–5,7–dihidro–4H–tieno[2,3–c]piran–2–ilcarbamoil) benzamida (Ejemplo 146a) (500 mg, 1,53 mmol) y NaOH (2 N, 2,1 mL) en EtOH (40 mL) se agitó a 100ºC bajo nitrógeno durante la noche. Luego de enfriarse hasta temperatura ambiente, la solución de reacción clara se filtró, y el filtrado se neutralizó cuidadosamente con 10% AcOH con agitación enérgica a 0ºC. El filtrado resultante se recogió mediante filtración, se lavó con agua y luego 20% EtOH en agua para proporcionar el producto final (280 mg, 82%) como un sólido blancuzco, el cual se secó bajo vacío durante la noche. P.f.: > 260ºC. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,83 (t, J = 5,6 Hz, 2H), 3,86 (t, J = 5,6 Hz, 2H), 4,58 (s, 2H), 7,23 (brs, 2H), 11,56 (brs, 1H). MS 224 (MH^+).

Ejemplo 146a: N–(3–ciano–5,7–dihidro–4H–tieno[2,3–c]piran–2–ilcarbamoil) benzamida

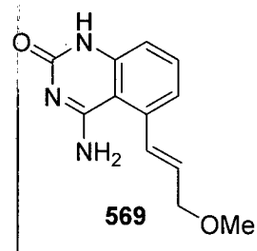
A una solución de 2–amino–5,7–dihidro–4H–tieno[2,3–c]piran–3–carbonitrilo (Ejemplo 146b) (400 mg, 2,22 mmol) en 1,4-dioxano (30 mL) se le adicionó isocianato de benzoilo (327 mg, 2,22 mmol). Luego la mezcla de reacción se agitó a temperatura ambiente bajo nitrógeno durante la noche. El precipitado se recogió mediante filtración, se lavó con 1,4-dioxano, y se secó al aire para proporcionar el compuesto del título (577 mg, 80%) como un sólido amarillo claro. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,62 (t, J = 5,2 Hz, 2H), 3,87 (t, J =

5,2 Hz, 2H), 4,62 (s, 2H), 7,56-7,53 (m, 2H), 7,67-7,65 (m, 1H), 8,04-8,01 (m, 2H), 11,60 (brs, 1H), 12,13 (brs, 1H).

Ejemplo 146b: 2–amino–5,7–dihidro–4H–tieno[2,3–c]piran–3–carbonitrilo

A una mezcla de dihidro–2H–piran–4(3H)–ona (820 mg, 8,19 mmol), malononitrilo (541 mg, 8,19 mmol) y azufre (263 mg, 8,19 mmol) en etanol (50 mL) se le adicionó trietilamina (1,14 mL, 8,19 mmol). Luego la mezcla de reacción se reflujó bajo nitrógeno durante la noche. Luego de enfriarse hasta temperatura ambiente, el precipitado se recogió mediante filtración, se lavó con etanol, y se secó al aire para proporcionar el compuesto del título (1,15 g, 78%) como un sólido marrón claro. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,43-2,40 (m, 2H), 3,80 (t, J = 5,6 Hz, 2H), 4,40 (t, J = 2,0 Hz, 2H), 7,09 (s, 2H). MS 181 (MH^+).

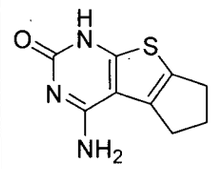
Ejemplo 147: (E)–4–amino–5–(3–metoxiprop–1–enil)quinazolin–2(1H)–ona



569

Preparada como en el Ejemplo 146 a partir de (*E*)–2–amino–6–(3–metoxiprop–1–enil)benzonitrilo (Ejemplo 97a) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,28 (s, 3H), 4,02 (dd, J = 6,0, 1,2 Hz, 2H), 6,13 (dt, J = 16,0, 3,8 Hz, 1H), 7,06 (d, J = 8,0 Hz, 1H), 7,23 (d, J = 8,0 Hz, 1H), 7,52 (t, J = 8,0 Hz, 1H), 7,80 (d, J = 16,0 Hz, 1H), 11,07 (s, 1H), 11,13 (s, 1H). ^{13}C RMN (DMSO-d_6) δ 58,0, 72,9, 111,4, 115,5, 121,9, 129,9, 131,2, 134,7, 140,2, 142,7, 150,6, 164,1.

Ejemplo 148: 4–amino–5,6–(2',3'–dihidro–1'H–ciclopenta[b])–tieno[2,3–d] pirimidin–2(1H)–ona–2,2–dióxido



570

Preparado como en el Ejemplo 4 a partir de N–(3–ciano–5,6–dihidro–4H–ciclopenta[b]tiofen–2–ilcarbamoil)benzamida (Ejemplo 148a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,33 (m, 2H), 2,76 (t, 2H), 2,87 (t, 2H), 7,51 (br-s, 2H), 11,56 (br-s, 1H). MS 208 (MH^+).

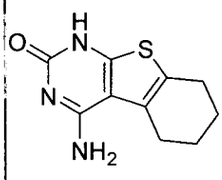
Ejemplo 148a: N–(3–ciano–5,6–dihidro–4H–ciclopenta[b]tiofen–2–il-carbamoil)benzamida

Preparada como en el Ejemplo 4a a partir de 2–amino–5,6–dihidro–4H–ciclopenta[b]tiofen–3–carbonitrilo (Ejemplo 148b). ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,34 (m, 2H), 2,72 (t, 2H), 2,82 (t, 2H), 7,52 (t, 2H), 7,65 (t, 1H), 8,01 (d, 2H), 11,56 (s, 1H), 12,06 (s, 1H)

Ejemplo 148b: 2–amino–5,6–dihidro–4H–ciclopenta[b]tiofen–3–carbonitrilo

Preparado como en el Ejemplo 5b a partir de ciclopentanona. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,23 (m, 2H), 2,53 (m, 2H), 2,63 (m, 2H), 7,00 (s, 2H)^{1}H RMN (400 MHz, DMSO-d_6) δ 2,23 (m, 2H), 2,53 (t, 2H), 2,62 (t, 2H), 7,00 (s, 2H).

Ejemplo 149: 4–amino–5,6–(1',2',3',4'–tetrahidrobenzo[b])–tieno[2,3–d]pirimidin–2(1H)–ona –2,2–dióxido



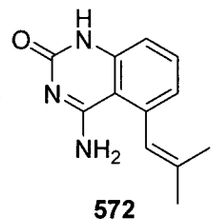
571

Preparado como en el Ejemplo 4 a partir de N–(3–ciano–4,5,6,7–tetrahidrobenzo[b]tiofen–2–ilcarbamoil)benzamida (Ejemplo 149a). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,73 (m, 4H), 2,57 (t, 2H), 2,72 (t, 2H). MS 222 (MH^+).

Ejemplo 149a: N–(3–ciano–4,5,6,7–tetrahidrobenzo[b]tiofen–2–ilcarbamoil)benzamida

Preparada como en el Ejemplo 4a a partir de 2–amino–4,5,6,7–tetrahidrobenzo[b]tiofen–3–carbonitrilo (Ejemplo 5b). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,75 (m, 4H), 2,51 (t, 2H), 2,60 (t, 2H), 7,54 (t, 2H), 7,66 (t, 1H), 8,02 (d, 2H), 11,57 (s, 1H), 12,06 (s, 1H).

Ejemplo 150: 4–amino–5–(2–metilprop–1–enil)quinazolin–2(1*H*)–ona



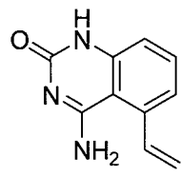
572

Una suspensión de *N*–(2–ciano–3–(2–metilprop–1–enil) fenil carbamoil) benzamida (Ejemplo 150a) (0,133 g, 0,416 mmol) en EtOH (3 mL) se trató con una solución de NaOH (2 M, 0,416 mL, 0,832 mmol) a temperatura ambiente. La mezcla obtenida se calentó a 90ºC durante 30 min, se enfrió hasta temperatura ambiente y se neutralizó con 10% AcOH. El producto precipitado se recogió mediante filtración para proporcionar 69,0 mg (77%) de 4–amino–5–(2–metilprop–1–enil)quinazolin–2(1*H*)–ona como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,60 (d, J = 1,2 Hz, 3H), 1,93 (d, J = 1,2 Hz, 3H), 6,58 (s, 1H), 6,67 (s amplio, 1H), 6,73 (m, 1H), 7,05 (m, 1H), 7,48 (m, 1H), 7,93 (s amplio, 1H), 10,72 (s amplio, 1H). MS 216 (MH^+).

Ejemplo 150a: *N*–(2–ciano–3–(2–metilprop–1–enil)fenilcarbamoil)benzamida

Se adicionó isocianato de benzoilo (88,1 mg, 0,60 mmol) a una solución de 2–amino–6–(2–metilprop–1–enil)benzonitrilo (Ejemplo 129b) (75,2 mg, 0,44 mmol) en 1,4-dioxano anhidro bajo nitrógeno, y se agitó a temperatura ambiente durante 12 h. La mezcla se concentró bajo vacío, y se purificó mediante cromatografía sobre gel de sílice eluyendo con gradiente solvente 0% a 15% MeOH en CH_2Cl_2, para proporcionar 125,0 mg (86%) de *N*–(2–ciano–3–(2–metilprop–1–enil)fenilcarbamoil)benzamida como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,80 (d, J = 1,2 Hz, 3H), 1,95 (d, J = 1,2 Hz, 3H), 6,40 (s, 1H), 7,19 (m, 1H), 7,55 (m, 2H), 7,67 (m, 2H), 8,03 (m, 2H), 8,13 (m, 1H), 11,33 (s, 1H), 11,48 (s, 1H).

Ejemplo 151: 4–amino–5–vinilquinazolin–2(1*H*)–ona



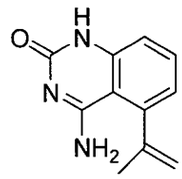
573

Preparada como en el Ejemplo 150 a partir de N–(2–ciano–3–vinilfenilcarbamoil)benzamida (Ejemplo 151a) en una cantidad de 20,0 mg (33%), como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 5,53 (m, 1H), 5,64 (m, 1H), 6,50 (s amplio, 1H), 6,98 (m, 1H), 7,08 (m, 1H), 7,37 (m, 1H), 7,50 (m, 1H), 8,0 (s amplio, 1H), 10,75 (s amplio, 1H). MS 188 (MH^+).

Ejemplo 151a: N–(2–ciano–3–vinilfenilcarbamoil)benzamida

Preparada como en el Ejemplo 150a a partir de 2–amino–6–vinilbenzonitrilo (Ejemplo 133b) en una cantidad de 99,3 mg (83%), como un sólido blanco.

Ejemplo 152: 4–amino–5–(prop–1–en–2–il)quinazolin–2(1*H*)–ona



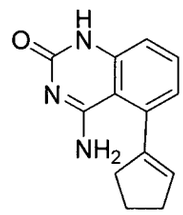
574

Preparada como en el Ejemplo 150 a partir de N–(2–ciano–3–(prop–1–en–2–il)fenilcarbamoil)benzamida (Ejemplo 152a) en una cantidad de 30,0 mg (47%), como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,07 (s, 3H), 5,14 (m, 1H), 5,43 (m, 1H), 6,67 (s amplio, 1H), 6,80 (m, 1H), 7,11 (m, 1H), 7,50 (m, 1H), 7,99 (s amplio, 1H), 10,81 (s amplio, 1H). MS 202 (MH^+).

Ejemplo 152a: N–(2–ciano–3–(prop–1–en–2–il)fenilcarbamoil)benzamida

Preparada como en el Ejemplo 150a a partir de 2–amino–6–(prop–1–en–2–il)benzonitrilo (Ejemplo 138b) en una cantidad de 96,0 mg (72%), como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,15 (s, 3H), 5,23 (m, 1H), 5,43 (m, 1H), 7,25 (m, 1H), 7,55 (m, 2H), 7,68 (m, 2H), 8,04 (m, 2H), 8,19 (m, 1H), 11,35 (s, 1H), 11,54 (s, 1H).

Ejemplo 153: 4–amino–5–ciclopentenilquinazolin–2(1*H*)–ona



575

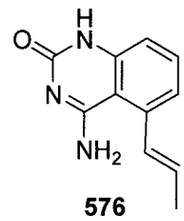
Preparada como en el Ejemplo 150 a partir de N–(ciano–3–ciclopentenilfenilcarbamoil)benzamida (Ejemplo 153a) en una cantidad de 60,0 mg (75%), como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,01 (m, 2H),

2,55 (m, 2H), 2,61 (m, 2H), 5,91 (s, 1H), 6,49 (s amplio, 1H), 6,81 (m, 1H), 7,08 (m, 1H), 7,48 (m, 1H), 7,88 (s amplio, 1H), 10,76 (s, 1H). MS 228 (MH^+).

Ejemplo 153a: N–(ciano–3–ciclopentenilfenilcarbamoil)benzamida

Preparada como en el Ejemplo 150a a partir de 2–amino–6–(ciclopenten–1–il)benzonitrilo (Ejemplo 135b) en una cantidad de 117,0 mg (93%), como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,99 (m, 2H), 2,57 (m, 2H), 2,78 (m, 2H), 6,45 (m, 1H), 7,26 (m, 1H), 7,57 (m, 2H), 7,68 (m, 2H), 8,06 (m, 2H), 8,15 (m, 1H), 11,34 (br s, 1H), 11,51 (s, 1H).

Ejemplo 154: (*E*)–4–amino–5–(prop–1–enil)quinazolin–2(1*H*)–ona



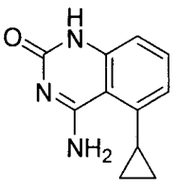
576

Preparada como en el Ejemplo 150 a partir de (*E*)–N–(2–ciano–3–(prop–1–enil)fenilcarbamoil)benzamida (Ejemplo 154a) en una cantidad de 13,0 mg (8%), como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,91 (m, 3H), 6,09 (m, 1H), 6,40 (s amplio, 1H), 6,91 (m, 2H), 7,03 (m, 1H), 7,45 (m, 1H), 7,9 (s amplio, 1H), 10,70 (s, 1H). MS 202 (MH^+).

Ejemplo 154a: (*E*)–N–(2–ciano–3–(prop–1–enil)fenilcarbamoil)benzamida

Preparada como en el Ejemplo 150a a partir de (*E*)–2–amino–6–(prop–1–enil)benzonitrilo (Ejemplo 130b) en una cantidad de 0,22 g (88%), como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 11,50 (s amplio, 1H), 11,34 (s amplio, 1H), 8,13 (d, J = 8,4 Hz, 1H), 8,02-8,08 (m, 2H), 7,64-7,70 (m, 2H), 7,52-7,59 (m, 2H), 7,20 (d, J = 8,0 Hz, 1H), 5,50-5,18 (m, 2H), 3,55-3,59 (m, 3H).

Ejemplo 155: 4–amino–5–ciclopropilquinazolin–2(1H)–ona

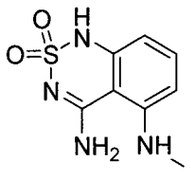


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Una solución de 2–amino–6–ciclopropilbenzonitrilo (Ejemplo 92a) (1,0 eq., 1,0 mmol, 158 mg) e isocianato de benzoilo (90% puro, 1,0 eq., 1,0 mmol, 1,171 g/mL, 140 μL) en dioxano (15 mL) se agitó a temperatura ambiente. Luego de 2 horas, los volátiles se removieron sobre un evaporador rotatorio. La N–benzoil urea cruda resultante se suspendió en EtOH (10 mL, 200 proof) y se adicionó NaOH (2,5 eq., 2,5 mmol, 1 N, 2,50 mL). La reacción se calentó hasta 75°C con agitación durante 7 horas. El solvente se evaporó y el residuo se diluyó con agua (10 mL). La mezcla de reacción se acidificó con 10% solución de ácido cítrico/agua y se tituló cuidadosmante hasta un pH 7-8 con solución saturada de $NaHCO_3$. El producto precipitado se recogió mediante filtración al vacío, lavando con agua. El residuo se suspendió en EtOH (3 mL, 200 proof) y se adicionó HCl (12,1 N, 3 mL). La mezcla se calentó hasta 90°C durante 1 hora. La mezcla de reacción se enfrió hasta temperatura ambiente y se diluyó con agua (20 mL), se filtró (frita PTFE de 0,45 μm), y el filtrado se concentró sobre un evaporador rotatorio. El residuo se purificó además mediante TLC preparativa (1000 μm, MeOH/DCM 10/90) y trituración con metanol a temperatura ambiente. La reacción proporciona 25 mg (12,4%) del compuesto del título como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO–d_6) δ 0,802 (m, 2H), 1,086 (m, 2H), 2,345 (m, 1H), 6,922 (d, J = 8 Hz, 1H), 7,000 (d, J = 8 Hz, 1H), 7,253 (br. s, 1H), 7,397 (t, J = 8 Hz, 1H), 8,022 (br. s, 1H), 10,644 (s, 1H). MS 202 (MH^+).

Ejemplo 156: N^5–metil–1H–benzo[c][1,2,6]tiadiazin–4,5–diamin–2,2–dióxido

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Preparado como en el Ejemplo 90 a partir de 2–amino–6–(metilamino)benzonitril sulfamida (Ejemplo 156a) para proporcionar N^5–metil–1H–benzo[c][1,2,6]tiadiazin–4,5–diamin–2,2–dióxido (27,7 mg, 45%). ^{1}H RMN (400MHz, DMSO-d_6) δ 2,67 (d, J = 2 Hz, 3H), 5,91 (bs, NH), 6,21-6,17 (m, 2H), 7,17 (t, J = 8 Hz, 1H), 7,51 (bs, 2H), 10,6 (bs, NH). MS 227 (MH^+).

Ejemplo 156a: 2–amino–6–(metilamino)benzonitril sulfamida

Preparada como en el Ejemplo 90a a partir de 2–amino–6–(metilamino)benzonitrilo (Ejemplo 156b) para proporcionar 2–amino–6–(metilamino)benzonitril sulfamida (65 mg, 30%). ^{1}H RMN (400MHz, $CDCl_3$) δ 2,88 (d, J = 5,2 Hz, 3H), 4,23 (bs, NH), 4,66 (bs, NH), 4,87 (bs, 2H), 6,44 (d, J = 8 Hz, 1H), 6,90 (d, J = 8 Hz, 1H), 7,39 (t, J = 8 Hz, 1H). MS 227 (MH^+).

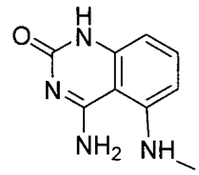
Ejemplo 156b: 2–amino–6–(metilamino)benzonitrilo

Preparado como en el Ejemplo 90b a partir de 2–metilamino–6–nitrobenzonitrilo (ejemplo 156b) para proporcionar 2–amino–6–(metilamino)benzonitrilo (0,30 g, 85%) como un aceite marrón el cual se utilizó en la etapa siguiente sin purificación adicional alguna. ^{1}H RMN (400MHz, $CDCl_3$) δ 2,87 (d, J = 5,2 Hz, 3H), 4,25 (bs, 2H), 4,47 (bs, NH), 5,96 (d, J = 8,8 Hz, 1H), 6,02 (d, J = 8,4 Hz, 1H), 7,13 (t, J = 8 Hz, 1H). Ms 148 (MH^+).

Ejemplo 156c: 2–metilamino–6–nitrobenzonitrilo

Preparado como en el Ejemplo 90c a partir de 2,6–dinitrobenzonitrilo y metilamina para proporcionar 2–metilamino–6–nitrobenzonitrilo (0,42 g, 79%). ^{1}H RMN (400MHz, DMSO-d_6) δ 2,85 (d, J = 5,2 Hz, 3H), 6,75 (d, J = 4,8 Hz, NH), 7,16 (d, J = 8,4 Hz, 1H), 7,45 (d, J = 7,6 Hz, 1H), 7,64 (t, J = 8,4 Hz, 1H).

Ejemplo 157: 4–amino–5–(metilamino)quinazolin–2(1H)–ona



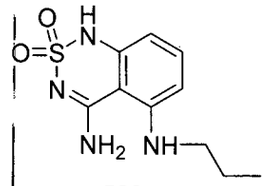
579

Una solución de N–(2–ciano–3–(metilamino)fenilcarbamoil)benzamida (Ejemplo 157a) (0,05 g, 0,17 mmol) y NaOH (2 N, 0,17 mL) en EtOH (6 mL) se agitó a 90ºC bajo nitrógeno durante media hora. La mezcla de reacción se enfrió hasta temperatura ambiente, y se concentró bajo vacío. Se adicionó H_2O (1 mL) y la mezcla de reacción se neutralizó hasta un pH ~ 4 con 10% AcOH. La precipitación resultante se filtró y se secó bajo vacío. El producto crudo se purificó mediante cromatografía preparativa de capa delgada utilizando una solución de DCM/MeOH (9:1) como eluyente, para proporcionar 4–amino–5–(metilamino)quinazolin–2(1H)–ona (18,2 mg, 56%). ^{1}H RMN (400MHz, DMSO-d_6) δ 2,76 (s, 3H), 6,10 (d, J = 7,6 Hz, 1H), 6,12 (d, J = 8 Hz, 1H), 7,13 (t, J = 8 Hz, 1H), 7,25 (bs, NH), 9,66 (bs, NH,) 10,13 (bs, 2H). MS 191 (MH^+).

Ejemplo 157a: N–(2–ciano–3–(metilamino)fenilcarbamoil)benzamida

A una solución de 2–amino–6–(metilamino)benzonitrilo (ejemplo 156b) (0,14 g, 0,97 mmol) en 1,4-dioxano (3 mL) se le adicionó isocianato de benzoilo (0,17 g, 1,17 mmol). La mezcla de reacción se agitó a temperatura ambiente bajo nitrógeno durante la noche. El precipitado obtenido se filtró y se secó bajo vacío para proporcionar N–(2–ciano–3–(metilamino)fenilcarbamoil)benzamida (57 mg, 20%). ^{1}H RMN (400MHz, DMSO-d_6) δ 2,75 (d, J = 4,4 Hz, 3H), 6,26 (d, J = 4,8 Hz, NH), 6,43 (d, J = 9,6 Hz, 1H), 7,40-7,43 (m, 2H), 7,51-7,55 (m, 2H), 7,63-7,65 (m, 1H), 8,01 (d, J = 8,4 Hz, 2H), 11,23 (s, NH), 11,30 (s, NH). MS 295 (MH^+).

Ejemplo 158: N^5–propil–1H–benzo[c][1,2,6]tiadiazin–4,5–diamin–2,2–dióxido



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Preparado como en el Ejemplo 90 a partir de 2–amino–6–(propilamino)benzonitril sulfamida (Ejemplo 158a) para proporcionar N^5–propil–1H–benzo[c][1,2,6]tiadiazin–4,5–diamin–2,2–dióxido (183 mg, 74%). ^{1}H RMN (400MHz, DMSO-d_6) δ 0,91 (t, J = 7,2 Hz, 3H), 1,57-1,63 (m, 2H), 2,48 (q, J = 7,2, 2H), 5,85-5,88 (m, NH), 6,27 (d, J = 8 Hz, 1H), 6,37 (d, J = 8,4 Hz, 1H), 7,24 (t, J = 8 Hz, 1H), 7,87 (bs, 2H), 10,65 (bs, NH). MS 255 (MH^+).

Ejemplo 158a: 2–amino–6–(propilamino)benzonitril sulfamida

Preparada como en el Ejemplo 90a a partir de 2–amino–6–(propilamino)benzonitrilo (Ejemplo 158b) para proporcionar 2–amino–6–(propilamino)benzonitril sulfamida (254 mg, 43%). ^{1}H RMN (400MHz, $CDCl_3$) δ 0,87 (t, J = 7,2 Hz, 3H), 1,48-1,57 (m, 2H), 3,10 (q, J = 6, J = 5,6, 2H), 5,86-5,89 (m, NH), 6,49 (d, J = 8,4 Hz, 1H), 6,69 (d, J = 7,6 Hz, 1H), 7,13 (s, 2H), 7,29 (t, J = 8 Hz, 1H), 9,06 (s, NH). MS 255 (MH^+).

Ejemplo 158b: 2–amino–6–(propilamino)benzonitrilo

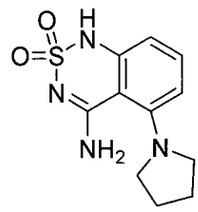
Preparado como en el Ejemplo 90b a partir de 2–propilamino–6–nitrobenzonitrilo (Ejemplo 158c) para proporcionar 2–amino–6–(propilamino)benzonitrilo (0,41 g, 91%) como un aceite marrón el cual se utilizó en la etapa siguiente sin purificación adicional alguna. MS 175 (MH^+).

Ejemplo 158c: 2–propilamino–6–nitrobenzonitrilo

Preparado como en el Ejemplo 90c a partir de 2,6–dinitrobenzonitrilo y propilamin 2–propilamino–6–nitrobenzonitrilo (0,53 g, 86%). ^{1}H RMN (400MHz, DMSO-d_6) δ 0,88 (t, J = 7,2 Hz, 3H), 1,51-1,57 (m, 2H), 3,22 (q, J = 5,6, J = 6,4,

2H), 6,60-6,63 (m, NH), 7,22 (d, J = 8,8 Hz, 1H), 7,40 (d, J = 7,6 Hz, 1H), 7,58 (t, J = 8,4 Hz, 1H).

Ejemplo 159: 5–(pirrolidin–1–il)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



581

Preparado como en el Ejemplo 90 a partir de 2–amino–6–(pirrolidin–1–il)benzonitril sulfamida (Ejemplo 159a) para proporcionar 5–(pirrolidin–1–il)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido (14,2 mg, 11%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,88-1,86 (m, 4H), 3,16-3,10 (m, br, 4H), 6,45 (d, J = 7,6 Hz, 1H), 6,64 (d, J = 8,4 Hz, 1H), 7,30 (t, J = 8,0 Hz, 1H), 7,83 (s, 1H, NH2), 8,14 (s, 1H, NH2), 10,79 (s, 1NH). MS 267 (MH^+).

Ejemplo 159a: 2–amino–6–(pirrolidin–1–il)benzonitril sulfamida

Preparada como en el Ejemplo 90a a partir de 2–amino–6–(pirrolidin–1–il)benzonitrilo (Ejemplo 159b) para proporcionar 2–amino–6–(pirrolidin–1–il)benzonitril sulfamida (0,34 g, 100%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,94-1,91 (m, 4H), 3,48-3,45 (m, 4H), 6,55 (d, J = 7,6 Hz, 1H), 6,81 (d, J = 8,0 Hz, 1H), 7,15 (s, 2H, NH_2), 7,32 (t, J = 8,0 Hz, 1H), 8,9 (s, 1NH). MS 267 (MH^+).

Ejemplo 159b: 2–amino–6–(pirrolidin–1–il)benzonitrilo

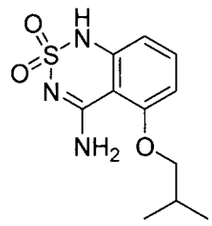
Preparado como en el Ejemplo 90b a partir de 2–nitro–6–(pirrolidin–1–il)benzonitrilo (ejemplo 159c) para proporcionar 2–amino–6–(pirrolidin–1–il)benzonitrilo (0,48 g, 85%) como un aceite marrón el cual se utilizó en la etapa siguiente sin purificación adicional alguna. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,91-

1,88 (m, 4H), 3,43-3,40 (m, 4H), 5,61 (s, 2H, NH_2), 5,86 (d, *J* = 8,8 Hz, 1H), 6,06 (d, *J* = 8,0 Hz, 1H), 6,99 (t, *J* = 8,0 Hz, 1H). MS 188 (MH^+).

Ejemplo 159c: 2–nitro–6–(pirrolidin–1–il)benzonitrilo

Preparado como en el Ejemplo 90c a partir de 2,6–dinitrobenzonitrilo y pirrolidina para proporcionar 2–nitro–6–(pirrolidin–1–il)benzonitrilo el cual se utilizó en la etapa siguiente sin purificación adicional alguna. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,97-1,94 (m, 4H), 3,60-3,57 (m, 4H), 7,22 (d, *J* = 8,0 Hz, 1H), 7,41 (d, *J* = 6,8 Hz, 1H), 7,58 (t, *J* = 8,0 Hz, 1H). MS 218 (MH^+).

Ejemplo 160: 4–amino–5–isobutoxi–*1H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



582

Preparado en la misma manera que el Ejemplo 111 a partir de 2–sulfamoilamino–6–isobutoxibenzonitrilo (Ejemplo 160a) para proporcionar 4–amino–5–isobutoxi–*1H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido (65 mg, 50%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,01 (d, *J* = 6,7 Hz, 6H), 2,06 (sept, *J* = 6,6 Hz, 1H), 3,90 (d, *J* = 6,2 Hz, 2H), 6,96 (d, *J* = 8,3 Hz, 1H), 7,15 (d, *J* = 8,0 Hz, 1H), 7,27 (br s, 2H), 7,56 (t, *J* = 8,7 Hz, 1H), 9,46 (s, 1H). MS 270 (MH^+).

Ejemplo 160a: 2–sulfamoilamino–6–isobutoxibenzonitrilo

Preparado en una manera similar al Ejemplo 111a a partir de 2–amino–6–isobutoxibenzonitrilo (Ejemplo 160b) para proporcionar 2–sulfamoilamino–6–isobutoxibenzonitrilo (130 mg, 50%). MS 191 (MH^+–NH_2SO_2).

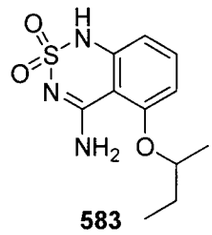
Ejemplo 160b: 2–amino–6–isobutoxibenzonitrilo

Preparado en una manera similar al Ejemplo 111b a partir de 2–isobutoxi–6–nitrobenzonitrilo (Ejemplo 160c) para proporcionar 2–amino–6–isobutoxibenzonitrilo. MS 191 (MH^+).

Ejemplo 160c: 2–isobutoxi–6–nitrobenzonitrilo

Preparado en una manera similar al Ejemplo 160c a partir de 2,6–dinitrobenzonitrilo e isobutanol para proporcionar 2–isobutoxi–6–nitrobenzonitrilo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,05 (d, J = 6,4 Hz, 6H), 2,11 (sept, J = 6,6 Hz, 1H), 4,07 (d, J = 6,5 Hz, 2H), 7,75 (dd, J = 8,0, 1,9 Hz, 1H), 7,91 (t, J = 8,2 Hz, 1H), 7,94 (dd, J = 8,2, 1,9 Hz, 1H).

Ejemplo 161: 4–amino–5–*sec*–butoxi–*1H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



583

Preparado en una manera similar al Ejemplo 111 a partir de 2–sulfamoilamino–6–*sec*–butoxibenzonitrilo (Ejemplo 161a) para proporcionar 4–amino–5–*sec*–butoxi–*1H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido (57 mg, 44%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,95 (t, J = 7,9 Hz, 3H), 1,28 (d, J = 5,9 Hz, 3H), 1,67 (m, J = 7,4 Hz, 2H), 4,57 (sext, J = 5,9 Hz, 1H), 6,98 (d, J = 8,7 Hz, 1H), 7,13 (d, J = 8,3 Hz, 1H), 7,27 (br s, 2H), 7,55 (t, J = 8,3 Hz, 1H), 9,41 (s, 1H). MS 270 (MH^+).

Ejemplo 161a: 2–sulfamoilamino–6–*sec*–butoxibenzonitrilo

Preparado en una manera similar al ejemplo 1a a partir de 2–amino–6–*sec*–butoxibenzonitrilo (Ejemplo 20b) para proporcionar 2–sulfamoilamino–6–*sec*–butoxibenzonitrilo. MS 191 (MH^+–NH_2SO_2).

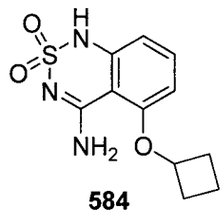
Ejemplo 161b: 2–amino–6–*sec*–butoxibenzonitrilo

Preparado en una manera similar al Ejemplo 111b a partir de 2–*sec*–butoxi–6–nitrobenzonitrilo (ejemplo 161c) para proporcionar 2–amino–6–*sec*–butoxibenzonitrilo. MS 191 (MH^+).

Ejemplo 161c: 2–*sec*–butoxi–6–nitrobenzonitrilo

Preparado en una manera similar al Ejemplo 161c a partir de 2,6–dinitrobenzonitrilo y *sec*–butanol para proporcionar 2–*sec*–butoxi–6–nitrobenzonitrilo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,98 (t, J = 7,5 Hz, 3H), 1,33 (d, J = 5,9 Hz, 3H), 1,73 (m, 2H), 4,76 (sext, J = 5,9 Hz, 1H), 7,78 (dd, J = 6,8, 2,8 Hz, 1H), 7,90 (m, 2H).

Ejemplo 162: 4–amino–ciclobutoxi–*1H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



584

Preparado en una manera similar al Ejemplo 111 a partir de 2–sulfamoilamino–6–ciclobutoxibenzonitrilo (Ejemplo 162a) para proporcionar 4–amino–ciclobutoxi–*1H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido (19,4 mg, 10%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,65 (m, 1H), 1,79 (m, 1H), 2,19 (m, 2H), 2,43 (m, 2H), 4,82 (m, 1H), 6,52 (d, J = 7,9 Hz, 1H), 6,58 (d, J = 8,2 Hz, 1H), 7,40 (t, J = 8,1 Hz, 1H), 7,78 (br s, 1H), 8,31 (br s, 1H), 10,92 (br s). MS 268 (MH^+).

Ejemplo 162a: 2–sulfamoilamino–6–ciclobutoxibenzonitrilo

Preparado en una manera similar al Ejemplo 111a a partir de 2–amino–6–ciclobutoxibenzonitrilo (Ejemplo 162b) para proporcionar 2–sulfamoilamino–6–ciclobutoxibenzonitrilo (231 mg, 100%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,67 (m, 1H), 1,82 (m, 1H), 2,08 (m, 2H), 2,47 (m, 2H), 4,83 (pent, J = 7,2 Hz, 1H), 6,79 (d, J = 8,2 Hz, 1H), 7,15 (d, J = 8,2 Hz, 1H), 7,28 (br s, 1H), 7,54 (t, J = 8,2 Hz, 1H), 9,46 (br s, 1H). MS 268 (MH^+).

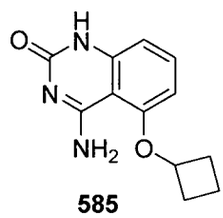
Ejemplo 162b: 2–amino–6–ciclobutoxibenzonitrilo

Preparado en una manera similar al Ejemplo 111b a partir de 2–ciclobutoxi–6–nitrobenzonitrilo (Ejemplo 162c) para proporcionar 2–amino–6–ciclobutoxibenzonitrilo (174 mg, 70%) como agujas blancas. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,65 (m, 1H), 1,81 (m, 1H), 2,06 (m, 2H), 2,44 (m, 2H), 4,72 (pent, J = 7,3 Hz, 1H), 6,00 (br s, 2H), 6,07 (d, J = 7,8 Hz, 1H), 6,34 (dd, J = 8,2, 0,8 Hz, 1H), 7,17 (t, J = 8,1 Hz, 1H). MS 189 (MH^+).

Ejemplo 162c: 2–ciclobutoxi–6–nitrobenzonitrilo

Preparado en una manera similar al Ejemplo 111c a partir de 2,6 dinitrobenzonitrilo y ciclobutanol para proporcionar 2–amino–6–ciclobutoxibenzonitrilo (298 mg, 34%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,69 (m, 1H), 1,85 (m, 1H), 2,14 (m, 2H), 2,52 (m, 2H), 4,98 (pent, J = 7,3 Hz, 1H), 7,55 (dd, J = 8,2, 1,1 Hz, 1H), 7,87 (t, J = 8,2 Hz, 1H), 7,92 (dd, J = 8,4, 1,3 Hz, 1H).

Ejemplo 163: 4–amino–5–ciclobutoxiquinazolin–2(*1H*)–ona



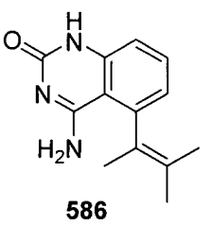
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Preparada en una manera similar al Ejemplo 111 a partir de *N*–(2–ciano–3–ciclobutoxifenilcarbamoil)benzamida (Ejemplo 163a) para proporcionar 4–amino–5–ciclobutoxiquinazolin–2(*1H*)–ona (19,4 mg, 76%) como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,68 (m, 1H), 1,84 (m, 1H), 2,20 (m, 2H), 2,49 (m, 2H), 4,87 (pent, J = 7,2 Hz, 1H), 7,52 (d, J = 8,2 Hz, 1H), 6,71 (d, J = 8,2 Hz, 1H), 7,92 (t, J = 8,2 Hz, 1H), 7,48 (br s, 1H), 7,88 (br s, 1H), 10,65 (br s, 1H). MS 232 (MH^+).

Ejemplo 163a: *N*–(2–ciano–3–ciclobutoxifenilcarbamoil)benzamida

A una solución de 2–amino–6–ciclobutoxibenzonitrilo (Ejemplo 162b) (30 mg, 0,16 mmol) en 1,4-dioxano (2 mL) se le adicionó isocianato de benzoilo (23 mg, 0,16 mmol). La reacción se agitó a ta bajo N_2 durante 19 horas. Una vez completa, la reacción se diluyó con EtOAc, se lavó con $NaHCO_3$ saturado (2x), agua, salmuera, se secó sobre $MgSO_4$, se filtró y se concentró para proporcionar *N*–(2–ciano–3–ciclobutoxifenilcarbamoil)benzamida (38 mg, 71%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,64 (m, 1H), 1,81 (m, 2H), 2,05 (m, 1H), 2,42 (m, 2H), 4,71 (pent, J = 7,1 Hz, 1H), 6,05 (d, J = 8,2 Hz, 1H), 6,33 (d, J = 8,3 Hz, 1H), 7,15 (t, J = 8,5 Hz, 1H), 7,45 (m, 1H), 7,56 (m, 2H), 7,87 (m, 1H), 8,05 (m, 1H), 11,35 (s, 1H).

Ejemplo 164: 4–amino–5–(3–metilbut–2–en–2–il)quinazolin–2(1H)–ona



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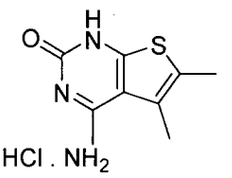
Preparada en una manera similar al Ejemplo 146 a partir de 1N–(2–ciano–3–(3–metilbut–2–en–2–il)fenilcarbamoil)benzamida (Ejemplo 164a) como un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,44 (s, 3H), 1,83 (s, 3H), 1,89 (s, 3H),

6,65 (dd, J = 7,2, 1,0 Hz, 1H), 6,69 (bs, 2H), 7,04 (dd, J = 7,2, 1,0 Hz, 1H), 7,48 (t, J = 7,2 Hz, 1H), 10,74 (s, 1H). MS 230 (MH^+).

Ejemplo 164a: N–(2–ciano–3–(3–metilbut–2–en–2–il) fenil carbamoil) benzamida

Preparada en una manera similar al Ejemplo 146a a partir de 2–amino–6–(3–metilbut–2–en–2–il)benzonitrilo (Ejemplo 98a) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,47 (s, 3H), 1,81 (s, 3H), 1,92 (s, 3H), 7,01-7,04 (m, 1H), 7,51-7,56 (m, 1H), 7,62-7,69 (m. 3H), 8,01-8,04 (m, 2H), 8,12-8,15 (m, 1H), 11,32 (s, 1H), 11,49 (s, 1H). MS 334 (MH^+).

Ejemplo 165: Síntesis mejorada de clorhidrato de 4–amino–5,6–dimetiltieno[2,3–d] pirimidin–2(1H)–ona



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Este ejemplo describe un método mejorado para preparar la sal HCl del compuesto 1. Específicamente, el método mejorado involucra un protocolo de lavado particular y la formación de la sal HCl como la etapa final. Cuando se compara con el método general para la preparación de sal HCl, este método proporciona un material significativamente más puro con una mejor solubilidad y facilidad de manipulación.

A una solución de 4–amino–5,6–dimetiltieno[2,3–d]pirimidin–2(1H)–ona (Ejemplo 165a) (1082 g, 5,54 moles) en agua (8,1 L) se le adicionó una solución etanólica de HCl (1,25 N en etanol 200 proof). La suspensión resultante se calentó hasta reflujo durante 15 minutos para proporcionar una solución clara. (En algunos casos se debe agregar H_2O:HCl 1,25 N 1:1 en etanol adicional para

obtener una solución clara). La solución se filtró mientras estaba caliente y el filtrado se enfrió hasta 0ºC mientras se agitaba. El precipitado resultante se recogió mediante filtración, y se lavó con acetona (3 x 5,4 L) y heptano (3 x 5,4 L). Los sólidos se colocaron en bandejas de secado y se secaron bajo vacío durante la noche para proporcionar clorhidrato de 4–amino–5,6–dimetiltieno[2,3–d]pirimidin–2(1H)–ona como un polvo blancuzco (1176 g, 92% de rendimiento). > 99% puro según se determinó mediante HPLC. P.f.: > 260ºC. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,30 (s, 6H), 8,56 (bs, 1H), 9,54 (bs, 1H), 12,92 (bs, 2H). ^{13}C RMN (400 MHz, DMSO-d_6) δ 12,2, 13,3, 106,5, 125,5, 125,7, 146,1, 154,9, 155,3. MS 196,2 (MH^+). Pureza según se determinó mediante HPLC, 99,64%.

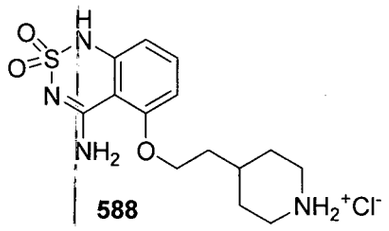
Ejemplo 165a: 4–amino–5,6–dimetiltieno[2,3–d]pirimidin–2(1H)–ona .

Se adicionó etanol a un frasco de tres bocas de 50 L (30,8 L) y se inició la agitación. Se adicionó N–(3–ciano–4,5–dimetiltiofen–2–ilcarbamoil)benzamida (Ejemplo 165b) (933 g, 3,12 mol) seguida por la adición de NaOH (2 N, 4,5 L). La mezcla de reacción se calentó hasta reflujo (~77ºC) y se agitó bajo nitrógeno durante 2,5 horas. Luego la solución se enfrió hasta 65ºC y se trató con carbón (233 g). Luego de agitar durante 30 minutos la solución caliente se filtró y el filtrado se enfrió lentamente hasta temperatura ambiente. El filtrado se neutralizó cuidadosamente con HCl 4 N con agitación enérgica, luego se enfrió además hasta -5ºC hasta 5ºC. El precipitado resultante se recogió mediante filtración, se lavó con agua (3 x 14 L), DMF (1 x 18,7 L), acetona (3 x 14 L) y agua (3 x 14 L). Los sólidos se colocaron en bandejas de secado y se secaron bajo vacío durante la noche para proporcionar 4–amino–5,6–dimetiltieno[2,3–d]pirimidin–2(1H)–tiona (573 g, 87%) como un sólido blancuzco. P.f.: > 260ºC. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,95 (bs, 1H), 2,25 (s, 3H), 2,16 (s, 3H). MS 196(MH^+). Pureza según se determinó mediante HPLC, 99,64%

Ejemplo 165b: N–(3–ciano–4,5–dimetiltiofen–2–ilcarbamoil)benzamida

A una solución de 2–amino–4,5–dimetiltiofen–3–carbonitrilo (1680 g, 11,04 mol) en 1,4-dioxano (42 L) se le adicionó isocianato de benzoilo (1624 g, 11,04 mol). Luego la mezcla de reacción se agitó a temperatura ambiente bajo nitrógeno durante la noche. El precipitado resultante se recogió mediante filtración, se lavó con 1,4-dioxano (3 x 1,7 l) and heptane (3 x 1,7 L), y se secó bajo vacío durante la noche para proporcionar N–(3–ciano–4,5–dimetiltiofen–2–ilcarbamoil)benzamida como un sólido blanco (2800 g, 84,7% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,10 (s, 3H), 2,24 (s, 3H), 7,52-7,56 (m, 2H), 7,64-7,69 (m, 1H), 8,01-8,03 (m, 2H), 11,57 (brs, 1H), 12,05 (brs, 1H). MS 300 (MH^+).

Ejemplo 166: Cloruro de 4–(2–(4–amino–*1H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido–5–iloxi)etil)piperidinio



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Se disolvió *terc*–butil–4–(2–(4–amino–*1H*–benzo[*c*][1,2,6]tiadiazin–2,2–dioxido–5–iloxi)etil)piperidin–1–carboxilato (Ejemplo 166a) (20 mg, 0,047 mmol) en una solución de HCl en EtOH (1 mL, 1,25 M). La reacción se agitó a reflujo bajo N_2. Una vez completa, el precipitado se recogió mediante filtración al vacío para proporcionar el producto deseado (17 mg, 100%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,38 (m, 2H), 1,73 (m, 1H), 1,81 (m, 2H), 1,87 (m, 2H), 2,84 (m, 2H), 3,24 (m, 2H), 4,21 (t, J = 6,4 Hz, 2H), 6,64 (d, J = 8,1 Hz, 1H), 6,78 (d, J = 8,3 Hz, 1H), 7,47 (t, J = 8,3 Hz, 1H), 7,81 (br s, 1H), 8,35 (br s, 1H), 8,59 (m, 1H), 8,85 (m, 1H), 10,99 (br s, 1H). MS 325 (MH^+).

Ejemplo 166a: 4–(2–(4–amino–*1H*–benzo[*c*][1,2,6]tiadiazin–2,2–dioxido–5–iloxi)etil)piperidin–1–carboxilato de *terc*–butilo

Preparado como en el Ejemplo 111 a partir de 4–(2–(2–ciano–3–(sulfamoilamino)fenoxi)etil)piperidin–1–carboxilato de *terc*–butilo (Ejemplo 166b) en 15% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,07 (qd, J = 12,8, 4,6 Hz, 2H), 1,40 (s, 9H), 1,60 (m, 1H), 1,70 (m, 2H), 1,79 (q, J = 6,7 Hz, 2H), 2,70 (m, 2H), 3,93 (m, 2H), 4,21 (t, J = 6,7 Hz, 2H), 6,62 (d, J = 8,1 Hz, 1H), 6,78 (d, J = 8,3 Hz, 1H), 7,46 (t, J = 8,3 Hz, 1H), 7,82 (br s, 1H), 8,34 (br s, 1H), 10,96 (br s, 1H).

Ejemplo166b: *terc*–butil–4–(2–(2–ciano–3–(sulfamoilamino)fenoxi)etil) piperidin–1–carboxilato

Preparado como en el Ejemplo 111a a partir de 4–(2–(3–amino–2–cianofenoxi)etil)piperidin–1–carboxilato de *terc*–butilo (Ejemplo 166c) en 72% de rendimiento como un jarabe claro. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,08 (m, 2H), 1,40 (s, 9H), 1,71 (m, 5H), 2,70 (m, 2H), 3,93 (m, 2H), 4,17 (t, J = 6,3 Hz, 2H), 6,98 (d, J = 8,6 Hz, 1H), 7,16 (d, J = 8,3 Hz, 1H), 7,28 (br s, 2H), 7,57 (t, J = 8,3 Hz, 1H), 9,45 (br s, 1H).

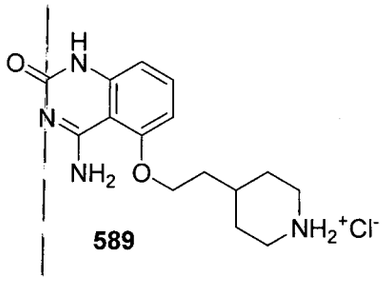
Ejemplo 166c: 4–(2–(3–amino–2–cianofenoxi)etil)piperidin–1–carboxilato de *terc*–butilo:

Preparado como en el Ejemplo 111b a partir de 4–(2–(2–ciano–3–nitrofenoxi)etil)piperidin–1–carboxilato de *terc*–butilo (Ejemplo 166d) en 36% como una espuma blanca. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,06 (m, 2H), 1,40 (s, 9H), 1,68 (m, 5H), 2,70 (m, 2H), 3,93 (m, 2H), 4,05 (t, J = 6,0 Hz, 2H), 5,98 (br s, 2H), 6,23 (d, J = 8,4 Hz, 1H), 6,34 (d, J = 8,4 Hz, 1H), 7,18 (t, J = 8,2 Hz, 1H).

Ejemplo 166d: *terc*–butil–4–(2–(2–ciano–3–nitrofenoxi)etil)piperidin–1–carboxilato:

A una suspensión de *terc*–butil–4–(2–hidroxietil)piperidin–1–carboxilato (769 μL, 3,50 mmol) y NaH (118 mg, 3,50 mmol, 60% dispersión en aceite mineral) en DMF seca (5 mL) a 0ºC, se le adicionó una solución de 2,6–dinitrobenzonitrilo (614 mg, 3,18 mmol) en DMF seca (4 mL). La reacción se agitó bajo N_2, entibiando hasta ta. Una vez completa, la reacción se inactivó con H_2O (50 mL), y el precipitado se recogió mediante filtración al vacío para proporcionar *terc*–butil–4–(2–(2–ciano–3–nitrofenoxi)etil)piperidin–1–carboxilato (955 mg, 80%) como un sólido tostado ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,09 (m, 2H), 1,40 (s, 9H), 1,73 (m, 5H), 2,70 (m, 2H), 3,94 (m, 2H), 4,32 (t, J = 6,8 Hz, 2H), 7,75 (m, 1H), 7,92 (m, 2H).

Ejemplo 167: Cloruro de 4–(2–(4–amino–2–oxo–1,2–dihidroquinazolin–5–iloxi)etil)piperidinio



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Preparado como en el Ejemplo 166 a partir de 4–(2–(4–amino–2–oxo–1,2–dihidroquinazolin–5–iloxi)etil)piperidin–1–carboxilato de *terc*–butilo (Ejemplo 167a) en 92% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,36 (m, 2H), 1,70 (m, 1H), 1,83 (q, J = 6,5 Hz, 2H), 1,88 (m, 2H), 2,84 (m, 2H), 3,26 (m, 2H), 4,36 (t, J = 6,4 Hz, 2H), 6,86 (d, J = 8,3 Hz, 1H), 6,99 (d, J = 8,3 Hz, 1H), 7,76 (t, J = 8,3 Hz, 1H), 8,50 (br s, 1H), 8,74 (br s, 1H), 8,98 (br s, 1H), 9,46 (br s, 1H), 11,99 (br s, 1H). MS 289 (MH^+).

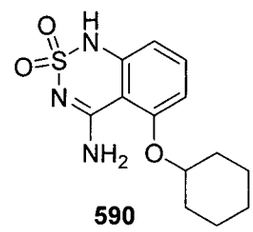
Ejemplo 167a: 4–(2–(4–amino–2–oxo–1,2–dihidroquinazolin–5–iloxi)etil) piperidin–1–carboxilato de *terc*–butilo

Preparado como en el Ejemplo 111 a partir de 4–(2–(3–(3–benzoilureido)–2–cianofenoxi)etil)piperidin–1–carboxilato de *terc*–butilo (Ejemplo 167b) en 31% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,08 (qd, J = 12,8, 4,6 Hz, 2H), 1,40 (s, 9H), 1,60 (m, 1H), 1,70 (m, 2H), 1,79 (q, J = 6,4 Hz, 2H), 2,69 (m, 2H), 3,93 (m, 2H), 4,23 (t, J = 6,9 Hz, 2H), 6,73 (m, 2H), 7,47 (t, J = 8,2 Hz, 1H), 7,57 (br s, 1H), 7,93 (br s, 1H), 10,73 (br s, 1H).

Ejemplo 167b: 4–(2–(3–(3–benzoilureido)–2–cianofenoxi)etil)piperidin–1–carboxilato de *terc*–butilo

Preparado como en el Ejemplo 146a a partir de 4–(2–(3–amino–2–cianofenoxi)etil)piperidin–1–carboxilato de *terc*–butilo (Ejemplo 167c) en 100% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,09 (m, 2H), 1,40 (s, 9H), 1,60 (m, 1H), 1,71 (m, 5H), 2,71 (m, 2H), 3,94 (m, 2H), 4,21 (t, J = 6,5 Hz, 2H), 7,01 (d, J = 8,5 Hz, 1H), 7,56 (t, J = 7,4 Hz, 2H), 7,47 (t, J = 8,2 Hz, 1H), 7,64 (t, J = 8,5 Hz, 1H), 7,68 (tt, J = 7,3, 1,5 Hz, 1H), 7,87 (d, J = 8,3 Hz, 1H), 8,05 (m, 2H), 11,35 (br s, 1H), 11,49 (br s, 1H) .

Ejemplo 168: 4–amino–5–(ciclohexiloxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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Preparado como en El ejemplo 111 a partir de 2–sulfamoilamino–6–hexiloxibenzonitrilo (Ejemplo 168a) en 63% de rendimiento como un sólido blanco cristalino. P.f.: 215–216ºC. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,30-1,71 (m, 8H), 1,99 (m, 2H), 4,63 (m, 1H), 6,60 (dd, J = 8,2, 0,8 Hz, 1H), 6,82 (d, J = 8,2 Hz, 1H),

7,45 (t, J = 8,3 Hz, 1H), 7,83 (br d, J = 2,0 Hz, 1H), 8,40 (br d, J = 2,4 Hz, 1H), 10,95 (br s, 1H). MS 296 (MH^+).

Ejemplo 168a: 2–sulfamoilamino–6–ciclohexiloxibenzonitrilo:

Preparado como en el Ejemplo 111a a partir de 2–amino–6–ciclohexiloxibenzonitrilo (Ejemplo 168b) en 91% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,37 (m, 3H), 1,51 (m, 3H), 1,70 (m, 2H), 1,85 (m, 2H), 4,55 (m, 1H), 6,98 (d, J = 8,1 Hz, 1H), 7,10 (d, J = 8,5 Hz, 1H), 7,24 (br s, 2H), 7,51 (t, J = 8,5 Hz, 1H), 9,39 (s, 1H).

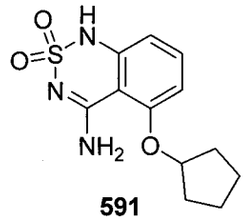
Ejemplo 168b: 2–amino–6–ciclohexiloxibenzonitrilo:

Preparado como en el Ejemplo 111b a partir de 2–nitro–6–ciclohexiloxibenzonitrilo para proporcionar 2–amino–6–ciclohexiloxibenzonitrilo (420 mg, 27%) como un jarabe verde. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,37 (m, 3H), 1,50 (m, 3H), 1,71 (m, 2H), 1,85 (m, 2H), 4,43 (m, 1 H), 5,94 (br s, 2H), 6,26 (d, J = 8,6 Hz, 1H), 6,31 (d, J = 8,1 Hz, 1H), 7,16 (t, J = 8,1 Hz, 1H). MS 215 (MH^+).

Ejemplo 168c: 2–nitro–6–ciclohexiloxibenzonitrilo:

Preparado como en el Ejemplo 166d a partir de 2–nitro–6–ciclohexiloxibenzonitrilo y ciclohexanol en 100% de rendimiento como un sólido tostado claro. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,45 (m, 4H), 1,60 (m, 2H), 1,74 (m, 2H), 1,90 (m, 2H), 4,76 (m, 1H), 7,79 (m, 1H), 7,89 (m, 2H).

Ejemplo 169: 4–amino–5–(ciclopentoxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–pentoxibenzonitrilo (Ejemplo 169a) en 38% de rendimiento como agujas blancuzcas P.f.: >260ºC. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,67 (m, 4H), 1,85 (m, 2H), 1,98 (m, 2H), 5,05 (m, 1H), 6,61 (d, J = 7,8 Hz, 1H), 6,76 (d, J = 7,8 Hz, 1H), 7,46 (t, J = 7,8 Hz, 1H), 7,72 (br s, 1H), 8,35 (br s, 1H), 10,96 (br s, 1H). MS 282 (MH^+).

Ejemplo 169a: 2–sulfamoilamino–6–ciclopentoxibenzonitrilo:

Preparado como en el Ejemplo 111a a partir de 2–amino–6–ciclopentoxibenzonitrilo (Ejemplo 169b) en 100% de rendimiento como un jarabe marrón claro. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,61 (m, 2H), 1,74 (m, 4H), 1,93 (m, 2H), 4,98 (m, 1H), 6,96 (d, J = 9,0 Hz, 1H), 7,14 (d, J = 8,2 Hz, 1H), 7,28 (br s, 2H), 7,55 (t, J = 8,2 Hz, 1H), 9,43 (s, 1H).

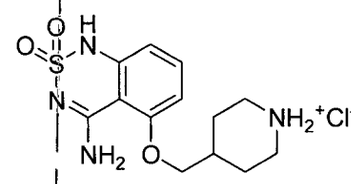
Ejemplo 169b: 2–amino–6–ciclopentoxibenzonitrilo:

Preparado como en el Ejemplo 111b a partir de 2–nitro–6–ciclopentoxibenzonitrilo (Ejemplo 169c) en 84% de rendimiento como un jarabe verde. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,58 (m, 2H), 1,71 (m, 4H), 1,89 (m, 2H), 4,84 (m, 1 H), 5,94 (br s, 2H), 6,20 (d, J = 8,0 Hz, 1H), 6,31 (d, J = 8,3 Hz, 1H), 7,17 (t, J = 8,3 Hz, 1H).

Ejemplo 169c: 2–nitro–6–ciclopentoxibenzonitrilo:

Preparado como en el Ejemplo 166d a partir de 2,6–dinitrobenzonitrilo y ciclopentanol en 78% de rendimiento como un sólido tostado claro. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,64 (m, 2H), 1,77 (m, 4H), 1,97 (m, 2H), 5,14 (m, 1H), 7,73 (m, 1H), 7,88 (m, 2H).

Ejemplo 170: Cloruro de 4–(2–(4–amino–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido–5–iloxi)metil)piperidinio



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Preparado como en el Ejemplo 166 a partir de 4–(2–(4–amino–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido–5–iloxi)metil)piperidin–1–carboxilato de *terc*–butilo (Ejemplo 170a) en 89% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,49 (m, 2H), 1,90 (d, J = 13,1 Hz, 2H), 2,23 (m, 1H), 2,89 (q, J = 11,6 Hz, 2H), 3,30 (d, J = 12,3 Hz, 2H), 4,09 (br s, J = 6,6 Hz, 2H), 6,65 (d, J = 8,2 Hz, 1H), 6,82 (d, J = 8,2 Hz, 1H), 7,48 (t, J = 8,2 Hz, 1H), 7,74 (br s, 1H), 8,33 (br s, 1H), 8,69 (m, 1H), 8,92 (m, 1H), 11,01 (s, 1H). MS 272 (MH^+).

Ejemplo 170a: 4–(2–(4–amino–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido–5–iloxi)metil)piperidin–1–carboxilato de *terc*–butilo

Preparado como en el Ejemplo 111 a partir de 4–((2–ciano–3–(sulfamoilamino)fenoxi)metil)piperidin–1–carboxilato de *terc*–butilo (Ejemplo 170b) en 91% como un sólido blanco. MS 355 ($MH^+ - C(CH_3)_3$).

Ejemplo 170b: 4–((2–ciano–3–(sulfamoilamino)fenoxi)metil)piperidin–1–carboxilato de *terc*–butilo

Preparado como en el Ejemplo 111a a partir de 4–((3–amino–2–cianofenoxi)metil)piperidin–1–carboxilato de *terc*–butilo (Ejemplo 170c) en 56% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,20 (m, 2H), 1,41 (s, 9H), 1,76 (d, J = 13,2 Hz, 2H), 1,97 (m, 2H), 4,00 (m, 4H), 6,96 (d, J = 8,6 Hz, 1H), 7,16 (d, J = 8,3 Hz, 1H), 7,28 (s, 2H), 7,57 (t, J = 8,3 Hz, 1H), 9,47 (s, 1H).

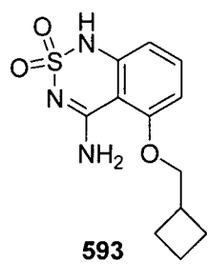
Ejemplo 170c: 4–((3–amino–2–cianofenoxi)metil)piperidin–1–carboxilato de *terc*–butilo

Preparado como en el Ejemplo 111b a partir de 4–((2–ciano–3–nitrofenoxi)metil)piperidin–1–carboxilato de *terc*–butilo (Ejemplo 170d) en 74% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,18 (qd, J = 12,6, 3,8 Hz, 2H), 1,41 (s, 9H), 1,74 (d, J = 12,6 Hz, 2H), 1,93 (m, 2H), 2,75 (m, 2H), 3,88 (d, J = 6,6 Hz, 2H), 3,99 (br d, J = 12,1 Hz, 2H), 6,00 (br s, 2H), 6,21 (d, J = 8,2 Hz, 1H), 6,34 (d, J = 8,3 Hz, 1H), 7,18 (t, J = 8,2 Hz, 1H).

Ejemplo 170d: 4–((2–ciano–3–nitrofenoxi)metil)piperidin–1–carboxilato de *terc*–butilo

Preparado como en el Ejemplo 111c a partir de 2,6–dinitrobenzonitrilo y 4–(hidroximetil)piperidin–1–carboxilato de *terc*–butilo en 73% como un sólido tostado. ^{1}H RMN (400 MHz, MeOD) δ 1,24 (qd, J = 12,8, 4,4 Hz, 2H), 1,41 (s, 9H), 1,78 (br d, J = 12,1 Hz, 2H), 2,02 (m, 2H), 2,77 (m, 2H), 4,00 (br d, J = 13,1 Hz, 2H), 4,15 (d, J = 6,3 Hz, 2H), 7,74 (dd, J = 7,5, 1,5 Hz, 1H), 7,91 (m, 2H).

Ejemplo 171: 4–amino–5–(ciclobutilmetoxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–ciclobutilmetoxibenzonitrilo (Ejemplo 171a) en 21% de rendimiento como un sólido amarillo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,88 (m, 4H), 2,08 (m, 2H), 2,86 (sept, J = 7,9 Hz, 1H), 4,16 (d, J = 6,9 Hz, 2H), 6,62 (dd, J = 8,2, 1,2 Hz, 1H), 6,77 (dd, J = 8,6, 0,7 Hz, 1H), 7,47 (t, J = 8,2 Hz, 1H), 7,76 (br s, 1H), 8,39 (br s, 1H), 10,98 (br s, 1H). MS 282 (MH^+).

Ejemplo 171a: 2–sulfamoilamino–6–ciclobutilmetoxibenzonitrilo

Preparado como en el Ejemplo 111a a partir de 2–amino–6–ciclobutilmetoxibenzonitrilo (Ejemplo 171b) en 94% de rendimiento como un sólido amarillo claro. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,94 (m, 4H), 2,12 (m, 2H), 2,86 (sept, J = 7,5 Hz, 1H), 4,13 (d, J = 6,3 Hz, 2H), 7,00 (d, J = 8,4 Hz, 1H), 7,19 (d, J = 8,2 Hz, 1H), 7,31, (br s, 2H), 7,60 (t, J = 8,4 Hz, 1H), 9,48 (br s, 1H).

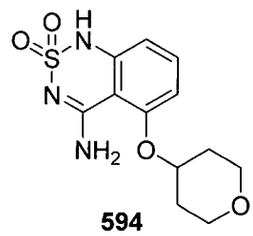
Ejemplo 171b: 2–amino–6–ciclobutilmetoxibenzonitrilo

Preparado como en el Ejemplo 111b a partir de 2–nitro–6–ciclobutilmetoxibenzonitrilo (Ejemplo 171c) en 41% de rendimiento como un aceite amarillo. MS 203 (MH^+).

Ejemplo 171c: 2–nitro–6–ciclobutilmetoxibenzonitrilo

Preparado como en el Ejemplo 166d a partir de 2,6–dinitrobenzonitrilo y ciclobutilmetanol en 68% como un sólido tostado. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,93 (m, 4H), 2,10 (m, 2H), 2,79 (m, 1H), 4,25 (d, J = 6,3 Hz, 2H), 7,74 (dd, J = 8,5, 2,2 Hz, 1H), 7,91 (m, 2H).

Ejemplo 172: 4–amino–5–(tetrahidro–2*H*–piran–4–iloxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–(tetrahidro–2*H*–piran–4–iloxi)benzonitrilo (Ejemplo 172a) en 69% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,77 (m, 2H), 2,05 (m, 2H), 3,51 (td, J = 11,6, 2,1 Hz, 2H), 3,85 (dt, J = 11,4, 3,9 Hz, 2H), 4,83 (sept, J

=4,1 Hz, 1H), 6,62 (d, *J* = 8,0 Hz, 1H), 6,88 (d, *J* = 8,4 Hz, 1H), 7,46 (t, *J* = 8,2 Hz, 1H), 7,78 (br s, 1H), 8,39 (br s, 1H), 10,96 (br s, 1H). MS 298 (MH^+).

Ejemplo 172a: 2–sulfamoilamino–6–(tetrahidro–2*H*–piran–4–iloxi)benzonitrilo

Preparado como en el Ejemplo 111a a partir de 2–amino–6–(tetrahidro–2*H*–piran–4–iloxi)benzonitrilo (Ejemplo 172b) en 58% como un sólido anaranjado claro. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,64 (m, 2H), 1,99 (m, 2H), 3,53 (ddd, *J* = 11,6, 8,3, 3,1 Hz, 2H), 3,85 (m, 2H), 4,80 (sept, *J* = 4,0 Hz, 1H), 7,07 (d, *J* = 8,3 Hz, 1H), 7,16 (d, *J* = 8,1 Hz, 1H), 7,28 (br s, 2H), 7,56 (t, *J* = 8,5 Hz, 1H), 9,47 (br s, 1H).

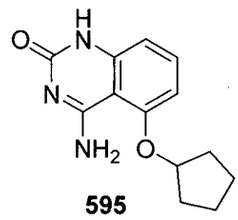
Ejemplo 172b: 2–amino–6–(tetrahidro–2*H*–piran–4–iloxi)benzonitrilo

Preparado como en el Ejemplo 111b a partir de 2–nitro–6–(tetrahidro–2*H*–piran–4–iloxi)benzonitrilo (Ejemplo 172c) en 49% como un jarabe anaranjado. MS 219 (MH^+).

Ejemplo 172c: 2–nitro–6–(tetrahidro–2*H*–piran–4–iloxi)benzonitrilo

Preparado como en el Ejemplo 166d a partir de 2,6–dinitrobenzonitrilo y tetrahidro–2*H*–piran–4–ol en 100% de rendimiento como un sólido tostado. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,69 (m, 2H), 2,03 (m, 2H), 3,56 (m, 2H), 3,87 (m, 2H), 4,98 (sept, *J* = 3,8 Hz, 1H), 7,90 (m, 3H).

Ejemplo 173: 4–amino–5–(ciclopentiloxi)quinazolin–2(1*H*)–ona



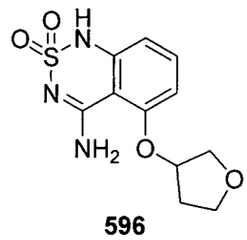
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Preparada como en el Ejemplo 111 a partir de *N*–(2–ciano–3–(ciclopentiloxi)fenilcarbamoil)benzamida (Ejemplo 173a) en 45% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,68 (m, 4H), 1,84 (m, 2H), 1,99 (m, 2H), 5,06 (m, 1H), 6,70 (d, J = 8,3 Hz, 2H), 7,43 (s, 1H), 7,45 (t, J = 8,2 Hz, 1H), 7,85 (br s, 1H), 10,65 (br s, 1H).

Ejemplo 173a: *N*–(2–ciano–3–(ciclopentiloxi)fenilcarbamoil)benzamida

Preparada como en el Ejemplo 146a a partir de 2–amino–6–ciclopentoxibenzonitrilo (Ejemplo 173b) en 70% de rendimiento como un sólido amarillo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,63 (m, 2H), 1,77 (m, 4H), 1,98 (m, 2H), 5,03 (m, 1H), 6,98 (d, J = 8,6 Hz, 1H), 7,55 (t, J = 7,6 Hz, 2H), 7,62 (t, J = 8,6 Hz, 1H), 7,67 (tt, J = 7,4, 1,2 Hz, 1H), 7,87 (d, J = 8,0 Hz, 1H), 8,06 (m, 2H), 11,37 (br s, 1H), 11,54 (br s, 1H).

Ejemplo 174: 4–amino–5–(tetrahidrofuran–3–iloxi)–1*H*–benzo[*c*][1,2,6] tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–(tetrahidrofuran–3–iloxi)benzonitrilo (Ejemplo 174a) en 33% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,07 (m, 1H), 2,26 (m, 1H), 3,74 (td, J = 8,4, 4,7 Hz, 1H), 3,84 (m, 2H), 3,95 (d, J = 10,4 Hz, 1H), 5,23 (m, 1H), 6,61 (d, J = 8,1 Hz, 1H), 6,73 (d, J = 8,4 Hz, 1H), 7,45 (t, J = 8,1 Hz, 1H), 7,64 (br s, 1H), 8,33 (br s, 1H), 10,97 (br s, 1H). MS 284 (MH^+).

Ejemplo 174a: 2–sulfamoilamino–6–(tetrahidrofuran–3–iloxi)benzonitrilo

Preparado como en el Ejemplo 111a a partir de 2–amino–6–(tetrahidrofuran–3–iloxi)benzonitrilo (Ejemplo 174b) en 40% de rendimiento como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,99 (m, 1H), 2,28 (m, 1H), 3,77 (td, J = 8,3, 4,7 Hz, 1H), 3,83 (m, 1H), 3,87 (d, J = 7,3 Hz, 1H), 3,92 (dd, J = 10,2, 4,4 Hz, 1H), 5,19 (m, 1H), 6,96 (d, J = 8,3 Hz, 1H), 7,18 (d, J = 8,3 Hz, 1H), 7,29 (s, 2H), 7,58 (t, J = 8,3 Hz, 1H), 9,49 (br s, 1H).

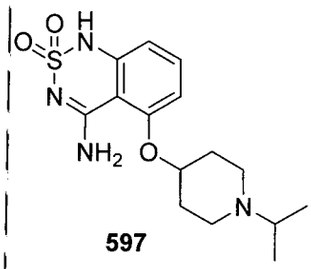
Ejemplo 174b: 2–amino–6–(tetrahidrofuran–3–iloxi)benzonitrilo

Preparado como en el Ejemplo 111b a partir de 2–nitro–6–(tetrahidrofuran–3–iloxi)benzonitrilo (Ejemplo 174c) en 97% de rendimiento como un jarabe marrón claro. MS 205 (MH^+).

Ejemplo174c: 2–nitro–6–(tetrahidrofuran–3–iloxi)benzonitrilo

Preparado como en el Ejemplo 166d a partir de 2,6–dinitrobenzonitrilo y tetrahidrofuran–3–ol en 50% de rendimiento como un sólido amarillo claro. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,04 (m, 1H), 2,32 (m, 1H), 3,81 (td, J = 8,3, 4,6 Hz, 1H), 3,89 (m, 2H), 3,98 (dd, J = 10,8, 4,5 Hz, 1H), 5,36 (m, 1H), 7,75 (dd, J = 8,1, 1,5 Hz, 1H), 7,91 (t, J = 8,2 Hz, 1H), 7,95 (dd, J = 8,2, 1,6 Hz, 1H).

Ejemplo 175: 4–amino–5–(1–isopropilpiperidin–4–iloxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–(1–isopropilpiperidin–4–iloxi)benzonitrilo (Ejemplo 175b) en 12% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,24 (d, J = 6,7 Hz, 6H),

2,11 (m, 2H), 2,28 (m, 2H), 3,13 (m, 4H), 4,87 (m, 1H), 6,67 (d, *J* = 8,0 Hz, 1H), 6,87 (d, *J* = 8,6 Hz, 1H), 7,49 (t, *J* = 8,3 Hz, 1H), 7,67 (br s, 1H), 8,43 (br s, 1H), 10,79 (br s, 1H). MS 339 (MH^+).

Ejemplo 175a: 2–sulfamoilamino–6–(1–isopropilpiperidin–4–iloxi)benzonitrilo

Preparado como en el Ejemplo 111a a partir de 2–amino–6–(1–isopropilpiperidin–4–iloxi)benzonitrilo (Ejemplo 175b). El producto se llevó a la etapa siguiente sin purificación adicional.

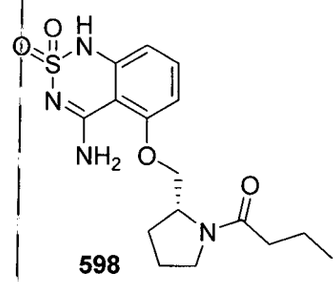
Ejemplo 175b: 2–amino–6–(1–isopropilpiperidin–4–iloxi)benzonitrilo

Preparado como en el Ejemplo 111b a partir de 2–nitro–6–(1–isopropilpiperidin–4–iloxi)benzonitrilo (Ejemplo 175c) en 80% de rendimiento como un jarabe marrón. MS 260 (MH^+).

Ejemplo 175c: 2–nitro–(1–isopropilpiperidin–4–iloxi)–6–benzonitrilo

Preparado como en el Ejemplo 166d a partir de 2,6–dinitrobenzonitrilo y 1–isopropilpiperidin–4–ol en 90% de rendimiento como un sólido tostado. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,99 (d, *J* = 6,8 Hz, 6H), 1,72 (m, 2H), 1,95 (m, 2H), 2,41 (m, 2H), 2,71 (m, 3H), 4,80 (m, 1H), 7,81 (dd, *J* = 8,2, 1,3 Hz, 1H), 7,89 (m, 2H).

Ejemplo 176: (*R*)–4–amino–5–((1–butirilpirrolidin–2–il)metoxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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A una solución de (*R*)–2–amino–6–((1–butirilpirrolidin–2–il)metoxi)benzonitrilo (84 mg, 0,29 mmol) (Ejemplo 176a) en acetonitrilo (9 mL), se le adicionó cloruro de sulfamoilo (70 mg, 0,60 mmol). La reacción se agitó a ta durante 20 h, y una vez completa se concentró *al vacío*. El residuo resultante se disolvió en EtOH (1 mL), y se adicionó NaOH acuoso 2 N (4 mL). La mezcla se reflujó durante 2 h, y una vez completa se enfrió hasta rt, se neutralizó con HCl 1 N y se agitó a 0°C. El precipitado resultante se recogió mediante filtración de vacío para proporcionar el producto deseado (38 mg, 35%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,89 (t, J = 7,3 Hz, 3H), 1,54 (sext, J = 7,3 Hz, 2H), 1,94 (m, 4H), 2,26 (t, J = 7,3 Hz, 2H), 3,49 (m, 2H), 4,10 (m, 1H), 4,25 (m, 1H), 4,43 (m, 1H), 6,62 (d, J = 8,2 Hz, 1H), 6,90 (d, J = 8,2 Hz, 1H), 7,45 (t, J = 8,2 Hz, 1H), 8,08 (br s, 1H), 8,34 (br s, 1H), 10,93 (br s, 1H). MS 367 (MH^+).

Ejemplo 176a: (*R*)–2–amino–6–((1–butirilpirrolidin–2–il)metoxi)benzonitrilo

Preparado como en el Ejemplo 111b a partir de (*R*)–2–((1–butirilpirrolidin–2–il)metoxi)–6–nitrobenzonitrilo (Ejemplo 176b) en 77% de rendimiento. MS 274 (MH^+).

Ejemplo 176b: (*R*)–2–((1–butirilpirrolidin–2–il)metoxi)–6–nitrobenzonitrilo

A una suspensión de cloruro de (*R*)–2–((2–ciano–3–nitrofenoxi)metil)pirrolidinio (140 mg, 0,49 mmol) (Ejemplo 176c) en THF (3 mL) se le adicionaron Et_3N (143 µL, 1,03 mmol) y cloruro de butirilo (56 µL, 0,54 mmol). La reacción se agitó durante 72 h a ta bajo N_2. Una vez completa, la reacción se filtró, y el filtrado se concentró para proporcionar (*R*)–2–((1–butirilpirrolidin–2–il)metoxi)–6–nitrobenzonitrilo (127 mg, 82%) como un jarabe amarillo. MS 318 (MH^+).

Ejemplo176c: Cloruro de (*R*)–2–((2–ciano–3–nitrofenoxi)metil)pirrolidinio

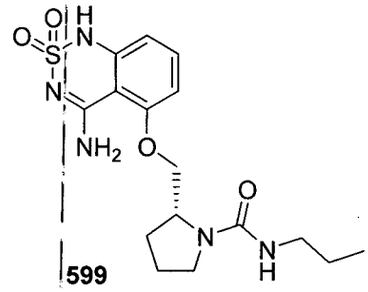
Preparado como en el Ejemplo 166 a partir de 2–((2–ciano–3–nitrofenoxi)metil)pirrolidin–1–carboxilato de (*R*)–*terc*–butilo (Ejemplo 176d) en

71% de rendimiento como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,92 (m, 2H), 2,14 (m, 2H), 3,28 (m, 2H), 4,07 (m, 2H), 4,50 (dd, J = 710,6, 6,4 Hz, 1H), 4,57 (dd, J = 10,9, 3,5 Hz, 1H), 7,77 (d, J = 8,0 Hz, 1H), 7,98 (m, 2H), 9,36 (br s, 1H), 9,74 (br s, 1H).

Ejemplo 176d: 2–((2–ciano–3–nitrofenoxi)metil)pirrolidin–1–carboxilato de (*R*)–*terc*–butilo

Preparado como en El ejemplo 166d a partir de 2,6–dinitrobenzonitrilo y 2–(hidroximetil)pirrolidin–1–carboxilato de(*R*)–*terc*–butilo en 87% de rendimiento como un sólido tostado. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,39 (s, 9H), 1,82 (m, 1H), 2,02 (m, 3H), 3,32 (m, 2H), 4,08 (m, 1H), 4,32 (m, 2H), 7,79 (d, J = 8,0 Hz, 1H), 7,91 (m, 2H).

Ejemplo 177: (*R*)–2–((4–amino–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dioxido–5–iloxi)metil)–*N*–propilpirrolidin–1–carboxamida



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Preparada como en el Ejemplo 176 a partir de (*R*)–2–((3–amino–2–cianofenoxi)metil)–*N*–propilpirrolidin–1–carboxamida (Ejemplo 177a) en 57% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,83 (t, J = 7,6 Hz, 3H), 1,42 (sext, J = 7,3 Hz, 2H), 1,90 (m, 4H), 3,00 (m, 2H), 3,20 (m, 1H), 3,43 (m, 2H), 4,01 (m, 1H), 4,16 (m, 1H), 4,33 (m, 1H), 6,27 (m, 1H), 6,61 (d, J = 8,4 Hz, 1H), 6,89 (d, J = 8,3 Hz, 1H), 7,45 (t, J = 8,2 Hz, 1H), 8,19 (br s, 1H), 8,27 (br s, 1H), 10,91 (s, 1H). MS 382 (MH^+).

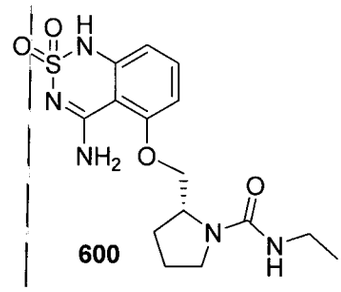
Ejemplo 177a: (*R*)–2–((3–amino–2–cianofenoxi)metil)–*N*–propilpirrolidin–1–carboxamida

Preparada como en el Ejemplo 111b a partir de (*R*)–2–((2–ciano–3–nitrofenoxi)metil)–*N*–propilpirrolidin–1–carboxamida (Ejemplo 177b) en 14% de rendimiento. MS 303 (MH^+).

