06-98495

Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

06-98495

21. EXPEDIENTE No.

54. TITULO: "DERIVADOS HETEROCICLICOS DE FENIL PROPANO-2-OL Y COMPUESTOS RELACIONADOS COMO MODULADORES DE LA ACTIVIDAD DE LA NOREPINEFRINA (NE) Y LA SEROTONINA (5-HT) Y LA RETOMA DE MONOAMINA PARA EL TRATAMIENTO DE SÍNTOMAS VASOMOTORES (VMS)"

51. CLASIFICACIÓN INTERNACIONAL: C07D 209/08, 209/30, 209/42, 265/36, 241/42, 235/06, 471/04; A61K 31/4045; A61P 15/10

71. SOLICITANTE: WYETH

DOMICILIO: Nueva Jersey, Estados Unidos

74. APODERADO: ALVARO CORREA ORDOÑEZ
T.P. 20.281

22. BOGOTA, D.C., Septiembre 29, 2006

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Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

30-10-06

(1) SOLICITUD DE :

[X]	Patente de Invención	[ ]	Patente de Modelo de Utilidad
[X]	Capítulo I.	[ ]	Capítulo II.

(2) SOLICITANTE (71)

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IDENTIFICACION

C.C. [ ] NIT [ ]

C.E. [ ] Otro [ ]

Cual

Número

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IDENTIFICACION

C.C. [X] NIT [ ]

C.E. [ ] Otro [ ]

Cual

Número 79.143.366 de Usaquén TP 20.281

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Nacionalidad o Domicilio: Estadounidenses a excepción de HEFFERNAN, Gavin David que es británico.

(5) PCT (85)

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(6) Título (54) DERIVADOS HETEROCICLICOS DE FENIL PROPANO-2-OL Y COMPUESTOS RELACIONADOS COMO MODULADORES DE LA ACTIVIDAD DE LA NOREPINEFRINA (NE) Y LA SEROTONINA (5-HT) Y LA RETOMA DE MONOAMINA PARA EL TRATAMIENTO DE SÍNTOMAS VASOMOTORES (VMS)

(7) Clasificación Internacional (51) C07D 209/08, 209/30, 209/42, 265/36, 241/42, 235/06, 471/04; A61K 31/4045; A61P 15/10

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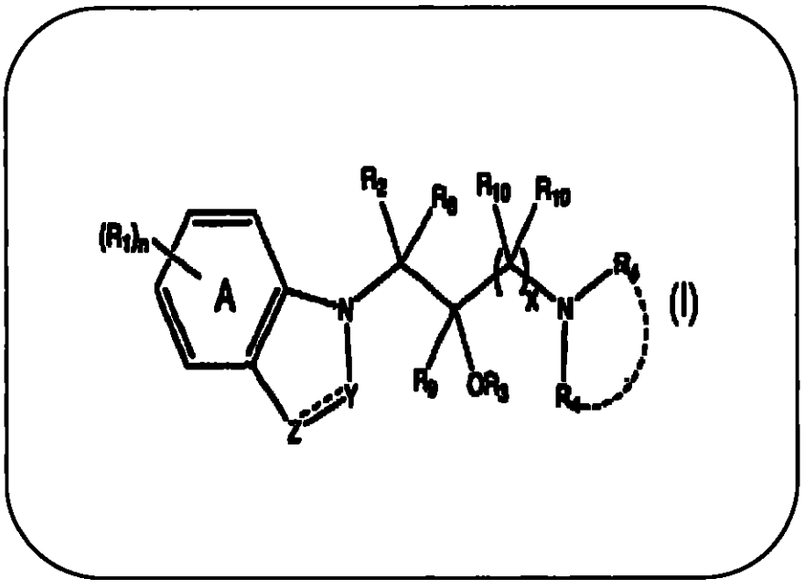
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(10) **ANEXOS**

- [ ] 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
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [ ] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar 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
- [ ] Arte final 12 x 12
- [ ] 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: Reporte de Búsqueda Internacional, Opinión Escrita, Notificación de presentación de documento de Prioridad, Solicitud de corrección al título, Extractos.

(11) **FIGURA CARATERISTICA**



(12) Solicito la concesión de la patente,

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA: _____

C.C. 79.143.366 de Usaquén T.P. 20.281

Instrucciones para la presentación de los anexos, ver reverso de esta página

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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[redacted]BECK LARA RODRIGUEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	49367693	24/08/2006	65,767,000.00

C O N C E P T O

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
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		TOTAL : $	463,000.00

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RESPONSABLE : _____

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(72) Inventors; and

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(74) Agents: LUCCI, Joseph et al.; Woodcock Washburn LLP, One Liberty Place, 46th Floor, Philadelphia, PA 19103 (US).

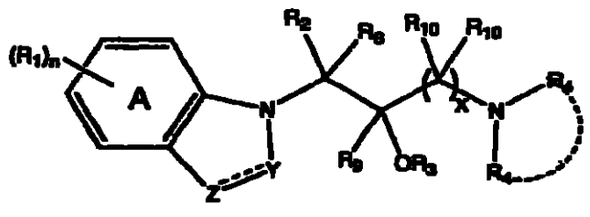
(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,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

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(54) Title: 1-(1H-INDOL-1-YL)-3-(4-METHYLPIPERAZIN-1-YL)-1-PHENYL PROPAN-2-OL DERIVATIVES AND RELATED COMPOUNDS AS MODULATORS OF THE NOREPINEPHRINE (NE) AND THE SEROTONINE (5-HT) ACTIVITY AND THE MONOAMINE REUPTAKE FOR THE TREATMENT OF VASOMOTOR SYMPTOMS (VMS)



(I)

(57) Abstract: The present invention is directed to phenylaminopropanol derivatives of formula (I): or a pharmaceutically acceptable salt thereof; wherein: the dotted line between Y and Z represents an optional double bond; the dotted line between the two R_4 groups represents an optional heterocyclic ring of 4 to 6 ring atoms that may be formed between the two R_4 groups, together with the nitrogen through which they are attached; Y is N, CR_6, or C=O; Z is N, CR_7, CR_3, or $C(R_3)_2$; R_2 is aryl substituted with 0-3 R_1 or heteroaryl substituted with 0-3 R_1; R_3 is H or C_1-C_4 alkyl; n is an integer form 0 to 4; x is an integer from 1 to 2; and the other substituents are defined in the claims; compositions containing these derivatives, and methods of their use for the prevention and treatment of conditions ameliorated by monoamine reuptake including, *inter alia*, vasomotor symptoms (VMS), sexual dysfunction, gastrointestinal and genitourinary disorders, chronic fatigue syndrome, fibromylagia syndrome, nervous system disorders, and combinations thereof, particularly those conditions selected form the group consisting of major depressive disorder, vasomotor symptoms, stress and urge urinary incontinence, fibromyalgia, pain, diabetic neuropathy, and combinations thereof.

WO 2005/097744 A1

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

1-(1H-INDOL-1-YL)-3-(4-METHYLPIPERAZIN-1-YL)-1-PHENYL PROPAN-2-OL DERIVATIVES AND RELATED COMPOUNDS AS MODULATORS OF THE NOREPINEPHRINE (NE) AND THE SEROTONINE (5-HT) ACTIVITY AND THE MONOAMINE REUPTAKE FOR THE TREATMENT OF VASOMOTOR SYMPTOMS (VMS)

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Application No. _____ filed March 28, 2005, which claims the benefit of U.S. Application No. 60/557,651 filed March 30, 2004 and U.S. Application No. 60/569,863 filed May 11, 2004, the entire disclosures of which are herein incorporated by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to phenylaminopropanol derivatives, compositions containing these derivatives, and methods of their use for the prevention and treatment of conditions ameliorated by monoamine reuptake including, *inter alia*, vasomotor symptoms (VMS), sexual dysfunction, gastrointestinal and genitourinary disorders, chronic fatigue syndrome, fibromylagia syndrome, nervous system disorders, and combinations thereof, particularly those conditions selected from the group consisting of major depressive disorder, vasomotor symptoms, stress and urge urinary incontinence, fibromyalgia, pain, diabetic neuropathy, and combinations thereof.

BACKGROUND OF THE INVENTION

[0003] Vasomotor symptoms (VMS), referred to as hot flushes and night sweats, are the most common symptoms associated with menopause, occurring in 60% to 80% of all women following natural or surgically-induced menopause. VMS are likely to be an adaptive response of the central nervous system (CNS) to declining sex steroids. To date, the most effective therapies for VMS are hormone-based treatments, including estrogens and/or some progestins. Hormonal treatments are very effective at alleviating VMS, but they are not appropriate for all women. It is well recognized that VMS are caused by fluctuations of sex steroid levels and can be disruptive and disabling in both males and females. A hot flush can last up to thirty minutes and vary in their frequency from several times a week to multiple

occurrences per day. The patient experiences a hot flash as a sudden feeling of heat that spreads quickly from the face to the chest and back and then over the rest of the body. It is usually accompanied by outbreaks of profuse sweating. It may sometimes occur several times an hour, and it often occurs at night. Hot flushes and outbreaks of sweats occurring during the night can cause sleep deprivation. Psychological and emotional symptoms observed, such as nervousness, fatigue, irritability, insomnia, depression, memory loss, headache, anxiety, nervousness or inability to concentrate are considered to be caused by the sleep deprivation following hot flush and night sweats (Kramer *et al.*, In: Murphy *et al.*, *3rd Int'l Symposium on Recent Advances in Urological Cancer Diagnosis and Treatment-Proceedings*, Paris, France: SCI: 3-7 (1992)).

[0004] Hot flushes may be even more severe in women treated for breast cancer for several reasons: 1) many survivors of breast cancer are given tamoxifen, the most prevalent side effect of which is hot flush, 2) many women treated for breast cancer undergo premature menopause from chemotherapy; 3) women with a history of breast cancer have generally been denied estrogen therapy because of concerns about potential recurrence of breast cancer (Loprinzi, *et al.*, *Lancet*, 2000, 356(9247): 2059-2063).

[0005] Men also experience hot flushes following steroid hormone (androgen) withdrawal. This is true in cases of age-associated androgen decline (Katovich, *et al.*, *Proceedings of the Society for Experimental Biology & Medicine*, 1990, 193(2): 129-35) as well as in extreme cases of hormone deprivation associated with treatments for prostate cancer (Berendsen, *et al.*, *European Journal of Pharmacology*, 2001, 419(1): 47-54. As many as one-third of these patients will experience persistent and frequent symptoms severe enough to cause significant discomfort and inconvenience.

[0006] The precise mechanism of these symptoms is unknown but generally is thought to represent disturbances to normal homeostatic mechanisms controlling thermoregulation and vasomotor activity (Kronenberg *et al.*, "Thermoregulatory Physiology of Menopausal Hot Flashes: A Review," *Can. J. Physiol. Pharmacol.*,

1987, 65:1312-1324).

[0007] The fact that estrogen treatment (*e.g.* estrogen replacement therapy) relieves the symptoms establishes the link between these symptoms and an estrogen deficiency. For example, the menopausal stage of life is associated with a wide range of other acute symptoms as described above and these symptoms are generally estrogen responsive.

[0008] It has been suggested that estrogens may stimulate the activity of both the norepinephrine (NE) and/or serotonin (5-HT) systems (*J. Pharmacology & Experimental Therapeutics*, 1986, 236(3) 646-652). It is hypothesized that estrogens modulate NE and 5-HT levels providing homeostasis in the thermoregulatory center of the hypothalamus. The descending pathways from the hypothalamus via brainstem/spinal cord and the adrenals to the skin are involved in maintaining normal skin temperature. The action of NE and 5-HT reuptake inhibitors is known to impinge on both the CNS and peripheral nervous system (PNS). The pathophysiology of VMS is mediated by both central and peripheral mechanisms and, therefore, the interplay between the CNS and PNS may account for the efficacy of dual acting SRI/NRIs in the treatment of thermoregulatory dysfunction. In fact, the physiological aspects and the CNS/PNS involvement in VMS may account for the lower doses proposed to treat VMS (Loprinzi, *et al., Lancet*, 2000, 356:2059-2063; Steams *et al., JAMA*, 2003, 289:2827-2834) compared to doses used to treat the behavioral aspects of depression. The interplay of the CNS/PNS in the pathophysiology of VMS and the presented data within this document were used to support the claims that the norepinephrine system could be targeted to treat VMS.

[0009] Although VMS are most commonly treated by hormone therapy (orally, transdermally, or via an implant), some patients cannot tolerate estrogen treatment (Berendsen, *Maturitas*, 2000, 36(3): 155-164, Fink *et al.*, *Nature*, 1996, 383(6598): 306). In addition, hormone replacement therapy is usually not recommended for women or men with or at risk for hormonally sensitive cancers (*e.g.* breast or prostate cancer). Thus, non-hormonal therapies (*e.g.* fluoxetine, paroxetine [SRIs] and clonidine) are being evaluated clinically. WO9944601 discloses a method for

decreasing hot flushes in a human female by administering fluoxetine. Other options have been studied for the treatment of hot flashes, including steroids, alpha-adrenergic agonists, and beta-blockers, with varying degree of success (Waldinger *et al.*, *Maturitas*, **2000**, 36(3): 165-168).

[0010] It has been reported that α_2-adrenergic receptors play a role in thermoregulatory dysfunctions (Freedman *et al.*, *Fertility & Sterility*, **2000**, 74(1): 20-3). These receptors are located both pre- and post-synaptically and mediate an inhibitory role in the central and peripheral nervous system. There are four distinct subtypes of the adrenergic$_{\alpha 2}$ receptors, *i.e.*, are α_{2A}, α_{2B}, α_{2C} and α_{2D} (Mackinnon *et al.*, *TIPS*, **1994**, 15: 119; French, *Pharmacol. Ther.*, **1995**, 68: 175). It has been reported that a non-select α_2-adrenoceptor antagonist, yohimbine, induces a flush and an α_2-adrenergic receptor agonist, clonidine, alleviates the yohimbine effect (Katovich, *et al.*, *Proceedings of the Society for Experimental Biology & Medicine*, **1990**, 193(2): 129-35, Freedman *et al.*, *Fertility & Sterility*, **2000**, 74(1): 20-3). Clonidine has been used to treat hot flush. However, using such treatment is associated with a number of undesired side effects caused by high doses necessary to abate hot flash described herein and known in the related arts.

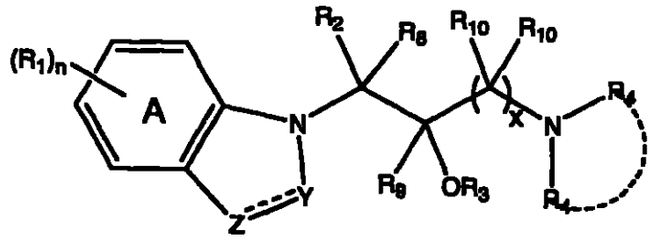
[0011] Given the complex multifaceted nature of thermoregulation and the interplay between the CNS and PNS in maintaining thermoregulatory homeostasis, multiple therapies and approaches can be developed to target vasomotor symptoms. The present invention focuses on novel compounds and compositions containing these compounds directed to these and other important uses.

SUMMARY OF THE INVENTION

[0012] The present invention is directed to phenylaminopropanol derivatives, compositions containing these derivatives, and methods of their use for the prevention and treatment of conditions ameliorated by monoamine reuptake including, *inter alia*, vasomotor symptoms (VMS), sexual dysfunction, gastrointestinal and genitourinary disorders, chronic fatigue syndrome, fibromylagia

syndrome, nervous system disorders, and combinations thereof, particularly those conditions selected from the group consisting of major depressive disorder, vasomotor symptoms, stress and urge urinary incontinence, fibromyalgia, pain, diabetic neuropathy, and combinations thereof.

[0013] In one embodiment, the present invention is directed to compounds of formula I:



I

or a pharmaceutically acceptable salt thereof;

wherein:

the dotted line between Y and Z represents an optional double bond;

the dotted line between the two R_4 groups represents an optional heterocyclic ring of 4 to 6 ring atoms that may be formed between the two R_4 groups, together with the nitrogen through which they are attached;

Y is N, CR_6, or C=O;

Z is N, NR_7, CR_5, or $C(R_5)_2$;

R_1 is, independently at each occurrence, alkyl, alkoxy, halo, CF_3, OCF_3, arylalkyloxy substituted with 0-3 R_{11}, aryloxy substituted with 0-3 R_{11}, aryl substituted with 0-3 R_{11}, heteroaryl substituted with 0-3 R_{11}, hydroxy, alkanoyloxy, nitro, nitrile, alkenyl, alkynyl, alkylsulfoxide, phenylsulfoxide substituted with 0-3 R_{11}, alkylsulfone, phenylsulfone substituted with 0-3 R_{11}, alkylsulfonamide, phenylsulfonamide substituted with 0-3 R_{11}, heteroaryloxy substituted with 0-3 R_{11}, heteroarylmethyloxy substituted with 0-3 R_{11}, alkylamido, or arylamido substituted with 0-3 R_{11}; or two adjacent R_1 also represent methylenedioxy;

R_2 is aryl substituted with 0-3 R_1 or heteroaryl substituted with 0-3 R_1;

R_3 is H or C_1-C_4 alkyl;

R_4 is, independently at each occurrence, H, C_1-C_4 alkyl, arylalkyl,

heteroarylmethyl, cycloheptylmethyl, cyclohexylmethyl, cyclopentylmethyl, or cyclobutylmethyl, or

both R_4 groups, together with the nitrogen through which they are attached, form a heterocyclic ring of 4 to 6 ring atoms, where one carbon may be optionally replaced with N, O, S, or SO_2, and where any carbon ring atom or additional N atom may be optionally substituted with C_1-C_4 alkyl, F, or CF_3;

R_5 is, independently at each occurrence, H, C_1-C_4 alkyl, aryl substituted with 0-3 R_1, or cyano; or when two R_5 are present, they form a carbocyclic ring of 3-7 carbons;

R_6 is H, C_1-C_4 alkyl, or cyano;

R_7 is H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, or aryl substituted with 0-3 R_1;

R_8 is H, or C_1-C_4 alkyl;

R_9 is H, or C_1-C_4 alkyl;

R_{10} is, independently at each occurrence, H, or C_1-C_4 alkyl; or R_{10} and R_4 together with the nitrogen to which R_4 is attached form a nitrogen-containing ring containing 3-6 carbon atoms;

n is an integer from 0 to 4;

x is an integer from 1 to 2; and

R_{11} is alkyl, alkoxy, halo, CF_3, OCF_3, hydroxy, alkanoyloxy, nitro, nitrile, alkenyl, alkynyl, alkylsulfoxide, alkylsulfone, alkylsulfonamide, or alkylamido; or two adjacent R_{11} also represent methylenedioxy;

wherein 1-3 carbon atoms in ring A may optionally be replaced with N.

[0014] In yet other embodiments, the present invention is directed to compositions, comprising:

a. at least one compound of formula I; and

b. at least one pharmaceutically acceptable carrier.

[0015] In another embodiment, the present invention is directed to methods for treating or preventing a condition ameliorated by monoamine reuptake in a subject in need thereof, comprising the step of:

administering to said subject an effective amount of a compound of formula I or pharmaceutically acceptable salt thereof.

The conditions ameliorated by monoamine reuptake include those selected from the group consisting of vasomotor symptoms, sexual dysfunction, gastrointestinal and genitourinary disorders, chronic fatigue syndrome, fibromylagia syndrome, nervous system disorders, and combinations thereof, particularly those conditions selected from the group consisting of major depressive disorder, vasomotor symptoms, stress and urge urinary incontinence, fibromyalgia, pain, diabetic neuropathy, and combinations thereof.

[0016] In another embodiment, the present invention is directed to methods for treating or preventing vasomotor symptoms in a subject in need thereof, comprising the step of:

administering to said subject an effective amount of at least one compound of formula I or pharmaceutically acceptable salt thereof.

[0017] In yet another embodiment, the present invention is directed to methods for treating or preventing a depression disorder in a subject in need thereof, comprising the step of:

administering to said subject an effective amount of at least one compound of formula I or pharmaceutically acceptable salt thereof.

[0018] In yet other embodiments, the present invention is directed to methods for treating or preventing sexual dysfunction in a subject in need thereof, comprising the step of:

administering to said subject an effective amount of at least one compound of formula I or pharmaceutically acceptable salt thereof.

[0019] In further embodiments, the present invention is directed to methods for treating or preventing pain in a subject in need thereof, comprising the step of:

administering to said subject an effective amount of at least one compound of formula I or pharmaceutically acceptable salt thereof.

[0020] In another embodiment, the present invention is directed to methods for treating or preventing gastrointestinal or genitourinary disorder, particularly stress

incontinence or urge urinary incontinence, in a subject in need thereof, comprising the step of:

administering to said subject an effective amount of a compound of formula I or pharmaceutically acceptable salt thereof.

[0021] In another embodiment, the present invention is directed to methods for treating or preventing chronic fatigue syndrome in a subject in need thereof, comprising the step of:

administering to said subject an effective amount of a compound of formula I or pharmaceutically acceptable salt thereof.

[0022] In another embodiment, the present invention is directed to methods for treating or preventing fibromylagia syndrome in a subject in need thereof, comprising the step of:

administering to said subject an effective amount of a compound of formula I or pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] The invention can be more fully understood from the following detailed description and the accompanying drawings that form a part of this application.

[0024] **Figure 1** is an overview of estrogen action on norepinephrine/serotonin mediated thermoregulation.

[0025] **Figure 2** is a schematic representation of the interactions of norepinephrine and serotonin and their respective receptors (5-HT_{2a}, α_1 and α_2-adrenergic).

DETAILED DESCRIPTION OF THE INVENTION

[0026] The present invention is directed to phenylaminopropanol derivatives, compositions containing these derivatives, and methods of their use for the

prevention and treatment of conditions ameliorated by monoamine reuptake including, *inter alia*, vasomotor symptoms (VMS), sexual dysfunction, gastrointestinal and genitourinary disorders, chronic fatigue syndrome, fibromylagia syndrome, nervous system disorders, and combinations thereof, particularly those conditions selected from the group consisting of major depressive disorder, vasomotor symptoms, stress and urge urinary incontinence, fibromyalgia, pain, diabetic neuropathy, and combinations thereof.

[0027] The following definitions are provided for the full understanding of terms and abbreviations used in this specification.

[0028] As used herein and in the appended claims, the singular forms "a," "an," and "the" include the plural reference unless the context clearly indicates otherwise. Thus, for example, a reference to "an antagonist" includes a plurality of such antagonists, and a reference to "a compound" is a reference to one or more compounds and equivalents thereof known to those skilled in the art, and so forth.

[0029] The abbreviations in the specification correspond to units of measure, techniques, properties, or compounds as follows: "min" means minutes, "h" means hour(s), "μL" means microliter(s), "mL" means milliliter(s), "mM" means millimolar, "M" means molar, "mmole" means millimole(s), "cm" means centimeters, "SEM" means standard error of the mean and "IU" means International Units. "Δ°C" and Δ "ED_{50} value" means dose which results in 50% alleviation of the observed condition or effect (50% mean maximum endpoint).

[0030] "Norepinephrine transporter" is abbreviated NET.

"Human norepinephrine transporter" is abbreviated hNET.

"Serotonin transporter" is abbreviated SERT.

"Human serotonin transporter" is abbreviated hSERT.

"Norepinephrine reuptake inhibitor" is abbreviated NRI.

"Selective norepinephrine reuptake inhibitor" is abbreviated SNRI.

"Serotonin reuptake inhibitor" is abbreviated SRI.

"Selective serotonin reuptake inhibitor" is abbreviated SSRI.

"Norepinephrine" is abbreviated NE.

"Serotonin is abbreviated 5-HT.

"Subcutaneous" is abbreviated sc.

"Intraperitoneal" is abbreviated ip.

"Oral" is abbreviated po.

[0031] In the context of this disclosure, a number of terms shall be utilized. The term "treatment" as used herein includes preventative (*e.g.*, prophylactic), curative or palliative treatment and "treating" as used herein also includes preventative, curative and palliative treatment.

[0032] The term "effective amount," as used herein, refers to an amount effective, at dosages, and for periods of time necessary, to achieve the desired result with respect to prevention or treatment of vasomotor symptoms, depression disorders, sexual dysfunction, or pain. In particular, with respect to vasomotor symptoms, "effective amount" refers to the amount of compound or composition of compounds that would increase norepinephrine levels to compensate in part or total for the lack of steroid availability in subjects subject afflicted with a vasomotor symptom. Varying hormone levels will influence the amount of compound required in the present invention. For example, the pre-menopausal state may require a lower level of compound due to higher hormone levels than the peri-menopausal state.

[0033] It will be appreciated that the effective amount of components of the present invention will vary from patient to patient not only with the particular compound, component or composition selected, the route of administration, and the ability of the components (alone or in combination with one or more combination drugs) to elicit a desired response in the individual, but also with factors such as the disease state or severity of the condition to be alleviated, hormone levels, age, sex, weight of the individual, the state of being of the patient, and the severity of the pathological condition being treated, concurrent medication or special diets then being followed by the particular patient, and other factors which those skilled in the art will recognize, with the appropriate dosage ultimately being at the discretion of the attendant physician. Dosage regimens may be adjusted to provide the improved

therapeutic response. An effective amount is also one in which any toxic or detrimental effects of the components are outweighed by the therapeutically beneficial effects.

[0034] Preferably, the compounds of the present invention are administered at a dosage and for a time such that the number of hot flushes is reduced as compared to the number of hot flushes prior to the start of treatment. Such treatment can also be beneficial to reduce the overall severity or intensity distribution of any hot flushes still experienced, as compared to the severity of hot flushes prior to the start of the treatment. With respect to depression disorders, sexual dysfunction, and pain, the compounds of the present invention are administered at a dosage and for a time such that there is the prevention, alleviation, or elimination of the symptom or condition.

[0035] For example, for an afflicted patient, compounds of formula I, or a pharmaceutically acceptable salt thereof, may be administered, preferably, at a dosage of from about 0.1 mg/day to about 500 mg/day, dosed one or two times daily, more preferably from about 1 mg/day to about 200 mg/day and most preferably from about 1 mg/day to 100 mg/day for a time sufficient to reduce and/ r substantially eliminate the number and/or severity of hot flushes or symptom or condition of the depression disorder, sexual dysfunction, or pain.

[0036] The terms "component," "composition of compounds," "compound," "drug," or "pharmacologically active agent" or "active agent" or "medicament" are used interchangeably herein to refer to a compound or compounds or composition of matter which, when administered to a subject (human or animal) induces a desired pharmacological and/or physiologic effect by local and/or systemic action.

[0037] The terms "component", "drug" or "pharmacologically active agent" or "active agent" or "medicament" are used interchangeably herein to refer to a compound or compounds or composition of matter which, when administered to an organism (human or animal) induces a desired pharmacologic and/or physiologic effect by local and/or systemic action.

[0038] The term "modulation" refers to the capacity to either enhance or inhibit a functional property of a biological activity or process, for example, receptor binding or signaling activity. Such enhancement or inhibition may be contingent on the occurrence of a specific event, such as activation of a signal transduction pathway and/or may be manifest only in particular cell types. The modulator is intended to comprise any compound, *e.g.*, antibody, small molecule, peptide, oligopeptide, polypeptide, or protein, preferably small molecule, or peptide.

[0039] As used herein, the term "inhibitor" refers to any agent that inhibits, suppresses, represses, or decreases a specific activity, such as serotonin reuptake activity or the norepinephrine reuptake activity.

[0040] The term "inhibitor" is intended to comprise any compound, *e.g.*, antibody, small molecule, peptide, oligopeptide, polypeptide, or protein, preferably small molecule or peptide, that exhibits a partial, complete, competitive and/or inhibitory effect on mammalian, preferably the human norepinephrine reuptake or both serotonin reuptake and the norepinephrine reuptake, thus diminishing or blocking, preferably diminishing, some or all of the biological effects of endogenous norepinephrine reuptake or of both serotonin reuptake and the norepinephrine reuptake.

[0041] Within the present invention, the compounds of formula I may be prepared in the form of pharmaceutically acceptable salts. As used herein, the term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic acids, including inorganic salts, and organic salts. Suitable non-organic salts include inorganic and organic acids such as acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, malic, maleic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric acid, p-toluenesulfonic and the like. Particularly preferred are hydrochloric, hydrobromic, phosphoric, and sulfuric acids, and most preferably is the hydrochloride salt.

[0042] "Administering," as used herein, means either directly administering a compound or composition of the present invention, or administering a prodrug, derivative or analog which will form an equivalent amount of the active compound or substance within the body.

[0043] The term "subject" or "patient" refers to an animal including the human species that is treatable with the compositions, and/or methods of the present invention. The term "subject" or "subjects" is intended to refer to both the male and female gender unless one gender is specifically indicated. Accordingly, the term "patient" comprises any mammal which may benefit from treatment or prevention of vasomotor symptoms, depression disorders, sexual dysfunction, or pain, such as a human, especially if the mammal is female, either in the pre-menopausal, peri-menopausal, or post-menopausal period. Furthermore, the term patient includes female animals including humans and, among humans, not only women of advanced age who have passed through menopause but also women who have undergone hysterectomy or for some other reason have suppressed estrogen production, such as those who have undergone long-term administration of corticosteroids, suffer from Cushing's syndrome or have gonadal dysgenesis. However, the term "patient" is not intended to be limited to a woman.

[0044] The terms "premature menopause" or "artificial menopause" refer to ovarian failure of unknown cause that may occur before age 40. It may be associated with smoking, living at high altitude, or poor nutritional status. Artificial menopause may result from oophorectomy, chemotherapy, radiation of the pelvis, or any process that impairs ovarian blood supply.

[0045] The term "pre-menopausal" means before the menopause, the term "peri-menopausal" means during the menopause and the term "post-menopausal" means after the menopause. "Ovariectomy" means removal of an ovary or ovaries and can be effected according to Merchenthaler *et al.*, *Maturitas*, 1998, 30(3): 307-316.

[0046] "Side effect" refers to a consequence other than the one(s) for which an agent or measure is used, as the adverse effects produced by a drug, especially on a tissue or organ system other then the one sought to be benefited by its administration. In the case, for example, of high doses of NRIs or NRI/SRI compounds alone, the term "side effect" may refer to such conditions as, for example, vomiting, nausea, sweating, and flushes (Janowsky, *et al., Journal of Clinical Psychiatry*, **1984**, 45(10 Pt 2): 3-9).

[0047] ""Alkyl," as used herein, refers to an optionally substituted, saturated straight, branched, or cyclic hydrocarbon having from about 1 to about 20 carbon atoms (and all combinations and subcombinations of ranges and specific numbers of carbon atoms therein), with from about 1 to about 8 carbon atoms being preferred, and with from about 1 to about 4 carbon atoms, herein referred to as "lower alkyl", being more preferred. Alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, cyclopentyl, isopentyl, neopentyl, n-hexyl, isohexyl, cyclohexyl, cyclooctyl, adamantyl, 3-methylpentyl, 2,2-dimethylbutyl, and 2,3-dimethylbutyl.

[0048] "Perfluorinated alkyl," as used herein, refers to an alkyl, as defined above, in which the hydrogens directly attached to the carbon atoms are completely replaced by fluorine.

[0049] "Alkenyl," as used herein, refers to an alkyl group of at least two carbon atoms having one or more double bonds, wherein alkyl is as defined herein. Alkenyl groups can be optionally substituted.

[0050] "Alkynyl," as used herein, refers to an alkyl group of at least two carbon atoms having one or more triple bonds, wherein alkyl is as defined herein. Alkynyl groups can be optionally substituted.

[0051] "Aryl" as used herein, refers to an optionally substituted, mono-, di-, tri-, or other multicyclic aromatic ring system having from about 5 to about 50 carbon atoms

(and all combinations and subcombinations of ranges and specific numbers of carbon atoms therein), with from about 6 to about 10 carbons being preferred. Non-limiting examples include, for example, phenyl, naphthyl, anthracenyl, and phenanthrenyl.

[0052] "Heteroaryl," as used herein, refers to an optionally substituted, mono-, di-, tri-, or other multicyclic aromatic ring system that includes at least one, and preferably from 1 to about 4 heteroatom ring members selected from sulfur, oxygen and nitrogen. Heteroaryl groups can have, for example, from about 3 to about 50 carbon atoms (and all combinations and subcombinations of ranges and specific numbers of carbon atoms therein), with from about 4 to about 10 carbons being preferred. Non-limiting examples of heteroaryl groups include, for example, pyrryl, furyl, pyridyl, 1,2,4-thiadiazolyl, pyrimidyl, thienyl, isothiazolyl, imidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, thiophenyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, purinyl, carbazolyl, benzimidazolyl, and isoxazolyl.

[0053] "Heterocyclic ring," as used herein, refers to a stable 5- to 7-membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic ring that is saturated, partially unsaturated or unsaturated (aromatic), and which contains carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S and including any bicyclic group in which any of the above defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. If specifically noted, a nitrogen atom in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds one, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than one. Examples of heterocycles include, but are not limited to, 1H-indazole, 2-pyrrolidonyl, 2H,6H-1,5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidonyl, 4aH-carbazole, 4H-quinolizinyl, 6H-1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl, benzofuranyl,

benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, carbazolyl, 4H-carbazolyl, α-, β-, or γ-carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl., oxazolyl, oxazolidinylpyrimidinyl, phenanthridinyl, phenanthrolinyl, phenoxazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, piperidonyl, 4-piperidonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, carbolinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, xanthenyl. Preferred heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, indolyl, benzimidazolyl, 1*H*-indazolyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, or isatinyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

[0054] "Alkoxy," as used herein, refers to the group R-O- where R is an alkyl group as defined herein.

[0055] "Aryloxy," as used herein, refers to the group R-O- where R is an aryl group, as defined herein.

[0056] "Heteroaryloxy," as used herein, refers to the group R-O- where R is a heteroaryl group, as defined herein.

[0057] "Alkanoyloxy," as used herein, refers to the group R-C(=O)-O- where R is an alkyl group of 1 to 5 carbon atoms.

[0058] "Alkylsulfoxide," as used herein, refers to as used herein, refers to –S(=O)-R, where R is alkyl, as defined above.

[0059] "Alkylsulfone," as used herein, refers to $-S(=O)_2-R$, where R is alkyl, as defined above.

[0060] "Alkylsulfonamide," as used herein, refers to $-NR-S(=O)_2-R$, where each R is independently, alkyl, as defined above or the NR part may also be NH.

[0061] "Phenylsulfonamide," as used herein, refers to $-NR-S(=O)_2$-phenyl, where R is H or alkyl, as defined above.

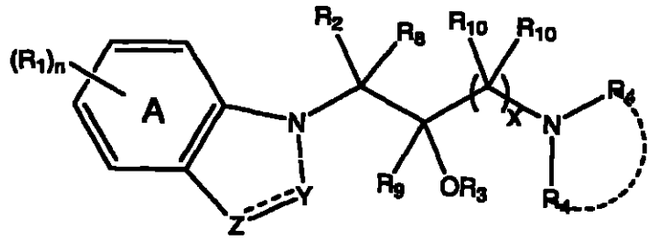
[0062] "Heteroarylmethyloxy," as used herein, refers to $-OCH_2-R$, where R is heteroaryl, as defined above.

[0063] "Alkylamido," as used herein, refers to –NR-C(=O)-R, where each R is independently, alkyl, as defined above, or the NR part may also be NH.

[0064] "Phenylamido," as used herein, refers to –NR-C(=O)-phenyl, where R is H or alkyl, as defined above.

[0065] "Halo," as used herein, refers to chloro, bromo, fluoro, and iodo.

[0066] In one embodiment, the present invention is directed to compounds of formula I:



I

or a pharmaceutically acceptable salt thereof;

wherein:

the dotted line between Y and Z represents an optional double bond;

the dotted line between the two R_4 groups represents an optional heterocyclic ring of 4 to 6 ring atoms that may be formed between the two R_4 groups, together with the nitrogen through which they are attached;

Y is N, CR_6, or C=O;

Z is N, NR_7, CR_5, or $C(R_5)_2$;

R_1 is, independently at each occurrence, alkyl, alkoxy, halo, CF_3, OCF_3, arylalkyloxy substituted with 0-3 R_{11}, aryloxy substituted with 0-3 R_{11}, aryl substituted with 0-3 R_{11}, heteroaryl substituted with 0-3 R_{11}, hydroxy, alkanoyloxy, nitro, nitrile, alkenyl, alkynyl, alkylsulfoxide, phenylsulfoxide substituted with 0-3 R_{11}, alkylsulfone, phenylsulfone substituted with 0-3 R_{11}, alkylsulfonamide, phenylsulfonamide substituted with 0-3 R_{11}, heteroaryloxy substituted with 0-3 R_{11}, heteroarylmethyloxy substituted with 0-3 R_{11}, alkylamido, or arylamido substituted with 0-3 R_{11}; or two adjacent R_1 also represent methylenedioxy;

R_2 is aryl substituted with 0-3 R_1 or heteroaryl substituted with 0-3 R_1;

R_3 is H or C_1-C_4 alkyl;

R_4 is, independently at each occurrence, H, C_1-C_4 alkyl, arylalkyl, heteroarylmethyl, cycloheptylmethyl, cyclohexylmethyl, cyclopentylmethyl, or cyclobutylmethyl, or

both R_4 groups, together with the nitrogen through which they are attached, form a heterocyclic ring of 4 to 6 ring atoms, where one carbon may be optionally replaced with N, O, S, or SO_2, and where any carbon ring atom or additional N atom may be optionally substituted with C_1-C_4 alkyl, F, or CF_3;

R_5 is, independently at each occurrence, H, C_1-C_4 alkyl, aryl substituted with

0-3 R_1, or cyano; or when two R_5 are present, they form a carbocyclic ring of 3-7 carbons;

R_6 is H, C_1-C_4 alkyl, or cyano;

R_7 is H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, or aryl substituted with 0-3 R_1;

R_8 is H, or C_1-C_4 alkyl;

R_9 is H, or C_1-C_4 alkyl;

R_{10} is, independently at each occurrence, H, or C_1-C_4 alkyl; or R_{10} and R_4 together with the nitrogen to which R_4 is attached form a nitrogen-containing ring containing 3-6 carbon atoms;

n is an integer from 0 to 4;

x is an integer from 1 to 2; and

R_{11} is alkyl, alkoxy, halo, CF_3, OCF_3, hydroxy, alkanoyloxy, nitro, nitrile, alkenyl, alkynyl, alkylsulfoxide, alkylsulfone, alkylsulfonamide, or alkylamido; or two adjacent R_{11} also represent methylenedioxy;

wherein 1-3 carbon atoms in ring A may optionally be replaced with N.