Ejemplo 177b: (*R*)–2–((2–ciano–3–nitrofenoxi)metil)–*N*–propilpirrolidin–1–carboxamida

Preparada como en el Ejemplo 176b a partir de cloruro de (*R*)–2–((2–ciano–3–nitrofenoxi)metil)pirrolidinio (Ejemplo 176c) e isocianato de propilo en 100% de rendimiento como un sólido amarillo claro. MS 333 (MH^+).

Ejemplo 178: (*R*)–2–((4–amino–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dioxido–5–iloxi)metil)–*N*–etilpirrolidin–1–carboxamida



600

Preparada como en el Ejemplo 176 a partir de (*R*)–2–((3–amino–2–cianofenoxi)metil)–*N*–etilpirrolidin–1–carboxamida (Ejemplo 178a) en 60% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,02 (t, J = 6,8 Hz, 3H), 1,90 (m, 4H), 3,08 (quint, J = 6,8 Hz, 2H), 3,20 (m, 2H), 4,01 (m, 1H), 4,16 (m, 1H), 4,33 (m, 1H), 6,27 (m, 1H), 6,62 (d, J = 8,4 Hz, 1H), 6,89 (d, J = 8,4 Hz, 1H), 7,46 (t, J = 8,4 Hz, 1H), 8,20 (br s, 1H), 8,27 (br s, 1H), 10,91 (s, 1H). MS 368 (MH^+).

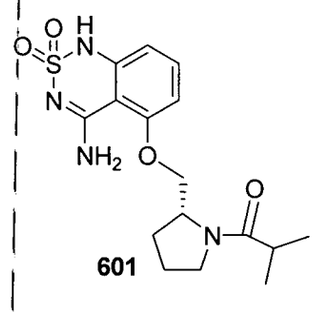
Ejemplo 178a: (*R*)–2–((3–amino–2–cianofenoxi)metil)–*N*–etilpirrolidin–1–carboxamida

Preparada como en el Ejemplo 111b a partir de (*R*)–2–((2–ciano–3–nitrofenoxi)metil)–*N*–etilpirrolidin–1–carboxamida (Ejemplo 178b) in 62% de rendimiento. MS 289 (MH^+).

Ejemplo 178b: (*R*)–2–((2–ciano–3–nitrofenoxi)metil)–*N*–etilpirrolidin–1–carboxamida

Preparada como en el Ejemplo 176b a partir de cloruro de (*R*)–2–((2–ciano–3–nitrofenoxi)metil)pirrolidinio (Ejemplo 176c) e isocianato de etilo en 95% de rendimiento como un sólido amarillo claro. MS 319 (MH^+).

Ejemplo 179: (*R*)–4–amino–5–((1–isobutirilpirrolidin–2–il)metoxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 176 a partir de (*R*)–2–amino–6–((1–isobutirilpirrolidin–2–il)metoxi)benzonitrilo (Ejemplo 179b) en 100% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,02 (d, J = 6,3 Hz, 6H), 1,94 (m, 4H), 2,70 (m, 1H), 3,55 (m, 2H), 4,12 (m, 1H), 4,24 (m, 1H), 4,43 (m, 1H), 6,62 (d, J = 7,9 Hz, 1H), 6,91 (d, J = 8,1 Hz, 1H), 7,47 (t, J = 8,1 Hz, 1H), 8,04 (br s, 1H), 8,34 (br s, 1H), 10,93 (br s, 1H). MS 367 (MH^+).

Ejemplo 179a: (*R*)–2–amino–6–((1–isobutirilpirrolidin–2–il)metoxi)benzonitrilo

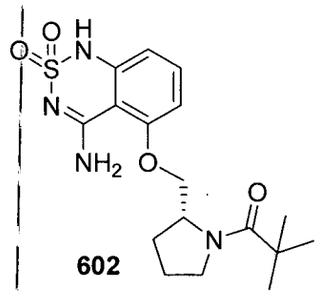
870

Preparado como en el Ejemplo 111b a partir de (*R*)–2–((1–isobutirilpirrolidin–2–il)metoxi)–6–nitrobenzonitrilo (Ejemplo 179b) en 80% de rendimiento como un jarabe claro. MS 288 (MH^+).

Ejemplo 179b: (*R*)–2–((1–isobutirilpirrolidin–2–il)metoxi)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 176b a partir de cloruro de (*R*)–2–((2–ciano–3–nitrofenoxi)metil)pirrolidinio y cloruro de isobutirilo en 100% de rendimiento como un sólido amarillo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,96 (dd, J = 6,6, 3,5 Hz, 6H), 1,93 (m, 4H), 2,14 (m, 1H), 2,66 (sept, J = 6,6 Hz, 1H), 3,55 (m, 1H), 4,28 (m, 3H), 7,79 (dd, J = 7,6, 1,8 Hz, 1H), 7,89 (m, 2H).

Ejemplo 180: (*R*)–4–amino–5–((1–pivaloilpirrolidin–2–il)metoxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 176 a partir de (*R*)–2–amino–6–((1–pivaloilpirrolidin–2–il)metoxi)benzonitrilo (Ejemplo 180a) en 64% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,18 (s, 9H), 1,92 (m, 4H), 3,55 (m, 1H), 3,73 (m, 1H), 4,13 (m, 1H), 4,27 (m, 1H), 4,48 (m, 1H), 6,62 (d, J = 8,2 Hz, 1H), 6,92 (d, J = 8,2 Hz, 1H), 7,47 (t, J = 8,2 Hz, 1H), 7,95 (br s, 1H), 8,37 (br s, 1H), 10,95 (br s, 1H). MS 381 (MH^+).

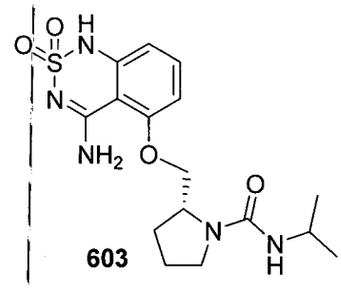
Ejemplo 180a: (*R*)–2–amino–6–((1–pivaloilpirrolidin–2–il)metoxi)benzonitrilo

Preparado como en el Ejemplo 111b a partir de (*R*)–2–((1–pivaloilpirrolidin–2–il)metoxi)–6–nitrobenzonitrilo (Ejemplo 180bW) en 91% de rendimiento como un jarabe claro. MS 302 (MH^+).

Ejemplo 180b: (*R*)–2–((1–pivaloilpirrolidin–2–il)metoxi)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 176b a partir de cloruro de (*R*)–2–((2–ciano–3–nitrofenoxi)metil)pirrolidinio y cloruro de pivaloilo en 99%. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,16 (s, 9H), 1,91 (m, 3H), 2,13 (m, 1H), 3,70 (m, 2H), 4,35 (m, 3H), 7,81 (dd, J = 7,5, 2,1 Hz, 1H), 7,92 (m, 2H).

Ejemplo 181: (*R*)–2–((4–amino–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dioxido–5–iloxi)metil)–*N*–isopropilpirrolidin–1–carboxamida



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Preparada como en el Ejemplo 176 a partir de (*R*)–2–((3–amino–2–cianofenoxi)metil)–*N*–isopropilpirrolidin–1–carboxamida (Ejemplo 181a) en 23% de rendimiento como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,05 (d, J = 6,4 Hz, 6H), 1,87 (m, 4H), 3,17 (m, 1H), 3,79 (m, 1H), 3,98 (m, 1H), 4,15 (m, 1H), 4,31 (m, 1H), 5,88 (d, J = 7,4 Hz, 1H), 6,59 (d, J = 8,2 Hz, 1H), 6,86 (d, J = 8,5 Hz, 1H), 7,43 (t, J = 8,2 Hz, 1H), 8,18 (br s, 1H), 8,23 (br s, 1H), 10,88 (s, 1H). MS 382 (MH^+).

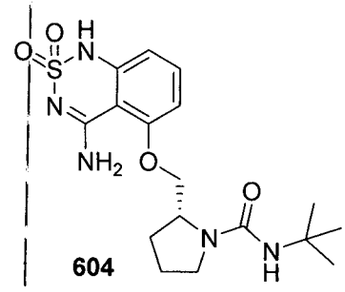
Ejemplo 181a: (*R*)–2–((3–amino–2–cianofenoxi)metil)–*N*–isopropilpirrolidin–1–carboxamida

Preparada como en el Ejemplo 111b a partir de (*R*)–2–((2–ciano–3–nitrofenoxi)metil)–*N*–isopropilpirrolidin–1–carboxamida (Ejemplo 181b) en 86% de rendimiento como un jarabe claro. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,07 (d, J = 5,9 Hz, 6H), 1,89 (m, 3H), 2,10 (m, 1H), 3,16 (m, 1H), 3,45 (m, 1H), 3,78 (m, 1H), 3,91 (m, 1H), 4,06 (m, 1H), 4,12 (m, 1H), 5,85 (d, J = 7,7 Hz, 1H), 6,00 (br s, 2H), 6,31 (d, J = 8,4 Hz, 1H), 6,34 (d, J = 8,4 Hz, 1H), 7,18 (t, J = 8,4 Hz, 1H).

Ejemplo 181b: (*R*)–2–((2–ciano–3–nitrofenoxi)metil)–*N*–isopropilpirrolidin–1–carboxamida

Preparada como en el Ejemplo 176b a partir de cloruro de (*R*)–2–((2–ciano–3–nitrofenoxi)metil)pirrolidinio (Ejemplo 176c) e isocianato de isopropilo en 100% de rendimiento como un sólido amarillo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,07 (d, J = 6,5 Hz, 6H), 1,91 (m, 3H), 2,13 (m, 1H), 3,17 (m, 1H), 3,79 (m, 1H), 4,19 (m, 2H), 4,32 (d, J = 8,8 Hz, 1H), 5,91 (d, J = 8,1 Hz, 1H), 7,89 (m, 3H).

Ejemplo 182: (*R*)–2–((4–amino–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dioxido–5–iloxi)metil)–*N*–*terc*–butilpirrolidin–1–carboxamida



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Preparada como en el Ejemplo 176 a partir de (*R*)–2–((3–amino–2–cianofenoxi)metil)–*N*–*terc*–butilpirrolidin–1–carboxamida (Ejemplo 182a) en 56% de rendimiento como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,27 (s, 9H), 1,89 (m, 4H), 3,21 (m, 1H), 4,02 (m, 1H), 4,19 (m, 1H), 4,34 (m, 1H), 5,35

(s, 1H), 6,62 (m, 1H), 6,86 (m, 1H), 7,46 (m, 1H), 8,23 (br s, 1H), 8,25 (br s, 1H), 10,91 (s, 1H). MS 396 (MH^+).

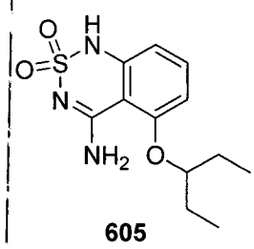
Ejemplo 182a: (*R*)–2–((3–amino–2–cianofenoxi)metil)–*N*–*terc*–butilpirrolidin–1–carboxamida

Preparada como en el Ejemplo 111b a partir de (*R*)–2–((2–ciano–3–nitrofenoxi)metil)–*N*–*terc*–butilpirrolidin–1–carboxamida (Ejemplo 182b) en 96% de rendimiento como un sólido blanco. MS 317 (MH^+).

Ejemplo 182b: (*R*)–2–((2–ciano–3–nitrofenoxi)metil)–*N*–*terc*–butilpirrolidin–1–carboxamida

Preparada como en el Ejemplo 176b a partir de cloruro de (*R*)–2–((2–ciano–3–nitrofenoxi)metil)pirrolidinio (Ejemplo 176c) e isocianato de *terc*–butilo en 100% de rendimiento como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,s7 (s, 9H), 1,86 (m, 1H), 1,95 (m, 2H), 2,12 (m, 1H), 3,18 (m, 1H), 3,37 (m, 1H), 4,20 (m, 1H), 4,23 (dd, J = 16,0, 6,3 Hz, 1H), 4,31 (dd, J = 9,7, 2,7 Hz, 1H), 5,36 (s, 1H), 7,84 (dd, J = 7,4, 0,9 Hz, 1H), 7,91 (m, 2H).

Ejemplo 183: 4–amino–5–(pentan–3–iloxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–(pentan–3–iloxi) benzonitrilo (Ejemplo 183a) en 48,7% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,91 (t, J = 7,6 Hz, 6H), 1,73 (m, 4H), 4,54 (m, 1H), 6,59

(dd, *J* = 8,4, 1,2 Hz, 1H), 6,79 (d, *J* = 8,0 Hz, 1H), 7,45 (t, *J* = 8,4 Hz, 1H), 7,84 (br d, *J* = 2,8 Hz, 1H), 8,38 (br d, *J* = 1,6 Hz, 1H), 10,96 (s, 1H). MS 284 (MH^+).

Ejemplo 183a: 2–sulfamoilamino–6–(pentan–3–iloxi)benzonitrilo:

Preparado como en el Ejemplo 111a a partir de 2–amino–6–(pentan–3–iloxi)benzonitrilo (Ejemplo 183b) en 68,1% de rendimiento. MS 284 (MH^+).

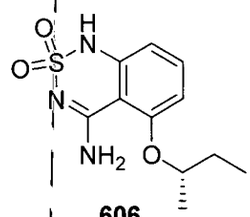
Ejemplo 183b: 2–amino–6–(pentan–3–iloxi)benzonitrilo:

Preparado como en el Ejemplo 111b a partir de 2–nitro–6–(pentan–3–iloxi)benzonitrilo (Ejemplo 183c) en 100% de rendimiento. MS 205 (MH^+).

Ejemplo 183c: 2–nitro–6–(pentan–3–iloxi)benzonitrilo:

Preparado como en el Ejemplo 111c a partir de pentan–3–ol y 2,6–dinitrobenzonitrilo en 86,5% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,94 (t, *J* = 7,6 Hz, 6H), 1,70 (m, 4H), 4,62 (m, 1H), 7,78 (dd, *J* = 7,2, 2,4 Hz, 1H), 7,88 (m, 2H).

Ejemplo 184: (*S*)–4–amino–5–(*sec*–butoxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de (*S*)–2–sulfamoilamino–6–*sec*–butoxibenzonitrilo (Ejemplo 184a) en 43,2% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) 0,94 (t, *J* = 7,6 Hz, 3H), 1,29 (d, *J* = 6,4 Hz, 1H), 1,69 (m, 2H), 4,72 (m, 1H), 6,59 (dd, *J* = 8,4, 1,2 Hz, 1H), 6,79 (d, *J* = 8,0 Hz, 1H), 7,45 (t, *J* = 8,4 Hz, 1H), 7,84 (br d, *J* = 2,8 Hz, 1H), 8,38 (br d, *J* = 1,6 Hz, 1H), 10,96 (s, 1H). MS 270 (MH^+).

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Ejemplo 184a: (*S*)–2–sulfamoilamino–6–*sec*–butoxibenzonitrilo:

Preparado como en el Ejemplo 111a a partir de (*S*)–2–amino–6–*sec*–butoxibenzonitrilo (Ejemplo 184b) en 69,1% de rendimiento. MS 270 (MH^+).

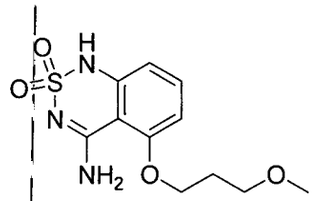
Ejemplo 184b: (*S*)–2–amino–6–*sec*–butoxibenzonitrilo:

Preparado como en el Ejemplo 111b a partir de (*S*)–2–*sec*–butoxi–6–nitrobenzonitrilo (Ejemplo 184c) en 100% de rendimiento. MS 191(MH^+).

Ejemplo 184c: (*S*)–2–*sec*–butoxi–6–nitrobenzonitrilo:

Preparado como en el Ejemplo 111c a partir de (*S*)–butan–2–ol y 2,6–dinitrobenzonitrilo en 85,2% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,94 (t, J = 7,6 Hz, 3H), 1,29 (d, J = 6,4 Hz, 1H), 1,69 (m, 2H), 4,72 (m, 1H), 7,74 (dd, J = 6,8, 2,4 Hz, 1H), 7,86 (m, 1H).

Ejemplo 185: (*S*)–4–amino–5–(metoxipropoxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–(3–metoxipropoxi)benzonitrilo (Ejemplo 185a) en 69,3% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,03 (m, 2H), 3,23 (s, 3H), 3,50 (t, J = 5,4 Hz, 2H), 4,18 (t, J = 5,6 Hz, 2H), 6,58 (dd, J = 8,0, 0,8 Hz, 1H), 6,70 (dd, J = 8,4, 0,8 Hz, 1H), 7,43 (t, J = 8,0 Hz, 1H), 78,22 (br s, 1H), 8,31 (br s, 1H), 10,90 (s, 1H). MS 286 (MH^+).

Ejemplo 185a: 2–sulfamoilamino–6–(3–metoxipropoxi)benzonitrilo:

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Preparado como en el Ejemplo 111a a partir de 2–amino–6–(3–metoxipropoxi)benzonitrilo (Ejemplo 185b) en 69,7% de rendimiento. MS 286 (MH^+).

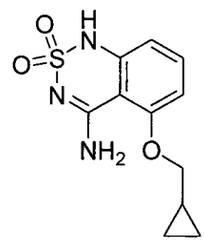
Ejemplo 185b: 2–amino–6–(3–metoxipropoxi)benzonitrilo:

Preparado como en el Ejemplo 111b a partir de 2–(3–metoxipropoxi)–6–nitrobenzonitrilo (Ejemplo 185c) en 100% de rendimiento. MS 207 (MH^+).

Ejemplo 185c: 2–(3–metoxipropoxi)–6–nitrobenzonitrilo:

Preparado como en el Ejemplo 111c a partir de 3–metoxipropan–1–ol y 2,6–dinitrobenzonitrilo en 63,6% de rendimiento. ^{1}H RMN (400 MHz, CDCl3) δ 2,16 (m, 2H), 3,36 (s, 3H), 3,63 (t, J = 5,6 Hz, 2H), 4,29 (t, J = 6,4 Hz, 2H), 7,35 (dd, J = 8,8, 0,8 Hz, 1H), 7,69 (t, J = 8,8 Hz, 1H), (dd, J = 8,4, 0,8 Hz, 1H).

Ejemplo 186: (*S*)–4–amino–5–(ciclopropilmetoxi)–1*H*–benzo[*c*][1,2,6] tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–(ciclopropilmetoxi)benzonitrilo (Ejemplo 186a) en 49,4% de rendimiento. P.f.: 246–247°C. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,39 (m, 2H), 1,60 (m, 2H), 1,36 (m, 1H), 4,02 (d, J = 7,2 Hz, 2H), 6,60 (dd, J = 8,4, 0,8 Hz, 1H), 6,73 (d, J = 8,4 Hz, 1H), 7,45 (t, J = 8,8 Hz, 1H), 7,99 (br d, J = 1,6 Hz, 1H), 8,41 (br d, J = 1,6 Hz, 1H), 10,96 (br s, 1H). MS 268 (MH^+).

Ejemplo 186a: 2–sulfamoilamino–6–(ciclopropilmetoxi)benzonitrilo:

Preparado como en el Ejemplo 111a a partir de 2–amino–6–(ciclopropilmetoxi)benzonitrilo (Ejemplo 186b) en 87,5% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,18 (m, 2H), 0,41 (m, 2H), 1,07 (m, 1H), 3,80 (d, J = 7,2 Hz, 2H), 6,76 (d, J = 8,0 Hz, 1H), 6,96 (d, J = 7,6 Hz, 1H), 7,09 (br s, 2H), 7,37 (t, 8,0 Hz, 1H). MS 268 (MH^+).

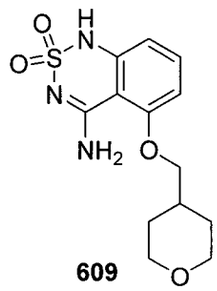
Ejemplo 186b: 2–amino–6–(ciclopropilmetoxi)benzonitrilo:

Preparado como en el Ejemplo 111b a partir de 2–(ciclopropilmetoxi)–6–benzonitrilo (Ejemplo 186c) en 100% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,35 (m, 2H), 0,58 (m, 2H), 1,23 (m, 1H), 3,86 (d, J = 7,6 Hz, 2H), 5,98 (br s, 2H), 6,20 (d, J = 8,0 Hz, 1H), 6,32 (dd, J = 8,8, 0,8 Hz, 1H), 7,17 (t, 8,8 Hz, 1H) MS 189 (MH^+).

Ejemplo 186c: 2–(ciclopropilmetoxi)–6–benzonitrilo:

Preparado como en el Ejemplo 111c a partir de 2,6–dinitrobenzonitrilo y ciclopropilmetanol en 90%. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,40 (m, 2H), 0,62 (m, 2H), 1,29 (m, 1H), 4,14 (d, J = 7,2 Hz, 2H), 7,71 (dd, J = 7,2, 1,2 Hz, 1H), 7,9 (m, 2H).

Ejemplo 187: 4–amino–5–(metoxitetrahidro–2*H*–piran–4–il)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–(tetrahidro–2*H*–piran–4–il)benzonitrilo (Ejemplo 187a) en 92% de rendimiento

como un sólido color crema. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,31 (m, 4H), 1,63 (br m, 4H), 3,31 (br m, 2H), 3,86 (br m, 2H), 4,01 (d, J = 6,8 Hz, 2H), 6,57 (d, J = 8,4 Hz, 1H), 6,71 (d, J = 8,0 Hz, 1H), 7,41 (t, J = 8,0 Hz, 1H), 7,68 (br, 1H), 8,24 (s, 1H), 10,90 (br, 1H). MS 312 (MH^+).

Ejemplo 187a: 2–sulfamoilamino–6–(tetrahidro–2*H*–piran–4–il)benzonitrilo

Preparado como en el Ejemplo 111a a partir de 2–amino–6–((tetrahidro–2*H*–piran–4–il)metoxi)benzonitrilo (Ejemplo 187b) en 51% de rendimiento como un sólido anaranjado. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,35 (m, 2H), 1,66 (br, 2H), 2,01 (br, 1H), 3,32 (br, 2H), 3,87 (br m, 2H), 3,96 (d, J = 6,4 Hz, 2H), 6,92 (d, J = 8,4 Hz, 1H), 7,12 (d, J = 8,4 Hz, 1H), 7,19 (br s, 2H), 7,52 (t, J = 8,4 Hz, 1H), 9,44 (br s, 1H).

Ejemplo 187b: 2–amino–6–((tetrahidro–2*H*–piran–4–il)metoxi)benzonitrilo

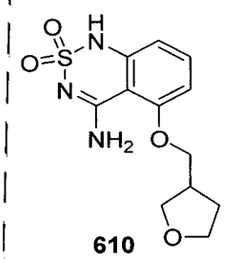
Preparado como en el Ejemplo 111b a partir de 2–nitro–6–((tetrahidro–2*H*–piran–4–il)metoxi)benzonitrilo (Ejemplo 187c) en 80% de rendimiento como un sólido amarillo. ^{1}H RMN (400MHz, DMSO-d_6) δ 1,32 (m, 2H), 1,64 (m, 2H), 1,97 (br, 1H), 3,31 (m, 2H), 3,86 (m, 4H), 5,97 (s, 2H), 6,19 (d, J = 8,4 Hz, 1H), 6,31 (d, 1H), 7,15 (t, J = 8,4 Hz, 1H).

Ejemplo 187c: 2–nitro–6–((tetrahidro–2*H*–piran–4–il)metoxi)benzonitrilo:

A una solución de tetrahidropiran–4–metanol (782 mg, 6,73 mmol) en THF (25 mL), se le adicionó lentamente nBuLi 1,38 M (4,13 mL, 5,70 mmol) en hexano a -78ºC bajo nitrógeno. A la hora se adicionó una solución de 2,6–dinitrobenzonitrilo (1,00 g, 5,18 mmol) en THF (25 mL). La reacción se agitó bajo N_2 durante la noche a ta, luego se inactivó con agua (100 mL). El precipitado se recogió mediante filtración para proporcionar 2–nitro–6–((tetrahidro–2*H*–piran–4–il)metoxi)benzonitrilo (1,13g, 83%) como un sólido marrón claro. ^{1}H RMN (400MHz, DMSO-d_6) δ 1,68 (m, 2H), 2,06 (br, 1H), 3,33 (m, 2H), 3,88 (m, 2H), 4,11 (d, J = 6,0 Hz, 2H), 7,72 (d, J = 6,0 Hz, 1H), 7,89-7,85 (m, 2H).

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Ejemplo 188: 4–amino–5–(metoxitetrahidrofuran–3–il)–1*H*–benzo[*c*][1,2,6] tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–(metoxitetrahidrofuran–3–il)benzonitrilo (Ejemplo 188a) en 26% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,64 (m, 1H), 1,99 (m, 1H), 2,73 (m, 1H), 3,56 (m, 2H), 3,67 (m, 1H), 3,75 (m, 1H), 4,04 (m, 2H), 6,51 (d, J = 8,4 Hz, 1H), 6,62 (d, J= 8,4 Hz, 1H), 7,34 (t, J = 8,0 Hz, 1H), 7,70 (br s, 1H), 8,09 (br s, 1H), 10,92 (br s, 1H), MS 298 (M H$^+$).

Ejemplo 188a: 2–sulfamoilamino–6–(metoxitetrahidrofuran–3–il)benzonitrilo

Preparado como en el Ejemplo 111a a partir de 2–amino–6–((tetrahidrofuran–3–il)metoxi)benzonitrilo (Ejemplo 188b) en 14% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,62 (m, 1H), 1,96 (m, 1H), 2,43 (m, 1H), 2,61 (m, 1H), 3,48 (m, 1H), 3,60 (m, 1H), 3,71 (m, 2H), 3,99 (m, 2H), 6,90 (d, J = 8,8 Hz, 1H), 7,09 (d, J = 8,0 Hz, 1H), 7,19 (s, 1H), 7,49 (t, J = 8,4 Hz, 1H), 9,42 (s, 1H).

Ejemplo 188b: 2–amino–6–((tetrahidrofuran–3–il)metoxi)benzonitrilo:

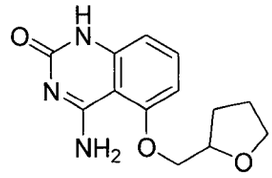
Preparado como en el Ejemplo 111b a partir de 2–nitro–6–((tetrahidrofuran–3–il)metoxi)benzonitrilo (Ejemplo 188c) en 99% de rendimiento como un aceite marrón dorado. MS 219 (MH$^+$).

Ejemplo 188c: 2–nitro–6–((tetrahidrofuran–3–il)metoxi)benzonitrilo:

Preparado como en el Ejemplo 166d a partir de 2,6–dinitrobenzonitrilo y 3–hidroximetiltetrahidrofurano en 48% de rendimiento como un sólido anaranjado-

rojo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,68 (m, 1H), 2,00 (m, 1H), 2,70 (m, 1H), 3,54 (m, 1H), 3,66 (m, 1H), 3,76 (m, 2H), 4,03 (m, 1H), 4,19 (m, 1H), 7,73 (d, J = 7,6 Hz, 1H), 7,90-7,95 (m, 2H).

Ejemplo 189: 4–amino–5–((tetrahidrofuran–2–il)metoxi)quinazolin–2(1*H*)–ona



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Preparada como en el Ejemplo 111 a partir de *N*–(2–ciano–3–((tetrahidrofuran–2–il)metoxi)fenilcarbamoil)benzamida (Ejemplo 189a) en 39% de rendimiento. ^{1}H RMN (400 MHz, *d*-DMSO) δ 1,65 (br m, 1H), 1,85 (br m, 2H), 1,99 (br m, 1H), 3,71 (m, 2H), 3,78 (m, 1H), 3,98 (m, 1H), 6,70-6,67 (m, 2H), 7,42 (t, J = 8,0 Hz, 1H), 7,62 (s, 1H), 7,88 (s, 1H), 10,62 (s, 1H).

Ejemplo 189a: *N*–(2–ciano–3–((tetrahidrofuran–2–il)metoxi)fenilcarbamoil) benzamida

Preparada como en el Ejemplo 146a a partir de 2–amino–6–((tetrahidrofuran–2–il)metoxi)benzonitrilo (Ejemplo 189b) en 45% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, *d*-DMSO) δ 1,98-1,74 (m, 4H), 3,54 (m, 1H), 3,69 (m, 1H), 4,20-4,07 (m, 3H), 6,97 (d, J = 8,8 Hz, 1H), 7,67-7,51 (m, 4H).

Ejemplo 189b: 2–amino–6–((tetrahidrofuran–2–il)metoxi)benzonitrilo

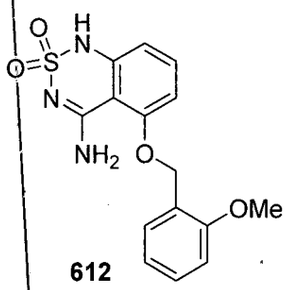
Preparado como en el Ejemplo 111b a partir de 2–nitro–6–((tetrahidrofuran–2–il)metoxi)benzonitrilo (Ejemplo 189c) en 92% de rendimiento como un aceite celeste claro. ^{1}H RMN (400 MHz, MeOD) δ 1,97-1,68 (m, 4H), 3,75-3,64 (m, 1H), 3,80-3,75 (m, 1H), 3,98-3,90 (m, 2H), 4,15-4,12 (m, 1H), 5,96 (s, 1H), 6,18 (d, J = 8,0 Hz, 1H), 6,31 (d, J = 8,0 Hz, 1H), 7,14 (t, J = 8,4 Hz, 1H).

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Ejemplo 189c: 2–nitro–6–((tetrahidrofuran–2–il)metoxi)benzonitrilo:

Preparado como en el Ejemplo 166d a partir de 2,6–dinitrobenzonitrilo y tetrafurfuril alcohol en 68% de rendimiento. ^{1}H RMN (400 MHz, MeOD) δ 2,10-1,70 (m, 7H), 3,68-3,66 (m, 1H), 3,80-3,78 (m, 1H), 4,29-4,20 (m, 3H), 7,72 (d, J = 6,0 Hz, 1H), 7,90-7,84 (m, 2H).

Ejemplo 190: 4–amino–5–(2–metoxibenciloxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–(4–metoxibenciloxi)benzonitrilo (Ejemplo 190a) en 85% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,81 (s, 3H), 5,25 (s, 2H), 6,59 (d, J = 8,4 Hz, 1H), 6,86 (d, J = 8,0 Hz, 1H), 6,96 (t, J = 7,2 Hz, 1H), 7,09 (d, J = 8,0 Hz, 1H), 7,37 (t, J = 8,0 Hz, 1H), 7,46-7,42 (m, 2H), 7,91 (s, 1H), 8,31 (s, 1H), 10,96 (s, 1H). MS 334 (MH^+).

Ejemplo 190a: 2–sulfamoilamino–6–(2–metoxibenciloxi)benzonitrilo

Preparado como en el Ejemplo 111a a partir de 2–amino–6–((tetrahidrofuran–2–il)metoxi)benzonitrilo (Ejemplo 190b) en 23% de rendimiento. ^{1}H RMN (400 MHz, *d*-DMSO) δ 3,80 (s, 3H), 6,88 (d, J = 8,4 Hz, 1H), 6,88 (d, J = 8,1 Hz 1H), 6,96 (t, J = 7,6 Hz, 1H), 7,06 (d, J = 8,0 Hz, 2H), 7,16 (d, J = 8,4 Hz, 1H), 7,39-7,33 (m, 5H), 7,45 (d, J = 7,2 Hz, 1H), 11,20 (s, 1H).

Ejemplo 190b: 2–amino–6–(2–metoxibenciloxi)benzonitrilo

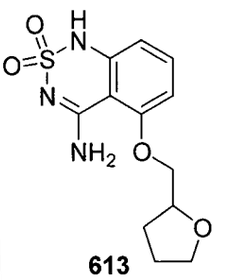
882

Preparado como en el Ejemplo 111b a partir de 2–nitro–6–(2–metoxibenciloxi)benzonitrilo (Ejemplo 190c) en 56% de rendimiento. ^{1}H RMN (400 MHz, MeOD) δ 3,79 (s, 3H), 5,04 (s, 2H), 6,30-6,26 (m, 2H), 7,06-6,94 (m, 3H), 7,33-7,28 (m, 3H), 7,54 (s, 1H).

Ejemplo 190c: 2–nitro–6–(2–metoxibenciloxi) benzonitrilo

Preparado como en el Ejemplo 111c a partir de 2,6–dinitrobenzonitrilo y 2–metoxibencil alcohol en 58% de rendimiento. ^{1}H RMN (400 MHz, DMSO) δ 3,82 (s, 3H), 5,34 (s, 2H), 6,99 (t, J = 7,6 Hz, 1H), 7,08 (d, J = 8,4 Hz, 1H), 7,37 (t, J = 8,4 Hz, 1H), 7,46 (d, J = 6,0 Hz, 1H), 7,81 (d, J = 7,6 Hz, 1H), 7,93-7,87 (m, 2H).

Ejemplo 191: 4–amino–5–(metoxitetrahidrofuran–2–il)–1*H*–benzo[*c*][1,2,6] tiadiazin–2,2–dióxido



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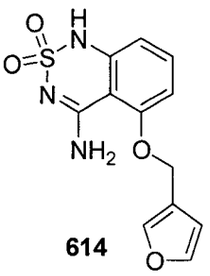
Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–(metoxitetrahidrofuran–2–il)benzonitrilo (Ejemplo 191a) en 100% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,65 (m, 1H), 1,86 (m, 1H), 1,98 (m, 1H), 3,69 (m, 1H), 3,78 (m, 1H), 3,98 (m, 1H) 4,25 (m, 1H), 6,61 (d, J = 7,2 Hz, 1H), 6,74 (d, J = 8,0 Hz, 1H).

Ejemplo 191a: 2–sulfamoilamino–6–(metoxitetrahidrofuran–2–il)benzonitrilo

Preparado como en el Ejemplo 111a a partir de 2–amino–6–((tetrahidrofuran–2–il)metoxi)benzonitrilo (Ejemplo 189b) en 79% de rendimiento como un sólido amarillo claro. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,02-1,68 (m, 2H),

3,66 (m, 1H), 3,81-3,76 (m, 1H), 4,20-4,03 (m, 3H), 6,93 (d, *J* = 8,4 Hz, 1H), 7,12 (d, *J* = 8,4 Hz, 1H), 7,23 (s, 1H), 7,53 (t, *J* = 8,4 Hz, 1H), 9,34 (br s, 1H).

Ejemplo 192: 4–amino–5–(furan–3-ilmetoxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–(furan–3-ilmetoxi)benzonitrilo (Ejemplo 192a) en 45% de rendimiento como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 5,11 (s, 2H), 6,54 (d, *J* = 0,4 Hz, 1H), 6,56 (s, 1H), 6,80 (d, *J* = 8,8 Hz, 1H), 7,39 (t, *J* = 8,4 Hz, 1H), 7,64 (s, 1H), 7,74 (s, 1H), 7,81 (s, 1H), 8,23 (s, 1H), 10,90 (s, 1H). MS 294 (MH^+).

Ejemplo 192a: 2–sulfamoilamino–6–(furan–3-ilmetoxi)benzonitrilo

Preparado como en el Ejemplo 111a a partir de 2–amino–6–(furan–3-ilmetoxi)benzonitrilo (Ejemplo 192b) en 57% de rendimiento como un sólido blancuzco. ^{1}H RMN (400 MHz, *d*-DMSO) δ 5,04 (s, 2H), 6,62 (s, 1H), 6,88 (d, *J* = 8,8 Hz, 1H), 7,15 (d, *J* = 8,1, 0,8 Hz, 1H), 7,35 (d, *J* = 8,8 Hz, 1H), 7,39–7,32 (m, 2H), 7,67 (s, 1H), 7,79 (s, 1H), 7,86 (s. 1H), 7,93 (s, 1H), 10,91 (s, 1H).

Ejemplo 192b: 2–amino–6–(furan–3-ilmetoxi)benzonitrilo

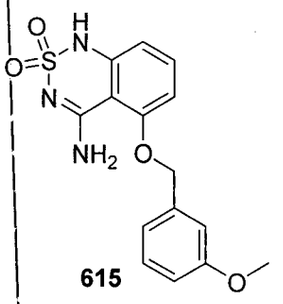
Preparado como en el Ejemplo 111b a partir de 2–nitro–6–(furan–3-ilmetoxi)benzonitrilo (Ejemplo 192c) en 21% de rendimiento como un aceite amarillo claro. ^{1}H RMN (400 MHz, *d*-DMSO) δ 4,92 (s, 2H), 6,31-6,26 (m, 2H), 6,59 (s, 1H), 6,99 (t, *J* = 8,4 Hz, 1H), 7,27 (s, 1H), 7,45 (s, 1H), 7,66 (s, 1H), 7,76 (s, 1H).

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Ejemplo 192c: 2–nitro–6–(furan–3-ilmetoxi)benzonitrilo

Preparado como en el Ejemplo 111c a partir de 2,6–dinitrobenzonitrilo y 3–furanmetanol en 100% de rendimiento. ^{1}H RMN (400 MHz, *d*-DMSO) δ 5,27 (s, 2H), 6,59 (s, 1H), 7,69 (s, 1H), 7,91-7,84 (m, 4H).

Ejemplo 193: 4–amino–5–(3–metoxibenciloxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–(3–metoxibenciloxi)benzonitrilo (Ejemplo 193a) en 54% de rendimiento. ^{1}H RMN (400 MHz, *d*-DMSO) δ 3,74 (s, 3H), 5,27 (s, 2H), 6,59 (d, J = 8,0 Hz, 1H), 6,79 (d, J = 8,0 Hz, 1H), 6,90 (d, J = 8,0 Hz, 1H), 7,04 (d, J = 7,2 Hz, 1H), 7,08 (s, 1H), 7,31 (t, J = 8,4 Hz, 1H), 7,42 (t, J = 8,0 Hz, 1H), 7,89 (br s, 1H), 8,32 (br s, 1H), 10,96 (br s, 1H). MS 334 (MH^+).

Ejemplo193a: 2–sulfamoilamino–6–(3–metoxibenciloxi)benzonitrilo

Preparado como en el Ejemplo 111a a partir de 2–amino–6–(3–metoxibenciloxi)benzonitrilo (Ejemplo 193b) en 17% de rendimiento como un sólido blanco. MS 334 (MH^+).

Ejemplo 193b: 2–amino–6–(3–metoxibenciloxi)benzonitrilo

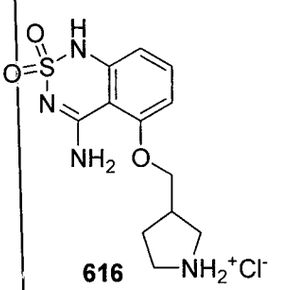
A una mezcla de 2–nitro–6–(3–metoxibenciloxi)benzonitrilo (Ejemplo 193c) (480 mg, 1,69 mmol) en acetona:agua 5:1 (9 mL) se le adicionaron zinc (552 mg, 8,44 mmol) y cloruro de amonio (911mg, 16,9 mmol). La reacción se agitó a

temperatura ambiente durante 30 minutos, luego se filtró y se concentró. El residuo se purificó mediante cromatografía flash (EtOAc:Hexano 55:45) para proporcionar 2–amino–6–(benciloxi)benzonitrilo (337 mg, 78%). ^{1}H RMN (400 MHz, *d*-DMSO) δ 3,73 (s, 3H), 5,04 (s, 1H), 6,27 (d, J = 8,0 Hz, 1H), 6,31 (d, J = 8,4 Hz, 1H), 7,06-6,97 (m, 3H), 7,27 (t, J = 8,0 Hz, 1H), 7,36 (s, 1H), 7,55 (s, 1H).

Ejemplo 193c: 2–(3–metoxibenciloxi)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 111c a partir de 2,6–dinitrobenzonitrilo y 3–metoxibencilalcohol en 83% de rendimiento. ^{1}H RMN (400 MHz, *d*-DMSO) δ 3,75 (s, 3H), 5,38 (s, 2H), 6,91 (d, J = 8,0 Hz, 1H), 7,04 (d, J = 7,6 Hz, 1H), 7,07 (s, 1H), 7,33 (t, J=8,0 Hz, 1H), 7,78 (d, J = 8,8 Hz, 4H), 7,93-7,87 (m, 2H).

Ejemplo 194: Cloruro de 4–(2–(4–amino–*1H*–benzo[*c*][1,2,6]tiadiazin–2,2–dioxido–5–iloxi)metil)pirrolidinio



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Preparado como en el Ejemplo 166 a partir de 3–(2–(4–amino–*1H*–benzo[*c*][1,2,6]tiadiazin–2,2–dioxido–5–iloxi)metil)pirrolidin–1–carboxilato de *terc*–butilo (Ejemplo 194a) en 27% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,72 (m, 1H), 2,07 (m, 1H), 2,52 (m, 1H), 2,64 (m, 1H), 2,94-2,74 (m, 3H), 3,79 (m, 2H), 6,26 (d, J = 8,0 Hz, 1H), 6,37 (d, J = 8,8 Hz, 1H), 7,09 (t, J = 8,0 Hz, 1H), 7,31 (br s, 1H), 7,96 (br s, 1H), 9,03 (br s, 1H).

Ejemplo 194a: 3–(2–(4–amino–*1H*–benzo[*c*][1,2,6]tiadiazin–2,2–dioxido–5–iloxi)metil)pirrolidin–1–carboxilato de *terc*–butilo

Preparado como en el Ejemplo 111 a partir de *terc*–butil–3–((2–ciano–3–(sulfamoilmetil)fenoxi)metil) pirrolidin–1–carboxilato (Ejemplo 194b) en 94% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,37 (s, 9H), 1,66 (br m, 1H), 1,97 (br m, 1H), 2,78 (br m, 1H), 3,48-3,20 (br m, 4H), 4,12 (br, m 2H), 6,60 (d, J = 8,0 Hz, 1H), 6,74 (d, J = 8,4Hz, 1H), 7,44 (t, J = 8,4 Hz, 1H), 7,70 (s, 1H), 8,33 (s, 1H), 10,95 (s, 1H).

Ejemplo 194b: 3–((2–ciano–3–(sulfamoilamino)fenoxi)metil)pirrolidin–1–carboxilato de *terc*–butilo

Preparado como en El ejemplo 111a a partir de 3–((3–amino–2–cianofenoxi)metil)pirrolidin–1–carboxilato de *terc*–butilo (Ejemplo 194c) en 47% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,37 (s, 9H), 1,70 (br, 1H), 1,97 (br, 1H), 2,63 (br, 1H), 3,47-2,98 (br m, 4H), 4,08 (br m, 2H), 6,94 (d, J = 8,8 Hz, 1H), 7,14 (d, J = 8,4 Hz, 1H), 7,24 (s, 1H), 7,48 (s, 1H), 7,54 (t, J = 8,0, 1H), 9,48 (br s, 1H).

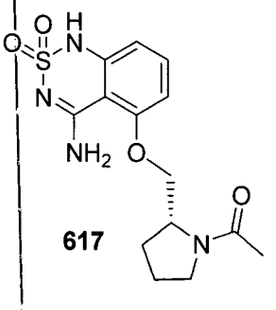
Ejemplo 194c: 3–((3–amino–2–cianofenoxi)metil)pirrolidin–1–carboxilato de *terc*–butilo

Preparado como en el Ejemplo 111b a partir de *terc*–butil–((2–ciano–3–nitorfenoxi)metil)pirrolidin–1–carboxilato (Ejemplo 194d) en 100% de rendimiento como un aceite claro. ^{1}H RMN (400MHz, DMSO-d_6) δ 1,37 (s, 9H), 1,69 (br, 1H), 1,96 (br, 1H), 2,59 (br, 1H), 3,07 (br, 1H), 3,23 (br, 1H), 3,35 (br, 1H), 3,40 (br, 1H), 3,96 (m, 2H), 5,98 (s, 2H), 6,20 (d, J = 8,0 Hz, 1H), 6,32 (d, J = 8,0 Hz, 1H), 7,15 (t, J = 8,4 Hz, 1H).

Ejemplo 194d: *terc*–butil–((2–ciano–3–nitorfenoxi)metil)pirrolidin–1–carboxilato

Preparado como en el Ejemplo 166d a partir de 2,6–dinitrobenzonitrilo y 3–(hidroximetil)pirrolidin–1–carboxilato de *terc*–butilo en 69% de rendimiento como un sólido amarillo. MS 347 (MH^+).

Ejemplo 195: (*R*)–4–amino–5–((1–acetilpirrolidin–2–il)metoxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 176 a partir de (*R*)–2–amino–6–((1–acetilpirrolidin–2–il)metoxi)benzonitrilo (Ejemplo 195a) en 31% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,90 (m, 4H), 2,00 (s, 3H), 3,49 (m, 2H), 4,09 (dd, J = 9,7, 6,1 Hz, 1H), 4,24 (dd, J = 9,8, 5,7 Hz, 1H), 4,41 (m, 1H), 6,62 (d, J = 8,2 Hz, 1H), 6,87 (d, J = 8,5 Hz, 1H), 7,46 (t, J = 8,3 Hz, 1H), 8,12 (br s, 1H), 8,33 (br s, 1H), 10,93 (br s, 1H). MS 339 (MH^+).

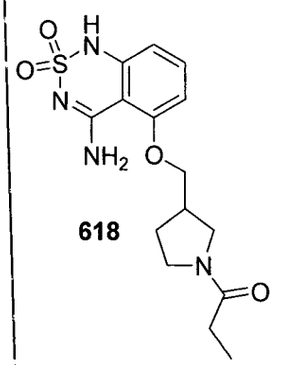
Ejemplo 195a: (*R*)–2–amino–6–((1–acetilpirrolidin–2–il)metoxi)benzonitrilo

Preparado como en el Ejemplo 111b a partir de (*R*)–2–((1–acetilpirrolidin–2–il)metoxi)–6–nitrobenzonitrilo (Ejemplo 195b) en 77% de rendimiento como un jarabe claro. MS 260 (MH^+).

Ejemplo 195b: (*R*)–2–((1–acetilpirrolidin–2–il)metoxi)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 176b a partir de cloruro de (*R*)–2–((2–ciano–3–nitrofenoxi)metil)pirrolidinio y cloruro de acetilo en 100% de rendimiento como un jarabe amarillo. MS 290 (MH^+).

Ejemplo 196: 4–amino–5–(metoxi–3–pirrolidin–1–propionil)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–((1–propionilpirrolidin–3–il)metoxibenzonitrilo (Ejemplo 196a) en 29% de rendimiento como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,95 (t, J = 7,6 Hz, 3H), 1,66 (m, 1H), 1,77 (m, 1H), 1,97 (m, 1H), 2,05 (m, 1H), 2,21 (q, J = 8,0 Hz, 2H), 2,74 (m, 1H), 2,86 (m, 1H), 3,63-3,23 (m, 4H), 4,13 (m, 2H), 6,60 (d, J = 8,0 Hz, 1H), 6,75 (d, J = 8,4 Hz, 1H), 7,44 (t, J = 8,0 Hz, 1H), 7,72 (s, 1H), 8,37-8,32 (m, 1H), 10,94 (s, 1H).

Ejemplo 196a: 2–sulfamoilamino–6–((1–propionilpirrolidin–3–il)metoxi-benzonitrilo

Preparado como en el Ejemplo 111a a partir de 2–amino–6–((1–propionilpirrolidin–3–il)metoxi)benzonitrilo (Ejemplo 196b) en 27% de rendimiento como un sólido blanco. MS 353 (MH^+).

Ejemplo 196b: 2–amino–6–((1–propionilpirrolidin–3–il)metoxi)benzonitrilo:

Preparado como en el Ejemplo 111b a partir de 2–nitro–6–((1–propionilpirrolidin–3–il)metoxi)benzonitrilo (Ejemplo 196c) en 100% de rendimiento como un aceite claro. MS 274 (MH^+).

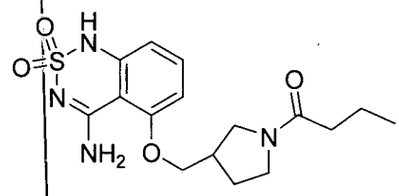
Ejemplo 196c: 2–nitro–6–((1–propionilpirrolidin–3–il)metoxi)benzonitrilo:

Preparado como en el Ejemplo 176b a partir de clorhidrato de 2–nitro–6–(pirrolidin–3-ilmetoxi)benzonitrilo (Ejemplo 196d) y cloruro de propionilo en 51% como un sólido amarillo. MS 304 (MH^+).

Ejemplo 196d: Clorhidrato de 2–nitro–6–(pirrolidin–3-ilmetoxi)benzonitrilo:

Preparado como en el Ejemplo 166 a partir de *terc*–butil–((2–ciano–3–nitrofenoxi)metil)pirrolidin–1–carboxilato (Ejemplo 194d) en 100% de rendimiento como un sólido amarillo. MS 248 (MH^+).

Ejemplo 197: 4–amino–5–(metoxi–3–pirrolidin–1–butiril)–1*H*–benzo[*c*][1,2,6] tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–((1–butirilpirrolidin–3–il)metoxibenzonitrilo (Ejemplo 197a) en 73% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,86 (t, J = 7,6 Hz, 3H), 1,48 (q, J = 7,6 Hz, 2H), 1,65 (m, 1H), 1,76 (m, 1H), 1,97 (m, 1H), 2,05 (m, 1H), 2,17 (t, J = 7,2 Hz, 2H), 2,74 (m, 1H), 2,85 (m, 1H), 3,10 (m, 1H), 3,64-3,23 (m, 4H), 4,12 (m, 1H), 6,60 (d, J = 8,0 Hz, 1H), 6,75 (d, J = 8,8 Hz, 1H), 7,44 (t, J = 8,4 Hz, 1H), 7,71 (s, 1H), 8,35-8,32 (m, 1H), 10,94 (s, 1H).

Ejemplo 197a: 2–sulfamoilamino–6–((1–butirilpirrolidin–3–il)metoxibenzonitrilo:

Preparado como en el Ejemplo 111a a partir de 2–amino–6–((1–butirilpirrolidin–3–il)metoxi)benzonitrilo (Ejemplo 197b) en 19% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,85 (t, J = 7,6 Hz, 3H), 1,48 (q, J = 7,6 Hz, 2H), 2,13-1,64 (m, 2H), 2,17 (m, 2H), 2,75-2,53 (m, 2H), 3,65-3,18 (m, 4H), 4,09 (m, 2H), 6,94 (m, 1H), 7,13 (m, 1H), 7,25 (s, 1H), 7,54 (m, 1H), 9,45 (m, 1H).

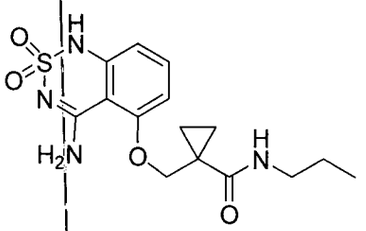
Ejemplo 197b: 2–amino–6–((1–butirilpirrolidin–3–il)metoxi)benzonitrilo:

Preparado como en El ejemplo 111b a partir de 2–nitro–6–((1–butirilpirrolidin–3–il)metoxi)benzonitrilo (Ejemplo 197c) en 100% de rendimiento como un aceite marrón. MS 288 (MH^+).

Ejemplo 197c: 2–nitro–6–((1–butirilpirrolidin–3–il)metoxi)benzonitrilo:

Preparado como en el Ejemplo 176b a partir de clorhidrato de 2–nitro–6–(pirrolidin–3-ilmetoxi)benzonitrilo (Ejemplo 196d) y cloruro de butirilo en 100% de rendimiento como un sólido anaranjado. MS 318 (MH^+).

Ejemplo 198: (E)–4–amino–5–(1–(propilcarbamoil)ciclopropilmetoxi)–1H–benzo[c][1,2,6]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 1–((2–ciano–3–(sulfamoilamino)fenoxi)metil)–N–propilciclopropanocarboxamida (Ejemplo 198a) en 94% de rendimiento como un sólido blanco. ^{1}H-RMN (400 MHz, DMSO-d_6) δ 10,95 (s amplio, 1H), 8,35 (s amplio, 1H), 7,95 (s amplio, 1H), 7,76 (t, J = 5,2 Hz, 1H), 7,45 (t, J = 8,0 Hz, 1H), 6,69 (d, J = 8,8 Hz, 1H), 6,61 (d, J = 7,6 Hz, 1H), 4,22 (s, 2H), 3,01 (q, J = 6,4 Hz, 2H), 1,40 (hex, J = 6,8 Hz, 2H), 1,12-1,18 (m, 2H), 0,88-0,95 (m, 2H), 0,80 (t, J = 7,6 Hz, 3H). MS 353 (MH^+).

Ejemplo 198a: 1–((2–ciano–3–(sulfamoilamino)fenoxi)metil)–N–propilciclopropanocarboxamida

Preparada como en el Ejemplo 111a a partir de 1–((3–amino–2–cianofenoxi)metil)–N–propilciclopropanocarboxamida (Ejemplo 198b) y cloruro de

sulfamoilo en 78% de rendimiento como un sólido blanco. ^{1}H-RMN (400 MHz, DMSO-d_6) δ 9,45 (s amplio, 1H), 7,51-7,61 (m, 2H), 7,26 (s amplio, 2H), 7,16 (d, J = 8,0 Hz, 1H), 6,91 (d, J = 8,4 Hz, 1H), 4,24 (s, 2H), 3,04 (q, J = 6,4 Hz, 2H), 1,43 (hex, J = 7,6 Hz, 2H), 1,08–1,14 (m, 2H), 0,83-0,88 (m, 2H), 0,82 (t, J = 7,2 Hz, 3H).

Ejemplo 198b: 1–((3–amino–2–cianofenoxi)metil)–N–propilciclopropano-carboxamida

Una solución de 1–(hidroximetil)–N–propilciclopropanocarboxamida (Ejemplo 198c) (0,67 g, 4,25 mmol) en THF anhidro (10 mL) se trató con NaH (0,17 g, 4,25 mmol, 60% suspensión en aceite mineral) a 0°C, bajo una atmósfera de nitrógeno. La mezcla obtenida se agitó a 0°C durante 10 min y a ta durante 30 min. Luego, se adicionó una solución de 2–amino–6–fluorbenzonitrilo (0,53 g, 3,86 mmol) en THF (5,0 mL) y la mezcla obtenida se calentó a reflujo durante la noche. La mezcla fría se inactivó con solución acuosa saturada de NH_4Cl (20 mL) y se extrajo con EtOAc (3x50 mL). El extracto combinado se lavó con salmuera, se secó sobre $MgSO_4$ anhidro, se filtró y se evaporó. El residuo se purificó mediante cromatografía sobre gel de sílice utilizando gradiente hexanos → hexanos/EtOAc (4:6), para proporcionar 0,75 g (71%) del compuesto del título como un sólido amarillo. ^{1}H-RMN (400 MHz, DMSO-d_6) δ 7,51 (t, J = 6,0 Hz, 1H), 7,17 (t, J = 8,0 Hz, 1H), 6,34 (d, J = 8,4 Hz, 1H), 6,19 (d, J = 8,4 Hz, 1H), 5,97 (s amplio, 2H), 4,13 (s, 2H), 3,04 (q, J = 6,4 Hz, 2H), 1,43 (hex, J = 6,8 Hz, 2H), 1,05-1,11 (m, 2H), 0,78-0,86 (m, 5H).

Ejemplo 198c: 1–(hidroximetil)–N–propilciclopropanocarboxamida

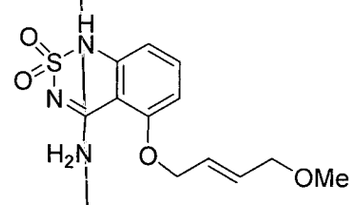
A una solución de 1–(propilcarbamoil)ciclopropanocarboxilato de etilo (Ejemplo 198d) (1,65 g, 8,27 mmol) en EtOH (70 mL) se le adicionó $NaBH_4$ (0,97 g, 25,64 mmol) a ta. La mezcla obtenida se agitó a ta durante 2 días, se inactivó con HCl 1,5 M y se concentró bajo presión reducida. La mezcla concentrada se

extrajo con EtOAc (4x70 mL), el extracto combinado se lavó con $NaHCO_3$ saturado y salmuera, y se secó sobre $MgSO_4$. El filtrado se evaporó y el residuo se purificó mediante cromatografía sobre gel de sílice utilizando el solvente gradiente hexanos → hexanos/EtOAc (1:9), para proporcionar 1,14 g (88%) del producto como un sólido blanco. ^{1}H-RMN (400 MHz, DMSO-d_6) δ 7,49 (s amplio, 1H), 5,09 (s amplio, 1H), 3,49 (s, 2H), 3,05 (q, J = 6,4 Hz, 2H), 1,41 (hex, J = 7,6 Hz, 2H), 0,86-0,91 (m, 2H), 0,83 (t, J = 7,2 Hz, 3H), 0,55-0,60 (m, 2H).

Ejemplo 198d: 1–(propilcarbamoil)ciclopropanocarboxilato de etilo

A una solución de ácido1–(etoxicarbonil)ciclopropancarboxílico (Wheeler, T. N.; Ray, J. A. *Synthetic Communications* **1988**, *18(2)*, 141) (1,52 g, 9,62 mmol) y *n*–propilamina (0,63 g, 10,58 mmol) en DMF anhidra (65 mL) a ta, se le adicionaron bajo una atmósfera de nitrógeno $NaHCO_3$ (4,04 g, 48,11 mmol), clorhidrato de N–(3–dimetilaminopropil)–N'–etilcarbodiimida (2,21 g, 11,54 mmol) e hidrato de 1–hidroxibenzotriazol (1,77 g, 11,54 mmol). Luego de agitarse a ta durante la noche, la mezcla se particionó entre agua (100 mL) y EtOAc (300 mL). La fase orgánica se separó, se lavó con agua y salmuera, y se secó sobre $MgSO_4$ anhidro. El filtrado se evaporó para proporcionar 1,65 g (86%) del producto crudo el cual se utilizó en la etapa siguiente sin purificación. ^{1}H-RMN (400 MHz, DMSO-d_6) δ 8,33 (s amplio, 1H), 4,08 (q, J = 6,8 Hz, 2H), 3,07 (q, J = 6,4 Hz, 2H), 1,43 (hex, J = 6,4 Hz, 2H), 1,31 (s, 4H), 1,17 (t, J = 6,4 Hz, 3H), 0,85 (t, J = 7,2 Hz, 3H).

Ejemplo 199: (*E*)–4–amino–5–(4–metoxibut–2–eniloxi)–1H–benzo[c][1,2,6] tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–(4–metoxibut–2–eniloxi)benzonitrilo (Ejemplo 199a) en 91% de rendimiento como un sólido blanco. ^{1}H-RMN (400 MHz, DMSO-d_6) δ 10,94 (s amplio, 1H), 8,34 (s amplio, 1H), 7,90 (s amplio, 1H), 7,45 (t, J = 8,4 Hz, 1H), 6,75 (d, J = 7,6 Hz, 1H), 6,61 (d, J = 8,0 Hz, 1H), 5,88–6,02 (m, 2H), 4,75-4,81 (m, 2H), 3,88-3,93 (m, 2H), 3,22 (s, 3H). MS 298 (MH^+).

Ejemplo 199a: 2–sulfamoilamino–6–(4–metoxibut–2–eniloxi)benzonitrilo

Preparado como en el Ejemplo 111a a partir de (*E*)–2–amino–6–(4–metoxibut–2–eniloxi)benzonitrilo (Ejemplo 199b) en 93% de rendimiento como un sólido blanco. ^{1}H-RMN (400 MHz, DMSO-d_6) δ 9,46 (s amplio, 1H), 7,56 (t, J = 8,4 Hz, 1H), 7,26 (s amplio, 2H), 7,15 (d, J = 8,0 Hz, 1H), 6,96 (d, J = 8,8 Hz, 1H), 5,84-6,00 (m, 2H), 4,68-4,76 (m, 2H), 3,89-3,95 (m, 2H), 3,23 (s, 3H).

Ejemplo 199b: (*E*)–2–amino–6–(4–metoxibut–2–eniloxi)benzonitrilo

A una solución de (*E*)–2–(4–metoxibut–2–eniloxi)–6–nitrobenzonitrilo (Ejemplo 199c) (0,25 g, 1,00 mmol) en una mezcla de AcOH, EtOH y agua (33 mL, 1:1:1) se le adicionó polvo de hierro (0,56 g, 10,00 mmol) a ta. La mezcla obtenida se agitó a ta durante 20 min, luego se calentó hasta 50°C durante 15 min adicionales, y se dejó enfriar. La suspensión se concentró bajo presión reducida; el residuo se trató con agua (50 mL) y se extrajo con EtOAc (4x50 mL). El extracto combinado se lavó con $NaHCO_3$ acuoso saturado y salmuera, y se secó sobre $MgSO_4$ anhidro. El filtrado se evaporó y el residuo se purificó mediante cromatografía flash sobre gel de sílice utilizando gradiente hexanos → hexanos/EtOAc (1:1), para proporcionar 0,19 g (86%) del compuesto del título como un sólido blanco. ^{1}H-RMN (400 MHz, DMSO-d_6) 7,17 (t, J = 8,4 Hz, 1H), 6,34 (d, J = 8,8 Hz, 1H), 6,22 (d, J = 8,4 Hz, 1H), 6,00 (s amplio, 2H), 5,82-5,96 (m, 2H), 4,56-4,62 (m, 2H), 3,88-3,93 (m, 2H), 3,23 (s, 3H).

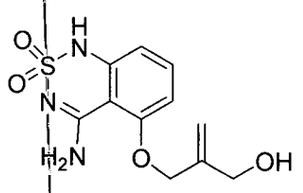
Ejemplo 199c: (*E*)–2–(4–metoxibut–2–eniloxi)–6–nitrobenzonitrilo

A una solución de (*E*)–2–(4–hidroxibut–2–eniloxi)–6–nitrobenzonitrilo (Ejemplo 199d) (0,50 g, 2,13 mmol) y 2,6–di–*terc*–butil–4–metilpiridina (2,18 g, 10,65 mmol) en CH_2Cl_2 (15,0 mL) a ta, se le adicionó bajo una atmósfera de nitrógeno tetrafluorborato de trimetiloxonio (1,58 g, 10,65 mmol). Luego de 1 h a ta, la reacción se inactivó con agua (50 mL) y se extrajo con EtOAc (4x50 mL). El extracto combinado se lavó con agua, HCl 1,5 M, $NaHCO_3$ acuoso saturado y salmuera, y se secó sobre $MgSO_4$ anhidro. El filtrado se evaporó y el residuo se purificó mediante cromatografía sobre gel de sílice utilizando el solvente gradiente hexanos → hexanos/EtOAc (3:7), para proporcionar 0,25 g (72%) del compuesto del título como un sólido amarillo. ^{1}H-RMN (400 MHz, DMSO-d_6) δ 7,84-7,92 (m, 2H), 7,68-7,73 (m, 1H), 5,82-6,03 (m, 2H), 4,82-4,88 (m, 2H), 3,87-3,93 (m, 2H), 3,21 (s, 3H).

Ejemplo 199d: (*E*)–2–(4–hidroxibut–2–eniloxi)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 166d a partir de (*E*)–but–2–en–1,4–diol (Miller, A. E. G.; Biss, J. W.; Schwartzman, L. H. *J. Org. Chem.* **1959**, *24*, 627 en 30% de rendimiento como un sólido amarillo. ^{1}H-RMN (400 MHz, DMSO-d_6) δ 7,83-7,94 (m, 2H), 7,67-7,74 (m, 1H), 5,97-6,07 (m, 1H), 5,78-5,89 (m, 1H), 4,80-89 (m, 3H), 3,94-4,02 (m, 2H).

Ejemplo 200: 4–amino–5–(2–(hidroximetil)aliloxi)–1H–benzo[c][1,2,6] tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de acetato de 2–((2–ciano–3–(sulfamoilamino)fenoxi)metil)alilo (Ejemplo 200a) en 44% de rendimiento como un sólido blanco. ^{1}H-RMN (400 MHz, DMSO-d_6) δ 10,95 (s amplio, 1H), 8,34 (s amplio, 1H), 8,01 (s amplio, 1H), 7,45 (t, J = 8,0 Hz, 1H), 6,76 (d, J = 8,4 Hz, 1H), 6,61 (d, J = 8,0 Hz, 1H), 5,26 (s, 1H), 5,20 (s, 1H), 5,14 (t, J = 5,2 Hz, 1H), 4,78 (s, 2H), 4,03 (d, J = 5,2 Hz, 2H). MS 284 (MH^+).

Ejemplo 200a: Acetato de 2–((2–ciano–3–(sulfamoilamino)fenoxi)metil)alilo

Preparado como en el Ejemplo 111a a partir de acetato de 2–((3–amino–2–cianofenoxi)metil)alilo (Ejemplo 200b) en 87% de rendimiento como un sólido blanco. ^{1}H-RMN (400 MHz, DMSO-d_6) δ 9,50 (s amplio, 1H), 7,57 (t, J = 8,4 Hz, 1H), 7,28 (s amplio, 2H), 7,17 (d, J = 8,0 Hz, 1H), 6,97 (d, J = 8,4 Hz, 1H), 5,39 (s amplio, 1H), 5,33 (s amplio, 1H), 4,74 (s, 2H), 4,63 (s, 2H), 2,05 (s, 3H).

Ejemplo 200b: Acetato de 2–((3–amino–2–cianofenoxi)metil)alilo

Preparado como en el Ejemplo 199b a partir de acetato de 2–((2–ciano–3–nitrofenoxi)metil)alilo (Ejemplo 200c) en 76% de rendimiento como un aceite amarillo. ^{1}H-RMN (400 MHz, DMSO-d_6) δ 7,18 (t, J = 8,4 Hz, 1H), 6,35 (d, J = 8,8 Hz, 1H), 6,23 (d, J = 8,0 Hz, 1H), 6,03 (s amplio, 2H), 5,34–5,38 (m, 1H), 5,28-5,31 (m, 1H), 4,61 (s, 4H), 2,05 (s, 3H).

Ejemplo 200c: Acetato de 2–((2–ciano–3–nitrofenoxi)metil)alilo

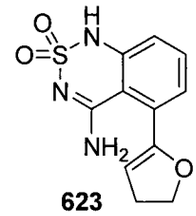
A una solución de 2–(2–(hidroximetil)aliloxi)–6–nitrobenzonitrilo (Ejemplo 200d) (0,40 g, 1,73 mmol), 4–dimetilaminopiridina (0,21 g, 1,73 mmol) y piridina (0,68 g, 8,64 mmol) en CH_2Cl_2 (10,0 mL) a 0ºC, se le adicionó Ac_2O (0,53 g, 5,19 mmol) bajo una atmósfera de nitrógeno. Luego de agitarse a 0ºC durante 10 min, la mezcla se agitó a ta durante la noche. La mezcla de reacción se diluyó con EtOAc (100 mL), se lavó con HCl 1,5 M, $NaHCO_3$ acuoso saturado y salmuera, y se secó sobre $MgSO_4$. El filtrado se evaporó y el residuo se purificó mediante cromatografía sobre gel de sílice utilizando el solvente gradiente hexanos →

hexanos/EtOAc (3:7), para proporcionar 0,40 g (84%) del compuesto del título como un sólido amarillo. ^{1}H-RMN (400 MHz, DMSO-d_6) δ 7,95 (dd, J = 8,4 Hz, J = 1,2 Hz, 1H), 7,91 (t, J = 8,4 Hz, 1H), 7,74 (dd, J = 8,4 Hz, J = 1,2 Hz, 1H), 5,43-5,46 (m, 1H), 5,36-5,40 (m, 1H), 4,90 (s, 2H), 4,66 (s, 2H), 2,05 (s, 3H).

Ejemplo 200d: 2–(2–(hidroximetil)aliloxi)–6–nitrobenzonitrilo

Preparado como en El ejemplo 166d a partir de 2,6–dinitrobenzonitrilo y 2–metilenopropan–1,3–diol en 55% de rendimiento como un sólido blanco. ^{1}H-RMN (400 MHz, DMSO-d_6) δ 7,93 (dd, J = 8,4 Hz, J = 0,8 Hz, 1H), 7,89 (t, J = 8,0 Hz, 1H), 7,73 (dd, J = 7,6 Hz, J = 0,8 Hz, 1H), 5,23–5,29 (m, 2H), 5,03 (t, J = 5,6 Hz, 1H), 4,85 (s, 2H), 4,06 (d, J = 5,2 Hz, 2H).

Ejemplo 201: 4–amino–5–(4,5–dihidrofuran–2–il)–1H–benzo[c][1,2,6] tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–(4,5–dihidrofuran–2–il)benzonitrilo (Ejemplo 201a) en 31% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,75-2,81 (m, 2H), 4,43 (t, J = 9,2 Hz, 2H), 5,35-5,36 (m, 1H), 7,07 (dd, J = 1,2, 8,0 Hz, 1H), 7,12 (dd, J = 1,2, 7,2 Hz, 1H), 7,50-7,54 (m, 1H), 8,2-8,4 (s amplio, 1H), 11,09 (s, 1H). MS 266 (MH^+).

Ejemplo 201a: 2–sulfamoilamino–6–(4,5–dihidrofuran–2–il)benzonitrilo

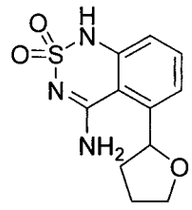
Preparado como en el Ejemplo 111a a partir de 2–amino–6–(4,5–dihidrofuran–2–il)benzonitrilo (Ejemplo 201b) en 19% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,82-2,88 (m, 2H), 4,45 (t, J = 9,6

Hz, 2H), 5,89 (t, *J* = 3,2 Hz, 1H), 7,29 (s, 2H), 7,47 (d, *J* = 7,2 Hz, 1H), 7,56 (d, *J* = 7,6 Hz, 1H), 7,67 (t, *J* = 8,0 Hz, 1H), 9,42 (s, 1H). MS 266 (MH^+).

Ejemplo 201b: 2–amino–6–(4,5–dihidrofuran–2–il)benzonitrilo

Se reflujaron 2–amino–6–bromobenzonitrilo (0,75 g, 3,81 mmol), (4,5–dihidrofuran–2–il)trimetilestannano (Menez, P.; Fargeas, V.; Poisson, J.; Ardisson, J.; Lallemand, J.–Y.; Pancrazi, A. *Tetrahedron Letters* **1994**, *35(42)*, 7767) (1,02 g, 4,38 mmol), y tetrakis(trifenilfosfin)paladio (0,33 g, 0,28 mmol) en tolueno (10,0 mL) bajo nitrógeno durante 1,5 h. Se adicionaron cloruro de amonio saturado (12 mL) e hidróxido de amonio (4 mL), y la mezcla se extrajo con EtOAc. La capa orgánica se concentró bajo vacío y el residuo se purificó mediante cromatografía sobre sílice utilizando 35% EtOAc/hexanos para proporcionar 0,48 g (68%) del compuesto del título como un aceite amarillo. ^{1}H RMN (400 MHz, Acetona-d_6) δ 2,78-2,83 (m, 2H), 4,40 (t, *J* = 9,2 Hz, 2H), 5,76 (t, *J* = 3,2 Hz, 1H), 6,04 (s, 2H), 6,77-6,80 (m, 2H), 7,28 (t, *J* = 8,0 Hz, 1H). MS 187 (MH^+).

Ejemplo 202: 4–amino–5–(tetrahidrofuran–2–il)–1H–benzo[c][1,2,6]tiadiazin–2,2–dióxido



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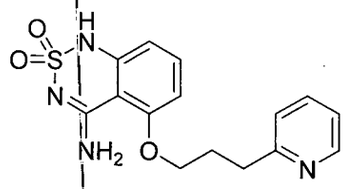
Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–(tetrahidrofuran–2–il)benzonitrilo (Ejemplo 202a) en 52% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,94-2,05 (m, 3H), 2,21-2,28 (m, 1H), 3,81-3,87 (m, 1H), 3,92-3,97 (m, 1H), 5,23-5,27 (m, 1H), 7,02 (d, *J* = 8,0 Hz,

1H), 7,30 (d, *J* = 7,6 Hz, 1H), 7,51 (t, *J* = 7,6 Hz, 1H), 7,9-8,5 (amplio, 2H), 10,94 (s, 1H). MS 268 (MH^+).

Ejemplo 202a: 2–sulfamoilamino–6–(tetrahidrofuran–2–il)benzonitrilo

Se reflujaron 2–amino–6–(4,5–dihidrofuran–2–il)benzonitrilo (Ejemplo 202b) (0,24 g, 1,28 mmol), 10% Pd/C (0,24 g), y formiato de amonio (2,40 g, 38,1 mmol) en MeOH (25 mL) bajo nitrógeno durante 1,5 h. Los sólidos insolubles se separaron mediante filtración y se descartaron, y el solvente se removió bajo vacío. El residuo resultante se disolvió en EtOAc, se lavó con Na_2CO_3 saturado y salmuera, se secó sobre $MgSO_4$ y se concentró bajo vacío. El residuo se disolvió en DMA anhidra (2,0 mL) y se trató con cloruro de sulfamoilo (0,11 g, 0,97 mmol). La mezcla de reacción se agitó bajo nitrógeno durante 30 minutos, se inactivó con agua (5,0 mL) y se extrajo con EtOAc (3x50 mL). El extracto combinado se secó sobre $MgSO_4$, se filtró y se concentró bajo vacío. El producto crudo se purificó mediante TLC prep sobre gel de sílice utilizando 65% EtOAc/hexanos para proporcionar 45,0 mg (13%) del compuesto del título como un sólido blanco. ^1H RMN (400 MHz, Acetona-d_6) δ 1,71-1,78 (m, 1H), 2,02-2,07 (m, 2H), 2,45-2,52 (m, 1H), 3,90-3,95 (m, 1H), 4,10-4,15 (m, 1H), 5,08 (t, *J* = 6,8 Hz, 1H), 6,6–6,8 (amplio, 2H), 7,36-7,39 (m, 1H), 7,62-7,63 (m, 2H), 8,22 (s amplio, 1H). MS 268 (MH^+).

Ejemplo 203: 4–amino–5–(3–(piridin–2–il)propoxi)–1H–benzo[c][1,2,6] tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–(3–(piridin–2–il)propoxi)benzonitrilo (Ejemplo 203a) en 58% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,37 (quint, J = 6,8 Hz, 2H), 2,89 (t, J = 7,2 Hz, 2H), 4,19 (t, J = 6,0 Hz, 2H), 6,60 (d, J = 8,4 Hz, 1H), 6,73 (d, J = 8,8 Hz, 1H), 7,19-7,22 (m, 1H), 7,29 (d, J = 8,0 Hz, 1H), 7,44 (t, J = 8,4 Hz, 1H), 7,68-7,72 (m, 1H), 7,92 (s, 1H), 8,36 (s, 1H), 8,49 (d, J = 4,0 Hz, 1H), 10,94 (s amplio, 1H). MS 333 (MH^+).

Ejemplo 203a: 2–sulfamoilamino–6–(3–(piridin–2–il)propoxi)benzonitrilo

Preparado como en el Ejemplo 111a a partir de 2–amino–6–(3–(piridin–2–il)propoxi)benzonitrilo (Ejemplo 203b) en 97% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,15 (quint, J = 6,4 Hz, 2H), 2,92 (t, J = 7,6 Hz, 2H), 4,15 (t, J = 6,0 Hz, 2H), 6,93 (d, J = 8,4 Hz, 1H), 7,14 (d, J = 8,4 Hz, 1H), 7,20-7,29 (m, 4H), 7,55 (t, J = 8,4 Hz, 1H), 7,68-7,72 (m, 1H), 8,48 (d, J = 4,8 Hz, 1H), 9,49 (s amplio, 1H). MS 333 (MH^+).

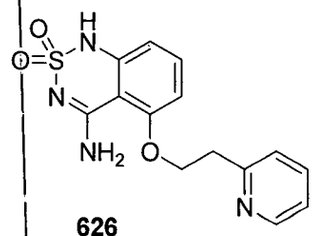
Ejemplo 203b: 2–amino–6–(3–(piridin–2–il)propoxi)benzonitrilo

Preparado como en el Ejemplo 199b a partir de 2–nitro–6–(3–(piridin–2–il)propoxi)benzonitrilo (Ejemplo 203c) en 85% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,12 (quint, J = 6,8 Hz, 2H), 2,90 (t, J = 7,2 Hz, 2H), 4,02 (t, J = 6,4 Hz, 2H), 5,99 (s, 2H), 6,18 (d, J = 8,0 Hz, 1H), 6,33 (d, J = 8,8 Hz, 1H), 7,14-7,22 (m, 2H), 7,26 (d, J = 8,0 Hz, 1H), 7,67-7,71 (m, 1H), 8,49 (d, J = 3,6 Hz, 1H). MS 254 (MH^+).

Ejemplo 203c: 2–nitro–6–(3–(piridin–2–il)propoxi)benzonitrilo

Preparado como en el Ejemplo 187c a partir de 3–(piridin–2–il)propan–1–ol 2,6–dinitrobenzonitrilo en 86% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,21 (quint, J = 6,4 Hz, 2H), 2,95 (t, J = 7,2 Hz, 2H), 4,31 (t, J = 6,4 Hz, 2H), 7,19-7,22 (m, 1H), 7,28 (d, J = 7,6 Hz, 1H), 7,67-7,74 (m, 2H), 7,86-7,92 (m, 2H), 8,48 (d, J = 4,8 Hz, 1H). MS 284 (MH^+).

Ejemplo 204: 4–amino–5–(2–(piridin–2–il)etoxi)–1H–benzo[c][1,2,6]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–(2–(piridin–2–il)etoxi)benzonitrilo (Ejemplo 204a) en 22% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,29 (t, J = 5,6 Hz, 2H), 4,46 (t, J = 5,6 Hz, 2H), 6,59 (d, J = 8,0 Hz, 1H), 6,75 (d, J = 8,8 Hz, 1H), 7,28-7,31 (m, 1H), 7,40-7,46 (m, 2H), 7,75-7,80 (m, 1H), 8,33-8,52 (m, 3H), 10,91 (s, 1H). MS 319 (MH^+).

Ejemplo 204a: 2–sulfamoilamino–6–(2–(piridin–2–il)etoxi)benzonitrilo

Preparado como en el Ejemplo 111a a partir de 2–amino–6–(2–(piridin–2–il)etoxi)benzonitrilo (Ejemplo 204b) en 67% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,22 (t, J = 6,4 Hz, 2H), 4,48 (t, J = 6,4 Hz, 2H), 7,00 (d, J = 8,8 Hz, 1H), 7,14 (d, J = 8,4 Hz, 1H), 7,23-7,26 (m, 3H), 7,39 (d, J = 7,6 Hz, 1H), 7,55 (t, J = 8,4 Hz, 1H), 7,73 (t, J = 7,2 Hz, 1H), 8,51 (d, J = 4,4 Hz, 1H), 9,42 (s, 1H). MS 319 (MH^+).