The dotted line in the ring fused to ring A represents an optional double bond between Y and Z. The dotted line between the two R_4 groups represents an optional heterocyclic ring of 4 to 6 ring atoms that may be formed between the two R_4 groups, together with the nitrogen through which they are attached.

[0067] In certain preferred embodiments of compounds of formula I, Y is N. In certain other preferred embodiments, Y is CR_6, preferably CH. In certain other preferred embodiments, Y is C=O.

[0068] In certain more preferred embodiments, Z is N. In certain preferred embodiments of compounds of formula I, Z is NR_7. In certain other more preferred embodiments, Z is CR_5. In yet certain other more preferred embodiments, Z is $C(R_5)_2$. In certain even more preferred embodiments, Z is CH, $C(CH_3)$, or C(CN).

[0069] In certain preferred embodiments of compounds of formula I, R_1 is, independently at each occurrence, alkyl, preferably C_1-C_4 alkyl, more preferably methyl. In certain other preferred embodiments, R_1 is, independently at each occurrence, alkoxy. In certain other preferred embodiments of compounds, R_1 is,

independently at each occurrence, halo, preferably F or Cl. In certain other preferred embodiments, R_1 is, independently at each occurrence, CF_3. In certain other preferred embodiments, R_1 is, independently at each occurrence, OCF_3. In certain other preferred embodiments, R_1 is, independently at each occurrence, benzyloxy substituted with 0-3 R_1. In certain other preferred embodiments, R_1 is, independently at each occurrence, aryloxy substituted with 0-3 R^1. In certain other preferred embodiments, R_1 is, independently at each occurrence, aryl substituted with 0-3 R_1. In certain other preferred embodiments, R_1 is, independently at each occurrence, heteroaryl substituted with 0-3 R_1. In certain other preferred embodiments, R_1 is, independently at each occurrence, hydroxy. In certain other preferred embodiments, R_1 is, independently at each occurrence, alkanoyloxy. In certain other preferred embodiments, R_1 is, independently at each occurrence, methylenedioxy. In certain other preferred embodiments, R_1 is, independently at each occurrence, nitro. In certain other preferred embodiments, R_1 is, independently at each occurrence, nitrile. In certain other preferred embodiments, R_1 is, independently at each occurrence, alkenyl. In certain other preferred embodiments, R_1 is, independently at each occurrence, alkynyl. In certain other preferred embodiments, R_1 is, independently at each occurrence, alkylsulfoxide. In certain other preferred embodiments, R_1 is, independently at each occurrence, phenylsulfoxide substituted with 0-3 R_1. In certain other preferred embodiments, R_1 is, independently at each occurrence, alkylsulfone. In certain other preferred embodiments, R_1 is, independently at each occurrence, phenylsulfone substituted with 0-3 R_1. In certain other preferred embodiments, R_1 is, independently at each occurrence, alkylsulfonamide. In certain other preferred embodiments, R_1 is, independently at each occurrence, phenylsulfonamide substituted with 0-3 R_1. In certain other preferred embodiments, R_1 is, independently at each occurrence, heteroaryloxy substituted with 0-3 R_1. In certain other preferred embodiments, R_1 is, independently at each occurrence, heteroarylmethyloxy substituted with 0-3 R_1. In certain other preferred embodiments, R_1 is, independently at each occurrence, alkylamido. In certain other preferred embodiments, R_1 is, independently at each occurrence, phenylamido substituted with 0-3 R_1.

[0070] In certain preferred embodiments of compounds of formula I, R_2 is aryl

substituted with 0-3 R_1, preferably substituted with no R_1. In certain preferred embodiments, R_2 is naphthyl substituted with 0-3 R_1, preferably substituted with no R_1. In certain preferred embodiments, R_2 is heteroaryl substituted with 0-3 R_1, preferably substituted with no R_1.

[0071] In certain preferred embodiments of compounds of formula I, R_3 is H. In certain other preferred embodiments, R_3 is C_1-C_4 alkyl, preferably C_1 alkyl.

[0072] In certain preferred embodiments of compounds of formula I, R_4 is, independently at each occurrence, H. In certain preferred embodiments, R_4 is, independently at each occurrence, C_1-C_4 alkyl, preferably C_1-C_3 alkyl, more preferably methyl, ethyl, isopropyl. In certain preferred embodiments of compounds of formula I, R_4 is, independently at each occurrence, benzyl. In certain preferred embodiments, R_4 is, independently at each occurrence, heteroarylmethyl. In certain preferred embodiments, R_4 is, independently at each occurrence, cycloheptylmethyl, cyclohexylmethyl, cyclopentylmethyl, or cyclobutylmethyl.

[0073] In certain preferred embodiments of compounds of formula I, both R_4 groups, together with the nitrogen through which they are attached, form a heterocyclic ring of 4 to 6 ring atoms, where one carbon may be optionally replaced with N, O, S, or SO_2, and where any carbon ring atom or additional N atom may be optionally substituted with C_1-C_4 alkyl, F, or CF_3. In certain more preferred embodiments, both R_4 groups, together with the nitrogen through which they are attached, form a pyridine, piperidine, piperazine, piperazine substituted with a methyl group, or morpholine ring.

[0074] In certain preferred embodiments of compounds of formula I, R_5 is, independently at each occurrence, H. In certain preferred embodiments of compounds, R_5 is, independently at each occurrence, C_1-C_4 alkyl, preferably methyl. In certain preferred embodiments of compounds, R_5 is, independently at each occurrence, aryl substituted with 0-3 R_1, preferably phenyl, tolyl, or xylyl. In certain preferred embodiments, R_5 is, independently at each occurrence, cyano.

[0075] In certain preferred embodiments of compounds of formula I , when two R_5 are present, when two R_5 are present, they form a carbocyclic ring of 3-7 carbons, preferably a cyclopentyl or cyclohexyl.

[0076] In certain preferred embodiments of compounds of formula I, R_6 is, independently at each occurrence, H. In certain preferred embodiments of compounds, R_6 is, independently at each occurrence, C_1-C_4 alkyl, preferably methyl. In certain preferred embodiments, R_6 is, independently at each occurrence, cyano.

[0077] In certain preferred embodiments of compounds of formula I, R_7 is, independently at each occurrence, H. In certain preferred embodiments of compounds, R_7 is, independently at each occurrence, C_1-C_8 alkyl, preferably C_1-C_4 alkyl, more preferably, methyl. In certain preferred embodiments of compounds, R_7 is, independently at each occurrence, C_3-C_8 cycloalkyl, preferably, cyclopentyl or cyclohexyl. In certain preferred embodiments of compounds, R_5 is, independently at each occurrence, aryl substituted with 0-3 R_1, preferably phenyl, tolyl, or xylyl.

[0078] In certain preferred embodiments of compounds of formula I, R_8 is, independently at each occurrence, H. In certain preferred embodiments of compounds, R_8 is, independently at each occurrence, C_1-C_4 alkyl, preferably methyl.

[0079] In certain preferred embodiments of compounds of formula I, R_9 is, independently at each occurrence, H. In certain preferred embodiments of compounds, R_9 is, independently at each occurrence, C_1-C_4 alkyl, preferably methyl.

[0080] In certain preferred embodiments of compounds of formula I, R_{10} is, independently at each occurrence, H. In certain preferred embodiments of compounds, R_{10} is, independently at each occurrence, C_1-C_4 alkyl, preferably methyl. In certain preferred embodiments of compounds of formula I, R_{10} and R_4 together with the nitrogen to which R_4 is attached form a nitrogen-containing ring containing 3-6 carbon atoms, especially, pyrrolidinyl, pyrrolyl, piperidinyl, pyridinyl, azepanyl, and azepinyl.

[0081] In certain preferred embodiments of compounds of formula I, n is an integer from 0 to 3. More preferably, n is 0 to 2. Even more preferably, n is 0 to 1. Yet more preferably, n is 0.

[0082] In certain preferred embodiments of compounds of formula I, x is an integer from 1 to 2. More preferably, x is 1.

[0083] In certain preferred embodiments of compounds of formula I, 1-2 carbon atoms in ring A may optionally be replaced with N. In certain preferred embodiments of compounds, one carbon atom in ring A may optionally be replaced with N. In certain preferred embodiments, no carbon atoms in ring A are replaced with N.

[0084] In certain preferred embodiments of compounds of formula I,

Y is N, CR_6, or C=O;

Z is N, NR_7, CR_5, or $C(R_5)_2$;

R_1 is, independently at each occurrence, alkyl, alkoxy, halo, CF_3, OCF_3, arylalkyloxy substituted with 0-3 R_{11}, aryloxy substituted with 0-3 R_{11}, aryl substituted with 0-3 R_{11}, heteroaryl substituted with 0-3 R_{11}, hydroxy, alkanoyloxy, nitro, nitrile, alkenyl, alkynyl, alkylsulfoxide, phenylsulfoxide substituted with 0-3 R_{11}, alkylsulfone, phenylsulfone substituted with 0-3 R_{11}, alkylsulfonamide, phenylsulfonamide substituted with 0-3 R_{11}, heteroaryloxy substituted with 0-3 R_{11}, heteroarylmethyloxy substituted with 0-3 R_{11}, alkylamido, or arylamido substituted with 0-3 R_{11}; or two adjacent R_1 also represent methylenedioxy;

R_2 is aryl substituted with 0-3 R_1 or heteroaryl substituted with 0-3 R_1;

R_3 is H

R_4 is, independently at each occurrence, H, or C_1-C_4 alkyl,

R_5 is, independently at each occurrence, H, C_1-C_4 alkyl, aryl substituted with 0-3 R_1, or cyano; or when two R_5 are present, they form a carbocyclic ring of 3-7 carbons;

R_6 is H, C1-C4 alkyl, or cyano;

R_7 is H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, aryl substituted with 0-3 R_1;

R_8 is H;

R_9 is H;

R_{10} is H;

n is an integer from 0 to 4;

x is 1;

R_{11} is alkyl, alkoxy, halo, CF_3, OCF_3, hydroxy, alkanoyloxy, nitro, nitrile, alkenyl, alkynyl, alkylsulfoxide, alkylsulfone, alkylsulfonamide, or alkylamido; or two adjacent R_{11} also represent methylenedioxy;

wherein 1-3 carbon atoms in ring A may optionally be replaced with N.

[0085] In certain preferred embodiments of compounds of formula I,

Y is CR_6;

Z is CR_5;

R_1 is, independently at each occurrence, alkyl, alkoxy, halo, CF_3, OCF_3, arylalkyloxy substituted with 0-3 R_{11}, aryloxy substituted with 0-3 R_{11}, aryl substituted with 0-3 R_{11}, heteroaryl substituted with 0-3 R_{11}, hydroxy, alkanoyloxy, nitro, nitrile, alkenyl, alkynyl, alkylsulfoxide, phenylsulfoxide substituted with 0-3 R_{11}, alkylsulfone, phenylsulfone substituted with 0-3 R_{11}, alkylsulfonamide, phenylsulfonamide substituted with 0-3 R_{11}, heteroaryloxy substituted with 0-3 R_{11}, heteroarylmethyloxy substituted with 0-3 R_{11}, alkylamido, or arylamido substituted with 0-3 R_{11}; or two adjacent R_1 also represent methylenedioxy;

R_2 is aryl substituted with 0-3 R_1 or heteroaryl substituted with 0-3 R_1;

R_3 is H or C_1-C_4 alkyl;

R_4 is, independently at each occurrence, H, C_1-C_4 alkyl, arylalkyl, heteroarylmethyl, cycloheptylmethyl, cyclohexylmethyl, cyclopentylmethyl, or cyclobutylmethyl;

R_5 is, independently at each occurrence, H, C_1-C_4 alkyl, aryl substituted with 0-3 R_1, or cyano; or when two R_5 are present, they form a carbocyclic ring of 3-7 carbons;

R_6 is H, C_1-C_4 alkyl, or cyano;

R_7 is H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or aryl substituted with 0-3 R_1;

R_8 is H or C_1-C_4 alkyl;

R_9 is H or C_1-C_4 alkyl;

R_{10} is, independently at each occurrence, H or C_1-C_4 alkyl; or R_{10} and R_4, together with the nitrogen to which R_4 is attached, form a nitrogen-containing ring

containing 3-6 carbon atoms;

n is an integer from 0 to 4;

x is an integer from 1 to 2; and

R_{11} is alkyl, alkoxy, halo, CF_3, OCF_3, hydroxy, alkanoyloxy, nitro, nitrile, alkenyl, alkynyl, alkylsulfoxide, alkylsulfone, alkylsulfonamide, or alkylamido; or two adjacent R_{11} also represent methylenedioxy;

wherein 1-3 carbon atoms in ring A may optionally be replaced with N.

[0086] In certain preferred embodiments of compounds of formula I,

Y is CR_6;

Z is $C(R_5)_2$;

R_1 is, independently at each occurrence, alkyl, alkoxy, halo, CF_3, OCF_3, arylalkyloxy substituted with 0-3 R_{11}, aryloxy substituted with 0-3 R_{11}, aryl substituted with 0-3 R_{11}, heteroaryl substituted with 0-3 R_{11}, hydroxy, alkanoyloxy, nitro, nitrile, alkenyl, alkynyl, alkylsulfoxide, phenylsulfoxide substituted with 0-3 R_{11}, alkylsulfone, phenylsulfone substituted with 0-3 R_{11}, alkylsulfonamide, phenylsulfonamide substituted with 0-3 R_{11}, heteroaryloxy substituted with 0-3 R_{11}, heteroarylmethyloxy substituted with 0-3 R_{11}, alkylamido, or arylamido substituted with 0-3 R_{11}; or two adjacent R_{11} also represent methylenedioxy;

R_2 is aryl substituted with 0-3 R_1 or heteroaryl substituted with 0-3 R_1;

R_3 is H or C_1-C_4 alkyl;

R_4 is, independently at each occurrence, H, C_1-C_4 alkyl, arylalkyl, heteroarylmethyl, cycloheptylmethyl, cyclohexylmethyl, cyclopentylmethyl, or cyclobutylmethyl;

R_5 is, independently at each occurrence, H, C_1-C_4 alkyl, aryl substituted with 0-3 R_1, or cyano; or when two R_5 are present, they form a carbocyclic ring of 3-7 carbons;

R_6 is H, C_1-C_4 alkyl, or cyano;

R_7 is H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, or aryl substituted with 0-3 R_1;

R_8 is H or C_1-C_4 alkyl;

R_9 is H or C_1-C_4 alkyl;

R_{10} is, independently at each occurrence, H or C_1-C_4 alkyl; or R_{10} and R_4, together with the nitrogen to which R_4 is attached, form a nitrogen-containing ring

containing 3-6 carbon atoms;

n is an integer from 0 to 4;

x is an integer from 1 to 2; and

R_{11} is alkyl, alkoxy, halo, CF_3, OCF_3, hydroxy, alkanoyloxy, nitro, nitrile, alkenyl, alkynyl, alkylsulfoxide, alkylsulfone, alkylsulfonamide, or alkylamido; or two adjacent R_{11} also represent methylenedioxy;

wherein 1-3 carbon atoms in ring A may optionally be replaced with N.

[0087] In certain preferred embodiments of compounds of formula I,

Y is C=O;

Z is $C(R_5)_2$;

R_1 is, independently at each occurrence, alkyl, alkoxy, halo, CF_3, OCF_3, arylalkyloxy substituted with 0-3 R_{11}, aryloxy substituted with 0-3 R_{11}, aryl substituted with 0-3 R_{11}, heteroaryl substituted with 0-3 R_{11}, hydroxy, alkanoyloxy, nitro, nitrile, alkenyl, alkynyl, alkylsulfoxide, phenylsulfoxide substituted with 0-3 R_{11}, alkylsulfone, phenylsulfone substituted with 0-3 R_{11}, alkylsulfonamide, phenylsulfonamide substituted with 0-3 R_{11}, heteroaryloxy substituted with 0-3 R_{11}, heteroarylmethyloxy substituted with 0-3 R_{11}, alkylamido, or arylamido substituted with 0-3 R_{11}; or two adjacent R_1 also represent methylenedioxy;

R_2 is aryl substituted with 0-3 R_1 or heteroaryl substituted with 0-3 R_1;

R_3 is H or C_1-C_4 alkyl;

R_4 is, independently at each occurrence, H, C_1-C_4 alkyl, arylalkyl, heteroarylmethyl, cycloheptylmethyl, cyclohexylmethyl, cyclopentylmethyl, or cyclobutylmethyl;

R_5 is, independently at each occurrence, H, C_1-C_4 alkyl, aryl substituted with 0-3 R_1, or cyano; or when two R_5 are present, they form a carbocyclic ring of 3-7 carbons;

R_6 is H, C_1-C_4 alkyl, or cyano;

R_7 is H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, or aryl substituted with 0-3 R_1;

R_8 is H or C_1-C_4 alkyl;

R_9 is H or C_1-C_4 alkyl;

R_{10} is, independently at each occurrence, H or C_1-C_4 alkyl; or R_{10} and R_4, together with the nitrogen to which R_4 is attached, form a nitrogen-containing ring

containing 3-6 carbon atoms;

n is an integer from 0 to 4;

x is an integer from 1 to 2; and

R_{11} is alkyl, alkoxy, halo, CF_3, OCF_3, hydroxy, alkanoyloxy, nitro, nitrile, alkenyl, alkynyl, alkylsulfoxide, alkylsulfone, alkylsulfonamide, or alkylamido; or two adjacent R_{11} also represent methylenedioxy;

wherein 1-3 carbon atoms in ring A may optionally be replaced with N.

[0088] In certain preferred embodiments of compounds of formula I,

Y is C=O;

Z is NR_7;

R_1 is, independently at each occurrence, alkyl, alkoxy, halo, CF_3, OCF_3, arylalkyloxy substituted with 0-3 R_{11}, aryloxy substituted with 0-3 R_{11}, aryl substituted with 0-3 R_{11}, heteroaryl substituted with 0-3 R_{11}, hydroxy, alkanoyloxy, nitro, nitrile, alkenyl, alkynyl, alkylsulfoxide, phenylsulfoxide substituted with 0-3 R_{11}, alkylsulfone, phenylsulfone substituted with 0-3 R_{11}, alkylsulfonamide, phenylsulfonamide substituted with 0-3 R_{11}, heteroaryloxy substituted with 0-3 R_{11}, heteroarylmethyloxy substituted with 0-3 R_{11}, alkylamido, or arylamido substituted with 0-3 R_{11}; or two adjacent R_{11} also represent methylenedioxy;

R_2 is aryl substituted with 0-3 R_1 or heteroaryl substituted with 0-3 R_1;

R_3 is H or C_1-C_4 alkyl;

R_4 is, independently at each occurrence, H, C_1-C_4 alkyl, arylalkyl, heteroarylmethyl, cycloheptylmethyl, cyclohexylmethyl, cyclopentylmethyl, or cyclobutylmethyl;

R_5 is, independently at each occurrence, H, C_1-C_4 alkyl, aryl substituted with 0-3 R_1, or cyano; or in the cases where two R_5 substitutions are present, they may form a carbocyclic ring of C_3-C_7;

R_6 is H, C_1-C_4 alkyl, or cyano;

R_7 is H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or aryl substituted with 0-3 R_1;

R_8 is H or C_1-C_4 alkyl;

R_9 is H or C_1-C_4 alkyl;

R_{10} is, independently at each occurrence, H or C_1-C_4 alkyl; R_{10} is, independently at each occurrence, H or C_1-C_4 alkyl; or R_{10} and R_4, together with the

nitrogen to which R_4 is attached, form a nitrogen-containing ring containing 3-6 carbon atoms;

n is an integer from 0 to 4;

x is an integer from 1 to 2; and

R_{11} is alkyl, alkoxy, halo, CF_3, OCF_3, hydroxy, alkanoyloxy, nitro, nitrile, alkenyl, alkynyl, alkylsulfoxide, alkylsulfone, alkylsulfonamide, or alkylamido; or two adjacent R_{11} also represent methylenedioxy;

wherein 1-3 carbon atoms in ring A may optionally be replaced with N.

[0089] Preferred compounds of formula I include:

1-(1H-indol-1-yl)-3-(4-methylpiperazin-1-yl)-1-phenylpropan-2-ol;

1-(5-fluoro-1H-indol-1-yl)-3-(4-methylpiperazin-1-yl)-1-phenylpropan-2-ol;

1-(1H-indol-1-yl)-3-morpholin-4-yl-1-phenylpropan-2-ol;

3-(dimethylamino)-1-(1H-indol-1-yl)-1-phenylpropan-2-ol;

3-(ethylamino)-1-(1H-indol-1-yl)-1-phenylpropan-2-ol;

1-(1H-indol-1-yl)-3-(isopropylamino)-1-phenylpropan-2-ol;

3-(benzylamino)-1-(1H-indol-1-yl)-1-phenylpropan-2-ol;

3-[(cyclohexylmethyl)amino]-1-(1H-indol-1-yl)-1-phenylpropan-2-ol;

3-[(cyclohexylmethyl)amino]-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

3-(isopropylamino)-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

3-(ethylamino)-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

1-(1H-indol-1-yl)-1-phenyl-3-piperazin-1-ylpropan-2-ol di;

1-(1H-indol-1-yl)-1-phenyl-3-[(pyridin-4-ylmethyl) amino]propan-2-ol;

1-(5-chloro-1H-indol-1-yl)-1-phenyl-3-piperidin-1-ylpropan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

3-amino-1-(1H-indol-1-yl)-1-phenylpropan-2-ol;

3-(ethylamino)-1-(5-fluoro-1H-indol-1-yl)-1-phenylpropan-2-ol;

3-amino-1-(5-fluoro-1H-indol-1-yl)-1-phenylpropan-2-ol;

1-(5-fluoro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

3-(methylamino)-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

3-amino-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

3-[thyl(methyl)amino]-1-(1H-indol-1-yl)-1-phenylpropan-2-ol;

1-(5-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(5-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-1-ol;

1-[2-hydroxy-3-(methylamino)-1-phenylpropyl]-1H-indole-3-carbonitrile;

1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

3-(methylamino)-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

1-(3-chlorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

1-(4-chlorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-[3-(trifluoromethoxy)phenyl]propan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-[2-(trifluoromethoxy)phenyl]propan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-[2-(trifluoromethoxy)phenyl]propan-2-ol;

1-(2-chlorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-[4-(trifluoromethoxy)phenyl]propan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-[4-(trifluoromethoxy)phenyl]propan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-[4-(trifluoromethoxy)phenyl]propan-2-ol;

4-amino-1-(3-chlorophenyl)-1-(1H-indol-1-yl)butan-2-ol

1-(3-bromophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

3-[2-hydroxy-1-(1H-indol-1-yl)-3-(methylamino)propyl]benzonitrile

1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-[3-(3-methylphenyl)-1H-indol-1-yl]propan-2-ol;

1-(4-fluorophenyl)-3-(methylamino)-1-(3-methyl-1H-indol-1-yl)propan-2-ol;

1-(2-fluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

1-(4-fluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-(3-methylphenyl)propan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-(2-methylphenyl)propan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-(2-methylphenyl)propan-2-ol;

3-(ethylamino)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)propan-2-ol;

1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-morpholin-4-ylpropan-2-ol;

1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-(propylamino)propan-2-ol;

1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-(4-methylpiperazin-1-yl)propan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-(4-methylphenyl)propan-2-ol;

1-(2,3-dihydro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(2,3-dihydro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-[3-(2-methylphenyl)-1H-indol-1-yl]propan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-(2-methyl-2,3-dihydro-1H-indol-1-yl)propan-2-ol;

1-(7-fluoro-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(7-fluoro-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

3-(methylamino)-1-(7-methyl-2,3-dihydro-1H-indol-1-yl)-1-phenylpropan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-(7-methyl-2,3-dihydro-1H-indol-1-yl)propan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-(5-methyl-2,3-dihydro-1H-indol-1-yl)propan-2-ol;

1-(1H-indol-1-yl)-1-(3-methoxyphenyl)-3-(methylamino)propan-2-ol;

1-(1H-indol-1-yl)-1-(4-methoxyphenyl)-3-(methylamino)propan-2-ol;

3-(methylamino)-1-(2-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

1-(1H-benzimidazol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

3-(methylamino)-1-(2-methyl-1H-benzimidazol-1-yl)-1-phenylpropan-2-ol;

1-(4-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(5-fluoro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(5-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(7-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(4-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(6-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(5-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(3-fluorophenyl)-1-(6-methoxy-1H-indol-1-yl)-3-(methylamino)propan-2-ol;

3-(methylamino)-1-phenyl-1-(1H-pyrrolo[2,3-b]pyridin-1-yl)propan-2-ol;

1-(5-chloro-2,3-dihydro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

3-(methylamino)-1-phenyl-1-(1H-pyrrolo[2,3-c]pyridin-1-yl)propan-2-ol;

1-(5-fluoro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

3-(methylamino)-1-(3-fluorophenyl)-1-(1H-pyrrolo[2,3-c]pyridin-1-yl)propan-2-ol;

1-(5-chloro-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

3-(methylamino)-1-(6-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

3-(methylamino)-1-(7-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-(5-methyl-1H-indol-1-yl)propan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-(7-methyl-1H-indol-1-yl)propan-2-ol;

3-(methylamino)-1-(4-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

3-(methylamino)-1-(5-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-(4-methyl-1H-indol-1-yl)propan-2-ol;

1-(3-ethyl-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-(3-phenyl-1H-indol-1-yl)propan-2-ol;

7-fluoro-1-[2hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one;

1-[2hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro- 2H-indol-2-one;

7-fluoro-1-[1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-3,3- dimethyl-1,3-dihydro-2H-indol-2-one;

1-(1H-indol-1-yl)-3-(methylamino)-1-(2-thienyl)propan-2-ol;

1(1H-indol-1-yl)-3-(methylamino)-1-(2-thienyl)propan-2-ol;

1'-[2-hydroxy-3-(methylamino)-1-phenylpropyl]spiro[cyclohexane-1,3'-indol]-2'(1'H)-one;

2-(3-fluorophenyl)-2-(1H-indol-1-yl)-1-[(2S)-pyrrolidin-2-yl]ethanol;

2-(3-fluorophenyl)-2-(1H-indol-1-yl)-1-[pyrrolidin-2-yl]ethanol;

1'-[2hydroxy-3-(methylamino)-1-phenylpropyl]spiro[cyclobutane-1,3'-indol]-2'(1'H)-one;

1'-[2hydroxy-3-(methylamino)-1-phenylpropyl]spiro[cyclopentane-1,3'-indol]-2'(1'H)-one;

1'-[2hydroxy-3-(methylamino)-1-phenylpropyl]spiro[cyclopropane-1,3'-indol]-2'(1'H)-one;

5-fluoro-1-[2hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one;

3-(cyclopropylamino)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)propan-2-ol;

7'-fluoro-1'-[2hydroxy-3-(methylamino)-1-phenylpropyl]spiro[cyclohexane-1,3'-indol]-2'(1'H)-one;

5'-bromo-1'-[2hydroxy-3-(methylamino)-1-phenylpropyl]spiro[cyclohexane-1,3'-indol]-2'(1'H)-one;

1-(3-fluorophenyl)-1-[3-(2-fluorophenyl)-1H-indol-1-yl]-3-(methylamino)propan-2-ol;

1-[3-(3,4-dichlorophenyl)-1H-indol-1-yl]-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(3-fluorophenyl)-1-[3-(3-fluorophenyl)-1H-indol-1-yl]-3-(methylamino)propan-2-ol;

1-(5-fluoro-3-methyl-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

3-amino-1-(5-fluoro-3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

1-(5-chloro-3-methyl-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

3amino-1-(5-chloro-3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

[3-(5-chloro-3-methyl-1H-indol-1-yl)-2-methoxy-3-phenylpropyl]methylamine;

1-(7-chloro-3-methyl-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

[3-(5-fluoro-3-methyl-1H-indol-1-yl)-2-methoxy-3-phenylpropyl]methylamine;

1-(4-bromo-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(4-bromo-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(5-bromo-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(5-bromo-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-[2-hydroxy-3-(methylamino)-1-phenylpropyl]-1H-indole-4-carbonitrile;

1-(6-bromo-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-[2-hydroxy-3-(methylamino)-1-phenylpropyl]-1H-indole-5-carbonitrile;

1-[1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-1H-indole-4-carbonitrile;

1-(6-bromo-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(6-fluoro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

3-amino-1-(3-fluorophenyl)-1-(1H-indol-1-yl)propan-2-ol;

1-(7-bromo-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-[3-(trifluoromethyl)phenyl]propan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-spiro[cyclohexane-1,3'-indol]-1'(2'H)-ylpropan-2-ol;

1-(2,3-dihydro-1H-indol-1-yl)-3-(methylamino)-1-[3-(trifluoromethyl)phenyl]propan-2-ol;

1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

1-(3,4-difluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-(3-methyl-1H-indol-1-yl)propan-2-ol;

1-(4-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(6-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(7-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(7-chloro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(4-chloro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(6-chloro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(5-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(5-chloro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(3-isopropyl-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(3-fluorophenyl)-1-(3-isopropyl-1H-indol-1-yl)-3-(methylamino)propan-2-ol;

1-(3,5-difluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

1-(3,5-difluorophenyl)-1-(2,3-dihydro-1H-indol-1-yl)-3-(methylamino)propan-2-ol;

4-amino-1-(3-fluorophenyl)-1-(1H-indol-1-yl)butan-2-ol;

1-(3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(3,5-difluorophenyl)-1-(3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)propan-2-ol;

1-(3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-(3-methyl-2,3-dihydro-1H-indol-1-yl)propan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-spiro[cyclopentane-1,3'-indol]-1'(2'H)-ylpropan-2-ol;

1-(3-fluorophenyl)-1-[3-(4-methoxyphenyl)-1H-indol-1-yl]-3-(methylamino)propan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-[3-(4-methylphenyl)-1H-indol-1-yl]propan-2-ol;

1-[3-(4-tert-butylphenyl)-1H-indol-1-yl]-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(3-fluorophenyl)-1-[3-(3-methoxyphenyl)-1H-indol-1-yl]-3-(methylamino)propan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-{3-[4-(trifluoromethyl)phenyl]-1H-indol-1-yl}propan-2-ol;

1-(3,5-difluorophenyl)-1-(6-fluoro-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)propan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-{3-[2-(trifluoromethyl)phenyl]-1H-indol-1-yl}propan-2-ol;

1-(3-fluorophenyl)-1-[3-(2-methoxyphenyl)-1H-indol-1-yl]-3-(methylamino)propan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-{3-[3-(trifluoromethyl)phenyl]-1H-indol-1-yl}propan-2-ol;

3-amino-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

1-(7-fluoro-3-methyl-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

3-amino-1-(7-fluoro-3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

1-(7-fluoro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(4-fluoro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(7-fluoro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(4-fluoro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-[5-(trifluoromethyl)-1H-indol-1-yl]propan-2-ol;

1-(6-fluoro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

3-(methylamino)-1-phenyl-1-[6-(trifluoromethyl)-1H-indol-1-yl]propan-2-ol;

3-(methylamino)-1-phenyl-1-[5-(trifluoromethyl)-1H-indol-1-yl]propan-2-ol;

1-(3-tert-butyl-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(1H-indol-1-yl)-2-methyl-3-(methylamino)-1-phenylpropan-2-ol;

3-(1H-indol-1-yl)-1-(methylamino)-3-phenylbutan-2-ol;

1-tert-butyl-3-[2hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2H-benzimidazol-2-one;

1-[2-hydroxy-3-(methylamino)-1-phenylpropyl]-3-propyl-1,3-dihydro-2H-benzimidazol-2-one;

5-bromo-1-[2hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one;

6-fluoro-1-[2hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one;

4-fluoro-1-[2hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one;

1-cyclobutyl-3-[2hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2H-benzimidazol-2-one;

5-fluoro-3-[2hydroxy-3-(methylamino)-1-phenylpropyl]-1-propyl-1,3-dihydro-2H-benzimidazol-2-one;

1-ethyl-3-[1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-1,3-dihydro-2H-benzimidazol-2-one;

1-ethyl-3-[2hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2H-benzimidazol-2-one;

4-fluoro-3-[2hydroxy-3-(methylamino)-1-phenylpropyl]-1-isopropyl-1,3-dihydro-2H-benzimidazol-2-one;

1-cyclopentyl-3-[2hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2H-benzimidazol-2-one;

1-[2hydroxy-3-(methylamino)-1-phenylpropyl]-3-isopropyl-1,3-dihydro-2H-benzimidazol-2-one;

3-[3(ethylamino)-2-hydroxy-1-phenylpropyl]-5-fluoro-1-isopropyl-1,3-dihydro-2H-benzimidazol-2-one;

1-[2hydroxy-3-(methylamino)-1-phenylpropyl]-3-methyl-1,3-dihydro-2H-benzimidazol-2-one;

1-ethyl-5-fluoro-3-[2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2H-benzimidazol-2-one;

1-ethyl-4-fluoro-3-[2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2H-benzimidazol-2-one;

4-fluoro-3-[1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-1-isopropyl-1,3-dihydro-2H-benzimidazol-2-one;

1-ethyl-4-fluoro-3-[2hydroxy-3-(methylamino)-1-(3-fluorophenyl)-propyl]-1,3-dihydro-2H-benzimidazol-2-one;

1-[1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one;

1-[3-(2,3-difluorophenyl)-1H-indol-1-yl]-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-[3-(2-chlorophenyl)-1H-indol-1-yl]-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol; and

pharmaceutically acceptable salts thereof, particularly hydrochloride and dihydrochloride salts thereof.

[0090] Particularly preferred compounds of formula I include:

(1RS,2SR)-1-(1H-indol-1-yl)-3-(4-methylpiperazin-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-1-(5-fluoro-1H-indol-1-yl)-3-(4-methylpiperazin-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-1-(1H-indol-1-yl)-3-morpholin-4-yl-1-phenylpropan-2-ol;

(1RS,2SR)-3-(dimethylamino)-1-(1H-indol-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-3-(ethylamino)-1-(1H-indol-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-1-(1H-indol-1-yl)-3-(isopropylamino)-1-phenylpropan-2-ol;

(1RS,2SR)-3-(benzylamino)-1-(1H-indol-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-3-[(cyclohexylmethyl)amino]-1-(1H-indol-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-3-[(cyclohexylmethyl)amino]-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-3-(isopropylamino)-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1RS,2SR)-3-(ethylamino)-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-1-(1H-indol-1-yl)-1-phenyl-3-piperazin-1-ylpropan-2-ol;

(1RS,2SR)-1-(1H-indol-1-yl)-1-phenyl-3-[(pyridin-4-ylmethyl) amino]propan-2-ol;

(1RS,2SR)-1-(5-chloro-1H-indol-1-yl)-1-phenyl-3-piperidin-1-ylpropan-2-ol;

(1RS,2RS)-1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol ;

(1RS,2SR)-3-amino-1-(1H-indol-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-3-(ethylamino)-1-(5-fluoro-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-3-amino-1-(5-fluoro-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-1-(5-fluoro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1RS,2SR)-3-(methylamino)-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1R,2S)-1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1RS,2SR)-3-amino-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-3-[ethyl(methyl)amino]-1-(1H-indol-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-1-(5-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1RS,2RS)-1-(5-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-1-ol;

1-[(1RS,2SR)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1H-indole-3-carbonitrile;

(1R,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2S)-1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-3-(methylamino)-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1S,2R)-1-(3-chlorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(4-chlorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-[3-(trifluoromethoxy)phenyl]propan-2-ol;

(1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-[2-(trifluoromethoxy)phenyl]propan-2-ol;

(1R,2S)-1-(1H-indol-1-yl)-3-(methylamino)-1-[2-(trifluoromethoxy)phenyl]propan-2-ol;

(1S,2R)-1-(2-chlorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

(1SR,2RS)-1-(1H-indol-1-yl)-3-(methylamino)-1-[4-(trifluoromethoxy)phenyl]propan-2-ol;

(1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-[4-(trifluoromethoxy)phenyl]propan-2-ol;

(1R,2S)-1-(1H-indol-1-yl)-3-(methylamino)-1-[4-(trifluoromethoxy)phenyl]propan-2-ol;

(1S,2R)-4-amino-1-(3-chlorophenyl)-1-(1H-indol-1-yl)butan-2-ol

(1S,2R)-1-(3-bromophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

3-[(1S,2R)-2-hydroxy-1-(1H-indol-1-yl)-3-(methylamino)propyl]benzonitrile

(1S,2R)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-[3-(3-methylphenyl)-1H-indol-1-yl]propan-2-ol;

(1S,2R)-1-(4-fluorophenyl)-3-(methylamino)-1-(3-methyl-1H-indol-1-yl)propan-2-ol;

(1S,2R)-1-(2-fluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(4-fluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-(3-methylphenyl)propan-2-ol;

(1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-(2-methylphenyl)propan-2-ol;

(1R,2S)-1-(1H-indol-1-yl)-3-(methylamino)-1-(2-methylphenyl)propan-2-ol;

(1S,2R)-3-(ethylamino)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-morpholin-4-ylpropan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-(propylamino)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-(4-methylpiperazin-1-yl)propan-2-ol;

(1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-(4-methylphenyl)propan-2-ol;

(1S,2R)-1-(2,3-dihydro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(2,3-dihydro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-[3-(2-methylphenyl)-1H-indol-1-yl]propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(2-methyl-2,3-dihydro-1H-indol-1-yl)propan-2-ol;

(1S,2R)-1-(7-fluoro-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(7-fluoro-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-3-(methylamino)-1-(7-methyl-2,3-dihydro-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(7-methyl-2,3-dihydro-1H-indol-1-yl)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(5-methyl-2,3-dihydro-1H-indol-1-yl)propan-2-ol;

(1S,2R)-1-(1H-indol-1-yl)-1-(3-methoxyphenyl)-3-(methylamino)propan-2-ol;

(1SR,2RS)-1-(1H-indol-1-yl)-1-(4-methoxyphenyl)-3-(methylamino)propan-2-ol;

(1RS,2SR)-3-(methylamino)-1-(2-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-1-(1H-benzimidazol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1RS,2SR)-3-(methylamino)-1-(2-methyl-1H-benzimidazol-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-1-(4-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(5-fluoro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(5-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(7-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(4-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(6-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1RS,2SR)-1-(5-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-1-(6-methoxy-1H-indol-1-yl)-3-(methylamino)propan-2-ol;

(1S,2R)-3-(methylamino)-1-phenyl-1-(1H-pyrrolo[2,3-b]pyridin-1-yl)propan-2-ol;

(1S,2R)-1-(5-chloro-2,3-dihydro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-3-(methylamino)-1-phenyl-1-(1H-pyrrolo[2,3-c]pyridin-1-yl)propan-2-ol;

(1S,2R)-1-(5-fluoro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-3-(methylamino)-1-(3-fluorophenyl)-1-(1H-pyrrolo[2,3-c]pyridin-1-yl)propan-2-ol;

(1S,2R)-1-(5-chloro-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-3-(methylamino)-1-(6-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1S,2R)-3-(methylamino)-1-(7-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(5-methyl-1H-indol-1-yl)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(7-methyl-1H-indol-1-yl)propan-2-ol;

(1S,2R)-3-(methylamino)-1-(4-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1S,2R)-3-(methylamino)-1-(5-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(4-methyl-1H-indol-1-yl)propan-2-ol;

(1S,2R)-1-(3-ethyl-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(3-phenyl-1H-indol-1-yl)propan-2-ol;

7-fluoro-1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3- dihydro-2H-indol-2-one;

1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro- 2H-indol-2-one;

7-fluoro-1-[(1S,2R)-1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one;

(1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-(2-thienyl)propan-2-ol;

(1R,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-(2-thienyl)propan-2-ol;

1'-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]spiro[cyclohexane-1,3'-indol]-2'(1'H)-one;

(1S,2R)-2-(3-fluorophenyl)-2-(1H-indol-1-yl)-1-[(2S)-pyrrolidin-2-yl]ethanol;

(1R,2S)-2-(3-fluorophenyl)-2-(1H-indol-1-yl)-1-[(2S)-pyrrolidin-2-yl]ethanol;

1'-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]spiro[cyclobutane-1,3'-indol]-2'(1'H)-one;

1'-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]spiro[cyclopentane-1,3'-indol]-2'(1'H)-one;

1'-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]spiro[cyclopropane-1,3'-indol]-2'(1'H)-one;

5-fluoro-1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one;

(1S,2R)-3-(cyclopropylamino)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)propan-2-ol;

7'-fluoro-1'-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]spiro[cyclohexane-1,3'-indol]-2'(1'H)-one;

5'-bromo-1'-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]spiro[cyclohexane-1,3'-indol]-2'(1'H)-one;

(1S,2R)-1-(3-fluorophenyl)-1-[3-(2-fluorophenyl)-1H-indol-1-yl]-3-(methylamino)propan-2-ol;

(1S,2R)-1-[3-(3,4-dichlorophenyl)-1H-indol-1-yl]-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-1-[3-(3-fluorophenyl)-1H-indol-1-yl]-3-(methylamino)propan-2-ol;

(1S,2R)-1-(5-fluoro-3-methyl-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S*,2R*)-3-amino-1-(5-fluoro-3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1S,2R)-1-(5-chloro-3-methyl-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-3-amino-1-(5-chloro-3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

[(2R,3S)-3-(5-chloro-3-methyl-1H-indol-1-yl)-2-methoxy-3-phenylpropyl]methylamine;

(1S,2R)-1-(7-chloro-3-methyl-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

[(2R,3S)-3-(5-fluoro-3-methyl-1H-indol-1-yl)-2-methoxy-3-phenylpropyl]methylamine;

(1S,2R)-1-(4-bromo-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(4-bromo-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(5-bromo-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(5-bromo-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1H-indole-4-carbonitrile;

(1S,2R)-1-(6-bromo-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1H-indole-5-carbonitrile;

1-[(1S,2R)-1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-1H-indole-4-carbonitrile;

(1S,2R)-1-(6-bromo-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(6-fluoro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-3-amino-1-(3-fluorophenyl)-1-(1H-indol-1-yl)propan-2-ol;

(1S,2R)-1-(7-bromo-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-[3-(trifluoromethyl)phenyl]propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-spiro[cyclohexane-1,3'-indol]-1'(2'H)-ylpropan-2-ol;

(1S,2R)-1-(2,3-dihydro-1H-indol-1-yl)-3-(methylamino)-1-[3-(trifluoromethyl)phenyl]propan-2-ol;

(1S,2S)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3,4-difluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(3-methyl-1H-indol-1-yl)propan-2-ol;

(1S,2R)-1-(4-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(6-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(7-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(7-chloro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(4-chloro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(6-chloro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(5-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(5-chloro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3-isopropyl-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-1-(3-isopropyl-1H-indol-1-yl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3,5-difluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3,5-difluorophenyl)-1-(2,3-dihydro-1H-indol-1-yl)-3-(methylamino)propan-2-ol;

(1S,2R)-4-amino-1-(3-fluorophenyl)-1-(1H-indol-1-yl)butan-2-ol;

(1S,2R)-1-(3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3,5-difluorophenyl)-1-(3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(3-methyl-2,3-dihydro-1H-indol-1-yl)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-spiro[cyclopentane-1,3'-indol]-1'(2'H)-ylpropan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-1-[3-(4-methoxyphenyl)-1H-indol-1-yl]-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-[3-(4-methylphenyl)-1H-indol-1-yl]propan-2-ol;

(1S,2R)-1-[3-(4-tert-butylphenyl)-1H-indol-1-yl]-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-1-[3-(3-methoxyphenyl)-1H-indol-1-yl]-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-{3-[4-(trifluoromethyl)phenyl]-1H-indol-1-yl}propan-2-ol;

(1S,2R)-1-(3,5-difluorophenyl)-1-(6-fluoro-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-{3-[2-(trifluoromethyl)phenyl]-1H-indol-1-yl}propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-1-[3-(2-methoxyphenyl)-1H-indol-1-yl]-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-{3-[3-(trifluoromethyl)phenyl]-1H-indol-1-yl}propan-2-ol;

(1S,2R)-3-amino-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1S,2R)-1-(7-fluoro-3-methyl-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-3-amino-1-(7-fluoro-3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1S,2R)-1-(7-fluoro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(4-fluoro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(7-fluoro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(4-fluoro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-[5-(trifluoromethyl)-1H-indol-1-yl]propan-2-ol;

(1S,2R)-1-(6-fluoro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-3-(methylamino)-1-phenyl-1-[6-(trifluoromethyl)-1H-indol-1-yl]propan-2-ol;

(1S,2R)-3-(methylamino)-1-phenyl-1-[5-(trifluoromethyl)-1H-indol-1-yl]propan-2-ol;

(1S,2R)-1-(3-tert-butyl-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(1H-indol-1-yl)-2-methyl-3-(methylamino)-1-phenylpropan-2-ol;

(2R,3S)-3-(1H-indol-1-yl)-1-(methylamino)-3-phenylbutan-2-ol;

1-tert-butyl-3-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2H-benzimidazol-2-one;

1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3-propyl-1,3-dihydro-2H-benzimidazol-2-one;

5-bromo-1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one;

6-fluoro-1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one;

4-fluoro-1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one;

1-cyclobutyl-3-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2H-benzimidazol-2-one;

5-fluoro-3-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1-propyl-1,3-dihydro-2H-benzimidazol-2-one;

1-ethyl-3-[(1S,2R)-1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-1,3-dihydro-2H-benzimidazol-2-one;

1-ethyl-3-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2H-benzimidazol-2-one;

4-fluoro-3-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1-isopropyl-1,3-dihydro-2H-benzimidazol-2-one;

1-cyclopentyl-3-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2H-benzimidazol-2-one;

1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3-isopropyl-1,3-dihydro-2H-benzimidazol-2-one;

3-[(1S,2R)-3-(ethylamino)-2-hydroxy-1-phenylpropyl]-5-fluoro-1-isopropyl-1,3-dihydro-2H-benzimidazol-2-one;

1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3-methyl-1,3-dihydro-2H-benzimidazol-2-one;

1-ethyl-5-fluoro-3-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2H-benzimidazol-2-one;

1-ethyl-4-fluoro-3-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2H-benzimidazol-2-one;

4-fluoro-3-[(1S,2R)-1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-1-isopropyl-1,3-dihydro-2H-benzimidazol-2-one;

1-ethyl-4-fluoro-3-[(1S,2R)-2-hydroxy-3-(methylamino)-1-(3-fluorophenyl)-propyl]-1,3-dihydro-2H-benzimidazol-2-one;

1-[(1S,2R)-1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one;

(1S,2R)-1-[3-(2,3-difluorophenyl)-1H-indol-1-yl]-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-[3-(2-chlorophenyl)-1H-indol-1-yl]-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol; and

pharmaceutically acceptable salts thereof, particularly hydrochloride and

dihydrochloride salts thereof.

[0091] Some of the compounds of the present invention may contain chiral centers and such compounds may exist in the form of stereoisomers (*i.e.* enantiomers). The present invention includes all such stereoisomers and any mixtures thereof including racemic mixtures. Racemic mixtures of the stereoisomers as well as the substantially pure stereoisomers are within the scope of the invention. The term "substantially pure," as used herein, refers to at least about 90 mole %, more preferably at least about 95 mole %, and most preferably at least about 98 mole % of the desired stereoisomer is present relative to other possible stereoisomers. Preferred enantiomers may be isolated from racemic mixtures by any method known to those skilled in the art, including high performance liquid chromatography (HPLC) and the formation and crystallization of chiral salts or prepared by methods described herein. See, for example, Jacques, *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen, S.H., *et al.*, *Tetrahedron*, 33:2725 (1977); Eliel, E.L. *Stereochemistry of Carbon Compounds*, (McGraw-Hill, NY, 1962); Wilen, S.H. *Tables of Resolving Agents and Optical Resolutions*, p. 268 (E.L. Eliel, Ed., University of Notre Dame Press, Notre Dame, IN 1972).

[0092] The present invention includes prodrugs of the compounds of formula I. "Prodrug," as used herein, means a compound which is convertible *in vivo* by metabolic means (*e.g.* by hydrolysis) to a compound of formula I. Various forms of prodrugs are known in the art, for example, as discussed in Bundgaard, (ed.), *Design of Prodrugs*, Elsevier (1985); Widder, *et al.* (ed.), *Methods in Enzymology*, vol. 4, Academic Press (1985); Krogsgaard-Larsen, et al., (ed). "Design and Application of Prodrugs," *Textbook of Drug Design and Development*, Chapter 5, 113-191 (1991), Bundgaard, *et al.*, *Journal of Drug Deliver Reviews*, 1992, 8:1-38, Bundgaard, *J. of Pharmaceutical Sciences*, 1988, 77:285 *et seq.*; and Higuchi and Stella (eds.) *Prodrugs as Novel Drug Delivery Systems*, American Chemical Society (1975).

[0093] Further, the compounds of formula I may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol,

and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purpose of the present invention.

[0094] The compounds of the present invention may be prepared in a number of ways well known to those skilled in the art. The compounds can be synthesized, for example, by the methods described below, or variations thereon as appreciated by the skilled artisan. All processes disclosed in association with the present invention are contemplated to be practiced on any scale, including milligram, gram, multigram, kilogram, multikilogram or commercial industrial scale.

[0095] As will be readily understood, functional groups present may contain protecting groups during the course of synthesis. Protecting groups are known *per se* as chemical functional groups that can be selectively appended to and removed from functionalities, such as hydroxyl groups and carboxyl groups. These groups are present in a chemical compound to render such functionality inert to chemical reaction conditions to which the compound is exposed. Any of a variety of protecting groups may be employed with the present invention. Protecting groups that may be employed in accordance with the present invention may be described in Greene, T.W. and Wuts, P.G.M., *Protective Groups in Organic Synthesis* 2d. Ed., Wiley & Sons, 1991.

[0096] Compounds of the present invention are suitably prepared in accordance with the following general description and specific examples. Variables used are as defined for formula I, unless otherwise noted. The reagents used in the preparation of the compounds of this invention can be either commercially obtained or can be prepared by standard procedures described in the literature. In accordance with this invention, compounds of formula I are produced by the following reaction schemes (***Scheme I-IV***).

[0097] The compounds of this invention contain chiral centers, proving for various stereoisomeric forms such as enantiomeric mixtures as well as optical isomers. The individual optical isomers can be prepared directly through asymmetric and/or

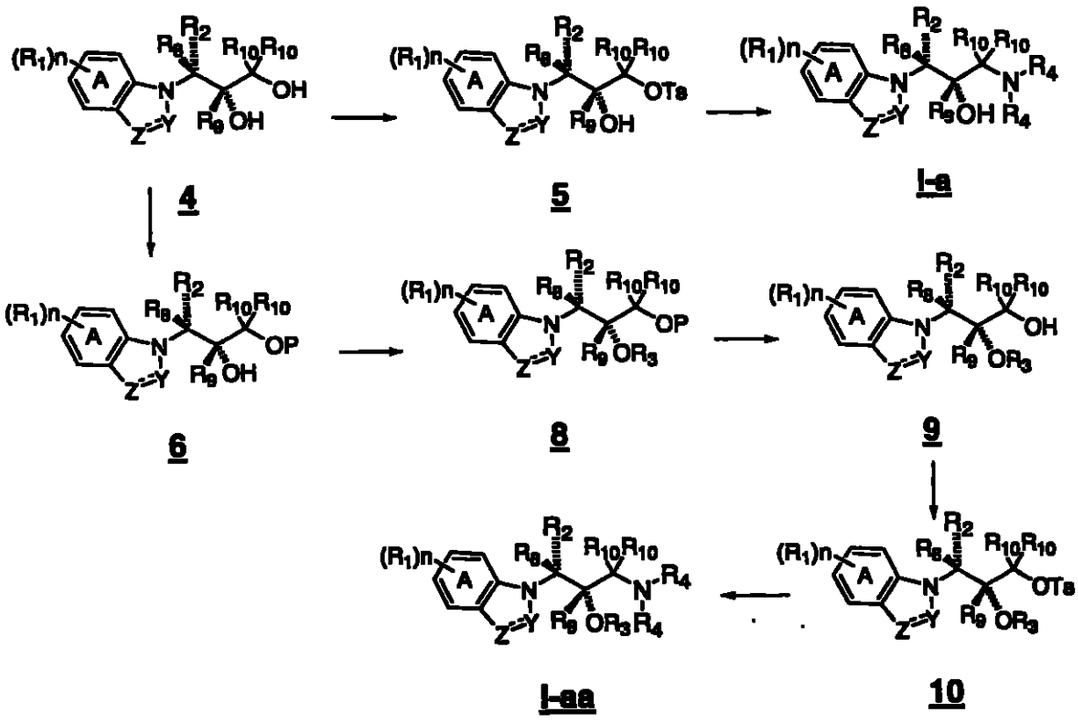
stereospecific synthesis or by conventional chiral separation of optical isomers from the enantiomeric mixture.

[0098] Compounds of the present invention are suitably prepared in accordance with the following general description and specific examples. Variables used are as defined for formula I, unless otherwise noted. The reagents used in the preparation of the compounds of this invention can be either commercially obtained or can be prepared by standard procedures described in the literature. In accordance with this invention, compounds of formula I are produced by the following reaction schemes (***Scheme I-IV***).

[0099] The compounds of this invention contain chiral centers, providing various stereoisomeric forms such as enantiomeric mixtures as well as optical isomers. The individual optical isomers can be prepared directly through asymmetric and/or stereospecific synthesis or by conventional chiral separation of optical isomers from the enantiomeric mixture.

[0100] In accordance with this invention, compounds of formula I are produced by the following reaction schemes (***Schemes I*** to ***IV***). Depending on the desired diastereomer, the compounds can be prepared via two different synthetic routes (A and B, ***Schemes I*** and ***II***). If it is desired to synthesize compounds of formula I-a, they can be prepared from compounds of formula 4 by selectively converting the primary alcohol into a leaving group and displacing it with a desired amine. (Route A, ***Scheme I***) Any conventional method for the selective conversion of a primary alcohol into a leaving group, and any conventional method for displacing a primary leaving group with an amine can be utilized for this conversion. In accordance with the preferred embodiment of this invention, the diol of formula 4 is treated with *para*-toluenesulfonyl chloride in pyridine to form the tosylate of formula 5, which is converted to the compound of formula I-a through treatment with an excess of alcoholic amine solution, either at room temperature or heated to about 40°C to about 80°C in a sealed tube. Compounds of formula I-a can be converted to a pharmaceutically acceptable salt using any conventional method.

Scheme I



Where: A, Y, Z, R_1, n, R_2, R_4, R_8, R_9, R_{10} are as previously described. R^3 = C_1-C_4 lower alkyl, P = protecting group; preferably trimethylsilyl, tert-butyldimethylsilyl, *para*-nitrobenzoyl; and OTs = *para*-toluenesulfonylate or any conventional leaving group

[0101] If it is desired to form compounds of formula I-aa, they can be prepared from compounds of formula 4 via selective protection of the primary alcohol, followed by alkylation of the secondary alcohol, and deprotection of the primary alcohol. Any conventional alcohol protecting groups can be utilized for this conversion and any method for the selective protection of a primary alcohol can be employed. According to the preferred embodiment of this invention, the reaction is carried out at low temperature in dichloromethane with trimethylsilyl chloride and triethylamine as base to form compounds of formula 6. Alkylation of the secondary alcohol can be accomplished via any conventional method of alkylating a secondary alcohol found in the literature. According to the preferred embodiment of this invention, compounds of formula 6 are reacted with an alkyl halide using sodium hydride as base to form compounds of formula 8, which can be deprotected to form compounds of formula 9 via any conventional method for deprotection of a primary alcohol.

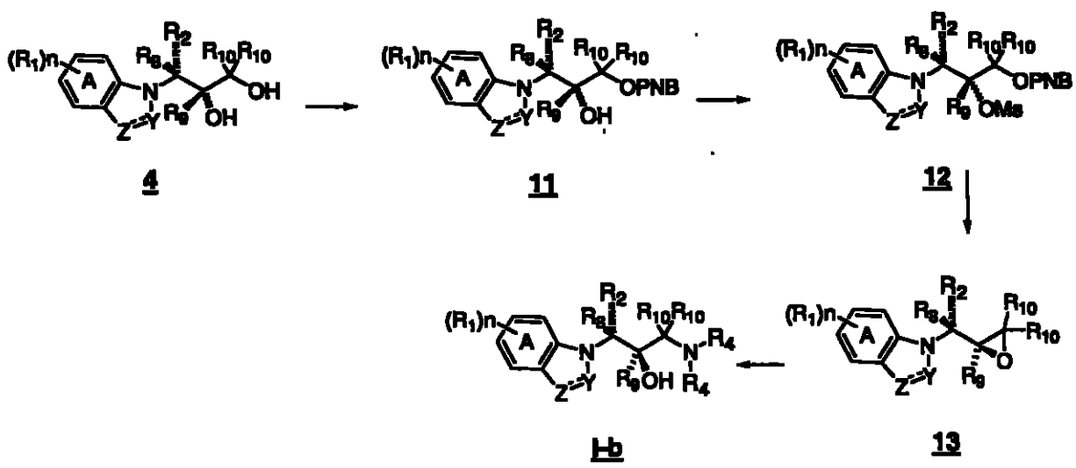
According to the preferred embodiment of this invention, compounds of formula 8 are treated with dilute aqueous hydrochloric acid or trifluoroacetic acid in dichloromethane to form compounds of formula 9. Conversion of the primary alcohol in compounds of formula 9 to complete the synthesis of compounds of formula I-aa can be performed as previously described for the synthesis of compounds of formula I-a. Compounds of formula I-aa can be converted to a pharmaceutically acceptable salt using any conventional method.

[0102] Alternatively, compounds of formula 10 can be prepared directly from compounds of formula 5. Any method of alkylating a hydroxyl group in the presence of a tosyl group can be employed for this conversion. In accordance with the preferred embodiment of this invention, compounds of formula 5 are treated with an alkyl trifluoromethanesulfonate, *e.g.* methyl trifluoromethanesulfonate, in the presence of a hindered base, *e.g.* 2,6-di-*tert*-butyl-4-methylpyridine. The reaction can be performed either at room temperature or heated to about 40°C to about 80°C. Compounds of formula 10 can be converted to compounds of formula I-aa as previously described for the synthesis of compounds of formula I-a. Compounds of formula I-aa can be converted to a pharmaceutically acceptable salt using any conventional method.

[0103] If it is desired to form compounds of I-b, they can also be prepared from compounds of formula 4 via Route B (***Scheme II***). This route involves the selective protection of the primary alcohol followed by conversion of the secondary alcohol to a leaving group. Any conventional method for the selective protection of a primary alcohol, and any conventional method for converting of a secondary alcohol into a leaving group can be utilized for this conversion. In accordance with the preferred embodiment of this invention, compounds of formula 4 are treated with *para*-nitrobenzoyl chloride in pyridine at low temperature (preferably below about 0°C) to form compounds of formula 11. Compounds of formula 11 can be converted to a secondary mesylate of formula 12 via reaction with methanesulfonyl chloride in dichloromethane using triethylamine as base. The reaction is preferably carried out at temperatures between about –15°C and about 10°C. Deprotection of the primary alcohol in compounds of formula 12 allows for the formation of a primary epoxide

through an S_N2 reaction resulting in an inversion of the stereocenter. Any conventional method for deprotection of a primary alcohol, and any conventional method for epoxide formation onto an alpha leaving group can be employed for this conversion. In accordance with the preferred embodiment of this invention, compounds of formula 12 are treated with an aqueous solution of a suitable base in organic solvent, preferably, aqueous sodium hydroxide in dioxane. The resulting epoxide of formula 13 can be ring-opened regioselectively with an amine to produce the desired aminoalcohol of formula I-b. Any conventional method for the regioselective ring opening of a primary epoxide can be employed for this conversion. In accordance with the preferred embodiment of this invention, compounds of formula 13 are treated with an excess of an alcoholic amine solution in a sealed flask, either at room temperature or heated to about 40°C to about 90°C. Compounds of formula I-b can be converted into a pharmaceutically acceptable salt using conventional methods.

Scheme II

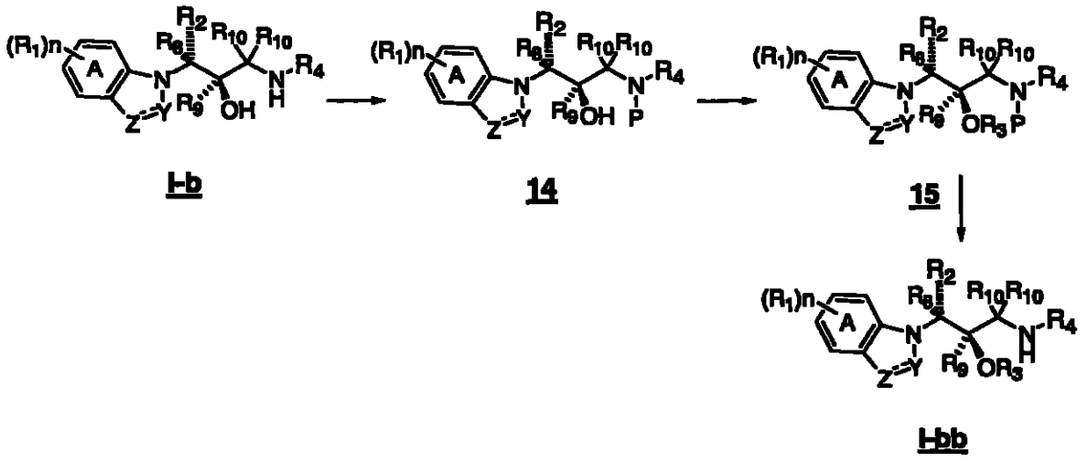


Where: A, Y, Z, R_1, n, R_2, and R_4, R_8, R_{10} are as previously described
R_9 is H
PNB = *para*-nitrobenzoyl or any conventional protecting group; and
OMs = methanesulfonate or any conventional leaving group

[0104] If it is desired to form compounds of formula I-bb, they can be made from compounds of formula I-b via protection of the amine, alkylation of the secondary

alcohol and deprotection of the amine (***Scheme III***). Any conventional method for protection of an amine, alkylation of a secondary alcohol, and deprotection of an amine can be utilized for this conversion. In accordance with the preferred embodiment of this invention, compounds of formula **I-b** are treated with boc anhydride, where boc = tert-butoxycarbonyl, to form compounds of formula **14** which can be alkylated with an alkyl halide using sodium hydride as base to form compounds of formula **15**. Deprotection is accomplished using an acid, preferably trifluoroacetic acid in dichloromethane to form compounds of formula **I-bb** that can be converted into a pharmaceutically acceptable salt using conventional methods.

Scheme III



I-b **14** **15** **I-bb**

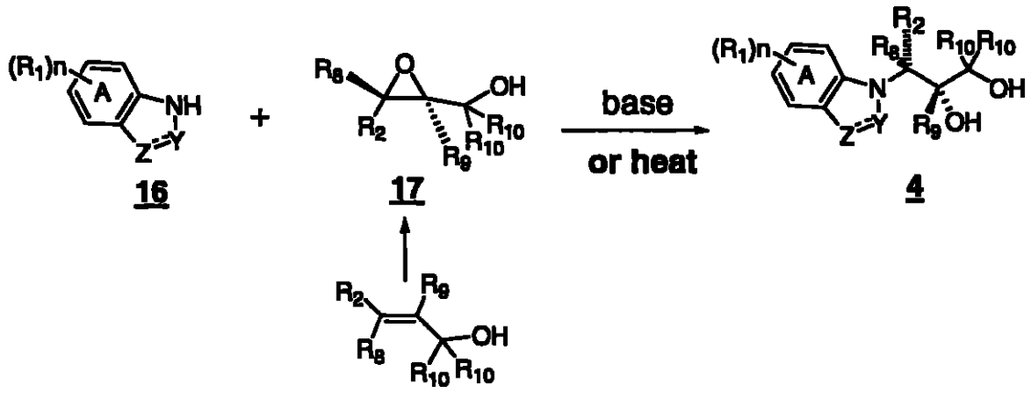
Where: A, Y, Z, R_1, n, R_2, and R_4, R_8, R_{10} are as previously described
R_9 is H
R_3 = C_1-C_3 lower alkyl, P = protecting group, preferably *tert*-butoxycarbonyl

[0105] Compounds of formula **4** are formed via a regio- and stereo-selective ring opening of an appropriately substituted epoxide of formula **17** (formed via an epoxidation of an appropriately substituted allylic alcohol) with an appropriately substituted compound of formula **16** (***Scheme IV***). Any conventional method for the regio- and stereo-selective ring opening of an epoxide can be employed for this conversion. In accordance with the preferred embodiment of this invention, compounds of formula **16** are treated with a base, *e.g.* sodium hydride, sodium *tert*-

butoxide, potassium hydroxide, potassium *tert*-butoxide or potassium hydroxide, then treated with the epoxide of formula 17. The epoxide of formula 17 can be pre-treated with a Lewis acid, *e.g.* titanium *iso*-propoxide, boron-trifluoride, etc. to ensure regio-selective ring-opening. The reaction occurs at room temperature over a duration of about 2 hours to about 72 hours. Alternatively, compounds of formula 16 that are suitably nucleophilic, *e.g.* indoline, can be heated with the epoxide of formula 17 at temperatures from about 50°C to about 170°C to form compounds of formula 4.

[0106] Epoxidation of trans-allylic alcohols can be performed either racemically or asymmetrically using methods described in the literature. In accordance with the preferred embodiment of this invention, racemic epoxidation is conducted with either peracetic acid or *meta*-chloroperbenzoic acid. If it is desired to produce a single enantiomer of compounds of formula I, asymmetric epoxidation of an allylic alcohol can be performed with *tert*-butylhydroperoxide or cumene hydroperoxide in the presence of the appropriate tartrate ester, titanium (IV) isopropoxide, and molecular sieves. This method is well established in the literature (*e.g.* K. B. Sharpless, *et. al.*, *J. Org. Chem.* 1986, *51*, 3710). Compounds of formula 16 and the starting allylic alcohols are either available from commercial sources or are accessible through methods well established in the literature.

Scheme IV



Where: A, Y, Z, R_1, n, R_8, R_9, R_{10} and R_2 are as previously described.

[0107] In other embodiments, the invention is directed to pharmaceutical compositions, comprising:

a. at least compound of formula I, or pharmaceutically acceptable salt thereof; and

b. at least one pharmaceutically acceptable carrier.

Generally, the compound of formula I, or a pharmaceutically acceptable salt thereof, will be present at a level of from about 0.1%, by weight, to about 90% by weight, based on the total weight of the pharmaceutical composition, based on the total weight of the pharmaceutical composition. Preferably, the compound of formula I, or a pharmaceutically acceptable salt thereof, will be present at a level of at least about 1%, by weight, based on the total weight of the pharmaceutical composition. More preferably, the compound of formula I, or a pharmaceutically acceptable salt thereof, will be present at a level of at least about 5%, by weight, based on the total weight of the pharmaceutical composition. Even more preferably, the norepinephrine reuptake inhibitor or a pharmaceutically acceptable salt thereof will be present at a level of at least about 10%, by weight, based on the total weight of the pharmaceutical composition. Yet even more preferably, the compound of formula I, or a pharmaceutically acceptable salt thereof, will be present at a level of at least about 25%, by weight, based on the total weight of the pharmaceutical composition.

[0108] Such compositions are prepared in accordance with acceptable pharmaceutical procedures, such as described *In Remington's Pharmaceutical Sciences*, 17th edition, ed. Alfonoso R. Gennaro, Mack Publishing Company, Easton, PA (1985). Pharmaceutically acceptable carriers are those that are compatible with the other ingredients in the formulation and biologically acceptable.

[0109] The compounds of this invention may be administered orally or parenterally, neat or in combination with conventional pharmaceutical carriers. Applicable solid carriers can include one or more substances that may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents or an encapsulating material. In powders, the carrier is a finely divided solid that is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a

carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

[0110] Liquid carriers may be used in preparing solutions, suspensions, emulsions, syrups, and elixirs. The active ingredient of this invention can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fat. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers, or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above, *e.g.* cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, *e.g.* glycols) and their derivatives, and oils (*e.g.* fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration.

[0111] Liquid pharmaceutical compositions, which are sterile solutions or suspensions, can be administered by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. Oral administration may be either liquid or solid composition form.

[0112] Preferably the pharmaceutical composition is in unit dosage form, *e.g.* as tablets, capsules, powders, solutions, suspensions, emulsions, granules, or suppositories. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example packeted powders, vials, ampoules, prefilled

syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

[0113] In another embodiment of the present invention, the compounds useful in the present invention may be administered to a mammal with one or more other pharmaceutical active agents such as those agents being used to treat any other medical condition present in the mammal. Examples of such pharmaceutical active agents include pain relieving agents, anti-angiogenic agents, anti-neoplastic agents, anti-diabetic agents, anti-infective agents, or gastrointestinal agents, or combinations thereof.

[0114] The one or more other pharmaceutical active agents may be administered in a therapeutically effective amount simultaneously (such as individually at the same time, or together in a pharmaceutical composition), and/or successively with one or more compounds of the present invention.

[0115] The term "combination therapy" refers to the administration of two or more therapeutic agents or compounds to treat a therapeutic condition or disorder described in the present disclosure, for example hot flush, sweating, thermoregulatory-related condition or disorder, or other. Such administration includes use of each type of therapeutic agent in a concurrent manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.

[0116] The route of administration may be any route, which effectively transports the active compound of formula I, or a pharmaceutically acceptable salt thereof, to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal, such as passive or iontophoretic delivery, or parenteral, *e.g.* rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment. Furthermore, the administration of compound of formula I, or pharmaceutically acceptable salt thereof, with other active ingredients may be concurrent or simultaneous.

[0117] It is believed that the present invention described presents a substantial breakthrough in the field of treatment, alleviation, inhibition, and/or prevention of conditions ameliorated by monoamine reuptake including, *inter alia*, vasomotor symptoms (VMS), sexual dysfunction, gastrointestinal and genitourinary disorders, chronic fatigue syndrome, fibromylagia syndrome, nervous system disorders, and combinations thereof, particularly those conditions selected from the group consisting of major depressive disorder, vasomotor symptoms, stress and urge urinary incontinence, fibromyalgia, pain, diabetic neuropathy, and combinations thereof.

[0118] Accordingly, in one embodiment, the present invention is directed to methods for treating or preventing a condition ameliorated by monoamine reuptake in a subject in need thereof, comprising the step of:

administering to said subject an effective amount of a compound of formula I or pharmaceutically acceptable salt thereof.

The conditions ameliorated by monoamine reuptake include those selected from the group consisting of vasomotor symptoms, sexual dysfunction, gastrointestinal and genitourinary disorders, chronic fatigue syndrome, fibromylagia syndrome, nervous system disorders, and combinations thereof, particularly those conditions selected from the group consisting of major depressive disorder, vasomotor symptoms, stress and urge urinary incontinence, fibromyalgia, pain, diabetic neuropathy, and combinations thereof.

[0119] "Vasomotor symptoms," "vasomotor instability symptoms" and "vasomotor disturbances" include, but are not limited to, hot flushes (flashes), insomnia, sleep disturbances, mood disorders, irritability, excessive perspiration, night sweats, fatigue, and the like, caused by, *inter alia*, thermoregulatory dysfunction.

[0120] The term "hot flush" is an art-recognized term that refers to an episodic disturbance in body temperature typically consisting of a sudden skin flushing, usually accompanied by perspiration in a subject.

[0121] The term "sexual dysfunction" includes, but is not limited to, condition relating to desire and/or arousal.

[0122] As used herein, "gastrointestinal and genitourinary disorders" includes irritable bowel syndrome, symptomatic GERD, hypersensitive esophagus, nonulcer dyspepsia, noncardiac chest pain, biliary dyskinesia, sphincter of Oddi dysfunction, incontinence (*i.e.*, urge incontinence, stress incontinence, genuine stress incontinence, and mixed incontinence)(including the involuntary voiding of feces or urine, and dribbling or leakage or feces or urine which may be due to one or more causes including but not limited to pathology altering sphincter control, loss of cognitive function, overdistention of the bladder, hyperreflexia and/or involuntary urethral relaxation, weakness of the muscles associated with the bladder or neurologic abnormalities), interstitial cystitis (irritable bladder), and chronic pelvic pain (including, but not limited to vulvodynia, prostatodynia, and proctalgia).

[0123] As used herein, "chronic fatigue syndrome" (CFS) is a condition characterized by physiological symptoms selected from weakness, muscle aches and pains, excessive sleep, malaise, fever, sore throat, tender lymph nodes, impaired memory and/or mental concentration, insomnia, disordered sleep, localized tenderness, diffuse pain and fatigue, and combinations thereof.

[0124] As used herein, "fibromyalgia syndrome" (FMS) includes FMS and other somatoform disorders, including FMS associated with depression, somatization disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder, undifferentiated somatoform disorder, and somatoform NOS. FMS and other somatoform disorders are accompanied by physiological symptoms selected from a generalized heightened perception of sensory stimuli, abnormalities in pain perception in the form of allodynia (pain with innocuous stimulation), abnormalities in pain perception in the form of hyperalgesia (increased sensitivity to painful stimuli), and combinations thereof.

[0125] As used herein, "nervous system disorders," includes addictive disorders (including those due to alcohol, nicotine, and other psychoactive substances) and

withdrawal syndrome, age-associated learning and mental disorders (including Alzheimer's disease), anorexia nervosa, bulimia nervosa, attention-deficit disorder with or without hyperactivity disorder bipolar disorder, pain, cyclothymic disorder, depression disorder (including major depressive disorder, refractory depression adolescent depression and minor depression), dysthymic disorder, generalized anxiety disorder (GAD), obesity (*i.e.*, reducing the weight of obese or overweight patients), obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorder, panic disorder, post-traumatic stress disorder, premenstrual dysphoric disorder (*i.e.*, premenstrual syndrome and late luteal phase dysphoric disorder), psychotic disorders (including schizophrenia, schizoaffective and schizophreniform disorders), seasonal affective disorder, sleep disorders (such as narcolepsy and enuresis), social phobia (including social anxiety disorder), selective serotonin reuptake inhibition (SSRI) "poop out" syndrome (*i.e.*, wherein a patient who fails to maintain a satisfactory response to SSRI therapy after an initial period of satisfactory response).

[0126] As used herein, "pain," includes both acute pain and chronic pain, which may be centralized pain, peripheral pain, or combination thereof. The term includes many different types of pains including, but not limited to, neuropathic pain, visceral pain, musculoskeletal pain, bony pain, cancer pain, inflammatory pain, and combinations thereof, such as lower back pain, atypical chest pain, headache such as cluster headache, migraine, herpes neuralgia, phantom limb pain, pelvic pain, myofascial face pain, abdominal pain, neck pain, central pain, dental pain, opioid resistant pain, visceral pain, surgical pain, bone injury pain, pain during labor and delivery, pain resulting from burns, post partum pain, angina pain, neuropathic pain such as peripheral neuropathy and diabetic neuropathy, post-operative pain, and pain which is co-morbid with nervous system disorders described herein.

[0127] As used herein, the term "acute pain" refers to centralized or peripheral pain that is intense, localized, sharp, or stinging, and/or dull, aching, diffuse, or burning in nature and that occurs for short periods of time.

[0128] As used herein, the term "chronic pain" refers to centralized or

peripheral pain that is intense, localized, sharp, or stinging, and/or dull, aching, diffuse, or burning in nature and that occurs for extended periods of time (*i.e.*, persistent and/or regularly reoccurring), including, for the purpose of the present invention, neuropathic pain and cancer pain. Chronic pain includes neuropathic pain, hyperalgesia, and/or allodynia.