Ejemplo 204b: 2–amino–6–(2–(piridin–2–il)etoxi)benzonitrilo

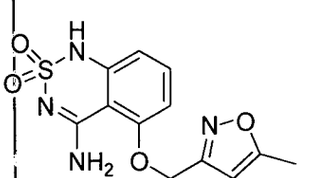
Preparado como en el Ejemplo 2b a partir de 2–nitro–6–(2–(piridin–2–il)propoxi)benzonitrilo (Ejemplo 221c) en 60% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,18 (t, J = 6,8 Hz, 2H), 4,36 (t, J = 6,8 Hz, 2H), 5,97 (s, 2H), 6,25 (d, J = 8,4 Hz, 1H), 6,32 (d, J = 8,4 Hz, 1H), 7,17 (t, J =

8,0 Hz, 1H), 7,22-7,26 (m, 1H), 7,37 (d, *J* = 8,0 Hz, 1H), 7,70-7,75 (m, 1H), 8,51 (d, *J* = 4,4 Hz, 1H). MS 240 (MH^+).

Ejemplo 204c: 2–nitro–6–(2–(piridin–2–il)etoxi)benzonitrilo

Preparado como en el Ejemplo 187c a partir de 2–(piridin–2–il)etanol y 2,6–dinitrobenzonitrilo en 82% de rendimiento como un sólido amarillo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,27 (t, *J* = 6,4 Hz, 2H), 4,64 (t, *J* = 6,4 Hz, 2H), 7,23-7,27 (m, 1H), 7,41 (d, *J* = 8,0 Hz, 1H), 7,71-7,79 (m, 2H), 7,86-7,91 (m, 2H), 8,50-8,52 (m, 1H). MS 270 (MH^+).

Ejemplo 205: 4–amino–5–((5–metilisoxazol–3–il)metoxi)–1H–benzo[c][1,2,6] tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–((5–metilisoxazol–3–il)metoxi)benzonitrilo (Ejemplo 205a) en 83% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,42 (s, 3H), 5,40 (s, 2H), 6,36 (s, 1H), 6,65 (d, *J* = 8,4 Hz, 1H), 6,81 (d, *J* = 8,4 Hz, 1H), 7,48 (t, *J* = 8,4 Hz, 1H), 8,06 (s, 1H), 8,40 (s, 1H), 11,02 (s, 1H). MS 309 (MH^+).

Ejemplo 205a: 2–sulfamoilamino–6–((5–metilisoxazol–3–il)metoxi)-benzonitrilo

Preparado como en el Ejemplo 111a a partir de 2–amino–6–((5–metilisoxazol–3–il)metoxi)benzonitrilo (Ejemplo 222b) en 85% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,42 (s, 3H), 5,32 (s, 2H), 6,34 (s, 1H), 7,07 (d, *J* = 8,0 Hz, 1H), 7,19 (d, *J* = 8,0 Hz, 1H), 7,30 (s, 2H), 7,59 (t, *J* = 8,8 Hz, 1H), 9,53 (s, 1H). MS 309 (MH^+).

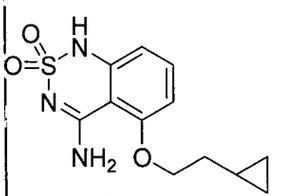
Ejemplo 205b: 2–amino–6–((5–metilisoxazol–3–il)metoxi)benzonitrilo

Preparado como en el Ejemplo 199b a partir de 2–((5–metilisoxazol–3–il)metoxi)–6–nitrobenzonitrilo (Ejemplo 205c) en 52% de rendimiento como un sólido amarillo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,42 (s, 3H), 5,19 (s, 2H), 6,07 (s, 2H), 6,31-6,33 (m, 2H), 6,37 (d, J = 8,4 Hz, 1H), 7,20 (t, J = 8,4 Hz, 1H). MS 230 (MH^+).

Ejemplo 205c: 2–((5–metilisoxazol–3–il)metoxi)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 187c a partir de (5–metilisoxazol–3–il)metanol y 2,6–dinitrobenzonitrilo en 86% de rendimiento como un sólido amarillo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,43 (d, J = 0,8 Hz, 3H), 5,50 (s, 2H), 6,38 (d, J = 0,4 Hz, 1H), 7,83 (dd, J = 1,2, 8,4 Hz, 1H), 7,91-7,98 (m, 2H). MS 260 (MH^+).

Ejemplo 206: 4–amino–5–(2–ciclopropiletoxi)–1H–benzo[c][1,2,6]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–(2–ciclopropiletoxi)benzonitrilo (Ejemplo 206a) en 94% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,11-0,15 (m, 2H), 0,43-0,48 (m, 2H), 0,77-0,81 (m, 1H), 1,73 (q, J = 6,8 Hz, 2H), 4,21 (t, J = 6,8 Hz, 2H), 6,61 (d, J = 8,0 Hz, 1H), 6,77 (d, J = 8,4 Hz, 1H), 7,46 (t, J = 8,4 Hz, 1H), 7,87 (s, 1H), 8,39 (s, 1H), 10,96 (s, 1H). MS 282 (MH^+).

Ejemplo 206a: 2–sulfamoilamino–6–(2–ciclopropiletoxi)benzonitrilo

Preparado como en el Ejemplo 111a a partir de 2–amino–6–(2–ciclopropiletoxi)benzonitrilo (Ejemplo 206b) en 80% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,13-0,17 (m, 2H), 0,41-0,46 (m, 2H), 0,82-0,87 (m, 1H), 1,64 (q, J = 6,4 Hz, 2H), 4,16 (t, J = 6,4 Hz, 2H), 6,96 (d, J = 8,0 Hz, 1H), 7,14 (d, J = 8,8 Hz, 1H), 7,27 (s, 2H), 7,56 (t, J = 8,8 Hz, 1H), 9,44 (s, 1H). MS 282 (MH^+).

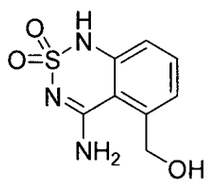
Ejemplo 206b: 2–amino–6–(2–ciclopropiletoxi)benzonitrilo

Preparado como en el Ejemplo 199b a partir de 2–(2–ciclopropiletoxi)–6–nitrobenzonitrilo (Ejemplo 206c) en 90% de rendimiento como un aceite amarillo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,13-0,16 (m, 2H), 0,40-0,45 (m, 2H), 0,81-0,85 (m, 1H), 1,61 (q, J = 6,8 Hz, 2H), 4,04 (t, J = 6,4 Hz, 2H), 5,97 (s, 2H), 6,21 (d, J = 8,0 Hz, 1H), 6,32 (d, J = 8,8 Hz, 1H), 7,17 (t, J = 8,4 Hz, 1H). MS 203 (MH^+).

Ejemplo 206c: 2–(2–ciclopropiletoxi)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 187c a partir de 2–ciclopropiletanol y 2,6–dinitrobenzonitrilo en 85% de rendimiento como un aceite amarillo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,15-0,20 (m, 2H), 0,43-0,47 (m, 2H), 0,84-0,89 (m, 1H), 1,69 (q, J = 6,8 Hz, 2H), 4,31 (t, J = 6,4 Hz, 2H), 7,73-7,76 (m, 1H), 7,86-7,93 (m, 2H). MS 233 (MH^+).

Ejemplo 207: 4–amino–5–(hidroximetil)–1H–benzo[c][1,2,6]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de acetato de 2–ciano–3–(sulfamoilamino)bencilo (Ejemplo 207a) en 53% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 4,60 (s, 2H), 6,62-6,63 (m, 1H), 7,04 (d, J = 8,0 Hz, 1H), 7,09 (d, J = 7,2 Hz, 1H), 7,51 (t, J = 7,6 Hz, 1H), 8,33 (s amplio, 1H), 8,86 (s amplio, 1H), 10,92 (s, 1H). MS 228 (MH^+).

Ejemplo 207a: Acetato de 2–ciano–3–(sulfamoilamino)bencilo

Preparado como en el Ejemplo 111a a partir de acetato de 3–amino–2–cianobencilo (Ejemplo 207b) en 90% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, Acetona–d_6) δ 2,09 (s, 3H), 5,24 (s, 2H), 6,76 (s amplio, 2H), 7,38 (dd, J = 0,8, 7,2 Hz, 1H), 7,66-7,75 (m, 2H), 8,40 (s amplio, 1H). MS 270 (MH^+).

Ejemplo 207b: Acetato de 3–amino–2–cianobencilo

Preparado como en el Ejemplo 199b a partir de acetato de 2–ciano–3–nitrobencilo (Ejemplo 207c) en 84% de rendimiento como un aceite amarillo. ^{1}H RMN (400 MHz, Metanol-d_4) δ 2,10 (s, 3H), 5,11 (s, 2H), 6,70 (d, J = 7,2 Hz, 1H), 6,78 (d, J = 8,8 Hz, 1H), 7,28 (t, J = 8,4 Hz, 1H). MS 191 (MH^+).

Ejemplo 207c: Acetato de 2–ciano–3–nitrobencilo

Se adicionó anhídrido acético (0,84 mL, 8,87 mmol) a una solución de 2–(hidroximetil)–6–nitrobenzonitrilo (Ejemplo 207d) (0,31 g, 1,77 mmol), piridina (0,86 mL, 10,6 mmol), y DMAP (0,22 g, 1,77 mmol) en CH_2Cl_2 (10 mL), y se agitó durante 24 h a ta. La mezcla se lavó una vez con AcOH (1 M, 20 mL), se secó con $MgSO_4$, se concentró, y se purificó mediante cromatografía sobre sílice utilizando CH_2Cl_2, para proporcionar el compuesto del título en una cantidad de 0,36 g (92%) como un sólido amarillo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,12 (s, 3H), 5,35 (s, 2H), 7,99 (t, J = 8,0 Hz, 1H), 8,06 (dd, J = 0,8, 8,0 Hz, 1H), 8,37 (dd, J = 0,8, 8,0 Hz, 1H).

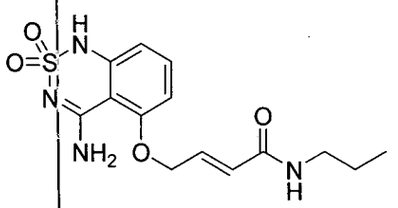
Ejemplo 207d: 2–(hidroximetil)–6–nitrobenzonitrilo

Se adicionó borohidruro de sodio (92,0 mg, 2,43 mmol) a una solución de 2–formil–6–nitrobenzonitrilo (Ejemplo 207e) (0,86 g, 4,88 mmol) en MeOH (38 mL) y THF (38 mL) a -8°C, y se agitó a esa temperatura durante no más de 30 min. La reacción se inactivó con HCl (6 M, 4,88 mL), seguido por la adición de agua (50 mL), y salmuera (50 mL). La mezcla se extrajo con EtOAc, el extracto combinado se secó sobre $MgSO_4$, se filtró y se concentró. El producto crudo se purificó mediante cromatografía sobre sílice utilizando el solvente gradiente $CH_2Cl_2 \rightarrow CH_2Cl_2$/MeOH (8:2) para proporcionar el compuesto del título en una cantidad de 0,32 g, (37%), el cual se utilizó inmmediatamente en la siguiente etapa. ^{1}H RMN (400 MHz, DMSO-d_6) δ 4,77 (d, J = 5,6 Hz, 2H), 5,87 (t, J = 5,6 Hz, 1H), 7,97 (t, J = 8,0 Hz, 1H), 8,07 (dd, J = 0,4, 8,0 Hz, 1H), 8,28 (dd, J = 0,8, 8,0 Hz, 1H).

Ejemplo 207e: 2–formil–6–nitrobenzonitrilo

Se adicionó 1,1–dimetoxi–*N*,*N*–dimetilmetanamina (13,56 mL, 102 mmol) a una solución de 2–metil–6–nitrobenzonitrilo (15,0 g, 92,5 mmol) en DMF anhidra (60 mL) bajo nitrógeno y se calentó a 130°C durante 15 h. Se adicionó hielo agua (300 mL), y el precipitado oscuro resultante se recogió mediante filtración y se secó bajo vacío. Se adicionaron buffer fosfato (pH 7, 350 mL) y luego $NaIO_4$ (40 g, 187 mmol) a una solución del precipitado oscuro en THF (350 mL) y se agitó a ta durante 3 h. La mezcla se extrajo con EtOAc, el extracto combinado se lavó con salmuera y se secó con $MgSO_4$. El filtrado se concentró y el residuo se purificó mediante cromatografía sobre sílice utilizando el gradiente solvente hexanos→EtOAc, para proporcionar 3,07 g (19%) del compuesto del título como un sólido amarillo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,15 (t, J = 8,4 Hz, 1H), 8,41 (dd, J = 1,2, 7,6 Hz, 1H), 8,62 (dd, J = 1,2, 8,4 Hz, 1H), 10,25 (s, 1H).

Ejemplo 208: (*E*)–4–amino–5–(4–oxo–4–(propilamino)but–2–eniloxi)–1H–benzo[c][1,2,6]tiadiazin–2,2–dióxido



630

Preparado como en el Ejemplo 111 a partir de (*E*)–4–(2–ciano–3–(sulfamoilamino)fenoxi)–N–propilbut–2–enamida (Ejemplo 208a) en 19% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, Acetona-d_6) δ 0,87 (t, J = 7,2 Hz, 3H), 1,47 (hex, J = 7,6 Hz, 2H), 3,11-3,17 (m, 4H), 5,35 (q, J = 7,2 Hz, 1H), 6,70 (d, J = 6,0 Hz, 1H), 6,77 (d, J = 8,0 Hz, 1H), 6,87 (d, J = 8,0 Hz, 1H), 7,2-7,5 (s amplio, 2H), 7,51 (t, J = 8,0 Hz, 1H), 8,19 (s amplio, 1H), 9,5-10,5 (s amplio, 1H). MS 339 (MH^+).

Ejemplo 208a: (*E*)–4–(2–ciano–3–(sulfamoilamino)fenoxi)–N–propilbut–2–enamida

Preparada como en el Ejemplo 111a a partir de (*E*)–4–(3–amino–2–cianofenoxi)–N–propilbut–2–enamida (Ejemplo 208b) en 87% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,84 (t, J = 7,2 Hz, 3H), 1,43 (hex, J = 6,8 Hz, 2H), 3,06 (q, J = 6,8 Hz, 2H), 4,90 (d, J = 2,8 Hz, 2H), 6,15 (d, J = 15,6 Hz, 1H), 6,70-6,77 (m, 1H), 6,91 (d, J 8,8 Hz, 1H), 7,17 (d, J = 8,4 Hz, 1H), 7,27 (s amplio, 2H), 7,57 (t, J = 8,8 Hz, 1H), 8,13-8,16 (m, 1H), 9,52 (s amplio, 1H). MS 339 (MH^+).

Ejemplo 208b: (*E*)–4–(3–amino–2–cianofenoxi)–N–propilbut–2–enamida

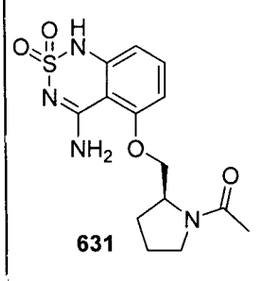
Preparada como en el Ejemplo 199b a partir de (*E*)–4–(2–ciano–3–nitrofenoxi)–N–propilbut–2–enamida (Ejemplo 208c) en 73% de rendimiento como un sólido amarillo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,84 (t, J = 7,2 Hz, 3H), 1,42 (hex, J = 7,2 Hz, 2H), 3,06 (q, J = 6,8 Hz, 2H), 4,77-4,79 (m, 2H), 6,04 (s, 2H),

6,11-6,20 (m, 2H), 6,35 (d, *J* = 8,4 Hz, 1H), 6,67-6,74 (m, 1H), 7,18 (t, *J* = 8,0 Hz, 1H), 8,11-8,14 (m, 1H). MS 260 (MH^+).

Ejemplo 208c: (*E*)–4–(2–ciano–3–nitrofenoxi)–N–propilbut–2–enamida

Se reflujaron (*E*)–4–bromo–N–propilbut–2–enamida (Elliott, M.; Farnham, A. W.; Janes, N. F.; Johnson, D. M.; Pulman, D. A. *Pesticide Science* **1987** *18(4)* 229) (0,14 g, 0,70 mmol), 2–hidroxi–6–nitrobenzonitrilo (0,14 g, 0,88 mmol), carbonato de potasio (0,39 g, 2,81 mmol), y 18–corona–6 (0,11 g, 0,42 mmol) en acetona (6 mL) durante 2 h, y luego se virtieron en hielo agua (45 mL). El precipitado resultante se recogió mediante filtración para proporcionar 0,16 g (79%) del compuesto del título como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,84 (t, *J* = 7,2 Hz, 3H), 1,42 (hex, *J* = 7,2 Hz, 2H), 3,06 (q, *J* = 6,8 Hz, 2H), 5,07 (d, *J* = 2,8 Hz, 2H), 6,16 (d, *J* = 16,0 Hz, 1H), 6,71–6,78 (m, 1H), 7,69 (d, *J* = 8,0 Hz, 1H), 7,88-7,96 (m, 2H), 8,11-8,14 (m, 1H).

Ejemplo 209: (*S*)–4–amino–5–((1–acetilpirrolidin–2–il)metoxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



631

Preparado como en el Ejemplo 176 a partir de (*S*)–2–amino–6–((1–acetilpirrolidin–2–il)metoxi)benzonitrilo (Ejemplo 209a) en 10% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,93 (m, 4H), 2,00 (s, 3H), 3,50 (m, 2H), 4,09 (dd, *J* = 10,0, 6,2 Hz, 1H), 4,24 (dd, *J* = 10,0, 5,6 Hz, 1H), 4,41 (m, 1H), 6,62 (d, *J* = 8,2 Hz, 1H), 6,87 (d, *J* = 8,5 Hz, 1H), 7,46 (t, *J* = 8,5 Hz, 1H), 8,12 (br s, 1H), 8,33 (br s, 1H), 10,93 (br s, 1H). MS 339 (MH^+).

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Ejemplo 209a: (*S*)–2–amino–6–((1–acetilpirrolidin–2–il)metoxi)benzonitrilo

A una suspensión de cloruro de (*S*)–2–((2–ciano–3–nitrofenoxi)metil)pirrolidinio (130 mg, 0,46 mmol) (Ejemplo 209b) en THF (5 mL) se le adicionaron Et_3N (135 μL, 0,97 mmol) y cloruro de acetilo (36 μL, 0,50 mmol). La reacción se agitó a ta durante 18 h, se filtró y se diluyó con EtOH (20 mL). La solución resultante se hidrogenó (20 Bar) utilizando 10% Pd/C como el catalizador. Una vez completa, la mezcla de reacción se concentró para proporcionar el compuesto del título (61 mg, 51%) como un jarabe claro. MS 260 (MH^+).

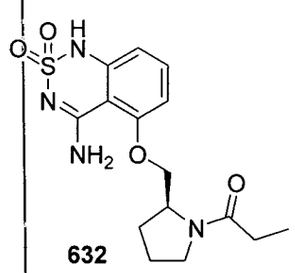
Ejemplo 209b: Cloruro de (*S*)–2–((2–ciano–3–nitrofenoxi)metil)pirrolidinio

Preparado como en el Ejemplo 166 a partir de (*S*)–*terc*–butil–2–((2–ciano–3–nitrofenoxi)metil)pirrolidin–1–carboxilato (Ejemplo 209c) en 81% de rendimiento como un sólido blancuzco. MS 248 (MH^+–HCl).

Ejemplo 209c: 2–((2–ciano–3–nitrofenoxi)metil)pirrolidin–1–carboxilato de (*S*)–*terc*–butilo

Preparado como en el Ejemplo 166d a partir de 2,6–dinitrobenzonitrilo y 2–(hidroximetil)pirrolidin–1–carboxilato de (*S*)–*terc*–butilo en 89% de rendimiento como un sólido tostado. ^1H RMN (400 MHz, DMSO-d_6) δ 1,40 (s, 9H), 1,81 (m, 1H), 2,03 (m, 3H), 3,32 (m, 2H), 4,08 (m, 1H), 4,33 (m, 2H), 7,79 (d, J = 7,8 Hz, 1H), 7,93 (m, 2H).

Ejemplo 210: (*S*)–4–amino–5–((1–propionilpirrolidin–2–il)metoxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



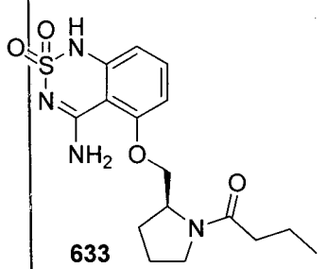
632

Preparado como en el Ejemplo 176 a partir de (*S*)–2–amino–6–((1–propionilpirrolidin–2–il)metoxi)benzonitrilo (Ejemplo 210a) en 17% de rendimiento como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,01 (t, J = 7,8 Hz, 3H), 1,95 (m, 4H), 2,31 (m, 2H), 3,48 (m, 2H), 4,11 (dd, J = 10,0, 6,4 Hz, 1H), 4,27 (dd, J = 9,8, 5,0 Hz, 1H), 4,43 (m, 1H), 6,64 (d, J = 7,9 Hz, 1H), 6,92 (d, J = 8,4 Hz, 1H), 7,48 (t, J = 8,2 Hz, 1H), 8,09 (br s, 1H), 8,34 (br s, 1H), 10,95 (br s, 1H). MS 353 (MH^+).

Ejemplo 210a: (*S*)–2–amino–6–((1–propionilpirrolidin–2–il)metoxi)benzonitrilo

Preparado como en el Ejemplo 209a a partir de cloruro de (*S*)–2–((2–ciano–3–nitrofenoxi)metil)pirrolidinio (Ejemplo 210b) y cloruro de propionilo en 90% de rendimiento como un jarabe claro. MS 274 (MH^+).

Ejemplo 211: (*S*)–4–amino–5–((1–butirilpirrolidin–2–il)metoxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



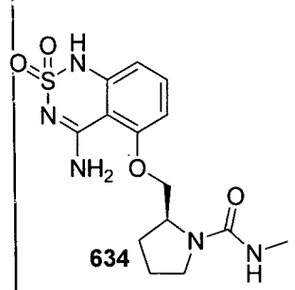
633

Preparado como en el Ejemplo 176 a partir de (*S*)–2–amino–6–((1–butirilpirrolidin–2–il)metoxi)benzonitrilo (Ejemplo 211a) en 78% de rendimiento como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,88 (t, J = 7,5 Hz, 3H), 1,54 (q, J = 7,5 Hz), 1,94 (m, 4H), 2,26 (t, J = 7,5 Hz, 2H), 3,48 (m, 2H), 4,10 (m, 1H), 4,25 (m, 1H), 4,43 (m, 1H), 6,62 (d, J = 8,1 Hz, 1H), 6,89 (d, J = 8,6 Hz, 1H), 7,47 (t, J = 8,3 Hz, 1H), 8,08 (br s, 1H), 8,32 (br s, 1H), 10,93 (br s, 1H). MS 367 (MH^+).

Ejemplo 211a: (*S*)–2–amino–6–((1–butirilpirrolidin–2–il)metoxi)benzonitrilo

Preparado como en el Ejemplo 209a a partir de cloruro de (*S*)–2–((2–ciano–3–nitrofenoxi)metil)pirrolidinio (Ejemplo 209b) y cloruro de butirilo en 90% de rendimiento como un sólido blanco. MS 288 (MH^+).

Ejemplo 212: (*S*)–2–((4–amino–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dioxido–5–iloxi)metil)–*N*–metilpirrolidin–1–carboxamida



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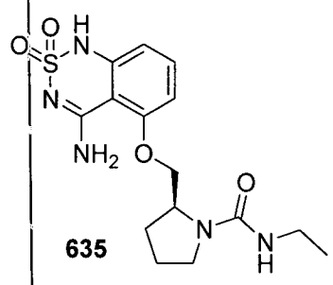
Preparada como en el Ejemplo 176 a partir de (*S*)–2–((3–amino–2–cianofenoxi)metil)–*N*–metilpirrolidin–1–carboxamida (Ejemplo 212a) en 30% de rendimiento como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,89 (m, 4H), 2,60 (d, J = 3,9 Hz, 3H), 3,20 (m, 2H), 4,01 (m, 1H), 4,16 (m, 1H), 4,32 (m, 1H), 6,23 (m, 1H), 6,62 (d, J = 8,2 Hz, 1H), 6,89 (d, J = 8,5 Hz, 1H), 7,46 (t, J = 8,2 Hz, 1H), 8,19 (br s, 1H), 8,27 (br s, 1H), 10,92 (s, 1H). MS 354 (MH^+).

Ejemplo 212a: (*S*)–2–((3–amino–2–cianofenoxi)metil)–*N*–metilpirrolidin–1–carboxamida

Preparada como en el Ejemplo 209a a partir de cloruro de (*S*)–2–((2–ciano–3–nitrofenoxi)metil)pirrolidinio (Ejemplo 209b) e isocianato de metilo en 53% de rendimiento como un sólido blanco. MS 275 (MH^+).

Ejemplo 213: (*S*)–2–((4–amino–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dioxido–5–iloxi)metil)–*N*–etilpirrolidin–1–carboxamida

911



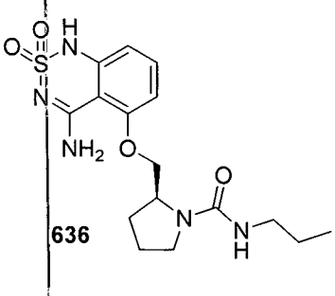
635

Preparada como en el Ejemplo 276 a partir de (*S*)–2–((3–amino–2–cianofenoxi)metil)–*N*–etilpirrolidin–1–carboxamida (Ejemplo 213a) en 68% de rendimiento como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,03 (t, J = 6,9 Hz, 6H), 1,90 (m, 4H), 3,08 (quint, J = 6,6 Hz, 2H), 3,20 (m, 1H), 3,31 (m, 1H), 4,00 (dd, J = 9,7, 6,7 Hz, 1H), 4,17 (dd, J = 9,7, 6,0 Hz, 1H), 4,33 (m, 1H), 6,27 (d, J = 5,7 Hz, 1H), 6,62 (d, J = 8,2 Hz, 1H), 6,89 (d, J = 8,3 Hz, 1H), 7,46 (t, J = 8,2 Hz, 1H), 8,20 (br s, 1H), 8,26 (br s, 1H), 10,91 (s, 1H). MS 368 (MH^+).

Ejemplo 213a: (*S*)–2–((3–amino–2–cianofenoxi)metil)–*N*–etilpirrolidin–1–carboxamida

Preparada como en el Ejemplo 209a a partir de cloruro de (*S*)–2–((2–ciano–3–nitrofenoxi)metil)pirrolidinio (Ejemplo 209bW) e isocianato de etilo en 100% de rendimiento como un sólido blanco. MS 289 (MH^+).

Ejemplo 214: (*S*)–2–((4–amino–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dioxido–5–iloxi)metil)–*N*–propilpirrolidin–1–carboxamida



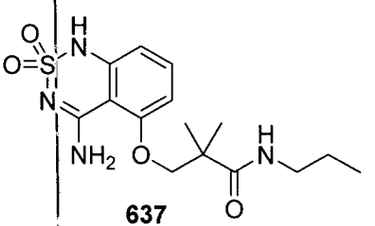
636

Preparada como en el Ejemplo 276 a partir de (*S*)–2–((3–amino–2–cianofenoxi)metil)–*N*–propilpirrolidin–1–carboxamida (Ejemplo 214a) en 37% de rendimiento como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,84 (t, *J* = 7,6 Hz, 6H), 1,43 (sext, *J* = 7,4 Hz, 2H), 1,92 (m, 4H), 3,01 (m, 2H), 3,21 (m, 1H), 3,33 (m, 1H), 4,02 (dd, *J* = 9,7, 6,4 Hz, 1H), 4,18 (dd, *J* = 9,7, 5,9 Hz, 1H), 4,34 (m, 1H), 6,27 (d, *J* = 5,6 Hz, 1H), 6,62 (d, *J* = 8,4 Hz, 1H), 6,89 (d, *J* = 8,6 Hz, 1H), 7,46 (t, *J* = 8,3 Hz, 1H), 8,20 (br s, 1H), 8,27 (br s, 1H), 10,91 (s, 1H). MS 382 (MH^+).

Ejemplo 214a: (*S*)–2–((3–amino–2–cianofenoxi)metil)–*N*–propilpirrolidin–1–carboxamida

Preparada como en el Ejemplo 209a a partir de cloruro de (*S*)–2–((2–ciano–3–nitrofenoxi)metil)pirrolidinio (Ejemplo 209b) e isocianato de propilo en 100% de rendimiento como un sólido blanco. MS 303 (MH^+).

Ejemplo 215: 3–(4–amino–2,2–dioxido–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)–2',2'–dimetil–N–propilpropanamida



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A una solución agitada de 3–(3–sulfamoilamino–2–cianofenoxi)–2,2–dimetil–N–propilpropanamida (18,52 g, 52,55 mmol) (Ejemplo 215a) en EtOH (150 mL) se le adicionó a temperatura ambiente solución de NaOH (2,0 N, 52,3 mL). Luego la mezcla de reacción se reflujó durante 2 hs hasta que la reacción estuvo completa mediante TLC. La solución se enfrió hasta 0ºC y se neutralizó cuidadosamente con 10% ácido acético y el precipitado se recogió mediante

filtración y se lavó con agua. El producto se purificó además mediante recristalización a partir de EtOH/H_2O (1:4), se secó bajo vacío para proporcionar el compuesto del título como un sólido blanco (13,5 g, 73%). P.f.: 225–226°C. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,75 (t, J = 7,4 Hz, 3H), 1,22 (s, 6H), 1,38 (m, 2H), 3,01 (q, J = 6,5 Hz, 2H), 4,07 (s, 2H), 6,59 (d, J = 8,0 Hz, 1H), 6,71 (d, J = 8,0 Hz, 1H), 7,44 (t, J = 8,0 Hz, 1H), 7,82 (t, J = 5,6 Hz, 1H), 7,92 (s, 1H), 8,33 (s, 1H), 10,93 (s, 1H). MS 355 (MH^+).

Ejemplo 215a: 3–(3–sulfamoilamino–2–cianofenoxi)–2,2–dimetil–N–propil–propanamida

A una solución de 3–(3–amino–2–cianofenoxi)–2,2–dimetil–N–propilpropanamida (16,5 g, 59,92 mmol) (Ejemplo 215b) en DMA (50 mL) se le adicionó cloruro de sulfamoilo (13,85 g, 119,84 mmol) a 0°C bajo nitrógeno. Luego la mezcla de reacción se agitó a temperatura ambiente bajo nitrógeno durante 3 hs después se diluyó con EtOAc, se lavó sucesivamente con $NaHCO_3$, salmuera, se secó sobre Na_2SO_4, se filtró y se evaporó para proporcionar el compuesto del título como un sólido blancuzco (18,52 g, 87%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,79 (t, J = 7,6 Hz, 3H), 1,20 (s, 6H), 1,38 (m, 2H), 3,01 (q, J = 6,5 Hz, 2H), 4,05 (s, 2H), 6,92 (d, J = 8,4 Hz, 1H), 7,13 (d, J = 8,4 Hz, 1H), 7,24 (s, 2H), 7,53 (t, J = 8,4 Hz, 1H), 7,55 (t, J = 5,6 Hz, 1H), 9,42 (s, 1H). MS 355 (MH^+).

Ejemplo 215b: 3–(3–amino–2–cianofenoxi)–2,2–dimetil–N–propilpropan-amida

Método A: A una solución de 3–(2–ciano–3–nitrofenoxi)–2,2–dimetil–N–propilpropanamida (305 mg, 1,0 mmol) (Ejemplo 215c) en EtOAc (20,0 mL) se le adicionó 10% Pd/C (50 mg). La suspensión se agitó bajo una atmósfera de H_2 a temperatura ambiente durante la noche. El Pd/C se separó mediante filtración, y se lavó con EtOAc. El filtrado se concentró bajo presión reducida y el residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con 50% EtOAc en

hexanos para proporcionar el compuesto del título (267 mg, 97%) como un sólido blanco. MS 276 (MH^+).

Método B: A una solución de 3–hidroxi–2,2–dimetil–N–propilpropanamida (20,2 g, 0,127 mol) (Ejemplo 215d) en THF seco (500 mL) se le adicionó cuidadosamente NaH (60% en aceite mineral, 7,64 g, 0,191 mol) en pequeñas porciones a 0°C bajo nitrógeno. Luego la mezcla de reacción se entibió hasta temperatura ambiente y se agitó bajo nitrógeno durante 1 h. A esta solución se le adicionó lentamente a temperatura ambiente 2–amino–6–fluorbenzonitrilo (17,3 g, 0,127 mol) en THF (100 mL) y la mezcla de reacción se reflujó durante la noche bajo nitrógeno después se enfrió hasta temperatura ambiente, se inactivó con salmuera, y se extrajo con EtOAc (3X). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se evaporaron y el residuo se cristalizó a partir de EtOAc/hexano para proporcionar el compuesto como un sólido blanco (16,5 g, 48%). MS 276 (MH^+).

Ejemplo 215c: 3–(2–ciano–3–nitrofenoxi)–2,2–dimetil–N–propilpropanamida

A una solución de 3–hidroxi–2,2–dimetil–N–propilpropanamida (1,59 g, 10,0 mmol) (Ejemplo 215d) en THF seco (30 mL) se le adicionó cuidadosamente NaH (60% en aceite mineral, 400 mg, 10,0 mmol) en pequeñas porciones a 0°C bajo nitrógeno. La mezcla de reacción se agitó a 0°C bajo nitrógeno durante 2 hs. A esta solución se le adicionó 2,6–dinitrobenzonitrilo (1,93, 10,0 mmol), y la solución de reacción se agitó a 0°C – ta bajo nitrógeno durante la noche. La mezcla de reacción se inactivó con salmuera, y se extrajo con EtOAc (3X). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4. Luego de la evaporación del solvente, el residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con 60% EtOAc en hexanos para

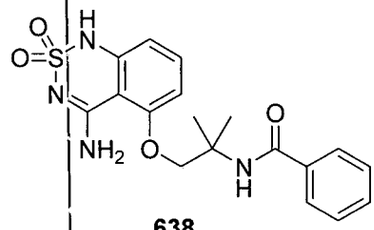
proporcionar el compuesto del título como un sólido amarillo pálido (2,21 g, 72%). MS 306 (MH^+).

Ejemplo 215d: 3–hidroxi–2,2–dimetil–N–propilpropanamida

Método A: Una solución de 3–hidroxi–2,2–dimetilpropanoato de metilo (2,64 g, 20 mmol) y n–propilamina (1,81 g, 30 mmol) se calentó a 190°C bajo microondas durante 10 hs. La amine en exceso se removió bajo vacío para proporcionar el compuesto del título como un aceite incoloro (3,18 g, 100%). MS 160 (MH^+).

Método B: A una solución de ácido 3–hidroxi–2,2–dimetilpropanoico (20,0 g, 0,169 mol), propilamina (15,3 mL, 0,186 mol), y HOBt (25,1 g, 0,186 mol) en diclorometano seco (500 mL) se le adicionó EDCI (35,6 g, 0,186 mmol) a temperatura ambiente bajo nitrógeno. Luego la mezcla de reacción se agitó a temperatura ambiente bajo nitrógeno durante la noche. La reacción se inactivó con salmuera, y se extrajo con EtOAc (8X). Las capas orgánicas combinadas se lavaron con solución saturada de $NaHCO_3$, HCl diluido, salmuera, y se secaron sobre Na_2SO_4. La evaporación del solvente bajo presión reducida proporcionó el compuesto del título como un aceite incoloro (19,2 g, 71%). MS 160 (MH^+).

Ejemplo 216: N–(1–(4–amino–2,2–dioxido–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)–2'–metilpropan–2'–il)benzamida



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Preparada como en el Ejemplo 215 a partir de N–(1–(3–sulfamoilamino–2–cianofenoxi)–2–metilpropan–2–il)benzamida (Ejemplo 216a) en 93% de

rendimiento como un sólido blanco. P.f.: 235–236ºC. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,47 (s, 6H), 4,38 (s, 2H), 6,61 (d, J = 8,4 Hz, 1H), 6,77 (d, J = 8,0 Hz, 1H), 7,39-7,51 (m, 4H), 7,75 (d, J = 7,6 Hz, 2H), 7,90 (s, 1H), 8,17 (s, 1H), 8,47 (s, 1H), 10,97 (s, 1H). MS 389 (MH^+).

Ejemplo 216a: N–(1–(3–sulfamoilamino–2–cianofenoxi)–2–metilpropan–2–il)benzamida

Preparada como en el Ejemplo 215a a partir de N–(1–(3–amino–2–cianofenoxi)–2–metilpropan–2–il)benzamida (Ejemplo 216b) en 98% de rendimiento como un sólido blanco. MS 389 (MH^+).

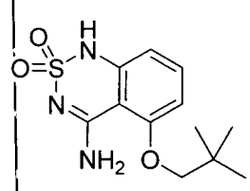
Ejemplo 216b: N–(1–(3–amino–2–cianofenoxi)–2–metilpropan–2–il)benzamida

Preparada como en el Ejemplo 215b (Método A) a partir de N–(1–(2–ciano–3–nitrofenoxi)–2–metilpropan–2–il)benzamida (Ejemplo 216c) en 96% de rendimiento como un sólido blanco. MS 310 (MH^+).

Ejemplo 216c: N–(1–(2–ciano–3–nitrofenoxi)–2–metilpropan–2–il)benzamida

Preparada como en el Ejemplo 215c a partir de N–(1–hidroxi–2–metilpropan–2–il)benzamida (Boyd, R.N.; Hansen, R.H. *J. Am. Chem. Soc.* **1953**, *75*, 5896) y 2,6–dinitrobenzonitrilo en 91% de rendimiento como un sólido amarillo pálido. MS 340 (MH^+).

Ejemplo 217: 5–(neopentiloxi)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



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Preparado como en el Ejemplo 215 a partir de 2–sulfamoilamino–6–(neopentiloxi)benzonitrilo (Ejemplo 217a) en 73% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,01 (s, 9H), 3,86 (s, 2H), 6,61 (d, J = 8,0 Hz, 1H), 6,77 (d, J = 8,0 Hz, 1H), 7,45 (t, J = 8,0 Hz, 1H), 7,66 (s, 1H), 8,49 (s, 1H), 10,99 (s, 1H). MS 284 (MH^+).

Ejemplo 217a: 2–sulfamoilamino–6–(neopentiloxi)benzonitrilo

Preparado como en el Ejemplo 215a a partir de 2–amino–6–(neopentiloxi)benzonitrilo (Ejemplo 217b) en 92% de rendimiento. MS 284 (MH^+).

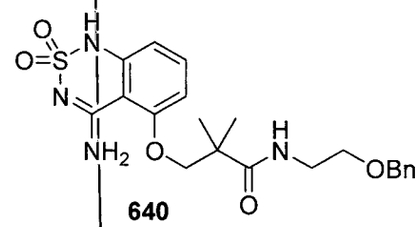
Ejemplo 217b: 2–amino–6–(neopentiloxi)benzonitrilo

Preparado como en el ejemplo 215b (Método A) a partir de 2–(neopentiloxi)–6–nitrobenzonitrilo (Ejemplo 217c) en 96% de rendimiento. MS 205 (MH^+).

Ejemplo 217c: 2–(neopentiloxi)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 215c a partir de 2,2–dimetilpropan–1–ol y 2,6–dinitrobenzonitrilo en 80% de rendimiento. MS 235 (MH^+).

Ejemplo 218: 3–(4–amino–2,2–dioxido–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)–N–(2''–(benciloxi)etil)–2',2'–dimetilpropanamida



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Preparada como en el Ejemplo 215 a partir de 3–(3–sulfamoilamino–2–cianofenoxi)–N–(2–(benciloxi)etil)–2,2–dimetilpropanamida (Ejemplo 218a) en 92% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,22 (s, 6H), 3,26 (q, J = 5,8 Hz, 2H), 3,41 (t, J = 5,8 Hz, 2H), 4,07 (s, 2H), 4,36 (s, 2H),

6,60 (d, J = 7,6 Hz, 1H), 6,71 (d, J = 7,6 Hz, 1H), 7,19-7,28 (m, 4H), 7,43 (t, J = 8,0 Hz, 2H), 7,91 (s, 1H), 7,97 (t, J = 5,8 Hz, 1H), 8,34 (s, 1H), 10,93 (s, 1H). MS 447 (MH^+).

Ejemplo 218a: 3–(3–sulfamoilamino–2–cianofenoxi)–N–(2–(benciloxi)etil)–2,2–dimetilpropanamida

Preparada como en el Ejemplo 215a a partir de 3–(3–amino–2–cianofenoxi)–N–(2–(benciloxi)etil)–2,2–dimetilpropanamida (Ejemplo 218b) en 100% de rendimiento. MS 447 (MH^+).

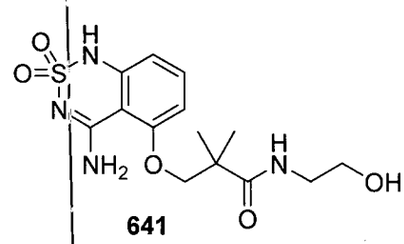
Ejemplo 218b: 3–(3–amino–2–cianofenoxi)–N–(2–(benciloxi)etil)–2,2–dimetil–propanamida

Preparada como en el Ejemplo 215b (Método B) a partir de N–(2–(benciloxi)etil)–3–hidroxi–2,2–dimetilpropanamida (Ejemplo 218c) y 2–amino–6–fluorbenzonitrilo en 82% de rendimiento. MS 368 (MH^+).

Ejemplo 218c: N–(2–(benciloxi)etil)–3–hidroxi–2,2–dimetilpropanamida

A una solución de ácido 3–hidroxi–2,2–dimetilpropanoico (2,36 g, 20 mmol), 2–(benciloxi)etanamina (3,02 g, 20 mmol), y HOBt (2,71 g, 20 mmol) en diclorometano seco (100 mL) se le adicionó EDCI (3,82 g, 20 mmol) a temperatura ambiente bajo nitrógeno. Luego la mezcla de reacción se agitó a temperatura ambiente bajo nitrógeno durante la noche. La reacción se inactivó con salmuera, y se extrajo con EtOAc (3X). Las capas orgánicas combinadas se lavó con solución saturada de $NaHCO_3$, HCl diluido, salmuera, y se secaron sobre Na_2SO_4. Luego de la evaporación del solvente, el residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con 40% EtOAc en hexanos para proporcionar el compuesto del título como un aceite incoloro (4,89 g) en 97% de rendimiento. MS 252 (MH^+).

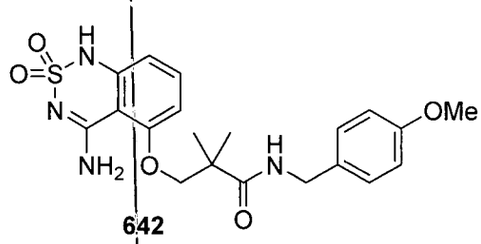
Ejemplo 219: 3–(4–amino–2,2–dioxido–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)–N–(2''–hidroxietil)–2',2'–dimetilpropanamida



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A una solución de 3–(4–amino–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)–2,2–dioxido–N–(2'–(benciloxi)etil)–2',2'–dimetilpropanamida (Ejemplo 218, 112 mg, 0,25 mmol) en EtOAc/EtOH/THF (1:1:1, 20,0 mL) se le adicionó 10% Pd/C (50 mg) y la suspensión se agitó bajo una atmósfera de H_2 a temperatura ambiente durante 2 hs. El Pd/C se separó mediante filtración, y se lavó con MeOH. La filtración se concentró bajo presión reducida, y el residuo se purificó mediante recristalización a partir de EtOH para proporcionar el compuesto del título como un sólido blanco (81 mg) en 90% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,22 (s, 6H), 3,11 (q, J = 6,0 Hz, 2H), 3,35 (q, J = 6,0 Hz, 2H), 4,05 (s, 2H), 4,61 (t, J = 6,0 Hz, 1H), 6,59 (d, J = 8,0 Hz, 1H), 6,70 (d, J = 8,0 Hz, 1H), 7,43 (t, J = 8,0 Hz, 1H), 7,78 (t, J = 6,0 Hz, 1H), 7,93 (s, 1H), 8,29 (s, 1H), 10,93 (s, 1H). MS 357 (MH^+).

Ejemplo 220: 3–(4–amino–2,2–dioxido–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)–N–(4''–metoxibencil)–2',2'–dimetilpropanamida



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Preparada como en el Ejemplo 215 a partir de 3–(3–sulfamoilamino–2–cianofenoxi)–N–(4–metoxibencil)–2,2–dimetilpropanamida (Ejemplo 220a) en 92% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,25 (s, 6H), 3,66 (s, 3H), 4,12 (s, 2H), 4,21 (d, J = 5,6 Hz, 2H), 6,61 (d, J = 8,4 Hz, 1H), 6,71 (d, J = 8,4 Hz, 1H), 6,73 (d, J = 8,0 Hz, 2H), 7,06 (d, J = 8,0 Hz, 2H), 7,44 (t, J = 8,4 Hz, 1H), 7,87 (s, 1H), 8,31 (s, 1H), 8,35 (t, J = 5,6 Hz, 1H), 10,95 (s, 1H). MS 433 (MH^+).

Ejemplo 220a: 3–(3–sulfamoilamino–2–cianofenoxi)–N–(4–metoxibencil)–2,2–dimetilpropanamida

Preparada como en el Ejemplo 215a a partir de 3–(3–amino–2–cianofenoxi)–N–(4–metoxibencil)–2,2–dimetilpropanamida (Ejemplo 220b) en 100% de rendimiento. MS 433 (MH^+).

Ejemplo 220b: 3–(3–amino–2–cianofenoxi)–N–(4–metoxibencil)–2,2–dimetil–propanamida

A una solución de 3–(2–ciano–3–nitrofenoxi)–N–(4–metoxibencil)–2,2–dimetil–propanamida (1,15 g, 3,0 mmol) (Ejemplo 220c) en diglime (30 mL) se le adicionó gota a gota una solución de $SnCl_2 \cdot 2H_2O$ (2,03 g, 9,0 mmol) en HCl concentrado (15 mL) a 0ºC. Luego la mezcla de reacción se agitó a 0ºC durante otra 1 h. La solución de reacción se neutralizó con NaOH 2 N a 0ºC, y se extrajo con EtOAc (2X). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4. Luego de la evaporación del solvente, el residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con 50% EtOAc en hexanos para proporcionar el compuesto del título como un sólido blanco (0,91 g) en 86% de rendimiento. MS 354 (MH^+).

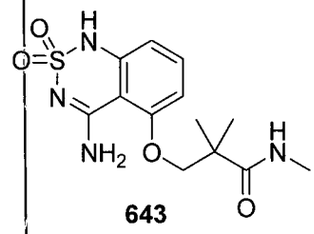
Ejemplo 220c: 3–(2–ciano–3–nitrofenoxi)–N–(4–metoxibencil)–2,2–dimetil–propanamida

Preparada como en el Ejemplo 215c a partir de 3–hidroxi–N–(4–metoxibencil)–2,2–dimetilpropanamida (Ejemplo 220d) y 2,6–dinitrobenzonitrilo en 95% de rendimiento como un sólido amarillo pálido. MS 384 (MH^+).

Ejemplo 220d: 3–hidroxi–N–(4–metoxibencil)–2,2–dimetilpropanamida

Preparada como en el Ejemplo 4c a partir de ácido 3–hidroxi–2,2–dimetilpropanoico y 4–metoxibencilamina en 97% de rendimiento como un sólido blanco. MS 238 (MH^+).

Ejemplo 221: 3–(4–amino–2,2–dioxido–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)–N,2',2'–trimetilpropanamida



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Preparada como en el Ejemplo 215 a partir de 3–(3–sulfamoilamino–2–cianofenoxi)–N,2,2–trimetilpropanamida (Ejemplo 221a) en 62% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,21 (s, 6H), 2,58 (d, J = 1,2 Hz, 3H), 4,05 (s, 2H), 6,60 (d, J = 8,0 Hz, 1H), 6,72 (d, J = 8,0 Hz, 1H), 7,44 (t, J = 8,0 Hz, 1H), 7,80 (q, J = 1,2 Hz, 1H), 7,96 (s, 1H), 8,33 (s, 1H), 10,93 (s, 1H). MS 327 (MH^+).

Ejemplo 221a: 3–(3–sulfamoilamino–2–cianofenoxi)–N,2,2–trimetilpropanamida

Preparada como en el Ejemplo 215a a partir de 3–(3–amino–2–cianofenoxi)–N,2,2–trimetilpropanamida (Ejemplo 221b) en 69% de rendimiento. MS 327 (MH^+).

Ejemplo 221b: 3–(3–amino–2–cianofenoxi)–N,2,2–trimetilpropanamida

Preparada como en el Ejemplo 215b (Método A) a partir de 3–(2–ciano–3–nitrofenoxi)–N,2,2–trimetilpropanamida (Ejemplo 221c) en 95% de rendimiento como un sólido blanco. MS 248 (MH^+).

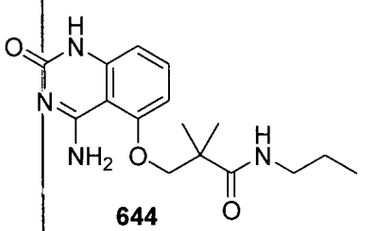
Ejemplo 221c: 3–(2–ciano–3–nitrofenoxi)–N,2,2–trimetilpropanamida

Preparada como en el Ejemplo 215c a partir de 3–hidroxi–N,2,2–trimetilpropanamida (Ejemplo 221d) y 2,6–dinitrobenzonitrilo en 77% de rendimiento como un sólido amarillo pálido. MS 378 (MH^+).

Ejemplo 221d: 3–hidroxi–N,2,2–trimetilpropanamida

Preparada como en el Ejemplo 215d a partir de 3–hidroxi–2,2–dimetilpropanoato y metilamina en 51% de rendimiento. MS 132 (MH^+).

Ejemplo 222: 3–(4–amino–2–oxo–1,2–dihidroquinazolin–5–iloxi)–2,2–dimetil–N–propilpropanamida



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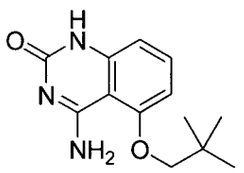
Una solución de N–(2–ciano–3–(2,2–dimetil–3–oxo–3–(propilamino)propoxi)–fenilcarbamoil)benzamida (Ejemplo 222a) (141 mg, 0,3 mmol) y NaOH (2 N, 0,3 mL) en EtOH (5 mL) se agitó a 100ºC bajo nitrógeno durante 2 hs. Luego de enfriarse hasta temperatura ambiente, la solución de reacción clara se filtró, y el filtrado se neutralizó cuidadosamente con 10% AcOH con agitación enérgica a 0ºC. El precipitado resultante se recogió mediante filtración, se lavó con agua y luego 20% EtOH en agua para proporcionar el producto final (81 mg) en 76% de rendimiento como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,73 (t, J = 7,4 Hz, 3H), 1,21 (s, 6H), 1,33-1,41 (m, 2H),

3,01 (q, J = 7,4 Hz, 2H), 4,08 (s, 2H), 6,64 (d, J = 8,0 Hz, 1H), 6,69 (d, J = 8,0 Hz, 1H), 7,42 (t, J = 8,0 Hz, 1H), 7,47 (s, 1H), 7,79 (t, J = 7,4 Hz, 1H), 7,84 (s, 1H), 10,60 (s, 1H). MS 319 (MH^+).

Ejemplo 222a: N–(2–ciano–3–(2,2–dimetil–3–oxo–3–(propilamino)propoxi) fenil–carbamoil)benzamida

Preparada como en el Ejemplo 146a a partir de 3–(3–amino–2–cianofenoxi)–2,2–dimetil–N–propil–propanamida (Ejemplo 215b, Método A) e isocianato de benzoilo en 85% de rendimiento como un sólido blanco. MS 423 (MH^+).

Ejemplo 223: 4–amino–5–(neopentiloxi)quinazolin–2(1H)–ona



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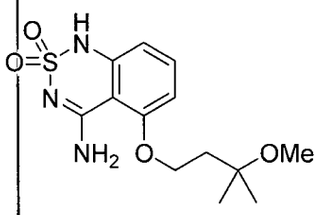
Preparada como en el Ejemplo 222 a partir de N–(2–ciano–3–(neopentiloxi)fenilcarbamoil)benzamida (Ejemplo 223a) en 90% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,03 (s, 9H), 3,90 (s, 2H), 5,96 (s, 2H), 6,15 (d, J = 7,6 Hz, 1H), 6,30 (d, J = 7,6 Hz, 1H), 7,14 (t, J = 7,6 Hz, 1H), 11,22 (s, 1H). MS 248 (MH^+).

Ejemplo 223a: N–(2–ciano–3–(neopentiloxi)fenilcarbamoil)benzamida

Preparada como en el Ejemplo 146a a partir de 2–amino–6–(neopentiloxi)–benzonitrilo (Ejemplo 217b) e isocianato de benzoilo en 96% de rendimiento como un sólido blanco. MS 352 (MH^+).

Ejemplo 224: 5–(3–metoxi–3–metilbutoxi)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido

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Preparado como en el Ejemplo 215 a partir de 2–sulfamoilamino–6–(3–metoxi–3–metilbutoxi)benzonitrilo (Ejemplo 224a) en 52% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,16 (s, 6H), 1,98 (t, J = 6,2 Hz, 2H), 3,09 (s, 3H), 4,18 (t, J = 6,2 Hz, 2H), 8,57 (d, J = 8,0 Hz, 1H), 6,73 (d, J = 8,0 Hz, 1H), 7,43 (t, J = 8,0 Hz, 1H), 8,25 (s, 1H), 8,30 (s, 1H), 10,89 (s, 1H). MS 314 (MH^+).

Ejemplo 224a: 2–sulfamoilamino–6–(3–metoxi–3–metilbutoxi)benzonitrilo

Preparado como en el Ejemplo 215a a partir de 2–amino–6–(3–metoxi–3–metilbutoxi)benzonitrilo (Ejemplo 224b) en 95% de rendimiento. MS 314 (MH^+).

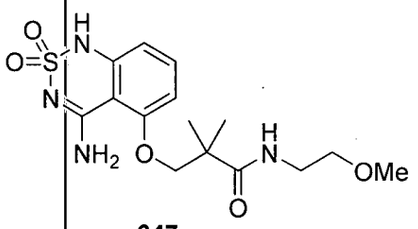
Ejemplo 224b: 2–amino–6–(3–metoxi–3–metilbutoxi)benzonitrilo

Preparado como en el Ejemplo 215b (Método A) a partir de 2–(3–metoxi–3–metilbutoxi)–6–nitrobenzonitrilo (Ejemplo 224c) en 62% de rendimiento. MS 235 (MH^+).

Ejemplo 224c: 2–(3–metoxi–3–metilbutoxi)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 215c a partir de 3–metoxi–3–metilbutan–1–ol y 2,6–dinitrobenzonitrilo en 52% de rendimiento. MS 265 (MH^+).

Ejemplo 225: 3–(4–amino–2,2–dioxido–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)–N–(2''–metoxietil)–2',2'–dimetilpropanamida



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Preparada como en el Ejemplo 215 a partir de 3–(3–sulfamoilamino–2–cianofenoxi)–N–(2–metoxietil)–2,2–dimetilpropanamida (Ejemplo 225a) en 12% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,21 (s, 6H), 3,13 (s, 3H), 3,17-3,22 (m, 2H), 3,28 (t, J = 6,0 Hz, 2H), 4,07 (s, 2H), 6,59 (d, J = 8,0 Hz, 1H), 6,71 (d, J = 8,0 Hz, 1H), 7,43 (t, J = 8,0 Hz, 1H), 7,87 (s, 1H), 7,91 (t, J = 5,6 Hz, 1H), 8,33 (s, 1H), 10,92 (s, 1H). MS 371 (MH^+).

Ejemplo 225a: 3–(3–sulfamoilamino–2–cianofenoxi)–N–(2–metoxietil)–2,2–dimetilpropanamida

Preparada como en el Ejemplo 215a a partir de 3–(3–amino–2–cianofenoxi)–N–(2–metoxietil)–2,2–dimetilpropanamida (Ejemplo 225b) en 41% de rendimiento. MS 371 (MH^+).

Ejemplo 225b: 3–(3–amino–2–cianofenoxi)–N–(2–metoxietil)–2,2–dimetil–propanamida

Preparada como en el Ejemplo 215b (Método A) a partir de 3–(2–ciano–3–nitrofenoxi)–N–(2–metoxietil)–2,2–dimetilpropanamida (Ejemplo 225c) en 91% de rendimiento. MS 292 (MH^+).

Ejemplo 225c: 3–(2–ciano–3–nitrofenoxi)–N–(2–metoxietil)–2,2–dimetil–propanamida

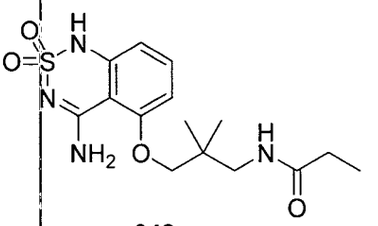
Preparada como en el Ejemplo 215c a partir de 3–hidroxi–N–(2–metoxietil)–2,2–dimetilpropanamida (Ejemplo 225d) y 2,6–dinitrobenzonitrilo en 55% de rendimiento. MS 322 (MH^+).

Ejemplo 225d: 3–hidroxi–N–(2–metoxietil)–2,2–dimetilpropanamida

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Preparada como en el Ejemplo 215d (Método A) a partir de 3–hidroxi–2,2–dimetilpropanoato de metilo y 2–metoxietanamina en 100% de rendimiento. MS 176 (MH^+).

Ejemplo 226: N–(3–(4–amino–)–2,2–dioxido–1H–benzo[c][1,2,6]tiadiazin–5–iloxi–2',2'–dimetilpropil)propionamida



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Preparada como en el Ejemplo 215a a partir de N–(3–(3–amino–2–cianofenoxi)–2,2–dimetilpropil)propionamida (Ejemplo 226a) y cloruro de sulfamoilo en 17% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,93-0,96 (m, 9H), 2,06-2,11 (m, 2H), 3,07 (d, J = 6,0 Hz, 2H), 3,74 (s, 2H), 6,58 (t, J = 8,4 Hz, 1H), 6,69 (d, J = 8,8 Hz, 1H), 7,41 (t, J = 8,4 Hz, 1H), 7,93-7,98 (m, 2H), 8,35 (brs, 1H), 10,91 (brs, 1H). MS 355 (MH^+).

Ejemplo 226a: N–(3–(3–amino–2–cianofenoxi)–2,2–dimetilpropil) propionamida

Preparada como en el Ejemplo 215b (Método A) a partir de N–(3–(2–ciano–3–nitrofenoxi)–2,2–dimetilpropil)propionamida (Ejemplo 226b) en 100% de rendimiento. MS 276 (MH^+).

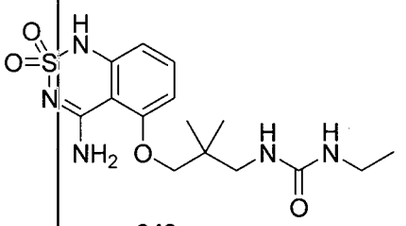
Ejemplo 226b: N–(3–(2–ciano–3–nitrofenoxi)–2,2–dimetilpropil)propionamida

Preparada como en el Ejemplo 215c a partir de N–(3–hidroxi–2,2–dimetilpropil)propionamida (Ejemplo 226c) y 2,6–dinitrobenzonitrilo en 68% de rendimiento. MS 306 (MH^+).

Ejemplo 226c: N–(3–hidroxi–2,2–dimetilpropil)propionamida

Preparada de acuerdo con la literatura (Boyd, R.N.; Hansen, R.H. *J. Am. Chem. Soc.* **1953**, *75*, 5896) a partir de 2–amino–2–metilpropan–1–ol y cloruro de benzoilo en 84% de rendimiento como un sólido blanco. MS 160 (MH^+).

Ejemplo 227: 1–(3–(4–amino–2,2–dioxido–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)–2',2'–dimetilpropil)–3'–etilurea



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Preparada como en el Ejemplo 215 a partir de 1–(3–(3–sulfamoilamino–2–cianofenoxi)–2,2–dimetilpropil)–3–etilurea (Ejemplo 227a) en 55% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,88-0,96 (m, 9H), 2,90-2,97 (m, 2H), 3,01 (d, J = 6,4 Hz, 2H), 3,72 (s, 2H), 5,75 (t, J = 5,6 Hz, 1H), 6,07 (t, J = 6,4 Hz, 1H), 6,56 (d, J = 8,4 Hz, 1H), 6,67 (d, J = 8,8 Hz, 1H), 7,39 (t, J = 8,4 Hz, 1H), 8,05 (brs, 1H), 8,25 (brs, 1H), 10,89 (s, 1H). MS 370 (MH^+).

Ejemplo 227a: 1–(3–(3–sulfamoilamino–2–cianofenoxi)–2,2–dimetilpropil)–3–etilurea

Preparada como en el Ejemplo 215a a partir de 1–(3–(3–amino–2–cianofenoxi)–2,2–dimetilpropil)–3–etilurea (Ejemplo 227b) en 100% de rendimiento. MS 370 (MH^+).

Ejemplo 227b: 1–(3–(3–amino–2–cianofenoxi)–2,2–dimetilpropil)–3–etilurea

Preparada como en el Ejemplo 215b (Método A) a partir de 1–(3–(2–ciano–3–nitrofenoxi)–2,2–dimetilpropil)–3–etilurea (Ejemplo 227c) en 90% de rendimiento. MS 291 (MH^+).

928

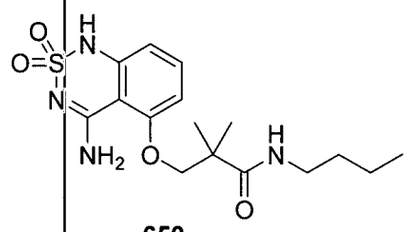
Ejemplo 227c: 1–(3–(2–ciano–3–nitrofenoxi)–2,2–dimetilpropil)–3–etilurea

Preparada como en el Ejemplo 215c a partir de 1–etil–3–(3–hidroxi–2,2–dimetilpropil)urea (Ejemplo 227d) y 2,6–dinitrobenzonitrilo en 47% de rendimiento. MS 321 (MH^+).

Ejemplo 227d: 1–etil–3–(3–hidroxi–2,2–dimetilpropil)urea

A una solución de 3–amino–2,2–dimetilpropan–1–ol (1,03 g, 10 mmol) en 1,4-dioxano seco (20 mL) se le adicionó gota a gota isocianato de etilo (0,71 g, 10 mmol) a temperatura ambiente bajo nitrógeno. Luego la mezcla de reacción se agitó a temperatura ambiente bajo nitrógeno durante la noche. El solvente se removió bajo presión reducida para proporcionar el compuesto del título como un aceite incoloro (1,74 g, 100%). MS 175 (MH^+).

Ejemplo 228: 3–(4–amino–2,2–dioxido–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)–N–butil–2',2'–dimetilpropanamida



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Preparada como en el Ejemplo 215 y 1a a partir de 3–(3–amino–2–cianofenoxi)–N–butil–2,2–dimetilpropanamida (Ejemplo 228a) y cloruro de sulfamoilo en 14% de rendimiento como un sólido blanco. ^1H RMN (400 MHz, DMSO-d_6) δ 0,78 (t, J = 7,2 Hz, 3H), 1,14-1,22 (m, 8H), 1,33-1,37 (m, 2H), 3,02-3,07 (m, 2H), 4,07 (s, 2H), 6,60 (d, J = 8,0 Hz, 1H), 6,71 (d, J = 8,8 Hz, 1H), 7,44 (t, J = 8,4 Hz, 1H), 7,80 (t, J = 5,6 Hz, 1H), 7,91 (s, 1H), 8,33 (s, 1H), 10,92 (s, 1H). MS 369 (MH^+).

Ejemplo 228a: 3–(3–amino–2–cianofenoxi)–N–butil–2,2–dimetilpropanamida .

Preparada como en el Ejemplo 215b (Método A) a partir de N–butil–3–(2–ciano–3–nitrofenoxi)–2,2–dimetilpropanamida (Ejemplo 228b) en 89% de rendimiento. MS 290 (MH^+).

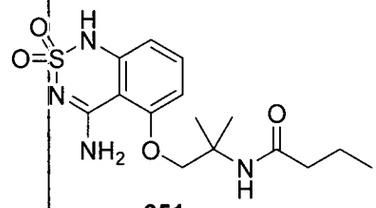
Ejemplo 228b: N–butil–3–(2–ciano–3–nitrofenoxi)–2,2–dimetilpropanamida

Preparada como en el Ejemplo 215c a partir de N–butil–3–hidroxi–2,2–dimetilpropanamida (Ejemplo 228c) y 2,6–dinitrobenzonitrilo en 66% de rendimiento. MS 320 (MH^+).

Ejemplo 228c: N–butil–3–hidroxi–2,2–dimetilpropanamida

Preparada como en el Ejemplo 215d (Método A) a partir de 3–hidroxi–2,2–dimetilpropanoato de metilo y n–butil amina en 100% de rendimiento. MS 174 (MH^+).

Ejemplo 229: N–(1–(4–amino–2,2–dioxido–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)–2'–metilpropan–2'–il)butiramida



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Preparada como en el Ejemplo 215 a partir de N–(1–(3–sulfamoilamino–2–cianofenoxi)–2–metilpropan–2–il)butiramida (Ejemplo 229a) e hidróxido de sodio en 54% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,78 (t, J = 7,2 Hz, 3H), 1,32 (s, 6H), 1,43-1,44 (m, 2H), 2,00 (t, J = 7,2 Hz, 2H), 4,24 (s, 2H), 6,60 (d, J = 8,0 Hz, 1H), 6,73 (d, J = 8,4 Hz, 1H), 7,44 (t, J = 8,4 Hz, 1H), 7,77 (s, 1H), 7,82 (s, 1H), 8,42 (s, 1H), 10,97 (s, 1H). MS 355 (MH^+).

Ejemplo 229a: N–(1–(3–sulfamoilamino–2–cianofenoxi)–2–metilpropan–2–il)–butiramida

Preparada como en el Ejemplo 215a a partir de N–(1–(3–amino–2–cianofenoxi)–2–metilpropan–2–il)butiramida (Ejemplo 229b) y cloruro de sulfamoilo en 100% de rendimiento. MS 355 (MH^+).

Ejemplo 229b: N–(1–(3–amino–2–cianofenoxi)–2–metilpropan–2–il) butiramida

Preparada como en el Ejemplo 215b (Método A) a partir de N–(1–(2–ciano–3–nitrofenoxi)–2–metilpropan–2–il)butiramida (Ejemplo 229c) en 100% de rendimiento. MS 276 (MH^+).

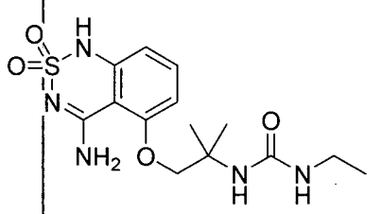
Ejemplo 229c: N–(1–(2–ciano–3–nitrofenoxi)–2–metilpropan–2–il)butiramida

Preparada como en el Ejemplo 215c a partir de N–(1–hidroxi–2–metilpropan–2–il)butiramida (Ejemplo 229d) y 2,6–dinitrobenzonitrilo en 72% de rendimiento. MS 306 (MH^+).

Ejemplo 229d: N–(1–hidroxi–2–metilpropan–2–il)butiramida

Preparada de acuerdo con la literatura (Boyd, R.N.; Hansen, R.H. *J. Am. Chem. Soc.* **1953**, *75*, 5896) a partir de 2–amino–2–metilpropan–1–ol y cloruro de butirilo en 32% de rendimiento. MS 160 (MH^+).

Ejemplo 230: 1–(1–(4–amino–2,2–dioxido–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)–2'–metilpropan–2'–il)–3'–etilurea



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Preparada como en el Ejemplo 215 a partir de 1–(1–(3–sulfamoilamino–2–cianofenoxi)–2–metilpropan–2–il)–3–etilurea (Ejemplo 230a) en 37% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,92 (t, J = 7,2 Hz, 3H), 1,27 (s, 6H), 2,90-2,93 (m, 2H), 4,21 (s, 2H), 5,63 (t, J = 5,2 Hz, 1H), 5,95 (s, 1H), 6,59 (d, J = 8,0 Hz, 1H), 6,72 (d, J = 8,4 Hz, 1H), 7,42 (t, J = 8,4 Hz, 1H), 7,94 (s, 1H), 8,34 (s, 1H), 10,94 (s, 1H). MS 356 (MH^+).

Ejemplo 230a: 1–(1–(3–sulfamoilamino–2–cianofenoxi)–2–metilpropan–2–il)–3–etilurea

Preparada como en el Ejemplo 215a a partir de 1–(1–(3–amino–2–cianofenoxi)–2–metilpropan–2–il)–3–etilurea (Ejemplo 230b) y cloruro de sulfamoilo en 100% de rendimiento. MS 356 (MH^+).

Ejemplo 230b: 1–(1–(3–amino–2–cianofenoxi)–2–metilpropan–2–il)–3–etilurea

Preparada como en el Ejemplo 215b (Método A) a partir de 1–(1–(2–ciano–3–nitrofenoxi)–2–metilpropan–2–il)–3–etilurea (Ejemplo 230c) en 86% de rendimiento. MS 277 (MH^+).

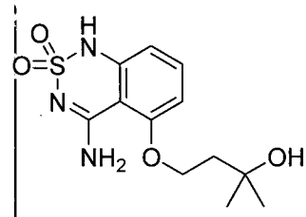
Ejemplo 230c: 1–(1–(2–ciano–3–nitrofenoxi)–2–metilpropan–2–il)–3–etilurea

Preparada como en el Ejemplo 215c a partir de 1–etil–3–(1–hidroxi–2–metilpropan–2–il)urea (Ejemplo 230d) y 2,6–dinitrobenzonitrilo en 65% de rendimiento. MS 307 (MH^+).

Ejemplo 230d: 1–etil–3–(1–hidroxi–2–metilpropan–2–il)urea

Preparada como en el Ejemplo 227d a partir de 2–amino–2–metilpropan–1–ol e isocianato de etilo en 94% de rendimiento. MS 161 (MH^+).

Ejemplo 231: 4–(4–amino–2,2–dioxido–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)–2'–metilbutan–2'–ol



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Preparado como en el Ejemplo 215 a partir de acetato de 4–(2–ciano–3–(sulfamoilamino)fenoxi)–2–metilbutan–2–ilo (Ejemplo 231a) en 20% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,15 (s, 6H), 1,89 (t, J = 6,4 Hz, 2H), 4,22 (t, J = 6,4 Hz, 2H), 4,62 (s,1H), 6,57 (d, J = 8,0 Hz, 1H), 6,73 (d, J = 8,4 Hz, 1H), 7,43 (t, J = 8,4 Hz, 1H), 8,22 (s, 1H), 8,30 (s, 1H), 10,87 (s, 1H). MS 300 (MH^+).

Ejemplo 231a: Acetato de 4–(2–ciano–3–(sulfamoilamino)fenoxi)–2–metilbutan–2–ilo

Preparado como en el Ejemplo 215a a partir de acetato de 4–(3–amino–2–cianofenoxi)–2–metilbutan–2–ilo (Ejemplo 231b) y cloruro de sulfamoilo en 100% de rendimiento. MS 342 (MH^+).

Ejemplo 231b: Acetato de 4–(3–amino–2–cianofenoxi)–2–metilbutan–2–ilo

Preparado como en el Ejemplo 215b (Método A) a partir de acetato de 4–(2–ciano–3–nitrofenoxi)–2–metilbutan–2–ilo (Ejemplo 231c). MS 263 (MH^+).

Ejemplo 231c: Acetato de 4–(2–ciano–3–nitrofenoxi)–2–metilbutan–2–ilo

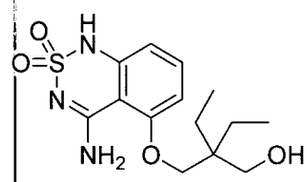
A una solución de 2–(3–hidroxi–3–metilbutoxi)–6–nitrobenzonitrilo (Ejemplo 231d) (250 mg, 1 mmol), trietilamina (3 equiv.), y DMAP (0,1 equiv.) en diclorometano seco (20 mL) se adicionó gota a gota cloruro de acetilo (1,5 equiv.) a 0ºC bajo nitrógeno. Luego la mezcla de reacción se agitó a 0ºC – temperatura ambiente durante la noche. La reacción se diluyó con EtOAc, se lavó con salmuera, y se secó sobre Na_2SO_4. Luego de la evaporación del solvente, el residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con 20%

EtOAc en hexanos para proporcionar el compuesto del título (137 mg, 47%). MS 293 (MH^+).

Ejemplo 231d: 2–(3–hidroxi–3–metilbutoxi)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 215c a partir de 3–metilbutan–1,3–diol y 2,6–dinitrobenzonitrilo en 81% de rendimiento. MS 251 (MH^+).

Ejemplo 232: 2–((4–amino–2,2–dioxido–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)metil)–2'–etilbutan–1'–ol



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Preparado como en el Ejemplo 215 a partir de acetato de 2–etil–2–((2–metil–3–(sulfamoilamino)fenoxi)metil)butilo (Ejemplo 232a) en 20% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,73-0,80 (m, 6H), 1,21-1,37 (m, 4H), 3,31-3,33 (m, 2H), 3,89 (s, 2H), 4,92 (brs, 1H), 6,56 (d, J = 8,0 Hz, 1H), 6,73 (d, J = 8,4 Hz, 1H), 7,40 (t, J = 8,4 Hz, 1H), 8,16 (brs, 2H), 10,91 (brs, 1H). MS 328 (MH^+).

Ejemplo 232a: Acetato de 2–((2–ciano–3–(sulfamoilamino)fenoxi)metil)–2–etilbutilo

Preparado como en el Ejemplo 215a a partir de acetato de 2–((3–amino–2–cianofenoxi)metil)–2–etilbutil (Ejemplo 232b) y cloruro de sulfamoilo en 90% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,80 (t, J = 7,6 Hz, 6H), 1,37-1,43 (m, 4H), 1,98 (s, 3H), 3,87 (s, 2H), 3,96 (s, 2H), 6,98 (d, J = 8,8 Hz, 1H), 7,13 (d, J = 8,4 Hz, 1H), 7,25 (s, 2H), 7,54 (t, J = 8,4 Hz, 1H), 9,46 (s, 1H).

Ejemplo 232b: Acetato de 2–((3–amino–2–cianofenoxi)metil)–2–etilbutilo

Preparado como en el Ejemplo 215b (Método A) a partir de acetato de 2–((2–ciano–3–nitrofenoxi)metil)–2–etilbutilo (Ejemplo 232c) en 91% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,79 (t, J = 7,6 Hz, 6H), 1,34-1,41 (m, 4H), 1,97 (s, 3H), 3,76 (s, 2H), 3,94 (s, 2H), 5,97 (s, 2H), 6,21 (d, J = 8,0 Hz, 1H), 6,31 (d, J = 8,4 Hz, 1H), 7,15 (t, J = 8,0 Hz, 1H). MS 291 (MH^+).

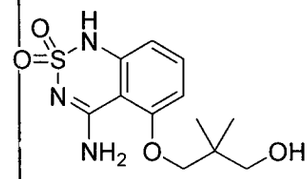
Ejemplo 232c: Acetato de 2–((2–ciano–3–nitrofenoxi)metil)–2–etilbutilo

Preparado como en el Ejemplo 231c a partir de 2–(2–etil–2–(hidroximetil)butoxi)–6–nitrobenzonitrilo (Ejemplo 232d) y cloruro de acetilo en 82% de rendimiento. MS 321 (MH^+).

Ejemplo 232d: 2–(2–etil–2–(hidroximetil)butoxi)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 215c a partir de 2,2–dietilpropan–1,3–diol y 2,6–dinitrobenzonitrilo en 86% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,80 (t, J = 7,6 Hz, 6H), 1,34 (q, J = 7,6 Hz, 4H), 3,33 (d, J = 5,6 Hz, 2H), 3,96 (s, 2H), 4,57 (t, J = 5,2 Hz, 1H), 7,74-7,76 (m, 1H), 7,84-7,90 (m, 2H).

Ejemplo 233: 3–(4–amino–2,2–dioxido–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)–2',2'–dimetilpropan–1'–ol



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Preparado como en el Ejemplo 215 a partir de acetato de 3–(2–ciano–3–(sulfamoil–amino)fenoxi)–2,2–dimetilpropilo (Ejemplo 233a) en 30% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,94 (s, 6H), 3,29-3,31 (m, 2H), 3,88 (s, 2H), 5,01 (t, J = 4,4 Hz, 1H), 6,58 (d, J = 8,4 Hz, 1H),

6,71 (d, *J* = 8,4 Hz, 1H), 7,42 (t, *J* = 8,0 Hz, 1H), 8,14 (s, 1H), 8,32 (s, 1H), 10,92 (s, 1H). MS 300 (MH^+).

Ejemplo 233a: Acetato de 3–(2–ciano–3–(sulfamoilamino)fenoxi)–2,2–dimetilpropilo

Preparado como en el Ejemplo 215a a partir de acetato de 3–(3–amino–2–cianofenoxi)–2,2–dimetilpropilo (Ejemplo 233b) y cloruro de sulfamoilo en 60% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,99 (s, 6H), 1,98 (s, 3H), 3,85 (s, 2H), 3,91 (s, 2H), 6,91 (d, *J* = 8,4 Hz, 1H), 7,12 (d, *J* = 8,0 Hz, 1H), 7,23 (s, 2H), 7,52 (t, *J* = 8,0 Hz, 1H), 9,45 (s, 1H).

Ejemplo 233b: Acetato de 3–(3–amino–2–cianofenoxi)–2,2–dimetilpropilo

Preparado como en el Ejemplo 215b (Método A) a partir de acetato de 3–(2–ciano–3–nitrofenoxi)–2,2–dimetilpropilo (Ejemplo 233c) en 77% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,98 (s, 6H), 2,00 (s, 3H), 3,75 (s, 2H), 3,90 (s, 2H), 5,99 (s, 2H), 6,17 (d, *J* = 8,4 Hz, 1H), 6,31 (d, *J* = 8,4 Hz, 1H), 7,15 (t, *J* = 8,0 Hz, 1H).

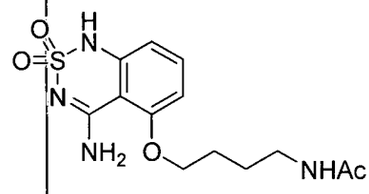
Ejemplo 233c: Acetato de 3–(2–ciano–3–nitrofenoxi)–2,2–dimetilpropilo

Preparado como en el Ejemplo 231c a partir de 2–(3–hidroxi–2,2–dimetilpropoxi)–6–nitrobenzonitrilo (Ejemplo 233d) y cloruro de acetilo en 66% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,04 (s, 6H), 2,00 (s, 3H), 3,95 (s, 2H), 4,02 (s, 2H), 7,70-7,72 (m, 1H), 7,85-7,92 (m, 2H).

Ejemplo 233d: 2–(3–hidroxi–2,2–dimetilpropoxi)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 215c a partir de 2,2–dimetilpropan–1,3–diol y 2,6–dinitrobenzonitrilo en 73% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,94 (s, 6H), 3,29-3,31 (m, 2H), 3,95 (s, 2H), 4,69 (t, *J* = 5,6 Hz, 1H), 7,69-7,71 (m, 1H), 7,84-7,90 (m, 2H).