[0129] As used herein, the term "neuropathic pain" refers to chronic pain caused by damage to or pathological changes in the peripheral or central nervous systems. Examples of pathological changes related to neuropathic pain include prolonged peripheral or central neuronal sensitization, central sensitization related damage to nervous system inhibitory and/or exhibitory functions and abnormal interactions between the parasympathetic and sympathetic nervous systems. A wide range of clinical conditions may be associated with or form the basis for neuropathic pain including, for example, diabetes, post traumatic pain of amputation (nerve damage cause by injury resulting in peripheral and/or central sensitization such as phantom limb pain), lower back pain, cancer, chemical injury, toxins, other major surgeries, peripheral nerve damage due to traumatic injury compression, post-herpetic neuralgia, trigeminal neuralgia, lumbar or cervical radiculopathies, fibromyalgia, glossopharyngeal neuralgia, reflex sympathetic dystrophy, casualgia, thalamic syndrome, nerve root avulsion, reflex sympathetic dystrophy or post thoracotomy pain, nutritional deficiencies, or viral or bacterial infections such as shingles or human immunodeficiency virus (HIV), and combinations thereof. Also included in the definition of neuropathic pain is a condition secondary to metastatic infiltration, adiposis dolorosa, burns, central pain conditions related to thalamic conditions, and combinations thereof.

[0130] As used herein, the term "hyperalgesia" refers to pain where there is an increase in sensitivity to a typically noxious stimulus.

[0131] As used herein, the term "allodynia" refers to an increase in sensitivity to a typically non-noxious stimulus.

[0132] As used herein, the term "visceral pain" refers to pain associated with or resulting from maladies of the internal organs, such as, for example, ulcerative colitis, irritable bowel syndrome, irritable bladder, Crohn's disease, rheumatologic (arthralgias), tumors, gastritis, pancreatitis, infections of the organs, biliary tract disorders, and combinations thereof.

[0133] As used herein, the term "female-specific pain" refers to pain that may be acute and/or chronic pain associated with female conditions. Such groups of pain include those that are encountered solely or predominately by females, including pain associated with menstruation, ovulation, pregnancy or childbirth, miscarriage, ectopic pregnancy, retrograde menstruation, rupture of a follicular or corpus luteum cyst, irritation of the pelvic viscera, uterine fibroids, adenomyosis, endometriosis, infection and inflammation, pelvic organ ischemia, obstruction, intra-abdominal adhesions, anatomic distortion of the pelvic viscera, ovarian abscess, loss of pelvic support, tumors, pelvic congestion or referred pain from non-gynecological causes, and combinations thereof.

[0134] In one embodiment, the present invention is directed to methods for treating or preventing vasomotor symptoms in a subject in need thereof, comprising the step of:

administering to said subject an effective amount of at least one compound of formula I or pharmaceutically acceptable salt thereof.

[0135] When estrogen levels are low or estrogen is absent, the normal levels between NE and 5-HT is altered and this altered change in neurotransmitter levels may result in changes in the sensitivity of the thermoregulatory center. The altered chemical levels may be translated in the thermoregulatory center as heat sensation and as a response, the hypothalamus may activate the descending autonomic pathways and result in heat dissipation via vasodilation and sweating (hot flush) (Figure 1). Accordingly, the estrogen deprivation may result in altered norepinephrine activity.

[0136] Norepinephrine synthesized in perikarya of the brainstem is released at the

nerve terminals in the hypothalamus and brainstem. In the hypothalamus, NE regulates the activity of neurons residing in the thermoregulatory center. In the brainstem, NE innervates serotoninergic neurons (5HT), and acting via adrenergic$_{\alpha 1}$ and adrenergic$_{\alpha 2}$ postsynaptic receptors, it stimulates the activity of the serotoninergic system. In response, 5-HT neurons also modulate the activity the thermoregulatory center and feedback to NE neurons. Via this feedback connection, 5-HT, acting via 5-HT$_{2a}$ receptors, inhibit the activity of NE neurons. Norepinephrine in the synaptic cleft is also taken up by NE transporter (NET) located in NE neurons. The transporter recycles NE and makes it available for multiple neurotransmission (Figure 2).

[0137] The present invention provides a treatment for vasomotor symptoms by methods of recovering the reduced activity of norepinephrine. Norepinephrine activity in the hypothalamus or in the brainstem can be elevated by (i) blocking the activity of the NE transporter, (ii) blocking the activity of the presynaptic adrenergic $_{\alpha 2}$ receptor with an antagonist, or (iii) blocking the activity of 5-HT on NE neurons with a 5-HT$_{2a}$ antagonist.

[0138] In another embodiment, the present invention is directed to methods for treating or preventing a depression disorder in a subject in need thereof, comprising the step of:

administering to said subject an effective amount of at least one compound of formula I or pharmaceutically acceptable salt thereof.

[0139] In yet other embodiments, the present invention is directed to methods for treating or preventing sexual dysfunction in a subject in need thereof, comprising the step of:

administering to said subject an effective amount of at least one compound of formula I or pharmaceutically acceptable salt thereof.

[0140] In another embodiment, the present invention is directed to methods for treating or preventing gastrointestinal or genitourinary disorder, particularly stress incontinence or urge urinary incontinence, in a subject in need thereof, comprising

the step of:

administering to said subject an effective amount of a compound of formula I or pharmaceutically acceptable salt thereof.

[0141] In another embodiment, the present invention is directed to methods for treating or preventing chronic fatigue syndrome in a subject in need thereof, comprising the step of:

administering to said subject an effective amount of a compound of formula I or pharmaceutically acceptable salt thereof.

[0142] In another embodiment, the present invention is directed to methods for treating or preventing fibromyalgia syndrome in a subject in need thereof, comprising the step of:

administering to said subject an effective amount of a compound of formula I or pharmaceutically acceptable salt thereof.

[0143] In further embodiments, the present invention is directed to methods for treating or preventing pain in a subject in need thereof, comprising the step of:

administering to said subject an effective amount of at least one compound of formula I or pharmaceutically acceptable salt thereof.

[0144] The pain may be, for example, acute pain (short duration) or chronic pain (regularly reoccurring or persistent). The pain may also be centralized or peripheral.

[0145] Examples of pain that can be acute or chronic and that can be treated in accordance with the methods of the present invention include inflammatory pain, musculoskeletal pain, bony pain, lumbosacral pain, neck or upper back pain, visceral pain, somatic pain, neuropathic pain, cancer pain, pain caused by injury or surgery such as burn pain or dental pain, or headaches such as migraines or tension headaches, or combinations of these pains. One skilled in the art will recognize that these pains may overlap one another. For example, a pain caused by inflammation may also be visceral or musculoskeletal in nature.

[0146] In a preferred embodiment of the present invention the compounds useful in the present invention are administered in mammals to treat chronic pain such as neuropathic pain associated for example with damage to or pathological changes in the peripheral or central nervous systems; cancer pain; visceral pain associated with for example the abdominal, pelvic, and/or perineal regions or pancreatitis; musculoskeletal pain associated with for example the lower or upper back, spine, fibromylagia, temporomandibular joint, or myofascial pain syndrome; bony pain associated with for example bone or joint degenerating disorders such as osteoarthritis, rheumatoid arthritis, or spinal stenosis; headaches such migraine or tension headaches; or pain associated with infections such as HIV, sickle cell anemia, autoimmune disorders, multiple sclerosis, or inflammation such as osteoarthritis or rheumatoid arthritis.

[0147] In a more preferred embodiment, the compounds useful in this invention are used to treat chronic pain that is neuropathic pain, visceral pain, musculoskeletal pain, bony pain, cancer pain or inflammatory pain or combinations thereof, in accordance with the methods described herein. Inflammatory pain can be associated with a variety of medical conditions such as osteoarthritis, rheumatoid arthritis, surgery, or injury. Neuropathic pain may be associated with for example diabetic neuropathy, peripheral neuropathy, post-herpetic neuralgia, trigeminal neuralgia, lumbar or cervical radiculopathies, fibromyalgia, glossopharyngeal neuralgia, reflex sympathetic dystrophy, casualgia, thalamic syndrome, nerve root avulsion, or nerve damage cause by injury resulting in peripheral and/or central sensitization such as phantom limb pain, reflex sympathetic dystrophy or postthoracotomy pain, cancer, chemical injury, toxins, nutritional deficiencies, or viral or bacterial infections such as shingles or HIV, or combinations thereof. The methods of use for compounds of this invention further include treatments in which the neuropathic pain is a condition secondary to metastatic infiltration, adiposis dolorosa, burns, or central pain conditions related to thalamic conditions.

[0148] As mentioned previously, the methods of the present invention may be used to treat pain that is somatic and/or visceral in nature. For example, somatic pain that can be treated in accordance with the methods of the present invention

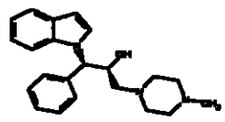
include pains associated with structural or soft tissue injury experienced during surgery, dental procedures, burns, or traumatic body injuries. Examples of visceral pain that can be treated in accordance with the methods of the present invention include those types of pain associated with or resulting from maladies of the internal organs such as ulcerative colitis, irritable bowel syndrome, irritable bladder, Crohn's disease, rheumatologic (arthralgias), tumors, gastritis, pancreatitis, infections of the organs, or biliary tract disorders, or combinations thereof. One skilled in the art will also recognize that the pain treated according to the methods of the present invention may also be related to conditions of hyperalgesia, allodynia, or both. Additionally, the chronic pain may be with or without peripheral or central sensitization.

[0149] The compounds useful in this invention may also be used to treat acute and/or chronic pains associated with female conditions, which may also be referred to as female-specific pain. Such groups of pain include those that are encountered solely or predominately by females, including pain associated with menstruation, ovulation, pregnancy or childbirth, miscarriage, ectopic pregnancy, retrograde menstruation, rupture of a follicular or corpus luteum cyst, irritation of the pelvic viscera, uterine fibroids, adenomyosis, endometriosis, infection and inflammation, pelvic organ ischemia, obstruction, intra-abdominal adhesions, anatomic distortion of the pelvic viscera, ovarian abscess, loss of pelvic support, tumors, pelvic congestion or referred pain from non-gynecological causes.

[0150] The present invention is further defined in the following Examples, in which all parts and percentages are by weight and degrees are Celsius, unless otherwise stated. It should be understood that these examples, while indicating preferred embodiments of the invention, are given by way of illustration only. From the above discussion and these examples, one skilled in the art can ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

EXAMPLES

[0151] EXAMPLE 1: (1RS,2SR)-1-(1H-indol-1-yl)-3-(4-methylpiperazin-1-yl)-1-phenyl propan-2-ol dihydrochloride



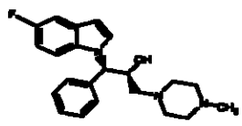
[0152] Step 1: A mixture of indole (2.34 g, 20 mmol) and pulverized solid potassium hydroxide (1.12 g, 20 mmol) was stirred for 30 minutes under nitrogen at room temperature. Trans-3-phenylglycidol (3.0 g, 20 mmol) in dimethylsulfoxide (1 mL) was then added and the mixture was stirred at 70°C for 2 hours until no epoxide remained. The mixture was then cooled and partitioned between water and dichloromethane. The organic layer was separated, washed with water several times, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified via Biotage chromatography (FlasH40i, silica, 10%, 20%, 30% ethyl acetate/hexane) to yield 1.92 g (36%) of (2RS,3RS)-3-indol-1-yl-3-phenyl-propane-1,2-diol as an oil. ^{1}HNMR (DMSO): δ3.27 (m, 2H, CH_2OH), δ4.45 (m, 1H, CHOH), δ4.80 (t, 1H, CH_2OH), δ5.20 (d, 1H, CHOH), δ5.60 (d, 1H, CHPh); MS (ESI) m/z 268 ($[M+H]^+$).

[0153] Step 2: A solution of (2RS,3RS)-3-indol-1-yl-3-phenyl-propane-1,2-diol (1.83 g, 6.8 mmol) and p-toluenesulfonyl chloride (1.31 g, 6.8 mmol) in anhydrous pyridine (10 mL) was stirred at room temperature under nitrogen for 15 hours. The mixture was then diluted with water (10 mL), quenched with a 2N aqueous solution of hydrochloric acid in an ice/water bath until the solution was pH = 3, and extracted with dichloromethane. The organic layer was washed with water again, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified via Biotage chromatography (FlasH40i, silica, 10%, 25% EtOAc/hexane) to yield 1.98 g (69%) of (2RS,3RS)-toluene-4-sulfonic acid 2-hydroxy-3-indol-1-yl-3-phenyl-propyl ester as a white solid. ^{1}HNMR (DMSO): δ3.70 and δ3.85 (dd and dd, 2H,

CH_2OTs), δ4.80 (m, 1H, CHOH), δ5.52 (d, 1H, CHPh), δ5.82 (d, 1H, CHOH); MS (ESI) m/z 422 ($[M+H]^+$).

[0154] Step 3: A mixture of (2RS,3RS)-toluene-4-sulfonic acid 2-hydroxy-3-indol-1-yl-3-phenyl-propyl ester (0.185 g, 0.4 mmol), 1-methyl piperazine (0.05 mL, 0.4 mmol) and potassium carbonate (0.07 g, 0.44 mmol) in acetonitrile (10 mL) was stirred at reflux under nitrogen for 24 hours. After cooling, the mixture was filtered and the filtrate was concentrated and purified via Biotage chromatography (5% methanol/dichloromethane) to give a white solid of (1RS,2SR)-1-(1H-indol-1-yl)-3-(4-methylpiperazin-1-yl)-1-phenylpropan-2-ol. The free base was dissolved in a minimum amount of ethanol and treated with a 1N ethereal solution of hydrochloric acid until the solution was pH = 3 followed by diethyl ether. The product was then crystallized by adding a minimum amount of hexane to afford the titled compound, (1RS,2SR)-1-(1H-Indol-1-yl)-3-(4-methylpiperazin-1-yl)-1-phenylpropan-2-ol dihydrochloride as an off-white solid. MS m/z 350 ($[M+H]^+$); HRMS: calcd for $C_{22}H_{27}N_3O$ + H+, 350.22269; found (ESI, [M+H]+), 350.2228.

[0155] EXAMPLE 2: (1RS,2SR)-1-(5-fluoro-1H-indol-1-yl)-3-(4-methylpiperazin-1-yl)-1-phenylpropan-2-ol dihydrochloride

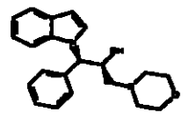


[0156] In an analogous manner to EXAMPLE 1, step 1 (2RS,3RS)-3-(5-fluoro-indol-1-yl)-3-phenyl-propane-1,2-diol was prepared from 5-fluoroindole and trans-3-phenylglycidol as an oil. MS (ESI) m/z 286 ($[M+H]^+$).

[0157] In an analogous manner to EXAMPLE 1, step 2 (2RS,3RS)-toluene-4-sulfonic acid 3-(5-fluoro-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester was prepared from (2RS,3RS)-3-(5-fluoro-indol-1-yl)-3-phenyl-propane-1,2-diol. MS (ESI) *m/z* 440 ($[M+H]^+$).

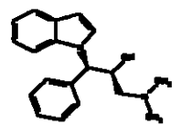
[0158] In an analogous manner to EXAMPLE 1, step 3 (1RS,2SR)-1-(5-fluoro-1H-indol-1-yl)-3-(4-methylpiperazin-1-yl)-1-phenylpropan-2-ol dihydrochloride was prepared from (2RS,3RS)-toluene-4-sulfonic acid 3-(5-fluoro-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester. MS m/z 368 ($[M+H]^+$); HRMS: calcd for $C_{22}H_{26}FN_3O$ + H+, 368.21327; found (ESI, [M+H]+), 368.213.

[0159] EXAMPLE 3: (1RS,2SR)-1-(1H-indol-1-yl)-3-morpholin-4-yl-1-phenylpropan-2-ol hydrochloride



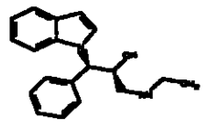
[0160] In an analogous manner to EXAMPLE 1, step 3 (1RS,2SR)-1-(1H-indol-1-yl)-3-(4-methylpiperazin-1-yl)-1-phenylpropan-2-ol hydrochloride was prepared from (2RS,3RS)-toluene-4-sulfonic acid 2-hydroxy-3-indol-1-yl-3-phenyl-propyl ester (EXAMPLE 1, step 3) and morpholine. MS (ESI) m/z 337 ($[M+H]^+$); HRMS: calcd for $C_{21}H_{24}N_2O_2$ + H+, 337.19105; found (ESI, [M+H]+), 337.1909.

[0161] EXAMPLE 4: (1RS,2SR)-3-(dimethylamino)-1-(1H-indol-1-yl)-1-phenylpropan-2-ol hydrochloride



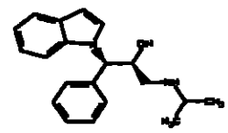
[0162] In an analogous manner to EXAMPLE 1, step 3 (1RS,2SR)-3-(dimethylamino)-1-(1H-indol-1-yl)-1-phenylpropan-2-ol hydrochloride was prepared from (2RS,3RS)-toluene-4-sulfonic acid 2-hydroxy-3-indol-1-yl-3-phenyl-propyl ester (EXAMPLE 1, step 3) and dimethylamine hydrochloride. MS (ES) m/z 295.2 ($[M+H]^+$); HRMS: calcd for $C_{19}H_{22}N_2O$ + H+, 295.18049; found (ESI, [M+H]+), 295.1829.

[0163] EXAMPLE 5: (1RS,2SR)-3-(ethylamino)-1-(1H-indol-1-yl)-1-phenylpropan-2-ol hydrochloride



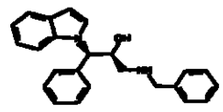
[0164] In an analogous manner to EXAMPLE 1, step 3, a solution of (2RS,3RS)-toluene-4-sulfonic acid 2-hydroxy-3-indol-1-yl-3-phenyl-propyl ester (EXAMPLE 1, step 3, 0.42 g, 1.0 mmol) and ethylamine (2 N solution in methanol, 5 mL) was stirred in a sealed flask at room temperature for 15 hours. After dilution with a saturated aqueous solution of sodium bicarbonate, the mixture was extracted with a solution of dichloromethane/isopropyl alcohol (3/1). The extract was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified on via Biotage chromatography (FlasH40i, silica, dichloromethane, 5% methanol/dichloromethane) to give an oil as free base of the expected product. The free base was dissolved in a minimum amount of ethanol and treated with a 1N ethereal solution of hydrochloric acid until the solution was pH = 3 followed by diethyl ether. The product was then crystallized by adding a minimum amount ethyl acetate to afford the titled compound, (1RS,2SR)-3-(ethylamino)-1-(1H-indol-1-yl)-1-phenylpropan-2-ol hydrochloride as a tan solid. MS (ES) m/z 295.2 ($[M+H]^+$); HRMS: calcd for $C_{19}H_{22}N_2O$ + H+, 295.18049; found (ESI, [M+H]+), 295.1797.

[0165] EXAMPLE 6: (1RS,2SR)-1-(1H-indol-1-yl)-3-(isopropylamino)-1-phenylpropan-2-ol hydrochloride



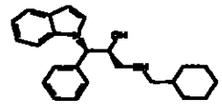
[0166] In an analogous manner to EXAMPLE 1, step 3 (1RS,2SR)-1-(1H-indol-1-yl)-3-(isopropylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2RS,3RS)-toluene-4-sulfonic acid 2-hydroxy-3-indol-1-yl-3-phenyl-propyl ester (EXAMPLE 1, step 3) and isopropylamine. MS (ES) m/z 309.2 ([M+H]$^+$); HRMS: calcd for $C_{20}H_{24}N_2O$ + H+, 309.19614; found (ESI, [M+H]+), 309.1971.

[0167] EXAMPLE 7: (1RS,2SR)-3-(benzylamino)-1-(1H-indol-1-yl)-1-phenylpropan-2-ol hydrochloride



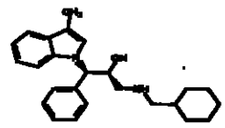
[0168] In an analogous manner to EXAMPLE 1, step 3 (1RS,2SR)-3-(benzylamino)-1-(1H-indol-1-yl)-1-phenylpropan-2-ol hydrochloride was prepared from (2RS,3RS)-toluene-4-sulfonic acid 2-hydroxy-3-indol-1-yl-3-phenyl-propyl ester (EXAMPLE 1, step 3) and benzylamine. MS (ES) m/z 357.2 ([M+H]$^+$); HRMS: calcd for $C_{24}H_{24}N_2O$ + H+, 357.19614; found (ESI, [M+H]+), 357.1962.

[0169] EXAMPLE 8: (1RS,2SR)-3-[(cyclohexylmethyl)amino]-1-(1H-indol-1-yl)-1-phenylpropan-2-ol hydrochloride



[0170] In an analogous manner to EXAMPLE 1, step 3 (1RS,2SR)-3-[(cyclohexylmethyl)amino]-1-(1H-indol-1-yl)-1-phenylpropan-2-ol hydrochloride was prepared from (2RS,3RS)-toluene-4-sulfonic acid 2-hydroxy-3-indol-1-yl-3-phenyl-propyl ester (EXAMPLE 1, step 3) and cyclohexyl methylamine. MS (ES) m/z 363.3 ($[M+H]^+$); HRMS: calcd for $C_{24}H_{30}N_2O$ + H+, 363.24309; found (ESI, [M+H]+), 363.2421.

[0171] EXAMPLE 9: (1RS,2SR)-3-[(cyclohexylmethyl)amino]-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol hydrochloride

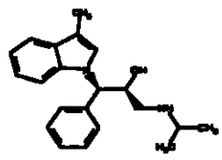


[0172] In an analogous manner to EXAMPLE 1, step 1 (2RS,3RS)-3-(3-methyl-indol-1-yl)-3-phenyl-propane-1,2-diol was prepared from 3-methylindole and trans-3-phenylglycidol as a yellow solid. MS (ESI) m/z 282 ($[M+H]^+$).

[0173] In an analogous manner to EXAMPLE 1, step 2 (2RS,3RS)-toluene-4-sulfonic acid 3-(3-methyl-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester was prepared from (2RS,3RS)-3-(3-methyl-indol-1-yl)-3-phenyl-propane-1,2-diol. MS (ESI) *m/z* 436 ($[M+H]^+$).

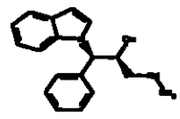
[0174] In an analogous manner to EXAMPLE 1, step 3 (1RS,2SR)-3-[(cyclohexylmethyl)amino]-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol hydro chloride was prepared from (2RS,3RS)-toluene-4-sulfonic acid 3-(3-methyl-indol-1-yl-2-hydroxy-3-phenyl-propyl ester and cyclohexyl methylamine. MS (ES) m/z 377.3 ($[M+H]^+$); HRMS: calcd for $C_{25}H_{32}N_2O$ + H+, 377.25874; found (ESI, [M+H]+), 377.2577.

[0175] EXAMPLE 10: (1RS,2SR)-3-(isopropylamino)-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol hydrochloride



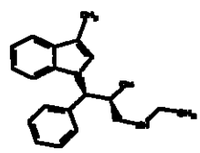
[0176] In an analogous manner to EXAMPLE 1, step 3 (1RS,2SR)-3-(isopropylamino)-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol hydrochloride was prepared from (2RS,3RS)-toluene-4-sulfonic acid 3-(3-methyl-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester (EXAMPLE 12, step 2) and isopropylamine. MS (ES) m/z 323.2 ([M+H]$^+$); HRMS: calcd for $C_{21}H_{26}N_2O$ + H+, 323.21179; found (ESI, [M+H]+), 323.2135.

[0177] EXAMPLE 11: (1RS,2SR)-1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride



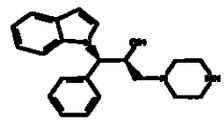
[0178] In an analogous manner to EXAMPLE 5, (1RS,2SR)-1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2RS,3RS)-toluene-4-sulfonic acid 2-hydroxy-3-indol-1-yl-3-phenyl-propyl ester (EXAMPLE 1, step 3) and methylamine (2N solution in methanol). MS (ESI) m/z 281 ([M+H]$^+$); HRMS: calcd for $C_{18}H_{20}N_2O$ + H+, 281.16484; found (ESI, [M+H]+), 281.166.

[0179] EXAMPLE 12: (1RS,2SR)-3-(ethylamino)-1-(3-methyl-1H-indol-1-yl)-1-phenyl propan-2-ol hydrochloride



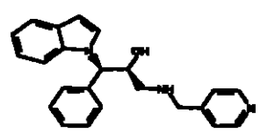
[0180] In an analogous manner to EXAMPLE 5, (1RS,2SR)-3-(ethylamino)-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol hydrochloride was prepared from (2RS,3RS)-toluene-4-sulfonic acid 3-(3-methyl-indol-1-yl-2-hydroxy-3-phenyl-propyl ester (EXAMPLE 12, step 2) and ethylamine (2N solution in methanol). MS (ESI) m/z 309 ([M+H]$^+$); HRMS: calcd for $C_{20}H_{24}N_2O$ + H+, 309.19614; found (ESI, [M+H]+), 309.198.

[0181] EXAMPLE 13: (1RS,2SR)-1-(1H-indol-1-yl)-1-phenyl-3-piperazin-1-ylpropan-2-ol dihydrochloride



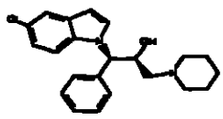
[0182] In an analogous manner to EXAMPLE 1, step 3 (2SR,3RS)-4-(2-hydroxy-3-Indol-1-yl-3-phenyl-propyl)-piperazine-1-carboxylic acid tert-butyl ester was prepared from (2RS,3RS)-toluene-4-sulfonic acid 2-hydroxy-3-Indol-1-yl-3-phenyl-propyl ester (EXAMPLE 1, step 3, 0.211g, 0.5 mmol) and *tert*-butyl-1-piperazine carboxylate (0.19 g, 1.0 mmol). The product was dissolved in diethyl ether (3 mL) and treated with a 4N solution of hydrochloric acid in dioxane (0.75 mL, 3.0 mmol). The reaction mixture was then stirred at room temperature for 15 hours, and the crude solid product was filtered and recrystallized from ethanol with a minimum amount of diethyl ether to give the titled compound, (1RS,2SR)-1-(1H-indol-1-yl)-1-phenyl-3-piperazin-1-ylpropan-2-ol dihydrochloride as a tan solid. MS (ESI) m/z 336 ([M+H]$^+$); HRMS: calcd for $C_{21}H_{25}N_3O$ + H+, 336.20704; found (ESI, [M+H]+), 336.2085.

[0183] EXAMPLE 14: (1RS,2SR)-1-(1H-indol-1-yl)-1-phenyl-3-[(pyridin-4-ylmethyl) amino]propan-2-ol hydrochloride



[0184] In an analogous manner to EXAMPLE 1, step 3 (1RS,2SR)-1-(1H-indol-1-yl)-1-phenyl-3-[(pyridin-4-ylmethyl)amino]propan-2-ol hydrochloride was prepared from (2RS,3RS)-toluene-4-sulfonic acid 2-hydroxy-3-indol-1-yl-3-phenyl-propyl ester (EXAMPLE 1, step 3) and pyridine-4-yl-methylamine. MS (ESI) m/z 358 ($[M+H]^+$); HRMS: calcd for $C_{23}H_{23}N_3O$ + H+, 358.19139; found (ESI, [M+H]+), 358.1928.

[0185] EXAMPLE 15: (1RS,2SR)-1-(5-chloro-1H-indol-1-yl)-1-phenyl-3-piperidin-1-ylpropan-2-ol hydrochloride

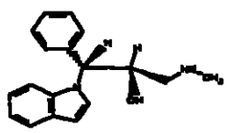


[0186] In an analogous manner to EXAMPLE 1, step 1 (2RS,3RS)-3-(5-chloro-indol-1-yl)-3-phenyl-propane-1,2-diol was prepared from 5-chloroindole and trans-3-phenylglycidol as an oil. MS (ESI) m/z 302 ($[M+H]^+$).

[0187] In an analogous manner to EXAMPLE 1, step 2 (2RS,3RS)-toluene-4-sulfonic acid 3-(5-chloro-indol-1-yl-2-hydroxy-3-phenyl-propyl ester was prepared from (2RS,3RS)-3-(5-chloro-indol-1-yl)-3-phenyl-propane-1,2-diol. MS (ESI) *m/z* 456 ($[M+H]^+$).

[0188] In an analogous manner to EXAMPLE 1, step 3 (1RS,2SR)-1-(5-chloro-1H-indol-1-yl)-1-phenyl-3-piperidin-1-ylpropan-2-ol hydrochloride was prepared from (2RS,3RS)-toluene-4-sulfonic acid 3-(5-chloro-indol-1-yl-2-hydroxy-3-phenyl-propyl ester and piperidine. MS m/z 369 ($[M+H]^+$); HRMS: calcd for $C_{22}H_{25}ClN_2O$ + H+, 369.17282; found (ESI, [M+H]+), 369.1725.

[0189] EXAMPLE 16: (1RS,2RS)-1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride



[0190] Step 2. To a solution of (2RS,3RS)-3-indol-1-yl-3-phenyl-propane-1,2-diol (EXAMPLE 1, step 1, 1.83 g, 6.9 mmol) in anhydrous pyridine (25 mL), *p*-nitrobenzoyl chloride (1.3 g, 6.9 mmol) in 1 mL of pyridine was added at –10°C dropwise. After stirring for 30 minutes, the reaction mixture was cooled with an ice

bath and quenched with water and a 2N aqueous solution of hydrochloric acid until the solution was pH=3 and xtracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated to give (2RS,3RS)-4-nitro-benzoic acid 2-hydroxy-3-indol-1-yl-3-phenyl-propyl ester quantitatively as a yellow solid. MS (ESI) m/z 417 ([M+H]$^+$).

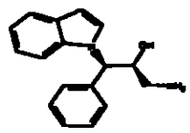
[0191] Step 3. To a solution of (2RS, 3RS)-4-nitro-benzoic acid 2-hydroxy-3-indol-1-yl-3-phenyl-propyl ester and triethylamine (1.4 mL, 10.5 mmol) in dichloromethane (20 mL) was added methanesulfonyl chloride (0.59 mL, 7.6 mmol) dropwise at 0 – 5°C with stirring. After stirring for 30 minutes, the mixture was washed with a 1N aqueous solution of hydrochloric acid, 5% aqueous sodium bicarbonate, and water, dried over anhydrous sodium sulfate, filtered, and concentrated to give a light yellow fluffy solid. The crude product was recrystallized from dichloromethane with a minimum amount of diethyl ether to give (2RS,3RS)-4-nitro-benzoic acid-3-indol-1-yl-2-methanesulfonyloxy-3-phenyl-propyl ester as a yellow solid. MS (ESI) m/z 495 ([M+H]$^+$).

[0192] Step 4. A solution of (2RS,3RS)-4-nitro-benzoic acid-3-indol-1-yl-2-methanesulfonyloxy-3-phenyl-propyl ester in dioxane (30 mL) and a 2N aqueous solution of sodium hydroxide (15 mL) were stirred at room temperature for 4 hours. The mixture was diluted with water and extracted with ethyl acetate. The extract was washed with 5% aqueous sodium carbonate and water, dried over anhydrous sodium sulfate, filtered, and concentrated to give (1RS,2SR)-1-(oxiranyl-phenyl-methyl)-1H-indole as an oil. MS (ESI) m/z 250 ([M+H]$^+$).

[0193] Step 5. (1RS,2SR)-1-(oxiranyl-phenyl-methyl)-1H-indole was treated with 5 mL of methylamine (2N solution in methanol) with stirring at room temperature for 15 hours. The reaction mixture was concentrated *in vacuo* and the crude product was recrystallized form dichloromethane. The free base of the expected product was dissolved in a minimum amount of dichloromethane, treated with a 1N ethereal solution of hydrochloric acid until the solution was pH = 3. The solid product was then recrystallized by adding an additional diethyl ether to give (1RS,2RS)-1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride as a light tan solid.

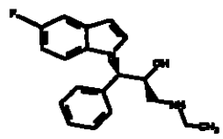
MS m/z 281 ([M+H]$^+$); HRMS: calcd for $C_{18}H_{20}N_2O$ + H+, 281.16484; found (ESI, [M+H]+), 281.1654.

[0194] EXAMPLE 17: (1RS,2SR)-3-amino-1-(1H-indol-1-yl)-1-phenylpropan-2-ol hydrochloride



In an analogous manner to EXAMPLE 5, (1RS,2SR)-3-amino-1-(1H-indol-1-yl)-1-phenylpropan-2-ol hydrochloride was prepared from (2RS,3RS)-toluene-4-sulfonic acid 2-hydroxy-3-indol-1-yl-3-phenyl-propyl ester (EXAMPLE 1, step 3, 0.42 g, 1.0 mmol) in a minimum amount of methanol and an excess of a 30% aqueous solution of ammonium hydroxide. The crude product was dissolved in n-hexane and filtered to give a white solid as a free base. The free base of the product was dissolved in a minimum amount of ethanol and treated with a 1N solution of ethereal hydrochloric acid until the solution was pH = 3 followed by diethyl ether. The product was then crystallized by adding a minimum amount of ethyl acetate to afford the titled compound as a tan solid. MS (ESI) m/z 267 ([M+H]$^+$); HRMS: calcd for $C_{17}H_{18}N_2O$ + H+, 267.14919; found (ESI, [M+H]+), 267.1493.

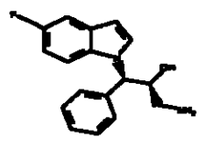
[0195] EXAMPLE 18: (1RS,2SR)-3-(ethylamino)-1-(5-fluoro-1H-indol-1-yl)-1-phenylpropan-2-ol hydrochloride



[0196] In an analogous manner to EXAMPLE 5, (1RS,2SR)-3-(ethylamino)-1-(5-fluoro-1H-indol-1-yl)-1-phenylpropan-2-ol hydrochloride was prepared from (2RS,3RS)-toluene-4-sulfonic acid 3-(5-fluoro-indol-1-yl-2-hydroxy-3-phenyl-propyl ester (EXAMPLE 2, step 2) and ethylamine (2N solution in methanol). MS (ES) m/z

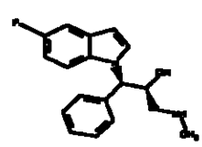
313.2 ([M+H]$^+$); HRMS: calcd for $C_{19}H_{21}FN_2O$ + H+, 313.17107; found (ESI, [M+H]+), 313.1706.

[0197] EXAMPLE 19: (1RS,2SR)-3-amino-1-(5-fluoro-1H-indol-1-yl)-1-phenylpropan-2-ol hydrochloride



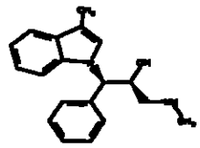
[0198] In an analogous manner to EXAMPLE 17, (1RS,2SR)-3-amino-1-(5-fluoro-1H-indol-1-yl)-1-phenylpropan-2-ol hydrochloride was prepared from (2RS, 3RS)-toluene-4-sulfonic acid 3-(5-fluoro-indol-1-yl-2-hydroxy-3-phenyl-propyl ester (EXAMPLE 2, step 2) and a 30% aqueous solution of ammonium hydroxide as a white solid. MS (ES) m/z 285.2 ([M+H]$^+$); HRMS: calcd for $C_{17}H_{17}FN_2O$ + H+, 285.13977; found (ESI, [M+H]+), 285.1403.

[0199] EXAMPLE 20: (1RS,2SR)-1-(5-fluoro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride



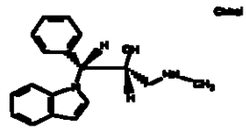
[0200] In an analogous manner to EXAMPLE 5, (1RS,2SR)-1-(5-fluoro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2RS,3RS)-toluene-4-sulfonic acid 3-(5-fluoro-indol-1-yl-2-hydroxy-3-phenyl-propyl ester (EXAMPLE 2, step 2) obtained and methylamine (2N solution in methanol). MS (ESI) m/z 299 ([M+H]$^+$); HRMS: calcd for $C_{18}H_{19}FN_2O$ + H+, 299.15542; found (ESI, [M+H]+), 299.1564.

[0201] EXAMPLE 21: (1RS,2SR)-3-(methylamino)-1-(3-methyl-1H-indol-1-yl)-1-phenyl propan-2-ol hydrochloride



[0202] In an analogous manner to EXAMPLE 5, (1RS,2SR)-3-(methylamino)-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol hydrochloride was prepared from (2RS, 3RS)-toluene-4-sulfonic acid 3-(3-methyl-indol-1-yl-2-hydroxy-3-phenyl-propyl ester (EXAMPLE 10, step 2) and methylamine (2N solution in methanol). MS (ESI) m/z 295 ($[M+H]^+$); HRMS: calcd for $C_{19}H_{22}N_2O$ + H+, 295.18049; found (ESI, [M+H]+), 295.1816.

[0203] EXAMPLE 22: (1R,2S)-1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride



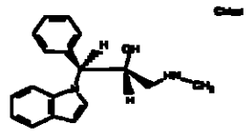
[0204] In an analogous manner to EXAMPLE 1, step 1 (2R,3R)-3-indol-1-yl-3-phenyl-propane-1,2-diol was prepared from indole and [(2S,3S)-3-phenyloxiran-2-yl]methanol as an oil. MS (ESI) m/z 286 ($[M+H]^+$).

[0205] In an analogous manner to EXAMPLE 1, step 2 (2R,3R)-toluene-4-sulfonic acid 3-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester was prepared from (2R,3R)-3-indol-1-yl-3-phenyl-propane-1,2-diol. MS (ESI) *m/z* 440 ($[M+H]^+$).

[0206] In an analogous manner to EXAMPLE 5, (1R,2S)-1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2R,3R)-toluene-4-sulfonic acid 3-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester and methylamine (2N solution in methanol) as a white solid. CD/MeOH = (+); e/e =

99.9% as determined by chiral HPLC; MS (ESI) m/z 281 ([M+H]$^+$); HRMS: calcd for $C_{18}H_{20}N_2O$ + H+, 281.16484; found (ESI, [M+H]+), 281.1649.

[0207] EXAMPLE 23: (1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol
hydrochloride



[0208] Racemic (1RS,2SR)-1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol (EXAMPLE 11) was dissolved in methanol. The resulting solution was injected onto the Supercritical Fluid Chromatography instrument. The baseline resolved enantiomers, using the conditions described below, were collected. The enantiomeric purity of each enantiomer was determined under the same Supercritical Fluid Chromatography conditions using a Chiralcel OJ-H 5u, 250 mm x 4.6 mm ID column at 2.0 mL/minutes flow rate using Analytical Supercritical Fluid Chromatography (Berger Instruments, Inc. Newark, DE USA).

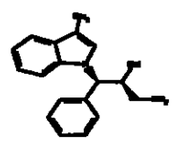
SFC Instrument: Berger MultiGram Prep SFC (Berger Instruments, Inc. Newark, DE 19702.

Column:	Chiralcel OJ-H; 5u; 250mm L x 20mm ID (Chiral Technologies, Inc, Exton, PA, USA)
Column temperature:	35°C
SFC Modifier:	20% MeOH with 1% diethylamine
Flow rate:	50 mL/min
Outlet Pressure:	100 bar
Detector:	UV at 218 nm

[0209] (1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol was isolated as a slower retention time peak with (-) rotation of chiral detection (CD) and e/e = 99.4% as determined by chiral HPLC. The isolated free base was

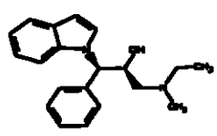
concentrated *in vacuo*, dissolved in minimum amount of ethanol and treated with a 1N ethereal solution of hydrochloric acid until the solution was pH = 3 followed by diethyl ether. The product was then crystallized by adding a minimum amount of ethyl acetate to afford the titled compound as a white solid of hydrochloride salt; MS (ESI) m/z 281 ([M+H]$^+$); HRMS: calcd for C18H20N2O + H+, 281.16484; found (ESI, [M+H]+), 281.1646.

[0210] EXAMPLE 24: (1RS,2SR)-3-amino-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol hydrochloride



In an analogous manner to EXAMPLE 17, (1RS,2SR)-3-amino-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol hydrochloride was prepared from (2RS, 3RS)-toluene-4-sulfonic acid 3-(3-methyl-indol-1-yl-2-hydroxy-3-phenyl-propyl ester (EXAMPLE 9, step 2) and a 30% aqueous solution of ammonium hydroxide as a tan solid. MS (ES) m/z 281.1 ([M+H]$^+$); HRMS: calcd for $C_{18}H_{20}N_{2O}$ + H+, 281.16484; found (ESI, [M+H]+), 281.1645.

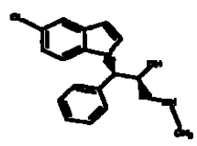
[0211] EXAMPLE 25: (1RS,2SR)-3-[ethyl(methyl)amino]-1-(1H-indol-1-yl)-1-phenylpropan-2-ol hydrochloride



[0212] In an analogous manner to EXAMPLE 5, (1RS,2SR)-3-[ethyl(methyl)amino]-1-(1H-indol-1-yl)-1-phenylpropan-2-ol hydrochloride was prepared from (1RS,2SR)-3- (methylamino)-1-(1H-indol-1-yl)-1-phenylpropan-2-ol (EXAMPLE 11) and ethylamine (2N solution in methanol) as a tan solid. MS (ES)

m/z 309.0 ([M+H]$^+$); HRMS: calcd for $C_{20}H_{24}N_2O$ + H+, 309.19614; found (ESI, [M+H]+), 309.1955.

[0213] EXAMPLE 26: (1RS,2SR)-1-(5-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride

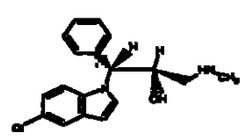


[0214] In an analogous manner to EXAMPLE 1, step 1 (2RS,3RS)-3-(5-chloro-indol-1-yl)-3-phenyl-propane-1,2-diol was prepared from 5-chloroindole and trans-3-phenylglycidol as an oil. MS (ESI) m/z 302 ([M+H]$^+$).

[0215] In an analogous manner to EXAMPLE 1, step 2 (2RS,3RS)-toluene-4-sulfonic acid 3-(5-chloro-indol-1-yl-2-hydroxy-3-phenyl-propyl ester was prepared from (2RS,3RS)-3-(5-chloro-indol-1-yl)-3-phenyl-propane-1,2-diol. MS (ESI) *m/z* 456 ([M+H]$^+$).

[0216] In an analogous manner to EXAMPLE 5, step 3 (1RS,2SR)-1-(5-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2RS,3RS)-toluene-4-sulfonic acid 3-(5-chloro-indol-1-yl-2-hydroxy-3-phenyl-propyl ester and methylamine (2N solution in methanol). MS (ESI) m/z 315 ([M+H]$^+$); HRMS: calcd for $C_{18}H_{19}ClN_2O$ + H+, 315.12587; found (ESI, [M+H]+), 315.1258.

[0217] EXAMPLE 27: (1RS,2RS)-1-(5-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-1-ol hydrochloride



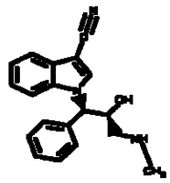
[0218] In an analogous manner to EXAMPLE 16, step 2 (2RS,3RS)-4-nitro-benzoic acid 3-(5-chloro-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester was prepared from (2RS,3RS)-3-(5-chloro-indol-1-yl)-3-phenyl-propane-1,2-diol (EXAMPLE1, step 1). MS (ESI) m/z 451 ([M+H]$^+$).

[0219] In an analogous manner to EXAMPLE 16, step 3 (2RS,3RS)-4-nitro-benzoic acid 3-(5-chloro-indol-1-yl)-2-methanesulfonyloxy-3-phenyl-propyl ester was prepared from (2RS,3RS)-4-nitro-benzoic acid 3-(5-chloro-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester. MS (ESI) m/z 529 ([M+H]$^+$).

[0220] In an analogous manner to EXAMPLE 16, step 4 (1RS,2SR)-5-chloro-1-(oxiranyl-phenyl-methyl)-1H-indole was prepared from (2RS,3RS)-4-nitro-benzoic acid 3-(5-chloro-indol-1-yl)-2-methanesulfonyloxy-3-phenyl-propyl ester. MS (ESI) m/z 284 ([M+H]$^+$).

[0221] In an analogous manner to EXAMPLE 16, step 5 (1RS,2RS)-1-(5-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride as a tan solid. MS (ESI) m/z 315 ([M+H]$^+$); HRMS: calcd for $C_{18}H_{19}ClN_2O$ + H+, 315.12587; found (ESI, [M+H]+), 315.1276.

[0222] EXAMPLE 28: 1-[(1RS,2SR)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1H-indole-3-carbonitrile hydrochloride

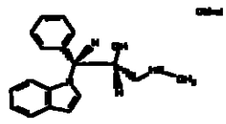


[0223] In an analogous manner to EXAMPLE 1, step 1 (2RS,3RS)-3-(3-cyano-indol-1-yl)-3-phenyl-propane-1,2-diol was prepared from 3-cyanoindole and trans-3-phenylglycidol as an oil. MS (ESI) m/z 293 ([M+H]$^+$).

[0224] In an analogous manner to EXAMPLE 1, step 2 (2RS,3RS)-toluene-4-sulfonic acid 3-(3-cyano-indol-1-yl-2-hydroxy-3-phenyl-propyl ester was prepared from (2RS,3RS)-3-(3-cyano-indol-1-yl)-3-phenyl-propane-1,2-diol. MS (ESI) *m/z* 447 ($[M+H]^+$).

[0225] In an analogous manner to EXAMPLE 1, step 3 (1RS,2SR)-1-(3-cyano-1H-indol-1-yl)-3-(4-methylpiperazin-1-yl)-1-phenylpropan-2-ol hydrochloride was prepared from (2RS,3RS)-toluene-4-sulfonic acid 3-(3-cyano-indol-1-yl-2-hydroxy-3-phenyl-propyl ester as a white solid. MS (ESI) m/z 306 ($[M+H]^+$); HRMS: calcd for $C_{19}H_{19}N_3O$ + H+, 306.16009; found (ESI, [M+H]+), 306.1614.

[0226] EXAMPLE 29: (1R,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride



[0227] Racemic (1RS,2RS)-1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol (EXAMPLE 16) was dissolved in methanol. The resulting solution was injected onto the Supercritical Fluid Chromatography instrument. The baseline resolved enantiomers, using the conditions described below, were collected. The enantiomeric purity of each enantiomer was determined under the same Supercritical Fluid Chromatography conditions using a Chiralcel OJ-H 5u, 250 mm x 4.6 mm ID column at 2.0 mL/minutes flow rate using Analytical Supercritical Fluid Chromatography (Berger Instruments, Inc. Newark, DE USA).

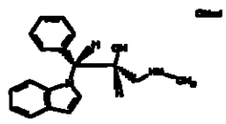
SFC Instrument:	Berger MultiGram Prep SFC (Berger Instruments, Inc. Newark, DE 19702.
Column:	Chiralcel OJ-H; 5u; 250mm L x 20mm ID (Chiral Technologies, Inc, Exton, PA, USA)
Column temperature:	35°C

SFC Modifier:	20% MeOH with 1% Ethanesulfonic acid
Flow rate:	50 mL/min
Outlet Pressure:	100 bar
Detector:	UV at 220 nm

[0228] (1R,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol was isolated as a faster retention time peak with (+) rotation of chiral detection (CD) and e/e = 99.9% as determined by chiral HPLC.

[0229] In an analogous manner as EXAMPLE 23, the titled compound was afforded as an off white solid of hydrochloride salt ; MS (ESI) m/z 306 ([M+H]$^+$); HRMS: calcd for C18H20N2O + H+, 281.16484; found (ESI, [M+H]+), 281.1654.

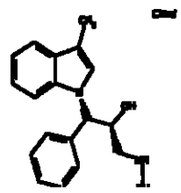
[0230] EXAMPLE 30: (1S,2S)-1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride



[0231] In an analogous manner to EXAMPLE 29, (1S,2S)-1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol was isolated as a slower retention time peak with (-) rotation of chiral detection (CD) and e/e = 99.9% as determined by chiral HPLC.

In an analogous manner as EXAMPLE 23, the titled compound was afforded as a white solid of hydrochloride salt; MS (ESI) m/z 306 ([M+H]$^+$); HRMS: calcd for C18H20N2O + H+, 281.16484; found (ESI, [M+H]+), 281.1655.

[0232] EXAMPLE 31: (1S,2R)-3-(methylamino)-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol hydrochloride

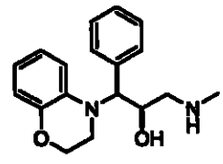


[0233] In an analogous manner to EXAMPLE 1, step 1 (2S,3S)-3-(3-methyl-indol-1-yl)-3-phenyl-propane-1,2-diol was prepared from 3-methylindole and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4) as an oil. MS (ESI) m/z 282 ($[M+H]^+$).

[0234] In an analogous manner to EXAMPLE 1, step 2 (2S,3S)-toluene-4-sulfonic acid 3-(3-methyl-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester was prepared from (2S,3S)-3-(3-methyl-indol-1-yl)-3-phenyl-propane-1,2-diol. MS (ESI) *m/z* 436 ($[M+H]^+$).

[0235] In an analogous manner to EXAMPLE 5, (1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2S,3S)-toluene-4-sulfonic acid 3-(3-methyl-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester and methylamine (2N solution in methanol) as a white solid. [□]D^{25}/MeOH= +116; CD/MeOH = (-); MS (ESI) m/z 295 ($[M+H]^+$); HRMS: calcd for $C_{19}H_{22}N_{2O}$ + H+, 295.18049; found (ESI, [M+H]+), 295.1816.

[0236] EXAMPLE 32: (1RS,2SR)-1-(2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-(methylamino)-1-phenylpropan-2-ol dihydrochloride



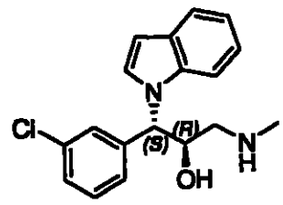
[0237] A mixture of 3,4-dihydro-2H-benzo[1,4]oxazine (2.027 g 15.00 mmol) and *trans*-ethyl-3-phenylglycidate (2.883 g, 15.00 mmol) was stirred at 135°C for 12 hours. After cooling, the viscous liquid was purified via Biotage Horizon (FLASH 40 M, silica, 10%, 20%, 30% EtOAc/hexane) and recrystallized (minimal warm chloroform/hexane/-20°C) to yield 4.261 g (87%) ethyl (2RS,3RS)-3-(2,3-dihydro-4H-

1,4-benzoxazin-4-yl)-2-hydroxy-3-phenylpropanoate as a white solid. MS (ESI) *m/z* 328.0 ([M+H]$^+$).

[0238] A mixture of ethyl (2RS,3RS)-3-(2,3-dihydro-4H-1,4-benzoxazin-4-yl)-2-hydroxy-3-phenylpropanoate (283 mg, 0.864 mmol) and ethanolic methylamine solution (5 mL, 33% in ethanol) was stirred at 70°C in a sealed tube for 5 hours. After cooling, all volatiles were removed under reduced pressure. The resulting yellow solid was purified via Biotage Horizon (FLASH 12 S, silica, 20%, 35%, 50% EtOAc/hexane) to yield 235 mg (87%) (2RS,3RS)-3-(2,3-dihydro-4H-1,4-benzoxazin-4-yl)-2-hydroxy-N-methyl-3 phenylpropanamide as a white solid. MS (ESI) *m/z* 311.0 ([M-H]$^-$).

[0239] A solution of (2RS,3RS)-3-(2,3-dihydro-4H-1,4-benzoxazin-4-yl)-2-hydroxy-N-methyl-3 phenylpropanamide (216 mg, 0.692 mmol) in dry tetrahydrofuran (3 mL) under nitrogen was treated dropwise with a solution of borane (1.0 M in tetrahydrofuran, 3.50 mL, 3.50 mmol), and the resulting solution was stirred at 70°C for 2 hours. After cooling in an ice bath, the reaction mixture was treated with a 2N aqueous solution of hydrochloric acid (1 mL), and the resulting mixture was heated at 50°C for 30 minutes. Tetrahydrofuran was removed under reduced pressure, and the aqueous residue was dissolved in water (5 mL) and washed with diethyl ether (10 mL). The aqueous layer was made alkaline with solid potassium carbonate and extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were washed with brine, dried (sodium sulfate) and concentrated under reduced pressure to yield 202 mg (98%) (1RS,2SR)-1-(2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-(methylamino)-1-phenylpropan-2-ol as a colorless oil. This oil was dissolved in ethanol (1 mL) and treated with a solution of hydrochloric acid (0.5 mL, 4M in 1,4-dioxane). All volatiles were again removed under reduced pressure. The resulting white solid was recrystallized (minimal warm ethanol/ethyl ether/-20°C) to yield 105 mg (41%) (1RS,2SR)-1-(2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-(methylamino)-1-phenylpropan-2-ol di hydrochloride as a white solid. MS (ESI) *m/z* 299.0 ([M+H]$^+$); HRMS: calcd for $C_{18}H_{22}N_2O_2$ + H+, 299.17540; found (ESI, [M+H]+), 299.1755.

[0240] EXAMPLE 33: (1*S*,2*R*)-1-(3-chlorophenyl)-1-(1*H*-indol-1-yl)-3-(methylamino)propan-2-ol hydrochloride



[0241] Step 1: A suspension of sodium hydride (60 % in mineral oil, 4.0 g, 100 mmol) in tetrahydrofuran (600 mL) was treated dropwise with diethyl ethoxycarbonylmethylphosphonate (20 mL, 100 mmol) at 23°C. After 1 hour s,3-chlorobenzaldehyde (9.3 mL, 82 mmol) was added. After an additional 1 hour, the reaction was quenched with water (20 mL) and concentrated under vacuum to remove tetrahydrofuran. The residue was taken up in ethyl acetate (300 mL), washed with water (5 x 300 mL) and brine (1 x 300 mL), dried (magnesium sulfate) and concentrated under vacuum to provide (2*E*)-3-(3-chlorophenyl)-acrylic acid ethyl ester (18 g, quantitative) as a clear, pale yellow oil. MS (ESI) *m/z* 210 ($[M+H]^+$).

[0242] Step 2: (2*E*)-3-(3-Chlorophenyl)-acrylic acid ethyl ester (17.6 g, 82 mmol) was dissolved in dry dichloromethane (300 mL), cooled to –78°C and treated with a solution of di-*iso*-butylaluminum hydride (1.0 M solution in hexane, 250 mL, 250 mmol) over 20 minutes. After 1.5 hours total, the reaction was quenched with methanol (75 mL) at –78°C, warmed to 23°C and treated with a saturated aqueous solution of potassium sodium tartrate (300 mL). The aqueous phase was separated and extracted with dichloromethane (2 x 300 mL). The combined extracts were washed with a saturated aqueous solution of sodium tartrate (450 mL), dried (sodium sulfate) and concentrated under vacuum to provide a cloudy yellow oil (14.6 g) that was pre-adsorbed on silica gel (25 g). Flash column chromatography (silica 250 g, 10 %, 20 % ethyl acetate/hexanes) provided (2*E*)-3-(3-chlorophenyl)prop-2-en-1-ol (12.4 g, 90 %) as a clear, colorless oil. MS (ESI) *m/z* 151 ($[M+H-H_2O]^+$).

[0243] Step 3: In an analogous manner to EXAMPLE 117, step 4, [(2*R*,3*R*)-3-(3-chlorophenyl)oxiran-2-yl]methanol was prepared from (2*E*)-3-(3-chlorophenyl)prop-2-en-1-ol. MS (ESI) *m/z* 167 ($[M+H-H_2O]^+$).

[0244] Step 4 (Method A): In an analogous manner to EXAMPLE 117, step 5, (2*S*,3*S*)-3-(3-chlorophenyl)-3-(1*H*-indol-1-yl)propane-1,2-diol was prepared from 1*H*-indole and [(2*R*,3*R*)-3-(3-chlorophenyl)oxiran-2-yl]methanol. MS (ES) *m/z* 302 ($[M+H]^+$).

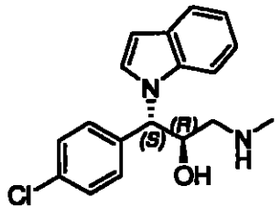
[0245] Step 4a (Method B): [(2*R*,3*R*)-3-(3-chlorophenyl)oxiran-2-yl]methanol (4.8 g, 26 mmol) and indoline (*d* 1.063, 2.9 mL, 26 mmol) were heated neat at 135°C in a sealed flask. After 1.5 hours, the cooled mixture was pre-adsorbed on silica gel (25 g). Flash column chromatography (silica 375 g, 20 %, 40 %, 80 % ethyl acetate/hexanes) provided (2*S*,3*S*)-3-(3-chlorophenyl)-3-(2,3-dihydro-1*H*-indol-1-yl)propane-1,2-diol (5.8 g, 73 %) as a white solid. MS (ES) *m/z* 304 ($[M+H]^+$).

[0246] Step 4b (Method B): A solution of (2*S*,3*S*)-3-(3-chlorophenyl)-3-(2,3-dihydro-1*H*-indol-1-yl)propane-1,2-diol (5.8 g, 19 mmol) in ca. 1:1 (v/v) toluene-dichloromethane (200 mL) was treated with a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (4.4 g, 19 mmol) in toluene (100 mL) at 0°C. After 30 minutes, the mixture was diluted with ethyl acetate (1 L) and washed with 5 % aqueous sodium carbonate (4 x 1 L), water (1 L) and brine (1 L), dried (magnesium sulfate) and concentrated under vacuum to give a dark oil (5.4 g) that was pre-adsorbed on silica gel (15 g). Flash column chromatography (silica 235 g, 20 %, 40 % ethyl acetate/hexanes) provided (2*S*,3*S*)-3-(3-chlorophenyl)-3-(1*H*-indol-1-yl)propane-1,2-diol, (4.7 g, 82 %) as a cloudy yellow oil. MS (ES) *m/z* 302 ($[M+H]^+$).

[0247] Step 5: In an analogous manner to EXAMPLE 1, step 2, (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-chlorophenyl)-2-hydroxy-3-indol-1-yl-propyl ester was prepared from (2*S*,3*S*)-3-(3-chlorophenyl)-3-(1*H*-indol-1-yl)propane-1,2-diol. MS (ES) *m/z* 456 ($[M+H]^+$).

[0248] Step 6: (2*S*,3*S*)-Toluene-4-sulfonic acid 3-(3-chlorophenyl)-2-hydroxy-3-indol-1-yl-propyl ester (0.60 g, 1.2 mmol) was treated with a solution of methylamine in methanol (2.0 M, 3 mL, 6 mmol) and the solution was stirred at 23°C for 18 hours. At this time, the solution was concentrated under vacuum and dissolved in diethyl ether (50 mL). The organic solution was washed with a 1 N aqueous solution of sodium hydroxide (50 mL), water (50 mL) and brine (50 mL), dried (sodium sulfate) and concentrated under vacuum to provide an orange foam (0.30 g) that was purified by reverse phase HPLC (90:10 water-acetonitrile to 50:50 water-acetonitrile containing 0.1 % trifluoroacetic acid @ 20 mL/min). The product fractions were concentrated under vacuum to remove acetonitrile and the aqueous solution was basified with a 2N aqueous solution of ammonium hydroxide. The resulting milky suspension was extracted with ethyl acetate (200 mL) and the organic phase was washed with water (200 mL) and brine (100 mL), dried (sodium sulfate) and concentrated under vacuum. The residue was dissolved in absolute ethanol (4 mL), treated with a 4 M hydrochloric acid in 1,4-dioxane (1.3 eq) and stirred for 10 minutes. The solution was concentrated under vacuum, then dissolved in absolute ethanol (3 mL) and left standing at 23°C overnight. Vacuum filtration provided (1*S*,2*R*)-1-(3-chlorophenyl)-1-(1*H*-indol-1-yl)-3-(methylamino)propan-2-ol hydrochloride (62 mg, 5 % for 3 steps) as a white crystalline solid. HRMS calcd for $C_{18}H_{19}ClN_2O + H^+$, 315.12587; found (ESI) 315.1267 ($[M+H]^+$).

[0249] EXAMPLE 34: (1*S*,2*R*)-1-(4-chlorophenyl)-1-(1*H*-indol-1-yl)-3-(methylamino)propan-2-ol hydrochloride



[0250] In an analogous manner to EXAMPLE 33, step 1 (2*E*)-3-(4-chlorophenyl)-acrylic acid ethyl ester was prepared from diethyl ethoxycarbonylmethylphosphonate and 4-chlorobenzaldehyde. MS (ESI) *m/z* 210 ($[M+H]^+$).

[0251] In an analogous manner to EXAMPLE 33, step 2 (2*E*)-3-(4-chlorophenyl)prop-2-en-1-ol was prepared from (2*E*)-3-(4-chlorophenyl)-acrylic acid ethyl ester. MS (ESI) *m/z* 151 ([M+H-H_2O]$^+$).

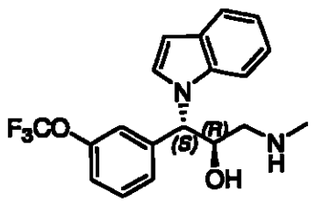
[0252] In an analogous manner to EXAMPLE 117, step 4, [(2*R*,3*R*)-3-(4-chlorophenyl)oxiran-2-yl]methanol was prepared from (2*E*)-3-(4-chlorophenyl)prop-2-en-1-ol. MS (ESI) *m/z* 167 ([M+H-H_2O]$^+$); [□□$_D$ +41 (c 0.0121 g/mL, DMSO); 99.2 % ee.

[0253] In an analogous manner to EXAMPLE 117, step 5, (2*S*,3*S*)-3-(4-chlorophenyl)-3-(1*H*-indol-1-yl)propane-1,2-diol was prepared from 1*H*-indole and [(2*R*,3*R*)-3-(4-chlorophenyl)oxiran-2-yl]methanol. MS (ES) *m/z* 302 ([M+H]$^+$).

[0254] In an analogous manner to EXAMPLE 1, step 2, (2*S*,3*S*)-toluene-4-sulfonic acid 3-(4-chlorophenyl)-2-hydroxy-3-indol-1-yl-propyl ester was prepared from (2*S*,3*S*)-3-(4-chlorophenyl)-3-(1*H*-indol-1-yl)propane-1,2-diol. MS (ES) *m/z* 456 ([M+H]$^+$).

[0255] In an analogous manner to EXAMPLE 33, step 6 (1*S*,2*R*)-1-(4-chlorophenyl)-1-(1*H*-indol-1-yl)-3-(methylamino)propan-2-ol hydrochloride was prepared from (2*S*,3*S*)-toluene-4-sulfonic acid 3-(4-chlorophenyl)-2-hydroxy-3-indol-1-yl-propyl ester and methylamine (2 N solution in methanol). HRMS: calcd for $C_{18}H_{19}ClN_2O$ + H^+, 315.12587; found (ESI) 315.124 ([M+H]$^+$).

[0256] EXAMPLE 35: (1*S*,2*R*)-1-(1*H*-Indol-1-yl)-3-(methylamino)-1-[3-(trifluoromethoxy)phenyl]propan-2-ol hydrochloride



[0257] In an analogous manner to EXAMPLE 33, step 1, (2*E*)-3-(3-trifluoromethoxy-phenyl)-acrylic acid ethyl ester was prepared from diethyl ethoxycarbonylmethylphosphonate and 3-(trifluoromethoxy)benzaldehyde. MS (ES) *m/z* 261 ($[M+H]^+$).

[0258] In an analogous manner to EXAMPLE 33, step 2, (2*E*)-3-[3-(trifluoromethoxy)phenyl]prop-2-en-1-ol was prepared from (2*E*)-3-(3-trifluoromethoxy-phenyl)-acrylic acid ethyl ester. MS (ES) *m/z* 201 ($[M+H-H_2O]^+$).

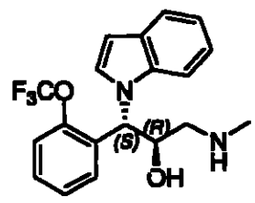
[0259] In an analogous manner to EXAMPLE 117, step 4, {(2*R*,3*R*)-3-[3-(trifluoromethoxy)phenyl]oxiran-2-yl}methanol was prepared from (2*E*)-3-[3-(trifluoromethoxy)phenyl]prop-2-en-1-ol. MS (ES) *m/z* 217 ($[M+H-H_2O]^+$); $[\square]_D^{25}$ = +30° (c = 0.0118 g/mL, DMSO); 84.4 % ee.

[0260] In an analogous manner to EXAMPLE 117, step 5, (2*S*,3*S*)-3-(1*H*-indol-1-yl)-3-[3-(trifluoromethoxy)phenyl]propane-1,2-diol was prepared from 1*H*-indole and {(2*R*,3*R*)-3-[3-(trifluoromethoxy)phenyl]oxiran-2-yl}methanol. MS (ES) *m/z* 352 ($[M+H]^+$).

[0261] In an analogous manner to EXAMPLE 1, step 2 (2*S*,3*S*)-toluene-4-sulfonic acid 2-hydroxy-3-indol-1-yl-3-(3-trifluoromethoxy-phenyl)-propyl ester was prepared from (2*S*,3*S*)-3-(1*H*-indol-1-yl)-3-[3-(trifluoromethoxy)phenyl]propane-1,2-diol. MS (ES) *m/z* 506 ($[M+H]^+$).

[0262] In an analogous manner to EXAMPLE 33, step 6 (1*S*,2*R*)-1-(1*H*-indol-1-yl)-3-(methylamino)-1-[3-(trifluoromethoxy)phenyl]propan-2-ol hydrochloride was prepared from (2*S*,3*S*)-toluene-4-sulfonic acid 2-hydroxy-3-indol-1-yl-3-(3-trifluoromethoxy-phenyl)-propyl ester and methylamine (2 N in methanol). MS (ES) *m/z* 365 ($[M+H]^+$).

[0263] EXAMPLE 36: (1*S*,2*R*)-1-(1*H*-indol-1-yl)-3-(methylamino)-1-[2-(trifluoromethoxy)phenyl]propan-2-ol hydrochloride



[0264] Step 1: In an analogous manner to EXAMPLE 33, step 1, (2*E*)-3-(2-trifluoromethoxy-phenyl)-acrylic acid ethyl ester was prepared from diethyl ethoxycarbonylmethylphosphonate and 2-(trifluoromethoxy)benzaldehyde. MS (ES) *m/z* 261 ($[M+H]^+$).

[0265] Step 2: In an analogous manner to EXAMPLE 33, step 2, (2*E*)-3-[2-(trifluoromethoxy)phenyl]prop-2-en-1-ol was prepared from (2*E*)-3-(2-trifluoromethoxy-phenyl)-acrylic acid ethyl ester. MS (ES) *m/z* 201 ($[M+H-H_2O]^+$).

[0266] Step 3: A solution of (2*E*)-3-[2-(trifluoromethoxy)phenyl]prop-2-en-1-ol (3.9 g, 18 mmol) in dichloromethane (90 mL) was treated with *meta*-chloroperoxybenzoic acid (77 %, 8.0 g, 36 mmol) at 23°C. After 5 hours, the reaction was quenched with a 1 N aqueous solution of sodium hydroxide (200 mL) with vigorous stirring and the phases were separated. The aqueous phase was extracted with diethyl ether (2 x 100 mL). The combined organic phases were washed with water (3 x 100 mL), dried (sodium sulfate) and concentrated under vacuum to provided a clear, colorless oil (3.8 g) that was pre-adsorbed on silica gel (6 g). Flash column chromatography (silica 60 g, 10 %, 20 % ethyl acetate/hexanes) provided {(2*RS*,3*RS*)-3-[2-(trifluoromethoxy)phenyl]oxiran-2-yl}methanol (2.4 g, 57 %) as a white solid. MS (ES) *m/z* 217 ($[M+H-H_2O]^+$).

[0267] {(2*RS*,3*RS*)-3-[2-(trifluoromethoxy)phenyl]oxiran-2-yl}methanol was dissolved in methanol. The resulting solution was injected onto the Supercritical Fluid Chromatography instrument, and the baseline resolved enantiomers were collected using the conditions described below. The enantiomeric purity of each enantiomer was determined under the same Supercritical Fluid Chromatography conditions using a Chiralpak AS-H 5u, 250 mm x 4.6 mm ID column at 2.0

mL/minutes flow rate using Analytical Supercritical Fluid Chromatography (Berger Instruments, Inc. Newark, DE USA).

SFC Instrument: Berger MultiGram Prep SFC (Berger Instruments, Inc. Newark, DE 19702.
Column: Chiralpak AS-H; 5u; 250mm L x 20mm ID (Chiral Technologies, Inc, Exton, PA, USA)
Column temperature: 35°C
SFC Modifier: 5% IPA/95% CO2
Flow rate: 35 mL/min
Outlet Pressure: 100 bar
Detector: UV at 220 nm

[0268] {(2*R*,3*R*)-3-[2-(trifluoromethoxy)phenyl]oxiran-2-yl}methanol was isolated as peak 1. MS (ES) *m/z* 217 ($[M+H-H_2O]^+$); $[\alpha]_D^{25}$ = +19.4° (c = 0.0102 g/mL, DMSO); > 99.9 % ee.

[0269] {(2*S*,3*S*)-3-[2-(trifluoromethoxy)phenyl]oxiran-2-yl}methanol was isolated as peak 2. MS (ES) *m/z* 217 ($[M+H-H_2O]^+$); $[\alpha]_D^{25}$ = -15.7° (c = 0.0125 g/mL, DMSO); 95.8 % ee.

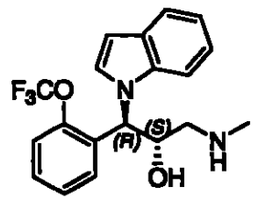
[0270] Step 4: In an analogous manner to EXAMPLE 117, step 5, (2*S*,3*S*)-3-(1*H*-indol-1-yl)-3-[2-(trifluoromethoxy)phenyl]propane-1,2-diol was prepared from 1*H*-indole and {(2*R*,3*R*)-3-[2-(trifluoromethoxy)phenyl]oxiran-2-yl}methanol, substituting sodium *tert*-butoxide in place of potassium hydride. MS (ES) *m/z* 352 ($[M+H]^+$).

[0271] Step 5: In an analogous manner to EXAMPLE 1, step 2, (2*S*,3*S*)-toluene-4-sulfonic acid 2-hydroxy-3-indol-1-yl-3-(2-trifluoromethoxy-phenyl)-propyl ester was prepared from (2*S*,3*S*)-3-(1*H*-indol-1-yl)-3-[2-(trifluoromethoxy)phenyl]propane-1,2-diol. MS (ES) *m/z* 506 ($[M+H]^+$).

[0272] Step 6: In an analogous manner to EXAMPLE 33, step 6 (1*S*,2*R*)-1-(1*H*-indol-1-yl)-3-(methylamino)-1-[2-(trifluoromethoxy)phenyl]propan-2-ol hydrochloride

was prepared from (2*S*,3*S*)-toluene-4-sulfonic acid 2-hydroxy-3-indol-1-yl-3-(2-trifluoromethoxy-phenyl)-propyl ester and methylamine (2 N in methanol). MS (ES) *m/z* 365 ([M+H]$^+$).

[0273] EXAMPLE 37: (1*R*,2*S*)-1-(1*H*-indol-1-yl)-3-(methylamino)-1-[2-(trifluoromethoxy)phenyl]propan-2-ol hydrochloride

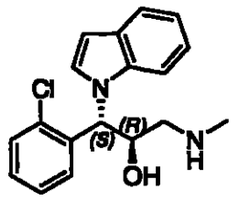


[0274] In an analogous manner to EXAMPLE 117, step 5, (2*R*,3*R*)-3-(1*H*-indol-1-yl)-3-[2-(trifluoromethoxy)phenyl]propane-1,2-diol was prepared from 1*H*-indole and {(2*S*,3*S*)-3-[2-(trifluoromethoxy)phenyl]oxiran-2-yl}methanol (EXAMPLE 36, step 3) substituting sodium *tert*-butoxide in place of potassium hydride. MS (ES) *m/z* 352 ([M+H]$^+$).

[0275] In an analogous manner to EXAMPLE 1, step 2, (2*R*,3*R*)-toluene-4-sulfonic acid 2-hydroxy-3-indol-1-yl-3-(2-trifluoromethoxy-phenyl)-propyl ester was prepared from (2*R*,3*R*)-3-(1*H*-indol-1-yl)-3-[2-(trifluoromethoxy)phenyl]propane-1,2-diol. MS (ES) *m/z* 506 ([M+H]$^+$).

[0276] In an analogous manner to EXAMPLE 33, step 6 (1*R*,2*S*)-1-(1*H*-indol-1-yl)-3-(methylamino)-1-[2-(trifluoromethoxy)phenyl]propan-2-ol hydrochloride was prepared from (2*R*,3*R*)-toluene-4-sulfonic acid 2-hydroxy-3-indol-1-yl-3-(2-trifluoromethoxy-phenyl)-propyl ester and methylamine (2 N in methanol). MS (ES) *m/z* 365 ([M+H]$^+$).

[0277] EXAMPLE 38: (1*S*,2*R*)-1-(2-chlorophenyl)-1-(1*H*-indol-1-yl)-3-(methylamino)propan-2-ol hydrochloride



[0278] In an analogous manner to EXAMPLE 33, step 1, (2*E*)-3-(2-chlorophenyl)-acrylic acid ethyl ester was prepared from diethyl ethoxycarbonylmethylphosphonate and 2-chlorobenzaldehyde. MS (ESI) *m/z* 210 ($[M+H]^+$).

[0279] In an analogous manner to EXAMPLE 33, step 2, (2*E*)-3-(2-chlorophenyl)prop-2-en-1-ol was prepared from (2*E*)-3-(2-chlorophenyl)-acrylic acid ethyl ester. MS (ESI) *m/z* 151 ($[M+H-H_2O]^+$).

[0280] In an analogous manner to EXAMPLE 36, step 3, [(2*RS*,3*RS*)-3-(2-chlorophenyl)oxiran-2-yl]methanol was prepared from (2*E*)-3-(2-chlorophenyl)prop-2-en-1-ol.

[0281] [(2*RS*,3*RS*)-3-(2-chlorophenyl)oxiran-2-yl]methanol was dissolved in methanol. The resulting solution was injected (50 mg/injection) onto the Supercritical Fluid Chromatography instrument, and the baseline resolved enantiomers were collected using the conditions described below. The enantiomeric purity of each enantiomer was determined under the same Supercritical Fluid Chromatography conditions using a Chiralpak AD-H 5u, 250 mm x 4.6 mm ID column at 2.0 mL/minutes flow rate using Analytical Supercritical Fluid Chromatography (Berger Instruments, Inc. Newark, DE USA).

SFC Instrument: Berger MultiGram Prep SFC (Berger Instruments, Inc. Newark, DE 19702.
Column: Chiralpak AD-H; 5u; 250mm L x 20mm ID (Chiral Technologies, Inc, Exton, PA, USA)
Column temperature: 35°C
SFC Modifier: 20% MeOH/80% CO2
Flow rate: 50 mL/min

Outlet Pressure: 100 bar
Detector: UV at 220 nm

[0282] [(2*S*,3*S*)-3-(2-chlorophenyl)oxiran-2-yl]methanol was isolated as peak 1. MS (ES) *m/z* 167 ($[M+H-H_2O]^+$); $[\alpha]_D^{25}$ = +2.6° (c = 0.0153 g/mL, DMSO); >99.8 % ee.