Ejemplo 234: N–(4–(4–amino–2,2–dioxido–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)butil)–acetamida



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Preparada como en el Ejemplo 215 a partir de N–(4–(2–ciano–3–(sulfamoilamino)fenoxi)butil)acetamida (Ejemplo 234a) en 30% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,48-1,51 (m, 2H), 1,77-1,81 (m, 5H), 3,03-3,08 (m, 2H), 4,14 (t, J = 6,0 Hz, 2H), 6,59 (d, J = 8,0 Hz, 1H), 6,73 (d, J = 8,4 Hz, 1H), 7,43 (t, J = 8,4 Hz, 1H), 7,78 (s,1H). 7,84 (brs, 1H), 8,32 (s,1H), 10,93 (s, 1H). MS 327 (MH^+).

Ejemplo 234a: N–(4–(2–ciano–3–(sulfamoilamino)fenoxi)butil)acetamida

Preparada como en el Ejemplo 215a a partir de N–(4–(3–amino–2–cianofenoxi)butil)acetamida (Ejemplo 234b) y cloruro de sulfamoilo en 100% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,51-1,54 (m, 2H), 1,70-1,73 (m, 2H), 1,77 (s, 3H), 3,04-3,09 (m, 2H), 4,09 (t, J = 6,4 Hz, 2H), 6,93 (d, J = 8,4 Hz, 1H), 7,13 (d, J = 8,0 Hz, 1H), 7,25 (s, 2H), 7,54 (t, J = 8,0 Hz, 1H), 7,85 (brs,1H), 9,42 (s, 1H).

Ejemplo 234b: N–(4–(3–amino–2–cianofenoxi)butil)acetamida

Preparada como en el Ejemplo 215b (Método A) a partir de N–(4–(2–ciano–3–nitrofenoxi)butil)acetamida (Ejemplo 234c) en 85% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,49-1,54 (m, 2H), 1,66-1,70 (m, 2H), 1,77 (s, 3H), 3,03-3,08 (m, 2H), 3,97 (t, J = 6,8 Hz, 2H), 5,95 (s, 2H), 6,18 (d, J = 8,0 Hz, 1H), 6,31 (d, J = 7,6 Hz, 1H), 7,15 (t, J = 8,4 Hz, 1H), 7,83 (brs,1H).

Ejemplo 234c: N–(4–(2–ciano–3–nitrofenoxi)butil)acetamida

A una solución de 2–(4–aminobutoxi)–6–nitrobenzonitrilo (Ejemplo 234d) (235 mg, 1,0 mmol), trietilamina (3 equiv.), y DMAP (0,1 equiv.) en diclorometano

seco (20 mL) se le adicionó gota a gota cloruro de acetilo (1,5 equiv.) a 0ºC bajo nitrógeno. Luego la mezcla de reacción se agitó a 0ºC – ta durante la noche. La reacción se diluyó con EtOAc, se lavó con salmuera, y se secó sobre Na_2SO_4. Luego de la evaporación del solvente, el residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con 50% EtOAc en hexanos para proporcionar el compuesto del título (158 mg, 57%). MS 278 (MH^+).

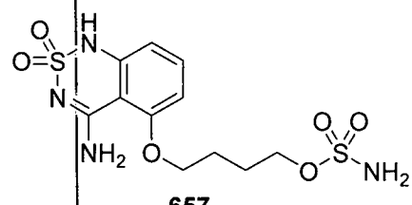
Ejemplo 234d: 2–(4–aminobutoxi)–6–nitrobenzonitrilo

Una solución de terc–butil 4–(2–ciano–3–nitrofenoxi)butilcarbamato (Ejemplo 234e) (671 mg, 2 mmol) en DCM/TFA (1:1, 20 mL) se agitó a temperatura ambiente durante 2 hs. El solvente se removió bajo vacío para proporcionar el compuesto del título (698 mg, 100%). MS 236 (MH^+).

Ejemplo 234e: 4–(2–ciano–3–nitrofenoxi)butilcarbamato de terc–butilo

Preparado como en el Ejemplo 215c a partir de 4–hidroxibutilcarbamato de terc–butilo y 2,6–dinitrobenzonitrilo en 7% de rendimiento como un sólido amarillo pálido. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,35 (s, 9H), 1,52-1,55 (m, 2H), 1,72-1,76 (m, 2H), 2,94-2,99 (m, 2H), 4,24 (t, J = 6,8 Hz, 2H), 6,86 (brs, 1H), 7,69-7,72 (m, 1H), 7,85-7,90 (m,2H).

Ejemplo 235: Sulfamato de 4–(4–amino–2,2–dioxido–1H–benzo[c][1,2,6] tiadiazin–5–iloxi)butilo



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Preparado como en el Ejemplo 215 a partir de sulfamato de 4–(2–ciano–3–(sulfamoilamino)fenoxi)butilo (Ejemplo 235a) en 31% de rendimiento. ^{1}H RMN

(400 MHz, DMSO-d_6) δ 1,74-1,79 (m, 2H), 1,85-1,91 (m, 2H), 4,07 (t, J = 6,4 Hz, 2H), 4,18 (t, J = 6,8 Hz, 2H), 6,58-6,60 (m, 1H), 6,74 (d, J = 8,4 Hz, 1H), 7,42-7,46 (m, 3H), 7,79 (s,1H), 8,32 (s, 1H), 10,93 (s,1H). MS 365 (MH^+).

Ejemplo 235a: Sulfamato de 4–(2–ciano–3–(sulfamoilamino)fenoxi)butilo

Preparado como en el Ejemplo 215a a partir de 2–amino–6–(4–(terc–butildimetilsililoxi)butoxi)benzonitrilo (Ejemplo 235b) y cloruro de sulfamoilo en 63% de rendimiento. MS 382 (M^++H_2O).

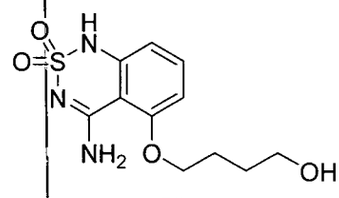
Ejemplo 235b: 2–amino–6–(4–(terc–butildimetilsililoxi)butoxi)benzonitrilo

Preparado como en el Ejemplo 215b (Método A) a partir de 2–(4–(terc–butildimetilsililoxi)butoxi)–6–nitrobenzonitrilo (Ejemplo 235c) en 76% de rendimiento. MS 321 (MH^+).

Ejemplo 235c: 2–(4–(terc–butildimetilsililoxi)butoxi)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 215c a partir de 4–(terc–butildimetil–sililoxi)butan–1–ol y 2,6–dinitrobenzonitrilo en 25% de rendimiento como un sólido amarillo pálido. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,01 (s, 6H), 0,81-0,83 (m, 9H), 1,61-1,66 (m, 2H), 1,76-1,81 (m, 2H), 3,63 (t, J = 6,8 Hz, 2H), 4,26 (t, J = 6,4 Hz, 2H), 7,68-7,70 (m, 1H), 7,84-7,89 (m, 2H).

Ejemplo 236: 4–(4–amino–2,2–dioxido–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)–butan–1'–ol

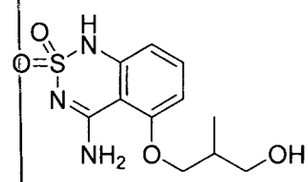


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Preparado como en el Ejemplo 215 a partir de sulfamato de 4–(2–ciano–3–(sulfamoilamino)fenoxi)butilo (Ejemplo 235a) en 2% de rendimiento. ^{1}H RMN (400

MHz, CD_3OD) δ 1,69-1,73 (m, 2H), 1,95-1,99 (m, 2H), 3,63 (t, J = 6,4 Hz, 2H), 4,24 (t, J = 6,4 Hz, 2H), 6,61-6,63 (m, 1H), 6,75-6,77 (m, 1H), 7,45 (m, J = 8,0 Hz, 1H). MS 286 (MH^+).

Ejemplo 237: 3–(4–amino–2,2–dioxido–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)–2'–metilpropan–1'–ol



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Preparado como en el Ejemplo 215 a partir de acetato de 3–(2–ciano–3–(sulfamoilamino)fenoxi)–2–metilpropilo (Ejemplo 237a) en 41% de rendimiento como un sólido blanco. ^1H RMN (400 MHz, DMSO-d_6) δ 0,94 (d, J = 6,4 Hz, 3H), 2,09-2,13 (m, 1H), 3,36-3,42 (m, 1H), 3,46-3,50 (m, 1H), 4,05 (d, J = 6,4 Hz, 2H), 4,84 (t, J = 5,6 Hz, 1H), 6,57 (d, J = 7,6 Hz, 1H), 6,70 (d, J = 8,4 Hz, 1H), 7,42 (t, J = 8,4 Hz, 1H), 8,05 (brs, 1H), 8,24 (brs, 1H), 10,91 (s, 1H). MS 286 (MH^+).

Ejemplo 237a: Acetato de 33–(2–ciano–3–(sulfamoilamino)fenoxi)–2–metilpropilo

Preparado como en el Ejemplo 215a a partir de acetato de 3–(3–amino–2–cianofenoxi)–2–metilpropilo (Ejemplo 237b) y cloruro de sulfamoilo en 78% de rendimiento. ^1H RMN (400 MHz, DMSO-d_6) δ 1,02 (d, J = 6,8 Hz, 3H), 2,01 (s, 3H), 2,23-2,27 (m, 1H), 3,99-4,07 (m, 4H), 6,94 (d, J = 8,8 Hz, 1H), 7,14 (d, J = 8,0 Hz, 1H), 7,26 (s, 2H), 7,55 (t, J = 8,0 Hz, 1H), 9,47 (s, 1H).

Ejemplo 237b: Acetato de 3–(3–amino–2–cianofenoxi)–2–metilpropilo

Preparado como en el Ejemplo 215b (Método A) a partir de acetato de 3–(2–ciano–3–nitrofenoxi)–2–metilpropilo (Ejemplo 237c) en 73% de rendimiento. ^1H RMN (400 MHz, DMSO-d_6) δ 0,99 (d, J = 7,2 Hz, 3H), 2,00 (s, 3H), 2,19-2,24 (m,

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1H), 3,91 (d, *J* = 5,2 Hz, 2H), 3,97-4,06 (m, 2H), 5,98 (s, 2H), 6,19 (d, *J* = 8,0 Hz, 1H), 6,32 (d, *J* = 8,4 Hz, 1H), 7,16 (t, *J* = 8,0 Hz, 1H).

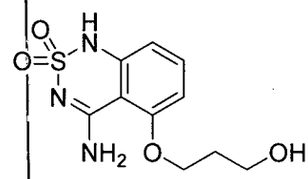
Ejemplo 237c: Acetato de 3–(2–ciano–3–nitrofenoxi)–2–metilpropilo

Preparado como en el Ejemplo 231c a partir de 2–(3–hidroxi–2–metilpropoxi)–6–nitrobenzonitrilo (Ejemplo 237d) y cloruro de acetilo en 41% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,04 (d, *J* = 6,8 Hz, 3H), 2,00 (s, 3H), 2,28-2,33 (m, 1H), 4,05-4,08 (m, 2H), 4,18 (d, *J* = 6,0 Hz, 2H), 7,71-7,73 (m, 1H), 7,86-7,92 (m, 2H).

Ejemplo 237d: 2–(3–hidroxi–2–metilpropoxi)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 215c a partir de 2–metilpropan–1,3–diol y 2,6–dinitrobenzonitrilo en 37% de rendimiento. MS 237 (MH^+).

Ejemplo 238: 3–(4–amino–2,2–dioxido–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)propan–1'–ol



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Preparado como en el Ejemplo 215 a partir de sulfamato de 3–(2–ciano–3–(sulfamoilamino)fenoxi)propilo (Ejemplo 238a) en 6% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,92-1,97 (m, 2H), 3,55-3,59 (m, 2H), 4,20 (t, *J* = 6,4 Hz, 2H), 4,79 (t, *J* = 4,8 Hz, 1H), 6,57-6,59 (m, 1H), 6,71-6,73 (m, 1H), 7,43 (t, *J* = 8,4 Hz, 1H), 8,12 (brs, 1H), 8,28 (brs, 1H), 10,90 (s, 1H). MS 272 (MH^+).

Ejemplo 238a: Sulfamato de 3–(2–ciano–3–(sulfamoilamino)fenoxi)propilo

Preparado como en el Ejemplo 215a a partir de 2–amino–6–(3–hidroxipropoxi)benzonitrilo (Ejemplo 238b) y cloruro de sulfamoilo en 30% de

rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,11-2,14 (m, 2H), 4,16-4,21 (m, 4H), 6,96 (d, J = 8,0 Hz, 1H), 7,15 (d, J = 7,6 Hz, 1H), 7,26 (s, 2H), 7,49 (s, 2H), 7,56 (t, J = 8,4 Hz, 1H), 9,46 (s, 1H).

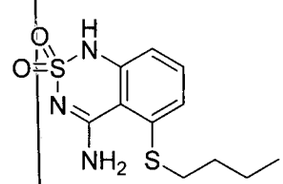
Ejemplo 238b: 2–amino–6–(3–hidroxipropoxi)benzonitrilo

Preparado como en el Ejemplo 215b (Método A) a partir de 2–(3–hidroxipropoxi)–6–nitrobenzonitrilo (Ejemplo 238c) en 100% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,79-1,85 (m, 2H), 3,52-3,56 (m, 2H), 4,04 (t, J = 6,4 Hz, 2H), 4,54 (t, J = 5,2 Hz, 1H), 5,93 (s, 2H), 6,19 (d, J = 8,0 Hz, 1H), 6,30 (d, J = 8,4 Hz, 1H), 7,15 (t, J = 8,0 Hz, 1H).

Ejemplo 238c: 2–(3–hidroxipropoxi)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 215c a partir de propan–1,3–diol y 2,6–dinitrobenzonitrilo dn 61% de rendimiento como un sólido amarillo pálido. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,89-1,93 (m, 2H), 3,56-3,61 (m, 2H), 4,30 (t, J = 6,4 Hz, 2H), 4,61 (t, J = 5,2 Hz, 1H), 7,71-7,74 (m, 1H), 7,85-7,91 (m, 2H).

Ejemplo 239: 5–(butiltio)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



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Preparado como en el Ejemplo 215 a partir de 2–sulfamoilamino–6–(butiltio)benzonitrilo (Ejemplo 239a) en 12% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,85 (t, J = 7,6 Hz, 3H), 1,34-1,41 (m, 2H), 1,49-1,56 (m, 2H), 2,97 (t, J = 7,2 Hz, 2H), 6,87 (d, J = 8,4 Hz, 1H), 7,12 (d, J = 7,6 Hz, 1H), 7,41 (t, J = 7,6 Hz, 1H), 8,12 (brs, 2H), 11,02 (brs, 1H). MS 286 (MH^+).

Ejemplo 239a: 2–sulfamoilamino–6–(butiltio)benzonitrilo

Preparado como en el Ejemplo 215a a partir de 2–amino–6–(butiltio)benzonitrilo (Ejemplo 239b) en 76% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,88 (t, J = 7,2 Hz, 3H), 1,36-1,45 (m, 2H), 1,54-1,61 (m, 2H), 3,07 (t, J = 7,6 Hz, 2H), 7,25-7,27 (m, 3H), 7,33-7,36 (m, 1H), 7,57 (t, J = 8,4 Hz, 1H), 9,50 (s, 1H).

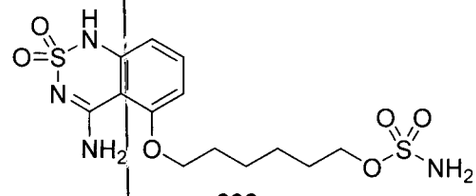
Ejemplo 239b: 2–amino–6–(butiltio)benzonitrilo

Preparado como en el Ejemplo 215b (Método A) a partir de 2–nitro–6–(butiltio)benzonitrilo (Ejemplo 239c) en 87% de rendimiento. ^{1}H RMN (400 MHz, $CDCl_3$) δ 0,93 (t, J = 7,2 Hz, 3H), 1,42-1,52 (m, 2H), 1,63-1,70 (m, 2H), 2,97 (t, J = 6,8 Hz, 2H), 4,43 (brs, 2H), 6,52-6,54 (m, 1H), 6,67-6,69 (m, 1H), 7,21 (t, J = 8,0 Hz, 1H).

Ejemplo 239c: 2–nitro–6–(butiltio)benzonitrilo

Preparado como en el Ejemplo 215c a partir de butan–1–tiol y 2,6–dinitrobenzonitrilo en 90% de rendimiento. ^{1}H RMN (400 MHz, $CDCl_3$) δ 0,97 (t, J = 7,2 Hz, 3H), 1,42-1,55 (m, 2H), 1,70-1,77 (m, 2H), 3,09 (t, J = 7,2 Hz, 2H), 7,63-7,69 (m, 2H), 7,99-8,01 (m, 1H).

Ejemplo 240: Sulfamato de 6–(4–amino–2,2–dioxido–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)hexilo



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Preparada como en el Ejemplo 215 a partir de sulfamato de 6–(2–ciano–3–(sulfamoilamino)fenoxi)hexilo (Ejemplo 240a) en 46% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,03-1,05 (m, 4H), 1,28 (m, 2H), 1,45 (m, 2H), 3,64 (t, J = 6,4 Hz, 2H), 3,78 (t, J = 6,4 Hz, 2H), 6,22 (d, J = 7,6 Hz, 1H), 6,37 (d, J = 7,6 Hz,

1H), 7,02 (s, 2H), 7,07 (t, J = 7,6 Hz, 1H), 7,44 (s, 1H), 7,96 (s, 1H), 10,56 (s, 1H). MS 393 (MH^+).

Ejemplo 240a: Sulfamato de 6–(2–ciano–3–(sulfamoilamino)fenoxi)hexilo

Preparado como en el Ejemplo 215a a partir de 2–amino–6–(6–hidroxi–hexiloxi)benzonitrilo (Ejemplo 240b) y cloruro de sulfamoilo en 20% de rendimiento. MS 393 (MH^+).

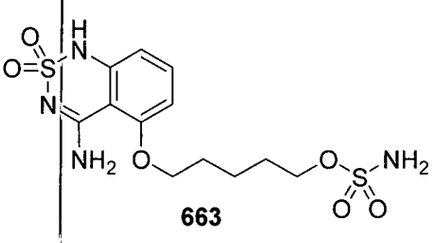
Ejemplo 240b: 2–amino–6–(6–hidroxihexiloxi)benzonitrilo

Preparado como en el Ejemplo 215b (Método A) a partir de 2–(6–hidroxihexiloxi)–6–nitrobenzonitrilo (Ejemplo 240c) en 99% de rendimiento. MS 235 (MH^+).

Ejemplo 240c: 2–(6–hidroxihexiloxi)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 215c a partir de hexan–1,6–diol y 2,6–dinitrobenzonitrilo en 88% de rendimiento como un sólido amarillo pálido. MS 265 (MH^+).

Ejemplo 241: Sulfamato de 5–(4–amino–2,2–dioxido–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)pentilo



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Preparado como en el Ejemplo 215 a partir de sulfamato de 5–(2–ciano–3–(sulfamoilamino)–fenoxi)pentilo (Ejemplo 241a) en 44% de rendimiento. ^1H RMN (400 MHz, DMSO-d_6) δ 1,09 (m, 2H), 1,33 (m, 2H), 1,47 (m, 2H), 3,66 (t, J = 6,6 Hz, 2H), 3,79 (t, J = 6,6 Hz, 2H), 6,22 (d, J = 8,0 Hz, 1H), 6,37 (d, J = 8,0 Hz, 1H), 7,03 (s, 2H), 7,07 (t, J = 8,0 Hz, 1H), 7,43 (s, 1H), 7,95 (s, 1H), 10,57 (s, 1H). MS 379 (MH^+).

Ejemplo 241a: Sulfamato de 5–(2–ciano–3–(sulfamoilamino)fenoxi)pentilo

Preparado como en el Ejemplo 215a a partir de 2–amino–6–(5–(terc–butildimetilsililoxi)pentiloxi)benzonitrilo (Ejemplo 241b) y cloruro de sulfamoilo en 26% de rendimiento. MS 379 (MH^+).

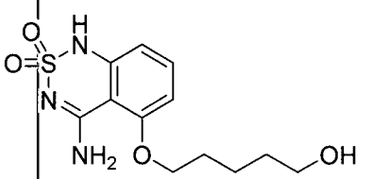
Ejemplo 241b: 2–amino–6–(5–(terc–butildimetilsililoxi)pentiloxi)benzonitrilo

Preparado como en el Ejemplo 215b (Método A) a partir de 2–(5–(terc–butildimetil–sililoxi)pentiloxi)–6–nitrobenzonitrilo (Ejemplo 241c) en 93% de rendimiento. MS 335 (MH^+).

Ejemplo 241c: 2–(5–(terc–butildimetilsililoxi)pentiloxi)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 215c a partir de 5–(terc–butildimetil–sililoxi)pentan–1–ol y 2,6–dinitrobenzonitrilo como un sólido amarillo pálido en 46% de rendimiento. MS 365 (MH^+).

Ejemplo 242: 5–(4–amino–2,2–dioxido–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)pentan–1'–ol



664

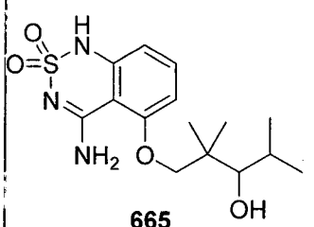
Preparado como en el Ejemplo 215 a partir de 2–sulfamoilamino–6–(5–hidroxi–pentiloxi)benzonitrilo (Ejemplo 242a) en 32% de rendimiento. ^1H RMN (400 MHz, DMSO-d_6) δ 1,39-1,49 (m, 4H), 1,77-1,84 (m, 2H), 3,31-3,44 (m, 2H), 4,14 (t, J = 6,4 Hz, 2H), 4,35 (m, 1H), 6,59 (d, J = 8,0 Hz, 1H), 6,74 (d, J = 8,0 Hz, 1H), 7,44 (t, J = 8,0 Hz, 1H), 7,81 (s, 1H), 8,34 (s, 1H), 10,93 (s, 1H). MS 300 (MH^+).

Ejemplo 242a: 2–sulfamoilamino–6–(5–hidroxipentiloxi)benzonitrilo

945

Preparado como en el Ejemplo 215a a partir de 2–amino–6–(5–(terc–butildimetilsililoxi)pentiloxi)benzonitrilo (Ejemplo 241b) y cloruro de sulfamoilo en 4% de rendimiento. MS 300 (MH^+).

Ejemplo 243: 1–(4–amino–2,2–dioxido–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)–2',2',4'–trimetilpentan–3'–ol



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Preparado como en el Ejemplo 215 a partir de acetato de 1–(2–ciano–3–(sulfamoilamino)–fenoxi)–2,2,4–trimetilpentan–3–ilo (Ejemplo 243a) en 35% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,76-0,78 (d, 3H), 0,93 (s, 6H), 1,05 (s, 3H), 1,86-1,89 (m, 1H), 3,18-3,19 (d, 1H), 3,73-3,75 (d, 1H), 3,99-4,02 (d, 1H), 4,98-4,99 (d, 1H), 6,57-6,59 (d, J = 8 Hz, 1H), 6,70-6,72 (d, J = 8 Hz,1H), 7,43 (t, J = 8 Hz, 1H), 8,29 (s, 1H), 8,43 (s, 1H), 10,88 (s, 1H). MS 342 (MH^+).

Ejemplo 243a: Acetato de 1–(2–ciano–3–(sulfamoilamino)fenoxi)–2,2,4–trimetilpentan–3–ilo

Preparado como en el Ejemplo 215a a partir de acetato de 1–(3–amino–2–cianofenoxi)–2,2,4–trimetilpentan–3–ilo (Ejemplo 243b) y cloruro de sulfamoilo en 90% de rendimiento. MS 384 (MH^+).

Ejemplo 243b: Acetato de 1–(3–amino–2–cianofenoxi)–2,2,4–trimetilpentan–3–ilo

Preparado como en el Ejemplo 215b (Método A) a partir de acetato de 1–(2–ciano–3–nitrofenoxi)–2,2,4–trimetilpentan–3–ilo (Ejemplo 243c) en 83% de rendimiento. MS 305 (MH^+).

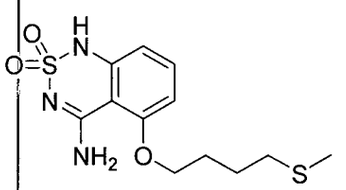
Ejemplo 243c: Acetato de 1–(2–ciano–3–nitrofenoxi)–2,2,4–trimetilpentan–3–ilo

Preparado como en el Ejemplo 231c a partir de 2–(3–hidroxi–2,2,4–trimetilpentiloxi)–6–nitrobenzonitrilo (Ejemplo 243d) y cloruro de acetilo en 50% de rendimiento. MS 335 (MH^+).

Ejemplo 243d: 2–(3–hidroxi–2,2,4–trimetilpentiloxi)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 215c a partir de 2,2,4–trimetilpentan–1,3–diol y 2,6–dinitrobenzonitrilo en 90% de rendimiento. MS 293 (MH^+).

Ejemplo 244: 5–(4–(metiltio)butoxi)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



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Preparado como en el Ejemplo 215 a partir de 2–sulfamoilamino–6–(4–(metiltio)butoxi)benzonitrilo (Ejemplo 244a) en 79% de rendimiento. ^1H RMN (400 MHz, DMSO-d_6) δ 1,63-1,67 (m, 2H), 1,86-1,90 (m, 2H), 2,02 (s, 3H), 2,48-2,53 (m, 2H), 4,16 (t, 2H), 6,57-6,60 (d, J=8,4 Hz, 1H), 6,72-6,74 (d, J = 8,4 Hz,1H), 7,43 (t, J=8 Hz, 1H), 7,80 (s, 1H), 8,35 (s, 1H), 10,92 (s, 1H). MS 316 (MH^+).

Ejemplo 244a: 2–sulfamoilamino–6–(4–(metiltio)butoxi)benzonitrilo

Preparado como en el Ejemplo 215a a partir de 2–amino–6–(4–(metiltio)–butoxi)benzonitrilo (Ejemplo 244b) y cloruro de sulfamoilo en 66% de rendimiento. MS 316 (MH^+).

947

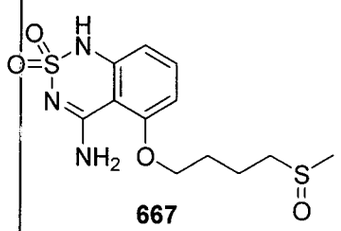
Ejemplo 244b: 2–amino–6–(4–(metiltio)butoxi)benzonitrilo

Preparado como en el Ejemplo 215b (Método A) a partir de 2–(4–(metiltio)butoxi)–6–nitrobenzonitrilo (Ejemplo 244c) en 95% de rendimiento. MS 237 (MH^+).

Ejemplo 244c: 2–(4–(metiltio)butoxi)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 215c a partir de 4–(metiltio)butan–1–ol y 2,6–dinitrobenzonitrilo en 89% de rendimiento. MS 267 (MH^+).

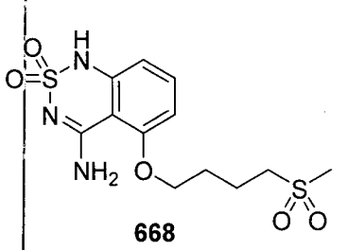
Ejemplo 245: 5–(4–(metilsulfinil)butoxi)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



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A una solución de 5–(4–(metiltio)butoxi)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido (Ejemplo 244) (79 mg, 0,25 mmol) en DCM/CH_3CO_2H (20:1, 20 mL) se le adicionó a temperatura ambiente MCPBA (1,0 equiv.). Luego la mezcla de reacción se agitó a temperatura ambiente durante la noche. El solvente se evaporó bajo presión reducida, y el residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con 15% MeOH en diclorometano para proporcionar el compuesto del título (74 mg, 90%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,74-1,77 (m, 2H), 1,88-1,95 (m, 2H), 2,50 (s, 3H), 2,68-2,73 (m, 1H), 2,77-2,83(m,1H), 4,19 (t, 2H), 6,58-6,60 (d, J = 8,4 Hz, 1H), 6,73-6,75 (d, J = 8,0 Hz, 1H), 7,44 (t, J = 8,0 Hz, 1H), 7,79 (s, 1H), 8,33 (s, 1H), 10,92 (s, 1H). MS 332 (MH^+).

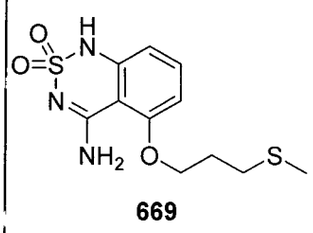
Ejemplo 246: 5–(4–(metilsulfonil)butoxi)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



668

Preparado como en el Ejemplo 245 a partir de 5–(4–(metiltio)butoxi)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido (Ejemplo 244) a través de la reacción con 3 equivalentes de MCPBA como un sólido blanco en 88% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,80-1,82 (m, 2H), 1,91-1,95 (m, 2H), 2,93 (s, 3H),3,18 (t, 2H), 4,18 (t, 2H), 6,58-6,60 (d, J = 8,4 Hz, 1H), 6,73-6,75 (d, J = 8,0 Hz, 1H), 7,44 (t, J = 8,0 Hz, 1H), 7,79 (s, 1H), 8,34 (s, 1H), 10,92 (s, 1H). MS 348 (MH^+).

Ejemplo 247: 5–(3–(metiltio)propoxi)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



669

Preparado como en el Ejemplo 215 a partir de 2–sulfamoilamino–6–(3–(metiltio)propoxi)benzonitrilo (Ejemplo 247a) en 69% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,05 (s, 3H), 2,08 (m, 2H), 2,59 (t, J = 7,2 Hz, 2H), 4,21 (t, J = 6,4 Hz, 2H), 6,59-6,61 (d, J = 8,0 Hz, 1H), 673-6,75 (d, J = 8,8 Hz,1H), 7,44 (t, J = 8,0 Hz, 1H), 7,79 (s, 1H), 8,33 (s, 1H), 10,93 (s, 1H). MS 302 (MH^+).

Ejemplo 247a: 2–sulfamoilamino–6–(3–(metiltio)propoxi)benzonitrilo

Preparado como en el Ejemplo 215a a partir de 2–amino–6–(3–

(metiltio)propoxi)benzonitrilo (Ejemplo 247b) y cloruro de sulfamoilo en 69% de rendimiento. MS 302 (MH^+).

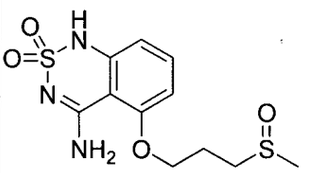
Ejemplo 247b: 2–amino–6–(3–(metiltio)propoxi)benzonitrilo

Preparado como en el Ejemplo 215b (Método A) a partir de 2–(3–(metiltio)propoxi)–6–nitrobenzonitrilo (Ejemplo 247c) en 98% de rendimiento. MS 223 (MH^+).

Ejemplo 247c: 2–(3–(metiltio)propoxi)–6–nitrobenzonitrilo

Preparada como en el Ejemplo 215c a partir de 4–(metiltio)butan–1–ol y 2,6–dinitrobenzonitrilo en 89% de rendimiento. MS 253 (MH^+).

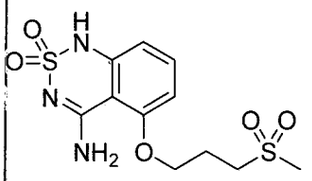
Ejemplo 248: 5–(3–(metilsulfinil)propoxi)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



670

Preparado como en el Ejemplo 245 a partir de 5–(3–(metiltio)propoxi)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido (Ejemplo 247) a través de la reacción con 1,0 equivalente de MCPBA como un sólido blanco en 90% de rendimiento. ^1H RMN (400 MHz, DMSO-d_6) δ 2,18-2,22 (m, 2H), 2,54 (s, 3H), 2,75-2,78 (m, 1H), 2,89-2,93 (m, 1H), 4,26 (t, J = 6,4Hz, 2H), 6,60-6,61 (d, J = 8,4 Hz, 1H), 6,73-6,75 (d, J = 8,0 Hz,1H), 7,44 (t, J = 8,0 Hz, 1H), 7,83 (s, 1H), 8,30 (s, 1H), 10,92 (s, 1H). MS 318 (MH^+).

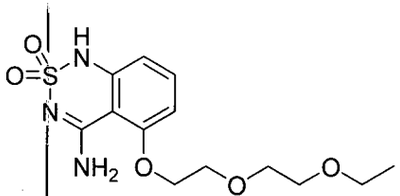
Ejemplo 249: 5–(3–(metilsulfonil)propoxi)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



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Preparado como en el Ejemplo 245 a partir de 5–(3–(metiltio)propoxi)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido (Ejemplo 247) a través de la reacción con 3,0 equivalentes de MCPBA en 87% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,24-2,27 (m, 2H), 3,00 (s, 3H), 3,26 (t, J = 7,6 Hz, 2H), 4,24 (t, J = 6,4 Hz, 2H), 6,60-6,62 (d, J = 8,0 Hz, 1H), 6,72-6,74 (d, J = 8,0 Hz,1H), 7,45 (t, J = 8,0 Hz, 1H), 7,79 (s, 1H), 8,31 (s, 1H), 10,93 (s, 1H). MS 334 (MH^+).

Ejemplo 250: 5–(2–(2–etoxietoxi)etoxi)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



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Preparado como en el Ejemplo 215 a partir de 2–sulfamoilamino–6–(2–(2–etoxietoxi)etoxi)benzonitrilo (Ejemplo 250a) en 52% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,05 (t, J = 7,2 Hz, 3H), 3,37-3,43 (m, 2H), 3,47 (t, 2H), 3,58 (t, 2H), 3,81 (t, 2H), 4,26 (t, 2H), 6,60-6,62 (d, J = 8,0 Hz, 1H), 673-6,75 (d, J = 8,0 Hz, 1H), 7,45 (t, J = 8,4 Hz, 1H), 7,99 (s, 1H), 8,32 (s, 1H), 10,97 (s, 1H). MS 330 (MH^+).

Ejemplo 250a: 2–sulfamoilamino–6–(2–(2–etoxietoxi)etoxi)benzonitrilo

Preparado como en el Ejemplo 215a a partir de 2–amino–6–(2–(2–etoxietoxi)etoxi)benzonitrilo (Ejemplo 250b) y cloruro de sulfamoilo en 69% de rendimiento. MS 330 (MH^+).

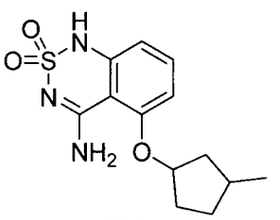
Ejemplo 250b: 2–amino–6–(2–(2–etoxietoxi)etoxi)benzonitrilo

Preparado como en el Ejemplo 215b (Método A) a partir de 2–(2–(2–etoxietoxi)etoxi)–6–nitrobenzonitrilo (Ejemplo 250c) en 98% de rendimiento. MS 251 (MH^+).

Ejemplo 250c: 2–(2–(2–etoxietoxi)etoxi)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 215c a partir de 2–(2–etoxietoxi)etanol y 2,6–dinitrobenzonitrilo en 66% de rendimiento. MS 281 (MH^+).

Ejemplo 251: 5–(3–metilciclopentiloxi)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



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Preparado como en el Ejemplo 215 a partir de 2–sulfamoilamino–6–(3–metilciclopentiloxi)benzonitrilo (Ejemplo 251a) en 45% de rendimiento. ^1H RMN (400 MHz, DMSO-d_6) δ 0,97-1,04 (m, 3H), 1,28-1,37 (m, 2H), 1,75-2,03 (m, 4H), 2,31-2,38 (m, 1H), 4,95-5,02 (m, 1H), 6,56-6,58 (d, J = 7,6 Hz,1H), 6,67-6,69 (d, J = 8,4 Hz, 1H),7,42 (t, J = 8,4 Hz, 1H), 7,69-7,72 (m, 1H), 8,30-8,36 (m, 1H), 10,92 (s, 1H). MS 296 (MH^+).

Ejemplo 251a: 2–sulfamoilamino–6–(3–metilciclopentiloxi)benzonitrilo

Preparado como en el Ejemplo 215a a partir de 2–amino–6–(3–metilciclopentiloxi)benzonitrilo (Ejemplo 251b) y cloruro de sulfamoilo en 52% de rendimiento. MS 296 (MH^+).

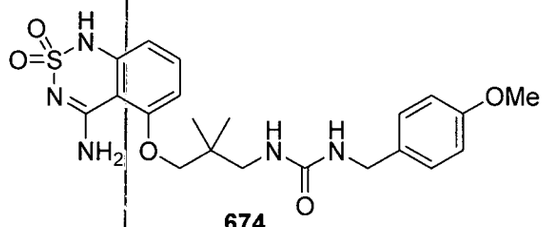
Ejemplo 251b: 2–amino–6–(3–metilciclopentiloxi)benzonitrilo

Preparado como en el Ejemplo 215b (Método A) a partir de 2–(3–metilciclopentiloxi)–6–nitrobenzonitrilo (Ejemplo 251c) en 98% de rendimiento. MS 217 (MH^+).

Ejemplo 251c: 2–(3–metilciclopentiloxi)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 215c a partir de 3–metilciclopentanol y 2,6–dinitrobenzonitrilo en 70% de rendimiento. MS 247 (MH^+).

Ejemplo 252: 1–(3–(4–amino–2,2–dioxido–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)–2',2'–dimetilpropil)–3'–(4''–metoxibencil)urea



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Preparada como en el Ejemplo 215 a partir de 1–(3–(3–sulfamoilamino–2–cianofenoxi)–2,2–dimetilpropil)–3–(4–metoxibencil)urea (Ejemplo 252a) en 77% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,92 (s, 6H), 3,06 (d, J = 6,4 Hz, 2H), 3,32 (s, 2H), 3,67 (s, 3H), 4,06 (d, J = 6,0 Hz, 2H), 6,29 (t, J = 6,0 Hz, 2H), 6,61 (d, J = 8,0 Hz, 1H), 6,71 (d, J = 8,0 Hz, 1H), 6,74 (d, J = 8,8 Hz, 2H), 7,06 (d, J = 8,8 Hz, 2H), 7,44 (t, J = 8,0 Hz, 1H), 8,12 (s, 1H), 8,34 (s, 1H), 10,90 (s, 1H). MS 462 (MH^+).

Ejemplo 252a: 1–(3–(3–sulfamoilamino–2–cianofenoxi)–2,2–dimetilpropil)–3–(4–metoxibencil)urea

Preparada como en el Ejemplo 215a a partir de 1–(3–(3–amino–2–cianofenoxi)–2,2–dimetilpropil)–3–(4–metoxibencil)urea (Ejemplo 252b) y cloruro de sulfamoilo en 100% de rendimiento. MS 462 (MH^+).

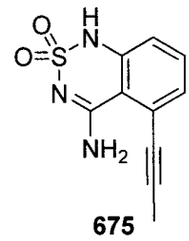
Ejemplo 252b: 1–(3–(3–amino–2–cianofenoxi)–2,2–dimetilpropil)–3–(4–metoxibencil)urea

Preparada como en el Ejemplo 215b (Método B) a partir de 1–(3–hidroxi–2,2–dimetilpropil)–3–(4–metoxibencil)urea (Ejemplo 252c) y 2–amino–6–fluorbenzonitrilo en 60% de rendimiento. MS 383 (MH^+).

Ejemplo 252c: 1–(3–hidroxi–2,2–dimetilpropil)–3–(4–metoxibencil)urea

Preparada como en el Ejemplo 227d a partir de 3–amino–2,2–dimetilpropan–1–ol e isocianato de 4–metoxibencilo en 100% de rendimiento. MS 267 (MH^+).

Ejemplo 253: 5–(prop–1–inil)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



675

Preparado como en el Ejemplo 215 a partir de 2–sulfamoilamino–6–(3–(trimetilsilil)prop–1–inil)benzonitrilo (Ejemplo 253a) en 10% de rendimiento. ^1H RMN (400 MHz, DMSO-d_6) δ 1,28 (s, 2H), 2,16 (s, 3H), 6,99-7,01 (d, J = 8,4 Hz, 1H), 7,21-7,23 (d, J = 7,8 Hz, 1H), 7,45 (t, J = 7,8 Hz, 1H). MS 236 (MH^+).

Ejemplo 253a: 2–sulfamoilamino–6–(3–(trimetilsilil)prop–1–inil)benzonitrilo

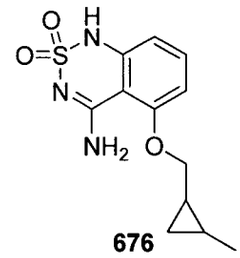
Una solución de 2–amino–6–(3–(trimetilsilil)prop–1–inil)benzonitrilo (Ejemplo 253b) (557 mg, 2,0 mmol) y $NH_2SO_2NH_2$ (0,96 g, 10 mmol) en 1,4–

dioxano seco (50 mL) se reflujó bajo nitrógeno durante 2 días. El solvente se evaporó bajo presión reducida, y el residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con 70% EtOAc en hexanos para proporcionar el compuesto del título (31 mg, 5%) como un sólido blanco. MS 308 (MH^+).

Ejemplo 253b: 2–amino–6–(3–(trimetilsilil)prop–1–inil)benzonitrilo

A una solución agitada de trimetil(prop–2–inil)silano (1,12 g, 10 mmol), 2–amino–6–bromobenzonitrilo (Klaubert, D. H.; Sellstedt, J. H.; Guinosso, C. J.; Capetola, R. J.; Bell, S. C. *J. Med. Chem.* **1981**, *24*, 742) (1,0 g, 5 mmol), CuI (0,01 equiv.) en trietilamina (50 mL) se le adicionó $Pd(PPh_3)_4$ (0,1 equiv.) a temperatura ambiente bajo nitrógeno. Luego la mezcla de reacción se reflujó bajo nitrógeno durante la noche. El solvente se evaporó, y el residuo se tituló con EtOAc/agua. La capa orgánica se separó, se lavó con salmuera, y se secó sobre Na_2SO_4. Luego de la evaporación del solvente, el residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con 15% EtOAc en hexanos para proporcionar el compuesto del título (1,43 g, 63%) as a como un líquido. MS 229 (MH^+).

Ejemplo 254: 5–((2–metilciclopropil)metoxi)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



676

Preparado como en el Ejemplo 111 a partir de 2–amino–6–((2–metilciclopropil)metoxi)benzonitril sulfamida (Ejemplo 254a) en 68% de rendimiento (mezcla de diastereoisómeros). ^1H RMN (400 MHz, DMSO-d_6) δ 0,17-

0,40 (m, 1H), 0,54-0,58 (m, 1H), 0,76-0,85 (m, 1H), 0,99-1,12 (m, 4H), 3,96-4,33 (m, 2H), 6,58-6,61 (m, 1H), 6,67-6,77 (m, 1H), 7,41-7,47 (m, 1H), 7,97 (s, NH), 8,38 (s, NH), 10,97 (s, NH). MS 282 (MH^+).

Ejemplo 254a: 2–amino–6–((2–metilciclopropil)metoxi)benzonitril sulfamida

Preparada como en el Ejemplo 90a a partir de 2–amino–6–((2–metilciclopropil)metoxi)benzonitrilo (Ejemplo 254b) en 100% de rendimiento. ^1H RMN (400 MHz, DMSO-d_6) δ 0,34-0,36 (m, 1H), 0,51-0,53 (m, 1H), 0,77-0,79 (m, 1H), 0,95-0,97 (m, 1H), 1,04-1,09 (m, 3H), 3,92-4,03 (m, 2H), 6,86-6,88 (bm, 1H), 7,11-7,18 (bm, 3H), 7,48-7,52 (bm, 1H), 9,53 (bs, NH). MS 282 (MH^+).

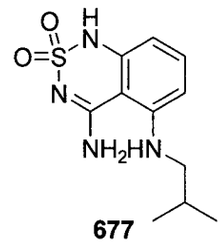
Ejemplo 254b: 2–amino–6–((2–metilciclopropil)metoxi)benzonitrilo

Una solución de 2–((2–metilciclopropil)metoxi)–6–nitrobenzonitrilo (Ejemplo 254c) (0,29 g, 1,25 mmol) en EtOAc/EtOH 1:1 (30 mL) se hidrogenó en un aparato H–cube utilizando 10% Pd/C como catalizador. La solución se evaporó para proporcionar 2–amino–6–((2–metilciclopropil)metoxi)benzonitrilo (0,20 g, 79%) como un aceite amarillo. MS 203 (MH^+).

Ejemplo 254c: 2–((2–metilciclopropil)metoxi)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 166d a partir de (2–metilciclopropil)metanol y 2,6–dinitrobenzonitrilo en 81% de rendimiento. MS 233 (MH^+).

Ejemplo 255: N5–isobutil–1H–benzo[c][1,2,6]tiadiazin–4,5–diamin–2,2–dióxido



677

Preparado como en el Ejemplo 111 a partir de 2–amino–6–(isobutilamino)benzonitril sulfamida (Ejemplo 255a) en 23% de rendimiento.1H RMN (400 MHz, DMSO-d_6) δ 0,95 (d, J = 6,8 Hz, 6H), 1,88-1,95 (m, 1H), 2,84 (t, J = 6,8 Hz, 2H), 5,87 (t, J = 6,4 Hz, NH), 6,31 (dd, J = 0,8 Hz, J = 8,0 Hz, 1H), 6,40 (d, J = 8,0 Hz, 1H), 7,26 (t, J = 8,4 Hz, 1H), 7,88 (s, NH_2), 10,70 (s, NH). MS 269 (MH^+).

Ejemplo 255a: 2–amino–6–(isobutilamino)benzonitril sulfamida

Preparada como en el Ejemplo 90a a partir de 2–amino–6–(isobutilamino)benzonitrilo (Ejemplo 255b) y utilizada en la siguiente etapa sin purificación adicional alguna. MS 269 (MH^+).

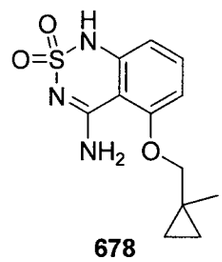
Ejemplo 255b: 2–amino–6–(isobutilamino)benzonitrilo

Preparado como en el Ejemplo 90b a partir de 2–(isobutilamino)–6–nitrobenzonitrilo (Ejemplo 255 en 66% de rendimiento. MS 190 (MH^+).

Ejemplo 255c: 2–(isobutilamino)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 90c a partir de 2,6–dinitrobenzonitrilo y metilamina en 92% de rendimiento. MS 220 (MH^+).

Ejemplo 256: 5–((1–metilciclopropil)metoxi)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



678

Preparado como en el Ejemplo 111 a partir de 2–amino–6–((1–metilciclopropil)metoxi)benzonitril sulfamida (Ejemplo 256a), en 39% de rendimiento. ^1H RMN (400 MHz, DMSO-d_6) δ 0,44-0,46 (m, 2H), 0,59-0,62 (m,

2H), 1,2 (s, 3H), 3,96 (s, 2H), 6,59 (d, J = 8,4 Hz, 1H), 6,66 (d, J = 8,0 Hz, 1H), 7,43 (t, J = 8,0 Hz, 1H), 7,83 (bs, NH), 8,40 (bs, NH), 9,45 (bs, NH). MS 282 (MH^+).

Ejemplo 256a: 2–amino–6–((1–metilciclopropil)metoxi)benzonitril sulfamida

Preparada como en el ejemplo 90a a partir de 2–amino–6–((1–metilciclopropil)metoxi)benzonitrilo (Ejemplo 256b) en 100% de rendimiento. ^1H RMN (400 MHz, DMSO-d_6) δ 0,40-0,43 (m, 2H), 0,53-0,56 (m, 2H), 1,20 (s, 3H), 3,89 (s, 2H), 6,85 (d, J = 8,0 Hz, 1H), 7,11-7,23 (bs, NH_2), 7,12 (d, J = 8,0 Hz, 1H), 7,51 (t, J = 8,4 Hz, 1H), 9,45 (bs, NH). MS 282 (MH^+).

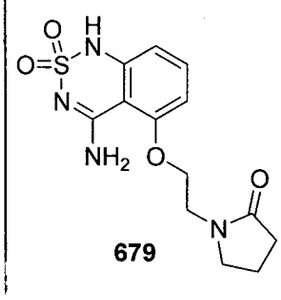
Ejemplo 256b: 2–amino–6–((1–metilciclopropil)metoxi)benzonitrilo

Preparado como en el Ejemplo 254b a partir de 2–((1–metilciclopropil)metoxi)–6–nitrobenzonitrilo (Ejemplo 256c) en 88% de rendimiento como un aceite amarillo. MS 203 (MH^+).

Ejemplo 256c: 2–((1–metilciclopropil)metoxi)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 166d a partir de (1–metilciclopropil)metanol y 2,6–dinitrobenzonitrilo en 65% de rendimiento. ^1H RMN (400 MHz, DMSO-d_6) δ 0,44-0,46 (m, 2H), 0,57-0,59 (m, 2H), 1,22 (s, 3H), 4,06 (s, 2H), 7,67 (dd, J = 1,6 Hz, J = 8,0 Hz, 1H), 7,85-7,92 (m, 2H).

Ejemplo 257: 1–(2–(4–amino–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)etil) pirrolidin–2–ona –2,2–dióxido



679

Preparado como en el Ejemplo 111 a partir de 2–amino–6–(2–(2–oxopirrolidin–1–il)etoxi)benzonitril sulfamida (Ejemplo 257a) en 45% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,94 (q, J = 7,2 Hz, 2H), 2,26 (t, J = 7,6 Hz, 2H), 3,43 (t, J = 7,2 Hz, 2H), 3,68 (t, J = 4,4 Hz, 2H), 4,23 (t, J = 4,4 Hz, 2H), 6,59 (d, J = 7,6 Hz, 1H), 6,70 (d, J = 8,8 Hz, 1H), 7,43 (t, J = 8,4 Hz, 1H), 7,82 (bs, NH), 8,21 (bs, NH), 10,98 (bs, NH). MS 325 (MH^+).

Ejemplo 257a: 2–amino–6–(2–(2–oxopirrolidin–1–il)etoxi)benzonitril sulfamida

Preparada como en el Ejemplo 90a a partir de 2–amino–6–(2–(2–oxopirrolidin–1–il)etoxi)benzonitrilo (Ejemplo 257b) en 100% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,94 (q, J = 8,4 Hz, 2H), 2,22 (t, J = 8,4 Hz, 2H), 3,50-3,58 (m, 4H), 4,21 (t, J = 4,8 Hz, 2H), 6,94 (bs, 1H), 7,17 (d, J = 7,6 Hz, 1H), 7,24 (bs, NH_2), 7,54 (t, J = 7,2 Hz, 1H), 9,49 (bs, NH). MS 325 (MH^+).

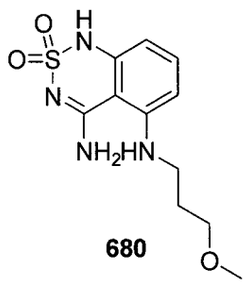
Ejemplo 257b: 2–amino–6–(2–(2–oxopirrolidin–1–il)etoxi)benzonitrilo

Preparado como en el Ejemplo 254b a partir de 2–nitro–6–(2–(2–oxopirrolidin–1–il)etoxi)benzonitrilo (Ejemplo 257c) utilizando trifluoretanol/hexafluorisopropanol (1:1) como solvente en 100% de rendimiento MS 246 (MH^+).

Ejemplo 257c: 2–nitro–6–(2–(2–oxopirrolidin–1–il)etoxi)benzonitrilo

Preparado como en el Ejemplo 166d a partir de 1–(2–hidroxietil)pirrolidin–2–ona y 2,6–dinitrobenzonitrilo en 74% de rendimiento. MS 276 (MH^+).

Ejemplo 258: N5–(3–metoxipropil)–1H–benzo[c][1,2,6]tiadiazin–4,5–diamin–2,2–dióxido



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Preparado como en el Ejemplo 90 a partir de 2–amino–6–(3–metoxipropilamino)benzonitril sulfamida (Ejemplo 258a) en 69% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,79-1,85 (m, 2H), 3,06 (q, J = 6,8 Hz, J = 6,8 Hz, 2H), 3,22 (s, 3H), 3,42 (t, , J = 6,0 Hz, 2H), 5,94 (t, J = 5,0 Hz, NH), 6,26 (d, J = 8,4 Hz, 1H), 6,34 (d, J = 8,0 Hz, 1H), 7,23 (t, J = 8,0 Hz, 1H),7,88 (s, NH_2), 10,64 (s, NH). MS 285 (MH^+).

Ejemplo 258a: 2–amino–6–(3–metoxipropilamino)benzonitril sulfamida

Preparada como en el Ejemplo 90a a partir de 2–amino–6–(3–metoxipropilamino)benzonitrilo en 65% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,74-1,79 (m, 2H), 3,19 (q, J = 6,8 Hz, J = 7,2 Hz, 2H), 3,22 (s, 3H), 3,39 (t, , J = 6,2 Hz, 2H), 5,96 (t, J = 5,6 Hz, NH), 6,47 (d, J = 8,8 Hz, 1H), 6,70 (d, J = 8,0 Hz, 1H), 7,09 (s, NH_2), 7,31 (t, J = 8,0 Hz, 1H), 9,09 (s, NH). MS 285 (MH^+).

Ejemplo 258b: 2–amino–6–(3–metoxipropilamino)benzonitrilo

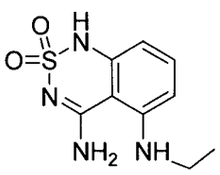
A una solución de 2–(3–metoxipropilamino)–6–nitrobenzonitrilo (Ejemplo 258c) (0,58 g, 2,48 mmol) en EtOH (20 mL) se le adicionó ciclohexeno (1,26 mL, 12,4 mmol). Luego se adicionó 10% Pd/C (1,32 g), y la mezcla de reacción se reflujó a 100°C durante 20 minutos, se enfrió hasta temperatura ambiente, se filtró a través de Celite que se lavó con EtOH (3x20 mL), y se evaporó para proporcionar 2–amino–6–(3–metoxipropilamino)benzonitrilo (0,43 g, 84%) como un aceite incoloro. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,71-1,77 (m, 2H), 3,10 (q, J = 6,8 Hz, J = 6,8 Hz, 2H), 3,22 (s, 3H), 3,37 (t, , J = 3,2 Hz, 2H), 5,55 (t, J = 5,2 Hz,

NH), 5,63 (s, NH_2), 5,79 (d, *J* = 7,6 Hz, 1H), 5,93 (d, *J* = 8,0 Hz, 1H), 6,98 (t, *J* = 8,0 Hz, 1H). MS 206 (MH^+).

Ejemplo 258c: 2–(3–metoxipropilamino)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 90c a partir de 2,6–dinitrobenzonitrilo y 3–metoxipropilamina en 83% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,76-1,81 (m, 2H), 3,23 (s, 3H), 3,28-3,33 (m, 2H), 3,40 (t, *J* = 5,6 Hz, 2H), 6,66 (t, *J* = 4,8 Hz, NH), 7,30 (d, *J* = 8,8 Hz, 1H), 7,42 (d, *J* = 8,0 Hz, 1H), 7,60 (t, *J* = 8,0 Hz, 1H).

Ejemplo 259: N5–etil–1H–benzo[c][1,2,6]tiadiazin–4,5–diamin–2,2–dióxido



681

Preparado como en el Ejemplo 111 a partir de 2–amino–6–(etilamino)benzonitril sulfamida (Ejemplo 259a) en 57% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,18 (t, J = 6,8 Hz, 3H), 2,99-3,06 (m, 2H), 5,87 (t, J = 5,2 Hz, NH), 6,30 (d, J = 7,6 Hz, 1H), 6,38 (d, J = 7,6 Hz, 1H), 7,26 (t, J = 8,0 Hz, 1H), 7,90 (s, NH_2), 10,68 (s, NH). MS 241 (MH^+).

Ejemplo 259a: 2–amino–6–(etilamino)benzonitril sulfamida

Preparada como en el Ejemplo 90a a partir de 2–amino–6–(etilamino)benzonitrilo (Ejemplo 259b) en 47% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,14 (t, J = 7,2 Hz, 3H), 3,15-3,22 (m, 2H), 5,84 (bs, NH), 6,48 (d, J = 8,8 Hz, 1H), 6,72 (d, J = 8,0 Hz, 1H), 7,02 (bs, NH_2), 7,31 (t, J = 8,0 Hz, 1H), 9,14 (bs, NH). MS 241 (MH^+).

Ejemplo 259b: 2–amino–6–(etilamino)benzonitrilo

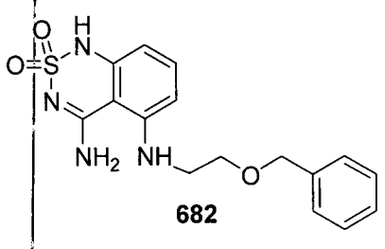
961

Preparado como en el Ejemplo 254b a partir de 2–(etilamino)–6–nitrobenzonitrilo (Ejemplo 259c) utilizando Trifluoretanol/Hexafluorisopropanol (2:1) como solvente, en 81% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,14 (t, J = 7,2 Hz, 3H), 3,15-3,22 (m, 2H), 5,41 (bt, J = 5,2 Hz, NH), 5,64 (s, NH_2), 5,82 (d, J = 8,0 Hz, 1H), 5,96 (d, J = 8,0 Hz, 1H), 7,00 (t, J = 8,4 Hz, 1H). MS 162 (MH^+).

Ejemplo 259c: 2–(etilamino)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 90c a partir de 2,6–dinitrobenzonitrilo y una solución de etilamina 2 M en THF en 88% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,13 (t, J = 7,6 Hz, 3H), 3,26-3,33 (m, 2H), 6,59 (bt, J = 5,2 Hz, NH), 7,22 (d, J = 9,2 Hz, 1H), 7,42 (d, J = 8,0 Hz, 1H), 7,60 (t, J = 8,4 Hz, 1H). MS 162 (M–Et).

Ejemplo 260: N5–(2–(benciloxi)etil)–1H–benzo[c][1,2,6]tiadiazin–4,5–diamin–2,2–dióxido



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Preparado como en el Ejemplo 90 a partir de 2–amino–6–(2–(benciloxi)etilamino)benzonitril sulfamida (Ejemplo 260a) en 68% de rendimiento. ^{1}H RMN (400MHz, DMSO-d_6) δ 3,25 (q, J = 5,2 Hz, J = 6,4 Hz, 2H), 3,64 (t, J = 5,6 Hz, 2H), 4,49 (s, 2H), 5,91 (t, J = 5,2 Hz, NH), 6,28 (d, J = 8,4 Hz, 1H), 6,40 (d, J = 8,4 Hz, 1H), 7,23 (t, J = 8,0 Hz, 1H), 7,25-7,35 (m, 5H), 7,90 (s, NH_2), 10,68 (s, NH). MS 347 (MH^+).

Ejemplo 260a: 2–amino–6–(2–(benciloxi)etilamino)benzonitril sulfamida

Preparada como en el Ejemplo 90a a partir de 2–amino–6–(2–(benciloxi)etilamino)benzonitrilo (Ejemplo 260b) en 45%. ^{1}H RMN (400MHz, $CDCl_3$) δ 3,36 (q, J = 5,2 Hz, J = 5,6 Hz, 2H), 3,57 (t, J = 5,6 Hz, 2H), 4,49 (s, 2H), 5,76 (t, J = 5,6 Hz, NH), 6,55 (d, J = 8,4 Hz, 1H), 6,72 (d, J = 8,0 Hz, 1H), 7,12 (s, NH_2), 7,25–7,32 (m, 6H), 9,12 (s, NH). MS 347 (MH^+).

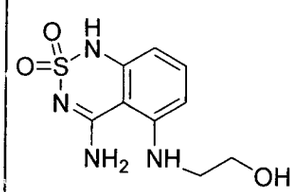
Ejemplo 260b: 2–amino–6–(2–(benciloxi)etilamino)benzonitrilo

Preparado como en el Ejemplo 90b a partir de 2–(2–(benciloxi)etilamino)–6–nitrobenzonitrilo (Ejemplo 260c) en 100% de rendimiento como un aceite marrón. ^{1}H RMN (400MHz, $CDCl_3$) δ 3,27 (q, J = 5,2 Hz, J = 6,0 Hz, 2H), 3,56 (t, J = 5,6 Hz, 2H), 4,49 (s, 2H), 5,34 (t, J = 5,6 Hz, NH), 5,67 (s, NH_2), 5,84 (d, J = 8,0 Hz, 1H), 5,95 (d, J = 8,4 Hz, 1H), 6,98 (t, J = 8,2 Hz, 1H), 7,30-7,34 (m, 5H). Ms 268 (MH^+).

Ejemplo 260c: 2–(2–(benciloxi)etilamino)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 90c a partir de 2–(benciloxi)etanamina y 2,6–dinitrobenzonitrilo en 77% de rendimiento. ^{1}H RMN (400MHz, DMSO-d_6) δ 3,49 (q, J = 5,2 Hz, J = 5,6 Hz, 2H), 3,59 (t, J = 5,6 Hz, 2H), 4,49 (s, 2H), 6,47 (t, J = 5,8 Hz, NH), 7,23-7,31 (m, 6H), 7,43 (d, J = 8,0 Hz, 1H), 7,58 (t, J = 8,4 Hz, 1H).

Ejemplo 261: 2–(4–amino–1H–benzo[c][1,2,6]tiadiazin–5–ilamino)etanol–2,2–dióxido

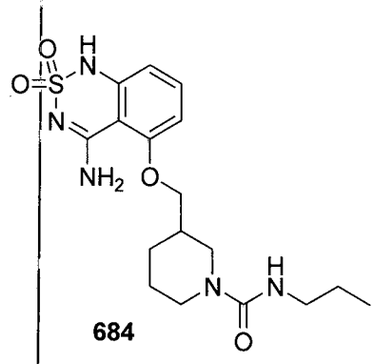


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Una solución de N^5–(2–(benciloxi)–etilamino)–1H–benzo[c][1,2,6]tiadiazin–4,5–diamin–2,2–dióxido (Ejemplo 260) (0,10 g, 0,29 mmol) en EtOH (20 mL) se

cargó con 30 mg de 10% Pd/C y un balón de H_2 y se agitó a temperatura ambiente durante 24 horas. La mezcla de reacción se filtró a través de Celite que se lavó con EtOH, las gases orgánicas combinadas se evaporaron, y el residuo se purificó mediante cromatografía flash utilizando una solución de DCM/MeOH (9:1) como eluyente, para proporcionar 2–(4–amino–1H–benzo[c][1,2,6]tiadiazin–5–ilamino)etanol–2,2–dióxido (64,8 mg, 87%). ^{1}H RMN (400MHz, DMSO-d_6) δ 3,11 (q, J = 5,6 Hz, J = 5,6 Hz, 2H), 3,58-3,59 (m, 2H), 4,84 (bs, 1H), 5,84 (t, J = 5,2 Hz, NH), 6,26 (d, J = 8,0 Hz, 1H), 6,37 (d, J = 8,4 Hz, 1H), 7,22 (t, J = 8,0 Hz, 1H), 7,86 (s, NH_2), 10,65 (bs, NH). MS 257 (MH^+).

Ejemplo 262: 3–((4–amino–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)metil)–N–propilpiperidin–1–carboxamida–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 3–((3–amino–2–cianofenoxi)metil)–N–propilpiperidin–1–carboxamida sulfamida (Ejemplo 262a) en 88% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,81 (t, J = 6,8 Hz, 3H), 1,23-1,43 (m, 4H), 1,60-1,63 (bm, 1H), 1,81-1,84 (bm, 1H), 1,99-2,05 (bm, 1H), 2,67-2,75 (m, 1H), 2,80-2,85 (m, 1H), 2,93-2,98 (m, 2H), 3,71 (bd, J = 12,8, 1H), 3,90 (bd, J = 10,8, 1H), 3,98-4,08 (m, 2H), 6,44 (d, J = 6,0 Hz, NH), 6,62 (d, J = 8,0 Hz, 1H), 6,76 (d, J = 8,4 Hz, 1H), 7,46 (t, J = 8,4 Hz, 1H), 7,80 (s, NH), 8,37 (s, NH), 10,95 (s, NH). MS 396 (MH^+).

Ejemplo 262a: 3–((3–amino–2–cianofenoxi)metil)–N–propilpiperidin–1 carboxamida sulfamida

Preparada como en el Ejemplo 90a a partir de 3–((3–amino–2–cianofenoxi)metil)–N–propilpiperidin–1–carboxamida (Ejemplo 262b) en 100% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,81 (t, J = 7,2 Hz, 3H), 1,31-1,44 (m, 4H), 1,61-1,64 (bm, 1H), 1,85-1,87 (bm, 2H), 2,60-2,75 (m, 2H), 2,94-2,98 (m, 2H), 3,78 (bd, J = 12,8 Hz, 1H), 3,93-3,97 (m, 1H), 4,01-4,10 (m, 2H), 6,38 (d, J = 6,0 Hz, NH), 6,96 (d, J = 8,8 Hz, 1H), 7,16 (d, J = 8,4 Hz, 1H), 7,27 (s, NH), 7,41 (s, NH), 7,57 (t, J = 8,4 Hz, 1H), 9,48 (s, NH). MS 396 (MH^+).

Ejemplo 262b: 3–((3–amino–2–cianofenoxi)metil)–N–propilpiperidin–1–carboxamida

Preparada como en el Ejemplo 254b a partir de 3–((2–ciano–3–nitrofenoxi)metil)–N–propilpiperidin–1–carboxamida (Ejemplo 262c) en 94% de rendimiento. MS 317 (MH^+).

Ejemplo 262c: 3–((2–ciano–3–nitrofenoxi)metil)–N–propilpiperidin–1–carboxamida

A una solución de clorhidrato de 2–nitro–6–(piperidin–3-ilmetoxi)benzonitrilo (Ejemplo 262d) (0,10 g, 0,34 mmol) en THF (6 mL) se le adicionaron trietilamina (0,10 mL, 0,76 mmol) e isocianato de propilo (0,05 mL, 0,52 mmol) y la mezcla de reacción se agitó a t.a. bajo nitrógeno durante 3 horas luego se filtró y se evaporó, para proporcionar 3–((2–ciano–3–nitrofenoxi)metil)–N–propilpiperidin–1–carboxamida (0,13 g, 100%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,81 (t, J = 7,2 Hz, 3H), 1,34-1,41 (m, 4H), 1,62-1,64 (bm, 1H), 1,87-1,95 (bm, 2H), 2,64-2,77 (m, 2H), 2,93-2,98 (m, 2H), 3,77 (bd, J = 12,8 Hz, 1H), 3,98 (bd, J = 12,8 Hz, 1H), 4,09-4,13 (m, 1H), 4,17-4,20 (m, 1H), 6,38 (d, J = 5,6 Hz, NH), 7,74 (bdd, J = 1,6 Hz, J = 8,0 Hz, 1H), 7,88-7,94 (m, 2H). MS 347 (MH^+).

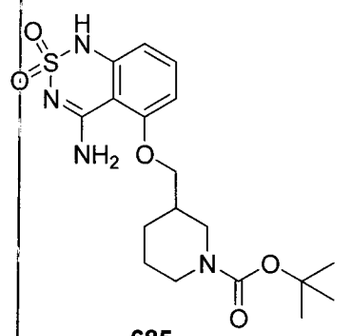
Ejemplo 262d: Clorhidrato de 2–nitro–6–(piperidin–3-ilmetoxi)benzonitrilo

Preparado como en el Ejemplo 166 a partir de 3–((2–ciano–3–nitrofenoxi)metil)piperidin–1–carboxilato de terc–butilo (Ejemplo 262e) en 98% de rendimiento. MS 262 (MH^+).

Ejemplo 262e: 3–((2–ciano–3–nitrofenoxi)metil)piperidin–1–carboxilato de terc–butilo

Preparado como en el Ejemplo 215c a partir de 3–(hidroximetil)piperidin–1–carboxilato de terc–butilo y 2,6–dinitrobenzonitrilo en 58% de rendimiento. MS 263 $[M+H–Boc]^+$.

Ejemplo 263: Terc–butil 3–((4–amino–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)metil)piperidin–1–carboxilato–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de terc–butil 3–((3–amino–2–cianofenoxi)metil)piperidin–1–carboxilato sulfamida (Ejemplo 263a), manteniendo el pH por encima de 3 luego de la acidificación, para proporcionar terc–butil 3–((4–amino–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)metil)piperidin–1–carboxilato–2,2–dióxido (33 mg, 23%). ^1H RMN (400 MHz, DMSO-d_6) δ 1,27-1,40 (bs, 11H), 1,62-1,66 (bm, 1H), 1,78-1,83 (bm, 1H), 2,05-2,12 (bm, 1H), 2,87-2,94 (m, 2H), 3,64-3,71 (bm, 1H), 3,83-3,86 (bm, 1H), 4,04 (bd, J = 7,2 Hz, 2H), 6,62 (d, J = 8,0 Hz, 1H), 6,77 (d, J = 8,4 Hz, 1H), 7,46 (t, J = 8,4 Hz, 1H), 7,76 (bs, NH), 8,37 (bs, NH), 10,95 (s, NH). MS 311 $[M+H–Boc]^+$.

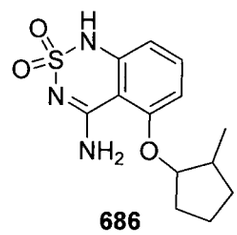
Ejemplo 263a: Terc–butil 3–((3–amino–2–cianofenoxi)metil)piperidin–1–carboxilato sulfamida

Preparada como en el Ejemplo 90a a partir de 3–((3–amino–2–cianofenoxi)metil)piperidin–1–carboxilato de terc–butilo (Ejemplo 263b). Luego de la extracción, se adicionó NaOH 1 M (1,56 mL, 1,56 mmol) al medio de reacción enfriado con hielo desencadenando la formación de un material pegajoso de color anaranjado. El agua se separó mediante vertido y el residuo se diluyó en EtOAc, y se extrajo, para proporcionar terc–butil 3–((3–amino–2–cianofenoxi)metil)piperidin–1–carboxilato sulfamida (0,15 g, 84%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,35-1,40 (bs, 11H), 1,63-1,66 (bm, 1H), 1,79-1,83 (bm, 1H), 1,88-1,93 (bm, 1H), 2,78-2,85 (m, 2H), 3,74-3,78 (bm, 1H), 3,92-4,04 (m, 3H), 6,96 (d, J = 8,4 Hz, 1H), 7,15 (d, J = 8,4 Hz, 1H), 7,27 (s, NH_2), 7,56 (t, J = 8,8 Hz, 1H), 9,47 (s, NH). MS 311 $[M+H–Boc]^+$.

Ejemplo 263b: 3–((3–amino–2–cianofenoxi)metil)piperidin–1–carboxilato de terc–butilo

Preparado como en el Ejemplo 254b a partir de 3–((2–ciano–3–nitrofenoxi)metil)piperidin–1–carboxilato de terc–butilo (Ejemplo 262e) en 100% de rendimiento como un aceite. MS 232 $[M+H–Boc]^+$.

Ejemplo 264: 4–amino–5–(*trans*–2–metilciclopentiloxi)–1*H*–benzo[*c*][1,2,6] tiadiazin–2,2–dióxido



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A una solución de 2–amino–6–(*trans*–2–metilciclopentiloxi)benzonitrilo (Ejemplo 264a) (150 mg, 0,694 mmol) en dimetilacetamida (3 mL) bajo N_2 se le adicionó cloruro de sulfamoilo (3 equiv.). La mezcla de reacción se agitó a temperatura ambiente bajo N_2 durante 2 horas, se diluyó con acetato de etilo (50 mL) y se inactivó con agua (20 mL). Las capas se separaron. El extracto orgánico se evaporó. Se adicionaron sucesivamente al residuo etanol (3 mL) y NaOH acuoso (2 N, 2,5 equiv.). La mezcla resultante se calentó a 90°C durante 16 horas. La elaboración se llevó a cabo como en el Ejemplo 111 para proporcionar el producto deseado (160 mg, 78%) como un polvo blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,02 (d, J = 6,4 Hz, 3H), 1,26 (m, 1H), 1,71 (br s, 3H), 1,89 (m, 1H), 2,12 (m, 1H), 2,24 (m, 1H), 4,55 (br s, 1H), 6,60 (d, J = 8,0 Hz, 1H), 6,71 (d, J = 8,0 Hz, 1H), 7,45 (t, J = 8,0 Hz, 1H), 7,73 (br s, 1H), 8,35 (br s, 1H), 10,96 (br s, 1H). MS 296 (MH^+).

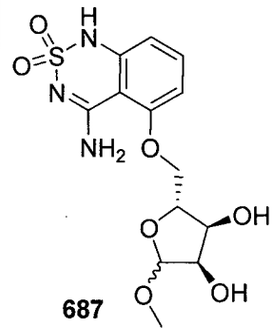
Ejemplo 264a: 2–amino–6–(*trans*–2–metilciclopentiloxi)benzonitrilo

Preparado como en el Ejemplo 111b a partir de 2–(*trans*–2–metilciclopentiloxi)–6–nitrobenzonitrilo (Ejemplo 264b) para proporcionar el compuesto del título en rendimiento cuantitativo como un aceite incoloro. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,04 (d, J = 7,2 Hz, 3H), 1,23 (m, 1H), 1,72 (m, 1H), 1,81 (m, 2 H), 1,99 (m, 2H), 2,26 (m, 1H), 4,28 (m, 1H), 4,36 (br s, 2H), 6,18 (d, J = 8,4 Hz, 1H), 6,18 (d, J = 8,4 Hz, 1H), 7,18 (t, J = 8,4 Hz, 1H). MS 296 (MH^+)

Ejemplo 264b: 2–(*trans*–2–metilciclopentiloxi)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 111c a partir de 2,6 dinitrobenzonitrilo y *trans*–2–metilciclopentanol en 65% como un sólido amarillo. MS 247 (MH^+).

Ejemplo 265: 4–amino–5–(((2*R*,3*S*,4*R*)–3,4–dihidroxi–5–metoxitetrahidrofuran–2–il)metoxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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A una solución de 4–amino–5–(((2*R*,3*S*,4*R*)–3,4,5–trihidroxitetrahidrofuran–2–il)metoxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido (Ejemplo 265a) (7 mg, 0,020 mmol) en metanol seco (1 mL) se le adicionó ácido trifluoracético (0,2 mL) y la mezcla se reflujó durante la noche. La solución resultante se evaporó hasta sequedad para proporcionar el compuesto del título como un polvo blanco (7,28 mg, 100%, mezcla de diastereómeros ~ 4/1). ^{1}H RMN (400 MHz, DMSO-d_6): δ [3,17 (s, ¾H)], 3,22 (s, 3H), 3,81 (d, J = 4,0 Hz, 1H), [3,93 (m, ½H)], 4,12 (m, 3H), 4,39 (m, 1H), 4,71 (s, 1H), [4,85 (d , J = 4,0 Hz, ¼H)], 5,44 (br s, 2H), 6,65 (d, J = 8,0 Hz, 1H), 6,81 (d, J = 8,0 Hz, 1H), 7,48 (t, J = 8,0 Hz, 1H), 7,95 (s, 1H), 8,41 (s, 1H), 11,00 (s, 1H), [11,01 (s, ¼H)].

Ejemplo 265a: 4–amino–5–(((2*R*,3*S*,4*R*)–3,4,5–trihidroxitetrahidrofuran–2–il)metoxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido

A una suspensión de 4–amino–5–(((3a*R*,4*R*,6*R*,6a*R*)–6–metoxi–2,2–dimetiltetrahidrofuro[3,4–*d*][1,3]dioxol–4–il)metoxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido (Ejemplo 265b) (15 mg, 0,038 mmol) en agua (1 mL) se le adicionó ácido trifluoracético (0,2 mL) y la mezcla se calentó durante la noche a 80ºC. La mezcla de reacción se evaporó hasta sequedad para proporcionar el compuesto del título como un sólido blanco en rendimiento cuantitativo (mezcla de diastereómeros ~ 10/1). ^{1}H RMN (400 MHz, DMSO-d_6): δ 3,71 (m, 4H), 4,12 (m, 3H), 4,35 (m, 1H), 5,02 (s, 1H), 6,63 (d, J = 8,0 Hz, 1H), 6,79 (d, J = 8,0 Hz, 1H),

7,47 (t, *J* = 8,0 Hz, 1H), 8,03 (br s, 1H), 8,31 (br s, 1H), 10,96 (br s, 1H), [11,00 (br s, 0,1H)].

Ejemplo 265b: 4–amino–5–(((3a*R*,4*R*,6*R*,6a*R*)–6–metoxi–2,2–dimetiltetrahidrofuro[3,4–*d*][1,3]dioxol–4–il)metoxi)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido

Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–(((3a*R*,4*R*,6*R*,6a*R*)–6–metoxi–2,2–dimetiltetrahidrofuro[3,4–*d*][1,3]dioxol–4–il)metoxi)benzonitrilo (Ejemplo 265c) en 78% de rendimiento como un sólido beige. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,28 (s, 3H), 1,41 (s, 3H), 3,18 (s, 3H), 4,00 (t, *J* = 9,2 Hz, 1H), 4,32 (dd, *J* = 5,2, 10,0 Hz, 1H), 4,59 (dd, *J* = 5,2, 8,8 Hz, 1H), 4,63 (d, *J* = 6,0 Hz, 1H), 4,82 (d, *J* = 6,0 Hz, 1H), 5,02 (s, 1H), 6,64 (d, *J* = 8,4 Hz, 1H), 6,70 (d, *J* = 8,4 Hz, 1H), 7,48 (t, *J* = 8,4 Hz, 1H), 7,98 (br s, 1H), 8,43 (br s, 1H), 11,02 (br s, 1H).

Ejemplo 265c: 2–sulfamoilamino–6–(((3a*R*,4*R*,6*R*,6a*R*)–6–metoxi–2,2–dimetiltetrahidrofuro[3,4–*d*][1,3]dioxol–4–il)metoxi)benzonitrilo

Preparado como en el Ejemplo 111a a partir de 2–amino–6–(((3a*R*,4*R*,6*R*,6a*R*)–6–metoxi–2,2–dimetiltetrahidrofuro[3,4–*d*][1,3]dioxol–4–il)metoxi)benzonitrilo (Ejemplo 265d) en 77% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,34 (s, 3H), 1,50 (s, 3H), 3,33 (s, 3H), 4,08 (m, 2H), 4,51 (dd, *J* = 6,4, 7,6 Hz, 1H), 4,65 (d, *J* = 6,0 Hz, 1H), 4,79 (d, *J* = 6,0 Hz, 1H), 5,01 (s, 1H), 5,25 (br s, 2H), 6,70 (d, *J* = 8,4 Hz, 1H), 7,28 (br s, 1H), 7,30 (d, *J* = 8,0 Hz, 1H), 7,51 (t, *J* = 8,4 Hz, 1H).

Ejemplo 265d: 2–amino–6–(((3a*R*,4*R*,6*R*,6a*R*)–6–metoxi–2,2–dimetiltetrahidrofuro[3,4–*d*][1,3]dioxol–4–il)metoxi)benzonitrilo

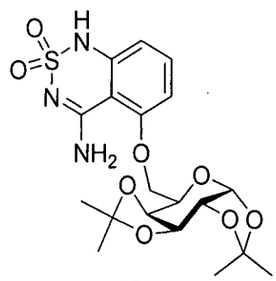
Preparado como en el Ejemplo 111b a partir de 2–(((3a*R*,4*R*,6*R*,6a*R*)–6–metoxi–2,2–dimetiltetrahidrofuro[3,4–d][1,3]dioxol–4–il)metoxi)–6–nitrobenzonitrilo (Ejemplo 252e) en 40% de rendimiento como un material incoloro pegajoso. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,33 (s, 3H), 1,49 (s, 3H), 3,33 (s, 3H), 4,05 (m, 2H),

4,45 (br s, 2H), 4,56 (dd, *J* = 6,0, 8,0 Hz, 1H), 4,65 (d, *J* = 6,0 Hz, 1H), 4,82 (br d, *J* = 6,0 Hz, 1H), 5,00 (s, 1H), 6,21 (dd, *J* = 0,8, 8,4 Hz, 1H), 6,33 (dd, *J* = 0,8, 8,4 Hz, 1H), 7,20 (t, *J* = 8,4 Hz, 1H).