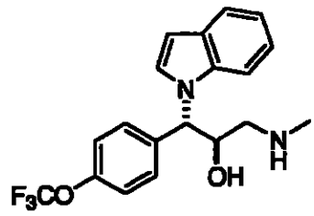
[0283] [(2*R*,3*R*)-3-(2-chlorophenyl)oxiran-2-yl]methanol was isolated as peak 2. MS (ES) *m/z* 167 ($[M+H-H_2O]^+$); $[\alpha]_D^{25}$ = -2.5° (c = 0.0139 g/mL, DMSO); >99.8 % ee.

[0284] In an analogous manner to EXAMPLE 117, step 5, (2*S*,3*S*)-3-(2-chlorophenyl)-3-(1*H*-indol-1-yl)propane-1,2-diol was prepared from 1*H*-indole and [(2*R*,3*R*)-3-(2-chlorophenyl)oxiran-2-yl]methanol, substituting sodium *tert*-butoxide in place of potassium hydride. MS (ES) *m/z* 302 ($[M+H]^+$).

[0285] In an analogous manner to EXAMPLE 1, step 2, (2*S*,3*S*)-toluene-4-sulfonic acid 3-(2-chlorophenyl)-2-hydroxy-3-indol-1-yl-propyl ester was prepared from (2*S*,3*S*)-3-(2-chlorophenyl)-3-(1*H*-indol-1-yl)propane-1,2-diol. MS (ES) *m/z* 456 ($[M+H]^+$).

[0286] In an analogous manner to EXAMPLE 33, step 6 (1*S*,2*R*)-1-(2-chlorophenyl)-1-(1*H*-indol-1-yl)-3-(methylamino)propan-2-ol hydrochloride was prepared from (2*S*,3*S*)-toluene-4-sulfonic acid 3-(2-chlorophenyl)-2-hydroxy-3-indol-1-yl-propyl ester and methylamine (2 N in methanol). MS (ES) *m/z* 315 ($[M+H]^+$).

[0287] EXAMPLE 39: (1*RS*,2*SR*)-1-(1*H*-indol-1-yl)-3-(methylamino)-1-[4-(trifluoromethoxy)phenyl]propan-2-ol hydrochloride



[0288] Step 1: In an analogous manner to EXAMPLE 33, step 1, (2*E*)-3-(4-trifluoromethoxy-phenyl)-acrylic acid ethyl ester was prepared from diethyl ethoxycarbonylmethylphosphonate and 4-(trifluoromethoxy)benzaldehyde. MS (ES) *m/z* 261([M+H]$^+$).

[0289] Step 2: In an analogous manner to EXAMPLE 33, step 2, (2*E*)-3-[4-(trifluoromethoxy)phenyl]prop-2-en-1-ol was prepared from (2*E*)-3-(4-trifluoromethoxy-phenyl)-acrylic acid ethyl ester. MS (ES) *m/z* 201 ([M+H-H_2O]$^+$).

[0290] Step 3: In an analogous manner to EXAMPLE 36, step 3, {(2*RS*,3*RS*)-3-[4-(trifluoromethoxy)phenyl]oxiran-2-yl}methanol was prepared from (2*E*)-3-[4-(trifluoromethoxy)phenyl]prop-2-en-1-ol . MS (ES) *m/z* 217 ([M+H-H_2O]$^+$).

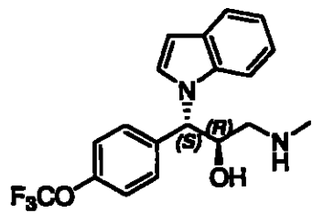
[0291] Step 4: In an analogous manner to EXAMPLE 33, step 4a (Method B), (2*RS*,3*RS*)-3-(2,3-dihydro-1*H*-indol-1-yl)-3-[4-(trifluoromethoxy)phenyl]propane-1,2-diol was prepared from indoline and {(2*RS*,3*RS*)-3-[4-(trifluoromethoxy)phenyl]oxiran-2-yl}methanol. MS (ES) *m/z* 354 ([M+H]$^+$).

[0292] Step 5: In an analogous manner to EXAMPLE 33, step 4b (Method B), (2*RS*,3*RS*)-3-(1*H*-indol-1-yl)-3-[4-(trifluoromethoxy)phenyl]propane-1,2-diol was prepared from (2*RS*,3*RS*)-3-(2,3-dihydro-1*H*-indol-1-yl)-3-[4-(trifluoromethoxy)phenyl]propane-1,2-diol. MS (ES) *m/z* 352 ([M+H]$^+$).

[0293] Step 6: In an analogous manner to EXAMPLE 1, step 2, (2*RS*,3*RS*)-toluene-4-sulfonic acid 2-hydroxy-3-indol-1-yl-3-(4-trifluoromethoxy-phenyl)-propyl ester was prepared from (2*RS*,3*RS*)-3-(1*H*-indol-1-yl)-3-[4-(trifluoromethoxy)phenyl]propane-1,2-diol . MS (ES) *m/z* 506 ([M+H]$^+$).

[0294] Step 7: In an analogous manner to EXAMPLE 33, step 6 (Method B), (1*RS*,2*SR*)-1-(1*H*-indol-1-yl)-3-(methylamino)-1-[4-(trifluoromethoxy)phenyl]propan-2-ol hydrochloride was prepared from (2*RS*,3*RS*)-toluene-4-sulfonic acid 2-hydroxy-3-indol-1-yl-3-(4-trifluoromethoxy-phenyl)-propyl ester and methylamine (2 N in methanol). MS (ES) *m/z* 365 ([M+H]$^+$).

[0295] EXAMPLE 40: (1*S*,2*R*)-1-(1*H*-indol-1-yl)-3-(methylamino)-1-[4-(trifluoromethoxy)phenyl]propan-2-ol hydrochloride



[0296] Step 1: (1*RS*,2*SR*)-1-(1*H*-indol-1-yl)-3-(methylamino)-1-[4-(trifluoromethoxy)phenyl]propan-2-ol hydrochloride (EXAMPLE 39, step 7) was dissolved in methanol. The resulting solution was injected (35 mg/injection) onto the Supercritical Fluid Chromatography instrument, and the baseline resolved enantiomers were collected using the conditions described below. The enantiomeric purity of each enantiomer was determined under the same Supercritical Fluid Chromatography conditions using a Chiralpak AD-H 5u, 250 mm x 4.6 mm ID column at 2.0 mL/minutes flow rate using Analytical Supercritical Fluid Chromatography (Berger Instruments, Inc. Newark, DE USA).

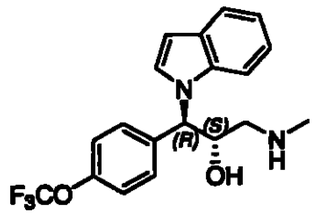
SFC Instrument: Berger MultiGram Prep SFC (Berger Instruments, Inc. Newark, DE 19702.
Column: Chiralpak AD-H; 5u; 250mm L x 20mm ID (Chiral Technologies, Inc, Exton, PA, USA)
Column temperature: 35°C
SFC Modifier: . 25% MeOH w/ 1.0%DEA/75% CO2
Flow rate: 50 mL/min

Outlet Pressure: 100 bar

Detector: UV at 220 nm

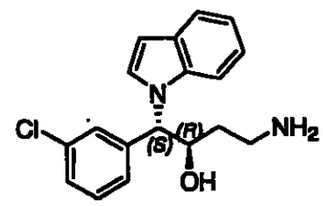
[0297] (1*S*,2*R*)-1-(1*H*-indol-1-yl)-3-(methylamino)-1-[4-(trifluoromethoxy)phenyl]propan-2-ol hydrochloride was isolated as peak 1 after neutralization and conversion of the free base to the hydrochloride salt according to EXAMPLE 33, step 6. MS (ES) *m/z* 365 ($[M+H]^+$); 98.4 % ee.

[0298] EXAMPLE 41: (1*R*,2*S*)-1-(1*H*-indol-1-yl)-3-(methylamino)-1-[4-(trifluoromethoxy)phenyl]propan-2-ol hydrochloride



[0299] (1*R*,2*S*)-1-(1*H*-indol-1-yl)-3-(methylamino)-1-[4-(trifluoromethoxy)phenyl]propan-2-ol hydrochloride (EXAMPLE 40, step 1) was isolated as peak 2 after neutralization and conversion of the free base to the hydrochloride salt according to EXAMPLE 33, step 6. MS (ES) *m/z* 365 ($[M+H]^+$); >99.9 % ee.

[0300] EXAMPLE 42: (1*S*,2*R*)-4-amino-1-(3-chlorophenyl)-1-(1*H*-indol-1-yl)butan-2-ol hydrochloride

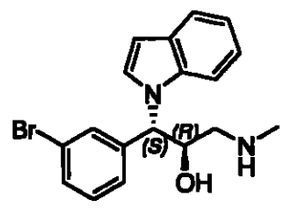


[0301] Step 1: A mixture of (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-chlorophenyl)-2-hydroxy-3-indol-1-yl-propyl ester (EXAMPLE 33, step 5, 1.9 g, 4.2 mmol) and

sodium cyanide (0.23 g, 4.7 mmol) in dry dimethylsulfoxide (20 mL) was heated at 100°C (microwave). After 15 minutes, the cooled solution was taken up in ethyl acetate (200 mL), washed with water (3 x 200 mL), dried (sodium sulfate) and concentrated under vacuum to give a tan foam (1.3 g) that was pre-adsorbed on silica gel (3 g). Flash column chromatography (silica 30 g, 10 %, 20 %, 40 % ethyl acetate/hexanes) provided (3*R*,4*S*)-4-(3-chlorophenyl)-3-hydroxy-4-indol-1-yl-butyronitrile (1.2 g, 92 %) as a tan foam. MS (ES) *m/z* 311 ($[M+H]^+$).

[0302] Step 2: A solution of (3*R*,4*S*)-4-(3-chlorophenyl)-3-hydroxy-4-indol-1-yl-butyronitrile (1.2 g, 3.9 mmol) in dry tetrahydrofuran (20 mL) was treated with diborane-tetrahydrofuran solution (1.0 M, 20 mL, 20 mmol) at 23°C. After 16 hours, the reaction was quenched with methanol (7 mL) at 23°C and the solution was concentrated under vacuum to give an off-white foam that was partitioned between diethyl ether (200 mL) and a 1 N aqueous solution of sodium hydroxide (200 mL). The organic phase was separated, washed with brine (200 mL), dried (sodium sulfate) and concentrated under vacuum to give a yellow foam (1.2 g) that was purified via Biotage chromatography [AnaLogix silica column, 2 x 40 g in series, dichloromethane to 5 % ammonia saturated methanol/dichloromethane] to provide (1*S*,2*R*)-4-amino-1-(3-chlorophenyl)-1-(1*H*-indol-1-yl)butan-2-ol (0.43 g, 36 %). The free base was converted to the hydrochloride salt as described in EXAMPLE 33, step 6, to provide (1*S*,2*R*)-4-amino-1-(3-chlorophenyl)-1-(1*H*-indol-1-yl)butan-2-ol hydrochloride (0.47 g, 34 %) as a foam. MS (ES) *m/z* 315 ($[M+H]^+$).

[0303] EXAMPLE 43: (1*S*,2*R*)-1-(3-bromophenyl)-1-(1*H*-indol-1-yl)-3-(methylamino)propan-2-ol hydrochloride



[0304] Step 1: In an analogous manner to EXAMPLE 33, step 1, (2*E*)-3-(3-bromophenyl)-acrylic acid ethyl ester was prepared from diethyl

ethoxycarbonylmethylphosphonate, and 3-bromobenzaldehyde. MS (ES) *m/z* 255 ([M+H]$^+$).

[0305] Step 2: In an analogous manner to EXAMPLE 33, step 2, (2*E*)-3-(3-bromophenyl)prop-2-en-1-ol was prepared from (2*E*)-3-(3-bromophenyl)-acrylic acid ethyl ester. MS (ES) *m/z* 195 ([M+H-H_2O]$^+$).

[0306] Step 3: In an analogous manner to EXAMPLE 117, step 4, [(2*R*,3*R*)-3-(3-bromophenyl)oxiran-2-yl]methanol was prepared from (2*E*)-3-(3-bromophenyl)prop-2-en-1-ol . MS (ES) *m/z* 211 ([M+H-H_2O]$^+$); 95 % ee.

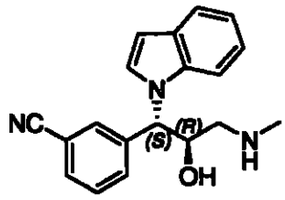
[0307] Step 4: In an analogous manner to EXAMPLE 33, step 4a (Method B), (2*S*,3*S*)-3-(3-bromophenyl)-3-(2,3-dihydro-1*H*-indol-1-yl)propane-1,2-diol was prepared from indoline and [(2*R*,3*R*)-3-(3-bromophenyl)oxiran-2-yl]methanol. MS (ES) *m/z* 348 ([M+H]$^+$).

[0308] Step 5: In an analogous manner to EXAMPLE 33, step 4b (Method B), (2*S*,3*S*)-3-(3-bromophenyl)-3-(1*H*-indol-1-yl)propane-1,2-diol was prepared from (2*S*,3*S*)-3-(3-bromophenyl)-3-(2,3-dihydro-1*H*-indol-1-yl)propane-1,2-diol. MS (ES) *m/z* 346 ([M+H]$^+$).

[0309] Step 6: In an analogous manner to EXAMPLE 1, step 2, (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-bromophenyl)-2-hydroxy-3-indol-1-yl-propyl ester was prepared from (2*S*,3*S*)-3-(3-bromophenyl)-3-(1*H*-indol-1-yl)propane-1,2-diol . MS (ES) *m/z* 500 ([M+H]$^+$).

[0310] Step 7: In an analogous manner to EXAMPLE 33, step 6 (1*S*,2*R*)-1-(3-bromophenyl)-1-(1*H*-indol-1-yl)-3-(methylamino)propan-2-ol hydrochloride was prepared from (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-bromophenyl)-2-hydroxy-3-indol-1-yl-propyl ester and methylamine (2 N solution in methanol). MS (ES) *m/z* 359 ([M+H]$^+$).

[0311] EXAMPLE 44: 3-[(1*S*,2*R*)-2-hydroxy-1-(1*H*-indol-1-yl)-3-(methylamino)propyl]benzonitrile hydrochloride

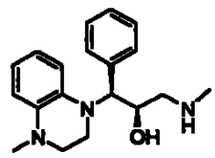


[0312] A mixture of (2*S*,3*S*)-3-(3-bromophenyl)-(1*H*-indol-1-yl)propane-1,2-diol (EXAMPLE 43, step 5, 1.4 g, 4.0 mmol), zinc (II) cyanide (4.7 g, 40 mmol) and tetrakis(triphenylphosphine)palladium (0) (0.46 g, 0.40 mmol) in de-gassed 1-methyl-2-pyrrolidinone (25 mL) was heated at 150°C in a sealed flask. After 3.5 hours, the cooled brown mixture was diluted with ethyl acetate (250 mL) and filtered through Celite. The filtrate was washed with water (5 x 250 mL) and brine (1 x 250 mL), dried (sodium sulfate), and concentrated under vacuum to give an amber oil (1.6 g) that was pre-adsorbed on silica gel (6 g). Flash column chromatography (silica 70 g, 30 %, 60 % ethyl acetate/hexanes) provided 3-[(1*S*,2*S*)-2,3-dihydroxy-1-(1*H*-indol-1-yl)propyl]benzonitrile (1.0 g, 83 %) as a pale yellow foam. MS (ES) *m/z* 293 ($[M+H]^+$).

[0313] In an analogous manner to EXAMPLE 1, step 2, (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-cyano-phenyl)-2-hydroxy-3-indol-1-yl-propyl ester was prepared from 3-[(1*S*,2*S*)-2,3-dihydroxy-1-(1*H*-indol-1-yl)propyl]benzonitrile. MS (ES) *m/z* 447 ($[M+H]^+$).

[0314] In an analogous manner to EXAMPLE 33, step 6 3-[(1*S*,2*R*)-2-hydroxy-1-(1H-indol-1-yl)-3-(methylamino)propyl]benzonitrile hydrochloride was prepared from (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-cyano-phenyl)-2-hydroxy-3-indol-1-yl-propyl ester and methylamine (2 N solution in methanol). MS (ESI) *m/z* 306 ($[M+H]^+$).

[0315] EXAMPLE 45: (1SR,2RS)-3-(methylamino)-1-(4-methyl-3,4-dihydroquinoxalin-1(2H)-yl)-1- phenylpropan-2-ol hydrochloride



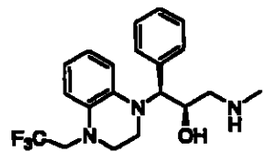
[0316] Step 1: In an analogous manner to EXAMPLE 53, step 3, 3-phenylglycidol was prepared from cinnamyl alcohol as a white solid. MS (ES) *m/z* 151.1 ($[M+H]^+$).

[0317] Step 2: In an analogous manner to EXAMPLE 47, step 4, (2SR,3SR)-3-(4-methyl-3,4-dihydroquinoxalin-1(2H)-yl)-3-phenylpropane-1,2-diol was prepared from 1-methyl-1,2,3,4-tetrahydroquinoxaline[1] and 3-phenylglycidol as a viscous colorless oil. MS (ES) *m/z* 299.0 ($[M+H]^+$); HRMS: calcd for $C_{18}H_{22}N_2O_2 + H^+$, 299.1760; found (ESI, $[M+H]^+$), 299.1739.

[0318] Step 3: In an analogous manner to EXAMPLE 47, step 6, (1SR,2RS)-3-(methylamino)-1-(4-methyl-3,4-dihydroquinoxalin-1(2H)-yl)-1-phenylpropan-2-ol hydrochloride was prepared from (2SR,3SR)-3-(4-methyl-3,4-dihydroquinoxalin-1(2H)-yl)-3-phenylpropane-1,2-diol as a white powder. MS (ES) *m/z* 312.0 ($[M+H]^+$); HRMS: calcd for $C_{19}H_{25}N_3O + H^+$, 312.2076; found (ESI, $[M+H]^+$), 312.2065.

[1] Cavagnol, J. C.; Wiselogle, F. Y. *J. Am. Chem. Soc.* **1947**, *69*, 795-799.

[0319] EXAMPLE 46: (1SR,2RS)-3-(methylamino)-1-phenyl-1-[4-(2,2,2-trifluoroethyl)-3,4- dihydroquinoxalin-1(2H)-yl]propan-2-ol hydrochloride

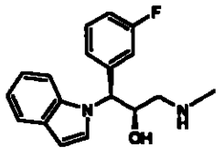


[0320] Compound 1-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroquinoxaline was obtained as a white powder side product of the reduction reaction of quinoxaline to 1,2,3,4-tetrahydroquinoxaline using sodium borohydride in trifluoroacetic acid.[2] MS (ES) *m/z* 217.1 ($[M+H]^+$).

[0321] In an analogous manner to EXAMPLE 47, step 4, (2SR,3SR)-3-(4-(2,2,2-trifluoroethyl)-3,4-dihydroquinoxalin-1(2H)-yl)-3-phenylpropane-1,2-diol was prepared from 1-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroquinoxaline and 3-phenylglycidol (EXAMPLE 45, step 1) as a viscous colorless oil.

[0322] In an analogous manner to EXAMPLE 47, step 6, (1SR,2RS)-3-(methylamino)-1-phenyl-1-[4-(2,2,2-trifluoroethyl)-3,4-dihydroquinoxalin-1(2H)-yl]propan-2-ol hydrochloride was prepared from (2SR,3SR)-3-(4-(2,2,2-trifluoroethyl)-3,4-dihydroquinoxalin-1(2H)-yl)-3-phenylpropane-1,2-diol as a white powder. MS (ES) *m/z* 380.0 ($[M+H]^+$); HRMS: calcd for $C_{20}H_{24}F_3N_3O + H^+$, 380.1950; found (ESI, $[M+H]^+$), 380.1934.

[0323] EXAMPLE 47: (1S,2R)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol hydrochloride



[2] Bugle, R. C.; Osteryoung, R. A. *J. Org. Chem.* **1979**, *44*, 1719-1720.

[0324] Step 1: To a mixture of *trans*-3-fluorocinnamic acid (50 g, 300 mmol) and iodomethane (300 mL) in acetone (1 L) was added portionwise cesium carbonate (147 g, 450 mmol, 1.5 equiv.), and the mixture was heated at 65ºC for 1.5 hours in a sealed reaction vessel. Upon cooling to room temperature, the reaction mixture was diluted with ethyl acetate (1 L), filtered through a pad of silica gel, and concentrated to give 47.33 g (87%) of *trans*-3-fluorocinnamic acid methyl ester as a colorless oil. MS (ES) *m/z* 180.0 (M^+).

[0325] Step 2: To a solution of *trans*-3-fluorocinnamic acid methyl ester (69.61 g, 386 mmol) in dry dichloromethane (1 L) at -78ºC under nitrogen was added dropwise diisobutylaluminum hydride (neat, 172 mL, 965 mmol, 2.5 equiv.) via an addition funnel. After the addition was complete, the reaction mixture was allowed to warm to -30ºC and stirred for an additional 1 hour, then quenched with methanol (150 mL). Upon warming to room temperature, the reaction mixture was treated with saturated aqueous solution of sodium/potassium tartrate (300 mL) and stirred for 30 minutes. The organic layer was washed sequentially with 1N aqueous hydrochloric acid solution, saturated aqueous sodium bicarbonate solution, brine, and dried (anhydrous sodium sulfate). The crude oil was purified by silica gel chromatography (0-50% ethyl acetate:hexane) to give 53.07 g (90%) of *trans*-3-fluorocinnamyl alcohol as a colorless oil. MS (ES) *m/z* 152.1 (M^+).

[0326] Step 3: An oven-dried, 3-neck, 2-L round bottom flask fitted with two oven-dried addition funnels and a rubber septum was charged with diisopropyl D-tartrate (11.55 g, 49.3 mmol, 0.30 equiv.), 4 Å powdered, activated molecular sieves (40 g) and dry dichloromethane (800 mL) under nitrogen. After being cooled to -25ºC, to the reaction mixture was added titanium isopropoxide (9.6 mL, 33 mmol, 0.20 equiv.) slowly via a hypodermic syringe. After stirring for 10 minutes, anhydrous *t*-butyl hydroperoxide (5.5 M in decane, 75.0 mL, 413 mmol, 2.5 equiv.) was added at a moderate rate via an addition funnel. The resulting mixture was stirred at -25ºC for 30 minutes. *trans*-3-Fluorocinnamyl alcohol (25.0 g, 164 mmol) in dry dichloromethane (50 mL) was added dropwise via an addition funnel while maintaining the temperature at -25ºC. After the addition, the reaction mixture was stirred at -25ºC for 1 hour and at -20ºC for another 3 hours. After the reaction was

complete, cooled aqueous sodium hydroxide solution (30%, 20 mL) saturated with sodium chloride was added slowly at -20°C. After diethyl ether (150 mL) was added, the cold bath was removed and the mixture was allowed to warm to ~ 5°C and stirred for 1 hour. Magnesium sulfate (anhydrous, 50 g) was added and the mixture was stirred for 20 minutes, then filtered through a pad of silica gel, and washed with ether (300 mL). The filtrate was concentrated and toluene was used to azeotropically remove excess *t*-butyl hydroperoxide. The residual oil was purified on silica gel (0-30% ethyl acetate:hexane) to give 24.80 g (90%) of [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol as a viscous, colorless oil. Percent ee: > 96.5%. MS (ESI) *m/z* 169.1 ($[M+H]^+$).

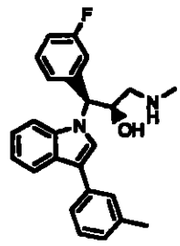
[0327] Step 4: A mixture of indoline (1.42 g, 11.89 mmol) and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (2.0 g, 11.89 mmol) was heated at 125°C for 5 hours in a sealed reaction vial. Upon cooling, the crude product was dissolved in ethyl acetate, absorbed on Fluorocil, and purified by Biotage chromatography (FlasH40i, silica, 0-55% EtOAc/hexane) to give 2.55 g (75%) of (2S,3S)-3-(2,3-dihydro-1H-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol as a colorless oil. MS (ESI) m/z 288.1 ($[M+H]^+$).

[0328] Step 5: A mixture of (2S,3S)-3-(2,3-dihydro-1H-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol (2.00 g, 6.96 mmol) and activated manganese dioxide (20.0 g, 230 mmol) in dichloromethane (30 mL) was stirred at 20°C for 3 hours. The mixture was diluted with ethyl acetate (15 mL), filtered through a pad of silica gel, and concentrated. The crude product was purified by Biotage chromatography (FlasH40i, silica, 0-70% EtOAc/hexane) to give 1.40 g (71%) of (2S,3S)-3-(3-fluorophenyl)-3-(1H-indol-1-yl)propane-1,2-diol as a colorless oil. MS (ESI) *m/z* 286.0 ($[M+H]^+$). HRMS: calcd for $C_{17}H_{16}FNO_2 + H^+$, 286.1238; found (ESI, $[M+H]^+$), 286.1239.

[0329] Step 6: To a solution of (2S,3S)-3-(2,3-dihydro-1H-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol (452 mg, 1.586 mmol) in dichloromethane (3 mL) under nitrogen was added triethylamine (1.1 mL, 7.93 mmol). The mixture was cooled to 0°C, and *para*-toluenesulfonyl chloride (423 mg, 2.22 mmol) was added

portionwise. The reaction mixture was stirred at 0°C for 1 hour and stored at 0°C overnight. Methylamine in absolute ethanol (8 M, 5 mL, 40 mmol) was added and the reaction mixture was sealed, and stirred overnight while warming to room temperature. All volatiles were removed under reduced pressure. The oil residue was dissolved in dichloromethane (20 mL), washed with aqueous potassium carbonate (5 mL), dried (anhydrous sodium sulfate), and concentrated. Purification by Biotage chromatography (FlasH12i, silica, 0-15% MeOH/dichloromethane/0.5% triethylamine) gave (1S,2R)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol, which was dissolved dichloromethane (5 mL) and treated with a 1M ethereal solution of hydrochloric acid (1.9 mL, 1.9 mmol). To the resulting solution was added hexane until white powder formed, which was collected, washed with hexane, and dried *in vacuo* to yield 209 mg (44%) of (1S,2R)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol hydrochloride as a white powder. MS (ES) *m/z* 299.0 ($[M+H]^+$); HRMS: calcd for $C_{18}H_{19}FN_2O + H^+$, 299.1554; found (ESI, $[M+H]^+$), 299.1553.

[0330] EXAMPLE 48: (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-[3-(3-methylphenyl)-1H-indol-1-yl]propan-2-ol hydrochloride



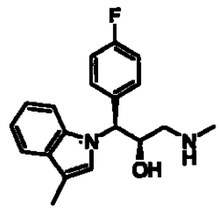
[0331] In an analogous manner to EXAMPLE 114, step 2, (2S,3S)-3-(3-fluorophenyl)-3-[3-[3-methylphenyl]-1H-indol-1-yl]propane-1,2-diol was prepared from (2*S*,3*S*)-3-(3-fluorophenyl)-3-(3-iodo-1*H*-indol-1-yl)propane-1,2-diol (EXAMPLE 114, step 1) and 3-methylbenzeneboronic acid.

[0332] In an analogous manner to EXAMPLE 1, step 2, (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-3-[3-(2-chlorophenyl)-indol-1-yl]-2-hydroxy-propyl ester was

prepared from (2S,3S)-3-(3-fluorophenyl)-3-{3-[3-methylphenyl]-1H-indol-1-yl}propane-1,2-diol.

[0333] In an analogous manner to EXAMPLE 5, (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-[3-(3-methylphenyl)-1H-indol-1-yl]propan-2-ol hydrochloride was prepared from (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-fluoro-phenyl)-3-[3-(3-methylphenyl)-indol-1-yl]-2-hydroxy-propyl ester and methylamine (2N solution in methanol). MS (ESI) *m/z* 389.2; HRMS: calcd for C25H25FN2O + H+, 389.20237; found (ESI, [M+H]+), 389.2005.

[0334] EXAMPLE 49: (1S,2R)-1-(4-fluorophenyl)-3-(methylamino)-1-(3-methyl-1H-indol-1-yl)propan-2-ol hydrochloride



[0335] Step 1: In an analogous manner to EXAMPLE 47, step 3, [(2R,3R)-3-(4-fluorophenyl)oxiran-2-yl]methanol was prepared from *trans*-4-fluorocinnamyl alcohol[3] as a white solid. Percent ee: > 97%. MS (ES) *m/z* 167.0 ([M-H]$^-$).

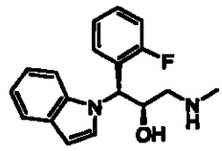
[0336] Step 2: In an analogous manner to EXAMPLE 117, step 5, (2S,3S)-3-(4-fluorophenyl)-3-(3-methyl-1H-indol-1-yl)propane-1,2-diol was prepared from 3-methylindole and [(2R,3R)-3-(4-fluorophenyl)oxiran-2-yl]methanol as a viscous, colorless oil. MS (ES) *m/z* 300.1 ([M+H]$^+$); HRMS: calcd for $C_{18}H_{18}FNO_2$ + H$^+$, 300.1400; found (ESI, [M+H]$^+$), 300.1406.

[0337] Step 3: In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(4-fluorophenyl)-3-(methylamino)-1-(3-methyl-1H-indol-1-yl)propan-2-ol hydrochloride

[3] Takeuchi, R.; Ue, N.; Tanabe, K.; Yamashita, K.; Shiga, N. *J. Am. Chem. Soc.*, 2001, *123*, 9525-9534.

was prepared from (2S,3S)-3-(4-fluorophenyl)-3-(3-methyl-1H-indol-1-yl)propane-1,2-diol as a white powder. MS (ESI) *m/z* 313.1 ([M+H]$^+$); HRMS: calcd for $C_{19}H_{21}FN_2O$ + H^+, 313.1711; found (ESI, [M+H]$^+$), 313.1727.

[0338] EXAMPLE 50: (1S,2R)-1-(2-fluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol hydrochloride



[0339] In an analogous manner to EXAMPLE 47, step 1, *trans*-2-fluorocinnamic acid methyl ester was prepared from *trans*-2-fluorocinnamic acid as a white solid. MS m/z 180.9 ([M+H]$^+$).

[0340] In an analogous manner to EXAMPLE 47, step 2, *trans*-2-fluorocinnamyl alcohol was prepared from *trans*-2-fluorocinnamic acid methyl ester as a colorless oil. MS (ESI) *m/z* 152.0 [M]$^+$; HRMS: calcd for C_9H_9FO, 152.0637; found (ESI, [M]$^+$), 152.0640.

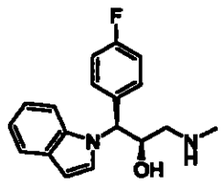
[0341] In an analogous manner to EXAMPLE 47, steps 3, [(2R,3R)-3-(2-fluorophenyl)oxiran-2-yl]methanol was prepared from *trans*-2-fluorocinnamyl alcohol as a white solid. MS m/z 169.0 ([M+H]$^+$).

[0342] In an analogous manner to EXAMPLE 117, step 5, (2S,3S)-3-(2-fluorophenyl)-3-(1H-indol-1-yl)propane-1,2-diol was prepared from indole and [(2R,3R)-3-(2-fluorophenyl)oxiran-2-yl]methanol as a viscous, colorless oil. MS (ES) *m/z* 286.2 ([M+H]$^+$); HRMS: calcd for $C_{17}H_{16}FNO_2$ + H^+, 286.1238; found (ESI, [M+H]$^+$), 286.1231.

[0343] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(2-fluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol hydrochloride was prepared from (2S,3S)-3-(2-fluorophenyl)-3-(3-methyl-1H-indol-1-yl)propane-1,2-diol

as a white powder. MS (ES) *m/z* 299.1 ([M+H]$^+$); HRMS: calcd for $C_{18}H_{19}FN_2O$ + H^+, 299.1554; found (ESI, [M+H]$^+$), 299.1557.

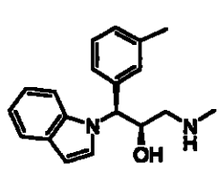
[0344] EXAMPLE 51: (1S,2R)-1-(4-fluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol hydrochloride



[0345] In an analogous manner to EXAMPLE 117, step 5, (2S,3S)-3-(4-fluorophenyl)-3-(1H-indol-1-yl)propane-1,2-diol was prepared from indole and [3-(4-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 49, step 1) as a viscous, colorless oil. MS (ES) *m/z* 286.1 ([M+H]$^+$); HRMS: calcd for $C_{17}H_{16}FNO_2$ + H^+, 286.1238; found (ESI, [M+H]$^+$), 286.1230.

[0346] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(4-fluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol hydrochloride was prepared from (2S,3S)-3-(4-fluorophenyl)-3-(1H-indol-1-yl)propane-1,2-diol as a white powder. MS (ES) *m/z* 299.1 ([M+H]$^+$).

[0347] EXAMPLE 52: (1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-(3-methylphenyl)propan-2-ol hydrochloride



[0348] In an analogous manner to EXAMPLE 47, step 1, *trans*-3-methylcinnamic acid methyl ester was prepared from *trans*-3-methylcinnamic acid.

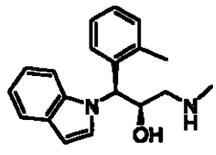
[0349] In an analogous manner to EXAMPLE 47, step 2, *trans*-3-methylcinnamyl alcohol was prepared from *trans*-3-methylcinnamic acid methyl ester as a colorless oil.

[0350] In an analogous manner to EXAMPLE 47, steps 3, [(2R,3R)-3-(3-methylphenyl)oxiran-2-yl]methanol was prepared from *trans*-3-methylcinnamyl alcohol as a colorless oil. HRMS: calcd for $C_{10}H_{12}O_2 + H^+$, 165.0916; found (ESI, $[M+H]^+$), 165.0926.

[0351] In an analogous manner to EXAMPLE 117, step 5, (2S,3S)-3-(1H-indol-1-yl)-3-(3-methylphenyl)propane-1,2-diol was prepared from indole and [(2R,3R)-3-(3-methylphenyl)oxiran-2-yl]methanol as a viscous, colorless liquid. MS (ES) *m/z* 282.1 ($[M+H]^+$); HRMS: calcd for $C_{18}H_{19}NO_2 + H^+$, 282.1494; found (ESI, $[M+H]^+$), 282.1488.

[0352] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-(3-methylphenyl)propan-2-ol hydrochloride was prepared from (2S,3S)-3-(1H-indol-1-yl)-3-(3-methylphenyl)propane-1,2-diol as a white powder. MS (ES) *m/z* 295.3 ($[M+H]^+$); HRMS: calcd for $C_{19}H_{20}N_2O + H^+$, 295.1805; found (ESI, $[M+H]^+$), 295.1799.

[0353] EXAMPLE 53: (1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-(2-methylphenyl)propan-2-ol hydrochloride



[0354] Step 1: In an analogous manner to EXAMPLE 47, step 1, *trans*-2-methylcinnamic acid methyl ester was prepared from *trans*-2-methylcinnamic acid.

[0355] Step 2: In an analogous manner to EXAMPLE 47, step 2, *trans*-2-methylcinnamyl alcohol was prepared from *trans*-2-methylcinnamic acid methyl ester as a colorless oil. MS (ES) *m/z* 146.9 ([M-H]$^-$).

[0356] Step 3: To a solution of *trans*-2-methylcinnamyl alcohol (1.50 g, 10.14 mmol) in dichloromethane (30 mL) was added sodium carbonate (1.50 g, 14.19 mmol). The mixture was cooled to 10°C and peracetic acid (32 wt %, 2.56 mL, 12.16 mmol) was added dropwise via an addition funnel. The reaction mixture was stirred for 3 hours while warming to room temperature, and quenched with saturated aqueous sodium sulfite solution (15 mL) slowly. More dichloromethane (30 mL) was added and the mixture was extracted. The organic layer was washed with brine, dried (anhydrous sodium sulfate), and concentrated. The oil residue was purified by silica gel chromatography (10-30% EtOAc/hexane) to give 920 mg (55%) of 3-(2-methylphenyl)glycidol as a colorless oil. HRMS: calcd for $C_{10}H_{12}O_2 + H^+$, 165.0916; found (ESI, $[M+H]^+$), 165.0936.

[0357] Step 4: In an analogous manner to EXAMPLE 117, step 5, (2SR,3SR)-3-(1H-indol-1-yl)-3-(2-methylphenyl)propane-1,2-diol was prepared from indole and 3-(2-methylphenyl)glycidol as a viscous, colorless liquid. MS (ES) *m/z* 282.2 ($[M+H]^+$); HRMS: calcd for $C_{18}H_{19}NO_2 + H^+$, 282.1494; found (ESI, $[M+H]^+$), 282.1499.

[0358] Step 5: In an analogous manner to EXAMPLE 47, step 6, (1SR,2RS)-1-(1H-indol-1-yl)-3-(methylamino)-1-(2-methylphenyl)propan-2-ol was prepared from (2SR,3SR)-3-(1H-indol-1-yl)-3-(2-methylphenyl)propane-1,2-diol as an oil.

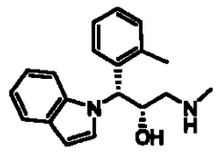
[0359] Step 6: Racemic (1SR,2RS)1-(1H-indol-1-yl)-3-(methylamino)-1-(2-methylphenyl)propan-2-ol was dissolved in ethanol (20 mg/mL). The resulting solution was stack injected onto the Supercritical Fluid Chromatography instrument at 1 mL increments. The baseline resolved enantiomers, using the conditions described below, were collected. The enantiomeric purity of each enantiomer was determined under similar Supercritical Fluid Chromatography conditions using a Chiralcel OJ-H 5u, 250 mm L x 4.6 mm ID column at 1.2 mL/minutes flow rate using

Analytical Supercritical Fluid Chromatography (Berger Instruments, Inc. Newark, DE USA).

SFC Instrument:	Berger MultiGram Prep SFC (Berger Instruments, Inc. Newark, DE 19702.
Column:	Chiralcel OJ-H; 5u; 250mm L x 20mm ID (Chiral Technologies, Inc., Exton, PA, USA)
Column temperature:	35°C
SFC Modifier:	15% MeOH with 1.0% DEA / 85% CO_2
Flow rate:	50 mL/min
Outlet Pressure:	100 bar
Detector:	UV at 220 nm

[0360] Step 7: In an analogous manner to EXAMPLE 144, step 2, (1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-(2-methylphenyl)propan-2-ol hydrochloride was prepared as a white solid, from (1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-(2-methylphenyl)propan-2-ol, which was isolated as Peak 1 of the chiral separation (step 6). Chiral purity: 100 %. MS (ESI) *m/z* 295.3 ($[M+H]^+$); HRMS: calcd for $C_{19}H_{22}N_2O + H^+$, 295.1805; found (ESI, $[M+H]^+$), 295.1795.

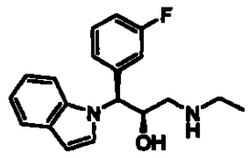
[0361] EXAMPLE 54: (1R,2S)-1-(1H-indol-1-yl)-3-(methylamino)-1-(2-methylphenyl)propan-2-ol hydrochloride



[0362] In an analogous manner to EXAMPLE 53, step 7, (1R,2S)-1-(1H-indol-1-yl)-3-(methylamino)-1-(2-methylphenyl)propan-2-ol hydrochloride was prepared as a white solid, from (1R,2S)-1-(1H-indol-1-yl)-3-(methylamino)-1-(2-methylphenyl)propan-2-ol, which was isolated as Peak 2 of the chiral separation

(EXAMPLE 53, step 6). Chiral purity: 100 %. MS (ESI) *m/z* 295.3 ($[M+H]^+$); HRMS: calcd for $C_{19}H_{22}N_2O$ + H^+, 295.1805; found (ESI, $[M+H]^+$), 295.1805.

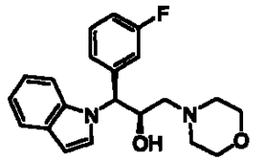
[0363] EXAMPLE 55: (1S,2R)-3-(ethylamino)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)propan-2-ol hydrochloride



[0364] Step 1: In an analogous manner to EXAMPLE 1, step 2, (2S,3S)-3-(3-fluorophenyl)-2-hydroxy-3-(1H-indol-1-yl)propyl 4-methylbenzenesulfonate was prepared from (2S,3S)-3-(3-fluorophenyl)-3-(1H-indol-1-yl)propane-1,2-diol (EXAMPLE 47, step 5) as an ivory solid. HRMS: calcd for $C_{24}H_{22}FN_2O_4S$ + H^+, 440.1326; found (ESI, $[M+H]^+$), 440.1345.

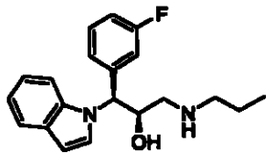
[0365] Step 2: (2S,3S)-3-(3-fluorophenyl)-2-hydroxy-3-(1H-indol-1-yl)propyl 4-methylbenzenesulfonate (200 mg, 0.456 mmol) was dissolved in a solution of ethylamine in methanol (2.0 M, 10 mL) and stirred for 12 hours in a sealed reaction vessel. All volatiles were removed under reduced pressure, and the liquid residue was dissolved in dichloromethane (15 mL), washed with a saturated aqueous solution of potassium carbonate, dried (anhydrous sodium sulfate), and concentrated. Purification of the liquid residue by Biotage chromatography (FlasH12i, silica, 0-15% MeOH/dichloromethane/0.5% triethylamine) gave (1S,2R)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-(ethylamino)propan-2-ol, which was used to prepare (1S,2R)-3-(ethylamino)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)propan-2-ol hydrochloride as a white powder in an analogous matter to EXAMPLE 144, step 2. Yield: 99 mg (70%). MS (ES) *m/z* 313.1 ($[M+H]^+$); HRMS: calcd for $C_{19}H_{21}FN_2O$ + H^+, 313.1716; found (ESI, $[M+H]^+$), 313.1716.

[0366] EXAMPLE 56: (1S,2R)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-morpholin-4-ylpropan-2-ol hydrochloride



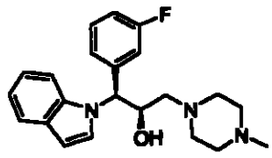
[0367] In an analogous manner to EXAMPLE 55, step 2, (1S,2R)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-morpholin-4-ylpropan-2-ol hydrochloride was prepared from morpholine and (2S,3S)-3-(3-fluorophenyl)-2-hydroxy-3-(1H-indol-1-yl)propyl 4-methylbenzenesulfonate (EXAMPLE 55, step 1) as a white powder. MS (ES) *m/z* 355.1 ($[M+H]^+$); HRMS: calcd for $C_{21}H_{23}FN_2O_2 + H^+$, 355.1816; found (ESI, $[M+H]^+$), 355.1822.

[0368] EXAMPLE 57: (1S,2R)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-(propylamino)propan-2-ol hydrochloride



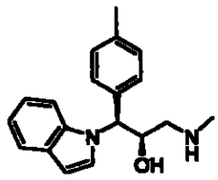
[0369] In an analogous manner to EXAMPLE 55, step 2, (1S,2R)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-(propylamino)propan-2-ol hydrochloride was prepared from propylamine and (2S,3S)-3-(3-fluorophenyl)-2-hydroxy-3-(1H-indol-1-yl)propyl 4-methylbenzenesulfonate (EXAMPLE 55, step 1) as a white powder. MS (ES) *m/z* 327.1 ($[M+H]^+$); HRMS: calcd for $C_{20}H_{23}FN_2O + H^+$, 327.1867; found (ESI, $[M+H]^+$), 327.1873.

[0370] EXAMPLE 58: (1S,2R)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-(4-methylpiperazin-1-yl)propan-2-ol dihydrochloride



[0371] In an analogous manner to EXAMPLE 55, step 2, (1S,2R)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-(4-methylpiperazin-1-yl)propan-2-ol dihydrochloride was prepared from 1-methylpiperazine and (2S,3S)-3-(3-fluorophenyl)-2-hydroxy-3-(1H-indol-1-yl)propyl 4-methylbenzenesulfonate (EXAMPLE 55, step 1) as a white powder. MS (ES) *m/z* 368.1 ($[M+H]^+$); HRMS: calcd for $C_{22}H_{26}FN_3O$ + H^+, 368.2133; found (ESI, $[M+H]^+$), 368.2138.

[0372] EXAMPLE 59: (1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-(4-methylphenyl)propan-2-ol hydrochloride



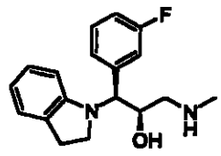
[0373] In an analogous manner to EXAMPLE 47, steps 3, [(2R,3R)-3-(4-methylphenyl)oxiran-2-yl]methanol was prepared from *trans*-4-methylcinnamyl alcohol[3] as a colorless oil. MS (ES) *m/z* 165.1 ($[M+H]^+$); HRMS: calcd for $C_{10}H_{12}O_2$ + H^+, 165.0916; found (ESI, $[M+H]^+$), 165.0937.

[0374] In an analogous manner to EXAMPLE 117, step 5, (2S,3S)-3-(1H-indol-1-yl)-3-(4-methylphenyl)propane-1,2-diol was prepared from indole and [(2R,3R)-3-(4-methylphenyl)oxiran-2-yl]methanol as a viscous colorless liquid. MS (ES) *m/z* 282.1 ($[M+H]^+$); HRMS: calcd for $C_{18}H_{19}NO_2$ + H^+, 282.1494; found (ESI, $[M+H]^+$), 282.1492.

[0375] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-(4-methylphenyl)propan-2-ol hydrochloride was prepared from (2S,3S)-3-(1H-indol-1-yl)-3-(4-methylphenyl)propane-1,2-diol as a white powder.

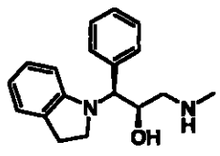
MS (ES) *m/z* 295.1 ([M+H]$^+$); HRMS: calcd for $C_{18}H_{22}N_2O$ + H^+, 295.1805; found (ESI, [M+H]$^+$), 295.1810.

[0376] EXAMPLE 60: (1S,2R)-1-(2,3-dihydro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride



[0377] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(2,3-dihydro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride was prepared from (2S,3S)-3-(2,3-dihydro-1H-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol (EXAMPLE 47, step 4) as a white solid. MS (ES) *m/z* 301.1 ([M+H]$^+$); HRMS: calcd for $C_{18}H_{21}FN_2O$ + H^+, 301.1711; found (ESI, [M+H]$^+$), 301.1716.

[0378] EXAMPLE 61: (1S,2R)-1-(2,3-dihydro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride

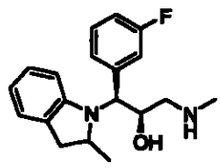


[0379] In an analogous manner to EXAMPLE 47, step 4, (2S,3S)-3-(2,3-dihydro-1H-indol-1-yl)-3-phenylpropane-1,2-diol was prepared from indoline and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4) as a viscous, colorless oil. MS (ES) *m/z* 270.2 ([M+H]$^+$); HRMS: calcd for $C_{17}H_{20}NO_2$ + H^+, 270.1494; found (ESI, [M+H]$^+$), 270.1493.

[0380] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(2,3-dihydro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2S,3S)-3-(2,3-dihydro-1H-indol-1-yl)-3-phenylpropane-1,2-diol as a white solid.

MS (ES) *m/z* 283.1 ($[M+H]^+$); HRMS: calcd for $C_{18}H_{21}N_2O + H^+$, 283.1805; found (ESI, $[M+H]^+$), 283.1810.

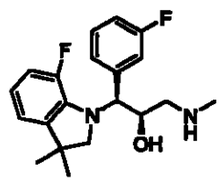
[0381] EXAMPLE 63: (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(2-methyl-2,3-dihydro-1H-indol-1-yl)propan-2-ol hydrochloride



[0382] In an analogous manner to EXAMPLE 47, step 4, (2S,3S)-3-(3-fluorophenyl)-3-(2-methyl-2,3-dihydro-1H-indol-1-yl)propane-1,2-diol was prepared from 2-methylindoline and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, step 3) as a viscous, colorless oil. MS (ES) *m/z* 302.1 ($[M+H]^+$); HRMS: calcd for $C_{18}H_{20}FNO_2 + H^+$, 302.1551; found (ESI, $[M+H]^+$), 302.1556.

[0383] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(2-methyl-2,3-dihydro-1H-indol-1-yl)propan-2-ol hydrochloride was prepared from (2S,3S)-3-(3-fluorophenyl)-3-(2-methyl-2,3-dihydro-1H-indol-1-yl)propane-1,2-diol as a white solid. MS (ES) *m/z* 315.0 ($[M+H]^+$); HRMS: calcd for $C_{19}H_{23}FN_2O + H^+$, 315.1867; found (ESI, $[M+H]^+$), 315.1850.

[0384] EXAMPLE 64: (1S,2R)-1-(7-fluoro-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride



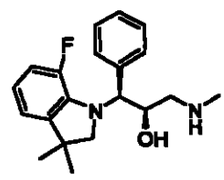
[0385] Step 1: A mixture of 7-fluoro-3,3-dimethyloxindole (EXAMPLE 99, step 5, 2.24 g 12.5 mmol) in toluene (15 mL) under nitrogen was heated at 80°C. Vitride

(65 wt% in toluene, 6 mL, 19.3 mmol) was added dropwise via an addition funnel. The resulting solution was stirred at 80°C for an additional 1.5 hours, then cooled in an ice bath. Aqueous sodium hydroxide solution (1N, 15 mL) was added slowly to quench the reaction. Water (15 mL) was added and the reaction mixture was extracted with ethyl acetate (20 mL). The organic layer was washed with brine, dried (anhydrous sodium sulfate), filtered through a pad of silica gel, and concentrated under reduced pressure to yield 1.68 g (82%) of 7-fluoro-3,3-dimethylindoline as a colorless oil. MS (ES) *m/z* 166.1 ($[M+H]^+$); HRMS: calcd for $C_{10}H_{12}FN + H^+$, 166.1032; found (ESI, $[M+H]^+$), 166.1040.

[0386] Step 2: In an analogous manner to EXAMPLE 47, step 4, (2S,3S)-3-(7-fluoro-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol was prepared from 7-fluoro-3,3-dimethylindoline and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, step 3) as a viscous, colorless oil. MS (ES) *m/z* 334.1 ($[M+H]^+$); HRMS: calcd for $C_{19}H_{21}F_2NO_2 + H^+$, 334.1613; found (ESI, $[M+H]^+$), 334.1616.

[0387] Step 3: In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(7-fluoro-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride was prepared from (2S,3S)-3-(7-fluoro-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol as a white solid. MS (ES) *m/z* 347 ($[M+H]^+$); HRMS: calcd for $C_{20}H_{24}F_2N_2O + H^+$, 347.1929; found (ESI, $[M+H]^+$), 347.1935.

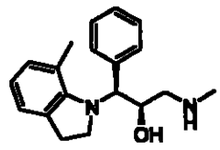
[0388] EXAMPLE 65: (1S,2R)-1-(7-fluoro-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride



[0389] In an analogous manner to EXAMPLE 47, step 4, (2S,3S)-3-(7-fluoro-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-3-phenylpropane-1,2-diol was prepared from 7-fluoro-3,3-dimethylindoline (EXAMPLE 64, step 1) and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4) as a viscous, colorless oil. MS (ES) *m/z* 316.1 ($[M+H]^+$); HRMS: calcd for $C_{19}H_{22}FNO_2$ + H^+, 316.1707; found (ESI, $[M+H]^+$), 316.1690.

[0390] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(7-fluoro-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2S,3S)-3-(7-fluoro-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-3-phenylpropane-1,2-diol as a white solid. HRMS: calcd for $C_{20}H_{25}FN_2O$ + H^+, 329.2029; found (ESI, $[M+H]^+$), 329.2041.

[0391] EXAMPLE 66: (1S,2R)-3-(methylamino)-1-(7-methyl-2,3-dihydro-1H-indol-1-yl)-1-phenylpropan-2-ol hydrochloride



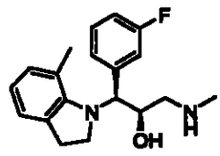
[0392] In an analogous manner to EXAMPLE 47, step 4, (2S,3S)-3-(7-methyl-2,3-dihydro-1H-indol-1-yl)-3-phenylpropane-1,2-diol was prepared from 7-methylindoline[4] and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4) as a viscous, colorless oil. MS (ES) *m/z* 284.2 ($[M+H]^+$); HRMS: calcd for $C_{18}H_{21}NO_2$ + H^+, 284.1651; found (ESI, $[M+H]^+$), 284.1650.

[0393] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-3-(methylamino)-1-(7-methyl-2,3-dihydro-1H-indol-1-yl)-1-phenylpropan-2-ol hydrochloride was prepared from (2S,3S)-3-(7-methyl-2,3-dihydro-1H-indol-1-yl)-3-phenylpropane-1,2-

[4] Gribble, G. W.; Hoffman, J. H. *Synthesis* **1977**, *12*, 859-860.

diol as a white solid. MS (ES) *m/z* 297.0 ($[M+H]^+$); HRMS: calcd for $C_{19}H_{24}N_2O$ + H^+, 297.1961; found (ESI, $[M+H]^+$), 297.1957.

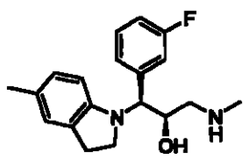
[0394] EXAMPLE 67: (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(7-methyl-2,3-dihydro-1H-indol-1-yl)propan-2-ol hydrochloride



[0395] In an analogous manner to EXAMPLE 47, step 4, (2S,3S)-3-(3-fluorophenyl)-3-(7-methyl-2,3-dihydro-1H-indol-1-yl)propane-1,2-diol was prepared from 7-methylindoline[4] and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, step 3) as a viscous, colorless oil. MS (ES) *m/z* 302.1 ($[M+H]^+$); HRMS: calcd for $C_{18}H_{20}FNO_2$ + H^+, 302.1551; found (ESI, $[M+H]^+$), 302.1551.

[0396] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(7-methyl-2,3-dihydro-1H-indol-1-yl)propan-2-ol hydrochloride was prepared from (2S,3S)-3-(3-fluorophenyl)-3-(7-methyl-2,3-dihydro-1H-indol-1-yl)propane-1,2-diol as a white solid. MS (ES) *m/z* 315.0 ($[M+H]^+$); HRMS: calcd for $C_{19}H_{23}FN_2O$ + H^+, 315.1873; found (ESI, $[M+H]^+$), 315.1862.

[0397] EXAMPLE 68: (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(5-methyl-2,3-dihydro-1H-indol-1-yl)propan-2-ol hydrochloride

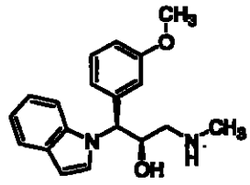


[0398] In an analogous manner to EXAMPLE 47, step 4, (2S,3S)-3-(3-fluorophenyl)-3-(5-methyl-2,3-dihydro-1H-indol-1-yl)propane-1,2-diol was prepared

from 5-methylindoline and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, step 3) as a viscous, colorless oil. MS (ES) *m/z* 302.1 ($[M+H]^+$); HRMS: calcd for $C_{18}H_{20}FNO_2$, 302.1551; found (ESI, $[M+H]^+$), 302.1551.

[0399] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(5-methyl-2,3-dihydro-1H-indol-1-yl)propan-2-ol hydrochloride was prepared from (2S,3S)-3-(3-fluorophenyl)-3-(5-methyl-2,3-dihydro-1H-indol-1-yl)propane-1,2-diol as a white solid. MS (ES) *m/z* 315.0 ($[M+H]^+$); HRMS: calcd for $C_{19}H_{23}FN_2O + H^+$, 315.1873; found (ESI, $[M+H]^+$), 315.1896.

[0400] EXAMPLE 69: (1*S*,2*R*)-1-(1*H*-indol-1-yl)-1-(3-methoxyphenyl)-3-(methylamino)propan-2-ol hydrochloride



[0401] In an analogous manner to EXAMPLE 33, step 1, ethyl (2*E*)-3-(3-methoxyphenyl)acrylate was prepared from 3-methoxybenzaldehyde and diethyl ethoxycarbonylmethylphosphonate. ^1H NMR (DMSO): □1.26 (t, 3H, OCH_2CH_3), □3.79 (s, 3H, OCH_3), □4.19 (q, 2H, OCH_2CH_3), □6.66 (d, 1H, CH=CHC(O)), □6.99 (m, 1H, CH=CH(CO)), □7.31 (m, 3H, ArH) and □7.62 (d, 1H, ArH).

[0402] In an analogous manner to EXAMPLE 33, step 2, (2*E*)-3-(3-methoxyphenyl)prop-2-en-1-ol was prepared from ethyl (2*E*)-3-(3-methoxyphenyl)acrylate. MS (ES) *m/z* 147.2 ($[M + H - H_2O]^+$).

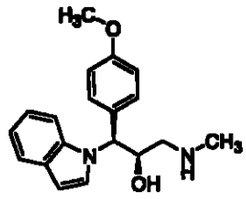
[0403] In analogous manner to EXAMPLE 117, step 4, [(2*R*,3*R*)-3-(3-methoxyphenyl)oxiran-2-yl]methanol was prepared from (2*E*)-3-(3-methoxyphenyl)prop-2-en-1-ol. MS (ES) *m/z* 222 ($[M+H + CH_3CN]^+$); 93.2 % ee.

[0404] In an analogous manner to EXAMPLE 117, step 5, (2*S*,3*S*)-3-(1*H*-indol-1-yl)-3-(3-methoxyphenyl)propane-1,2-diol was prepared from 1*H*-indole and [(2*R*,3*R*)-3-(3-methoxyphenyl)oxiran-2-yl]methanol. MS (ES) *m/z* 298.2 ([M+H]$^+$).

[0405] In an analogous manner to EXAMPLE 1, step 2, (2*S*,3*S*)-toluene-4-sulfonic acid 2-hydroxy-3-(1*H*-indol-1-yl)-3-(3-methoxyphenyl)-propyl ester was prepared from (2*S*,3*S*)-3-(1*H*-indol-1-yl)-3-(3-methoxyphenyl)propane-1,2-diol. MS (ES) *m/z* 452.2 ([M+H]$^+$).

[0406] In an analogous manner to EXAMPLE 33, step 6 (1*S*,2*R*)-1-(1*H*-indol-1-yl)-1-(3-methoxyphenyl)-3-(methylamino)propan-2-ol hydrochloride was prepared from (2*S*,3*S*)-toluene-4-sulfonic acid 2-hydroxy-3-(1*H*-indol-1-yl)-3-(3-methoxyphenyl)-propyl ester. MS (ES) *m/z* 311.3 ([M+H]$^+$); HRMS: calcd for $C_{19}H_{22}N_2O_2$ + H$^+$, 311.17540; found (ESI, [M+H]$^+$), 311.1758.

[0407] EXAMPLE 70: (1*SR*,2*RS*)-1-(1*H*-indol-1-yl)-1-(4-methoxyphenyl)-3-(methylamino)propan-2-ol hydrochloride



[0408] A mixture of methyl *trans*-3-(4-methoxyphenyl)glycidate (2.11 g, 10.1 mmol) and indoline (1.14 mL, 10.1 mmol) was heated to 135°C in a sealed tube for 16 hours. The cooled reaction mixture was then directly purified by flash chromatography (silica, 20%, 30% ethyl acetate/hexane) to yield 2.94 g (89%) of methyl (2*SR*,3*SR*)-3-(2,3-dihydro-1*H*-indol-1-yl)-2-hydroxy-3-(4-methoxyphenyl) propanoate as a yellow solid. MS (ES) *m/z* 328.2 ([M+H]$^+$); HRMS: calcd for $C_{19}H_{21}NO_4$ + H$^+$, 328.15434; found (ESI, [M+H]$^+$), 328.1536.

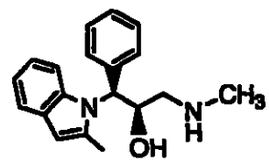
[0409] To a solution of methyl (2*SR*,3*SR*)-3-(2,3-dihydro-1*H*-indol-1-yl)-2-hydroxy-3-(4-methoxyphenyl)propanoate (2.63 g, 8.0 mmol) in anhydrous toluene (50 mL) at

0°C under nitrogen was added a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.87 g, 8.2 mmol) in anhydrous toluene (50 mL) over 5 minutes. The reaction mixture was stirred 0°C to room temperature for 1.5 hours then quenched by the addition of 7% w/v aqueous sodium carbonate solution (100 mL). The resulting biphasic mixture was stirred vigorously for 5 minutes then partitioned between ethyl acetate (300 mL) and 7% w/v aqueous sodium carbonate (250 mL). The organic phase was separated, washed with 7% w/v aqueous sodium carbonate solution (3 x 250 mL), water (250 mL) and saturated brine (250 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a lilac solid. Purification by flash chromatography (silica, 20%, 30% ethyl acetate/hexane) afforded 2.5 g (96%) of methyl (2*SR*,3*SR*)-2-hydroxy-3-(1*H*-indol-1-yl)-3-(4-methoxyphenyl)propanoate as a cream solid. MS (ES) *m/z* 326.3 ($[M+H]^+$); HRMS: calcd for $C_{19}H_{19}NO_4 + H^+$, 326.13869; found (ESI, $[M+H]^+$), 326.1378.

[0410] A solution of methyl (2*SR*,3*SR*)-2-hydroxy-3-(1*H*-indol-1-yl)-3-(4-methoxyphenyl)propanoate (2.43 g, 7.5 mmol) in methylamine solution (33% wt. in absolute ethanol, 40 mL) was heated to 75°C in a sealed tube for 1 hour . The cooled reaction mixture was then concentrated under reduced pressure to afford a yellow syrup. Purification by crystallization from 80% chloroform/hexane (50 mL) afforded 1.93 g (80%) of (2*SR*,3*SR*)-2-hydroxy-3-(1*H*-indol-1-yl)-3-(4-methoxyphenyl)-*N*-methylpropanamide as a white crystalline solid. MS (ES) *m/z* 323.2 ($[M-H]^-$); HRMS: calcd for $C_{19}H_{20}N_2O_3 + H^+$, 325.15467; found (ESI, $[M+H]^+$), 325.1562.

[0411] To a solution of (2*SR*,3*SR*)-2-hydroxy-3-(1*H*-indol-1-yl)-3-(4-methoxyphenyl)-*N*-methylpropanamide (900 mg, 2.8 mmol) in anhydrous tetrahydrofuran (50 mL) at room temperature under nitrogen was added dropwise a solution of borane-tetrahydrofuran complex (1.0 M in tetrahydrofuran, 13.9 mL, 13.9 mmol) and the mixture heated to reflux for 3 hours. The reaction mixture was then cooled to 50°C, methanol (20 mL) was added, and the mixture stirred at 50°C for 1 hour . The cooled reaction mixture was then concentrated under reduced pressure to afford a white solid. Purification by flash chromatography (silica, 15% methanol/dichloromethane) afforded 272 mg (32%). of (1*SR*,2*RS*)-1-(1*H*-indol-1-yl)-1-(4-methoxyphenyl)-3-(methylamino)propan-2-ol as a yellow syrup. The product was dissolved in absolute ethanol (4 mL), a solution of hydrogen chloride (4 M in 1,4-dioxane, 0.28 mL, 1.12 mmol) added, the solution stirred for 10 minutes then concentrated under reduced pressure to afford a white foam. Crystallization from 1 : 1 : 1 v/v absolute ethanol : diethyl ether : hexane (12 mL) at -35°C afforded 81.3 mg (8%) of (1*SR*,2*RS*)-1-(1*H*-indol-1-yl)-1-(4-methoxyphenyl)-3-(methylamino)propan-2-ol hydrochloride as a hygroscopic white solid. MS (ES) *m/z* 311.3 ($[M+H]^+$); HRMS: calcd for $C_{19}H_{22}N_2O_2 + H^+$, 311.17540; found (ESI, $[M+H]^+$), 311.176.

[0412] EXAMPLE 71: (1RS,2SR)-3-(methylamino)-1-(2-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol hydrochloride



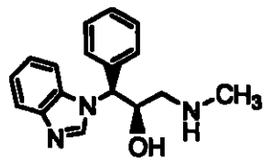
[0413] Step 1: A mixture of sodium hydride (60% in mineral oil, 0.40 g, 10 mmol) and *tert*-butanol (5 mL) was stirred for 15 minutes under nitrogen at room temperature. 2-Methylindole (1.31 g, 10 mmol) in methylene chloride (2 mL) was then added and the mixture was stirred for an additional 30 minutes. at room temperature. A pre-mixed solution of titanium isopropoxide (3.55 mL, 12 mmol) and *trans*-3-phenylglycidol (1.5g, 10 mmol) in methylene chloride (2 mL) was added, and the reaction mixture was stirred at room temperature for 15 hours until no epoxide remained as determined by tlc. The mixture was filtered through a Celite pad, and the filtrate was then treated with a 2N aqueous solution of hydrochloric acid (50 mL) with stirring over 30 minutes. The organic layer was separated and the aqueous layer was extracted with methylene chloride several times. The combined extracts were washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified via Biotage Horizon (Flash 40 M, silica, gradient from 10% ethyl acetate/hexane to 65% ethyl acetate/hexane) to yield (2RS,3RS)-3-(2-methyl-indol-1-yl)-3-phenyl-propane-1,2-diol as a white solid. MS (ESI) m/z 282 ($[M+H]^+$).

[0414] In an analogous manner to EXAMPLE 1, step 2 (2RS,3RS)-toluene-4-sulfonic acid 3-(2-methyl-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester was prepared from (2RS,3RS)-3-(2-methyl-indol-1-yl)-3-phenyl-propane-1,2-diol as an oil. MS (ESI) m/z 436 ($[M+H]^+$).

[0415] In an analogous manner to EXAMPLE 5, (1RS,2SR)-3-(methylamino)-1-(2-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol hydrochloride was prepared from (2RS,3RS)-toluene-4-sulfonic acid 3-(2-methyl-indol-1-yl)-2-hydroxy-3-phenyl-propyl

ester and methylamine (2N solution in methanol) as a tan solid. MS (ES) m/z 295.0; HRMS: calcd for C19H22N2O + H+, 295.18049; found (ESI, $[M+H]^+$), 295.1818.

[0416] EXAMPLE 72: (1RS,2SR)-1-(1H-benzimidazol-1-yl)-3-(methylamino)-1-phenyl propan-2-ol hydrochloride

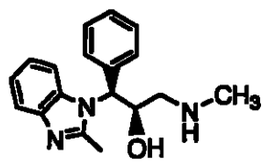


[0417] In an analogous manner to EXAMPLE 17, step 1 (2RS,3RS)-3-(1H-benzimidazol-1-yl)-3-phenyl-propane-1,2-diol was prepared from benzimidazole and trans-3-phenylglycidol as an oily solid. MS (ESI) m/z 269 ($[M+H]^+$).

[0418] In an analogous manner to EXAMPLE 1, step 2 (2RS,3RS)-toluene-4-sulfonic acid 3-benzoimidazol-1-yl-2-hydroxy-3-phenyl-propyl ester was prepared from (2RS,3RS)-1-(1H-benzimidazol-1-yl)-3-phenyl-propane-1,2-diol as a white solid. MS (ESI) m/z 423 ($[M+H]^+$).

[0419] In an analogous manner to EXAMPLE 5, (1RS,2SR)-1-(1H-benzimidazo-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2RS,3RS)- toluene-4-sulfonic acid 3-benzoimidazol-1-yl-2-hydroxy-3-phenyl-propyl ester and methylamine (2N solution in methanol) as a white solid. MS (ES) m/z 282.1; HRMS: calcd for C17H19N3O + H+, 282.16009; found (ESI, $[M+H]^+$), 282.1617.

[0420] EXAMPLE 73: (1RS,2SR)-3-(methylamino)-1-(2-methyl-1H-benzimidazol-1-yl)-1-phenylpropan-2-ol hydrochloride

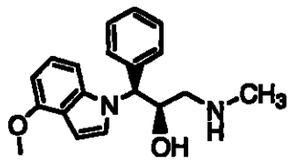


[0421] In an analogous manner to EXAMPLE 17, step 1 (2RS,3RS)-3-(2-methyl-1H-benzimidazol-1-yl)-3-phenyl-propane-1,2-diol was prepared from 2-methylbenzimidazole and trans-3-phenylglycidol as a yellow solid. MS (ESI) m/z 283 ($[M+H]^+$).

[0422] In an analogous manner to EXAMPLE 1, step 2 (2RS,3RS)-toluene-4-sulfonic acid 2-hydroxy-3-(2-methyl-benzoimidazol-1-yl)-3-phenyl-propyl ester was prepared from (2RS,3RS)-3-(2-methyl-1H-benzimidazol-1-yl)-3-phenyl-propane-1,2-diol as a white solid. MS (ESI) m/z 437 ($[M+H]^+$).

[0423] In an analogous manner to EXAMPLE 5, (1RS,2SR)-1-(2-methyl-1H-benzimidazo-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2RS,3RS)-toluene-4-sulfonic acid 2-hydroxy-3-(2-methyl-benzoimidazol-1-yl)-3-phenyl-propyl ester and methylamine as a white solid. MS (ES) m/z 296.1; SHRMS: calcd for C18H21N3O + H+, 296.17574; found (ESI, $[M+H]^+$), 296.1752.

[0424] EXAMPLE 74: (1RS,2SR)-1-(4-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenyl propan-2-ol hydrochloride

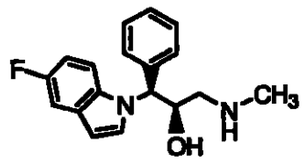


[0425] In an analogous manner to EXAMPLE 17, step 1 (2RS,3RS)-3-(4-methoxy-1H-indol-1-yl)-3-phenyl-propane-1,2-diol was prepared from 4-methoxyindole and trans-3-phenylglycidol as an oil. MS (ESI) m/z 298 ($[M+H]^+$).

[0426] In an analogous manner to EXAMPLE 1, step 2 (2RS,3RS)-toluene-4-sulfonic acid 2-hydroxy-3-(4-methoxy-indol-1-yl)-3-phenyl-propyl ester was prepared from (2RS,3RS)-3-(4-methoxy-1H-indol-1-yl)-3-phenyl-propane-1,2-diol as a white solid. MS (ESI) m/z 452 ($[M+H]^+$).

[0427] In an analogous manner to EXAMPLE 5, (1RS,2SR)-3-(4-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2RS,3RS)-toluene-4-sulfonic acid 2-hydroxy-3-(4-methoxy-indol-1-yl)-3-phenyl-propyl ester and methylamine as a white solid. MS (ESI) m/z 311; HRMS: calcd for C19H22N2O2 + H+, 311.17540; found (ESI, $[M+H]^+$), 311.1772

[0428] EXAMPLE 75: (1S,2R)-1-(5-fluoro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride

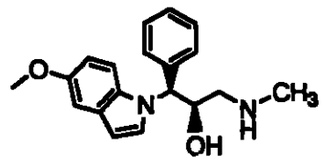


[0429] In an analogous manner to EXAMPLE 17, step 1 (2S,3S)-3-(5-fluoro-1H-indol-1-yl)-3-phenyl-propane-1,2-diol was prepared from 5-fluoroindole and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4) as an oil. MS (ESI) m/z 286 ($[M+H]^+$).

[0430] In an analogous manner to EXAMPLE 1, step 2 (2S,3S)-toluene-4-sulfonic acid 3-(5-fluoro-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester was prepared from (2S,3S)-3-(5-fluoro-1H-indol-1-yl)-3-phenyl-propane-1,2-diol as an oil. MS (ESI) m/z 438 ($[M+H]^+$).

[0431] In an analogous manner to EXAMPLE 5, (1S,2R)-1-(5-fluoro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2S,3S)-toluene-4-sulfonic acid 3-(5-fluoro-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester and methylamine as a white solid. MS (ES) m/z 299.1; HRMS: calcd for C18H19FN2O + H+, 299.15542; found (ESI, $[M+H]^+$), 299.1556.

[0432] EXAMPLE 76: (1S,2R)-1-(5-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride

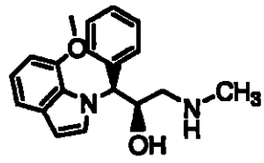


[0433] In an analogous manner to EXAMPLE 17, step 1 (2S,3S)-3-(5-methoxy-1H-indol-1-yl)-3-phenyl-propane-1,2-diol was prepared from 5-methoxyindole and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4) as an oil. MS (ESI) m/z 298 ($[M+H]^+$).

[0434] In an analogous manner to EXAMPLE 1, step 2 (2S,3S)-toluene-4-sulfonic acid 3-(5-methoxy-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester was prepared from (2S,3S)-3-(5-methoxy-1H-indol-1-yl)-3-phenyl-propane-1,2-diol as an oil. MS (ESI) m/z 452 ($[M+H]^+$).

[0435] In an analogous manner to EXAMPLE 5, (1S,2R)-1-(5-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2S,3S)- toluene-4-sulfonic acid 3-(5-methoxy-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester and methylamine as a white solid. MS (ES) m/z 311.1; HRMS: calcd for C19H22N2O2 + H+, 311.17540; found (ESI, $[M+H]^+$), 311.1745.

[0436] EXAMPLE 77: (1S,2R)-1-(7-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride

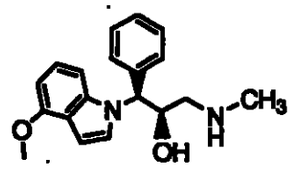


[0437] In an analogous manner to EXAMPLE 17, step 1 (2S,3S)-3-(7-methoxy-1H-indol-1-yl)-3-phenyl-propane-1,2-diol was prepared from 7-methoxyindole and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4) as an oil. MS (ESI) m/z 298 ($[M+H]^+$).

[0438] In an analogous manner to EXAMPLE 1, step 2 (2S,3S)-toluene-4-sulfonic acid 3-(7-methoxy-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester was prepared from (2S,3S)-3-(7-methoxy-1H-indol-1-yl)-3-phenyl-propane-1,2-diol as an oil. MS (ESI) m/z 452 ($[M+H]^+$).

[0439] In an analogous manner to EXAMPLE 5, (1S,2R)-1-(7-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2S,3S)-toluene-4-sulfonic acid 3-(7-methoxy-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester and methylamine as a white solid. MS (ES) m/z 311.1; HRMS: calcd for C19H22N2O2 + H+, 311.17540; found (ESI, $[M+H]^+$), 311.1753.

[0440] EXAMPLE 78: (1S,2R)-1-(4-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenyl propan-2-ol hydrochloride

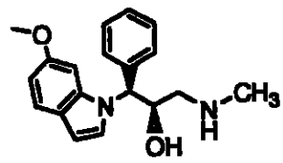


[0441] In an analogous manner to EXAMPLE 17, step 1 (2S,3S)-3-(4-methoxy-1H-indol-1-yl)-3-phenyl-propane-1,2-diol was prepared from 4-methoxyindole and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4) as an oil. MS (ESI) m/z 298 ($[M+H]^+$).

[0442] In an analogous manner to EXAMPLE 1, step 2 (2S,3S)- toluene-4-sulfonic acid 3-(4-methoxy-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester was prepared from (2S,3S)-3-(4-methoxy-1H-indol-1-yl)-3-phenyl-propane-1,2-diol as an oil. MS (ESI) m/z 452 ($[M+H]^+$).

[0443] In an analogous manner to EXAMPLE 5, (1S,2R)-1-(4-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2S,3S)- toluene-4-sulfonic acid 3-(4-methoxy-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester and methylamine as a white solid. MS (ESI) m/z 311; HRMS: calcd for C19H22N2O2 + H+, 311.17540; found (ESI, $[M+H]^+$), 311.175.

[0444] EXAMPLE 79: (1S,2R)-1-(6-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenyl propan-2-ol hydrochloride

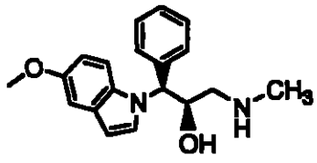


[0445] In an analogous manner to EXAMPLE 17, step 1 (2S,3S)-3-(6-methoxy-1H-indol-1-yl)-3-phenyl-propane-1,2-diol was prepared from 6-methoxyindole and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4) as an oil. MS (ESI) m/z 298 ($[M+H]^+$).