Ejemplo 265e: 2-(((3a*R*,4*R*,6*R*,6a*R*)-6-metoxi-2,2-dimetiltetrahidrofuro[3,4-*d*][1,3]dioxol-4-il)metoxi)-6-nitrobenzonitrilo

Preparado como en el Ejemplo 111c a partir de 2,6 dinitrobenzonitrilo y *(*(3a*R*,4*R*,6*R*,6a*R*)-6-metoxi-2,2-dimetiltetrahidrofuro[3,4-*d*][1,3]dioxol-4-il)metanol en 70% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,33 (s, 3H), 1,49 (s, 3H), 3,32 (s, 3H), 4,23 (d, *J* = 2,0 Hz, 1H), 4,24 (s, 1H), 4,60 (br t, *J* = 6,0 Hz, 1H), 4,67 (d, *J* = 6,0 Hz, 1H), 4,86 (br d, *J* = 6,0 Hz, 1H), 5,01 (s, 1H), 7,35 (d, *J* = 8,4 Hz, 1H), 7,72 (t, *J* = 8,4 Hz, 1H), 7,87 (dd, *J* = 0,8, 8,4 Hz, 1H).

Ejemplo 266: 4-amino-5-(((3a*R*,5a*S*,8a*S*,8b*S*)-2,2,7,7-tetrametiltetrahidro-3a*H*-bis[1,3]dioxolo[4,5-*b*:4',5'-*d*]piran-5-il)metoxi)-1*H*-benzo[*c*][1,2,6]tiadiazin-2,2-dióxido



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Preparado como en el Ejemplo 264 a partir de 2-amino-6-(((3a*R*,5a*S*,8a*S*,8b*S*)-2,2,7,7-tetrametiltetrahidro-3a*H*-bis[1,3]dioxolo[4,5-*b*:4',5'-*d*]piran-5-il)metoxi)benzonitrilo (Ejemplo 266a) en 72% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,29 (s, 3H), 1,31 (s, 3H), 1,38 (s, 3H), 1,43 (s, 3H), 4,07 (m, 2H), 4,19 (br d, *J* = 8,4 Hz, 1H), 4,36 (dd, *J* = 1,2, 8,0

Hz, 1H), 4,41 (dd, *J* = 2,4, 5,2 Hz, 1H), 4,44 (dd, *J* = 2,4, 10,0 Hz, 1H), 4,67 (dd, *J* = 2,4, 8,0 Hz, 1H), 5,51 (d, *J* = 4,8 Hz, 1H), 6,63 (d, *J* = 8,0 Hz, 1H), 6,77 (d, *J* = 8,4 Hz, 1H), 7,45 (t, *J* = 8,4 Hz, 1H), 7,86 (br s, 1H), 8,41 (br s, 1H), 10,98 (br s, 1H). MS 456 (MH^+).

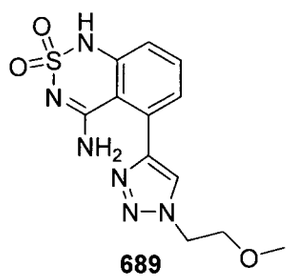
Ejemplo 266a: 2–amino–6–(((3a*R*,5a*S*,8a*S*,8b*S*)–2,2,7,7–tetrametiltetrahidro–3a*H*–bis[1,3]dioxolo[4,5–*b*:4',5'–*d*]piran–5–il)metoxi)benzonitrilo

Preparado como en el Ejemplo 111b a partir de 2–nitro–6–(((3a*R*,5a*S*,8a*S*,8b*S*)–2,2,7,7–tetrametiltetrahidro–3a*H*–bis[1,3]dioxolo[4,5–*b*:4',5'–*d*]piran–5–il)metoxi)benzonitrilo (Ejemplo 266b) en rendimiento cuantitativo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,28 (s, 3H), 1,31 (s, 3H), 1,37 (s, 3H), 1,39 (s, 3H), 4,05 (m, 2H), 4,16 (dd, *J* = 4,0, 8,8 Hz, 1H), 4,37 (m, 2H), 4,67 (dd, *J* = 2,4, 8,0 Hz, 1H), 5,47 (d, *J* = 4,8 Hz, 1H), 6,01 (br s, 2H), 6,23 (d, *J* = 8,0 Hz, 1H), 6,35 (d, *J* = 8,4 Hz, 1H), 7,17 (t, *J* = 8,4 Hz, 1H).

Ejemplo 266b: 2–nitro–6–(((3a*R*,5a*S*,8a*S*,8b*S*)–2,2,7,7–tetrametiltetrahidro–3a*H*–bis[1,3]dioxolo[4,5–*b*:4',5'–*d*]piran–5–il)metoxi)benzonitrilo

Preparado como en el Ejemplo 111c a partir de 2,6 dinitrobenzonitrilo y ((3a*R*,5a*S*,8a*S*,8b*S*)–2,2,7,7–tetrametiltetrahidro–3a*H*–bis[1,3]dioxolo[4,5–*b*:4',5'–*d*]piran–5–il)metanol en 59% de rendimiento como un material blanco pegajoso. MS 408 (MH^+), 424 (MH_2O^+).

Ejemplo 267: 4–amino–5–(1–(2–metoxietil)–1*H*–1,2,3–triazol–4–il)–1*H*–benzo[c][1,2,6]tiadiazin–2,2–dióxido



689

Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–(1–(2–metoxietil)–1*H*–1,2,3–triazol–4–il)benzonitrilo (Ejemplo 267a) en 78% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,27 (s, 3H), 3,78 (t, J = 5,2 Hz, 2H), 4,59 (t, J = 5,2 Hz, 2H), 6,90 (br s, 1H), 7,09 (dd, J = 0,8, 8,0 Hz, 1H), 7,20 (dd, J = 0,8, 7,6 Hz, 1H), 7,58 (t, J = 7,6 Hz, 1H), 8,15 (br s, 1H), 8,32 (s, 1H), 11,09 (br s, 1H). MS 323 (MH^+).

Ejemplo 267a: 2–sulfamoilamino–6–(1–(2–metoxietil)–1*H*–1,2,3–triazol–4–il)benzonitrilo

Preparado como en el Ejemplo 111a a partir de 2–amino–6–(1–(2–metoxietil)–1*H*–1,2,3–triazol–4–il)benzonitrilo (Ejemplo 267b) en 90% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,28 (s, 3H), 3,79 (t, J = 5,2 Hz, 2H), 4,66 (t, J = 5,2 Hz, 2H), 7,32 (br s, 2H), 7,60 (dd, J = 1,2, 8,0 Hz, 1H), 7,76 (t, J = 8,0 Hz, 1H), 7,82 (dd, J = 1,2, 8,0 Hz, 1H), 8,64 (s, 1H), 9,52 (br s, 1H).

Ejemplo 267b: 2–amino–6–(1–(2–metoxietil)–1*H*–1,2,3–triazol–4–il) benzonitrilo

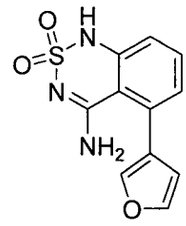
A una solución de 1–bromo–2–metoxietano (5,00 g, 35,97 mmol) en DMF (25 mL), se le adicionó azida de sodio (3 equiv.) y la mezcla se calentó a 50°C durante 48 horas. La mezcla de reacción se diluyó con agua (75 mL) y se extrajo con dietil éter. El extracto orgánico se secó sobre $MgSO_4$ y se concentró para proporcionar 1–azido–2–metoxietano como un líquido amarillo. Esta azida (200 mg, 1,94 mmol) se adicionó a una solución de 2–amino–6–etinilbenzonitrilo (250 mg, 1,76 mmol) (Ejemplo 267c) en H_2O/*terc*–BuOH = 1:2 (15 mL) y la solución se trató sucesivamente con ascorbato de sodio (0,264 mmol) y $CuSO_4$ (0,035 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 48 horas, se diluyó con agua y se extrajo con acetato de etilo. El extracto orgánico se secó sobre $MgSO_4$ y se purificó sobre gel de sílice (acetato de etilo/hexano 6:4) para

proporcionar el compuesto del título como un sólido blanco en 88% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,26 (s, 3H), 3,78 (t, J = 5,2 Hz, 2H), 4,23 (t, J = 5,2 Hz, 2H), 6,13 (br s, 2H), 6,80 (dd, J = 1,2, 8,4 Hz, 1H), 7,09 (dd, J = 1,2, 7,6 Hz, 1H), 7,36 (t, J = 8,4 Hz, 1H), 8,52 (s, 1H). MS 244 (MH^+).

Ejemplo 267c: 2–amino–6–etinilbenzonitrilo

A una solución de 2–amino–6–bromobenzonitrilo (1,25 g, 6,34 mmol) y etiniltrimetilsilano (2,42 g, 12,7 mmol) en Et_3N seco (15 mL) se le adicionó bajo N_2 Cu(I) (60 mg), $Pd(PPh_3)_4$ (360 mg) y la mezcla se agitó a 80°C durante 20 horas. La mezcla de reacción se enfrió hasta temperatura ambiente, se diluyó con acetato de etilo y se lavó con salmuera. La capa orgánica se evaporó y el residuo se disolvió en metanol (20 mL), se trató con solución de NaOH acuosa 1 M (1,05 equiv.) y se agitó a temperatura ambiente durante 1 hora. El metanol se separó mediante evaporación y el residuo acuoso se extrajo con CH_2Cl_2, se secó sobre $MgSO_4$, y se purificó sobre gel de sílice (acetato de etilo/hexanos 75/25) para proporcionar el producto deseado en 93% de rendimiento como un sólido amarillo claro. ^{1}H RMN (400 MHz, DMSO-d_6) δ 4,54 (s, 1H), 6,24 (br s, 2H), 6,76 (dd, J = 0,8, 7,6 Hz, 1H), 6,82 (dd, J = 0,8, 8,4 Hz, 1H), 7,28 (dd, J = 7,6, 8,4 Hz, 1H). MS 143 (MH^+).

Ejemplo 268: 4–amino–5–(furan–3–il)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–(furan–3–il)benzonitrilo (Ejemplo 268a) en 47% de rendimiento como un sólido beige. ^{1}H

RMN (400 MHz, DMSO-d_6) δ 6,34 (br s, 1H), 6,51 (dd, J = 0,8, 2,0 Hz, 1H), 7,03 (m, 2H), 7,52 (dd, J = 7,6, 8,0 Hz, 1H), 7,79 (t, J = 1,6 Hz, 1H), 7,93 (dd, J = 0,8, 1,6 Hz, 1H), 8,23 (br s, 1H), 11,09 (s,1H). MS 264 (MH^+)

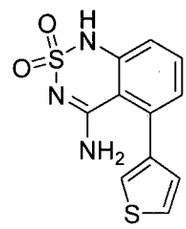
Ejemplo 268a: 2–sulfamoilamino–6–(furan–3–il)benzonitrilo

Preparado como en el Ejemplo 111a a partir de 2–amino–6–(furan–3–il)benzonitrilo (Ejemplo 268b) en 63% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 6,97 (dd, J = 0,8, 2,0 Hz, 1H), 7,29 (br s, 2H), 7,46 (dd, J = 0,8, 7,6 Hz, 1H), 7,54 (dd, J = 0,8, 8,0 Hz, 1H), 7,69 (t, J = 8,0 Hz, 1H), 7,85 (t, J = 1,6 Hz, 1H), 8,21 (dd, J = 0,8, 1,6 Hz, 1H), 9,48 (br s, 1H).

Ejemplo 268b: 2–amino–6–(furan–3–il)benzonitrilo

Preparado como en el Ejemplo 129c partir de ácido furan–3–ilborónico y 2–amino–6–bromobenzonitrilo en 74% de rendimiento como un sólido amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 4,51 (br s, 2H), 6,66 (dd, J = 1,2, 8,4 Hz, 1H), 6,78 (dd, J = 1,2, 2,0 Hz, 1H), 6,82 (dd, J = 1,2, 8,0 Hz, 1H), 7,31 (t, J = 8,0 Hz, 1H), 7,50 (t, J = 1,6 Hz, 1H), 7,95 (dd, J = 1,2, 1,6 Hz, 1H).

Ejemplo 269: 4–amino–5–(tiofen–3–il)–1*H*–benzo[*c*][1,2,6]tiadiazin–2,2–dióxido



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Preparado como en el Ejemplo 111 a partir de 2–sulfamoilamino–6–(tiofen–3–il)benzonitrilo (Ejemplo 269a) en 52% de rendimiento como un sólido beige. ^{1}H RMN (400 MHz, DMSO-d_6) δ 5,82 (br s, 1H), 7,05 (m, 3H), 7,54 (t, J = 8,0 Hz, 1H), 7,67 (m, 1H), 8,15 (br s, 1H), 11,13 (s,1H). MS 280 (MH^+).

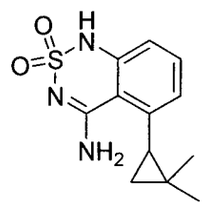
Ejemplo 269a: 2–sulfamoilamino–6–(tiofen–3–il)benzonitrilo

Preparado como en el Ejemplo 111a a partir de 2–amino–6–(tiofen–3–il)benzonitrilo (Ejemplo 269b) en 60% de rendimiento como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,31 (br s, 2H), 7,42 (dd, J = 1,2, 2,8 Hz, 1H), 7,43 (d, J = 1,6 Hz, 1H), 7,57 (dd, J = 0,8, 8,0 Hz, 1H), 7,70 (t, J = 8,0 Hz, 1H), 7,73 (dd, J = 2,8, 4,8 Hz, 1H), 7,88 (dd, J = 1,2, 2,8 Hz, 1H), 9,48 (br s, 1H).

Ejemplo 269b: 2–amino–6–(tiofen–3–il)benzonitrilo

Preparado como en el Ejemplo 129c partir de ácido tiofen–3–ilborónico y 2–amino–6–bromobenzonitrilo en 94% de rendimiento como un sólido beige. ^{1}H RMN (400 MHz, DMSO-d_6) δ 6,08 (br s, 2H), 6,70 (dd, J = 1,2, 7,6 Hz, 1H), 6,77 (dd, J = 1,2, 8,4 Hz, 1H), 7,31 (dd, J = 7,6, 8,4 Hz, 1H), 7,38 (dd, J = 1,2, 4,8 Hz, 1H), 7,66 (dd, J = 2,8, 4,8 Hz, 1H), 7,78 (dd, J = 1,2, 2,8 Hz, 1H).

Ejemplo 270: 5–(2,2–dimetilciclopropil)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



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Una solución de 2–amino–6–(2,2–dimetilciclopropil)benzonitrilo (381 μmol, 71 mg) (Ejemplo 270a) y cloruro de sulfamoilo (572 μmol, 66 mg) en DMA (1 mL) se agitó a temperatura ambiente. Luego de 1 hora, la mezcla de reacción se diluyó con NaOH (1 N, 572 μmol, 572 μL) y agua (~30 mL). El precipitado se separó mediante filtración, se lavó con agua (3 X 5 mL) luego se disolvió en EtOH (10 mL) y se adicionó NaOH (1 N, 953 μL). La reacción se calentó hasta 80°C con agitación. Luego de la terminación el solvente se evaporó y el residuo se particionó entre agua (20 mL) y éter (5 mL).La capa acuosa se extrajo con éter (2

X 5 mL), luego se acidificó hasta un pH ~3 con HCl 1 N. El precipitado se recogió, se lavó con agua, se secó al vacío para proporcionar el producto deseado (59 mg, 58%) como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,610 (m, 1H), 0,63 (s, 3H), 0,89 (m, 1H), 1,20 (s, 3H), 2,48 (m, 1H), 6,88 (d, J = 8 Hz, 1H), 6,92 (d, J = 8 Hz, 1H), 7,21 (br. s, 1H), 7,39 (t, J = 8 Hz, 1H), 8,42 (br. s, 1H), 10,74 (s, 1H). MS 266 (MH^+).

Ejemplo 270a: 2–amino–6–ciclopropilbenzonitrilo

A una solución desgasificada de 2–amino–6–bromobenzonitrilo (851 μmol, 168 mg), ácido 2,2–dimetilciclopropilborónico (1,106 μmol, 126 mg) (Ejemplo 270b), y Cs_2CO_3 (2,979 mmol, 970 mg) en DME (3,4 mL) y agua (850 μL) se le adicionó bajo nitrógeno tetrakis(trifenilfosfin)paladio (0) (43 μmol, 50 mg) y la mezcla de reacción se sometió a microondas durante 2 horas a 160°C. La mezcla de reacción se enfrió hasta temperatura ambiente y se extrajo con EtOAc (3 X 5 mL). Las capas orgánicas combinadas se lavaron una vez con salmuera (5 mL), se secaron sobre sulfato de sodio, se filtraon y se evaporaron. El producto crudo se purificó sobre gel de sílice (EtOAc/hexanos 10%–40%) para proporcionar el producto deseado (71 mg, 45%) como un sólido ceroso, amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 0,82 (m, 1H), 0,82 (s, 3H), 0,85 (m, 1H), 1,33 (s, 3H), 1,92 (m, 1H), 4,36 (br. s, 2H), 6,47 (d, J = 8 Hz, 1H), 6,56 (d, J = 8 Hz, 1H), 7,20 (t, J = 8 Hz, 1H).

Ejemplo 270b: Ácido 2,2–dimetilciclopropilborónico

A una solución de 1–bromo–2,2–dimetilciclopropano (7,48 mmol, 1,115 g) (Ejemplo 270c) en THF anhidro (20 mL) se le adicionó gota a gota a -78°C bajo nitrógeno tBuLi (8,23 mmol, 1,7 M en pentano, 4,85 mL). Luego de 1 hora a -78°C, se adicionó borato de trimetilo (8,23 mmol, 920 μL) y la mezcla de reacción se agitó durante 2 horas a -78°C, se entibió hasta temperatura ambiente, se agitó durante 1 hora, y se inactivó con solución de NH_4Cl sat. (20 mL). La mezcla de

reacción se diluyó hasta un volumen total de 100 mL con DCM y se trató con HCl (6 N en agua, 22,45 mmol, 3,74 mL). Las capas se separaron, la capa acuosa se extrajo con diclorometano (2 X 50 mL), las capas orgánicas combinadas se lavaron con salmuera (25 mL), se secaron sobre sulfato de sodio, se filtraron y se evaporaron. El residuo se diluyó con acetona (50 mL) y unas pocas gotas de agua, luego se concentró al vacío cuidadosamente para proporcionar 214 mg (25,1%) de producto como un sólido blancuzco. ^{1}H RMN (400 MHz, acetona-d_6) δ 0,00 (m, 1H), 0,13 (m, 1H), 0,755 (d of d, J = 4 Hz, 8 Hz, 1H), 0,865 (d of d, J = 4 Hz, 8 Hz, 1H), 1,39 (s, 3H), 1,46 (s, 3H), 6,81 (s, 2H).

Ejemplo 270c: 1–bromo–2,2–dimetilciclopropano

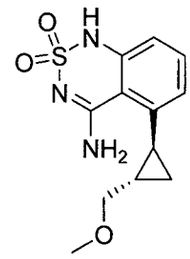
A una suspensión de Zinc (polvo fino, 319,4 mmol, 20,88 g) en EtOH (20 mL) se le adicionó HCl (12 N, 5 mL) a 0ºC. Se adicionó a la mezcla durante 5 minutos con agitación una solución de 1,1–dibromo–2,2–dimetilciclopropano (18,2 g) (Ejemplo 270d) en EtOH (20 mL). La mezcla de reacción se dejó entibiar lentamente hasta temperatura ambiente durante la noche. Las sales de zinc se separaron mediante filtración a través de una almohadilla de Celite, el Celite se lavó con EtOH (50 mL), y la solución resultante se particionó entre agua (200 mL) y pentano (200 mL). La capa acuosa se extrajo además con pentano (2 X 100 mL), y los extractos orgánicos combinados se lavaron sucesivamente con agua (4 X 75 mL), salmuera (25 mL), se secaron sobre sulfato de sodio, se filtraron, y se evaporaron para proporcionar el producto (1,115 g , 9,4%) como un líquido volátil, incoloro. ^{1}H RMN (400 MHz, acetona-d_6) δ 0,602 (d of d, J = 4 Hz, 6 Hz, 1H), 1,025 (d of d, J = 6 Hz, 8 Hz, 1H), 1,116 (s, 3H), 1,233 (s, 3H), 2,963 (d of d, J = 4 Hz, 8 Hz, 1H).

Ejemplo 270d: 1,1–dibromo–2,2–dimetilciclopropano

A una solución de pentano (200 mL) enfriada hasta -5ºC se le adicionó isobutileno (457,7 mmol, 25,68 g) seguido por terc–butóxido de potasio (549,2

mmol, 61,63 g). Luego se adicionó gota a gota bromoformo (457,7 mmol, 40,0 mL) con agitación enérgica durante aproximadamente 1 hora a -5ºC. La mezcla de reacción se dejó entibiar lentamente hasta temperatura ambiente y luego se particionó entre pentano (100 mL) y agua (200 mL). La capa acuosa se extrajo con pentano (2 X 50 mL) y las capas orgánicas combinadas se lavaron con agua (4 X 75 mL), salmuera (50 mL), se secaron sobre sulfato de sodio, se filtraron y se evaporaron. El residuo anaranjado se presionó a través de un tapón de sílice eluyendo con pentano. El solvente se evaporó para proporcionar el producto deseado (65,70 g, 57,3%) como un aceite incoloro. ^{1}H RMN (400 MHz, acetona-d_6) δ 1,392 (s, 6H), 1,505 (s, 2H).

Ejemplo 271: (±)–trans–5–(2–(metoximetil)ciclopropil)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



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Preparado como en el Ejemplo 270 a partir de (±)–trans–2–amino–6–(2–(metoximetil)ciclopropil)benzonitrilo (Ejemplo 271a) y cloruro de sulfamoilo en 34% como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,976 (m, 1H), 1,172 (m, 1H), 1,340 (m, 1H), 2,282 (m, 1H), 3,175 (d of d, J = 8 Hz, 10 Hz, 1H), 3,252 (s, 3H), 3,576 (d of d, J = 5 Hz, 10 Hz, 1H), 6,802 (d, J = 8 Hz, 1H), 6,855 (d, J = 8 Hz, 1H), 7,376 (t, J = 8 Hz, 1H), 8,396 (br. s, 1H), 8,473 (br. s, 1H), 10,823 (s, 1H). MS 282 (MH^+).

Ejemplo 271a: (±)–trans–2–amino–6–(2–(metoximetil)ciclopropil)benzonitrilo

Preparado como en el Ejemplo 270a a partir de ácido (±)–trans–2–(metoximetil)ciclopropilborónico (ejemplo 271b) y 2–amino–6–bromobenzonitrilo en 64% de rendimiento como un sólido ceroso amarillento marrón. ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,932 (m, 2H), 1,341 (m, 1H), 1,879 (m, 1H), 2,324 (s, 3H), 3,351 (d, J = 6 Hz, 2H), 5,896 (br. s, 2H), 6,148 (d, J = 8 Hz, 1H), 6,550 (d, J = 8 Hz, 1H), 7,130 (t, J = 8 Hz, 1H).

Ejemplo 271b: Ácido (±)–trans–2–(metoximetil) ciclopropilborónico

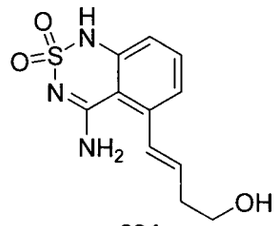
A una solución de (±)–trans–2–(metoximetil)ciclopropil)–4,4,5,5–tetrametil–1,3,2–dioxaborolano (10,0 mmol, 2,121 g) (Ejemplo 271c) disuelta en THF (64 mL) se le adicionaron $NaIO_4$ (30,0 mmol, 6,417 g) y agua (16 mL). La mezcla de reacción se agitó a temperatura ambiente durante 3 minutos luego se trató con HCl acuoso (2 N, 3,33 mL). La mezcla de reacción se agitó durante una hora a temperatura ambiente, se particionó con EtOAc (100 mL), la capa acuosa se extrajo con EtOAC (2 X 50 mL), las capas orgánicas combinadas se lavaron con salmuera (25 mL), se secaron sobre sulfato de sodio, se filtraron, y se evaporaron. La mezcla se recogió en acetona, se trató con unas pocas gotas de agua, y se evaporó cuidadosamente hasta un aceite viscoso, el cual se solidificó lentamente a temperatura ambiente para proporcionar el producto deseado en rendimiento cuantitativo. ^{1}H RMN (400 MHz, DMSO-d_6) δ -0,467 (m, 1H), 0,324 (m, 1H), 0,532 (m, 1H), 1,055 (m, 1H), 3,099 (d of d, J = 7 Hz, 10 Hz, 1H), 3,186 (d of d, J = 7 Hz, 10 Hz, 1H), 3,206 (s, 3H), 7,344 (s, 2H).

Ejemplo 271c: (±)–trans–2–(metoximetil)ciclopropil)–4,4,5,5–tetrametil–1,3,2–dioxaborolano

A una solución de (E)–2–(3–metoxiprop–1–enil)–4,4,5,5–tetrametil–1,3,2–dioxaborolano (32,2 mmol, 6,3710 g) en tolueno anhidro (50 mL) bajo nitrógeno se le adicionó dietil zinc (0,59 M en hexanos, 32,2 mmol, 54,6 mL), seguido por CH_2I_2 (45,08 mmol, 3,63 mL). El frasco se calentó hasta 50°C bajo nitrógeno. Luego de

4 horas, se adicionó otra porción de dietil zinc (54,6 mL) y CH_2I_2 (3,63 mL) y se calentó durante la noche bajo nitrógeno. La mezcla de reacción se enfrió hasta temperatura ambiente y se inactivó con NH_4Cl acuoso saturado (50 mL). La mezcla de reacción se particionó con éter (200 mL), las capas se separaron, la capa orgánica se lavó con salmuera (25 mL), se secó sobre sulfato de sodio, se filtró y se evaporó. El residuo se purificó sobre gel de sílice (EtOAc/hexanos 1% a 15%) para proporcionar el producto deseado (5,552 g, 81,3%) como un aceite amarillo claro. ^{1}H RMN (400 MHz, acetona) δ 0,012 (m, 1H), 0,804 (m, 1H), 0,944 (m, 1H), 1,172 (m, 1H), 3,484 (dd, J = 6 Hz, 10 Hz, 1H), 3,553 (dd, J = 6 Hz, 10 Hz, 1H), 3,570 (s, 3H).

Ejemplo 272: (E)–4–(4–amino–2,2–dioxo–1H–benzo[c][1,2,6]tiadiazin–5–il)but–3–en–1–ol

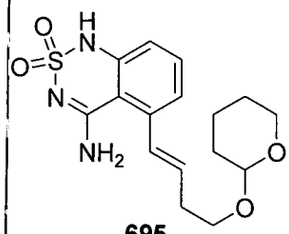


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A una solución de (E)–5–(4–(tetrahidro–2H–piran–2–iloxi)but–1–enil)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido (322 μmol, 43 mg) (Ejemplo 273) en THF (860 L) se le adicionó AcOH (1,7 mL) y agua (430 μL) y la solución se calentó durante la noche a 45ºC. La solución se enfrió hasta temperatura ambiente y el solvente se evaporó. El residuo se trituró con agua en ebullición luego se enfrió hasta temperatura ambiente. El sóido resultante se recogió y se lavó con agua para proporcionar el producto deseado (69 mg, 80%) como un sólido amarillo claro. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,365 (q, J = 6 Hz, 2H), 3,568 (q, J = 6 Hz, 2H), 4,681 (t, J = 6 Hz, 1H), 6,186 (d de t, J = 7 Hz, 16 Hz, 1H),

6,786 (d, *J* = 16 Hz, 1H), 6,922 (d, J = 8 Hz, 1H), 7,022 (br. s, 1H), 7,088 (d, J = 8 Hz, 1H), 7,468 (t, *J* = 8 Hz, 1H), 8,388 (br. s, 1H), 10,935 (s, 1H). MS 268 (MH^+).

Ejemplo 273: (E)–5–(4–(tetrahidro–2H–piran–2–iloxi)but–1–enil)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



695

Preparado como en el Ejemplo 270 a partir de (E)–2–amino–6–(4–(tetrahidro–2H–piran–2–iloxi)but–1–enil)benzonitrilo (Ejemplo 273a) y cloruro de sulfamoilo en 61% de rendimiento como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,459 (m, 4H), 1,610 (m, 2H), 1,700 (m, 2H), 2,479 (q, J = 6 Hz, 2H), 3,428 (m, 1H), 3,528 (m, 1H), 3,765 (m, 2H), 4,579 (m, 1H), 6,200 (d de t, *J* = 7 Hz, 16 Hz, 1H), 6,823 (d, *J* = 16 Hz, 1H), 6,867 (br. s, 1H), 6,931 (d, *J* = 8 Hz, 1H), 7,087 (d, *J* = 8 Hz, 1H), 7,472 (t, *J* = 8 Hz, 1H), 8,401 (br. s, 1H), 10,945 (s, 1H). MS 352 (MH^+).

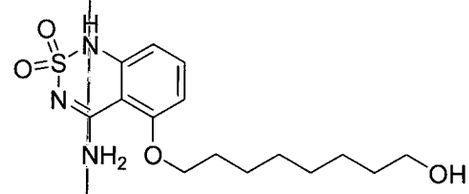
Ejemplo 273a: (E)–2–amino–6–(4–(tetrahidro–2H–piran–2–iloxi)but–1–enil)benzonitrilo

Preparado como en el Ejemplo 270a a partir de (E)–4,4,5,5–tetrametil–2–(4–(tetrahidro–2H–piran–2–iloxi)but–1–enil)–1,3,2–dioxaborolano (Ejemplo 273b) y 2–amino–6–bromobenzonitrilo en 47% de rendimiento como una goma amarilla. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,570 (m, 4H), 1,727 (m, 2H), 1,837 (m, 2H), 2,565 (q, *J* = 6 Hz, 2H), 3,541 (m, 2H), 3,879 (m, 2H), 4,387 (br. s, 2H), 4,635 (m, 1H), 6,423 (d de t, *J* = 7 Hz, 16 Hz, 1H), 6,586 (d, *J* = 8 Hz, 1H), 6,710 (d, *J* = 16 Hz, 1H), 6,905 (d, *J* = 8 Hz, 1H), 7,237 (t, *J* = 8 Hz, 1H).

Ejemplo 273b: (E)–4,4,5,5–tetrametil–2–(4–(tetrahidro–2H–piran–2–iloxi)but–1–enil)–1,3,2–dioxaborolano

Se trató 2–(but–3–iniloxi)tetrahidro–2H–pirano puro (12,8 mmol, 2,0 mL) con pinacolborano (19,1 mmol, 2,78 mL) a 60°C bajo nitrógeno. Luego de 2 horas, se adicionó otra porcóon de pinacolborano (12,8 mmol, 1,86 mL) y se continuó calentando a 60°C. Luego de 8 horas, la mezcla de reacción se diluyó con hexanos (30 mL) y se trató gota a gota con agua (1 mL), agitando hasta que cesó la evolución del gas. Las capas se separaron, la capa acuosa se extrajo con hexanos (2 X 5 mL), las capas orgánicas combinadas se lavaron con salmuera (5 mL), se secaron sobre sulfato de magnesio, se filtraron, y se evaporaron. El producto crudo se purificó sobre gel de sílice (EtOAc/hexanos 10% a 30%) para proporcionar el producto (1,73 g, 48% de rendimiento) como un aceite. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,262 (s, 3H), 1,531 (m, 2H), 1,699 (m, 1H), 1,812 (m, 1H), 2,469 (d of q, J = 2 Hz, 7 Hz, 2H), 3,495 (m, 1H), 3,832 (m, 2H), 4,593 (d of d, J = 3 Hz, 4 Hz, 1H), 5,523 (d de t, J = 2 Hz, 18 Hz, 1H), 6,634 (d de t, J = 7 Hz, 18 Hz, 1H).

Ejemplo 274: 8–(4–amino–2,2–dioxo–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)octan–1–ol



696

A una solución de acetato de 8–(3–amino–2–cianofenoxi)octilo (746 μmol, 227 mg) en DMA (3 mL) se le adicionaron cloruro de sulfamoilo (1,492 mmol, 172 mg) y piridina (4,476 mmol, 362 μL). La mezcla de reacción se agitó a

temperatura ambiente hasta la terminación, luego se inactivó con $NaHCO_3$ sat. (15 mL) y se adicionó NaCl sólido. El precipitado se recogió y se lavó con agua. El precipitado húmedo se suspendió en EtOH (15 mL) y se trató con NaOH (8,952 mmol, 1 N, 8,95 mL). La mezcla de reacción se reflujó hasta la terminación luego se enfrió hasta temperatura ambiente. La mayor parte del EtOH y el agua se removieron al vacío, luego la mezcla de reacción se disolvió en agua (15 mL), se extrajo con éter (3 X 5 mL), se filtró a través de una frita PTFE de 0,45 μm, luego se acidificó con 10% solución de ácido cítrico/agua hasta un pH 4–5. El precipitado se separó mediante filtración, se lavó con agua y se secó para proporcionar 146 mg (57,3%) del producto deseado como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,265 (m, 6H), 1,380 (m, 4H), 1,785 (pentete, J = 7 Hz, 2H), 3,348 (q, J = 6 Hz, 2H), 4,303 (t, J = 5 Hz, 2H), 6,580 (d, J = 8 Hz, 1H), 6,724 (d, J = 8 Hz, 1H), 7,428 (t, J = 8 Hz, 1H), 7,796 (br. s, 1H), 8,329 (br. s, 1H), 10,922 (s, 1H). MS 342 (MH^+).

Ejemplo 274a: Acetato de 8–(3–amino–2–cianofenoxi)octilo

Una solución de acetato de 8–(2–ciano–3–nitrofenoxi)octilo (802 μmol, 268 mg) (Ejemplo 274c) en EtOH (15 mL) se hidrogenó en un aparato H–cube utilizando 10% Pd/C como catalizador. La solución se evaporó para proporcionar acetato de 8–(3–amino–2–cianofenoxi)octilo (244 mg, 244 mg). MS 305 (MH^+)

Ejemplo 274b: Acetato de 8–(2–ciano–3–nitrofenoxi)octilo

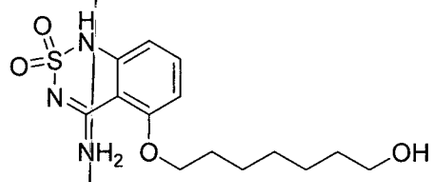
Se disolvió 2–(8–hidroxioctiloxi)–6–nitrobenzonitrilo (804 μmol, 235 mg) (Ejemplo 274c) en DCM seco (10 mL), se enfrió hasta 0ºC, y se trató sucesivamente con piridina (3,216 mmol, 260 μL) y cloruro de acetilo (1,608 mmol, 114 μL). La mezcla de reacción se agitó y se dejó entibiar lentamente hasta temperatura ambiente. Cuando la reacción estuvo completa, los volátiles se removieron al vacío y el producto crudo se purificó sobre gel de sílice (10% a 50%

EtOAc en hexanos) para proporcionar el producto deseado (268 mg, 100%). MS 335 (MH^+).

Ejemplo 274c: 2–(8–hidroxioctiloxi)–6–nitrobenzonitrilo

A una solución de 1,8–octanodiol (3,87 mmol, 566 mg) en THF (seco, 10 mL) se le adicionaron 2,6–dinitrobenzonitrilo (1,29 mmol, 250 mg) y DBU (1,30 mmol, 194 μL). La mezcla de reacción se agitó durante 24 horas a temperatura ambiente y se evaporó. El residuo oleoso se trituró con 10% ácido cítrico/agua y se adicionó NaCl sólido. El precipitado se recogió, se lavó con agua, se secó al vacío y se purificó sobre gel de sílice (40% a 100% EtOAc en hexanos) para proporcionar el producto deseado (235 mg, 62,3%) como un sólido ligeramente rosado. MS 293 (MH^+).

Ejemplo 275: 7–(4–amino–2,2–dioxo–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)heptan–1–ol



697

Preparado como en el Ejemplo 274 a partir de acetato de 7–(3–amino–2–cianofenoxi)heptilo (Ejemplo 275a) y cloruro de sulfamoilo en 79,4% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,320 (m, 4H), 1,405 (m, 4H), 1,811 (pentete, J = 7 Hz, 2H), 3,378 (q, J = 6 Hz, 2H), 4,154 (t, J = 6 Hz, 2H), 4,331 (t, J = 5 Hz, 1H), 6,605 (d, J = 8 Hz, 1H), 6,752 (d, J = 8 Hz, 1H), 7,454 (t, J = 8 Hz, 1H), 7,823 (br. s, 1H), 8,358 (br. s, 1H), 10,946 (s, 1H). MS 328 (MH^+).

Ejemplo 275a: Acetato de 7–(3–amino–2–cianofenoxi)heptilo

Preparado como en el Ejemplo 274a a partir de acetato de 7–(2–ciano–3–nitrofenoxi)heptilo (Ejemplo 275b) en 89% de rendimiento. MS 291 (MH^+)

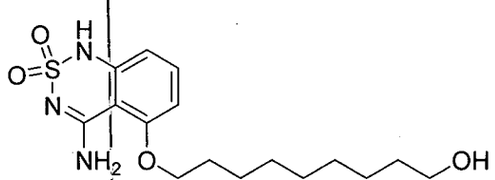
Ejemplo 275b: Acetato de 7–(2–ciano–3–nitrofenoxi)heptilo

Preparado como en el Ejemplo 274b a partir de 2–(7–hidroxiheptiloxi)–6–nitrobenzonitrilo (Ejemplo 275c) en 100% de rendimiento. MS 321 (MH^+).

Ejemplo 275c: 2–(7–hidroxiheptiloxi)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 274c (excepto que DBU se reemplazó con KOtBu) a partir de 1,7–heptanodiol en 65% de rendimiento. MS 279 (MH^+).

Ejemplo 276: 9–(4–amino–2,2–dioxo–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)nonan–1–ol



698

Preparado como en el Ejemplo 274 a partir de acetato de 9–(3–amino–2–cianofenoxi)nonilo (Ejemplo 276a) y cloruro de sulfamoilo en 62,3% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,250 (m, 8H), 1,381 (m, 4H), 1,791 (pentete, J = 7 Hz, 2H), 3,349 (q, J = 6 Hz, 2H), 4,135 (t, J = 6 Hz, 2H), 4,301 (t, J = 5 Hz, 1H), 6,585 (d, J = 8 Hz, 1H), 6,728 (d, J = 8 Hz, 1H), 7,434 (t, J = 8 Hz, 1H), 7,798 (br. s, 1H), 8,329 (br. s, 1H), 10,924 (s, 1H). MS 356 (MH^+).

Ejemplo 276a: Acetato de 9–(3–amino–2–cianofenoxi)nonilo

Preparado como en el Ejemplo 274a a partir de acetato de 9–(2–ciano–3–nitrofenoxi)nonilo (Ejemplo 276b) en 99,3% de rendimiento. MS 319 (MH^+)

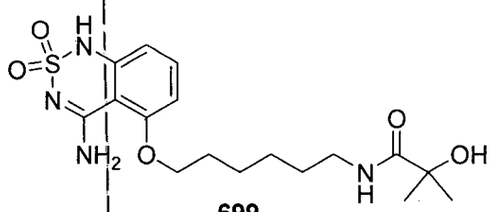
Ejemplo 276b: Acetato de 9–(2–ciano–3–nitrofenoxi)nonilo

Preparado como en el Ejemplo 274b a partir de 2–(9–hidroxinoniloxi)–6–nitrobenzonitrilo (Ejemplo 276c) en 100% de rendimiento. MS 349 (MH^+).

Ejemplo 276c: 2–(9–hidroxinoniloxi)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 274c (excepto que DBU se reemplazó con 1,1,3,3–tetrametilguanidina) a partir de 1,9–nonanodiol y 2,6–dinitrobenzonitrilo en 30,7% de rendimiento. MS 307 (MH^+).

Ejemplo 277: N–(6–(4–amino–2,2–dioxo–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)hexil)–2–hidroxi–2–metilpropanamida



699

Preparada como en el Ejemplo 274 a partir de acetato de 1–(6–(3–amino–2–cianofenoxi)hexilamino)–2–metil–1–oxopropan–2–ilo (Ejemplo 277a) en 65,5% de rendimiento. ^1H RMN (400 MHz, DMSO-d_6) δ 1,201 (s, 6H), 1,289 (m, 2H), 1,399 (m, 4H), 1,790 (pentete, J = 7 Hz, 2H), 3,036 (q, J = 6 Hz, 2H), 4,130 (t, J = 6 Hz, 2H), 5,272 (s, 1H), 6,587 (d, J = 8 Hz, 1H), 6,728 (d, J = 8 Hz, 1H), 7,436 (t, J = 8 Hz, 1H), 7,594 (br. t, 1H), 7,804 (br. s, 1H), 8,326 (br. s, 1H), 10,924 (s, 1H). MS 399 (MH^+).

Ejemplo 277a: Acetato de 1–(6–(3–amino–2–cianofenoxi)hexilamino)–2–metil–1–oxopropan–2–ilo

Preparado como en el Ejemplo 274a a partir de acetato de 1–(6–(2–ciano–3–nitrofenoxi)hexilamino)–2–metil–1–oxopropan–2–ilo (Ejemplo 274b) en 94,4% de rendimiento. MS 362 (MH^+)

Ejemplo 277b: Acetato de 1–(6–(2–ciano–3–nitrofenoxi)hexilamino)–2–metil–1–oxopropan–2–ilo

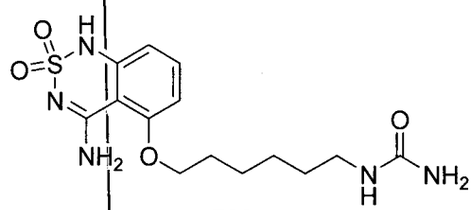
A una solución de 6–(2–ciano–3–nitrofenoxi)hexilcarbamato de terc–butilo (333 μmol, 121 mg) (Ejemplo 277c) en dixoano (2 mL) se le adicionó HCl con. (1 mL). Luego de 15 minutos, la solución se concentró al vacío y se secó sobre alto

vacío. La sal de HCl cruda se suspendió en DCM (seco, 10 mL) y se trató con piridina (2,664 mmol, 215 μL) y acetato de 1–cloro–2–metil–1–oxopropan–2–ilo (1,332 mmol, 193 μL). La mezcla de reacción se reflujó bajo una atmósfera de nitrógeno hasta que estuvo clara (6 h), luego se enfrió hasta temperatura ambiente y los volátiles se removieron al vacío. El residuo se purificó sobre gel de sílice (40% a 100% EtOAc en hexanos) para proporcionar el producto (117 mg, 90%) como un aceite pesado amarillo claro. MS 392 (MH^+).

Ejemplo 277c: 6–(2–ciano–3–nitrofenoxi)hexilcarbamato de terc–butilo

Preparado como en el Ejemplo 215c a partir de 6–hidroxihexilcarbamato de terc–butilo en 53,8% de rendimiento como un sólido amarillo claro. MS 364 (MH^+).

Ejemplo 278: 1–(6–(4–amino–2,2–dioxo–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)hexil)urea

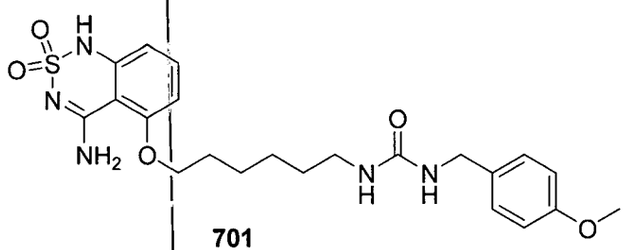


700

Una solución de 1–(6–(4–amino–2,2–dioxo–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)hexil)–3–(4–metoxibencil)urea (122 μmol, 58 mg) (Ejemplo 279) en DCM (2,5 mL) se trató con TFA (2,5 mL). La mezcla de reacción se agitó a temperatura ambiente durante 4 horas, luego los volátiles se removieron bajo una corriente de nitrógeno. El residuo oleoso se trituró con éter, el precipitado se recogió, se lavó con éter, luego se disolvió en MeOH y se evaporó para proporcionar el producto deseado (44 mg,100% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,364 (m, 6H), 1,812 (pentete, J = 7 Hz, 2H), 2,943 (br t, 2H), 4,154 (d, J = 7 Hz, 2H), 4,131 (t, J = 7 Hz, 2H), 5,349 (br. s, 2H), 5,894 (br. s, 1H), 6,607 (d, J = 8 Hz, 1H), 6,752

(d, J = 8 Hz, 1H), 7,456 (t, J = 8 Hz, 1H), 7,824 (br. s, 1H), 8,351 (br. s, 1H), 10,945 (s, 1H). MS 356 (MH^+).

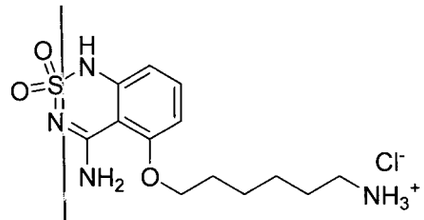
Ejemplo 279: 1–(6–(4–amino–2,2–dioxo–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)hexil)–3–(4–metoxibencil)urea



701

A una suspensión de cloruro de 6–(4–amino–2,2–dioxo–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)hexan–1–aminio (166 μmol, 52 mg) (Ejemplo 280) en DCM seco (6 mL) se le adicionaron sucesivamente Et_3N (332 μmol, 46 μL) y 1–(isocianatometil)–4–metoxibenceno (183 μmol, 26 μL). La reacción se agitó durante 48 horas a temperatura ambiente luego se concentró al vacío. El residuo se lavó con agua, se secó, luego se purificó sobre gel de sílice (20% a 100% EtOAc en hexanos) para proporcionar el producto deseado (64 mg, 81,0% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,296 (m, 2H), 1,371 (m, 4H), 1,791 (pentete, J = 8 Hz, 2H), 2,980 (q, J = 6 Hz, 2H), 3,695 (s, 3H), 4,086 (d, J = 6 Hz, 2H), 4,131 (t, J = 6 Hz, 2H), 5,836 (br. t, J = 5 Hz, 1H), 6,141 (br. t, J = 6 Hz, 1H), 6,585 (d, J = 8 Hz, 1H), 6,727 (d, J = 8 Hz, 1H), 6,840 (d, J = 9 Hz, 2H), 7,137 (d, J = 9 Hz, 2H), 7,433 (t, J = 8 Hz, 1H), 7,803 (br. s, 1H), 8,321 (br. s, 1H), 10,926 (s, 1H). MS 476 (MH^+).

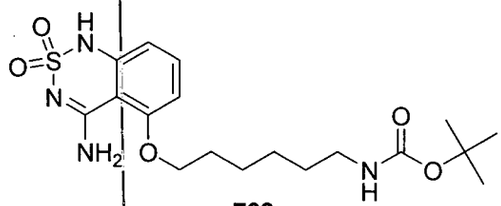
Ejemplo 280: Cloruro de 6–(4–amino–2,2–dioxo–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)hexan–1–aminio



702

A una solución de 6–(4–amino–2,2–dioxo–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)hexilcarbamato de terc–butilo (118 mg, 286 umol) (Ejemplo 281) en dioxano (2 mL) se le adicionó HCl con. (1 mL) y la solución se agitó a temperatura ambiente durante 15 minutos. Los solventes se removieron al vacío y el residuo se trituró con etanol caliente. Luego de enfriarse hasta temperatura ambiente, el precipitado se recogió, se lavó con etanol caliente, y se secó al vacío para proporcionar el producto deseado 56 mg (62,9%) como un polvo blancuzco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,367 (m, 4H), 1,529 (pentete, J = 7 Hz, 2H), 1,795 (pentete, J = 7 Hz, 2H), 2,741 (br m, 2H), 4,144 (t, J = 7 Hz, 2H), 6,596 (d, J = 8 Hz, 1H), 6,733 (d, J = 8 Hz, 1H), 7,440 (t, J = 8 Hz, 1H), 7,725 (br. s, 3H), 7,795 (br. s, 1H), 8,350 (br. s, 1H), 10,954 (s, 1H). MS 313 (MH^+).

Ejemplo 281: 6–(4–amino–2,2–dioxo–1H–benzo[c][1,2,6]tiadiazin–5–iloxi)hexilcarbamato de terc–butilo



703

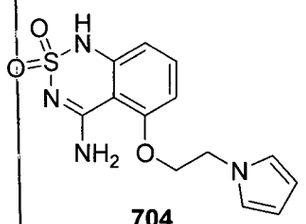
Preparado como en el Ejemplo 274 a partir de 6–(3–amino–2–cianofenoxi)hexilcarbamato de terc–butilo (Ejemplo 281a) y cloruro de sulfamoilo en 59,5% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,274 (m, 2H), 1,339 (s, 9H), 1,361 (m, 4H), 1,779 (pentete, J = 7 Hz, 2H), 2,878 (q, J = 6 Hz, 2H),

4,122 (t, *J* = 6 Hz, 2H), 6,580 (d, *J* = 8 Hz, 1H), 6,722 (d, *J* = 8 Hz, 1H), 6,75 (br t, *J* = 6 Hz, 1H), 7,428 (t, *J* = 8 Hz, 1H), 7,798 (br. s, 1H), 8,323 (br. s, 1H), 10,921 (s, 1H). MS 413 (MH^+).

Ejemplo 281a: 6–(3–amino–2–cianofenoxi)hexilcarbamato de terc–butilo

Preparado como en el Ejemplo 274a a partir de 6–(2–ciano–3–nitrofenoxi)hexilcarbamato de terc–butilo (ejemplo 277c) en rendimiento cuantitativo. MS 334 (MH^+).

Ejemplo 282: 5–(2–(1H–pirrol–1–il)etoxi)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



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Preparado como en el Ejemplo 274 a partir de 2–(2–(1H–pirrol–1–il)etoxi)–6–aminobenzonitrilo (Ejemplo 282a) y cloruro de sulfamoilo en 66,6% de rendimiento. ^1H RMN (400 MHz, DMSO-d_6) δ 4,392 (m, 4H), 5,992 (t, *J* = 2 Hz, 2H), 6,595 (d, *J* = 8 Hz, 1H), 6,693 (d, *J* = 8 Hz, 1H), 6,816 (t, *J* = 2 Hz, 2H), 7,428 (t, *J* = 8 Hz, 1H), 7,482 (br. s, 1H), 8,288 (br. s, 1H), 10,930 (s, 1H). MS 307 (MH^+).

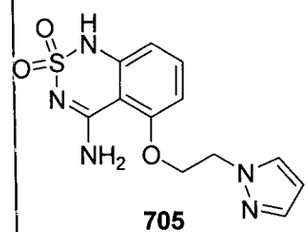
Ejemplo 282a: 2–(2–(1H–pirrol–1–il)etoxi)–6–aminobenzonitrilo

Preparado como en el Ejemplo 274a a partir de 2–(2–(1H–pirrol–1–il)etoxi)–6–nitrobenzonitrilo (Ejemplo 282b) en 85,2% de rendimiento. MS 228 (MH^+).

Ejemplo 282b: 2–(2–(1H–pirrol–1–il)etoxi)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 166d a partir de 2–(1H–pirrol–1–il)etanol y 2,6–dinitrobenzonitrilo, en 42,5% de rendimiento. MS 258 (MH^+).

Ejemplo 283: 5–(2–(1H–pirazol–1–il)etoxi)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



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Preparado como en el Ejemplo 274 a partir de 2–(2–(1H–pirazol–1–il)etoxi)–6–aminobenzonitrilo (Ejemplo 283a) y cloruro de sulfamoilo en 54,5% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 4,406 (t, J = 5 Hz, 2H), 4,630 (t, J = 5 Hz, 2H), 6,266 (t, J = 2 Hz, 1H), 6,593 (d, J = 8 Hz, 1H), 6,689 (d, J = 8 Hz, 1H), 7,445 (br s, 1H), 7,425 (t, J = 8 Hz, 1H), 7,805 (d, J = 2 Hz, 1H), 8,224 (br. s, 1H), 8,301 (br. s, 1H), 10,904 (s, 1H). MS 308 (MH^+).

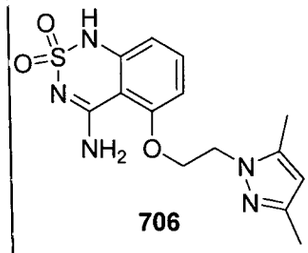
Ejemplo 283a: 2–(2–(1H–pirazol–1–il)etoxi)–6–aminobenzonitrilo

Preparado como en el Ejemplo 274a a partir de 2–(2–(1H–pirazol–1–il)etoxi)–6–nitrobenzonitrilo (Ejemplo 283b) en 46,2% de rendimiento. MS 229 (MH^+).

Ejemplo 283b: 2–(2–(1H– pirazol –1–il)etoxi)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 215c a partir de 2–(1H–pirazol–1–il)etanol y 2,6–dinitrobenzonitrilo en 89,2% de rendimiento. MS 259 (MH^+).

Ejemplo 284: 5–(2–(3,5–dimetil–1H–pirazol–1–il)etoxi)–1H–benzo[c][1,2,6]tiadiazin–4–amin–2,2–dióxido



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Preparado como en el Ejemplo 274 a partir de 2–(2–(3,5–dimetil–1H–pirazol–1–il)etoxi)–6–aminobenzonitrilo (Ejemplo 284a) y cloruro de sulfamoilo en 18,2% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,066 (s, 3H), 2,215 (s, 3H), 4,313 (t, J = 4 Hz, 2H), 4,397 (t, J = 4 Hz, 2H), 5,801 (s, 1H), 6,584 (d, J = 8 Hz, 1H), 6,645 (d, J = 8 Hz, 1H), 7,418 (t, J = 8 Hz, 1H), 8,395 (br. s, 1H), 8,677 (br. s, 1H), 10,885 (s, 1H). MS 336 (MH^+).

Ejemplo 284a: 2–(2–(3,5–dimetil–1H–pirazol–1–il)etoxi)–6–aminobenzonitrilo

Preparado como en el Ejemplo 274a a partir de 2–(2–(3,5–dimetil–1H–pirazol –1–il)etoxi)–6–nitrobenzonitrilo (Ejemplo 284b) en 69,3% de rendimiento. MS 257 (MH^+).

Ejemplo 284b: 2–(2–(3,5–dimetil–1H–pirazol–1–il)etoxi)–6–nitrobenzonitrilo

Preparado como en el Ejemplo 215c a partir de 2–(3,5–dimetil–1H–pirazol–1–il)etanol y 2,6–dinitrobenzonitrilo en 90,7% de rendimiento. MS 287 (MH^+).

EXPERIMENTO 4: Ensayo biológico

Un derivado de línea celular HEK293 (Chandrashekar *et al.*, *Cell* 100, 703-711, 2000) el cual expresa de modo estable Gα15 y hT1R2/hT1R3 (Li *et al.*, *Proc Natl Acad Sci Estados Unidos* 99, 4692-4696, 2002) (véase también, la Publicación Internacional No. WO 03/001876) se utilinzó en ensayos biológicos en

asociación con la identificación de compuestos con propiedades de mejoramiento del sabor dulce.

Los compuestos se seleccionaron inicialmente en base a su actividad en la línea celular hT1R2/hT1R3-HEK293-Gα15 Li *et al.*, *supra*. La actividad se determinó utilizando un ensayo de captación de imágenes fluorométricas automatizado en un instrumento FLIPR (Fluormetric Intensity Plate Reader, Molecular Devices, Sunnyvale, CA) (designado ensayo FLIPR). Se sembraron células a partir de un clon (designado clon S-9) dentro de placas de 384 pocillos (a aproximadamente 50.000 células por pocillo) en un medio que contenía DMEM con Baja Glucosa (Invitrogen, Carlsbad, CA), 10% suero bovino fetal dializado (Invitrogen, Carlsbad, CA), 100 Unidades/ml de Penicilina G, y 100 µg/ml de Estreptomicina (Invitrogen, Carlsbad, CA) (Li et al., 2002) (véase también, la Publicación Internacional No. WO 03/001876).

Las células S-9 cells se cultivaronn durante 24 horas a 37°C. Luego las células S-9 se cargaron con el colorante de calcio Fluo-3AM (Molecular Probes, Eugene, OR), 4 µM en buffer fosfato salino (D-PBS) (Invitrogen, Carlsbad, CA), durante 1 hora a temperatura ambiente. Luego del reemplazo con 25 µl de D-PBS, se llevó a cabo la estimulación en el instrumento FLIPR y a temperatura ambiente mediante la adición de 25 µl de D-PBS suplementado con los compuestos en concentraciones correspondientes a tres veces el nivel final deseado (Estimulación 1).

Las células se incubaron con los compuestos durante 7,5 minutos y luego se llevó a cabo otra estimulación en el instrumento FLIPR mediante la adición de 25 µl de D-PBS suplementado con una concentración sub-óptima de edulcorantes (produciendo aproximadamente 5% a 20% de actividad del receptor) (Estimulación 2).

Alternativamente luego del reemplazo con 25 µl de D-PBS por pocillo, se llevó a cabo la estimulación en el instrumento FLIPR a temperatura ambiente mediante la adición de 25 µl de D-PBS suplementado con diferentes estímulos.

Los edulcorantes típicos utilizados incluyen, pero no se limitan a D-Glucosa, D-Fructosa, Sucralosa, Aspartame y Sacarosa. Luego se cuantificó la actividad del receptor mediante la determinación de los máximos incrementos de fluorescencia (utilizando una excotación de 480 nm y una emisión de 535 nm) luego de la normalización hasta la intensidad de la fluorescencia basal medida antes de la estimulación. Los compuestos que produjeron un incremento en la actividad del receptor mediada por edulcorante se seleccionaron para la caracterización y cuantificación adicionales de las potenciales propiedades de mejoramiento.

En este ensayo siguiente, una concentración fija de compuestos se adicionó en duplicados a 10 columnas consecutivas (20 pocillos en total) durante la estimulación 1. Las concentraciones de compuesto típicas evaluadas fueron 300 µM, 100 µM, 50 µM, 30 µM, 10 µM, 3 µM y 1 µM, 0,3 µM, 0,1 µM, o 0,03 µM. Luego del período de incubación de 7,5 minutos, concentraciones en aumento de edulcorante (para generar una curva de respuesta a la dosis) se presentaron en los pocillos, en duplicados, durante la estimulación 2. La eficacia relativa de los compuestos en el mejoramiento del receptor se determinó calculando la magnitud de un cambio en la CE_{50} para el edulcorante. El mejoramiento se definió como una relación ($CE_{50}R$) que corresponde a la CE_{50} de los edulcorantes, determinada en ausencia del compuesto de ensayo, dividida por la CE_{50} del edulcorante, determinada en presencia del compuesto de ensayo. En algunas realizaciones, los compuestos tienen una $CE_{50}R$ entre aproximadamente 1 (*por ejemplo,* >1) y aproximadamente 1000. En otras realizaciones, los compuestos tienen una $CE_{50}R$ entre aproximadamente 1,25 y aproximadamente 500. Todavía en otras

realizaciones, los compuestos tienen una $CE_{50}R$ entre aproximadamente 1,50 y aproximadamente 100. Aún en otras realizaciones, los compuestos tienen una $CE_{50}R$ entre aproximadamente 1 (*por ejemplo,* >1) y aproximadamente 50.

Todavía en otra realización, los compuestos a aproximadamente 50 µM tienen una $CE_{50}R$ entre aproximadamente 1 (*por ejemplo,* >1) y aproximadamente 1000, entre aproximadamente 1,25 y aproximadamente 500, entre aproximadamente 1,50 y aproximadamente 100, o entre aproximadamente 1 (*por ejemplo,* >1) y aproximadamente 50. Los resultados del ensayo para los compuestos se ilustran en la tabla a continuación.

En un ejemplo ilustrativo, la $CE_{50}R$ de la sucralosa preincubada a 50 µM para un grupo de compuestos específicos de la presente invención generalmente tiene un rango desde 0,73 hasta 5,20, mientras que la $CE_{50}R$ de la sucralosa de coestimulación a 50 µM para el mismo grupo de compuestos generalmente tiene un rango desde 0,72 hasta 4,46. En otro ejemplo ilustrativo, la $CE_{50}R$ de la sacarosa coestimulada a 50 µM para un grupo de compuestos específicos de la presente invención generalmente tiene un rango desde 1,30 hasta 4,35, la $CE_{50}R$ de la sucralosa de coestimulación a 50 µM para el mismo grupo de compuestos generalmente tiene un rango desde 1,73 hasta 24,09, y la $CE_{50}R$ de la fructosa de coestimulación a 50 µM para el mismo grupo de compuestos generalmente tiene un rango desde 0,81 hasta 4,46. En otro ejemplo ilustrativo, la $CE_{50}R$ de la sacarosa coestimulada a 50 µM para un grupo de compuestos específicos de la presente invención generalmente tiene un rango desde 1,05 hasta 2,44, la $CE_{50}R$ de la sucralosa de coestimulación a 50 µM para el mismo grupo de compuestos generalmente tiene un rango desde 1,57 hasta 11,63, y la $CE_{50}R$ de la fructosa de coestimulación a 50 µM para el mismo grupo de compuestos generalmente tiene un rango desde 0,99 hasta 1,78. En otro ejemplo ilustrativo, la $CE_{50}R$ de la sacarosa coestimulada a 50 µM para un grupo de compuestos específicos de la

presente invención generalmente tiene un rango desde 1,27 hasta 116,56, la $CE_{50}R$ de la sucralosa de coestimulación a 50 μM para el mismo grupo de compuestos generalmente tiene un rango desde 1,48 hasta 157,63, y la $CE_{50}R$ de la fructosa de coestimulación a 50 μM para el mismo grupo de compuestos generalmente tiene un rango desde 0,68 hasta 9,56. En otro ejemplo ilustrativo, la $CE_{50}R$ de la sacarosa coestimulada a 50 μM para un grupo de compuestos específicos de la presente invención generalmente tiene un rango desde 0,88 hasta 36,66, la $CE_{50}R$ de la sucralosa de coestimulación a 50 μM para el mismo grupo de compuestos generalmente tiene un rango desde 1,07 hasta 101,15, y la $CE_{50}R$ de la fructosa de coestimulación a 50 μM para el mismo grupo de compuestos generalmente tiene un rango desde 0,71 hasta 7,09. En otro ejemplo ilustrativo, la $CE_{50}R$ de la sacarosa coestimulada a 50 μM para un grupo de compuestos específicos de la presente invención generalmente tiene un rango desde 1,39 hasta 17,17, la $CE_{50}R$ de la sucralosa de coestimulación a 50 μM para el mismo grupo de compuestos generalmente tiene un rango desde 3,80 hasta 49,89, y la $CE_{50}R$ de la fructosa de coestimulación a 50 μM para el mismo grupo de compuestos generalmente tiene un rango desde 0,92 hasta 6,07. En otro ejemplo ilustrativo, la $CE_{50}R$ de la sacarosa coestimulada a 50 μM para un grupo de compuestos específicos de la presente invención generalmente tiene un rango desde 1,30 hasta 56,27, la $CE_{50}R$ de la sucralosa de coestimulación a 50 μM para el mismo grupo de compuestos generalmente tiene un rango desde 1,26 hasta 204,98, y la $CE_{50}R$ de la fructosa de coestimulación a 50 μM para el mismo grupo de compuestos generalmente tiene un rango desde 1,14 hasta 8,37.

Número de Compuesto	Sucralosa Preincubada $CE_{50}R$ (50 μM)	Sucralosa de $CE_{50}R$ (50 μM)
B	5,20	4,46
B1	2,41	1,93
B2	2,19	2,44
B3	2,19	3,77
B4	1,73	4,14
B5	1,58	2,98
B6	1,00	1,32
B7	1,02	1,38
B8	1,12	1,12
B9	1,11	1,07
B10	0,86	1,01
B11	1,08	1,11
B12	0,73	0,78
B13	0,95	0,97
B14	1,11	1,06
B15	0,84	1,05
B16	0,99	1,11
B17	0,90	1,04
B18	0,86	
B19	1,03	1,09
B20	1,06	
B22	0,92	0,98
B23	1,10	1,89
B24	0,87	1,12
B25		1,10
B26		0,99
B27		0,86
B28		0,96
B29		0,72
B30		1,16
B31		1,25
B32	1,03	1,35
B33	0,87	1,36
B34	1,23	0,74
B35	0,99	
B36	0,99	
B37	0,90	0,96
B38		0,93
B39		1,07
B40	0,89	
B41		0,82
B42	1,15	1,02
B43	0,98	1,35

EXPERIMENTO 5: Medición del Sabor Dulce y del Mejoramiento del Sabor Dulce Utilizando Panelistas Humanos que Llevaron a Cabo un Ensayo en Escala

Las muestras de ensayo que contenían los compuestos experimentales se compararon con una curva de respuesta a la dosis en cuanto a las concentraciones de intensidad de dulzor percibida de los edulcorantes (tales como, por ejemplo, sucralosa, sacarosa, fructosa y otros edulcorantes) para determinar la intensidad de dulzor equivalente.

Un grupo de ocho o más panelistas probaron las soluciones que incluían los edulcorantes en diversas concentraciones, así como también el compuesto experimental con y sin edulcorante adicionado. Luego los panelistas evaluaron la intensidad de dulzor de todas las muestras en una escala de línea horizontal estructurada, establecida desde 0 hasta 15, donde 0 es igual a no dulzor y 15 es igual a un dulzor equivalente a una muestra de 15% sacarosa. Los puntajes para la intensidad de dulzor se promediaron entre los panelistas. Luego utilizando los puntajes promedio y/o la ecuación de la línea para la curva de respuesta a la dosis de edulcorante, se determinaron las concentraciones de dulzor equivalentes para las muestras que contenían los compuestos experimentales.

Previamente los sujetos se habían familiarizado con el atributo clave del sabor y se capacitaron para utilizar la escala lineal de 0 a 15 puntos. Los sujetos se abstuvieron de comer o beber (excepto agua) durante al menos 1 hora antes del ensayo. Los sujetos comieron una galletita salada y se enjuagaron con agua varias veces para limpiarse la boca.

Las soluciones de edulcorante se proporcionan en un amplio rango de concentraciones tales como 100 ppm, 200 ppm, 300 ppm, 400 ppm, y 500 ppm para la sucralosa, o entre 0% y 12% para la sacarosa o la fructosa, con el objeto de crear una curva de respuesta a la dosis. Las muestras que contenían el

compuesto experimental se prepararon tanto solas como en una solución de sucralosa de 100 ppm o en una solución de fructosa o sacarosa 6%. Todas las muestras se elaboraron en buffer de bajo sodio pH 7,1. Con el objeto de auxiliar en la dispersión, las soluciones se pueden elaborar en 0,1% etanol.

Las soluciones se dispensaron en volúmenes de 20 ml dentro de tazas para muestras de 29,6 ml (1 oz.) y se sirvieron a los sujetos a temperatura ambiente. Toas las muestras se presentaron en orden contrabalanceado aleatorizado para reducir el sesgo de respuesta. Además, se pueden utilizar dos sesiones de ensayo para examinar la precisión del panel.

Los sujetos probaron cada muestra individualmente y evaluaron la intensidad de dulzor en la escala lineal antes de probar la muestra siguiente. Todas las muestras se expectoraron. Los sujetos pueden volver a probar las muestras pero solamente pueden utilizar el volumen de muestra proporcionado. Los sujetos deben enjuagarse con agua entre las muestras. Se puede requerir la ingestión de una galletita sin sal entre las muestras dependiendo de las muestras que se prueben.

Los puntajes para cada muestra se promediaron entre los sujetos y se calculó el error standard. La curva de respuesta a la dosis se ploteó gráficamente, y ello puede utilizarse para asegurarse de que el panel está evaluando con precisión; *es decir*, el incremento de la concentración de sucralosa debería corresponder a mayores puntajes promedio en cuanto al dulzor. Se pueden utilizar los ensayos ANOVA de 2 vías (siendo los factores las muestras y los panelistas) y de comparación múltiple (tal como el ensayo de Diferencia Honestamente Significativa de Tukey) para determinar las diferencias entre las muestras y/o los panelistas. Se puede utilizar un ANOVA de 3 vías, con las sesiones como el tercer factor, para determinar si existe cualquier diferencia en las evaluaciones entre las sesiones.

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Los compuestos ensayados en este Experimento, a saber, los compuestos C1 a C21, constituyen compuestos representativos de la presente invención que incluyen los compuestos de la Fórmula estructural (I) y sus fórmulas subgenéricas.

A continuación se encuentran los resultados de los ensayos de sabor en humanos con un compuesto **C1**. La Tabla 1 indica que 100 µM de compuesto **C1** en 100 ppm de sucralosa tiene un dulzor equivalente a 200 ppm de sucralosa. La Tabla 2 indica que 100 µM de compuesto **C1** solo no tiene dulzor, y por consiguiente se puede definir como un verdadero mejorador dulce.

Tabla 1. Puntajes de dulzor promedio para diversas muestras de sucralosa, que incluyen 100 ppm de sucralosa con 100 µM de compuesto **C1**, n = 32 (16 Panelistas x 2 replicados). Valor de Tukey = 1,409 (α = 0,05).

Muestra	Promedio	Error Standard	Significancia de HSD de Tukey (5%)
100 ppm de Sucralosa	6,3	0,3	A
100 ppm de Sucralosa + 100 µM de C1	10,2	0,5	B
200 ppm de Sucralosa	10,4	0,5	B
300 ppm de Sucralosa	11,5	0,4	Bc
400 ppm de Sucralosa	12,3	0,4	C

Tabla 2. Puntajes de dulzor promedio para 100 µM de compuesto C1 y buffer de bajo sodio, n = 15 (15 Panelistas x 1 rep). Valor de Tukey = 0,186 (α = 0,05).

Muestra	Promedio	Error Standard	Significancia de HSD de Tukey (5%)
Buffer de Bajo Sodio (no contiene edulcorantes)	0,1	0,1	A
100 µM de 7	0,1	0,1	A

A continuación se muestran los resultados de los ensayos de sabor en humanos con el compuesto **C2**. La Tabla 3 indica que 100 µM de compuesto en 100 ppm de sucralosa tiene un dulzor equivalente a aproximadamente 600 ppm de sucralosa. La Tabla 4 muestra una curva de respuesta a la dosis del compuesto **C2** con 100 ppm de sucralosa lo cual demuestra que el dulzor de la sucralosa mejora significativamente a través de la adición de cantidades en aumento del compuesto **C2**. La Tabla 5 indica que 100 µM de compuesto **C2** solo tiene poco dulzor o no lo tiene, y por consiguiente se puede definir como un verdadero mejorador dulce.

Tabla 3. Puntajes de dulzor promedio, n = 12 (12 Panelistas x 1 rep). Valor de Tukey = 2,449 (α = 0,05), 2,209 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
100 ppm de Sucralosa	7,4	1,7	0,5	a	a
200 ppm de Sucralosa	10,4	1,9	0,6	b	b
300 ppm de Sucralosa	10,5	2,8	0,8	b	b
400 ppm de Sucralosa	11,2	2,4	0,7	bc	bc
600 ppm de Sucralosa	13,0	1,4	0,4	c	c

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100 µM de C2 + 100 ppm de Sucralosa	13,3	1,6	0,5	c	c

Tabla 4. Puntajes de dulzor promedio, n = 26 (14 Panelistas x 1 rep; 12 panelistas x 1 rep). Valor de Tukey = 1,584 (α = 0,05), 1,452 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
100 ppm de sucralosa	6,3	1,5	0,3	a	a
100 ppm de sucralosa + 3,12 µM de C2	7,4	1,7	0,3	ab	ab
100 ppm de sucralosa + 6,25 µM de C2	8,4	1,8	0,4	bc	bc
100 ppm de sucralosa + 12,5 µM de C2	9,1	1,9	0,4	cd	cd
200 ppm de sucralosa	9,5	2,0	0,4	cd	cd
300 ppm de sucralosa	10,3	2,7	0,5	d	d
100 ppm de sucralosa + 25 µM C2	10,3	1,6	0,3	d	d
400 ppm de sucralosa	12,1	1,9	0,4	e	e
100 ppm sucralosa + 50 µM C2	12,3	1,5	0,3	e	e

Tabla 5. Puntajes de dulzor promedio, n = 12 (12 Panelistas x 1 rep). Valor de Tukey = 0,809 (α = 0,05), 0,723 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
0% Sacarosa	0,0	0,0	0,0	a	a
100 µM de C2 en LSB	0,2	0,3	0,1	a	a

2% Sacarosa	2,4	1,0	0,3	b	b

A continuación se muestran los resultados de los ensayos de sabor en humanos con el compuesto **C3**. La Tabla 6 indica que 100 µM de compuesto en 100 ppm de sucralosa tiene un dulzor equivalente a aproximadamente entre 200 y 300 ppm de sucralosa. La Tabla 7 indica que 100 µM de compuesto **C3** solo no tiene dulzor, y por consiguiente se puede definir como un verdadero mejorador dulce.

Tabla 6. Puntajes de dulzor promedio, n = 13 (13 Panelistas x 1 rep). Valor de Tukey = 2,333 (α = 0,05), 2,087 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
100 ppm de Sucralosa	6,5	1,3	0,4	a	a
200 ppm de Sucralosa	9,1	2,0	0,6	b	b
100 ppm de Sucralosa + 100 µM de C3	9,8	1,8	0,5	b	bc
300 ppm de Sucralosa	10,8	2,8	0,8	b	bc
400 ppm de Sucralosa	11,2	2,3	0,6	b	c

Tabla 7. Puntajes de dulzor promedio, n = 13 (13 Panelistas x 1 rep). Valor de Tukey = 0,906 (α = 0,05), 0,811 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
100 µM de C3 en LSB	0,0	0,0	0,0	a	a
0% Sacarosa	0,0	0,1	0,0	a	a

2% Sacarosa	1,8	1,0	0,3	b	b

A continuación se muestran los resultados de los ensayos de sabor en humanos con un compuesto **C4**. La Tabla 8 indica que 100 µM de compuesto **C4** en 6% sacarosa tiene un dulzor equivalente a 8% sacarosa. La Tabla 9 indica que 100 µM de compuesto **C4** solo no tiene dulzor, y por consiguiente se puede definir como un verdadero mejorador dulce.

Tabla 8. Puntajes de dulzor promedio para diversas muestras de sacarosa, que incluyen 6% sacarosa con 100 µM de compuesto **C4**, n = 28 (14 Panelistas x 2 replicados). Valor de Tukey = 1,091 (α = 0,05), 0,976 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
6% Sacarosa	6,6	1,0	0,2	a	a
8% Sacarosa	8,1	2,1	0,4	b	b
6% Sacarosa + 100 µM de C4	8,1	1,1	0,2	b	b
9% Sacarosa	8,6	1,9	0,4	bc	b
10% Sacarosa	9,6	0,6	0,1	c	c

Tabla 9. Puntajes de dulzor promedio, n = 14 (14 Panelistas x 1 rep). Valor de Tukey = 0,876 (α = 0,05), 0,784 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
100 µM de C4 en LSB	0,3	0,6	0,2	a	a
0% Sacarosa	0,3	1,1	0,3	a	a
2% Sacarosa	2,2	0,6	0,2	b	b

4% Sacarosa	4,0	0,9	0,2	c	c
6% Sacarosa	5,5	0,9	0,2	d	d

A continuación se muestran los resultados de los ensayos de sabor en humanos con un compuesto **C5**. La Tabla 10 indica que 100 µM de compuesto **C5** en 6% sacarosa tiene un dulzor equivalente a 9% sacarosa. La Tabla 11 indica que 100 µM de compuesto **C5** solo no tiene dulzor, y por consiguiente se puede definir como un verdadero mejorador dulce.

Tabla 10. Dulzor Promedio, n = 24 (12 Panelistas x 2 rep). Valor de Tukey = 0,832 (α = 0,05), 0,744 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
6% Sacarosa	7,3	1,3	0,3	a	a
8% Sacarosa	7,9	1,3	0,3	ab	ab
9% Sacarosa	8,6	1,1	0,2	bc	bc
6% Sacarosa + 100 µM de C5	8,8	0,9	0,2	cd	c
10% Sacarosa	9,6	0,7	0,1	d	d

Tabla 11. Dulzor Promedio, n = 14 (14 Panelistas x 1 rep). Valor de Tukey = 0,981 (α = 0,05), 0,877 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
LSB + 100 µM de C5	0,2	0,5	0,1	a	a
0% Sacarosa	0,4	1,5	0,4	a	a
2% Sacarosa	2,1	0,8	0,2	b	b

4% Sacarosa	3,9	0,7	0,2	c	c
6% Sacarosa	5,7	0,7	0,2	d	d

A continuación se muestran los resultados de los ensayos de sabor en humanos con un compuesto **C6**. La Tabla 12 indica que 100 µM de compuesto **C6** en 6% sacarosa tiene un dulzor equivalente a aproximadamente 10% sacarosa. La Tabla 13 indica que 100 µM de compuesto **C6** solone no tiene dulzor, y por consiguiente se puede definir como un verdadero mejorador dulce.

Tabla 12. Dulzor Promedio, n = 28 (14 Panelistas x 2 rep). Valor de Tukey = 0,818 (α = 0,05), 0,732 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
6% Sacarosa	6,8	1,2	0,2	a	a
8% Sacarosa	8,3	1,1	0,2	b	b
9% Sacarosa	8,6	1,3	0,3	bc	bc
6% Sacarosa + 100 µM de C6	9,3	1,0	0,2	cd	cd
10% Sacarosa	9,5	0,7	0,1	d	d

Tabla 13. Dulzor Promedio, n = 14 (14 Panelistas x 1 rep). Valor de Tukey = 1,238 (α = 0,05), 1,107 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
0% Sacarosa	0,0	0,1	0,0	a	a
LSB + 100 µM de C6	0,2	0,5	0,1	a	a
2% Sacarosa	1,9	0,9	0,2	b	b

4% Sacarosa	3,9	1,3	0,4	c	c
6% Sacarosa	5,5	2,0	0,5	d	d

A continuación se muestran los resultados de los ensayos de sabor en humanos con un compuesto **C7**. La Tabla 14 indica que 50 µM de compuesto **C7** en 6% sacarosa tiene un dulzor equivalente a aproximadamente 9% sacarosa.

Tabla 14. Dulzor Promedio, n = 26 (13 Panelistas x 2 rep). Valor de Tukey = 0,762 (α = 0,05), 0,682 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
6% Sacarosa	6,5	1,0	0,2	a	a
8% Sacarosa	8,5	1,3	0,2	b	b
9% Sacarosa	8,7	1,4	0,3	b	b
6% Sacarosa + 50 µM de C7	8,9	1,1	0,2	bc	b
10% Sacarosa	9,7	0,9	0,2	c	c

A continuación se muestran los resultados de los ensayos de sabor en humanos con un compuesto **C8**. La Tabla 15 indica que 100 µM de compuesto **C8** en 6% sacarosa tiene un dulzor equivalente a aproximadamente 8% sacarosa. La La Tabla 16 indica que 100 µM de compuesto **C8** solo no tiene dulzor, y por consiguiente se puede definir como un verdadero mejorador dulce.

Tabla 15. Dulzor Promedio, n = 28 (14 Panelistas x 2 rep). Valor de Tukey = 0,859 (α = 0,05), 0,768 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)

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6% Sacarosa	7,0	1,3	0,3	a	a
6% Sacarosa + 100 µM de C8	8,2	1,3	0,3	b	b
8% Sacarosa	8,4	1,5	0,3	bc	bc
9% Sacarosa	9,0	1,0	0,2	bc	c
10% Sacarosa	9,1	1,0	0,2	c	c

Tabla 16. Dulzor Promedio, n = 14 (14 Panelistas x 1 rep). Valor de Tukey = 1,029 (α = 0,05), 0,921 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
0% Sacarosa	0,0	0,0	0,0	a	a
100 µM de C8 en LSB	0,2	0,3	0,1	a	a
2% Sacarosa	2,0	0,9	0,2	b	b
4% Sacarosa	4,1	1,4	0,4	c	c
6% Sacarosa	5,7	1,4	0,4	d	d

A continuación se muestran los resultados de los ensayos de sabor en humanos con un compuesto **C9**. La Tabla 17 indica que desde aproximadamente 40 hasta aproximadamente 55 µM de compuesto **C9** en 100 ppm de sucralosa tiene un dulzor equivalente a aproximadamente 400 ppm de sucralosa. La Tabla 18 indica que from desde aproximadamente 40 hasta aproximadamente 55 µM de compuesto **C9** solo no tiene dulzor, y por consiguiente se puede definir como un verdadero mejorador dulce.

Tabla 17. Dulzor Promedio, n = 28 (14 Panelistas x 2 rep). Valor de Tukey = 1,304 (α = 0,05), 1,178 (α = 0,10).

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Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
100 ppm de Sucralosa	6,5	2,0	0,4	a	a
200 ppm de Sucralosa	9,0	1,8	0,3	b	b
300 ppm de Sucralosa	10,9	1,6	0,3	c	c
100 ppm de Sucralosa + 40-55 µM de C9	12,2	1,3	0,3	cd	d
400 ppm de Sucralosa	12,3	1,8	0,3	d	d

Tabla 18. Dulzor Promedio, n = 22 (11 Panelistas x 2 rep). Valor de Tukey = 0,693 (α = 0,05), 0,619 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
LSB + 40-55 µM de C9	0,1	0,4	0,1	a	a
0% Sacarosa	0,2	0,6	0,1	a	a
2% Sacarosa	2,4	0,8	0,2	b	b
4% Sacarosa	4,2	1,1	0,2	c	c
6% Sacarosa	5,9	1,1	0,2	d	d

A continuación se muestran los resultados de los ensayos de sabor en humanos con un compuesto **C10**. La Tabla 19 indica que 25 µM de compuesto **C10** en 6% sacarosa tiene un dulzor equivalente a aproximadamente 8% sacarosa.

Tabla 19. Dulzor Promedio, n = 28 (14 Panelistas x 2 rep). Valor de Tukey = 0,747 (α = 0,05), 0,668 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
6% Sacarosa	7,3	1,4	0,3	a	a
6% Sacarosa + 25 µM de C10	8,4	1,1	0,2	b	b
8% Sacarosa	8,6	1,2	0,2	bc	bc
9% Sacarosa	9,1	0,9	0,2	cd	cd
10% Sacarosa	9,7	0,5	0,1	d	d

La Tabla 20 indica que 25 µM de compuestos **C10** solos no tienen dulzor, y por consiguiente se pueden definir como verdaderos mejoradores dulces.

Tabla 20. Dulzor Promedio, n = 14 (14 Panelistas x 1 rep). Valor de Tukey = 0,957 (α = 0,05), 0,856 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
0% Sacarosa	0,2	0,5	0,1	a	a
LSB + 25 µM de C10	0,2	0,6	0,1	a	a
2% Sacarosa	2,8	1,5	0,4	b	b
4% Sacarosa	4,7	1,0	0,3	c	c
6% Sacarosa	5,9	0,5	0,1	d	d

A continuación se muestran los resultados de los ensayos de sabor en humanos con un compuesto **C11**. La Tabla 21 indica que 50 µM de compuesto **C11** en 6% sacarosa tiene un dulzor equivalente a aproximadamente 8% sacarosa.

Tabla 21. Dulzor Promedio, n = 15 (15 Panelistas x 1 rep). Valor de Tukey = 0,905 (α = 0,05), 0,810 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
6% Sacarosa	6,5	0,9	0,2	a	a
8% Sacarosa	8,3	0,9	0,2	b	b
6% Sacarosa + 50 µM de C11	8,4	1,0	0,2	b	b
10% Sacarosa	9,4	0,9	0,2	c	c
9% Sacarosa	9,4	0,7	0,2	c	c

A continuación se muestran los resultados de los ensayos de sabor en humanos con un compuesto **C12**. La Tabla 22 indica que 50 µM de compuesto **C12** en 6% sacarosa tiene un dulzor equivalente a aproximadamente 9% -10% sacarosa.

Tabla 22. Dulzor Promedio, n = 26 (13 Panelistas x 2 rep). Valor de Tukey = 0,492 (α = 0,05), 0,440 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
6% Sacarosa	6,5	0,8	0,2	a	a
8% Sacarosa	8,2	1,0	0,2	b	b
6% Sacarosa + 50 µM de C12	9,0	0,8	0,2	c	c
9% Sacarosa	9,2	0,7	0,1	c	c
10% Sacarosa	9,4	0,9	0,2	c	c

A continuación se muestran los resultados de los ensayos de sabor en humanos con un compuesto **C13**. La Tabla 23 indica que 25 µM de compuesto **C13** en 6% sacarosa tiene un dulzor equivalente a aproximadamente 8% sacarosa.

Tabla 23. Dulzor Promedio, n = 26 (13 Panelistas x 2 rep). Valor de Tukey = 0,636 (α = 0,05), 0,569 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
6% Sacarosa	6,8	1,0	0,2	a	a
6% Sacarosa + 25 µM de C13	8,6	1,1	0,2	b	b
8% Sacarosa	8,7	1,0	0,2	b	b
9% Sacarosa	9,5	0,7	0,1	c	c
10% Sacarosa	9,5	0,8	0,2	c	c

A continuación se muestran los resultados de los ensayos de sabor en humanos con un compuesto **C14**. La Tabla 24 indica que 50 µM de compuesto **C14** en 6% sacarosa tiene un dulzor equivalente a aproximadamente 8%-9% sacarosa.

Tabla 24. Dulzor Promedio, n = 26 (12 Panelistas x 1 rep; 14 Panelistas x 1 rep). Valor de Tukey = 0,782 (α = 0,05), 0,701 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
6% Sacarosa	6,5	1,0	0,2	a	a
8% Sacarosa	8,4	1,2	0,2	b	b

6% Sacarosa + 50 µM de C14	8,7	1,3	0,2	bc	bc
9% Sacarosa	9,2	1,2	0,2	c	cd
10% Sacarosa	9,4	0,7	0,1	c	d

A continuación se muestran los resultados de los ensayos de sabor en humanos con un compuesto **C15**. La Tabla 25 indica que 50 µM de compuesto **C15** en 6% sacarosa tiene un dulzor equivalente a aproximadamente 9%-10% sacarosa.

Tabla 25. Dulzor Promedio, n = 25 (11 Panelistas x 1 rep; 14 Panelistas x 1 rep). Valor de Tukey = 0,688 (α = 0,05), 0,617 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
6% Sacarosa	6,7	0,9	0,2	a	a
8% Sacarosa	8,1	1,0	0,2	b	b
6% Sacarosa + 50 µM de C15	9,1	1,1	0,2	c	c
10% Sacarosa	9,2	0,9	0,2	c	c
9% Sacarosa	9,3	0,7	0,1	c	c

A continuación se muestran los resultados de los ensayos de sabor en humanos con el compuesto **C16**. La Tabla 26 indica que 25 µM de compuesto **C16** en 6% sacarosa tiene un dulzor equivalente a aproximadamente 10%-12% sacarosa. La Tabla 27 muestra una curva de respuesta a la dosis del compuesto **C16** con 6% sacarosa lo cual demuestra que el dulzor de la sacarosa mejora significativamente a través de la adición de cantidades en aumento del compuesto **C16**. La Tabla 28 indica que 14,11 µM de compuesto **C16** en 50 ppm de sucralosa tiene un dulzor equivalente a aproximadamente 200 ppm-300 ppm de sucralosa.

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La Tabla 29 indica que 25 µM de compuesto **C16** en 6% fructosa tiene un dulzor equivalente a entre 6% y 8% fructosa. La Tabla 29 indica que 25 µM de compuesto **C16** solo tiene poco dulzor o no lo tiene, y por consiguiente se puede definir como un verdadero mejorador dulce.

Tabla 26. Dulzor Promedio, n = 24 (12 Panelistas x 2 rep). Valor de Tukey = 1,079 (α = 0,05), 0,974 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
6% Sacarosa	6,2	1,5	0,3	a	a
8% Sacarosa	8,3	1,1	0,2	b	b
9% Sacarosa	9,3	1,4	0,3	bc	c
10% Sacarosa	9,8	1,2	0,2	cd	cd
6% Sacarosa + 25 µM de C16	10,6	1,7	0,3	de	de
12% Sacarosa	11,1	1,4	0,3	e	e

Tabla 27. Dulzor Promedio, n = 30 (15 Panelistas x 2 rep). Valor de Tukey = 1,138 (α = 0,05), 1,043 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
6% Sacarosa	6,7	1,0	0,2	a	a
6% Sacarosa + 2,82 µM de C16	7,5	1,6	0,3	ab	ab
6% Sacarosa + 5,64 µM de C16	8,0	1,1	0,2	b	b
8% Sacarosa	8,3	1,7	0,3	b	b
6% Sacarosa + 11,29 µM de C16	10,1	1,5	0,3	c	c

6% Sacarosa + 19,75 µM de C16	10,3	1,7	0,3	cd	cd
10% Sacarosa	10,3	1,8	0,4	cd	cd
6% Sacarosa 28,22 µM de C16	10,9	1,4	0,3	cd	cd
12% Sacarosa	11,2	1,0	0,2	d	d

Tabla 28. Dulzor Promedio, n = 28 (14 Panelistas x 2 rep). Valor de Tukey = 0,969 (α = 0,05), 0,881 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
50 ppm de Sucralosa	4,3	0,7	0,1	a	a
100 ppm de Sucralosa	6,2	1,6	0,3	b	b
150 ppm de Sucralosa	8,2	1,8	0,3	cd	cd
200 ppm de Sucralosa	8,9	1,6	0,3	de	d
50 ppm de Sucralosa + 14,11 µM de C16	9,9	2,3	0,4	ef	e
300 ppm de Sucralosa	10,3	1,7	0,3	f	e

Tabla 29. Dulzor Promedio, n = 26 (13 Panelistas x 2 rep). Valor de Tukey = 0,714 (α = 0,05), 0,639 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
6% Fructosa	6,9	1,0	0,2	a	a
6% Fructosa + 25 µM de C16	7,8	1,1	0,2	b	b
8% Fructosa	8,6	0,8	0,2	c	c
9% Fructosa	9,3	0,7	0,1	cd	d

10% Fructosa	9,5	0,7	0,1	d	d

Tabla 30. Dulzor Promedio, n = 30 (15 Panelistas x 2 rep). Valor de Tukey = 0,535 (α = 0,05), 0,479 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
0% Sacarosa	0,2	0,5	0,1	a	a
LSB + 25 µM de C16	0,6	0,8	0,2	a	a
2% Sacarosa	2,3	0,8	0,2	b	b
4% Sacarosa	4,2	1,2	0,2	c	c
6% Sacarosa	5,8	0,6	0,1	d	d

A continuación se muestran los resultados de los ensayos de sabor en humanos con el compuesto **C17**. La Tabla 31 indica que 8 µM de compuesto **C17** en 6% sacarosa tiene un dulzor equivalente a aproximadamente 9%-10% sacarosa. La Tabla 32 indica que 8 µM de compuesto **C17** solo tiene poco dulzor o no lo tiene, y por consiguiente se puede definir como un verdadero mejorador dulce.

Tabla 31. Dulzor Promedio, n = 28 (14 Panelistas x 2 rep). Valor de Tukey = 0,657 (α = 0,05), 0,588 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
6% Sacarosa	6,8	1,2	0,2	a	a
8% Sacarosa	8,5	0,9	0,2	b	b
9% Sacarosa	8,6	0,8	0,2	b	b

6% Sacarosa + 8 µM de C17	9,0	1,1	0,2	bc	bc
10% Sacarosa	9,6	0,6	0,1	c	c

Tabla 32. Dulzor Promedio, n = 28 (14 Panelistas x 2 rep). Valor de Tukey = 0,467 (α = 0,05), 0,425 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
0% Sacarosa	0,1	0,4	0,1	a	a
LSB + 8 µM de C17	0,2	0,5	0,1	a	a
2% Sacarosa	2,3	0,7	0,1	c	c
4% Sacarosa	4,5	1,0	0,2	d	d
6% Sacarosa	5,8	0,6	0,1	e	e

EXPERIMENTO 6: Medición del Sabor Dulce y del Mejoramiento del Sabor Dulce Utilizando Panelistas Humanos que Llevaron a Cabo un Ensayo de Comparación Pareado

Las muestras de ensayo que contienen los compuestos experimentales se presentan en pares al panelista y se le pide que determine cuál de las muestras es más dulce. Un grupo de 10-16 o más panelistas participaron en cada ensayo. Los sujetos se abstuvieron de comer o beber (excepto agua) durante al menos 1 hora antes del ensayo. Los sujetos se enjuagaron con agua varias veces para limpiarse la boca.

Todas las muestras se preparan con etanol para asegurar la dispersión del compuesto en solución. Ellos incluye muestras sin compuesto; todas las soluciones se balancean en 0,1% etanol.

Las muestras también se preparan con buffer de bajo sodio (pH 7,1) en lugar de agua. El buffer contiene 0,952 g de KCl, 5,444 g de Na_2HPO_4, y 0,952 g de KH_2PO_4 en 40 L de agua DIUF. Los volúmenes de las muestras son usualmente de 20 ml.

En un ensayo de comparación pareado, al panelista se le presentan dos muestras diferentes y se le pide que identifique a la muestra que es más dulce. Las muestras dentro de un ensayo de comparación pareado se presentan en un orden contrabalanceado, aleatorizado. Los panelistas tienen una espera de hasta 1 minuto entre los ensayos de sabor para eliminar de su boca cualquiera de los sabores.

Se utilizan tablas de probabilidad binomial para determiner la probabilidad de que la cantidad de respuestas correctas tengan lugar para cada ensayo en alfa=0,05.

A continuación se muestran los resultados de los ensayos de sabor en humanos con un compuesto **C18**. La Tabla 33 indica que los panelistas percibieron 6% Fructosa + 100 μM de **C18** como significativamente más dulce que una solución de 6% Fructosa ($p<0,05$)

Tabla 33. Muestra seleccionada como más dulce por los panelistas: n = 26 (13 panelistas x 2 reps).

Muestras	**Total**
6% Fructosa	6
6% Fructosa + 100 μM de 568	20
Total	26
Confianza	0,991

6% Fructosa + 100 µM de C18 (valor p)	0,009

A continuación se muestran los resultados de los ensayos de sabor en humanos con un compuesto **C19**. La Tabla 34 indica que los panelistas percibieron 6% Fructosa + 100 µM de **C19** como significativamente más dulce que una solución de 6% Fructosa ($p<0,05$)

Tabla 34. Muestra seleccionada como más dulce por los panelistas: n = 24 (12 panelistas x 2 reps).

Muestras	**Total**
6% Fructosa	6
6% Fructosa + 100 µM de C19	18
Total	24
Confianza	0,977
6% Fructosa + 100 µM de C19 (valor p)	0,023

A continuación se muestran los resultados de los ensayos de sabor en humanos con un compuesto **C20**. La Tabla 34 indica que los panelistas percibieron 6% Fructosa + 100 µM de **C20** como significativamente más dulce que una solución de 6% Fructosa ($p<0,05$). La Tabla 36 indica que 100 µM de compuesto **C20** solo tiene poco dulzor por sí mismo o no lo tiene (Experimento 5).

Tabla 35. Muestra seleccionada como más dulce por los panelistas: n = 19 (19 Panelistas x 1 rep).

Muestras	Ensayo 1	Total
6% Fructosa	0	0
6% Fructosa + 100 µM de C20	19	19
Total	19	19

Tabla 36. Dulzor Promedio, n = 13 (13 Panelistas x 1 rep). Valor de Tukey = 0,753 (α = 0,05), 0,674 (α = 0,10).

Tratamiento	Promedio	DS	Er St	Tukey (5%)	Tukey (10%)
0% Fructosa	0,2	0,5	0,1	a	a
LSB + 100 µM de C20	0,2	0,5	0,1	a	a
2% Fructosa	2,3	0,7	0,2	b	b
4% Fructosa	4,2	1,1	0,3	c	c
6% Fructosa	5,9	0,3	0,1	d	d

A continuación se muestran los resultados de los ensayos de sabor en humanos con un compuesto **C21**. La Tabla 37 indica que los panelistas percibieron 6% Fructosa + 25 µM de **C21** como significativamente más dulce que una solución de 6% Fructosa ($p<0,05$). La Tabla 38 indica que los panelistas percibieron que 6% Fructosa + 25 µM de **C21** tiene la misma intensidad de dulzor que una solución de 7% Fructosa.

Tabla 37. Muestra seleccionada como más dulce por los panelistas: n = 25 (25 Panelistas x 1 rep).

Muestras	Ensayo 1
6% Fructosa	5
6% Fructosa + 25 µM de C21	20
Total	25
Confianza	0,999
6% Fructosa + 25 µM de C21 (valor p)	0,001

Table 38. Muestra seleccionada como más dulce por los panelistas: n = 25 (25 Panelistas x 1 rep).

Muestras	Ensayo 1
7% Fructosa	13
6% Fructosa + 25 µM de C21	12
Total	25
Confianza	0,166
6% Fructosa + 25 µM de C21 (valor p)	0,834

EXPERIMENTO 7. Determinaciónde la Solubilidad de los Compuestos de la Presente Invención y de Sus Sales HCl en Propilen Glicol

La solubilidad de los compuestos presentes y de sus sales HCl en propilen glicol se determinó a través del método de agitación en frasco. Aproximadamente

1022

50 mg del compuesto de ensayo se pesaron y se adicionaron a un vial de vidrio de 4 mL, y luego se adicionó al vial 1 mL de propilen glicol. El vial se sonicó durante 10 minutos y luego se agitó durante 24 hs en un agitador orbital fijo en 300 rpm. Una alícuota de 200 µL de la solución se transfirió desde el vial hacia un vial centrífugo de 1,5 mL y se centrifugó a 12.500 rpm durante 10 min. Una alícuota de 50 µL del sobrenadante se diluyó 100 veces con propilen glicol. Luego 50 µL de esta solución se diluyeron además 100 veces con agua y se analizaron mediante cromatografía líquida espectrometría de masas (columna C18 con elución gradiente con una velocidad de flujo de 2,0 mL/min, agua con 0,1% ácido trifluoracético como fase móvil A y metanol con 0,1% ácido trifluoracético como fase móvil B, el % de fase móvil B aumentando desde 5% hasta 95% en 0,6 min y luego siendo mantenido a 95% durante 1,4 min). El resultado de un ensayo de solubilidad ejemplificativo se muestra en la Tabla A.

Tabla A. Solubilidad del Compuesto C2 y de Su Sal HCl

Compuesto	**Solubilidad Promedio (mM)**	**Desviación Standard (mM)**
C2	**6,2**	**1,7**
C2.clorhidrato	**45,7**	**3,0**

Todas las publicaciones y solicitudes de patentes en la presente se incorporan como referencia en la misma extensión que si se indicara específicamente e individualmente que cada publicación o solicitud de patente individual se incorpore como referencia.

La descripción detallada precedentemente se ha proporcionado solamente para brindar claridad a la comprensión y no deben interpretarse limitaciones innecessarias a partir de la misma puesto que las modificaciones serán obvias para aquéllos expertos en la técnica. Ello no constituye una admisión de que cualquier información proporcionada en la presente constituya técnica previa o sea relevante para las invenciones reivindicadas actualmente, o de que cualquier publicación a la que se efectúe referencia específicamente o implícitamente constituya técnica previa.

A menos que se definan de otro modo, todos los términos técnicos y científicos utilizados en la presente tienen el mismo significado que el comprendido normalmente por un experto en la técnica a la cual pertenece esta invención.

En la presente se describen realizaciones de esta invención, que incluyen el mejor modo conocido por los inventores para llevar a cabo la invención. Las variaciones de esas realizaciones preferidas puede tornarse evidente para aquéllos de pericia corriente en la técnica luego de la lectura de la descripción precedente. Los inventores esperan que los expertos empleen dichas variaciones según sea apropiado, y los inventores pretenden que la invención se practique de otro modo al descripto específicamente en la presente. En consecuencia, esta invención incluye todas las modificaciones y equivalentes de la materia objeto citadas en las reivindicaciones anexas a la misma según lo permita la ley aplicable. Más aún, cualquier combinación de los elementos descriptos precedentemente en todas las posibles variaciones de los mismos se encuentra comprendida por la invención a menos que se indicara lo contrario en la presente o que de otro modo se encontrara claramente contradicho por el contexto.

REIVINDICACIONES

1. Un método de cribado para un candidato de un modificador del ligando del receptor quimiosensorial que comprende

determinar si una entidad de ensayo es adecuada para interactuar con un receptor quimiosensorial *a través de* un primer sitio de interacción dentro del dominio Venus atrapamoscas del receptor quimiosensorial.

2. El método de la reivindicación 1, en donde el primer sitio de interacción del dominio Venus atrapamoscas del receptor quimiosensorial incluye uno o más residuos de interacción del dominio Venus atrapamoscas del receptor quimiosensorial.

3. El método de la reivindicación 1, en donde el primer sitio de interacción del dominio Venus atrapamoscas del receptor quimiosensorial incluye uno o más espacios de interacción del dominio Venus atrapamoscas del receptor quimiosensorial.

4. El método de la reivindicación 1, en donde el primer sitio de interacción del dominio Venus atrapamoscas incluye un espacio de interacción identificado en base a uno o más residuos de interacción.

5. El método de la reivindicación 1, en donde el primer sitio de interacción del dominio Venus atrapamoscas del receptor quimiosensorial incluye uno o más residuos de interacción, los cuales son identificados en base a análisis de mutagénesis del dominio Venus atrapamoscas.

6. El método de la reivindicación 1, en donde el primer sitio de interacción del dominio Venus atrapamoscas es identificado en base a modelación computacional, cristalografía de rayos X, o una combinación de los mismos.

7. El método de la reivindicación 1, en donde el primer sitio de interacción del dominio Venus atrapamoscas es identificado en base a uno o más ligandos de receptores quimiosensoriales conocidos.

8. El método de la reivindicación 1, en donde el primer sitio de interacción del dominio Venus atrapamoscas es identificado en base a uno o más modificadores de ligandos de receptores quimiosensoriales conocidos.

9. El método de la reivindicación 1, en donde el primer sitio de interacción del dominio Venus atrapamoscas es identificado en base a un ligando del receptor quimiosensorial predeterminado.

10. El método de la reivindicación 1, en donde el primer sitio de interacción del dominio Venus atrapamoscas está predeterminado.

11. El método de la reivindicación 1, en donde el primer sitio de interacción del dominio Venus atrapamoscas se encuentra en el dominio Venus atrapamoscas de T1R2.

12. El método de la reivindicación 1, en donde el primer sitio de interacción del dominio Venus atrapamoscas se encuentra en el dominio Venus atrapamoscas de T1R2 y es identificado en presencia del dominio Venus atrapamoscas de T1R3.

13. El método de la reivindicación 1, en donde la determinación se lleva a cabo in silico.

14. Un método de cribado para un candidato de un modificador del ligando del receptor quimiosensorial que comprende

determinar si una entidad de ensayo es adecuada para interactuar con un receptor quimiosensorial *a través de* un primer sitio de interacción dentro del dominio Venus atrapamoscas del receptor quimiosensorial,

en donde el primer sitio de interacción se identifica a la luz de un segundo sitio de interacción identificado en base a la interacción entre un ligando del receptor quimiosensorial y el receptor quimiosensorial.

15. El método de la reivindicación 14, en donde el primer y el segundo sitio de interacción se encuentran en el dominio Venus atrapamoscas de T1R2.

16. El método de la reivindicación 14, el primer y el segundo sitio de interacción se encuentran en el dominio Venus atrapamoscas de T1R2 y son identificados en presencia del dominio Venus atrapamoscas de T1R3.

17. El método de la reivindicación 1, en donde el primer sitio de interacción incluye un residuo de interacción seleccionado del grupo integrado por los aminoácidos N143, S144, e I167 de un T1R2 humano y una combinación de los mismos.

18. El método de la reivindicación 1, en donde el primer sitio de interacción incluye un residuo de interacción seleccionado del grupo integrado por los aminoácidos S40, S144, S165, Y103, D142, y P277 de un T1R2 humano y una combinación de los mismos.

19. El método de la reivindicación 1, en donde el primer sitio de interacción incluye un residuo de interacción seleccionado del grupo integrado por los aminoácidos K65, R383, D307, E302, y D278 de un T1R2 humano y una combinación de los mismos.

20. El método de la reivindicación 1, en donde el primer sitio de interacción incluye un residuo de interacción seleccionado del grupo integrado por los aminoácidos I167, P185, T184, T326, E302, V384, A305, I325, I306, R383, D307, E382, D278, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, y S168 de un T1R2 humano y una combinación de los mismos.

21. El método de la reivindicación 1, en donde el primer sitio de interacción incluye un residuo de interacción seleccionado del grupo integrado por los aminoácidos N143, S144, I167, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, P185, T184, T326, E302, V384, A305, I325, I306, D307, E382, I279, I67, V66, V309, S303, T242, F103, Q328, y S168 de un T1R2 humano y una combinación de los mismos.

22. El método de la reivindicación 1, en donde el primer sitio de interacción incluye un grupo de residuos de interacción seleccionados del grupo integrado por 1) N143, S144, e I167 de un T1R2 humano, 2) S40, S144, S165, Y103, D142, P277 de un T1R2 humano, 3) K65, R383, D307, E302, y D278 de un T1R2 humano, 4) I167, P185, T184, T326, E302, V384, A305, I325, I306, R383, D307, E382, D278, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, y S168 de un T1R2 humano, 5) N143, S144, I167, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, P185, T184, T326, E302, V384, A305, I325,

I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, y S168 de un T1R2 humano, y 6) una combinación de los mismos.

23. El método de la reivindicación 1, en donde el primer sitio de interacción incluye un residuo de interacción seleccionado del grupo integrado por los aminoácidos K65, D278, L279, D307, R383 y V384 de un T1R2 humano y una combinación de los mismos y en donde una entidad de ensayo adecuada para interactuar con el primer sitio de interacción del receptor quimiosensorial es indicativa de un candidato de un mejorador del ligando del receptor quimiosensorial.

24. El método de la reivindicación 1, en donde el primer sitio de interacción incluye un residuo de interacción seleccionado del grupo integrado por los aminoácidos S40, S144, Y103, D142, P277 de un T1R2 humano y una combinación de los mismos en donde una entidad de ensayo adecuada para interactuar con el primer sitio de interacción del receptor quimiosensorial es indicativa de un candidato de un mejorador para la sacarosa o la sucralosa.

25. El método de la reivindicación 1, en donde la entidad de ensayo consiste en una estructura de compuesto diseñada.

26. El método de la reivindicación 1, en donde el ligando del receptor quimiosensorial es una entidad gustativa dulce seleccionada del grupo integrado ácido ciclámico, mogrosida, tagatosa, maltosa, galactosa, manosa, sacarosa, fructosa, lactosa, aspartame, derivados de aspartame, neotame, sacarina, sucralosa, acesulfame K, glucosa, eritritol, D-triptófano, glicina, manitol, sorbitol, maltitol, lactitol, isomalt, jarabe de glucosa hidrogenado (HGS), hidrolizado de

almidón hidrogenado (HSH), esteviosida, rebaudiosida A, glucósidos dulces basados en Ste*via*, alitame, carrelame, edulcorantes basados en guanidina, tagatosa, xilitol, y jarabe de maíz de alta fructosa.

27. Un método de cribado para un candidato de un modificador del receptor quimiosensorial que comprende

determinar si una entidad de ensayo es adecuada para interactuar con un receptor quimiosensorial *a través de* un sitio de interacción dentro del dominio Venus atrapamoscas del receptor quimiosensorial,

en donde el sitio de interacción incluye un residuo de interacción seleccionado del grupo integrado por N143, S144, I167, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, P185, T184, T326, E302, V384, A305, I325, I306, D307, E382, I279, I67, V66, V309, S303, T242, F103, Q328, y S168 de T1R2 humano y una combinación de los mismos,

en donde una entidad de ensayo adecuada para interactuar con el sitio de interacción del receptor quimiosensorial es indicativa de un candidato de un modificador del receptor quimiosensorial.

28. El método de la reivindicación 27, en donde el sitio de interacción incluye un residuo de interacción seleccionado del grupo integrado por los aminoácidos N143, S144, e I167 de un T1R2 humano y una combinación de los mismos.

29. El método de la reivindicación 27, en donde el sitio de interacción incluye un residuo de interacción seleccionado del grupo integrado por los aminoácidos S40, S144, Y103, D142, y P277 de un T1R2 humano y una combinación de los mismos.

30. El método de la reivindicación 27, en donde el sitio de interacción incluye un residuo de interacción seleccionado del grupo integrado por I167, P185, T184, T326, E302, V384, A305, I325, I306, R383, D307, E382, D278, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, y S168 de un T1R2 humano y una combinación de los mismos.

31. El método de la reivindicación 27, en donde el sitio de interacción se encuentra en el dominio Venus atrapamoscas de T1R2.

32. El método de la reivindicación 27, en donde el sitio de interacción se encuentra en el dominio Venus atrapamoscas de T1R2 y es identificado en presencia del dominio Venus atrapamoscas de T1R3.

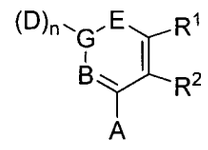
33. El método de la reivindicación 27, en donde la determinación se lleva a cabo *in silico*.

34. El método de la reivindicación 27, en donde la entidad de ensayo consiste en una estructura de compuesto diseñada.

35. Un modificador del ligando del receptor quimiosensorial identificado a través del método de la reivindicación 1.

36. Un modificador del receptor quimiosensorial identificado a través del método de la reivindicación 27.

37. Un mejorador del ligando del receptor quimiosensorial identificado a través del método de la reivindicación 1 y que tiene la Fórmula estructural (I):



(I)

o un tautómero, sal, solvato, y/o éster del mismo, en donde:

G forma un enlace único o bien con D o E y un enlace doble con el otro de D o E;

R^1 es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, $-NO_2$, $-OR^3$, $-S(O)_aR^3$, $-NR^3R^4$, $-CONR^3R^4$, $-CO_2R^3$, $-NR^3CO_2R^4$, $-NR^3CONR^4R^5$, $-NR^3CSNR^4R^5$, $-NR^3C(=NH)NR^4R^5$, $-SO_2NR^3R^4$, $-NR^4SO_2R^3$, $-NR^3SO_2NR^4R^5$, $-B(OR^3)(OR^4)$, $-P(O)(OR^3)(OR^4)$ o $-P(O)(R^3)(OR^4)$;

R^2 es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, $-NO_2$, $-OR^6$, $-S(O)_bR^6$, $-NR^6R^7$, $-CONR^6R^7$, $-CO_2R^6$, $-NR^6CO_2R^7$, $-NR^6CONR^7R^8$, $-NR^6CSNR^7R^8$, $-NR^6C(=NH)NR^7R^8$, $-SO_2NR^5R^6$, $-NR^5SO_2R^6$, $-NR^5SO_2NR^6R^7$, $-B(OR^5)(OR^6)$, $-P(O)(OR^5)(OR^6)$, o $-P(O)(R^5)(OR^6)$; o alternativamente, R^1 y R^2, conjuntamente con los átomos a los cuales ellos están unidos, forman un anillo arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido ring en donde el anillo está opcionalmente fusionado a otro anillo arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido;

con la condición de que R^1 y R^2 no sean ambos hidrógeno;

A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, halo, -CN, $-NO_2$, $-OR^9$, $-S(O)_cR^9$, $-NR^9COR^{10}$, $-NHOR^9$, $-NR^9R^{10}$, $-NOR^9$, $-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$, $-NR^9C(=NH)NR^{10}R^{11}$, $-B(OR^{10})(OR^{11})$, $-P(O)(OR^{10})(OR^{11})$ o $-P(O)(R^{10})(OR^{11})$;

B es -N- o $-C(R^{12})-$;

R^{12} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, $-NR^{13}R^{14}$, -CN, $-OR^{13}$, $-S(O)_dR^{13}$, $-CO_2R^{13}$ o $-CONR^{13}R^{14}$;

G es -C- o $-S(O)_2-$;

siempre que cuando G sea $-S(O)_2-$, entonces G forme un enlace único con E;

cuando el enlace entre D y G es un enlace único, entonces D es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, $-OR^{15}$, -NH-OR^{15}, $-S(O)_eR^{15}$, $-NR^{15}R^{16}$, $-NH-NHR^{15}$, $-CO_2R^{15}$, o $-CONR^{15}R^{16}$;

cuando G forma un enlace doble con D, entonces D es =O, =S , $=N-OR^{15}$, o $=N-NHR^{15}$;

n es 0 cuando G es $-S(O)_2-$, y n es 1 cuando G es -C-;

E es $-NR^{17}-$, -N- o $-C(R^{18})-$;

siempre que E sea $-NR^{17}-$ solamente cuando G forme un enlace único con E; R^{17} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido,

heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido o $-CO_2R^{19}$;

R^{18} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, $-NR^{20}R^{21}$, -CN, $-OR^{20}$, $-S(O)_fR^{20}$, $-CO_2R^{20}$ o $-CONR^{20}R^{21}$;

a, b, c, d, e y f son independientemente 0, 1 o 2; y

R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{13}, R^{14}, R^{15}, R^{16}, R^{18}, R^{20}, y R^{21} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido; o alternativamente, R^3 y R^4, R^4 y R^5, R^6 y R^7, R^7 y R^8, R^9 y R^{10}, R^{10} y R^{11}, R^{13} y R^{14}, R^{15} y R^{16}, o R^{20} y R^{21}, conjuntamente con los átomos a los cuales ellos están unidos, forman un anillo cicloheteroalquilo o cicloheteroalquilo sustituido.

38. Un método de modulación de la actividad de un ligando del receptor quimiosensorial que comprende poner en contacto un modificador del ligando del receptor quimiosensorial con una célula que contiene un dominio Venus atrapamoscas de T1R2 en presencia de un ligando del receptor quimiosensorial, en donde el modificador del ligando del receptor quimiosensorial interactúa con un sitio de interacción del receptor quimiosensorial.

39. El método de la reivindicación 38, en donde el sitio de interacción del receptor quimiosensorial incluye un residuo de interacción seleccionado del grupo integrado por los aminoácidos N143, S144, e I167 de un T1R2 humano y una combinación de los mismos.

40. El método de la reivindicación 38, en donde el sitio de interacción del receptor quimiosensorial incluye un residuo de interacción seleccionado del grupo integrado por los aminoácidos S40, S144, S165, Y103, D142, y P277 de un T1R2 humano y una combinación de los mismos.

41. El método de la reivindicación 38, en donde el sitio de interacción del receptor quimiosensorial incluye un residuo de interacción seleccionado del grupo integrado por los aminoácidos K65, R383, D307, E302, y D278 de un T1R2 humano y una combinación de los mismos.

42. El método de la reivindicación 38, en donde el sitio de interacción del receptor quimiosensorial incluye un residuo de interacción seleccionado del grupo integrado por los aminoácidos I167, P185, T184, T326, E302, V384, A305, I325, I306, R383, D307, E382, D278, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, y S168 de un T1R2 humano y una combinación de los mismos.

43. El método de la reivindicación 38, en donde el sitio de interacción incluye un residuo de interacción seleccionado del grupo integrado por los aminoácidos N143, S144, I167, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, P185, T184, T326, E302, V384, A305, I325, I306, D307, E382, I279, I67, V66, V309, S303, T242, F103, Q328, y S168 de un T1R2 humano y una combinación de los mismos.

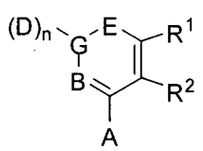
44. El método de la reivindicación 38, en donde el sitio de interacción incluye un grupo de residuos de interacción de K65, D278, L279, D307, R383, y V384 de

un T1R2 humano y en donde el modificador del ligando del receptor quimiosensorial mejora la actividad de un ligando del receptor quimiosensorial.

45. El método de la reivindicación 38, en donde el sitio de interacción incluye un grupo de residuos de interacción de S40, S144, Y103, D142, y P277 de un T1R2 humano y en donde el ligando del receptor quimiosensorial está seleccionado del grupo integrado por sacarosa y sucralosa.

46. El método de la reivindicación 38, en donde el modificador del ligando del receptor quimiosensorial estabiliza una conformación cerrada dentro de un dominio Venus atrapamoscas de T1R2 formada por la interacción entre el ligando del receptor quimiosensorial y el receptor quimiosensorial.

47. El método de la reivindicación 38, en donde el modificador del ligando del receptor quimiosensorial es un mejorador del ligando del receptor quimiosensorial y tiene la Fórmula estructural (I):



(I)

o un tautómero, sal, solvato, y/o éster del mismo, en donde:

G forma un enlace único o bien con D o E y un enlace doble con el otro de D o E;

R^1 es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido,

-CN, -NO_2, -OR^3, -$S(O)_aR^3$, -NR^3R^4, -$CONR^3R^4$, -CO_2R^3, -$NR^3CO_2R^4$, -$NR^3CONR^4R^5$, -$NR^3CSNR^4R^5$, -$NR^3C(=NH)NR^4R^5$, -$SO_2NR^3R^4$, -$NR^4SO_2R^3$, -$NR^3SO_2NR^4R^5$, -$B(OR^3)(OR^4)$, -$P(O)(OR^3)(OR^4)$ o -$P(O)(R^3)(OR^4)$;

R^2 es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, -NO_2, -OR^6, -$S(O)_bR^6$, -NR^6R^7, -$CONR^6R^7$, -CO_2R^6, -$NR^6CO_2R^7$, -$NR^6CONR^7R^8$, -$NR^6CSNR^7R^8$, -$NR^6C(=NH)NR^7R^8$, -$SO_2NR^5R^6$, -$NR^5SO_2R^6$, -$NR^5SO_2NR^6R^7$, -$B(OR^5)(OR^6)$, -$P(O)(OR^5)(OR^6)$, o -$P(O)(R^5)(OR^6)$; o alternativamente, R^1 y R^2, conjuntamente con los átomos a los cuales ellos están unidos, forman un anillo arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido en donde el anillo está opcionalmente fusionado a otro anillo arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido;

con la condición de que R^1 y R^2 no sean ambos hidrógeno;

A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, halo, -CN, -NO_2, -OR^9, -$S(O)_cR^9$, -NR^9COR^{10}, -$NHOR^9$, -NR^9R^{10}, -NOR^9, -$CONR^9R^{10}$, -CO_2R^9, -$NR^9CO_2R^{10}$, -$NR^9CONR^{10}R^{11}$, -$NR^9CSNR^{10}R^{11}$, -$NR^9C(=NH)NR^{10}R^{11}$, -$B(OR^{10})(OR^{11})$, -$P(O)(OR^{10})(OR^{11})$ o -$P(O)(R^{10})(OR^{11})$;

B es -N- o -$C(R^{12})$-;

R^{12} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -$NR^{13}R^{14}$, -CN, -OR^{13}, -$S(O)_dR^{13}$, -CO_2R^{13} o -$CONR^{13}R^{14}$;

G es -C- o -$S(O)_2$-;

siempre que cuando G sea -$S(O)_2$-, entonces G forme un enlace único con E;

cuando el enlace entre D y G es un enlace único, entonces D es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -OR^{15}, -NH-OR^{15}, -$S(O)_eR^{15}$, -$NR^{15}R^{16}$, -NH-NHR^{15}, -CO_2R^{15}, o -$CONR^{15}R^{16}$;

cuando G forma un enlace doble con D, entonces D es =O, =S , =N-OR^{15}, o =N-NHR^{15};

n es 0 cuando G es -$S(O)_2$-, y n es 1 cuando G es -C-;

E es -NR^{17}-, -N- o -$C(R^{18})$-;

siempre que E sea -NR^{17}- solamente cuando G forme un enlace único con E; R^{17} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido o -CO_2R^{19};

R^{18} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -$NR^{20}R^{21}$, -CN, -OR^{20}, -$S(O)_fR^{20}$, -CO_2R^{20} o -$CONR^{20}R^{21}$;

a, b, c, d, e y f son independientemente 0, 1 o 2; y

R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{13}, R^{14}, R^{15}, R^{16}, R^{18}, R^{20}, y R^{21} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido; o alternativamente, R^3 y R^4, R^4 y R^5, R^6 y R^7, R^7 y R^8, R^9 y R^{10}, R^{10} y

R^{11}, R^{13} y R^{14}, R^{15} y R^{16}, o R^{20} y R^{21}, conjuntamente con los átomos a los cuales ellos están unidos, forman un anillo cicloheteroalquilo o cicloheteroalquilo sustituido.

48. El método de la reivindicación 38, en donde la célula contiene un dominio Venus atrapamoscas de T1R2 dentro de una vía de GPCR.

49. El método de la reivindicación 38, en donde el modificador del ligando del receptor quimiosensorial se proporciona en una composición comestible.

50. El método de la reivindicación 38, en donde el modificador del ligando del receptor quimiosensorial se proporciona en una composición medicinal.

51. El método de la reivindicación 38, en donde el modificador del ligando del receptor quimiosensorial se proporciona en un producto alimenticio o de bebida.

52. Un modificador del ligando del receptor quimiosensorial, en donde en presencia de un ligando del receptor quimiosensorial éste interactúa con un dominio Venus atrapamoscas de T1R2 *a través* de al menos tres residuos de interacción seleccionados del grupo integrado por N143, S144, I167, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, y S168 de un T1R2 humano.

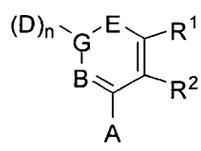
53. El modificador del ligando del receptor quimiosensorial de la reivindicación 52, en donde éste interactúa con un dominio Venus atrapamoscas de T1R2 *a través de* un grupo de aminoácidos seleccionados del grupo integrado por 1)

N143, S144, e I167 de un T1R2 humano, 2) S40, S144, S165, Y103, D142, P277 de un T1R2 humano, 3) K65, R383, D307, E302, y D278 de un T1R2 humano, 4) I167, P185, T184, T326, E302, V384, A305, I325, I306, R383, D307, E382, D278, I279, I67, V66, V309, D142, S165, S40, S303, T242, F103, Q328, y S168 de un T1R2 humano, y 5) N143, S144, I167, S40, S144, S165, Y103, D142, P277, K65, R383, D307, E302, D278, P185, T184, T326, E302, V384, A305, I325, I306, E382, I279, I67, V66, V309, S303, T242, F103, Q328, y S168 de un T1R2 humano.

54. El modificador del ligando del receptor quimiosensorial de la reivindicación 52, en donde éste interactúa con un dominio Venus atrapamoscas de T1R2 *a través de* un grupo de aminoácidos K65, D278, L279, D307, R383, y V384 de un T1R2 humano y en donde éste mejora la actividad de un ligando del receptor quimiosensorial.

55. El modificador del ligando del receptor quimiosensorial de la reivindicación 52, en donde éste interactúa con un dominio Venus atrapamoscas de T1R2 *a través de* un grupo de aminoácidos de S40, S144, Y103, D142, P277 de un T1R2 humano en presencia de sacarosa o sucralosa y en donde éste mejora la actividad de la sacarosa o sucralosa.

56. El modificador del ligando del receptor quimiosensorial de la reivindicación 52 es un compuesto que tiene la Fórmula estructural (I):



(I)

o un tautómero, sal, solvato, y/o éster del mismo, en donde:

G forma un enlace único o bien con D o E y un enlace doble con el otro de D o E;

R^1 es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, $-NO_2$, $-OR^3$, $-S(O)_aR^3$, $-NR^3R^4$, $-CONR^3R^4$, $-CO_2R^3$, $-NR^3CO_2R^4$, $-NR^3CONR^4R^5$, $-NR^3CSNR^4R^5$, $-NR^3C(=NH)NR^4R^5$, $-SO_2NR^3R^4$, $-NR^4SO_2R^3$, $-NR^3SO_2NR^4R^5$, $-B(OR^3)(OR^4)$, $-P(O)(OR^3)(OR^4)$ o $-P(O)(R^3)(OR^4)$;

R^2 es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, $-NO_2$, $-OR^6$, $-S(O)_bR^6$, $-NR^6R^7$, $-CONR^6R^7$, $-CO_2R^6$, $-NR^6CO_2R^7$, $-NR^6CONR^7R^8$, $-NR^6CSNR^7R^8$, $-NR^6C(=NH)NR^7R^8$, $-SO_2NR^5R^6$, $-NR^5SO_2R^6$, $-NR^5SO_2NR^6R^7$, $-B(OR^5)(OR^6)$, $-P(O)(OR^5)(OR^6)$, o $-P(O)(R^5)(OR^6)$; o alternativamente, R^1 y R^2, conjuntamente con los átomos a los cuales ellos están unidos, forman un anillo arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido ring en donde el anillo está opcionalmente fusionado a otro anillo arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido;

con la condición de que R^1 y R^2 no sean ambos hidrógeno;

A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, halo, -CN, $-NO_2$, $-OR^9$, $-S(O)_cR^9$, $-NR^9COR^{10}$, $-NHOR^9$, $-NR^9R^{10}$, $-NOR^9$,

$-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$, $-NR^9C(=NH)NR^{10}R^{11}$, $-B(OR^{10})(OR^{11})$, $-P(O)(OR^{10})(OR^{11})$ o $-P(O)(R^{10})(OR^{11})$;

B es -N- o $-C(R^{12})-$;

R^{12} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, $-NR^{13}R^{14}$, -CN, $-OR^{13}$, $-S(O)_dR^{13}$, $-CO_2R^{13}$ o $-CONR^{13}R^{14}$;

G es -C- o $-S(O)_2-$;

siempre que cuando G sea $-S(O)_2-$, entonces G forme un enlace único con E;

cuando el enlace entre D y G es un enlace único, entonces D es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, $-OR^{15}$, $-NH-OR^{15}$, $-S(O)_eR^{15}$, $-NR^{15}R^{16}$, $-NH-NHR^{15}$, $-CO_2R^{15}$, o $-CONR^{15}R^{16}$;

cuando G forma un enlace doble con D, entonces D es =O, =S , $=N-OR^{15}$, r $=N-NHR^{15}$;

n es 0 cuando G es $-S(O)_2-$, y n es 1 cuando G es -C-;

E es $-NR^{17}-$, -N- o $-C(R^{18})-$;

siempre que E sea $-NR^{17}-$ solamente cuando G forme un enlace único con E; R^{17} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido o $-CO_2R^{19}$;

R^{18} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido,

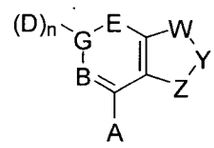
heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, $-NR^{20}R^{21}$, -CN, $-OR^{20}$, $-S(O)_fR^{20}$, $-CO_2R^{20}$ o $-CONR^{20}R^{21}$;

a, b, c, d, e y f son independientemente 0, 1 o 2; y

R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{13}, R^{14}, R^{15}, R^{16}, R^{18}, R^{20}, y R^{21} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido; o alternativamente, R^3 y R^4, R^4 y R^5, R^6 y R^7, R^7 y R^8, R^9 y R^{10}, R^{10} y R^{11}, R^{13} y R^{14}, R^{15} y R^{16}, o R^{20} y R^{21}, conjuntamente con los átomos a los cuales ellos están unidos, forman un anillo cicloheteroalquilo o cicloheteroalquilo sustituido.

57. El compuesto de la reivindicación 56, en donde R^1 y R^2, conjuntamente con los átomos a los cuales ellos están unidos, forman un anillo arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido en donde el anillo está opcionalmente fusionado a otro anillo arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido.

58. El compuesto de la reivindicación 56, que tiene la Fórmula estructural (II),



(II)

en donde:

Y forma un enlace único o bien con W o Z y un enlace doble con el otro de W o Z;

W es -C(R^{24})-, -S-, -N-, -N(R^{25})-, u -O-;

Y es -C(R^{26})- o -N-;

Z es -C(R^{27})-, -S-, -N-, -N(R^{28})-, u -O-;

R^{24} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, -NO_2, -OR^{29}, -$S(O)_gR^{29}$, -$NR^{29}R^{30}$, -$CONR^{29}R^{30}$, -CO_2R^{29}, -$SO_2NR^{29}R^{30}$, -$NR^{29}SO_2R^{30}$, -$B(OR^{29})(OR^{30})$, -$P(O)(OR^{29})(OR^{30})$ o -$P(O)(R^{29})(OR^{30})$;

R^{26} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, halo, -CN, -NO_2, -OR^{31}, -$S(O)_hR^{31}$, -$OCOR^{31}$, -$NR^{31}R^{32}$, -$CONR^{31}R^{32}$, -CO_2R^{31}, -$SO_2NR^{31}R^{32}$, -$NR^{31}SO_2R^{32}$, -$B(OR^{31})(OR^{32})$, -$P(O)(OR^{31})(OR^{32})$ o -$P(O)(R^{31})(OR^{32})$;

R^{27} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, halo, -CN, -NO_2, -OR^{33}, -$S(O)_iR^{33}$, -$OCOR^{33}$, -$NR^{33}R^{34}$, -$CONR^{33}R^{34}$, -COR^{33}, -CO_2R^{33}, -$SO_2NR^{33}R^{34}$, -$NR^{33}SO_2R^{34}$, -$B(OR^{33})(OR^{34})$, -$P(O)(OR^{33})(OR^{34})$ o -$P(O)(R^{33})(OR^{34})$ o alternativamente R^{24} y R^{26} o R^{26} y R^{27} conjuntamente con los átomos a los cuales ellos están unidos forman un anillo cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido;

g, h e i son independientemente 0 o 1;

R^{25} y R^{28} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido,

heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido; y

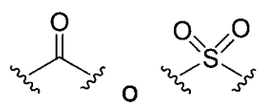
R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, y R^{34} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido; o alternativamente R^{29} y R^{30}, R^{31} y R^{32} o R^{33} y R^{34} conjuntamente con los átomos a los cuales ellos están unidos forman un anillo cicloheteroalquilo o cicloheteroalquilo sustituido; y

con las siguientes condiciones:

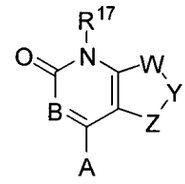
(a) cuando W es -O- o -S- o -NR^{25}, entonces Z es –$C(R^{27})$ o -N-; y

(b) cuando Z es -O- o -S- o -NR^{28}, entonces W es -$C(R^{24})$ o -N-.

59. El compuesto de la reivindicación 58, en donde $(D)_n$-G es



60. El compuesto de la reivindicación 58, que tiene la Fórmula estructural (IIa):



(IIa)

con las siguientes condiciones:

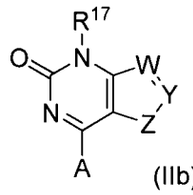
(a) cuando W es -O- o -S- o -NR^{25}, entonces Z es –$C(R^{27})$ o -N-;

(b) cuando Z es -O- o -S- o -NR^{28}, entonces W es -$C(R^{24})$ o -N-; y

(c) cuando B es -N-, entonces A no es halo.

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61. El compuesto de la reivindicación 60, que tiene la Fórmula estructural (IIb):



(IIb)

en donde:

W es -C(R^{24})- o -N-;

Y es -C(R^{26})- o -N-; y

Z es -S-, -N(R^{28})- u -O-.

62. El compuesto de la reivindicación 61, en donde

W es -C(R^{24})-, e

Y es -C(R^{26})-.

63. El compuesto de la reivindicación 62, en donde

R^{24} es hidrógeno, alquilo, alquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, -CN, -NO_2, -OR^{29}, -$S(O)_gR^{29}$, -$OCOR^{29}$, -$NR^{29}R^{30}$, -$CONR^{29}R^{30}$ o -CO_2R^{29}; y

R^{26} es hidrógeno, alquilo, alquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, -CN, -NO_2, -OR^{31}, -$OCOR^{31}$, -$S(O)_hR^{31}$, -$NR^{31}R^{32}$, -$CONR^{31}R^{32}$ o -CO_2R^{31}.

64. El compuesto de la reivindicación 63, en donde

R^{24} es hidrógeno, -CF_3, alquilo o alquilo sustituido; y

R^{26} es hidrógeno, -CF_3, alquilo o alquilo sustituido.

65. El compuesto de la reivindicación 62, en donde

A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, -CN, $-NO_2$, $-S(O)_cR^9$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$ o $-NR^9CO_2R^{10}$;

R^{17} es hidrógeno, alquilo, alquilo sustituido, arilalquilo, o arilalquilo sustituido;

R^{24} es hidrógeno, alquilo, alquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, -CN, $-NO_2$, $-OR^{29}$, $-S(O)_gR^{29}$, $-OCOR^{29}$, $-NR^{29}R^{30}$, $-CONR^{29}R^{30}$ o $-CO_2R^{29}$; y

R^{26} es hidrógeno, alquilo, alquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, -CN, $-NO_2$, $-OR^{31}$, $-S(O)_hR^{31}$, $-OCOR^{31}$, $-NR^{31}R^{32}$, $-CONR^{31}R^{32}$ o $-CO_2R^{31}$.

66. El compuesto de la reivindicación 62, en donde

A es $-NR^9COR^{10}$, $-NHOR^9$, $-NR^9R^{10}$, $-NOR^9$, $-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-OR^9$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$ o $-NR^9C(=NH)NR^{10}R^{11}$;

R^{17} es hidrógeno, alquilo, alquilo sustituido, arilalquilo, o arilalquilo sustituido; R^{24} es hidrógeno, alquilo, alquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, -CN, $-NO_2$, $-OR^{29}$, $-S(O)_gR^{29}$, $-OCOR^{29}$, $-NR^{29}R^{30}$, $-CONR^{29}R^{30}$ o $-CO_2R^{29}$; y

R^{26} es hidrógeno, alquilo, alquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, -CN, $-NO_2$, $-OR^{31}$, $-S(O)_hR^{31}$, $-OCOR^{31}$, $-NR^{31}R^{32}$, $-CONR^{31}R^{32}$ o $-CO_2R^{31}$.

67. El compuesto de la reivindicación 66, en donde

A es -OH, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHOCH_3$, $-NOCH_3$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$,

$-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$ o $-CH_2NHC(O)CH_3$;

R^{17} es hidrógeno, metilo, etilo, propilo, *iso*-propilo, *n*-butilo, *iso*-butilo, *sec*-butilo, *t*-butilo, fenilo o bencilo;

R^{24} es hidrógeno, $-CF_3$, metilo, etilo, propilo, *iso*-propilo, *n*-butilo, *iso*-butilo, *sec*-butilo o *t*-butilo; y R^{26} es hidrógeno, $-CF_3$, metilo, etilo, propilo, *iso*-propilo, *n*-butilo, *iso*-butilo, *sec*-butilo o *t*-butilo.

68. El compuesto de la reivindicación 67, en donde

A es $-NH_2$,

R^{17} es hidrógeno o metilo,

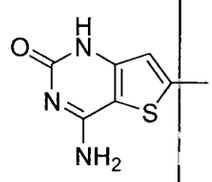
R^{24} es hidrógeno, $-CF_3$, metilo o etilo, y

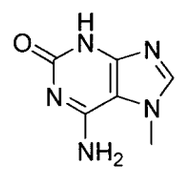
R^{26} es hidrógeno, $-CF_3$, metilo o etilo.

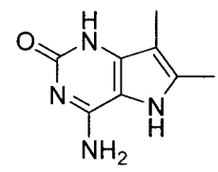
69. El compuesto de cualquiera de las reivindicaciones 62 a 68, en donde R^{28} es hidrógeno, alquilo o arilalquilo.

70. El compuesto de cualquiera de las reivindicaciones 62 a 68, en donde R^{28} es hidrógeno, metilo o bencilo.

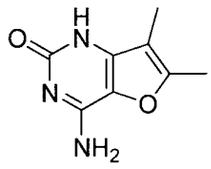
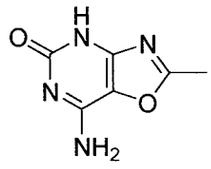
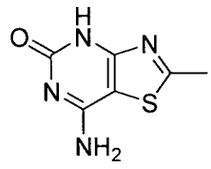
71. El compuesto de la reivindicación 61 que tiene la Fórmula estructural seleccionada del grupo integrado por:



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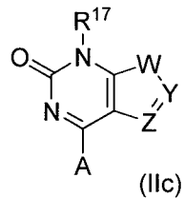
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, y 
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o un tautómero, sal, solvato, y/o éster del mismo.

72. El compuesto de la reivindicación 71, en donde la sal es la sal clorhidrato o trifluoracetato.

73. El compuesto de la reivindicación 60, que tiene la Fórmula estructural (IIc):


(IIc)

en donde,

W es -S-, -N(R^{25})-, u -O-;

Y es -C(R^{26})- o -N-; y

Z es -C(R^{27})- o -N-.

74. El compuesto de la reivindicación 73, en donde

Y es -C(R^{26})-, y

Z es -C(R^{27})-.

75. El compuesto de la reivindicación 74, en donde

R^{27} es hidrógeno, alquilo, alquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, -CN, -NO_2, -OR^{33}, -$S(O)_iR^{33}$, -$OCOR^{33}$, -$NR^{33}R^{34}$, -$CONR^{33}R^{34}$ o -CO_2R^{33}; y

R^{26} es hidrógeno, alquilo, alquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, -CN, $-NO_2$, $-OR^{31}$, $-S(O)_hR^{31}$, $-OCOR^{31}$, $-NR^{31}R^{32}$, $-CONR^{31}R^{32}$ o $-CO_2R^{31}$.

76. El compuesto de la reivindicación 74, en donde

R^{26} y R^{27} conjuntamente con el átomo al cual ellos están unidos forman un anillo cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido.

77. El compuesto de la reivindicación 74, en donde

A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, $-NR^9COR^{10}$, $-NHOR^9$, $-NOR^9$, $-OR^9$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$ o $-NR^9C(=NH)NR^{10}R^{11}$, -CN, $-NO_2$, $-S(O)_cR^9$, $-NR^9R^{10}$, $-C(O)NR^9R^{10}$, $-CO_2R^9$ o $-NR^9CO_2R^{10}$; y

R^{17} es hidrógeno, alquilo, alquilo sustituido, arilalquilo, o arilalquilo sustituido.

78. El compuesto de la reivindicación 74, en donde

A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, $-NR^9COR^{10}$, $-NHOR^9$, $-NOR^9$, $-OR^9$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$ o $-NR^9C(=NH)NR^{10}R^{11}$, -CN, $-NO_2$, $-S(O)_cR^9$, $-NR^9R^{10}$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-CO_2R^9$ o $-NR^9CO_2R^{10}$;

R^{17} es hidrógeno, alquilo, alquilo sustituido, arilalquilo, o arilalquilo sustituido;

R^{27} es hidrógeno, alquilo, alquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, -CN, $-NO_2$, $-OR^{33}$, $-S(O)_iR^{33}$, $-OCOR^{33}$, $-NR^{33}R^{34}$, $-C(O)NR^{33}R^{34}$ o $-CO_2R^{33}$; y

R^{26} es hidrógeno, alquilo, alquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, -CN, $-NO_2$, $-OR^{31}$, $-S(O)_hR^{31}$, $-OC(O)R^{31}$,

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$-NR^{31}R^{32}$, $-C(O)NR^{31}R^{32}$ o $-CO_2R^{31}$, o alternativamente R^{26} y R^{27} conjuntamente con el(os) átomo(s) al(os) cual(es) ellos están unidos forman un anillo cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido.

79. El compuesto de la reivindicación 78, en donde

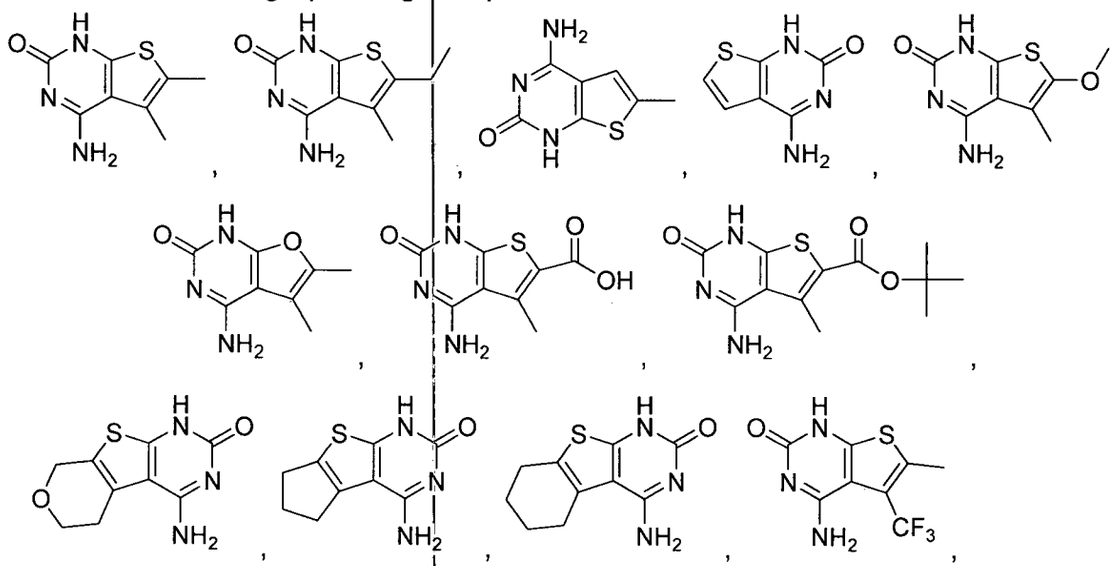
A es $-NH_2$;

R^{17} es hidrógeno, metilo, etilo, propilo, *iso*-propilo, *n*-butilo, *iso*-butilo, *sec*-butilo, *t*-butilo, fenilo o bencilo;

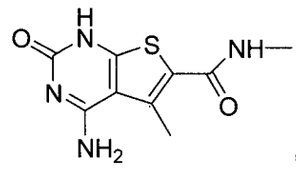
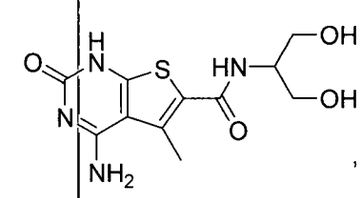
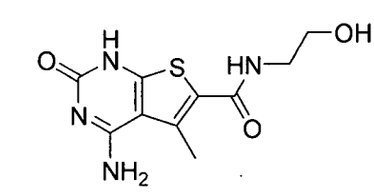
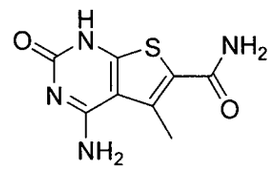
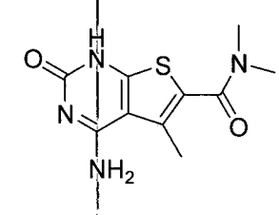
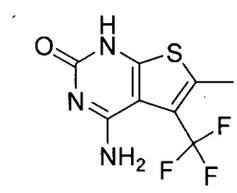
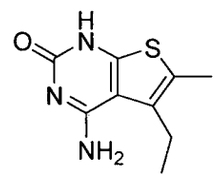
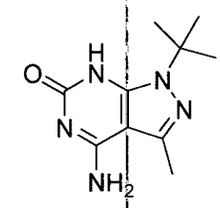
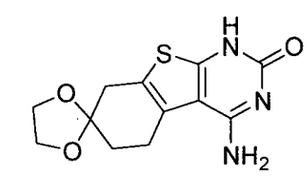
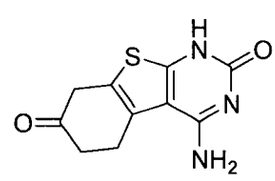
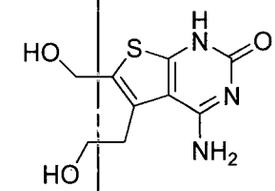
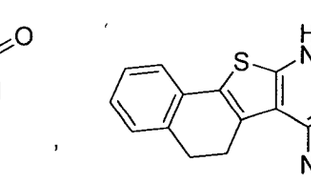
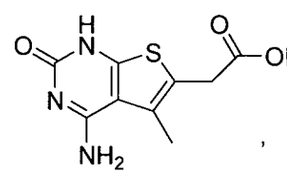
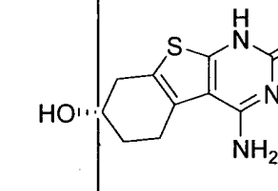
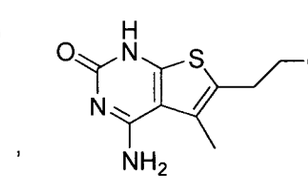
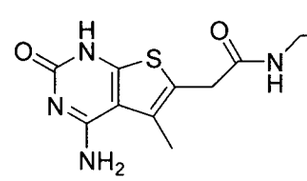
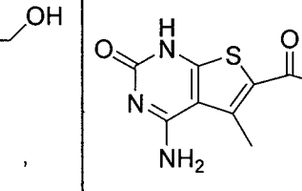
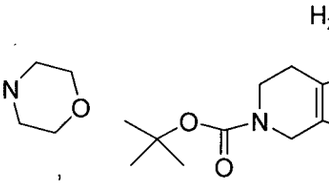
R^{26} y R^{27} son independientemente hidrógeno, alcanilo, alcanilo sustituido, alcoxi, ácido carboxílico, amida de ácido carboxílico, o éster de ácido carboxílico;

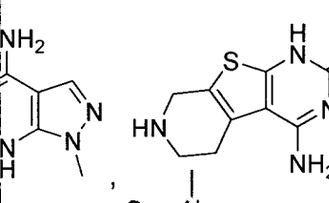
o alternativamente, R^{26} y R^{27} conjuntamente con el(os) átomo(s) al(os) cual(es) ellos están unidos forman un anillo cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido.

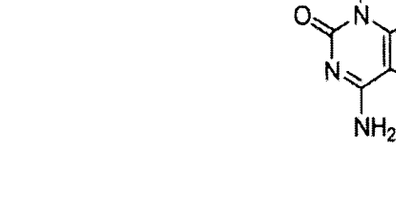
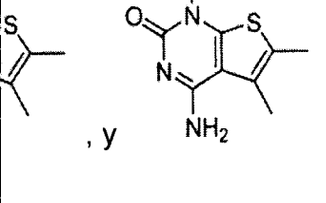
80. El compuesto de la reivindicación 73, que tiene la Fórmula estructural seleccionada del grupo integrado por:



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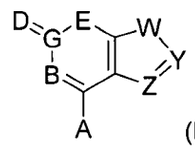
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o un tautómero, sal, solvato, y/o éster del mismo.

81. El compuesto de la reivindicación 80, en donde la sal es la sal clorhidrato o trifluoracetato.

82. El compuesto de la reivindicación 58, que tiene la Fórmula estructural (IIe):



(IIe)

en donde,

G forma un enlace único con E y un enlace doble con D;

B es -N-;

E es $-NR^{17}-$;

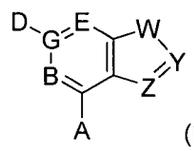
D es =S , $=N-OR^{15}$, o $=N-NHR^{15}$;

W es -S-, $-N(R^{25})-$ u -O-;

Y es $-C(R^{26})-$; y

Z es $-C(R^{27})-$.

83. El compuesto de la reivindicación 58, que tiene la Fórmula estructural (IIf):



(IIf)

en donde,

G forma un enlace doble con E y un enlace único con D;

B es -N-;

E es -N-;

D es $-OR^{15}$, $-NH-OR^{15}$, $-NH-NHR^{15}$, $-S(O)_eR^{15}$, o $-NR^{15}R^{16}$;

W es -S-, $-N(R^{25})-$ u -O-;

Y es $-C(R^{26})-$; y

Z es $-C(R^{27})-$.

84. El compuesto de la reivindicación 82 u 83, en donde A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, $-OR^9$, $-SR^9$, -CN, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$ o $-NR^9C(=NH)NR^{10}R^{11}$.

85. El compuesto de la reivindicación 84, en donde

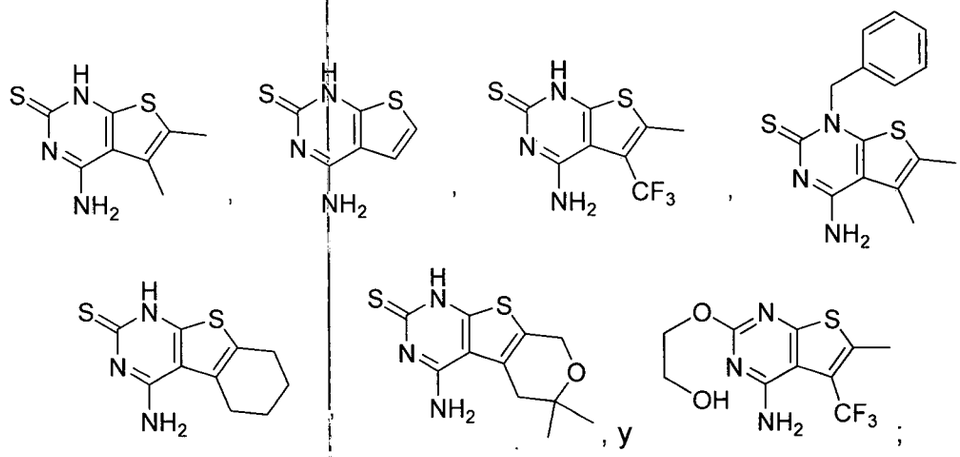
R^{17} es hidrógeno, alquilo, alquilo sustituido, arilalquilo, o arilalquilo sustituido;

R^{26} y R^{27} son independientemente hidrógeno, alcanilo, alcanilo sustituido, alcoxi;

o alternativamente, R^{26} y R^{27} conjuntamente con el(os) átomo(s) al(os) cual(es) ellos están unidos forman un anillo cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido.

86. El compuesto de la reivindicación 82 u 83, que tiene la Fórmula estructural seleccionada del grupo integrado por

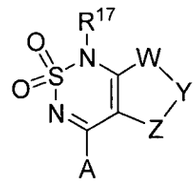
1054



o un tautómero, sal, solvato, y/o éster del mismo.

87. El compuesto de la reivindicación 86, en donde la sal es la sal clorhidrato o trifluoracetato.

88. El compuesto de la reivindicación 58, que tiene la Fórmula estructural (IId):



(IId)

con las siguientes condiciones:

(a) cuando W es -O- o -S- o -NR^{25}, entonces Z es –$C(R^{27})$ o -N-; y

(b) cuando Z es -O- o -S- o -NR^{28}, entonces W es -$C(R^{24})$ o -N-.

89. El compuesto de la reivindicación 88, en donde

W es -S-, NR^{25}, -O-;

Y es -CR^{26}-;

Z es -$C(R^{27})$-; y

W e Y forman un enlace único e Y y Z forman un enlace doble.

90. El compuesto de la reivindicación 88, en donde

W es -C(R^{24})-;

Y es -CR^{26}-;

Z es -S-, -NR^{28}-, -O-; y

W e Y forman un enlace doble e Y y Z forman un enlace único.

91. El compuesto de la reivindicación 88, en donde

W es -S-, NR^{25}, -O-;

Y es -N-;

Z es -C(R^{27})-; y

W e Y forman un enlace único e Y y Z forman un enlace doble.

92. El compuesto de la reivindicación 88, en donde

W es - NR^{25};

Y es -N-; y

Z es -C(R^{27})-; y

Y forma un enlace único con cada uno de W y un enlace doble con Z.

93. El compuesto de cualquiera de las reivindicaciones 88 a 92, en donde A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, -OR^9, -SR^9, -CN, -NR^9R^{10}, -CONR^9R^{10}, -CO_2R^9, -N$R^9CO_2R^{10}$, -NR^9CON$R^{10}R^{11}$, -NR^9CSN$R^{10}R^{11}$ o -NR^9C(=NH)N$R^{10}R^{11}$.

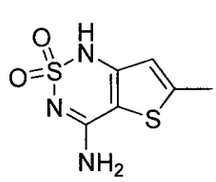
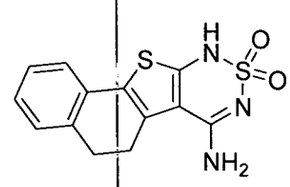
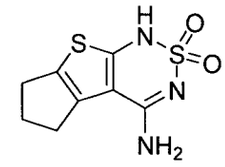
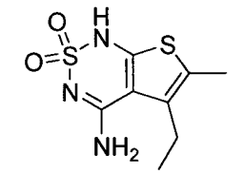
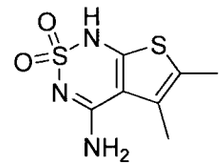
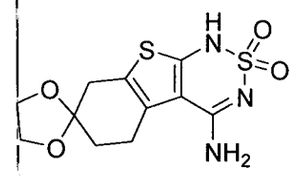
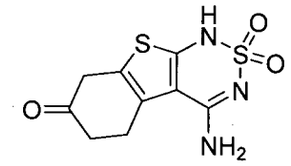
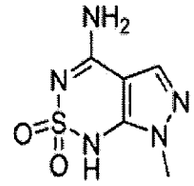
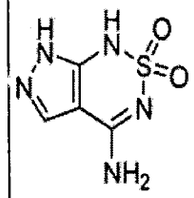
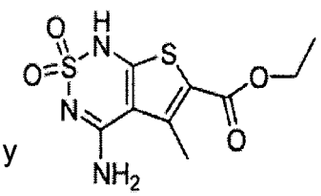
94. El compuesto de la reivindicación 93, en donde R^{17} es hidrógeno.

95. El compuesto de la reivindicación 94, en donde

R^{26} y R^{27} son independientemente hidrógeno, alcanilo, alcanilo sustituido, alcoxi, ácido carboxílico, éster de ácido carboxílico;

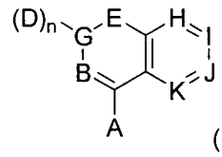
o alternativamente, R^{26} y R^{27} conjuntamente con el(os) átomo(s) al(os) cual(es) ellos están unidos forman un anillo ciclialquilo o cicloalquilo sustituido.

96. El compuesto de la reivindicación 88, que tiene la Fórmula estructural seleccionada del grupo integrado por:


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o un tautómero, sal, solvato, y/o éster del mismo.

97. El compuesto de la reivindicación 56 que tiene la Fórmula estructural (III):



(III)

en donde:

H es -C(R^{35})- o -N-;

I es -C(R^{36}) o -N-;

J es -C(R^{37})- o -N-;

K es -C(R^{38})- o -N-;

R^{35} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, -NO_2, -OR^{39}, -$S(O)_jR^{39}$, -$OCOR^{39}$, -$NR^{39}R^{40}$, -$CONR^{39}R^{40}$, -CO_2R^{39}, -$SO_2NR^{39}R^{40}$, -$NR^{39}SO_2R^{40}$, -$B(OR^{39})(OR^{40})$, -$P(O)(OR^{39})(OR^{40})$ o -$P(O)(R^{39})(OR^{40})$;

R^{36} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, -NO_2, -OR^{41}, -$S(O)_kR^{41}$, -$OCOR^{41}$, -$NR^{41}R^{42}$, -$CONR^{41}R^{42}$, -CO_2R^{41}, -$SO_2NR^{41}R^{42}$, -$NR^{41}SO_2R^{42}$, -$B(OR^{41})(OR^{42})$, -$P(O)(OR^{41})(OR^{42})$ o -$P(O)(R^{41})(OR^{42})$;

R^{37} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, -NO_2, -OR^{43}, -$S(O)_lR^{43}$, -$OCOR^{43}$, -$NR^{43}R^{44}$, -$CONR^{43}R^{44}$, -CO_2R^{43}, -$SO_2NR^{43}R^{44}$, -$NR^{43}SO_2R^{44}$, -$B(OR^{43})(OR^{44})$, -$P(O)(OR^{43})(OR^{44})$ o -$P(O)(R^{43})(OR^{44})$;

R^{38} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo,

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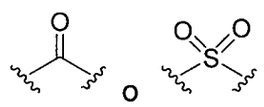
arilalquilo sustituido, acilo, acilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, $-NO_2$, $-OR^{45}$, $-S(O)_mR^{45}$, $-OCOR^{45}$, $-NR^{45}R^{46}$, $-CONR^{45}R^{46}$, $-COR^{45}$, $-CO_2R^{45}$, $-SO_2NR^{45}R^{46}$, $-NR^{45}SO_2R^{46}$, $-B(OR^{45})(OR^{46})$, $-P(O)(OR^{45})(OR^{46})$ o $-P(O)(R^{45})(OR^{46})$; o alternativamente R^{36} y R^{37} o R^{37} y R^{38} tomados conjuntamente con el átomo al cual ellos están unidos, forman un anillo cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo, o cicloheteroalquilo sustituido;

j, k, l y m son independientemente 0, 1 o 2; y

R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, y R^{46} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido o alternativamente R^{39} y R^{40}, R^{41} y R^{42}, R^{43} y R^{44} o R^{45} y R^{46} conjuntamente con los átomos a los cuales ellos están unidos forman un anillo cicloheteroalquilo o cicloheteroalquilo sustituido;

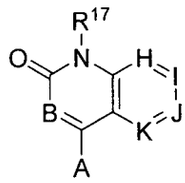
con la condición de que a lo sumo, dos de H, I, J y K sean -N-.

98. El compuesto de la reivindicación 97, en donde $(D)_n$-G es



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99. El compuesto de la reivindicación 97, que tiene la Fórmula estructural (IIIa):



(IIIa)

100. El compuesto de la reivindicación 99, en donde A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, $-OR^9$, $-NO_2$, $-S(O)_cR^9$, $-NHOR^9$, $-NR^9COR^{10}$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$, o $-NR^9C(=NH)NR^{10}R^{11}$.

101. El compuesto de la reivindicación 100, en donde A es -OH, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHOCH_3$, $-NOCH_3$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$ o $-CH_2NHC(O)CH_3$.

102. El compuesto de la reivindicación 99, en donde R^{17} es hidrógeno, alquilo, alquilo sustituido, arilalquilo, o arilalquilo sustituido.

103. El compuesto de la reivindicación 102, en donde R^{17} es hidrógeno, metilo, etilo, propilo, *iso*-propilo, *n*-butilo, *iso*-butilo, *sec*-butilo, *t*-butilo, fenilo o bencilo.

104. El compuesto de la reivindicación 99, en donde

H es $-C(R^{35})-$;

I es $-C(R^{36})$;

J es $-C(R^{37})-$; y

K es $-C(R^{38})-$.

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105. El compuesto de la reivindicación 99, en donde

A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, -CN, -OR^9, -NO_2, -$S(O)_cR^9$, -$NHOR^9$, -NR^9COR^{10}, -NR^9R^{10}, -$CONR^9R^{10}$, -CO_2R^9 o -$NR^9CO_2R^{10}$; y

R^{17} es hidrógeno, alquilo, alquilo sustituido, arilalquilo, o arilalquilo sustituido.

106. El compuesto de la reivindicación 99, en donde

A es -OH, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -$NHOCH_3$, -$NOCH_3$, -$NHC(O)CH_3$, -$NHC(O)OCH_3$, -$NHC(O)NH_2$, -$NHC(S)NH_2$, -$NHC(NH)NH_2$, -CN, -CH_2OH, -CH_2NH_2, -CH_2NHCH_3, -$CH_2N(CH_3)_2$, -CO_2H, -$CONH_2$, -$CONHCH_3$ o -$CH_2NHC(O)CH_3$; y

R^{17} es hidrógeno, metilo, etilo, propilo, *iso*-propilo, *n*-butilo, *iso*-butilo, *sec*-butilo, *t*-butilo, fenilo o bencilo.

107. El compuesto de la reivindicación 99, en donde

R^{35} es hidrógeno, alquilo, alquilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, -CN, -NO_2, -OR^{39}, -$S(O)_jR^{39}$, -$OCOR^{39}$, -$NR^{39}COR^{40}$, -$CONR^{39}R^{40}$, -CO_2R^{39}, $NR^{39}R^{40}$, -$SO_2NR^{39}R^{40}$, o -$NR^{39}SO_2R^{40}$;

R^{36} es hidrógeno, alquilo, alquilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, -CN, -NO_2, -OR^{41}, -$S(O)_jR^{41}$, -$OCOR^{41}$, $NR^{41}R^{42}$, -$NR^{41}COR^{42}$, -$CONR^{41}R^{42}$, -CO_2R^{41}, -$SO_2NR^{41}R^{42}$, o -$NR^{41}SO_2R^{42}$;

R^{37} es hidrógeno, alquilo, alquilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, -CN, -NO_2, -OR^{43}, -$S(O)_jR^{43}$, -$OCOR^{43}$, $NR^{43}R^{44}$, -$NR^{43}COR^{44}$, -$CONR^{43}R^{44}$, -CO_2R^{43}, -$SO_2NR^{43}R^{44}$, o -$NR^{43}SO_2R^{44}$; o alternativamente R^{36} y R^{37}, conjuntamente con los átomos a los cuales ellos están unidos, forman un anillo cicloheteroalquilo o cicloheteroalquilo sustituido; y

R^{38} es hidrógeno, alquilo, alquilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, -CN, $-NO_2$, $-OR^{45}$, $-S(O)_jR^{45}$, $-OCOR^{45}$, $NR^{45}R^{46}$, $-NR^{45}COR^{46}$, $-CONR^{45}R^{46}$, $-CO_2R^{45}$, $-SO_2NR^{45}R^{46}$, $-NR^{45}SO_2R^{46}$.

108. El compuesto de la reivindicación 107, en donde

R^{38} es hidrógeno, alcanilo, alcanilo sustituido, alquenilo, alquenilo sustituido, cicloalcanilo, cicloalcanilo sustituido, cicloalquenilo, cicloalquenilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, -CN, $-NO_2$, $-OR^{45}$, $-S(O)_jR^{45}$, $-OCOR^{45}$, $NR^{45}R^{46}$, $-NR^{45}COR^{46}$, $-CONR^{45}R^{46}$, $-CO_2R^{45}$, $-SO_2NR^{45}R^{46}$, $-NR^{45}SO_2R^{46}$.

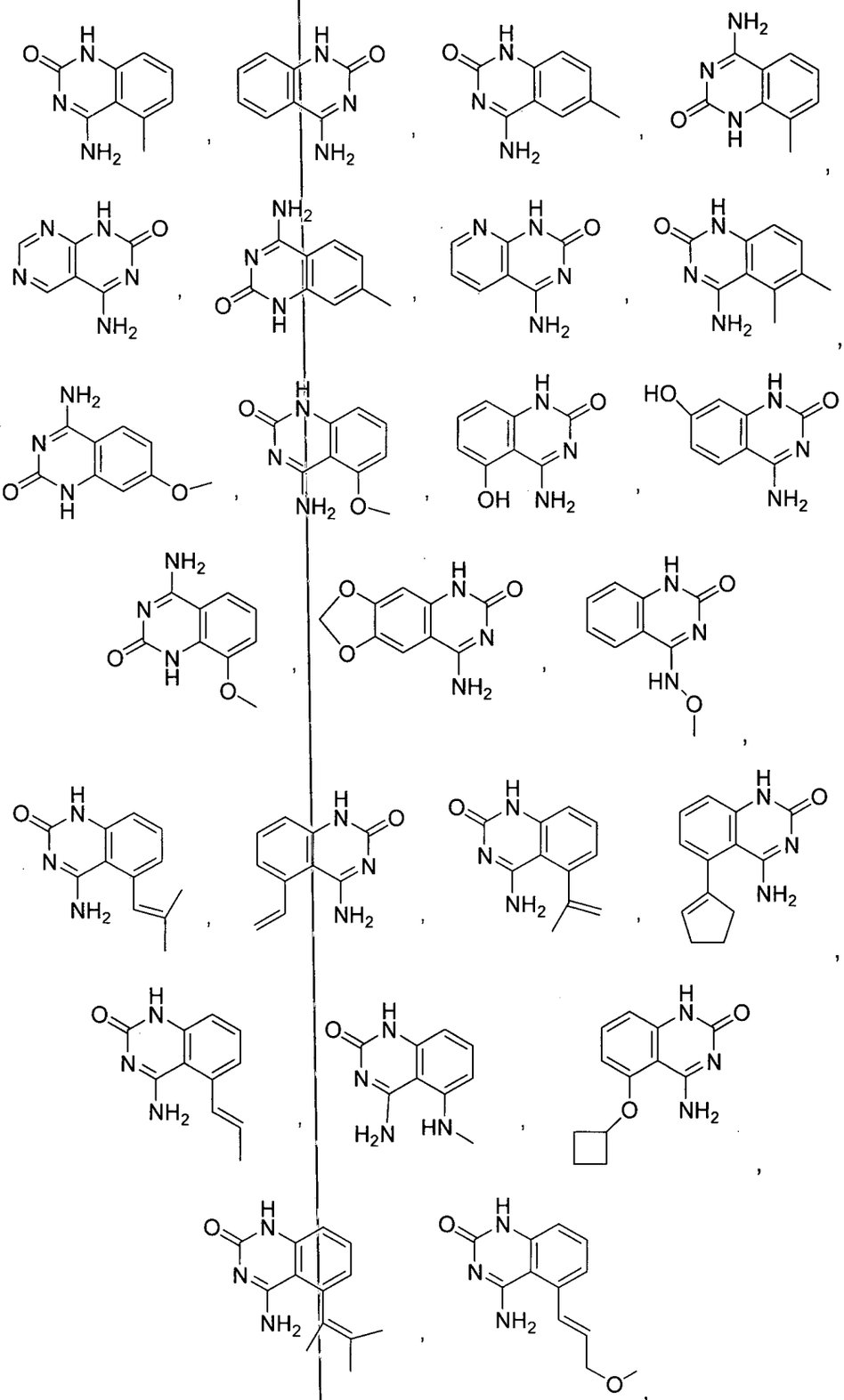
109. El compuesto de la reivindicación 107, en donde

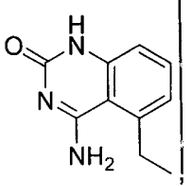
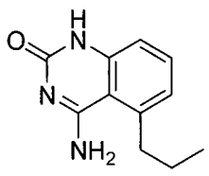
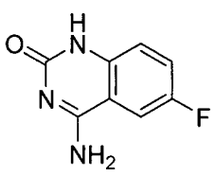
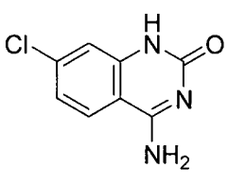
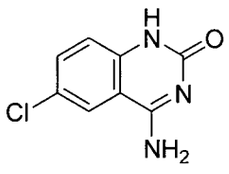
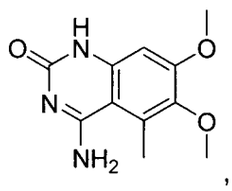
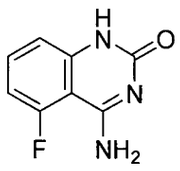
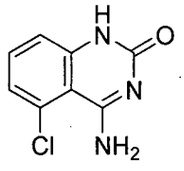
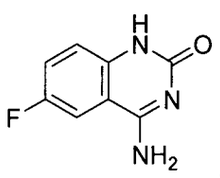
A es $-NH_2$,

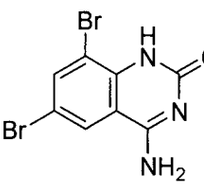
R^{17} es hidrógeno, metilo, etilo o bencilo; y

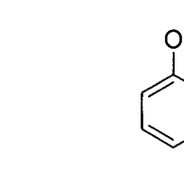
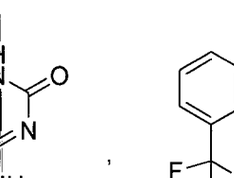
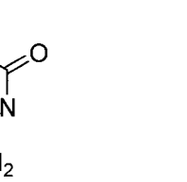
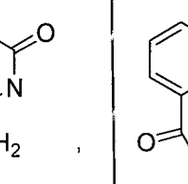
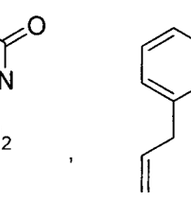
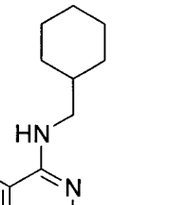
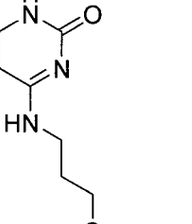
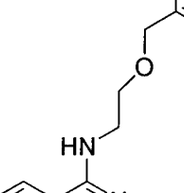
R^{35}, R^{36}, R^{37} y R^{38} son independientemente hidrógeno, flúor, cloro, bromo, metilo, trifluormetilo, etilo, isopropilo, ciclopropilo, propenilo, metilpropenilo, butenilo, metilbutenilo, propenilo sustituido, metilpropenilo sustituido, butenilo sustituido, metilbutenilo sustituido, -NH-alcanilo, -NH-(alcanilo sustituido), -OH, $-OCH_3$, -O-cicloalcanilo, –O-bencilo, $-CO_2H$.

110. El compuesto de la reivindicación 99 que tiene la Fórmula estructural seleccionada del grupo integrado por




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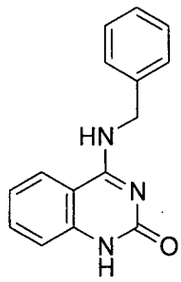
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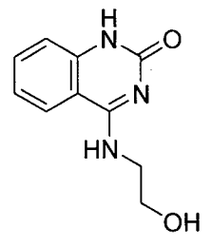
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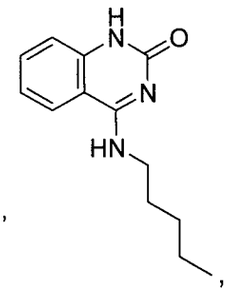
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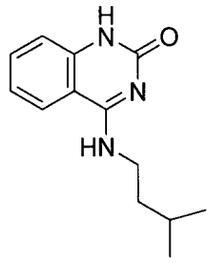
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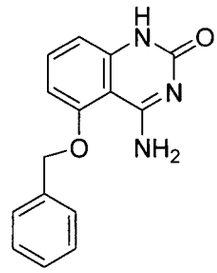
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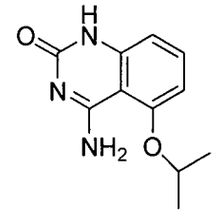


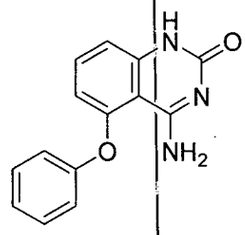


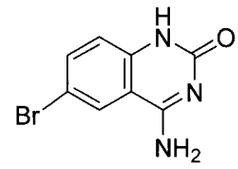


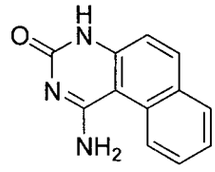


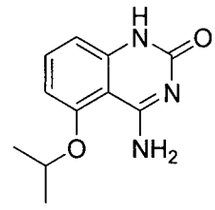


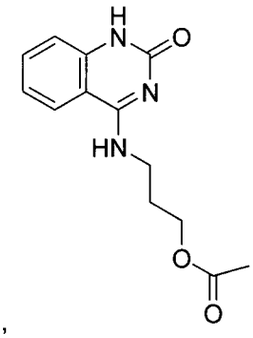


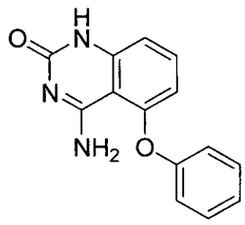


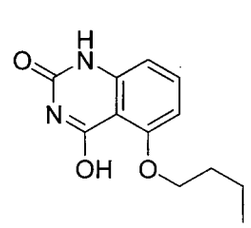


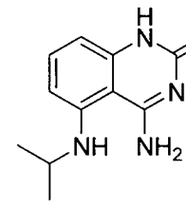




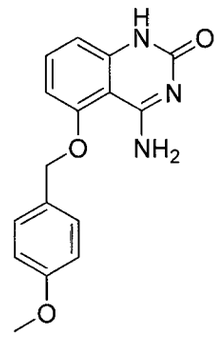
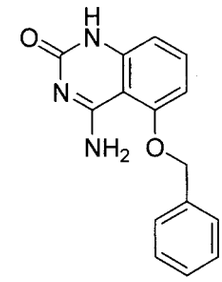
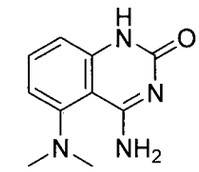
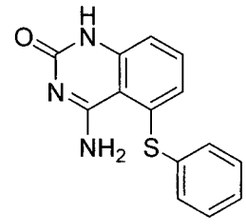
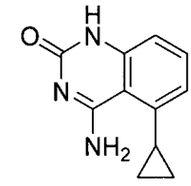
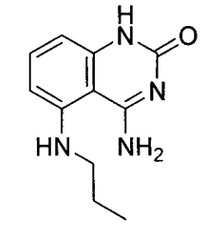
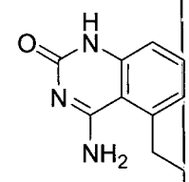
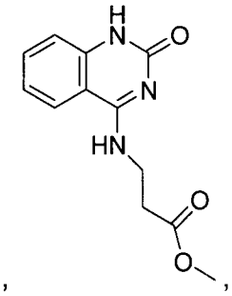
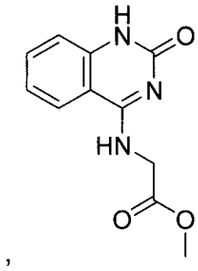
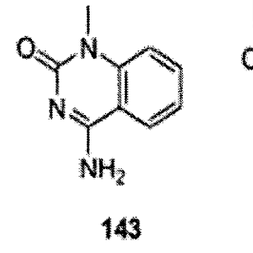
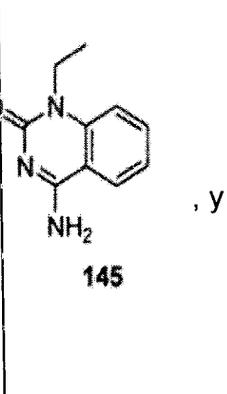
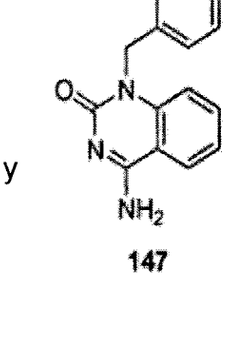
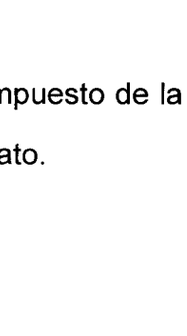
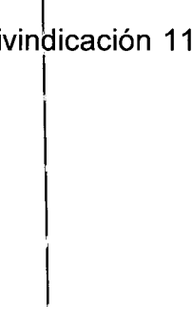
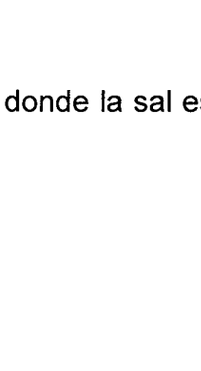








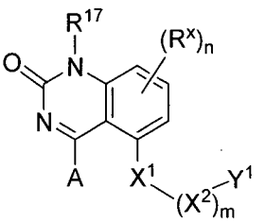
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o un tautómero, sal, solvato, y/o éster del mismo.

111. El compuesto de la reivindicación 110, en donde la sal es la sal clorhidrato o trifluoracetato.

112. El compuesto de la reivindicación 99, que tiene la Fórmula estructural (IIIa1):



(IIIa1)

en donde,

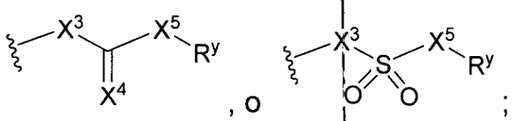
A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, $-OR^9$, $-NO_2$, $-S(O)_cR^9$, $-NOR^9$, $-NHOR^9$, $-NR^9COR^{10}$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$ o $-NR^9CO_2R^{10}$;

R^{17} es hidrógeno, alquilo, alquilo sustituido, arilalquilo, o arilalquilo sustituido; X^1 es $-CH_2-$, $-O-$, $-NR^9-$, $-S-$, $-S(O)-$, o $-S(O)_2-$;

X^2 es alquileno, alquileno sustituido, heteroalquileno, o heteroalquileno sustituido;

m es 0 o 1;

Y^1 es cicloheteroalquilo, cicloheteroalquilo sustituido, o



;

X^3 y X^5 son independientemente un enlace covalente, $-O-$ o $-NR^9-$;

X^4 es O, NR^9, $N-OR^9$, o S;

R^x es halo, $-NO_2$, -CN, -OH, $-NH_2$, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido;

n es 0, 1, 2, o 3;

R^Y es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido, $-NR^9R^{10}$; y

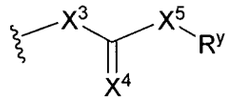
cada R^9 y R^{10} es independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido;

con la condición de que cuando X^1 sea –O– o –S–, y m sea cero; entonces X^3 no sea –O–.

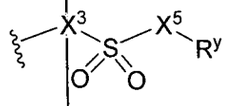
113. El compuesto de la reivindicación 112, en donde

X^1 es $-CH_2-$; e

Y^1 es



, o



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114. El compuesto de la reivindicación 112, en donde

X^1 es –O–, $-NR^9-$, o –S–;

m es 0 o 1, y

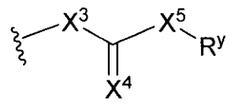
Y^1 es cicloheteroalquilo o cicloheteroalquilo sustituido.

115. El compuesto de la reivindicación 112, en donde

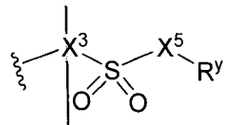
X^1 es –O–, $–NR^9–$, o –S–;

m es 1, e

Y^1 es



, o



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116. El compuesto de cualquiera de las reivindicaciones 112, 114, y 115, en donde

X^2 es metileno, etileno, propileno, dimetiletileno, metilciclopropileno, o ciclopropilmetileno.

117. El compuesto de cualquiera de las reivindicaciones 112 a 116, en donde A es hidrógeno, alquilo, alquilo sustituido, -CN, $-OR^9$, $-NO_2$, $-S(O)_cR^9$, $-NOR^9$, $-NHOR^9$, $-NR^9COR^{10}$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$ o $-NR^9CO_2R^{10}$.

118. El compuesto de cualquiera de las reivindicaciones 112 a 116, en donde R^{17} es hidrógeno, alquilo, alquilo sustituido.

119. El compuesto de la reivindicación 112, en donde Y^1 es cicloheteroalquilo o cicloheteroalquilo sustituido.

120. El compuesto de la reivindicación 119, en donde Y^1 rs piperidinilo, piperidinilo sustituido, tetrahidrofuranilo, tetrahidrofuranilo sustituido, tetrahidropiranilo, tetrahidropiranilo sustituido, dihidrofuranilo, dihidrofuranilo sustituido, pirrolidinilo, pirrolidinilo sustituido, oxetanilo, u oxetanilo sustituido.

121. El compuesto de la reivindicación 119 o 120, en donde el cicloheteroalquilo sustituido comprende uno o más sustituyentes seleccionados del grupo integrado por alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, $-OR^9$, $-NO_2$, $-S(O)_cR^9$, $-NOR^9$, $-NHOR^9$, $-NR^9COR^{10}$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$, y $-NR^9CO_2R^{10}$.

122. El compuesto de la reivindicación 112, en donde X^4 es O.

123. El compuesto de la reivindicación 112, en donde $-X^3-C(X^4)-X^5-$ es –C(O)-,
-C(O)-NH-, -NH-C(O)-, -NH-C(O)-NH-, -C(O)-O-, -O-C(O)-, -O-C(O)-O-, -NH-C(O)-O-, -O-C(O)-NH-, –C(NH)-, -C(NH)-NH-, -NH-C(NH)-, -NH-C(NH)-NH-, -C(NH)-O-, -O-C(NH)-, -O-C(NH)-O-, -NH-C(NH)-O-, -O-C(NH)-NH-, -C(N-OH)-, o -C(S)-.

124. El compuesto de la reivindicación 112, en donde

A es hidrógeno, alquilo, alquilo sustituido, o $-NR^9R^{10}$;

R^{17} es hidrógeno; e

Y^1 es piperidinilo, piperidinilo sustituido, tetrahidrofuranilo, tetrahidrofuranilo sustituido, tetrahidropiranilo, tetrahidropiranilo sustituido, dihidrofuranilo, dihidrofuranilo sustituido, pirrolidinilo, pirrolidinilo sustituido, oxetanilo, u oxetanilo sustituido.

125. El compuesto de la reivindicación 112, en donde

A es hidrógeno, alquilo, alquilo sustituido, o $-NR^9R^{10}$;

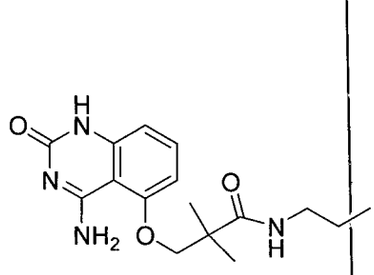
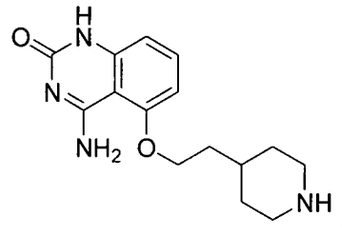
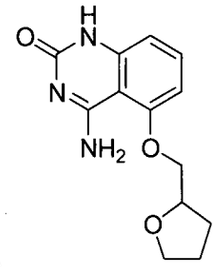
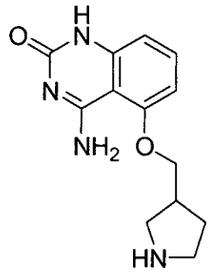
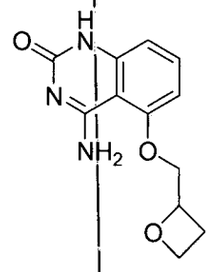
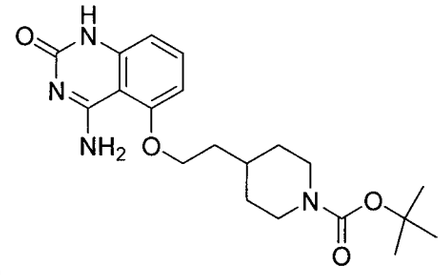
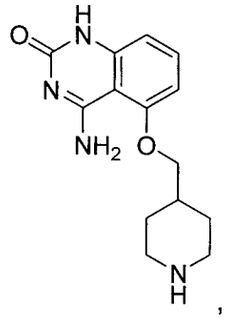
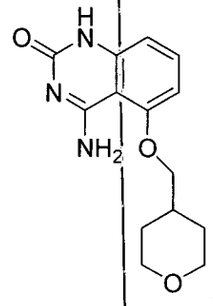
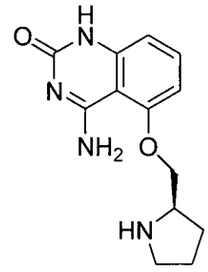
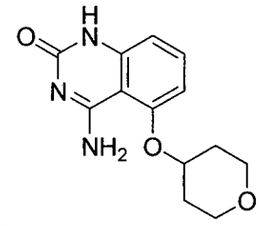
R^{17} es hidrógeno;

Y^1 es $-X^3-C(X^4)-X^5-$; y

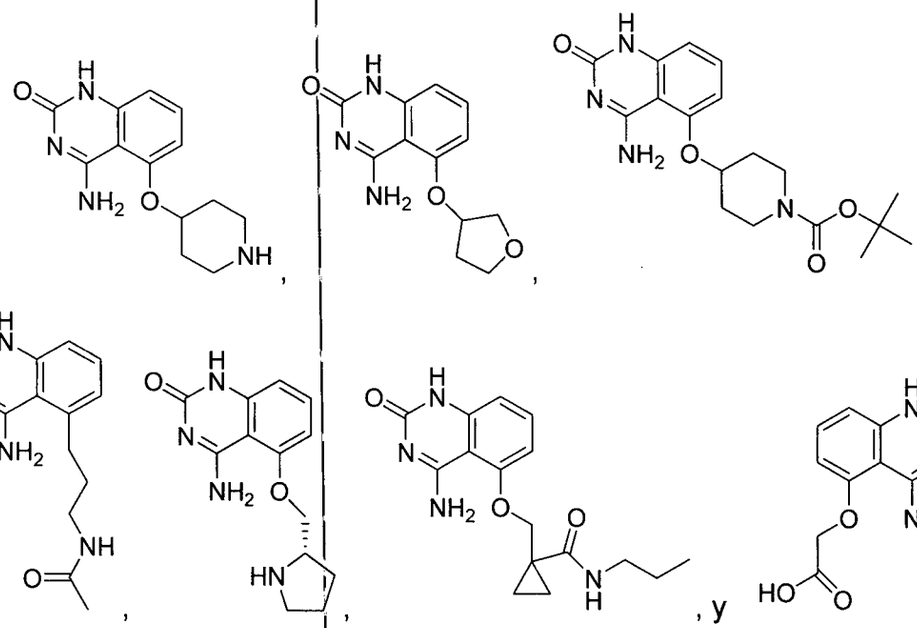
$-X^3-C(X^4)-X^5-$ es –C(O)-, -C(O)-NH-, -NH-C(O)-, -NH-C(O)-NH-, -C(O)-O-,

-O-C(O)-, -O-C(O)-O-, -NH-C(O)-O-, -O-C(O)-NH-, –C(NH)-, -C(NH)-NH-, -NH-C(NH)-, -NH-C(NH)-NH-, -C(NH)-O-, -O-C(NH)-, -O-C(NH)-O-, -NH-C(NH)-O-, -O-C(NH)-NH-, -C(N-OH)-, o -C(S)-.

126. El compuesto de la reivindicación 112, que tiene la Fórmula estructural seleccionada del grupo integrado por


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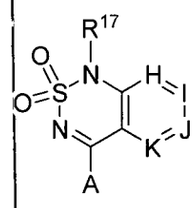
1071



o un tautómero, sal, solvato, y/o éster del mismo.

127. El compuesto de la reivindicación 122, en donde la sal es la sal clorhidrato o trifluoracetato.

128. El compuesto de la reivindicación 97, que tiene la Fórmula estructural (IIIb):



(IIIb).

129. El compuesto de la reivindicación 128, en donde A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, -CN, $-NO_2$, $-OR^9$, $-S(O)_cR^9$, $-NR^9COR^{10}$, $-NHOR^9$, $-NR^9R^{10}$, $-NOR^9$, $-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$, o $-NR^9C(=NH)NR^{10}R^{11}$.

130. El compuesto de la reivindicación 128, en donde R^{17} es hidrógeno, alquilo, o alquilo sustituido.

131. El compuesto de la reivindicación 128, en donde

A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, $-OR^1$, $-SR^1$, $-CN$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$ o $-NR^9C(=NH)NR^{10}R^{11}$; y

R^{17} es hidrógeno, alquilo, o alquilo sustituido.

132. El compuesto de la reivindicación 128, en donde

H es $-C(R^{35})-$ o $-N-$;

I es $-C(R^{36})-$;

J es $-C(R^{37})-$; y

K es $-C(R^{38})-$ o $-N-$.

133. El compuesto de la reivindicación 128, en donde

H es $-C(R^{35})-$;

I es $-C(R^{36})-$;

J es $-C(R^{37})-$; y

K es $-C(R^{38})-$.

134. El compuesto de la reivindicación 128, en donde

R^{35} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo

sustituido, -CN, -NO_2, -OR^{39}, -$S(O)_jR^{39}$, -$OCOR^{39}$, -$NR^{39}R^{40}$, -$CONR^{39}R^{40}$, -CO_2R^{39}, -$SO_2NR^{39}R^{40}$, -$NR^{39}SO_2R^{40}$;

R^{36} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido, -CN, -NO_2, -OR^{41}, -$S(O)_kR^{41}$, -$OCOR^{41}$, -$NR^{41}R^{42}$, -$CONR^{41}R^{42}$, -CO_2R^{41}, -$SO_2NR^{41}R^{42}$, -$NR^{41}SO_2R^{42}$;

R^{37} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido, -CN, -NO_2, -OR^{43}, -$S(O)_lR^{43}$, -$OCOR^{43}$, -$NR^{43}R^{44}$, -$CONR^{43}R^{44}$, -CO_2R^{43}, -$SO_2NR^{43}R^{44}$, -$NR^{43}SO_2R^{44}$;

R^{38} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido, -CN, -NO_2, -OR^{45}, -$S(O)_mR^{45}$, -$OCOR^{45}$, -$NR^{45}R^{46}$, -$CONR^{45}R^{46}$, -COR^{45}, -CO_2R^{45}, -$SO_2NR^{45}R^{46}$, -$NR^{45}SO_2R^{46}$.

135. El compuesto de la reivindicación 128, en donde

A es -NH_2,

R^{17} es hidrógeno, metilo, etilo o bencilo; y

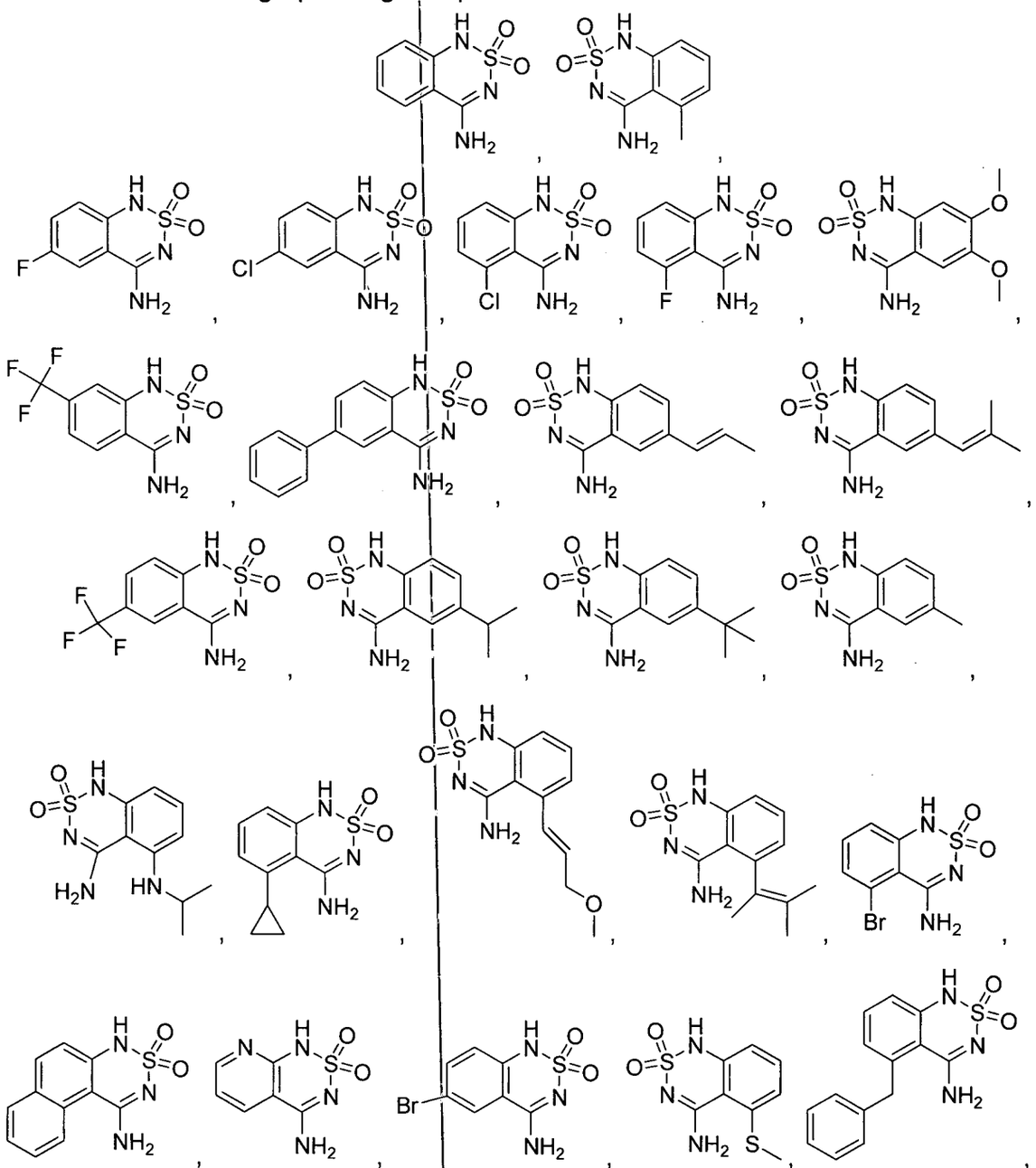
R^{35}, R^{36}, R^{37} y R^{38} son independientemente hidrógeno, flúor, cloro, bromo,

-CN, alcanilo, alcanilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, cicloalcanilo, cicloalcanilo sustituido, cicloalquenilo, cicloalquenilo sustituido, heteroalcanilo, heteroalcanilo sustituido, cicloheteroalquilo, cicloheteroalquilo sustituido, -O-alcanilo, -O-(alcanilo sustituido), -O-alquenilo, -O-

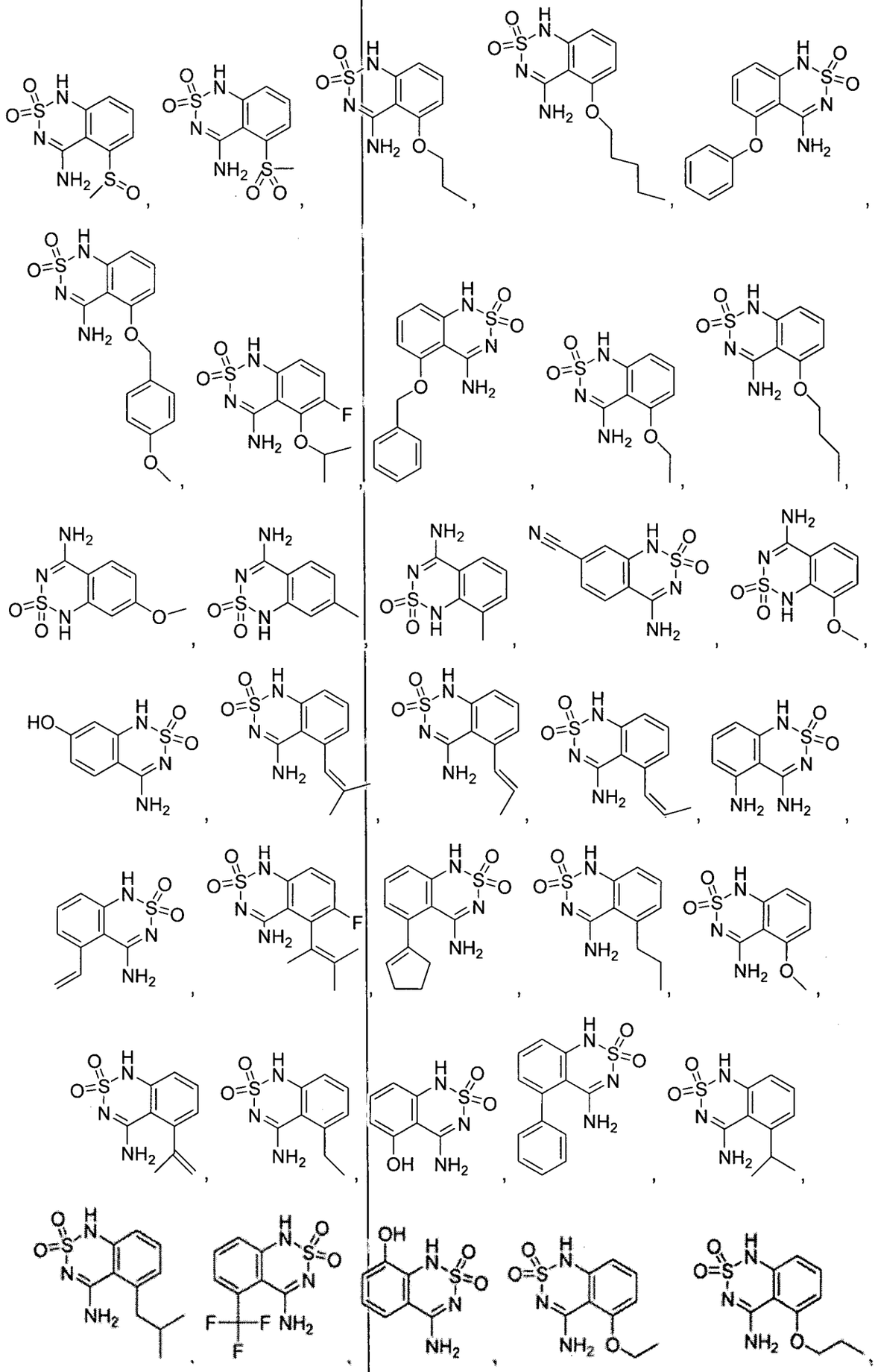
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(alquenilo sustituido), -NH-alcanilo, -NH-(alcanilo sustituido), -NH-alquenilo, -NH-(alquenilo sustituido), -S-alcanilo, -S-(alcanilo sustituido), -S-alquenilo, o -S-(alquenilo sustituido).

136. Un compuesto de la reivindicación 128 que tiene la fórmula estructural seleccionada del grupo integrado por:

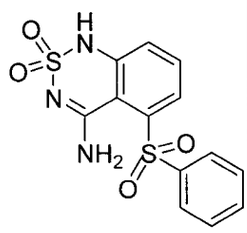


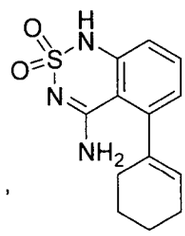
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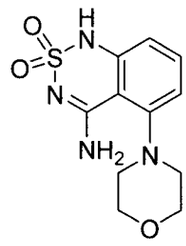


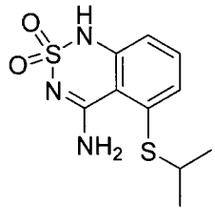
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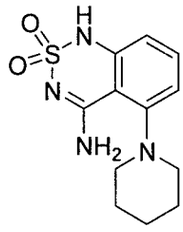
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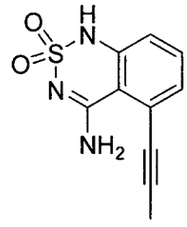


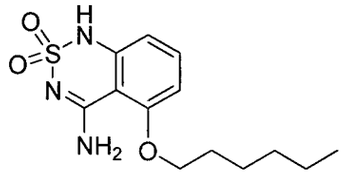


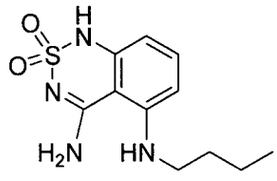


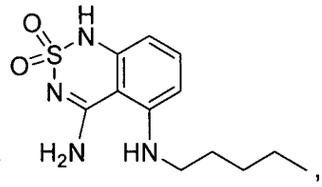


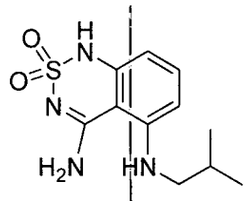


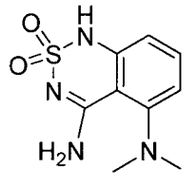


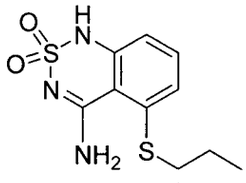


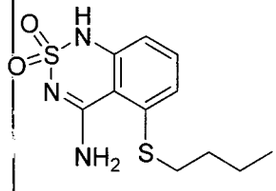


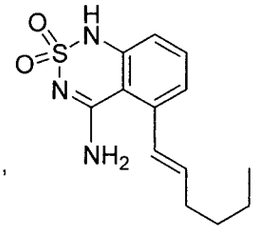


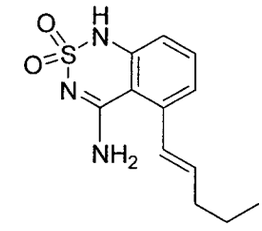




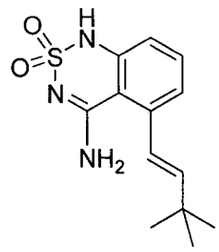
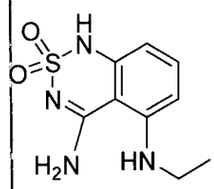
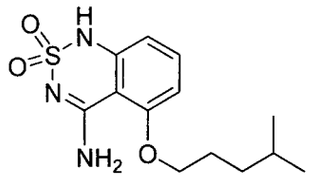
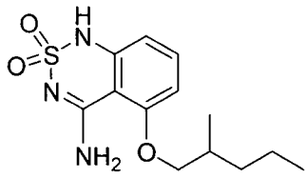
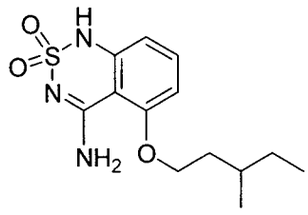
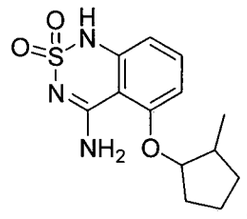
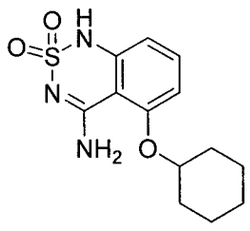
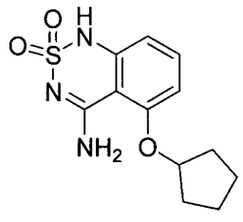
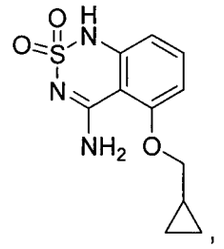
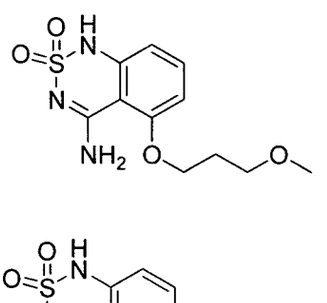
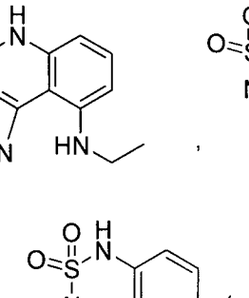
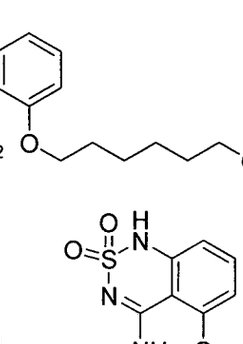
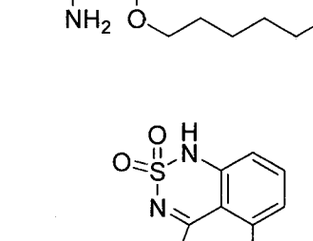
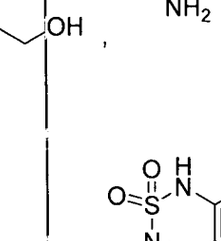
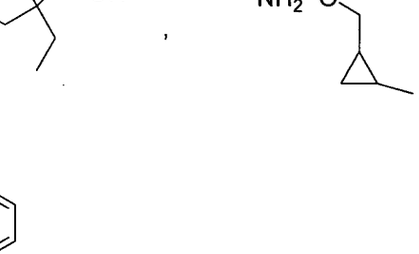
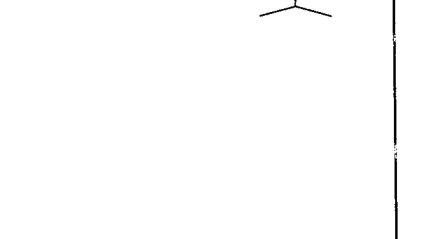
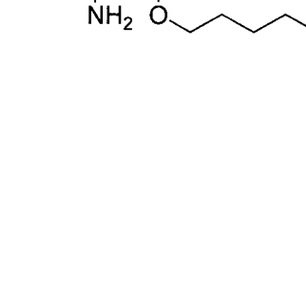








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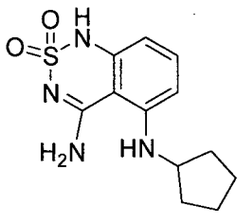

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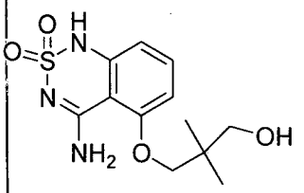
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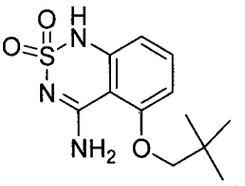
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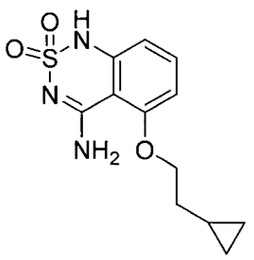
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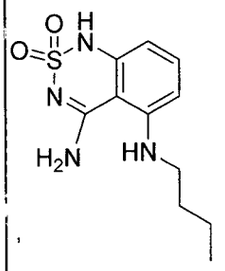
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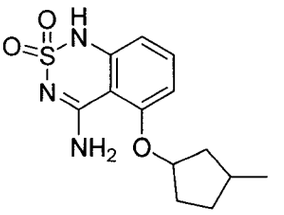


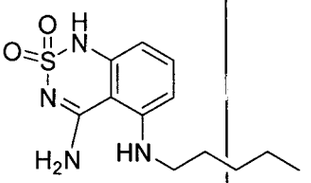


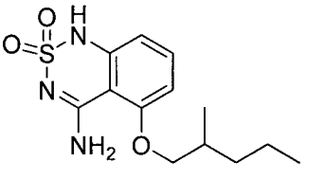


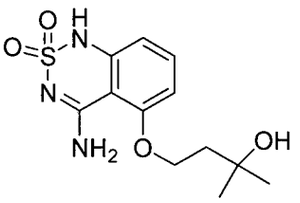


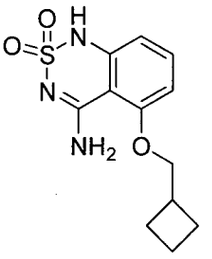


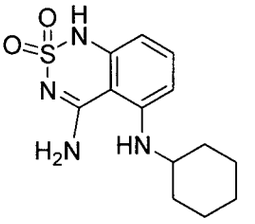


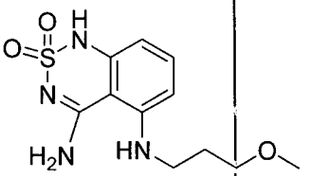


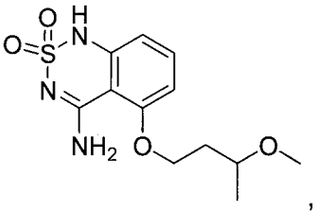


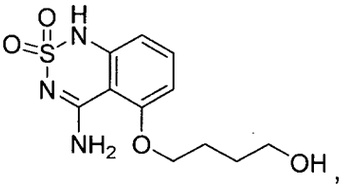


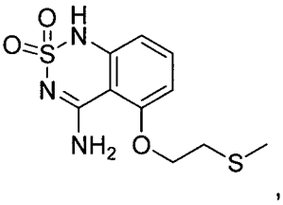


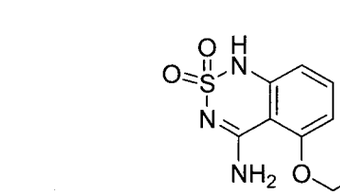


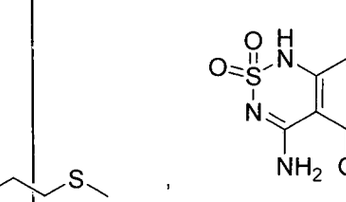


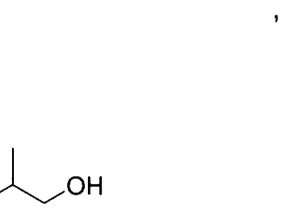




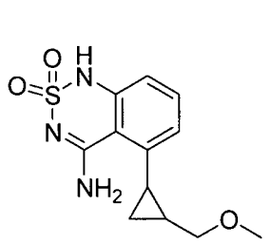


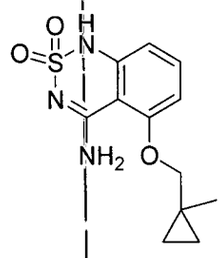


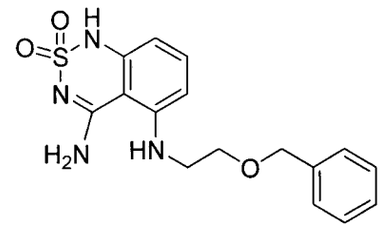


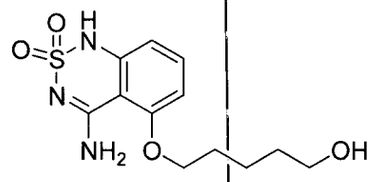


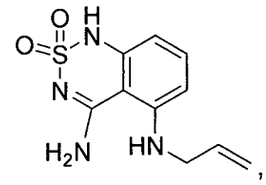


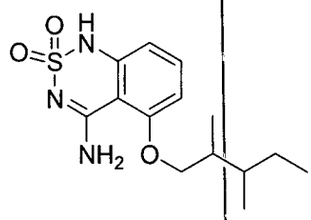


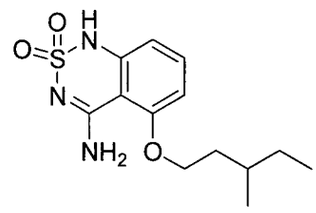


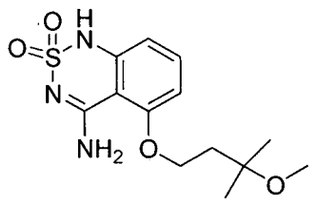


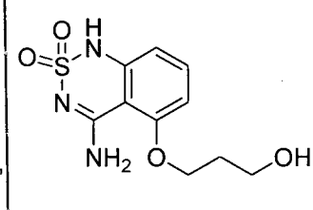


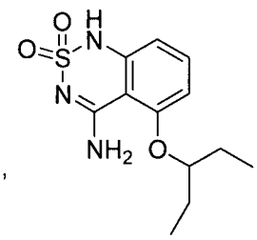


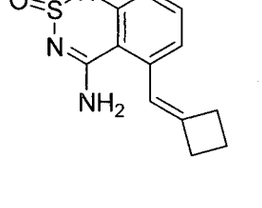


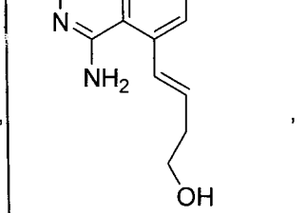


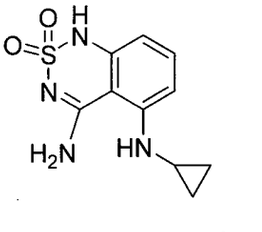


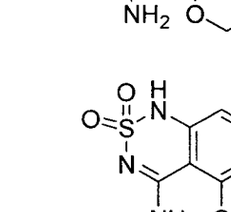


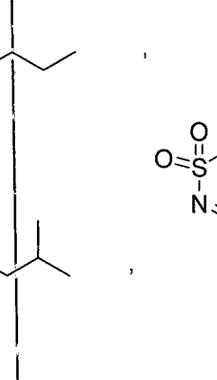


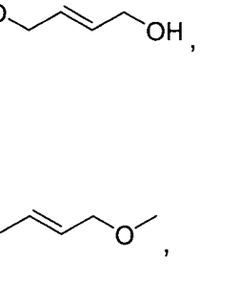


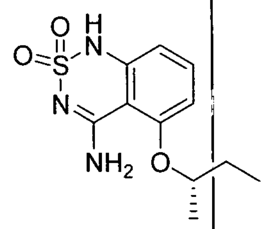
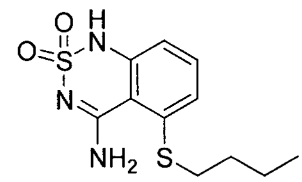
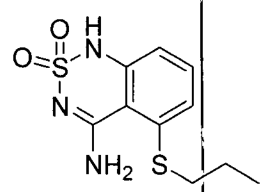
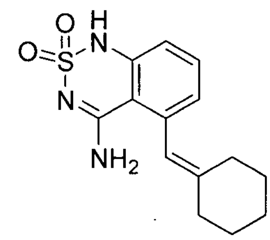
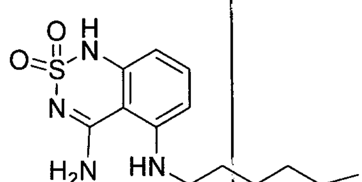
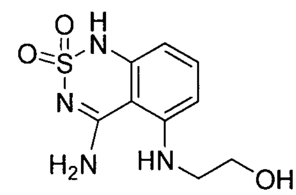
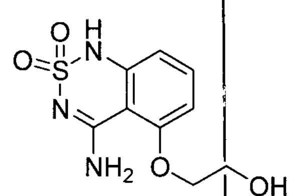
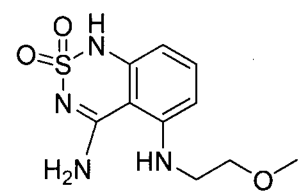
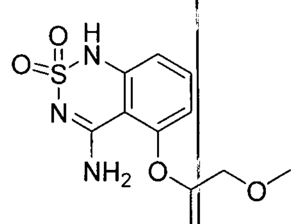
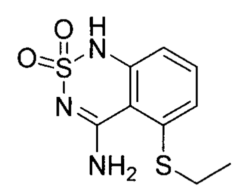
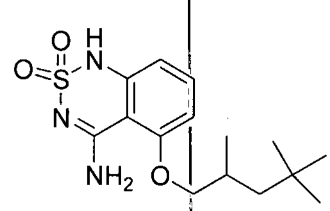
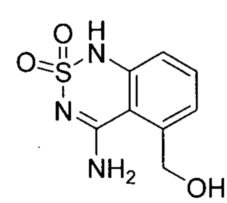
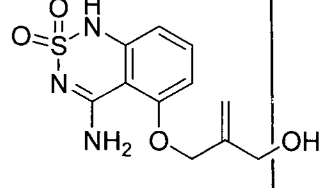
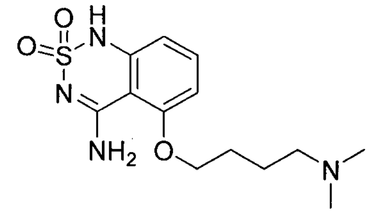




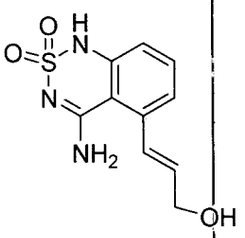


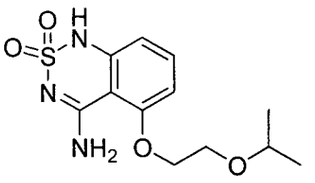


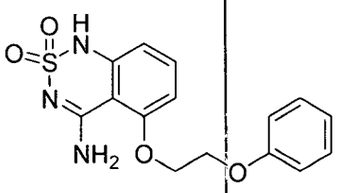


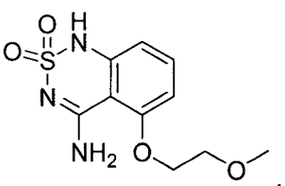

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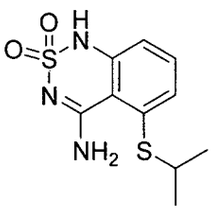
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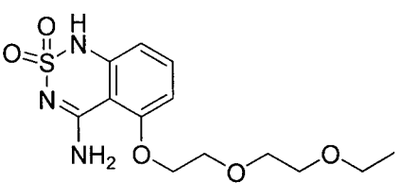


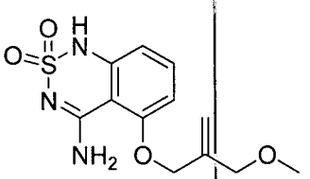


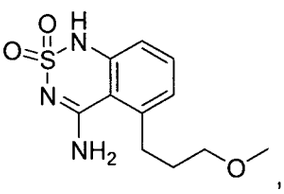


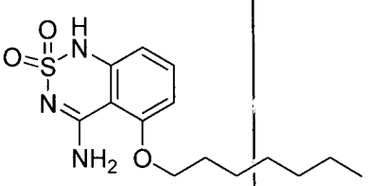


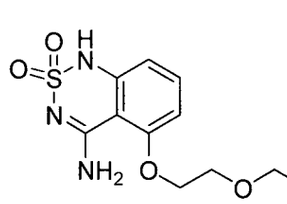


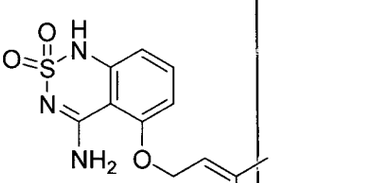


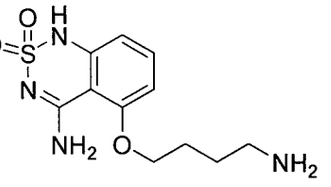


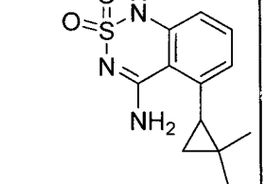


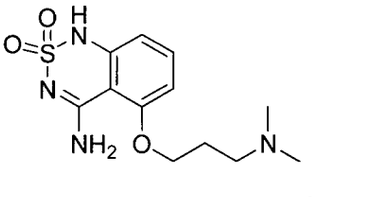




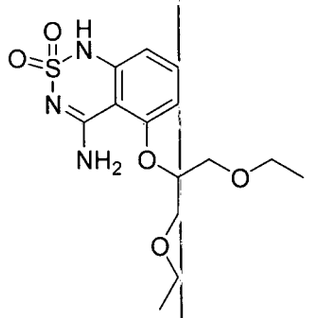


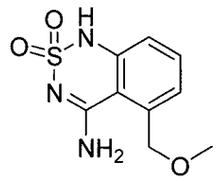


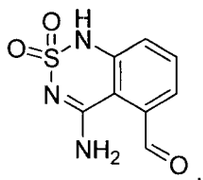


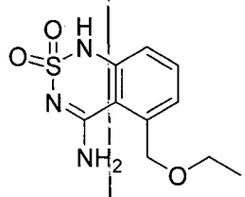


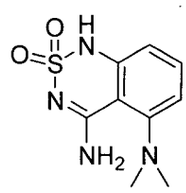
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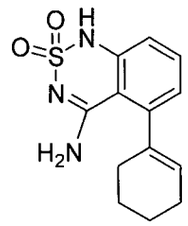


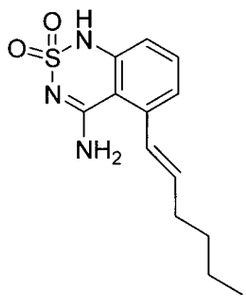


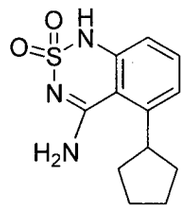


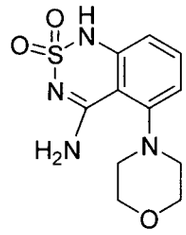


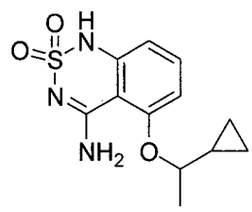


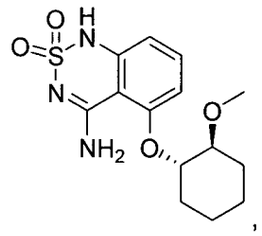


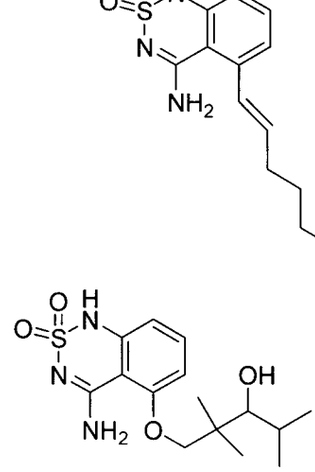


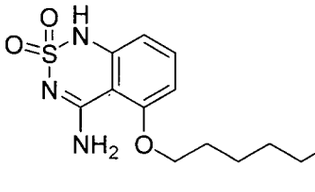


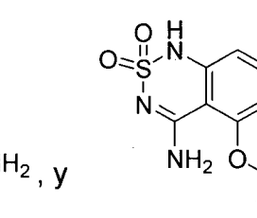


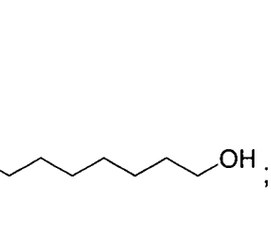


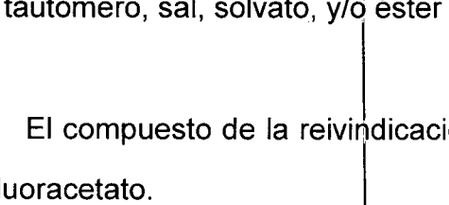


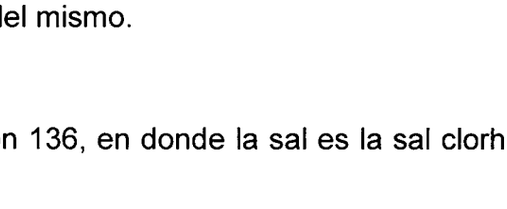








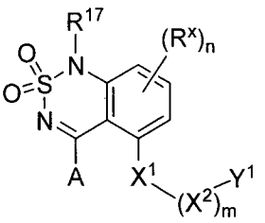




o un tautómero, sal, solvato, y/o éster del mismo.

137. El compuesto de la reivindicación 136, en donde la sal es la sal clorhidrato o trifluoracetato.

138. El compuesto de la reivindicación 128, que tiene la Fórmula estructural (IIIb1):



(IIIb1)

en donde,

A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, $-OR^9$, $-NO_2$, $-S(O)_cR^9$, $-NOR^9$, $-NHOR^9$, $-NR^9COR^{10}$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$ o $-NR^9CO_2R^{10}$;

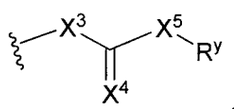
R^{17} es hidrógeno, alquilo, alquilo sustituido, arilalquilo, o arilalquilo sustituido;

X^1 es $-CH_2-$, $-O-$, $-NR^9-$, $-S-$, $-S(O)-$, o $-S(O)_2-$;

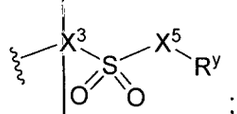
X^2 es alquileno, alquileno sustituido, heteroalquileno, o heteroalquileno sustituido;

m es 0 o 1;

Y^1 es heteroarilo, heteroarilo sustituido, cicloheteroalquilo, cicloheteroalquilo sustituido, o



, o



;

X^3 y X^5 son independientemente un enlace covalente, $-O-$ o $-NR^9-$;

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X^4 es O, NR^9, N-OR^9, o S;

R^x es halo, -NO_2, -CN, -OH, -NH_2, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido;

n es 0, 1, 2, o 3;

R^Y es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido, -NR^9R^{10}; y

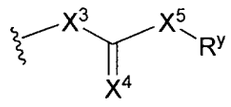
cada R^9 y R^{10} es independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido;

con la condición de que cuando X^1 sea –O– o –S–, y m sea cero; entonces X^3 no sea –O–.

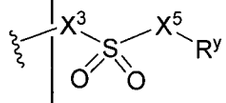
139. El compuesto de la reivindicación 138, en donde

X^1 es $–CH_2–$; e

Y^1 es



, o



.

140. El compuesto de la reivindicación 138, en donde

X^1 es –O–, $–NR^9–$, o –S–;

m es 0 o 1, e

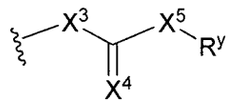
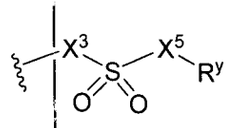
Y^1 es cicloheteroalquilo o cicloheteroalquilo sustituido.

141. El compuesto de la reivindicación 138, en donde

X^1 es –O–, –NR^9–, o –S–;

m es 1, e

Y^1 es


, o

.

142. El compuesto de cualquiera de las reivindicaciones 138, 140, y 141, en donde

X^2 es alcanileno, alcanileno sustituido, heteroalcanileno, heteroalcanileno sustituido, alquenileno, alquenileno sustituido, heteroalquenileno, o heteroalquenileno sustituido.

143. El compuesto de cualquiera de las reivindicaciones 138, 140, y 141, en donde

X^2 es metileno, etileno, propileno, *iso*-propileno, butileno, *iso*-butileno, *sec*-butileno, pentileno, hexileno, heptileno, dimetiletileno, metilciclopropileno, ciclopropilmetileno, etenileno, propenileno, o butenileno.

144. El compuesto de la reivindicación 138, en donde A es hidrógeno, alquilo, alquilo sustituido, -CN, -NO_2, -OR^9, -$S(O)_cR^9$, -NR^9COR^{10}, -$NHOR^9$, -NR^9R^{10}, -NOR^9, -$CONR^9R^{10}$, -CO_2R^9, -$NR^9CO_2R^{10}$, -$NR^9CONR^{10}R^{11}$, -$NR^9CSNR^{10}R^{11}$, -$NR^9C(=NH)NR^{10}R^{11}$.

145. El compuesto de la reivindicación 138, en donde R^{17} es hidrógeno, alquilo, o alquilo sustituido.

146. El compuesto de la reivindicación 138, en donde Y^1 es cicloheteroalcanilo, cicloheteroalcanilo sustituido, cicloheteroalquenilo, o cicloheteroalquenilo sustituido.

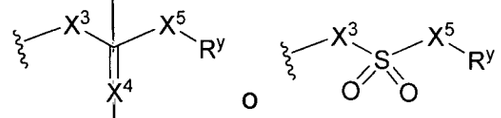
147. El compuesto de la reivindicación 146, en donde Y^1 es piperidinilo, piperidinilo sustituido, tetrahidrofuranilo, tetrahidrofuranilo sustituido, tetrahidropiranilo, tetrahidropiranilo sustituido, dihidrofuranilo, dihidrofuranilo sustituido, pirrolidinilo, pirrolidinilo sustituido, oxetanilo, oxetanilo sustituido, un anillo sacárido o su derivado, un anillo sacárido sustituido o su derivado.

148. El compuesto de la reivindicación 138, en donde Y^1 es heteroarilo o heteroarilo sustituido.

149. El compuesto de la reivindicación 148, en donde Y^1 es piridinilo, piridinilo sustituido, pirrolilo, pirrolilo sustituido, furanilo, furanilo sustituido, pirazolilo, pirazolilo sustituido, isoxazolilo, isoxazolilo sustituido, oxazolilo, y oxazolilo sustituido.

150. El compuesto de la reivindicación 146 o 147, en donde el cicloheteroalcanilo sustituido o el cicloheteroalquenilo sustituido comprende uno o más sustituyentes seleccionados del grupo integrado por alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, $-OR^9$, $-NO_2$, $-S(O)_cR^9$, $-NOR^9$, $-NHOR^9$, $-NR^9COR^{10}$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$, y $-NR^9CO_2R^{10}$.

151. El compuesto de la reivindicación 138, en donde Y es



o

.

152. El compuesto de la reivindicación 151, en donde X^4 es O.

153. El compuesto de la reivindicación 138, en donde $-X^3-C(X^4)-X^5-$ es –C(O)-,
-C(O)-NH-, -NH-C(O)-, -NH-C(O)-NH-, -C(O)-O-, -O-C(O)-, -O-C(O)-O-, -NH-C(O)-O-, -O-C(O)-NH-, –C(NH)-, -C(NH)-NH-, -NH-C(NH)-, -NH-C(NH)-NH-, -C(NH)-O-, -O-C(NH)-, -O-C(NH)-O-, -NH-C(NH)-O-, -O-C(NH)-NH-, -C(N-OH)-, o -C(S)-.

154. El compuesto de la reivindicación 138, en donde

A es hidrógeno, alquilo, alquilo sustituido, o $-NR^9R^{10}$;

R^{17} es hidrógeno; e

Y^1 es piperidinilo, piperidinilo sustituido, tetrahidrofuranilo, tetrahidrofuranilo sustituido, tetrahidropiranilo, tetrahidropiranilo sustituido, dihidrofuranilo, dihidrofuranilo sustituido, pirrolidinilo, pirrolidinilo sustituido, oxetanilo, oxetanilo sustituido, un anillo monosacárido, un anillo monosacárido sustituido, piridinilo, piridinilo sustituido, pirrolilo, pirrolilo sustituido, furanilo, furanilo sustituido, pirazolilo, pirazolilo sustituido, isoxazolilo, isoxazolilo sustituido, oxazolilo, u oxazolilo sustituido.

155. El compuesto de la reivindicación 138, en donde

A es hidrógeno, alquilo, alquilo sustituido, o $-NR^9R^{10}$;

R^{17} es hidrógeno;

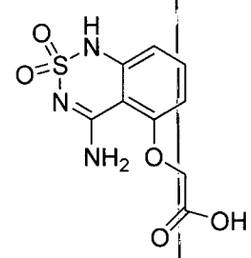
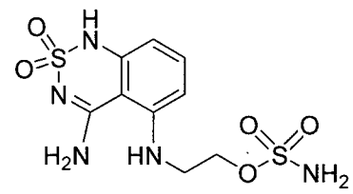
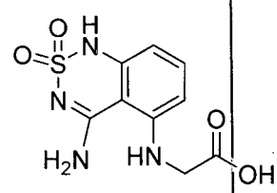
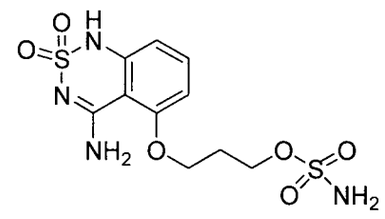
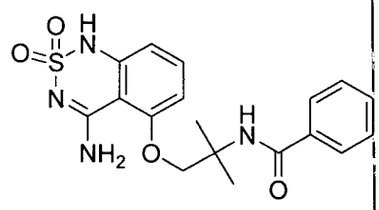
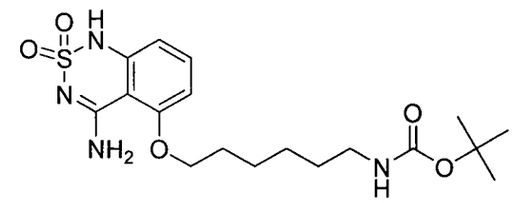
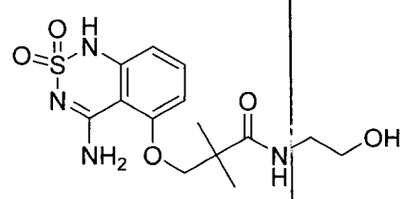
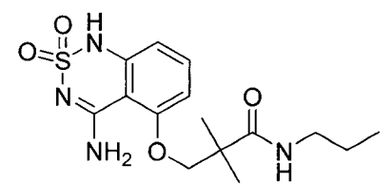
Y^1 es $-X^3-C(X^4)-X^5-$; y

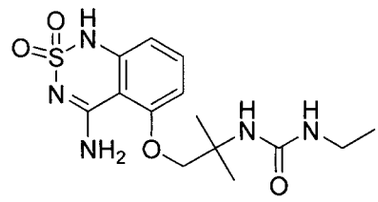
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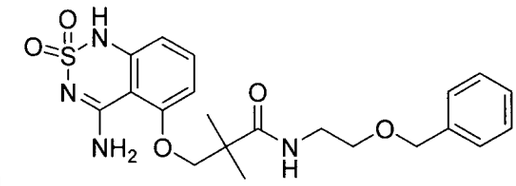
$-X^3-C(X^4)-X^5-$ es –C(O)-, -C(O)-NH-, -NH-C(O)-, -NH-C(O)-NH-, -C(O)-O-,

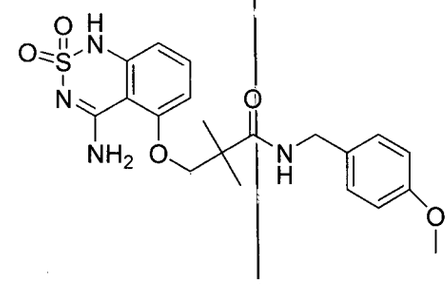
-O-C(O)-, -O-C(O)-O-, -NH-C(O)-O-, -O-C(O)-NH-, –C(NH)-, -C(NH)-NH-, -NH-C(NH)-, -NH-C(NH)-NH-, -C(NH)-O-, -O-C(NH)-, -O-C(NH)-O-, -NH-C(NH)-O-, -O-C(NH)-NH-, $-S(O)_2-$, $-NH-S(O)_2-$, $-S(O)_2-NH-$, $-O-S(O)_2-$, $-S(O)_2-O-$, -C(N-OH)-, o -C(S)-.

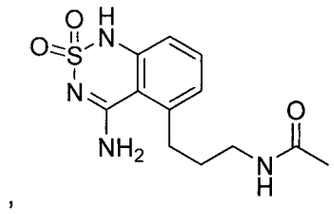
156. El compuesto de la reivindicación 138, que tiene la Fórmula estructural seleccionada del grupo integrado por

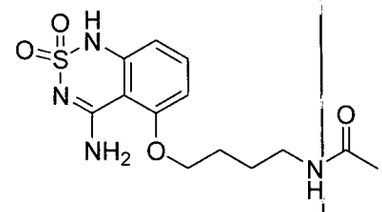

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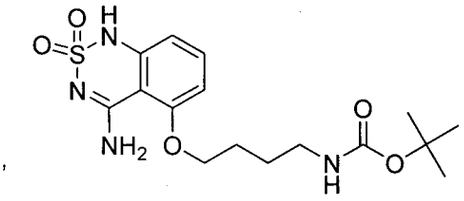


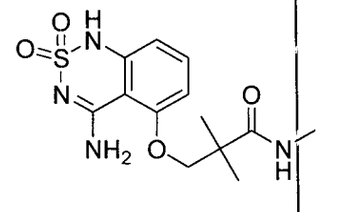


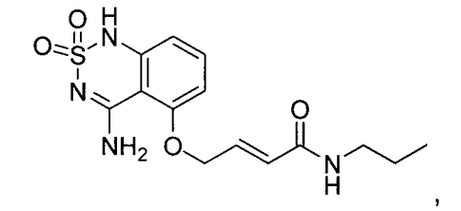


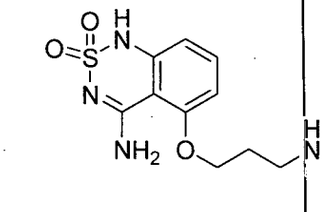


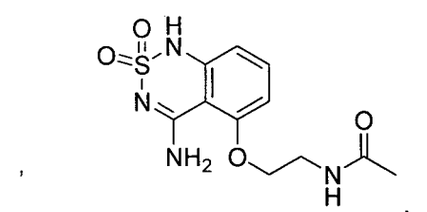


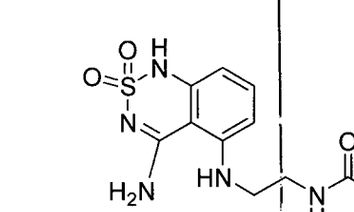


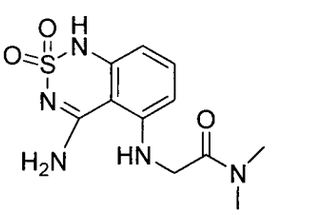


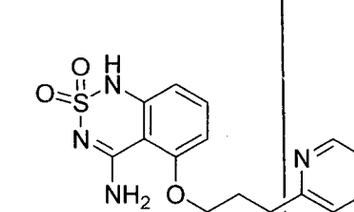


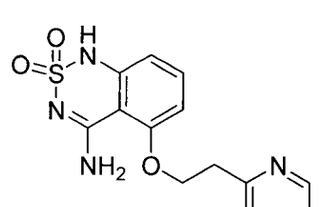


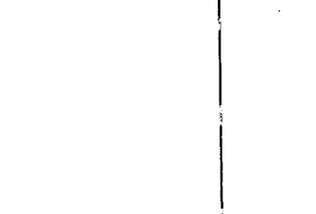




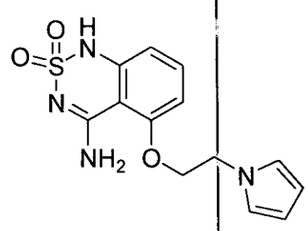


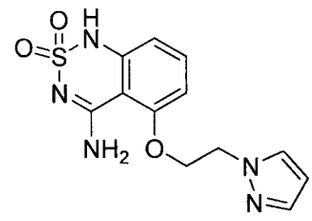


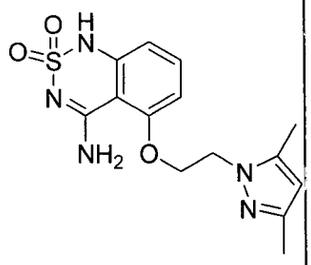


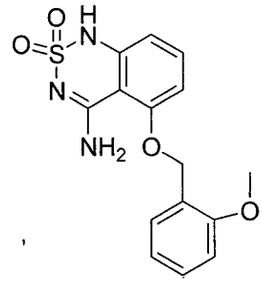


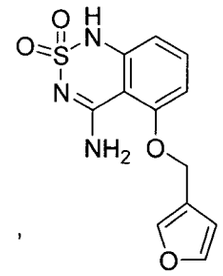
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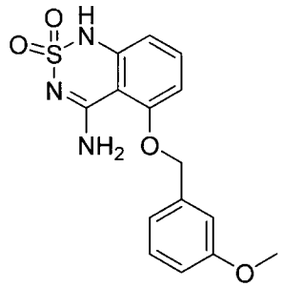


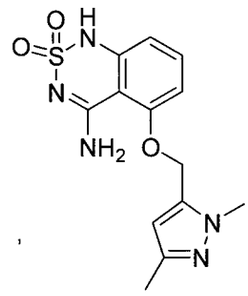


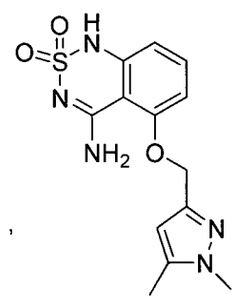


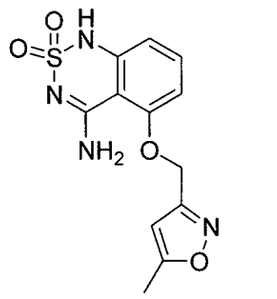


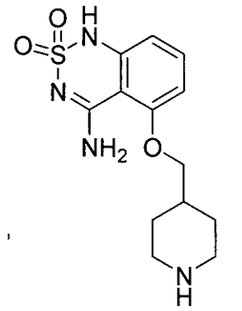


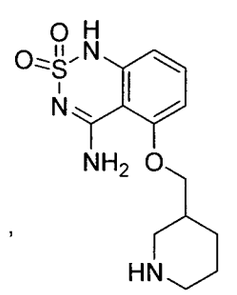


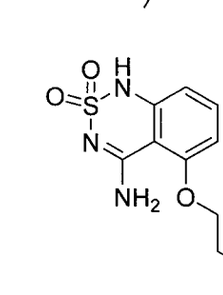


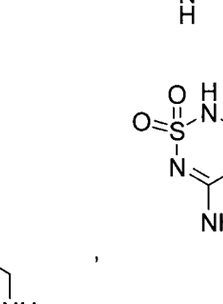


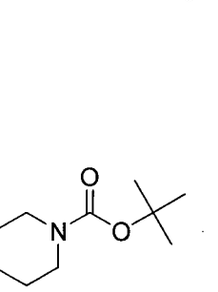


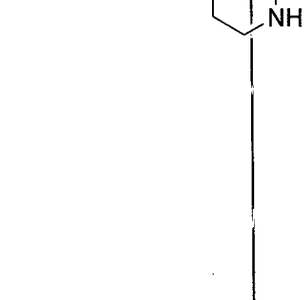




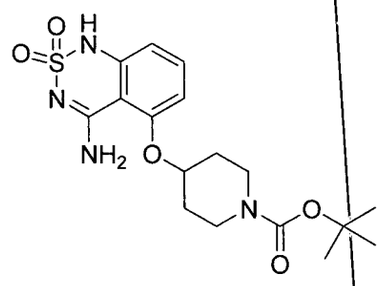


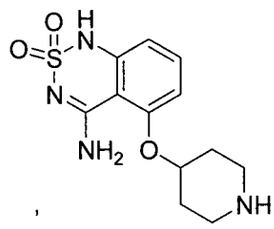


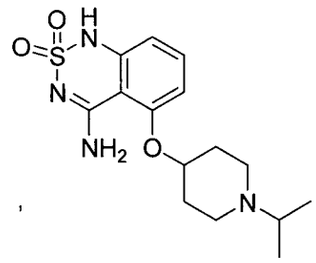


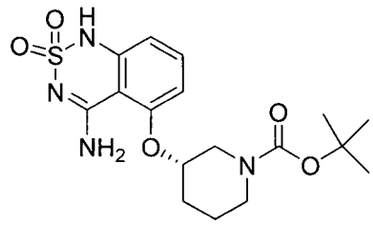


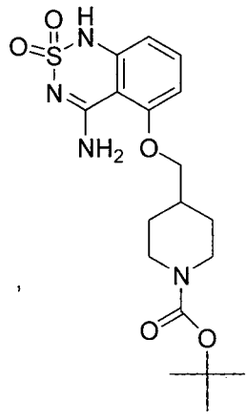
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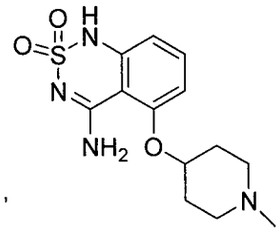


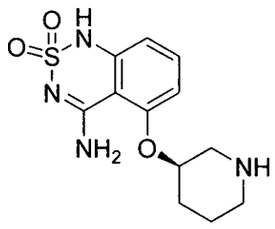


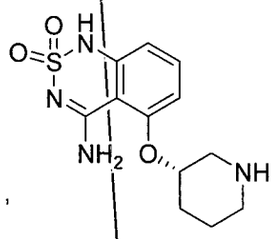


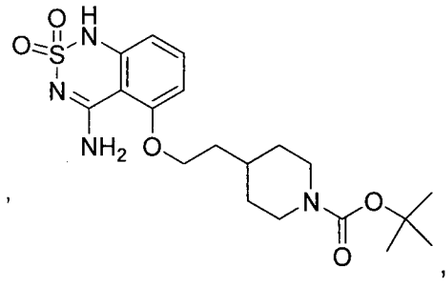


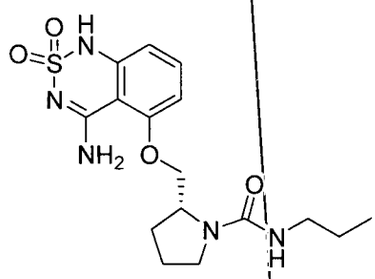


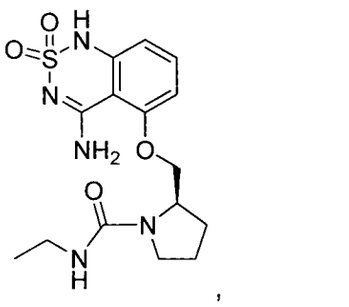


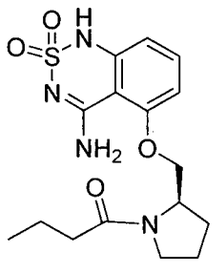


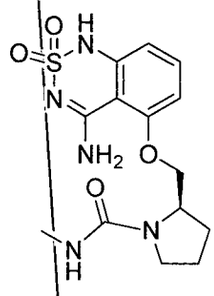


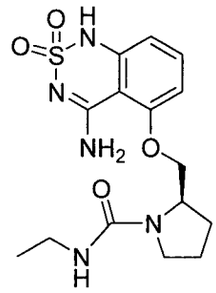


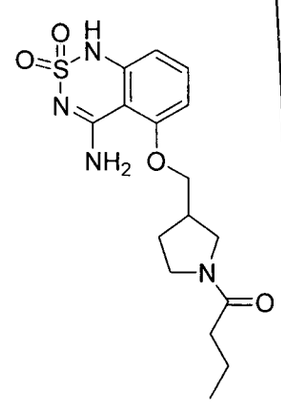


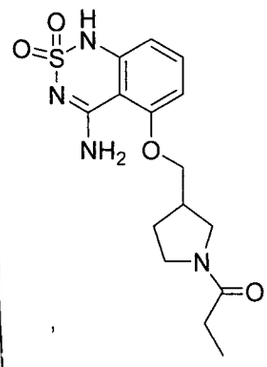


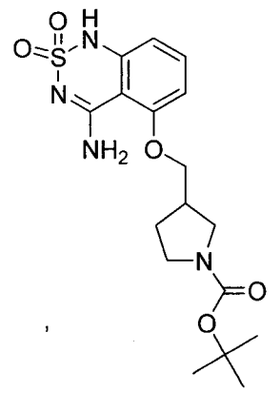


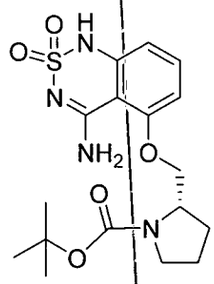


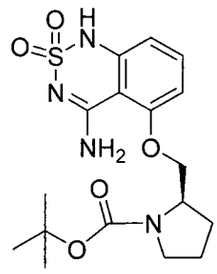


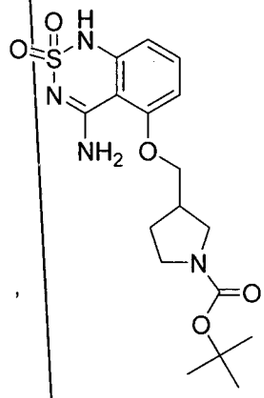


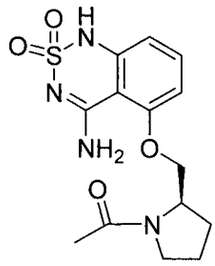


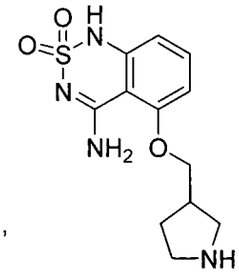


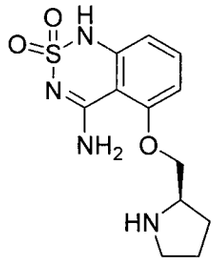


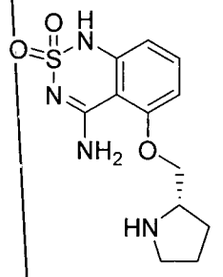




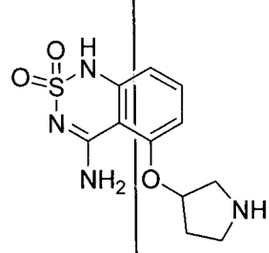


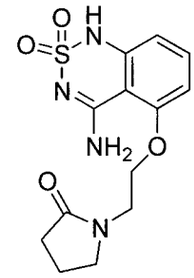


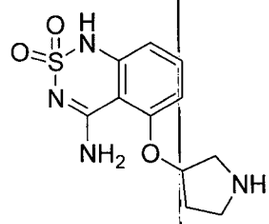


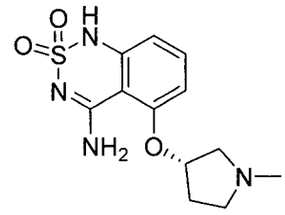


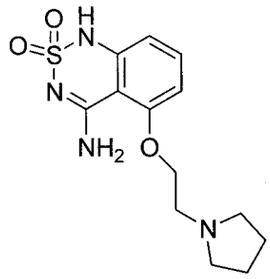
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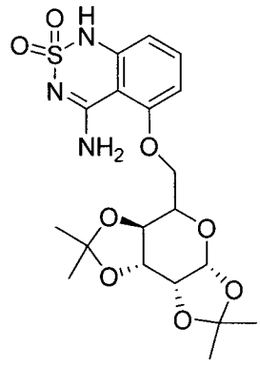


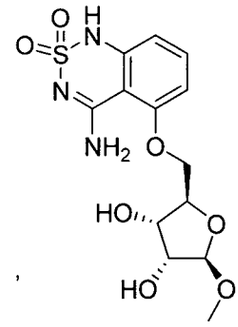


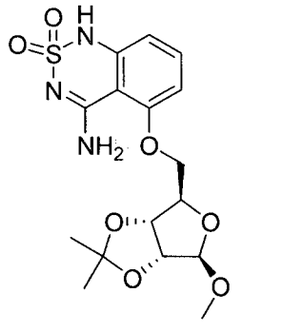


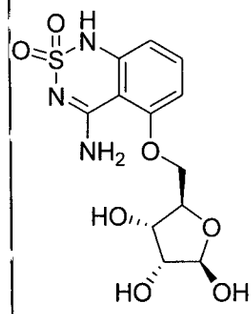


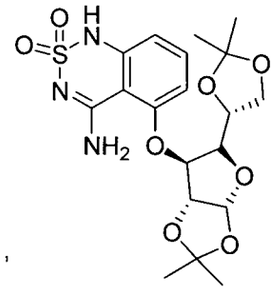


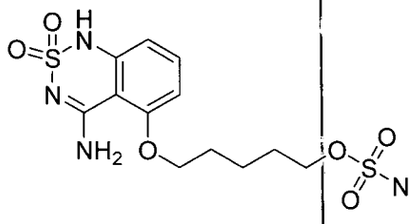


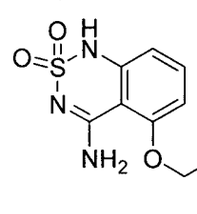




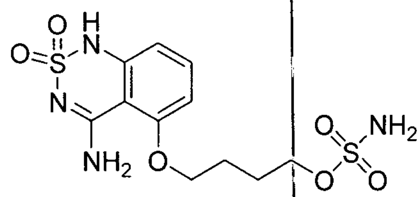
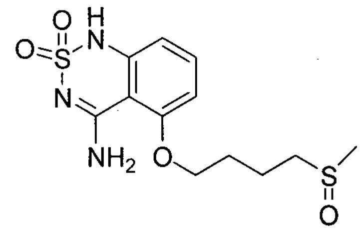
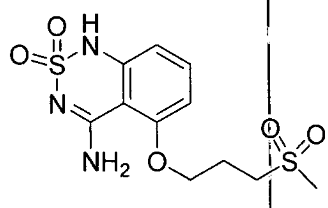
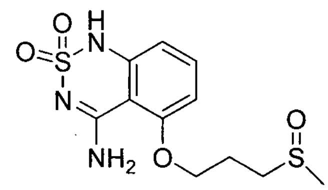
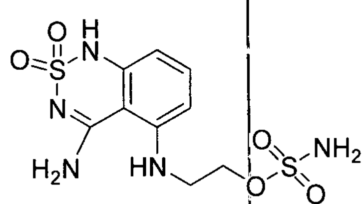
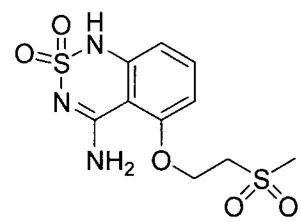
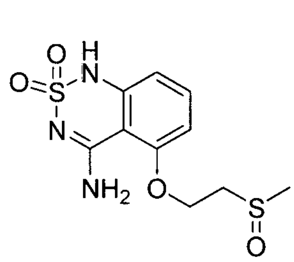
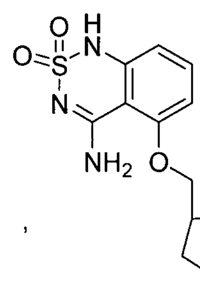
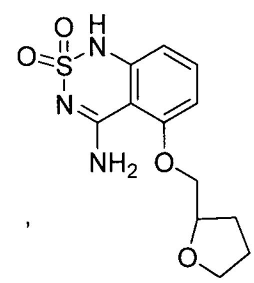
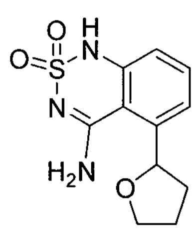
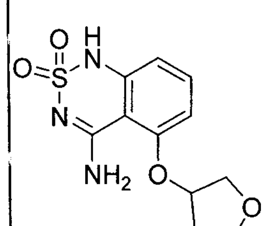
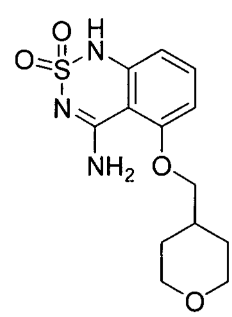
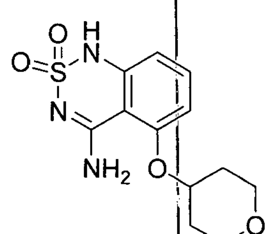
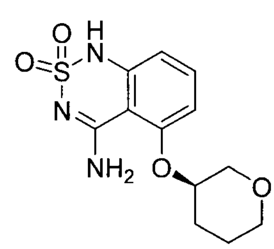




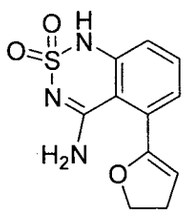


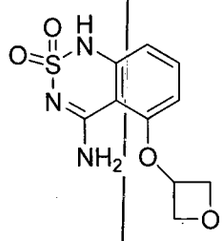


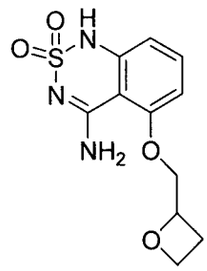
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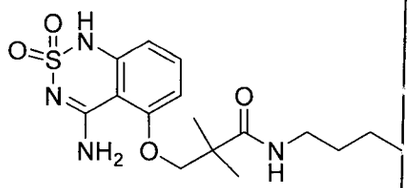
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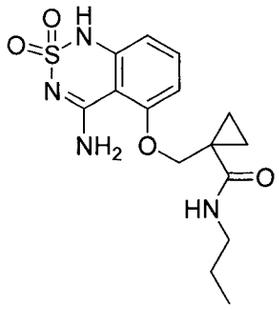
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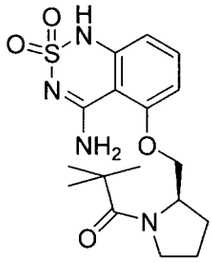


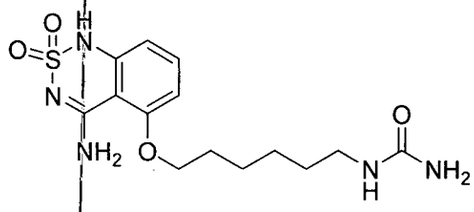


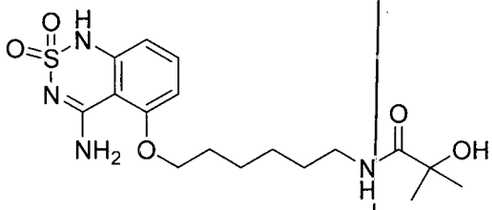


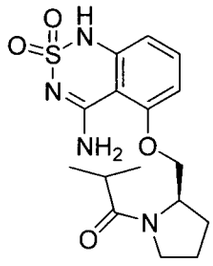


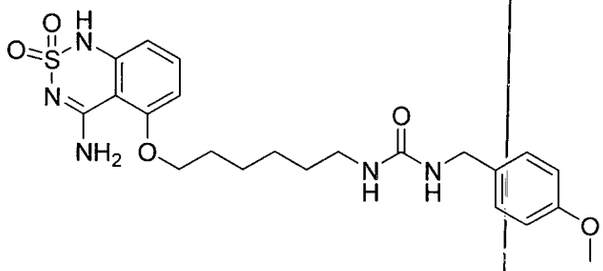


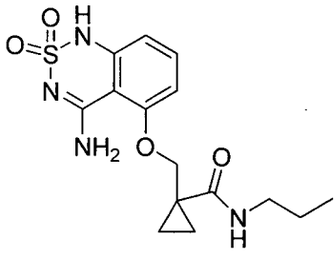


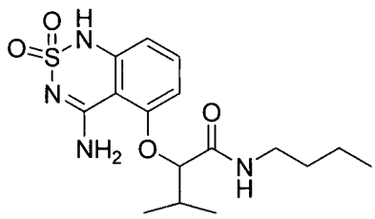


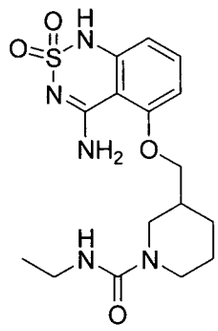


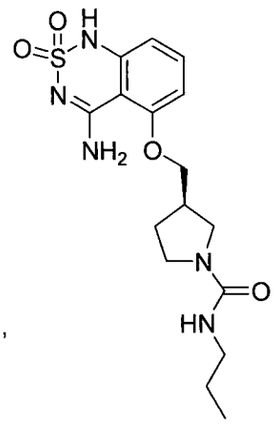


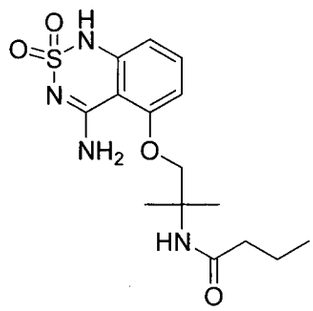


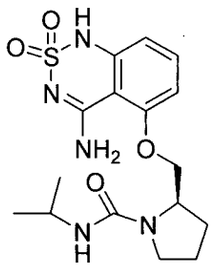


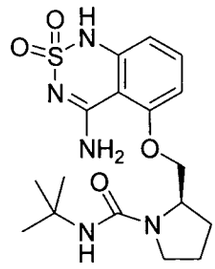


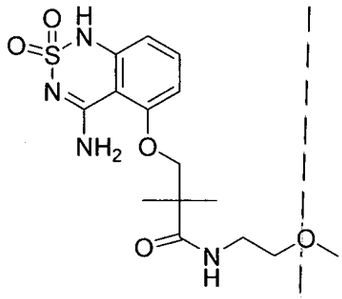


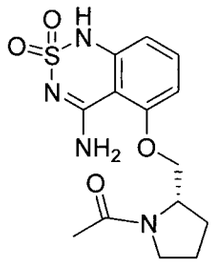


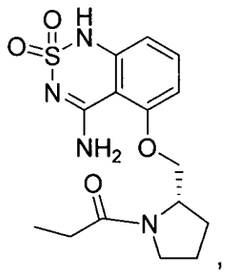


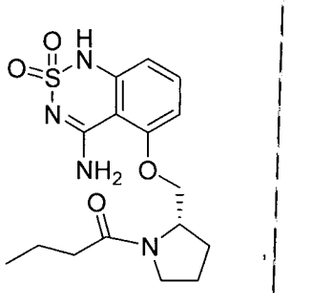


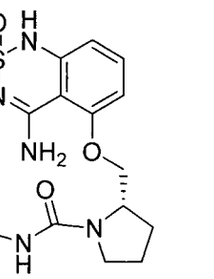


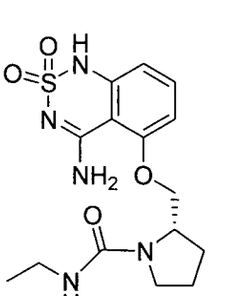




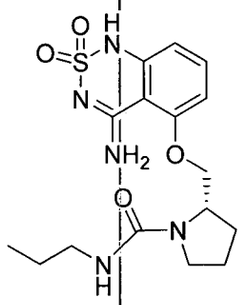




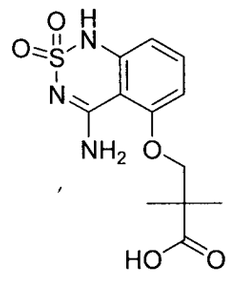




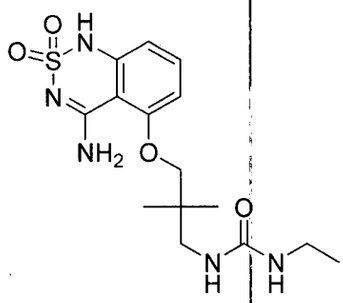
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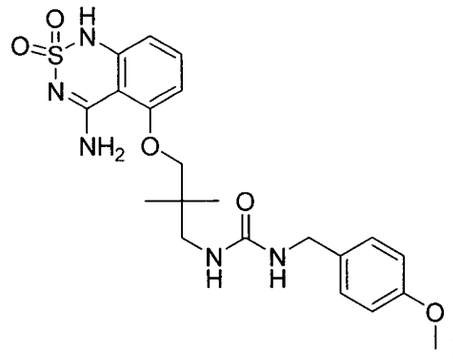
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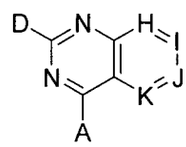


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o un tautómero, sal, solvato, y/o éster del mismo.

157. El compuesto de la reivindicación 156, en donde la sal es una sal clorhidrato o trifluoracetato.

158. El compuesto de la reivindicación 97, que tiene la fórmula estructural (IIIc)



(IIIc)

en donde:

D es halo, $-OR^{15}$, $-NH-OR^{15}$, $-NH-NHR^{15}$, $-S(O)_eR^{15}$, o $-NR^{15}R^{16}$.

159. El compuesto de la reivindicación 158, en donde

R^{35}, R^{36}, R^{37}, y R^{38} son independientemente hidrógeno, alquilo, o alquilo sustituido.

160. El compuesto de la reivindicación 159, en donde

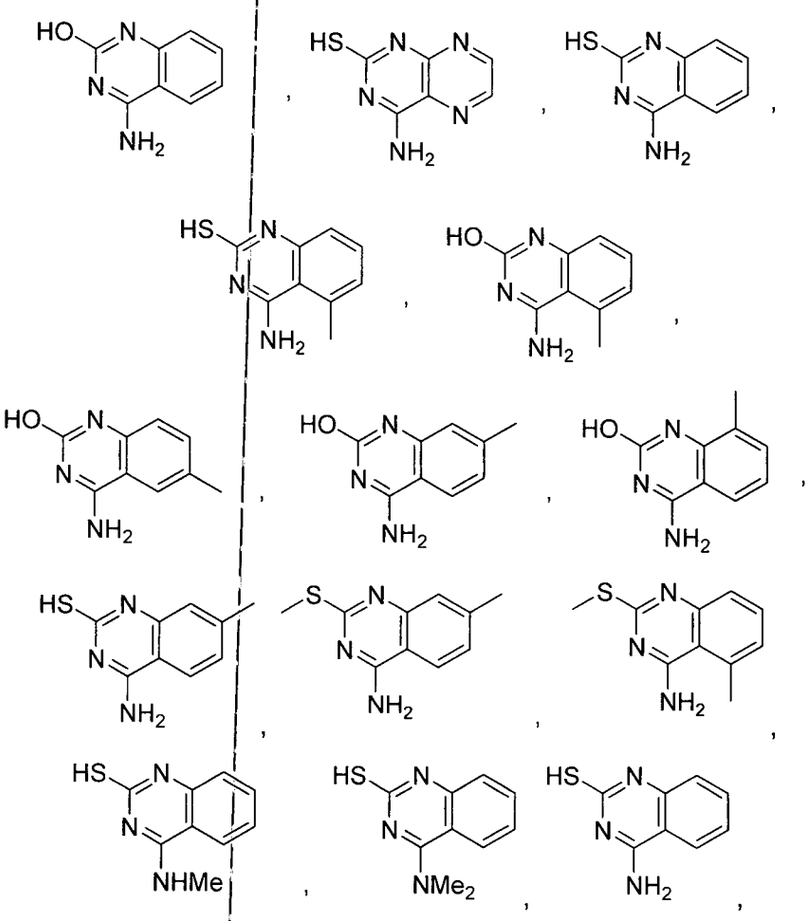
H es -C(R^{35})-;

I es -C(R^{36});

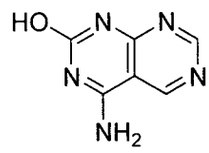
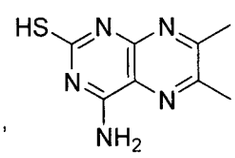
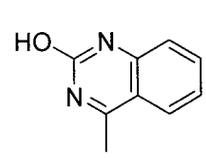
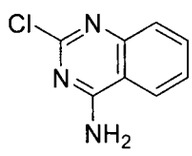
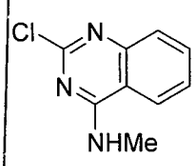
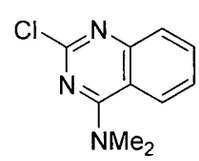
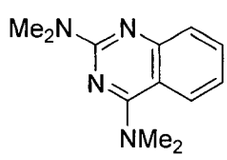
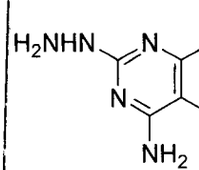
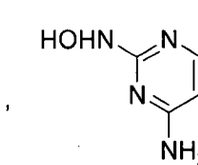
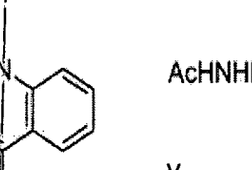
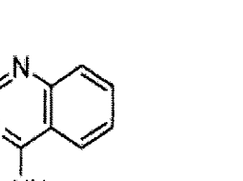
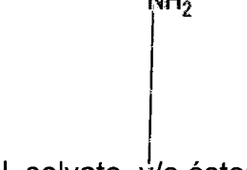
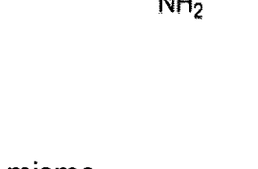
J es -C(R^{37})-; y

K es -C(R^{38})-.

161. El compuesto de la reivindicación 158, que tiene la fórmula estructural seleccionada del grupo integrado por



1099

, y

;

o un tautómero, sal, solvato, y/o éster del mismo.

162. El compuesto de la reivindicación 161, en donde la sal es la sal clorhidrato o trifluoracetato.

163. El compuesto de la reivindicación 97, que tiene la Fórmula estructural (XI):

(XI)

en donde,

R^{12} es hidrógeno, -OH, -SH, -CN, $-CH_2OH$ o $-CO_2H$;

D es -OH o -SH; y

A es -OH, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, o $-CH_2NHC(O)CH_3$;

siempre que cuando R^{12} sea hidrógeno, entonces R^{35}, R^{36}, R^{37}, y R^{38} no sean hidrógeno.

164. El compuesto de la reivindicación 163, en donde

R^{12} es -OH, -SH, -CN, $-CH_2OH$ o $-CO_2H$; y

A es $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, o $-CH_2NHC(O)CH_3$.

165. El compuesto de la reivindicación 164, en donde

cuando R^{36}, R^{37}, R^{38} y R^{35} son hidrógeno, D es –OH, y A es $-CO_2H$; entonces R^{12} no es $-CO_2H$ u -OH;

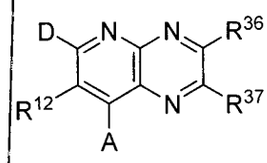
cuando R^{36}, R^{37}, R^{38} y R^{35} son hidrógeno, D es –OH, y A es $–NH_2$; entonces R^{12} no es $-CO_2H$ o CN;

cuando R^{36}, R^{38} y R^{35} son hidrógeno, R^{37} es -OMe, D es –OH, y A es $-CH_2OH$; entonces R^{12} no es $-CH_2OH$; y

cuando R^{36}, R^{38} y R^{35} son hidrógeno, R^{37} es hidrógeno o metilo, D es –OH, y A es $–CO_2H$; entonces R^{12} no es -SH.

166. El compuesto de la reivindicación 97, que tiene la Fórmula estructural (XII):

1101



(XII)

en donde

R^{12} es hidrógeno, -OH, -SH, -CN, $-CH_2OH$ o $-CO_2H$;

D es -SH u –OH;

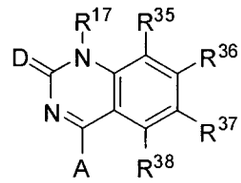
A es -OH, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, o $-CH_2NHC(O)CH_3$;

R^{36} es hidrógeno, $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, $-CH_3$, $-C_2H_5$, $-CH(CH_3)_2$, $-CH_2OH$, $-CH_2OCH_3$, -CN, $-C(O)NR^{41}R^{42}$, $-CO_2R^{41}$, $-SO_2NR^{39}R^{40}$, $-NR^{39}SO_2R^{40}$, $-B(OR^{39})(OR^{40})$, $-P(O)(OR^{39})(OR^{40})$ o $-P(O)(R^{39})(OR^{40})$; y

R^{37} es hidrógeno, $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, $-CH_3$, $-C_2H_5$, $-CH(CH_3)_2$, $-CH_2OH$, $-CH_2OCH_3$, -CN, $-C(O)NR^{43}R^{44}$, $-CO_2R^{43}$, $-SO_2NR^{43}R^{44}$, $-NR^{43}SO_2R^{44}$, $-B(OR^{43})(OR^{44})$, $-P(O)(OR^{43})(OR^{44})$ o $-P(O)(R^{43})(OR^{44})$.

167. El modificador del ligando de la reivindicación 166, en donde R^{12} es -OH, -SH, -CN, $-CH_2OH$ o $-CO_2H$.

168. El compuesto de la reivindicación 97, que tiene la Fórmula estructural (XIII):



(XIII)

en donde:

D es =O o =S;

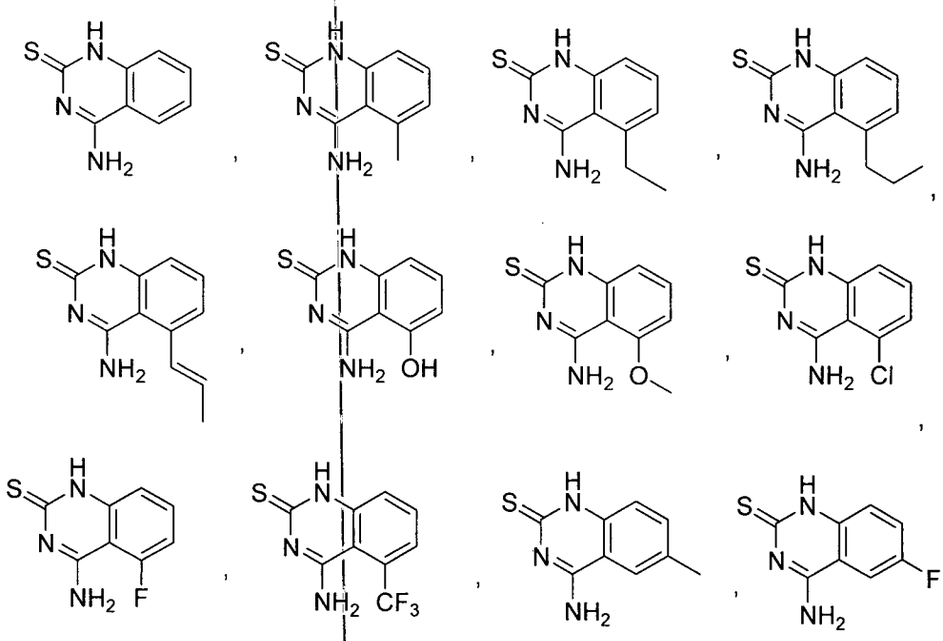
A es -OH, NH_2, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, o $-CH_2NHC(O)CH_3$;

R^{17} es hidrógeno, alquilo, arilo, arilalquilo.

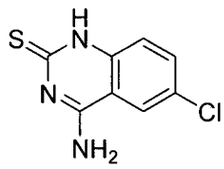
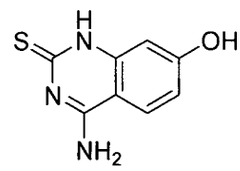
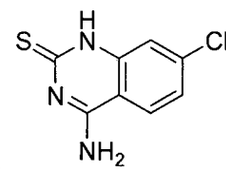
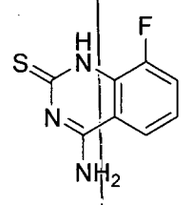
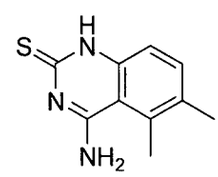
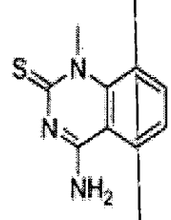
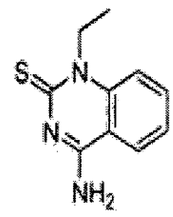
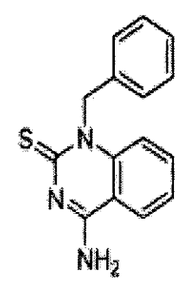
169. El compuesto de la reivindicación 168, en donde

cuando A es $-NH_2$, y R^{35}, R^{36}, R^{37} y R^{38} son hidrógeno; entonces R^{17} no es metilo, etilo o fenilo.

170. El compuesto de la reivindicación 168, que tiene la fórmula estructural seleccionada del grupo integrado por



1103

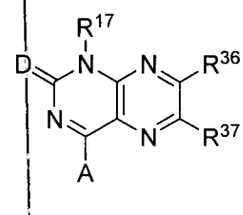









;

o un tautómero, sal, solvato, y/o éster del mismo.

171. El compuesto de la reivindicación 170, en donde la sal es la sal clorhidrato o trifluoracetato.

172. El compuesto de la reivindicación 97, que tiene la Fórmula estructural (XIV):



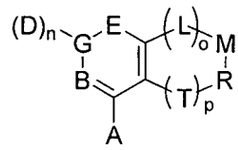
(XIV),

en donde:

A es -OH, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, o $-CH_2NHC(O)CH_3$;

R^{17} es alquilo, arilo, o arilalquilo.

173. El compuesto de la reivindicación 56, que tiene la Fórmula estructural (IV):



(IV)

en donde:

L es $-CHR^{60}-$, $-NR^{47}$, -O- o -S-;

M es $-CHR^{61}-$, $-NR^{48}$, -O- o -S-;

R es $-CHR^{62}-$, $-NR^{49}$, -O- o -S-;

T es $-CHR^{63}-$, $-NR^{50}$, -O- o -S-;

o y p son independientemente 0, 1, o 2;

R^{60} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido, -CN, $-NO_2$, $-OR^{64}$, $-S(O)_tR^{64}$, $-OCOR^{64}$, $-NR^{64}COR^{65}$, $-NR^{64}R^{65}$, $-CONR^{64}R^{65}$, $-CO_2R^{64}$, $-SO_2NR^{64}R^{65}$, $-NR^{64}SO_2R^{65}$, $-B(OR^{64})(OR^{65})$, $-P(O)(OR^{64})(OR^{65})$ o $-P(O)(R^{64})(OR^{65})$;

R^{61} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido, -CN, $-NO_2$, $-OR^{66}$, $-S(O)_uR^{66}$, $-OCOR^{66}$, $-NR^{66}COR^{67}$, $-NR^{66}R^{67}$, $-CONR^{66}R^{67}$,

$-CO_2R^{66}$, $-SO_2NR^{66}R^{67}$, $-NR^{66}SO_2R^{67}$, $-B(OR^{66})(OR^{67})$, $-P(O)(OR^{66})(OR^{67})$ o $-P(O)(R^{66})(OR^{67})$;

R^{62} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido, -CN, $-NO_2$, $-OR^{68}$, $-S(O)_vR^{68}$, $-OCOR^{68}$, $-NR^{68}COR^{69}$, $-NR^{68}R^{69}$, $-CONR^{68}R^{69}$, $-CO_2R^{68}$, $-SO_2NR^{68}R^{69}$, $-NR^{68}SO_2R^{69}$, $-B(OR^{68})(OR^{69})$, $-P(O)(OR^{68})(OR^{69})$ o $-P(O)(R^{68})(OR^{69})$;

R^{63} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido, -CN, $-NO_2$, $-OR^{70}$, $-S(O)_xR^{70}$, $-OCOR^{70}$, $-NR^{70}COR^{71}$, $-NR^{70}R^{71}$, $-CONR^{70}R^{71}$, $-CO_2R^{70}$, $-SO_2NR^{70}R^{71}$, $-NR^{70}SO_2R^{71}$, $-B(OR^{70})(OR^{71})$, $-P(O)(OR^{70})(OR^{71})$ o $-P(O)(R^{70})(OR^{71})$; o alternativamente R^{60} y R^{61}, R^{61} y R^{62}, o R^{62} y R^{63} conjuntamente con los átomos a los cuales ellos están unidos forman un anillo arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloheteroalquilo o cicloheteroalquilo sustituido;

t, u, v y x son independientemente 0, 1 o 2;

R^{64} a R^{71} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido o alternativamente R^{64} y R^{65}, R^{66} y R^{67}, R^{68} y R^{69}, o R^{70} y R^{71} conjuntamente con los átomos a los cuales ellos están unidos forman un anillo cicloheteroalquilo o cicloheteroalquilo sustituido; y

R^{47} a R^{50} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido,

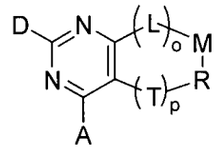
heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido;

con la condición de que a lo sumo solamente uno de L, M, R y T sea un heteroátomo.

174. El compuesto de la reivindicación 173, en donde B es -N-, y E es $-NR^{17}-$ o -N-.

175. El compuesto de la reivindicación 174, en donde G es -C-.

176. El compuesto de la reivindicación 175, que tiene la Fórmula estructural (XV):



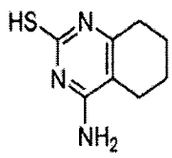
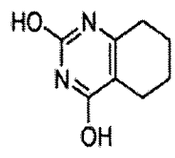
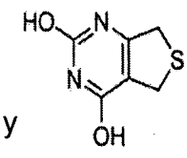
XV

en donde:

D es -SH u –OH; y

A es -OH, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, o $-CH_2NHC(O)CH_3$.

177. El compuesto de la reivindicación 176, que tiene la fórmula estructural seleccionada del grupo integrado por



, y

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o un tautómero, sal, solvato, y/o éster del mismo.

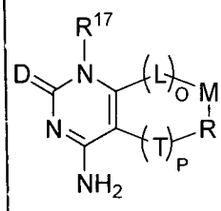
178. El compuesto de la reivindicación 177, en donde la sal es la sal clorhidrato o trifluoracetato.

179. El compuesto de la reivindicación 174, en donde

A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, $-OR^9$, $-SR^9$, $-CN$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-CO_2R^9$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{11}$, $-NR^9CSNR^{10}R^{11}$ o $-NR^9C(=NH)NR^{10}R^{11}$; y

D es =O, =S , $=N-OR^{15}$.

180. El compuesto de la reivindicación 174, que tiene la Fórmula estructural (IVb):

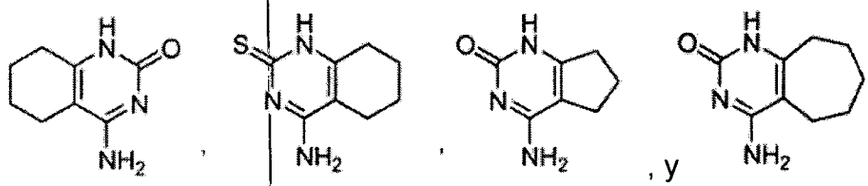

(IVb),

en donde,

L es $-CHR^{60}-$; M es $-CHR^{61}-$; R es $-CHR^{62}-$; T es $-CHR^{63}-$.

181. El compuesto de la reivindicación 180, que tiene la fórmula estructural seleccionada del grupo integrado por:

1108

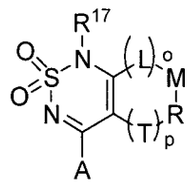


;

o un tautómero, sal, solvato, y/o éster del mismo.

182. El compuesto de la reivindicación 181, en donde la sal es la sal clorhidrato o trifluoracetato.

183. El compuesto de la reivindicación 173, que tiene la Fórmula estructural (IVa):



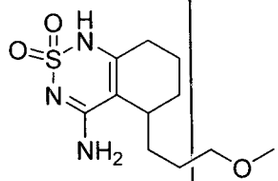
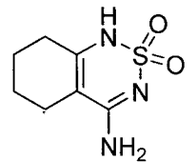
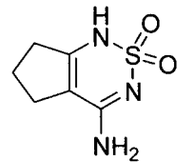
(IVa).

184. El compuesto de la reivindicación 183, en donde L es -CHR^{60}-; M es -CHR^{61}-; R es -CHR^{62}-; y T es -CHR^{63}-.

185. El compuesto de la reivindicación 184, en donde A es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, -OR^9, -SR^9, -CN, -NR^9R^{10}, -$CONR^9R^{10}$, -CO_2R^9, -$NR^9CO_2R^{10}$, -$NR^9CONR^{10}R^{11}$, -$NR^9CSNR^{10}R^{11}$ o -$NR^9C(=NH)NR^{10}R^{11}$.

186. El compuesto de la reivindicación 183, que tiene la fórmula estructural seleccionada del grupo integrado por:

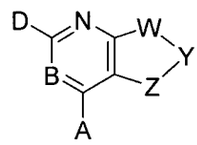
1109

o un tautómero, sal, solvato, y/o éster del mismo.

187. El compuesto de la reivindicación 186, en donde la sal es la sal clorhidrato o trifluoracetato.

188. El compuesto de la reivindicación 58, que tiene la Fórmula estructural (Va):



(Va)

en donde:

D es hidrógeno, alquilo, arilo, halo, -OH, $-NH_2$, $-SR^{15}$, $-CH_3$, $-CO_2H$ o $-CONH_2$;

A es $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHC(NH)NH_2$, -CN, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, o $-CH_2NHC(O)CH_3$; y

R^{15} es hidrógeno, alquilo, alquilo sustituido, arilalquilo.

189. El compuesto de la reivindicación 188, en donde

Y forma un enlace único con W y un enlace doble con Z;

W es $-C(R^{24})-$ o –N-;

Y es $–C(R^{26})-$ o –N-; y

Z es –S-, $-N(R^{28})$, u –O-.

1110

190. El compuesto de la reivindicación 188, en donde

Y forma un enlace doble con W y un enlace único con Z;

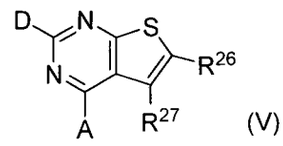
W es –S-, -N(R^{25}), u –O-

Y es –C(R^{26})- o –N-; y

Z es -C(R^{27})- o –N-.

191. El compuesto de la reivindicación 189 or 190, en donde B es –C(R^{12})-.

192. El compuesto de la reivindicación 188, que tiene la Fórmula estructural (V):



(V)

en donde:

R^{26} es hidrógeno, alquilo, halo, -CO_2R^{54}, -$CONR^{54}R^{55}$, -$SO_2NR^{54}R^{55}$, -$NR^{54}SO_2R^{55}$, -$B(OR^{54})(OR^{55})$, -$P(O)(OR^{54})(OR^{55})$ or -$P(O)(R^{54})(OR^{55})$;

R^{27} es hidrógeno, alcoxi, alquilo, alquilo sustituido, halo, -CN, -$C(O)NR^{56}R^{57}$, -CO_2R^{56}, -$SO_2NR^{56}R^{57}$, -$NR^{56}SO_2R^{57}$, -$B(OR^{56})(OR^{57})$, -$P(O)(OR^{56})(OR^{57})$ or -$P(O)(R^{56})(OR^{57})$; o alternativamente R^{52} and R^{53} conjuntamente con los átomos a los cuales ellos están unidos forman un anillo cicloheteroalquilo o cicloheteroalquilo sustituido ring and

R^{54}, R^{55}, R^{56}, and R^{57} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido; o alternativamente R^{54} and R^{55} or R^{56} and R^{57} conjuntamente con los átomos a los cuales ellos están

unidos forman un anillo cicloheteroalquilo o cicloheteroalquilo sustituido ring;

siempre que cuando R^{26} and R^{27} are hidrógeno, and D is –SH; then A is $-NH_2$.

193. El compuesto de la reivindicación 192, en donde

cuando D es metilo, A es dimetilamino, y R^{53} es hidrógeno; entonces R^{52} no es metilo, etilo o carboxilo;

cuando D es metilo, A es dimetilamino, y R^{53} es metilo; entonces R^{52} no es metilo;

cuando D es $-SCH_3$, A es dimetilamino, y R^{53} es hidrógeno; entonces R^{52} no es carboetoxi;

cuando D es hidrógeno, A es dimetilamino, y R^{53} es hidrógeno; entonces R^{52} no es carboxilo o carboetoxi;

cuando D es hidrógeno, A es dimetilamino y R^{53} es metilo; entonces R^{52} no es metilo;

cuando D es hidrógeno, A es metilamino y R^{53} es hidrógeno; entonces R^{52} no es metilo, etilo o carboetoxi;

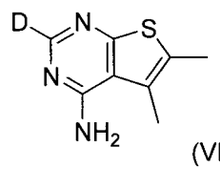
cuando D es hidrógeno, A es metilamino y R^{53} es metilo; entonces R^{52} no es metilo o carboetoxi;

cuando D es hidrógeno, A es metilamino y R^{53} es $-CH_2NMe$; entonces R^{52} no es metilo o carboetoxi;

cuando D es fenilo, A es metilamino y R^{53} es hidrógeno entonces R^{52} no es metilo; y

cuando D es fenilo, A es $-NH(CO)CH_3$ y R^{53} es metilo entonces R^{52} no es carbometoxi.

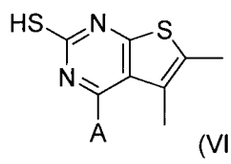
194. El modificador del ligando de la reivindicación 192, que tiene la fórmula estructural (VI):



(VI),

en donde D es hidrógeno, $-CH_3$, $-C_2H_5$, fenilo o bencilo.

195. El compuesto de la reivindicación 192, que tiene la fórmula estructural (VII):



(VII),

en donde A es hidrógeno, $-CH_3$, $-C_2H_5$, fenilo o bencilo.

196. El compuesto de la reivindicación 192, que tiene la fórmula estructural (VIII):

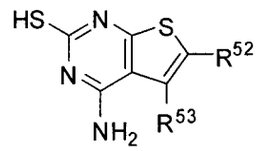


(VIII)

en donde

R^9 y R^{10} son independientemente hidrógeno, $-CH_3$, $-C_2H_5$, fenilo o bencilo; y siempre que ambos R^9 y R^{10} no sean hidrógeno.

197. El compuesto de la reivindicación 192, que tiene la fórmula estructural (IX):



(IX)

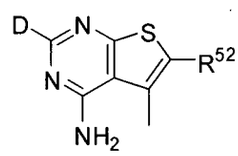
en donde

R^{52} es alquilo, alquilo sustituido, -CN, $-C(O)NR^{54}R^{55}$, $-CO_2R^{54}$, $-SO_2NR^{54}R^{55}$, $-NR^{54}SO_2R^{55}$, $-B(OR^{54})(OR^{55})$, $-P(O)(OR^{54})(OR^{55})$, o $-P(O)(R^{54})(OR^{55})$;

R^{53} es alquilo, CO_2R^{56} o $-CONR^{56}R^{57}$, $-SO_2NR^{56}R^{57}$, $-NR^{56}SO_2R^{57}$, $-B(OR^{56})(OR^{57})$, $-P(O)(OR^{56})(OR^{57})$ o $-P(O)(R^{56})(OR^{57})$; y

R^{54} a R^{57} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido; o alternativamente R^{52} y R^{53} conjuntamente con los átomos a los cuales ellos están unidos forman un anillo cicloheteroalquilo o cicloheteroalquilo sustituido.

198. El compuesto de la reivindicación 192, que tiene la fórmula estructural (X):



(X)

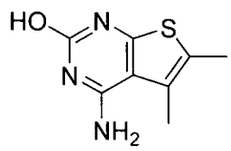
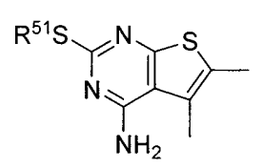
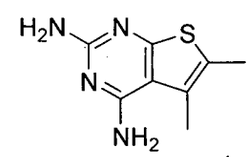
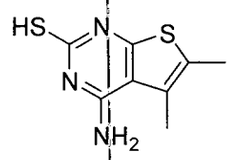
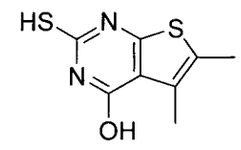
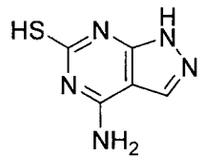
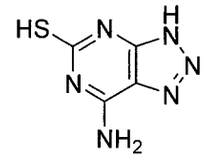
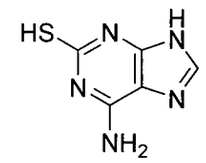
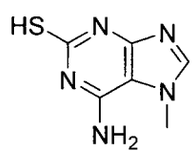
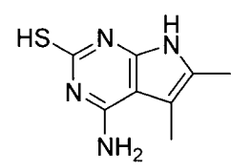
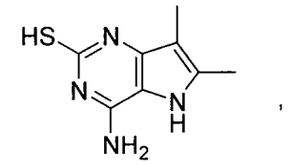
en donde,

D es -OH, -SH o $-NH_2$,

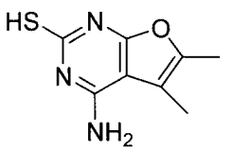
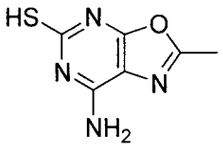
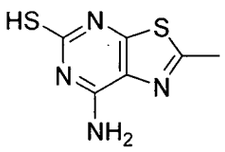
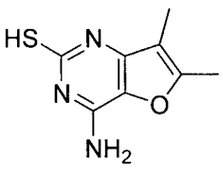
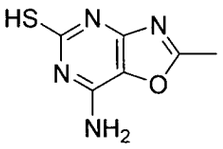
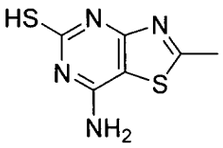
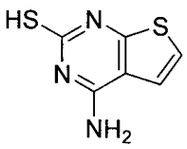
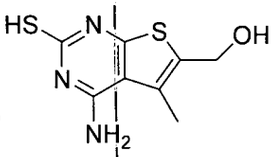
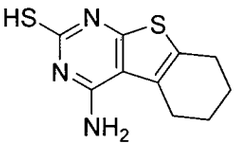
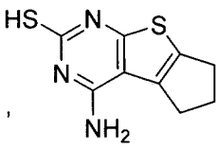
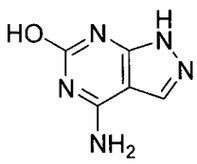
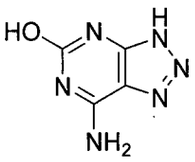
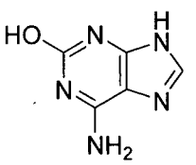
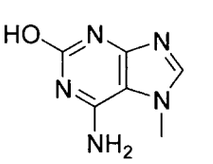
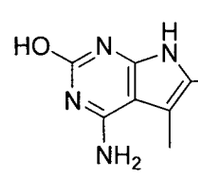
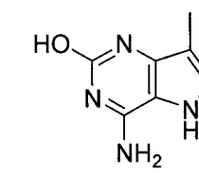
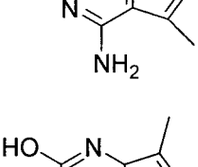
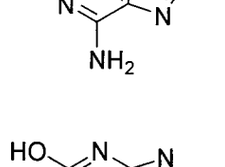
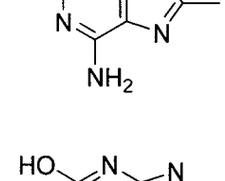
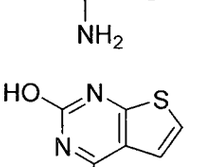
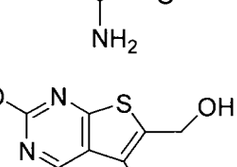
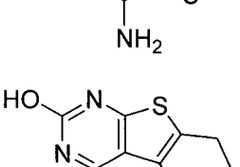
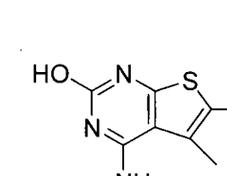
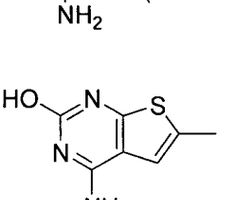
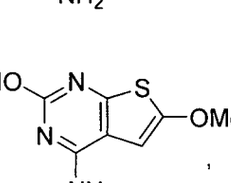
R^{52} es alquilo, alquilo sustituido, alcoxi, -CN, $-C(O)NR^{54}R^{55}$, $-CO_2R^{54}$, $-SO_2NR^{54}R^{55}$, $-NR^{54}SO_2R^{55}$, $-B(OR^{54})(OR^{55})$, $-P(O)(OR^{54})(OR^{55})$, $-P(O)(R^{54})(OR^{55})$, y

R^{54} y R^{55} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido; o alternativamente R^{54} y R^{55} conjuntamente con los átomos a los cuales ellos están unidos forman un anillo cicloheteroalquilo o cicloheteroalquilo sustituido.

199. El compuesto de la reivindicación 188, que tiene la fórmula estructural seleccionada del grupo integrado por


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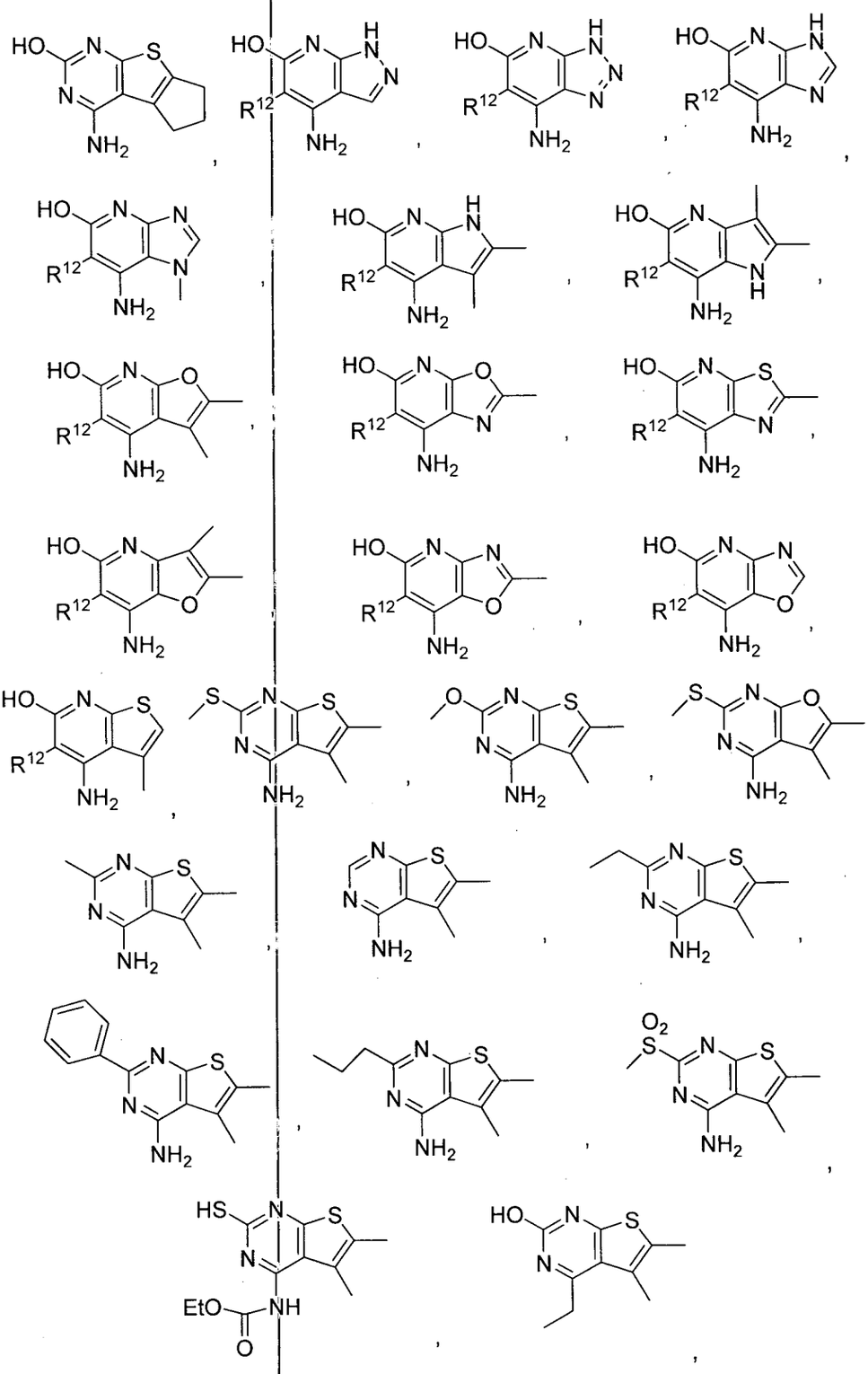
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en donde,

R^{12} es –OH, -SH, -CN, $-CH_2OH$, o $-CO_2H$; y

R^{51} es $-CH_3$, $-CH_2CH_3$, bencilo, o $-CH_2CO_2CH_2CH_3$;

o un tautómero, sal, solvato, y/o éster del mismo.

200. El compuesto de la reivindicación 199, en donde la sal es la sal clorhidrato o trifluoracetato.

201. Una composición ingerible que comprende el modificador del ligando del receptor quimiosensorial de la reivindicación 52.

202. La composición ingerible de la reivindicación 201, seleccionada del grupo integrado por una composición comestible, una composición medicinal, una composición farmacéutica, y las combinaciones de las mismas.

203. La composición ingerible de la reivindicación 201, seleccionada del grupo integrado por producto alimenticio o de bebida, producto no comestible, y las combinaciones de los mismos.

204. La composición ingerible de la reivindicación 203, en donde el producto alimenticio o de bebida está seleccionados del grupo integrado por la categoría Sopas; la categoría Alimentos Procesados Secos; la categoría Bebidas; la categoría Comidas Preparadas; la categoría Alimentos Enlatados o Conservados; la categoría Alimentos Procesados Congelados; la categoría Alimentos Procesados Enfriados; la categoría Alimentos "Snack"; la categoría Productos Horneados; la categoría Golosinas; la categoría Productos Lácteos; la categoría Helados; la categoría Reemplazo de Comidas; la categoría Pastas y Fideos; la categoría Salsas, Aderezos, Condimentos; la categoría Alimentos para Bebés; la

categoría Alimentos para Untar; recubrimientos, garrapiñados, o glaseados dulces; y las combinaciones de los mismos.

205. La composición ingerible de la reivindicación 203, en donde el producto no comestible está seleccionado del grupo integrado por productos nutricionales y suplementos dietarios, farmacéuticos, medicaciones sin receta médica, productos de cuidado oral, y cosméticos.

206. La composición ingerible de la reivindicación 201, en donde el modificador del ligando del receptor quimiosensorial es un compuesto que tiene la Fórmula estructural (I) según de describió en la reivindicación 56, o un tautómero, sal, solvato, y/o éster del mismo.

207. La composición ingerible de la reivindicación 201, que comprende al menos aproximadamente 0,0001 ppm del modificador del ligando del receptor quimiosensorial.

208. La composición ingerible de la reivindicación 201, que comprende desde aproximadamente 0,0001 ppm hasta aproximadamente 10 ppm del modificador del ligando del receptor quimiosensorial.

209. La composición ingerible de la reivindicación 201, que comprende desde aproximadamente 0,01 ppm hasta aproximadamente 100 ppm del modificador del ligando del receptor quimiosensorial.

210. La composición ingerible de la reivindicación 201, que comprende desde aproximadamente 10 ppm hasta aproximadamente 100.000 ppm del modificador del ligando del receptor quimiosensorial.

211. La composición ingerible de la reivindicación 201, que comprende además uno o más edulcorantes.

212. La composición ingerible de la reivindicación 211, en donde el edulcorante está seleccionado del grupo integrado por sacarosa, fructosa, glucosa, galactosa, manosa, lactosa, tagatosa, maltos, jarabe de maíz (que incluye jarabe de maíz de alta fructosa), D-triptófano, glicina, eritritol, isomalt, lactitol, manitol, sorbitol, xilitol, maltodextrina, maltitol, isomalt, jarabe de glucosa hidrogenado (HGS), hidrolizado de almidón hidrogenado (HSH), esteviosida, rebaudiosida A, otros glucósidos dulces basados en Ste*via*, carrelame, otros edulcorantes basados en guanidina, sacarina, acesulfame-K, ciclamato, sucralosa, alitame, mogrosida, neotame, aspartame, otros derivados de aspartame, y las combinaciones de los mismos.

213. La composición ingerible de la reivindicación 206, en donde el modificador del ligando del receptor quimiosensorial es un compuesto que tiene la Fórmula estructural (II) según se describió en la reivindicación 58 o la Fórmula estructural (III) según se describió en la reivindicación 97, o un tautómero, sal, solvato, y/o éster del mismo.

214. La composición ingerible de la reivindicación 206, en donde el modificador del ligando del receptor quimiosensorial tiene la Fórmula estructural (IIa) según se describió en la reivindicación 60, la Fórmula estructural (IIc) según se describió en la reivindicación 73, la Fórmula estructural (IIIb) según se describió en la reivindicación 124, o la Fórmula estructural (IIIb1) según se describió en la reivindicación 133, o un tautómero, sal, solvato, y/o éster del mismo.

215. La composición ingerible de la reivindicación 202, en donde la composición farmacéutica comprende un compuesto que tiene la Fórmula estructural (I) según se describió en la reivindicación 56, o un tautómero, sal, solvato, y/o éster del mismo; y un vehículo farmacéuticamente aceptable.

216. Un método de mejoramiento del sabor dulce de una composición ingerible que comprende poner en contacto a la composición ingerible o a los precursores de la misma con un modificador del ligando del receptor quimiosensorial para formar una composición ingerible modificada.

217. El método de la reivindicación 216, en donde la composición ingerible está seleccionada del grupo integrado por una composición comestible, una composición medicinal, una composición farmacéutica, y las composiciones de las mismas.

218. El método de la reivindicación 216, en donde la composición ingerible está seleccionada del grupo integrado por productos alimenticios o de bebidas, productos no comestibles, y las combinaciones de los mismos.

219. El método de la reivindicación 216, en donde la composición ingerible modificada comprende al menos aproximadamente 0,001 ppm del modificador del ligando del receptor quimiosensorial.

220. El método de la reivindicación 216, en donde la composición ingerible modificada comprende desde aproximadamente 0,001 ppm hasta aproximadamente 100.000 ppm del modificador del ligando del receptor quimiosensorial.

221. El método de la reivindicación 216, en donde el modificador del ligando del receptor quimiosensorial es un compuesto que tiene la Fórmula estructural (I) según se describió en la reivindicación 56, o un tautómero, sal, solvato, y/o éster del mismo.

222. El método de la reivindicación 216, en donde el mejorador del ligando del receptor quimiosensorial es un compuesto que tiene la Fórmula estructural (II) según se describió en la reivindicación 58 o la Fórmula estructural (III) según se describió en la reivindicación 97, o un tautómero, sal, solvato, y/o éster del mismo.

223. El método de la reivindicación 216, en donde el mejorador del ligando del receptor quimiosensorial tiene la Fórmula estructural (IIa) según se describió en la reivindicación 60, la Fórmula estructural (IIc) según se describió en la reivindicación 73, la Fórmula estructural (IIIb) según se describió en la reivindicación 128, o la Fórmula estructural (IIIb1) según se describió en la reivindicación 138, o un tautómero, sal, solvato, y/o éster del mismo.

224. Un método para tratar una afección asociada con un receptor quimiosensorial que comprende administrar a un sujeto que necesita dicho tratamiento una cantidad efectiva de una entidad seleccionada del grupo integrado por un modificador del receptor quimiosensorial, un modificador del ligando del receptor quimiosensorial, y una combinación de los mismos, en donde la entidad interactúa con un sitio de interacción del receptor quimiosensorial.

225. El método de la reivindicación 224, en donde la afección asociada con un receptor quimiosensorial es el gusto.

226. El método de la reivindicación 224, en donde la afección asociada con un receptor quimiosensorial consiste en una afección asociada con el sistema gastrointestinal o con trastornos metabólicos.

227. El método de la reivindicación 224, en donde la afección asociada con un receptor quimiosensorial consiste en una afección asociada con un trastorno gastrointestinal funcional.

228. El método de la reivindicación 224, en donde la afección asociada con un receptor quimiosensorial consiste en una afección asociada con células que expresan un T1R.

229. El método de la reivindicación 224, en donde la afección asociada con un receptor quimiosensorial consiste en una afección asociada con células productoras de hormonas que expresan un T1R.

230. El método de la reivindicación 224, en donde la entidad consiste en un modificador del ligando del receptor quimiosensorial.

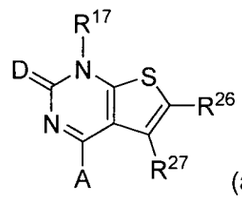
231. El método de la reivindicación 230, en donde el modificador del ligando del receptor quimiosensorial es un compuesto que tiene la Fórmula estructural (I) según se describió en la reivindicación 56, o un tautómero, sal, solvato, y/o éster del mismo.

232. El método de la reivindicación 230, en donde el modificador del ligando del receptor quimiosensorial es un compuesto que tiene la Fórmula estructural (II)

según se describió en la reivindicación 58 o la Fórmula estructural (III) según se describió en la reivindicación 97, o un tautómero, sal, solvato, y/o éster del mismo.

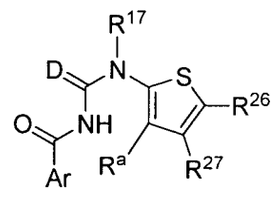
233. El método de la reivindicación 230, en donde el modificador del ligando del receptor quimiosensorial tiene la Fórmula estructural (IIa) según se describió en la reivindicación 60, la Fórmula estructural (IIc) según se describió en la reivindicación 73, la Fórmula estructural (IIIb) según se describió en la reivindicación 128, o la Fórmula estructural (IIIb1) según se describió en la reivindicación 138, o un tautómero, sal, solvato, y/o éster del mismo.

234. Un proceso para preparar un compuesto que tiene la Fórmula estructural (a):



(a),

que comprende hacer reaccionar un compuesto que tiene la Fórmula estructural (b)



(b)

con una base,

en donde:

D es oxígeno o azufre;

A es $-NH_2$ u $-OR^b$;

R^{17} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, o arilalquilo sustituido;

R^{26} y R^{27} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, heteroarilalquilo sustituido, -CN, $-NO_2$, $-OR^{31}$, $-S(O)_hR^{31}$, $-NR^{31}R^{32}$, $-CONR^{31}R^{32}$, $-CO_2R^{31}$, $-SO_2NR^{31}R^{32}$, o $-NR^{31}SO_2R^{32}$; o alternativamente R^{26} y R^{27}, conjuntamente con los átomos a los cuales ellos están unidos, forman un anillo cicloalquilo, cicloalquilo sustituido, heterocicloalquilo, o heterocicloalquilo sustituido;

Ar es arilo o arilo sustituido; y

R^a es -CN, $-C(O)R^b$, $-C(O)OR^b$, $-C(O)N(R^b)_2$;

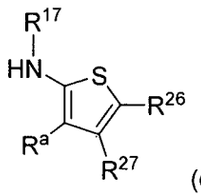
cada R^b es independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, o heteroarilalquilo sustituido;

h es 0, 1 o 2; y

R^{31} y R^{32} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido; o alternativamente R^{31} y R^{32}, conjuntamente con los átomos a los cuales ellos están unidos, forman un anillo cicloheteroalquilo o cicloheteroalquilo sustituido.

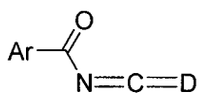
235. El proceso de la reivindicación 234, en donde la base es una base inorgánica.

236. El proceso de la reivindicación 234, en donde el compuesto que tiene la Fórmula estructural (b) se prepara haciendo reaccionar un compuesto que tiene la Fórmula estructural (c):



(c),

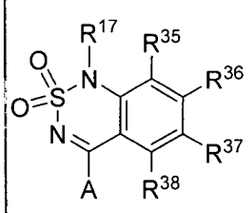
con un compuesto que tiene la Fórmula estructural (d):



(d).

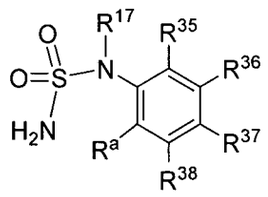
237. El proceso de la reivindicación 234 o 236, en donde Ar es fenilo o fenilo sustituido.

238. Un proceso para preparar un compuesto que tiene la Fórmula estructural (e):



(e),

que comprende hacer reaccionar un compuesto que tiene la Fórmula estructural (f)



(f),

con una base,

en donde:

A es $-NH_2$ u $-OR^b$;

R^{17} es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, o arilalquilo sustituido;

R^{35}, R^{36}, R^{37}, y R^{38} son cada uno independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, halo, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido, -CN, $-NO_2$, $-OR^{41}$, $-S(O)_kR^{41}$, $-NR^{41}R^{42}$, $-CONR^{41}R^{42}$, $-CO_2R^{41}$, $-SO_2NR^{41}R^{42}$, y $-NR^{41}SO_2R^{42}$; o alternativamente, R^{35} y R^{36}, R^{36} y R^{37}, o R^{37} y R^{38}, conjuntamente con los átomos a los cuales ellos están unidos, forman un anillo cicloalquilo, cicloalquilo sustituido, heterocicloalquilo, o heterocicloalquilo sustituido;

R^a es -CN, $-C(O)R^b$, $-C(O)OR^b$, $-C(O)N(R^b)_2$;

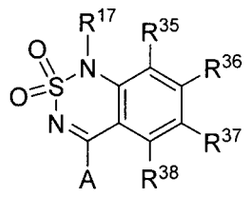
cada R^b es independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido, heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo, o heteroarilalquilo sustituido; y

R^{41} y R^{42} son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, arilalquilo, arilalquilo sustituido, acilo, acilo sustituido,

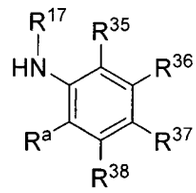
heteroalquilo, heteroalquilo sustituido, heteroarilo, heteroarilo sustituido, heteroarilalquilo o heteroarilalquilo sustituido; o alternativamente R^{41} y R^{42}, conjuntamente con los átomos a los cuales ellos están unidos, forman un anillo cicloheteroalquilo o cicloheteroalquilo sustituido.

239. El proceso de la reivindicación 238, en donde la base es una base inorgánica.

240. Un proceso para preparar un compuesto que tiene la Fórmula estructural (e):


(e),

que comprende hacer reaccionar un compuesto que tiene la Fórmula estructural (g)


(g)

con $NH_2S(O)_2NH_2$ o Cl-$S(O)_2$-NH_2 en presencia de una base para proporcionar directamente un compuesto que tiene la Fórmula estructural (e); o alternativamente para proporcionar el compuesto que tiene la fórmula estructural

(f) de la reivindicación 221 el cual se hace reaccionar además con una base para proporcionar un compuesto que tiene la Fórmula estructural (e).

241. El proceso de la reivindicación 240, en donde la base es una base orgánica.

MODULACIÓN DE RECEPTORES QUIMIOSENSORIALES Y LIGANDOS RELACIONADOS CON LOS MISMOS

RESUMEN

La presente invención incluye métodos para identificar modificadores de receptores quimiosensoriales y sus ligandos, *por ejemplo*, mediante la determinación de si una entidad de ensayo es adecuada para interactuar con uno o más sitios de interacción dentro de los dominios Venus atrapamoscas de los receptores quimiosensoriales, y modificadores capaces de modular receptores quimiosensoriales y sus ligandos. La presente invención también incluye modificadores de receptores quimiosensoriales y sus ligandos que tienen la Fórmula (I), sus subgéneros, y compuestos específicos. Más aún, la presente invención incluye composiciones ingeribles que comprenden los modificadores de receptores quimiosensoriales y sus ligandos y métodos de utilización de los modificadores de receptores quimiosensoriales y sus ligandos para mejorar el sabor dulce de una composición ingerible o para tratar una afección asociada con un receptor quimiosensorial. Además, la presente invención incluye procesos para preparar los modificadores de receptores quimiosensoriales y sus ligandos.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO PROPIETARIOS

PATENTE DE INVENCION ____ PCT __X__ MODELO DE UTILIDAD ____ DISEÑO INDUSTRIAL ___

(21) Nº de solicitud:
(22) Fecha de solicitud:
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(71)Solicitante(s) **SENOMYX INC.**

(72) Inventor(es) **VER ANEXO No. 1**

(74) Apoderado: **DRA. MARGARITA CASTELLANOS ABONDANO**

(30) Prioridad	(31) **No. Prioridad**	32) **Fecha**	(33) **País**
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(54) Titulo: **MODULACION DE RECEPTORES QUIMIOSENSORIALES Y LIGANDOS RELACIONADOS CON LOS MISMOS**

(72) Inventor(es) **ANEXO No. 1**

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Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

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(72) Inventor(es) **CATHERINE TAC-HDJIAN**
DONALD S. KARANEWSKY
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Reivindicación(es):

1. Un método de cribado para un candidato de un modificador del ligando del receptor quimiosensorial que comprende

determinar si una entidad de ensayo es adecuada para interactuar con un receptor quimiosensorial *a través de* un primer sitio de interacción dentro del dominio Venus atrapamoscas del receptor quimiosensorial.

2. El método de la reivindicación 1, en donde el primer sitio de interacción del dominio Venus atrapamoscas del receptor quimiosensorial incluye uno o más residuos de interacción del dominio Venus atrapamoscas del receptor quimiosensorial.

3. El método de la reivindicación 1, en donde el primer sitio de interacción del dominio Venus atrapamoscas del receptor quimiosensorial incluye uno o más espacios de interacción del dominio Venus atrapamoscas del receptor quimiosensorial.

4. El método de la reivindicación 1, en donde el primer sitio de interacción del dominio Venus atrapamoscas incluye un espacio de interacción identificado en base a uno o más residuos de interacción.

5. El método de la reivindicación 1, en donde el primer sitio de interacción del dominio Venus atrapamoscas del receptor quimiosensorial incluye uno o más residuos de interacción, los cuales son identificados en base a análisis de mutagénesis del dominio Venus atrapamoscas.

6. El método de la reivindicación 1, en donde el primer sitio de interacción del dominio Venus atrapamoscas es identificado en base a modelación computacional, cristalografía de rayos X, o una combinación de los mismos.

7. El método de la reivindicación 1, en donde el primer sitio de interacción del dominio Venus atrapamoscas es identificado en base a uno o más ligandos de receptores quimiosensoriales conocidos.

8. El método de la reivindicación 1, en donde el primer sitio de interacción del dominio Venus atrapamoscas es identificado en base a uno o más modificadores de ligandos de receptores quimiosensoriales conocidos.

9. El método de la reivindicación 1, en donde el primer sitio de interacción del dominio Venus atrapamoscas es identificado en base a un ligando del receptor quimiosensorial predeterminado.

10. El método de la reivindicación 1, en donde el primer sitio de interacción del dominio Venus atrapamoscas está predeterminado.

11. El método de la reivindicación 1, en donde el primer sitio de interacción del dominio Venus atrapamoscas se encuentra en el dominio Venus atrapamoscas de T1R2.

12. El método de la reivindicación 1, en donde el primer sitio de interacción del dominio Venus atrapamoscas se encuentra en el dominio Venus atrapamoscas de T1R2 y es identificado en presencia del dominio Venus atrapamoscas de T1R3.

13. El método de la reivindicación 1, en donde la determinación se lleva a cabo in silico.

14. Un método de cribado para un candidato de un modificador del ligando del receptor quimiosensorial que comprende

determinar si una entidad de ensayo es adecuada para interactuar con un receptor quimiosensorial *a través de* un primer sitio de interacción dentro del dominio Venus atrapamoscas del receptor quimiosensorial,

en donde el primer sitio de interacción se identifica a la luz de un segundo sitio de interacción identificado en base a la interacción entre un ligando del receptor quimiosensorial y el receptor quimiosensorial.

15. El método de la reivindicación 14, en donde el primer y el segundo sitio de interacción se encuentran en el dominio Venus atrapamoscas de T1R2.

16. El método de la reivindicación 14, el primer y el segundo sitio de interacción se encuentran en el dominio Venus atrapamoscas de T1R2 y son identificados en presencia del dominio Venus atrapamoscas de T1R3....



FIG. 5

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Bogotá,
2020

Doctor(a)
MARGARITA CASTELLANOS ABONDANO

REFERENCIA	Radicación No.	9 139683
	Solicitud internacional	PCT/US2008/065650
	Fecha inicio fase nacional	08/01/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	21306

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 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.

2. 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, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

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.

Continua en la página siguiente...

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Radicación No.:9 139683

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 05 FEB. 2010
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Industria y Comercio
SUPERINTENDENCIA

Bogotá,
2020

Doctor(a)
MARGARITA CASTELLANOS ABONDANO
Apoderado(a) y/o Representante de
SENOMYX INCORPORATED

REFERENCIA	Radicación No.	9 139683
	Solicitud internacional	PCT/US2008/065650
	Fecha inicio fase nacional	08/01/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	1308

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de quince reivindicaciones, es necesario que cancele la tasa establecida por cada reivindicación adicional presentada, de conformidad con lo dispuesto en la resolución de tasas vigente para la fecha de presentación de la solicitud, so pena de que no sean tenidas en cuenta dentro del presente trámite administrativo.

En consecuencia, con fundamento en lo previsto por el artículo 12 del Código Contencioso Administrativo, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio atienda el requerimiento aquí señalado. Lo anterior, con el alcance que para tal efecto establece el artículo 13 de la misma codificación, respecto de las reivindicaciones adicionales.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del titulo primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 05 FEB. 2010
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