[0446] In an analogous manner to EXAMPLE 1, step 2 (2S,3S)-toluene-4-sulfonic acid 3-(6-methoxy-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester was prepared from (2S,3S)-3-(6-methoxy-1H-indol-1-yl)-3-phenyl-propane-1,2-diol as an oil. MS (ESI) m/z 452 ($[M+H]^+$).

[0447] In an analogous manner to EXAMPLE 5, (1S,2R)-1-(6-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2S,3S)- toluene-4-sulfonic acid 3-(6-methoxy-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester and methylamine as a white solid. MS (ESI) m/z 311; HRMS: calcd for C19H22N2O2 + H+, 311.17540; found (ESI, $[M+H]^+$), 311.1757.

[0448] EXAMPLE 80: (1RS,2SR)-1-(5-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenyl propan-2-ol hydrochloride

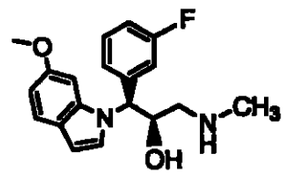


[0449] In an analogous manner to EXAMPLE 17, step 1 (2RS,3RS)-3-(5-methoxy-1H-indol-1-yl)-3-phenyl-propane-1,2-diol was prepared from 5-methoxyindole and trans-3-phenylglycidol as an oil. MS (ESI) m/z 298 ($[M+H]^+$).

[0450] In an analogous manner to EXAMPLE 1, step 2 (2RS,3RS)- toluene-4-sulfonic acid 3-(5-methoxy-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester was prepared from (2RS,3RS)-3-(5-methoxy-1H-indol-1-yl)-3-phenyl-propane-1,2-diol as an oil. MS (ESI) m/z 452 ($[M+H]^+$).

[0451] In an analogous manner to EXAMPLE 5, (1RS,2SR)-1-(5-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2RS,3RS)- toluene-4-sulfonic acid 3-(5-methoxy-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester and methylamine as a white solid. MS (ESI) m/z 311; HRMS: calcd for C19H22N2O2 + H+, 311.17540; found (ESI, $[M+H]^+$), 311.1756.

[0452] EXAMPLE 81: (1S,2R)-1-(3-fluorophenyl)-1-(6-methoxy-1H-indol-1-yl)-3-(methyl- amino)propan-2-ol hydrochloride

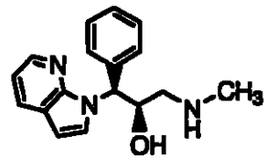


[0453] In an analogous manner to EXAMPLE 17, step 1 (2S,3S)-3-(6-methoxy-1H-indol-1-yl)-3-(3-fluorophenyl)-propane-1,2-diol was prepared from 6-methoxyindole and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, step 3) as an oil. MS (ESI) m/z 316 ($[M+H]^+$).

[0454] In an analogous manner to EXAMPLE 1, step 2 (2S,3S)-toluene-4-sulfonic acid 3-(6-methoxy-indol-1-yl)-2-hydroxy-3-(3-fluorophenyl)-propyl ester was prepared from (2S,3S)-3-(6-methoxy-1H-indol-1-yl)-3-(3-fluorophenyl)-propane-1,2-diol as an oil. MS (ESI) m/z 470 ($[M+H]^+$).

[0455] In an analogous manner to EXAMPLE 5, (1S,2R)-1-(3-fluorophenyl)-1-(6-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2S,3S)-toluene-4-sulfonic acid 3-(6-methoxy-indol-1-yl)-2-hydroxy-3-(3-fluorophenyl)-propyl ester and methylamine as a white solid. MS (ES) m/z 329.2; HRMS: calcd for C19H21FN2O2 + H+, 329.16598; found (ESI, $[M+H]^+$), 329.1663.

[0456] EXAMPLE 82: (1S,2R)-3-(methylamino)-1-phenyl-1-(1H-pyrrolo[2,3-b]pyridin-1-yl)propan-2-ol

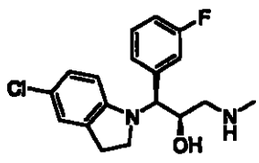


[0457] In an analogous manner to EXAMPLE 17, step 1 (2S,3S)-3-phenyl-3-(1H-pyrrolo[2,3-b]pyridin-1-yl)propane-1,2-diol was prepared from 7-azaindole and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4) as a white solid. MS (ES) m/z 269.2; HRMS: calcd for C16H16N2O2 + H+, 269.12845; found (ESI, $[M+H]^+$), 269.13.

[0458] In an analogous manner to EXAMPLE 1, step 2 (2S,3S)-toluene-4-sulfonic acid 2-hydroxy-3-phenyl-3-pyrrolo[2,3-b]pyridin-1-yl-propyl ester was prepared from (2S,3S)-3-phenyl-3-(1H-pyrrolo[2,3-b]pyridin-1-yl)propane-1,2-diol as an oil. MS (ESI) m/z 423 ($[M+H]^+$).

[0459] In an analogous manner to EXAMPLE 5, (1S,2R)-3-(methylamino)-1-phenyl-1-(1H-pyrrolo[2,3-b]pyridin-1-yl)propan-2-ol was prepared from (2S,3S)-toluene-4-sulfonic acid 2-hydroxy-3-phenyl-3-pyrrolo[2,3-b]pyridin-1-yl-propyl ester and methylamine as a white solid. MS (ES) m/z 282.3; HRMS: calcd for C17H19N3O + H+, 282.16009; found (ESI, $[M+H]^+$), 282.16.

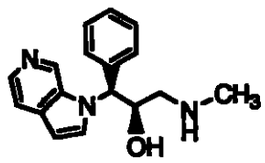
[0460] EXAMPLE 83: (1S,2R)-1-(5-chloro-2,3-dihydro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride



[0461] In an analogous manner to EXAMPLE 47, step 4, (2S,3S)-3-(5-chloro-2,3-dihydro-1H-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol was prepared from 5-chloroindoline and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, step 3) as a viscous, colorless oil. MS (ES) *m/z* 322.1 ($[M+H]^+$); HRMS: calcd for $C_{17}H_{17}ClFNO_2 + H^+$, 322.1005; found (ESI, $[M+H]^+$), 322.1005.

[0462] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(5-chloro-2,3-dihydro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride was prepared from (2S,3S)-3-(5-chloro-2,3-dihydro-1H-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol as a white solid. MS (ES) *m/z* 335.1 ($[M+H]^+$); HRMS: calcd for $C_{18}H_{20}ClFN_2O + H^+$, 335.1326; found (ESI, $[M+H]^+$), 335.1349.

[0463] EXAMPLE 84: (1S,2R)-3-methylamino-1-phenyl-1-(1H-pyrrolo[2,3-c]pyridin-1-yl) propan-2-ol dihydrochloride



[0464] In an analogous manner to EXAMPLE 17, step 1 (2S,3S)-3-(7-chloro-1H-pyrrolo[2,3-c]pyridin-1-yl)-3-phenylpropane-1,2-diol was prepared from 7-chloro-1H-pyrrolo[2,3-c]pyridine[5] and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4) as an oil. MS (ES) m/z 303 ($[M+H]^+$).

[0465] In an analogous manner to EXAMPLE 1, step 2 (2S,3S)-toluene-4-sulfonic acid 3-(7-chloro-pyrrolo[2,3-c]pyridin-1-yl)-2-hydroxy-3-phenyl-propyl ester was prepared from (2S,3S)-3-(7-chloro-pyrrolo[2,3-c]pyridin-1-yl)-3-phenyl-propane-1,2-diol as an oil. MS (ESI) m/z 457 ($[M+H]^+$).

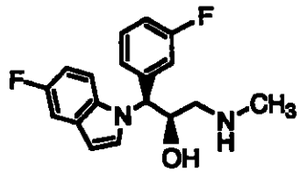
[0466] In an analogous manner to EXAMPLE 5, (1S,2R)-1-(7-chloro-pyrrolo[2,3-c]pyridine-1-yl)-3-methylamino-1-phenyl-propan-2-ol was prepared from (2S,3S)-

[5] Zhang, Z., et al., *J. Org. Chem.* 2002, *67*, 2345-2347

toluene-4-sulfonic acid 3-(7-chloro-pyrrolo[2,3-c]pyridin-1-yl)-2-hydroxy-3-phenyl-propyl ester and methylamine as a white solid. MS (ES) m/z 316.1 ([M+H]$^+$).

[0467] Step 4: (1S,2R)-1-(7-chloro-pyrrolo[2,3-c]pyridine-1-yl)-3-methylamino-1-phenyl-propan-2-ol (0.12 g, 0.38 mmol) was dissolved in ethanol (20 mL) and treated with 10% palladium on carbon. The reaction mixture placed under 50 psi of hydrogen on a Parr shaker for 15 hours. The reaction mixture was filtered through a Celite pad and the filtrate was concentrated *in vacuo*. The crude product was purified via Biotage Horizon (Flash 25 S, silica, gradient from 30% to 100% of 0.9% ammonium hydroxide in 10% methanol-methylene chloride/methylene chloride) to give a white solid as the free base of the expected product. The free base was dissolved in a minimum amount of ethanol and treated with a 1N ethereal solution of hydrochloric acid until the solution was pH = 3 followed by diethyl ether. The product was then crystallized by adding a minimum amount of ethyl acetate to afford the titled compound, (1S,2R)-3-methylamino-1-phenyl-1-(1H-pyrrolo[2,3-c]pyridin-1-yl)-propan-2-ol dihydrochloride as a white solid. MS (ES) m/z 282.1.

[0468] EXAMPLE 85: (1S,2R)-1-(5-fluoro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methyl- amino)propan-2-ol hydrochloride

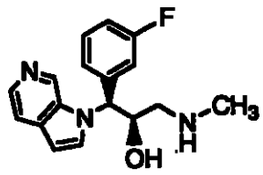


[0469] In an analogous manner to EXAMPLE 17, step 1 (2S,3S)-3-(5-fluoro-1H-indol-1-yl)-3-(3-fluorophenyl)-propane-1,2-diol was prepared from 5-fluoroindole and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, step 3) as an oil. MS (ESI) m/z 304 ([M+H]$^+$).

[0470] In an analogous manner to EXAMPLE 1, step 2 (2S,3S)-toluene-4-sulfonic acid 3-(5-fluoro-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester was prepared from (2S,3S)-3-(5-fluoro-1H-indol-1-yl)-3-(3-fluorophenyl)-propane-1,2-diol as an oil. MS (ESI) m/z 458 ([M+H]$^+$).

[0471] In an analogous manner to EXAMPLE 5, (1S,2R)-1-(5-fluoro-1H-indol-3-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride was prepared from (2S,3S)-toluene-4-sulfonic acid 3-(5-fluoro-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester and methylamine as a light tan solid. MS (ES) m/z 317.2; HRMS: calcd for C18H18F2N2O + H+, 317.14599; found (ESI, $[M+H]^+$), 317.1472.

[0472] EXAMPLE 86: (1S,2R)-3-methylamino-1-(3-fluorophenyl)-1-(1H-pyrrolo[2,3-c]pyridin-1-yl) propan-2-ol dihydrochloride



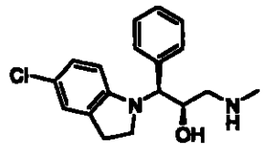
[0473] In an analogous manner to EXAMPLE 17, step 1 (2S,3S)-3-(7-chloro-pyrrolo[2,3-c]pyridin-1-yl)-3-(3-fluorophenyl)-propane-1,2-diol was prepared from 7-chloro-1H-pyrrolo[2,3-c]pyridine[5] and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, step 3) as an oil. MS (ESI) m/z 321 ($[M+H]^+$).

[0474] In an analogous manner to EXAMPLE 1, step 2 (2S,3S)-toluene-4-sulfonic acid 3-(7-chloro-pyrrolo[2,3-c]pyridin-1-yl)-2-hydroxy-3-(3-fluorophenyl)-propyl ester was prepared from (2S,3S)-3-(7-chloro-pyrrolo[2,3-c]pyridin-1-yl)-3-(3-fluorophenyl)-propane-1,2-diol as an oil. MS (ESI) m/z 475 ($[M+H]^+$).

[0475] In an analogous manner to EXAMPLE 5, (1S,2R)-1-(7-chloro-pyrrolo[2,3-c]pyridine-1-yl)-3-methylamino-1-(3-fluorophenyl)-propan-2-ol was prepared from (2S,3S)-toluene-4-sulfonic acid 3-(7-chloro-pyrrolo[2,3-c]pyridin-1-yl)-2-hydroxy-3-(3-fluorophenyl)-propyl ester and methylamine as a white solid. MS (ESI) m/z 334 ($[M+H]^+$).

[0476] In an analogous manner to EXAMPLE 84, step 4 (1S,2R)-3-methylamino-1-(3-fluorophenyl)-1-(1H-pyrrolo[2,3-c]pyridin-1-yl)-propan-2-ol dihydrochloride was prepared from (1S,2R)-1-(7-chloro-pyrrolo[2,3-c]pyridine-1-yl)-3-methylamino-1-(3-fluorophenyl)-propan-2-ol as a white solid. MS (ESI) m/z 282.1 ($[M+H]^+$).

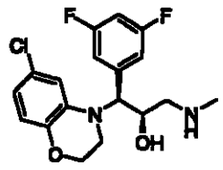
[0477] EXAMPLE 87: (1S,2R)-1-(5-chloro-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride



[0478] In an analogous manner to EXAMPLE 47, step 4, (2S,3S)-3-(5-chloro-2,3-dihydro-1H-indol-1-yl)-3-phenylpropane-1,2-diol was prepared from 5-chloroindoline and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4) as a viscous, colorless oil. MS (ES) *m/z* 304.1 ($[M+H]^+$); HRMS: calcd for $C_{17}H_{18}ClNO_2$ + H^+, 304.1099; found (ESI, $[M+H]^+$), 304.1081.

[0479] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(5-chloro-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from 2S,3S)-3-(5-chloro-2,3-dihydro-1H-indol-1-yl)-3-phenylpropane-1,2-diol as a white powder. MS (ES) *m/z* 317.1 ($[M+H]^+$); HRMS: calcd for $C_{18}H_{21}ClN_2O$ + H^+, 317.1421; found (ESI, $[M+H]^+$), 317.1431.

[0480] EXAMPLE 88: (1S,2R)-1-(6-chloro-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-1-(3,5-difluorophenyl)-3-(methylamino)propan-2-ol hydrochloride

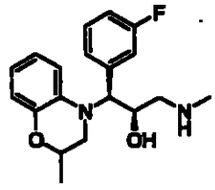


[0481] Step 1: In an analogous manner to EXAMPLE 165, step 1, 6-chloro-3,4-dihydro-2H-1,4-benzoxazine was prepared from 6-chloro-2H-1,4-benzoxazin-3(4H)-one as a yellow solid. MS (ES) *m/z* 170.0 ($[M+H]^+$); HRMS: calcd for C_8H_8ClNO + H^+, 170.0367; found (ESI, $[M+H]^+$), 170.0365.

[0482] Step 2: In an analogous manner to EXAMPLE 47, step 4, (2S,3S)-3-(6-chloro-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-(3,5-difluorophenyl)propane-1,2-diol was prepared from 6-chloro-3,4-dihydro-2H-1,4-benzoxazine and [(2R,3R)-3-(3,5-difluorophenyl)oxiran-2-yl]methanol (EXAMPLE 157, step 3) as a viscous, yellowish liquid. MS (ES) *m/z* 356.1 ($[M+H]^+$); HRMS: calcd for $C_{17}H_{16}ClF_2NO_3 + H^+$, 356.0860; found (ESI, $[M+H]^+$), 356.0869.

[0483] Step 3: In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(6-chloro-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-1-(3,5-difluorophenyl)-3-(methylamino)propan-2-ol hydrochloride was prepared from (2S,3S)-3-(6-chloro-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-(3,5-difluorophenyl)propane-1,2-diol as a white powder. MS (ES) *m/z* 369.1 ($[M+H]^+$); HRMS: calcd for $C_{18}H_{19}ClF_2N_2O_2 + H^+$, 369.1176; found (ESI, $[M+H]^+$), 369.1178.

[0484] EXAMPLE 89: (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(2-methyl-2,3-dihydro-4H-1,4-benzoxazin-4-yl)propan-2-ol hydrochloride

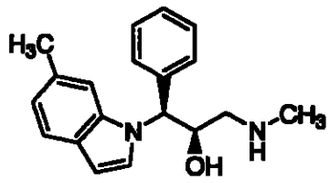


[0485] In an analogous manner to EXAMPLE 165, step 1, 2-methyl-3,4-dihydro-2H-1,4-benzoxazine was prepared from 2-methyl-2H-1,4-benzoxazin-3(4H)-one[6] as a brown oil. MS (ES) *m/z* 149.9 ($[M+H]^+$).

[0486] In an analogous manner to EXAMPLE 47, step 4, (2S,3S)-3-(3-fluorophenyl)-3-(2-methyl-2,3-dihydro-4H-1,4-benzoxazin-4-yl)propane-1,2-diol was prepared from 2-methyl-3,4-dihydro-2H-1,4-benzoxazine and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, step 3) as a viscous, brown liquid. MS (ES) *m/z* 318.2 ($[M+H]^+$); HRMS: calcd for $C_{18}H_{20}FNO_3 + H^+$, 318.1500; found (ESI, $[M+H]^+$), 318.1513.

[0487] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(2-methyl-2,3-dihydro-4H-1,4-benzoxazin-4-yl)propan-2-ol hydrochloride was prepared from (2S,3S)-3-(3-fluorophenyl)-3-(2-methyl-2,3-dihydro-4H-1,4-benzoxazin-4-yl)propane-1,2-diol as a white powd r. MS (ES) *m/z* 331.0 ($[M+H]^+$); HRMS: calcd for $C_{19}H_{23}FN_2O_2 + H^+$, 331.1816; found (ESI, $[M+H]^+$), 331.1804.

[0488] EXAMPLE 90: (1*S*,2*R*)-3-(methylamino)-1-(6-methyl-1*H*-indol-1-yl)-1-phenylpropan-2-ol hydrochloride



[0489] In an analogous manner to EXAMPLE 117, step 5 (2S,3S)-3-(6-methyl-1H-indol-1-yl)-3-phenylpropane-1,2-diol was prepared from 6-methylindole and 2*R*,3*R*-(+)-3-phenylglycidol as an oil. MS (ESI) m/z 282 ($[M+H]^+$).

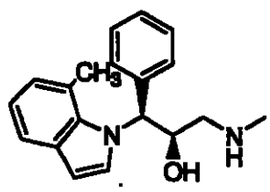
[0490] In an analogous manner to EXAMPLE 1, step 2 (2S,3S)-toluene-4-sulfonic acid 3-(6-methyl-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester was prepared from (2S,3S)-3-(6-methyl-1H-indol-1-yl)-3-phenylpropane-1,2-diol MS (ESI) *m/z* 436 ($[M+H]^+$).

[0491] In an analogous manner to EXAMPLE 5 (1*S*,2*R*)-3-(methylamino)-1-(6-methyl-1*H*-indol-1-yl)-1-phenylpropan-2-ol hydrochloride was prepared from (2S,3S)-toluene-4-sulfonic acid 3-(6-methyl-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester and methylamine (2N solution in methanol); MS (ESI) *m/z* 295 ($[M+H]^+$); HRMS: calcd for C19H22N2O + H+, 295.18049; found (ESI-FT/MS, [M+H]1+), 295.1809.

[0492] EXAMPLE 91: (1*S*,2*R*)-3-(methylamino)-1-(7-methyl-1*H*-indol-1-yl)-1-phenylpropan-2-ol hydrochloride

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[8] Wheeler, K. W. *J. Med. Pharm. Chem.* 1962, *5*, 1378-1383.

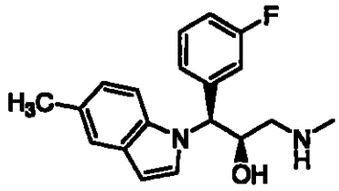


[0493] In an analogous manner to EXAMPLE 117, step 5 (2S,3S)-3-(7-methyl-1H-indol-1-yl)-3-phenylpropane-1,2-diol was prepared from 7-methylindole and 2*R*,3*R*-(+)-3-phenylglycidol as an oil. MS (ESI) m/z 282 ([M+H]$^+$).

[0494] In an analogous manner to EXAMPLE 1, step 2 (2S,3S)-toluene-4-sulfonic acid 3-(7-methyl-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester was prepared from (2S,3S)-3-(7-methyl-1H-indol-1-yl)-3-phenylpropane-1,2-diol MS (ESI) *m/z* 436 ([M+H]$^+$).

[0495] In an analogous manner to EXAMPLE 5 (1*S*,2*R*)-3-(methylamino)-1-(7-methyl-1*H*-indol-1-yl)-1-phenylpropan-2-ol hydrochloride was prepared from (2S,3S)-toluene-4-sulfonic acid 3-(7-methyl-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester and methylamine (2N solution in methanol); MS (ESI) *m/z* 295 ([M+H]$^+$); HRMS: calcd for C19H22N2O + H+, 295.18049; found (ESI-FT/MS, [M+H]1+), 295.1809.

[0496] EXAMPLE 92: ((1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(5-methyl-1H-indol-1-yl)propan-2-ol hydrochloride

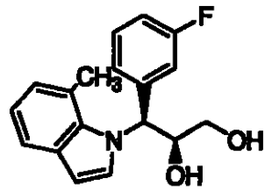


[0497] In an analogous manner to EXAMPLE 117, step 5 (2S,3S)-3-(3-fluorophenyl)-3-(5-methyl-1H-indol-1-yl)propane-1,2-diol was prepared from 5-methylindole and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (see EXAMPLE 47, step 3) as an oil. MS (ESI) m/z 300 ([M+H]$^+$).

[0498] In an analogous manner to EXAMPLE 1, step 2 (2S,3S)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-3-(5-methyl-indol-1-yl)-2-hydroxy-propyl ester was prepared from (2S,3S)-3-(3-fluorophenyl)-3-(5-methyl-1H-indol-1-yl)propane-1,2-diol MS (ESI) *m/z* 454 ($[M+H]^+$).

[0499] In an analogous manner to EXAMPLE 5 ((1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(5-methyl-1H-indol-1-yl)propan-2-ol hydrochloride was prepared from (2S,3S)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-3-(5-methyl-indol-1-yl)-2-hydroxy-propyl ester and methylamine (2N solution in methanol); MS (ESI) *m/z* 313 ($[M+H]^+$); HRMS: calcd for C19H21FN2O + H+, 313.17107; found (ESI-FTMS, [M+H]1+), 313.17163.

[0500] EXAMPLE 93: ((1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(7-methyl-1H-indol-1-yl)propan-2-ol hydrochloride



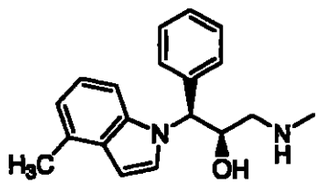
[0501] In an analogous manner to EXAMPLE 117, step 5 (2S,3S)-3-(3-fluorophenyl)-3-(7-methyl-1H-indol-1-yl)propane-1,2-diol was prepared from 7-methylindole and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (see EXAMPLE 47, step 3) as an oil. MS (ESI) m/z 300 ($[M+H]^+$).

[0502] In an analogous manner to EXAMPLE 1, step 2 (2S,3S)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-3-(7-methyl-indol-1-yl)-2-hydroxy-propyl ester was prepared from (2S,3S)-3-(3-fluorophenyl)-3-(7-methyl-1H-indol-1-yl)propane-1,2-diol MS (ESI) *m/z* 454 ($[M+H]^+$).

[0503] In an analogous manner to EXAMPLE 5 ((1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(7-methyl-1H-indol-1-yl)propan-2-ol hydrochloride was prepared from (2S,3S)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-3-(7-methyl-indol-1-yl)-2-hydroxy-propyl ester and methylamine (2N solution in methanol); MS (ESI) *m/z* 313

([M+H]$^+$); HRMS: calcd for C19H21FN2O + H+, 313.17107; found (ESI-FTMS, [M+H]1+), 313.17141.

[0504] EXAMPLE 94: (1*S*,2*R*)-3-(methylamino)-1-(4-methyl-1*H*-indol-1-yl)-1-phenylpropan-2-ol hydrochloride



[0505] In an analogous manner to EXAMPLE 117, step 5 (2S,3S)-3-(4-methyl-1H-indol-1-yl)-3-phenylpropane-1,2-diol was prepared from 4-methylindole[7] and 2*R*,3*R*-(+)-3-phenylglycidol as an oil. MS (ESI) m/z 282 ([M+H]$^+$).

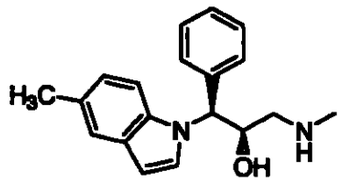
[0506] In an analogous manner to EXAMPLE 1, step 2 (2S,3S)-toluene-4-sulfonic acid 3-(4-methyl-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester was prepared from (2S,3S)-3-(4-methyl-1H-indol-1-yl)-3-phenylpropane-1,2-diol MS (ESI) *m/z* 436 ([M+H]$^+$).

[0507] In an analogous manner to EXAMPLE 5 (1*S*,2*R*)-3-(methylamino)-1-(4-methyl-1*H*-indol-1-yl)-1-phenylpropan-2-ol hydrochloride was prepared from (2S,3S)-toluene-4-sulfonic acid 3-(4-methyl-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester and methylamine (2N solution in methanol); MS (ESI) *m/z* 295 ([M+H]$^+$); HRMS: calcd for C19H22N2O + H+, 295.18049; found (ESI-FT/MS, [M+H]1+), 295.1811.

[0508] EXAMPLE 95: (1*S*,2*R*)-3-(methylamino)-1-(5-methyl-1*H*-indol-1-yl)-1-phenylpropan-2-ol hydrochloride

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[7] Raucher, Stanley; Koolpe, Gary A. *J. Org. Chem.* 1983, 48(12), 2066-9

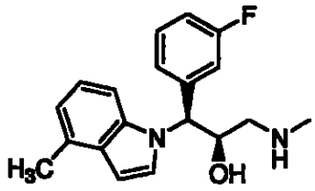


[0509] In an analogous manner to EXAMPLE 117, step 5 (2S,3S)-3-(5-methyl-1H-indol-1-yl)-3-phenylpropane-1,2-diol was prepared from 5-methylindole and *2R,3R*-(+)-3-phenylglycidol as an oil. MS (ESI) m/z 282 ([M+H]$^+$).

[0510] In an analogous manner to EXAMPLE 1, step 2 (2S,3S)-toluene-4-sulfonic acid 3-(5-methyl-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester was prepared from (2S,3S)-3-(5-methyl-1H-indol-1-yl)-3-phenylpropane-1,2-diol MS (ESI) *m/z* 436 ([M+H]$^+$).

[0511] In an analogous manner to EXAMPLE 5 (1*S*,2*R*)-3-(methylamino)-1-(5-methyl-1*H*-indol-1-yl)-1-phenylpropan-2-ol hydrochloride was prepared from (2S,3S)-toluene-4-sulfonic acid 3-(5-methyl-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester and methylamine (2N solution in methanol); MS (ESI) *m/z* 295 ([M+H]$^+$); HRMS: calcd for C19H22N2O + H+, 295.18049; found (ESI-FT/MS, [M+H]1+), 295.1812.

[0512] EXAMPLE 96: ((1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(4-methyl-1H-indol-1-yl)propan-2-ol hydrochloride

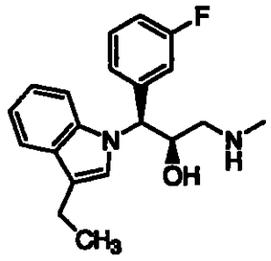


[0513] In an analogous manner to EXAMPLE 117, step 5 (2S,3S)-3-(3-fluorophenyl)-3-(4-methyl-1H-indol-1-yl)propane-1,2-diol was prepared from 4-methylindole[7] and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (see EXAMPLE 47, step 3) as an oil. MS (ESI) m/z 300 ([M+H]$^+$).

[0514] In an analogous manner to EXAMPLE 1, step 2 (2S,3S)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-3-(4-methyl-indol-1-yl)-2-hydroxy-propyl ester was prepared from (2S,3S)-3-(3-fluorophenyl)-3-(4-methyl-1H-indol-1-yl)propane-1,2-diol MS (ESI) *m/z* 454 ([M+H]$^+$).

[0515] In an analogous manner to EXAMPLE 5 ((1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(4-methyl-1H-indol-1-yl)propan-2-ol hydrochloride was prepared from (2S,3S)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-3-(4-methyl-indol-1-yl)-2-hydroxy-propyl ester and methylamine (2N solution in methanol); MS (ESI) *m/z* 313 ([M+H]$^+$); HRMS: calcd for C19H21FN2O + H+, 313.17107; found (ESI-FT/MS, [M+H]1+), 313.171.

[0516] EXAMPLE 97: ((1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(3-ethyl -1H-indol-1-yl)propan-2-ol hydrochloride



[0517] In an analogous manner to EXAMPLE 117, step 5 (2S,3S)-3-(3-fluorophenyl)-3-(3-ethyl-1H-indol-1-yl)propane-1,2-diol was prepared from 3-ethylindole[8] and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (see EXAMPLE 47, step 3) as an oil. MS (ESI) m/z 314 ([M+H]$^+$).

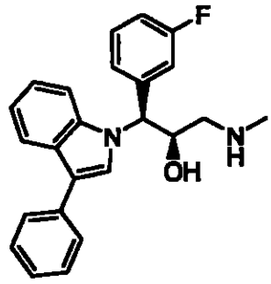
[0518] In an analogous manner to EXAMPLE 1, step 2 (2S,3S)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-3-(3-ethyl-indol-1-yl)-2-hydroxy-propyl ester was prepared

[8] Ainsworth, D. P.; Suschitzky, Hans *J. Chem Soc. [Section] C: Organic* 1967, (4), 315-19

from (2S,3S)-3-(3-fluorophenyl)-3-(3-ethyl-1H-indol-1-yl)propane-1,2-diol MS (ESI) *m/z* 468 ([M+H]$^+$).

[0519] In an analogous manner to EXAMPLE 5 ((1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(3-ethyl-1H-indol-1-yl)propan-2-ol hydrochloride was prepared from (2S,3S)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-3-(3-ethyl-indol-1-yl)-2-hydroxy-propyl ester and methylamine (2N solution in methanol); MS (ESI) *m/z* 327 ([M+H]$^+$); HRMS: calcd for C20H23FN2O + H+, 327.18672; found (ESI, [M+H]+), 327.1871.

[0520] EXAMPLE 98: ((1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(3-phenyl -1H-indol-1-yl)propan-2-ol hydrochloride



[0521] In an analogous manner to EXAMPLE 117, step 5 (2S,3S)-3-(3-fluorophenyl)-3-(3-phenyl-1H-indol-1-yl)propane-1,2-diol was prepared from 3-phenylindole[9] and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (see EXAMPLE 47, step 3) as an oil; MS (ESI) m/z 362 ([M+H]$^+$).

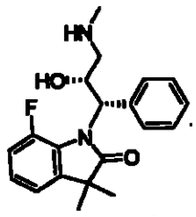
[0522] In an analogous manner to EXAMPLE 1, step 2 (2S,3S)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-3-(3-phenyl-indol-1-yl)-2-hydroxy-propyl ester was prepared from (2S,3S)-3-(3-fluorophenyl)-3-(3-phenyl-1H-indol-1-yl)propane-1,2-diol MS (ESI) *m/z* 516 ([M+H]$^+$).

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[9] Cacchi, Sandro; Fabrizi, Giancarlo; Marinelli, Fabio; Moro, Leonardo; Pace, Paola *Synlett* 1997, (12), 1363-1366.

[0523] In an analogous manner to EXAMPLE 5 ((1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(3-phenyl-1H-indol-1-yl)propan-2-ol hydrochloride was prepared from (2S,3S)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-3-(3-phenyl-indol-1-yl)-2-hydroxy-propyl ester and methylamine (2N solution in methanol); MS (ESI) *m/z* 375 ([M+H]$^+$); HRMS: calcd for C24H23FN2O + H+, 375.18672; found (ESI, [M+H]+), 375.1886.

[0524] EXAMPLE 99: 7-fluoro-1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3- dihydro-2H-indol-2-one hydrochloride



[0525] Step 1: A mixture of sodium perborate tetrahydrate (65 g, 422 mmol) in glacial acetic acid (250 mL) was stirred at 80ºC . 2,6-Difluoroaniline (11.0 g, 85 mmol) in glacial acetic acid (50 mL) was added slowly to the mixture. The temperature was maintained between 80 – 90°C for 1 hour. The cooled reaction mixture was poured into water and extracted twice with diethyl ether. The combined organic layers were washed with a dilute solution of sodium bicarbonate, dried over anhydrous magnesium sulfate and evaporated. The residue was purified via Biotage chromatography (FlashH90i, silica, 10% THF/hexane) and the product washed with hexane to afford 2,6-difluoronitrobenzene (7.0 g) (52%). MS (ESI) m/z 160 ([M+H]$^+$).

[0526] Step 2: To a solution of 2,6-difluoronitrobenzene (5.0 g, 31.44 mmol) in dry *N,N*-dimethylformamide (50 mL) was added potassium carbonate (4.41 g, 32 mmol) and dimethylmalonate (3.6 mL, 31.44 mmol). The reaction mixture was heated to 65ºC and stirred for 24 hours. After cooling to room temperature, the mixture was neutralized with a dilute aqueous solution of hydrochloric acid and extracted with diethyl ether. The ethereal layer was dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Crystallization from 5% ethyl acetate/hexane gave 4.6 g

(54%) 2-(6-fluoro-2-nitro-phenyl)-malonic acid dimethyl ester. MS (ESI) m/z 272 $[M+H]^+$).

[0527] Step 3: 2-(6-Fluoro-2-nitro-phenyl)-malonic acid dimethyl ester (12 g, 44 mmol) in a 6N aqueous solution of hydrochloric acid (200 mL) was heated at reflux for 4 hours. The mixture was cooled, diluted with 250 mL of water and extracted with diethyl ether. The ethereal layer was dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Crystallization from 5% ethyl acetate/hexane gave 7.6 g of (6-fluoro-2-nitro-phenyl)-acetic acid (54%). MS (ESI) m/z 200 ($[M+H]^+$).

[0528] Step 4: A mixture of (6-fluoro-2-nitro-phenyl)-acetic acid (9.6 g, 48 mmol) and 10% palladium on carbon (1.3 g) in acetic acid (100 ml) was hydrogenated at 50 psi for 24 hours. The catalyst was removed by filtration through Celite and the solvent was evaporated. The residue was then dissolved in ethanol (100 mL) and pyridinium *para*-toluenesulfonate (50 mg) was added and the mixture heated at reflux for 1 hour s. The mixture was cooled, poured into water, extracted with ethyl acetate and dried over anhydrous magnesium sulfate. The solvent was filtered and concentrated *in vacuo*. The solid was triturated with 5% ethyl acetate/hexane to give 6.0 g (83%) 7-fluoro-1,3-dihydro-indol-2-one. MS (ESI) m/z 152, $[M+H]^+$).

[0529] Step 5: 7-Fluoro-1,3-dihydro-indol-2-one (7.3 g, 48 mmol) and lithium chloride (6.67 g, 158 mmol) were dissolved in tetrahydrofuran (200 mL). The solution was cooled to –78ºC and *n*- butyllithium (40 mL, 100 mmol) was added slowly over a 15 minute period. After 20 minutes at –78ºC, methyl iodide (6 mL, 96 mmol) was added and the mixture allowed to warm to room temperature. After 24 hours, the mixture was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The crude product was purified via Biotage chromatography (Flash40i, silica, 10% then 20% ethyl acetate/hexane) gave 4.1 g (48%) 7-fluoro-3,3-dimethyl-1,3-dihydro-2H-indol-2-one. MS (ESI) m/z 180, $[M+H]^+$).

[0530] Step 6: A mixture of sodium hydride (244 mg, 6.1 mmol, 60% in mineral oil) and 7-fluoro-3,3-dimethyl-1,3-dihydro-2H-indol-2-one (1.1 g, 6.1 mmol) in dry

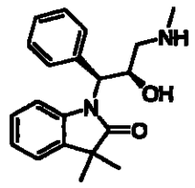
N,N-dimethylformamide (3.5 mL) was stirred at room temperature for 20 minutes. [(2R, 3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4, 460 mg, 3.0 mmol) was added and the mixture was heated to 60ºC under nitrogen. After 20 minutes, additional [(2R, 3R)-3-phenyloxiran-2-yl]methanol (230 mg) was added followed by another addition of [(2R, 3R)-3-phenyloxiran-2-yl]methanol (230 mg) 30 minutes later. The reaction was monitored by tlc (1:1 hexane: ethyl acetate) for the disappearance of starting epoxide. The reaction mixture was poured into a 2N aqueous solution of hydrochloric acid and diluted with ethyl acetate. The layers were separated and the organic layer was washed with water and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give 1.8 g of a yellow oil as crude product. The crude product was purified via Biotage chromatography (FlasH40i, silica, 6:1 to 1:1 hexane: ethyl acetate) to yield 450 mg (23%) of 1-[(1S,2S)-2,3-dihydroxy-1-phenylpropyl]-7-fluoro-3,3-dimethyl-1,3-dihydro-2H- indol-2-one as a yellow oil. MS (ESI) m/z 330 $[(M+H)^+]$.

[0531] Step 7: A solution of 1-[(1S,2S)-2,3-dihydroxy-1-phenylpropyl]-7-fluoro-3,3-dimethyl-1,3-dihydro-2H- indol-2-one (870 mg, 2.6 mmol) in dry pyridine (7.5 mL) was cooled to 0ºC. *para*-Toluenesulfonyl chloride (524 mg, 2.75 mmol) and 4-dimethylaminopyridine(50 mg) were added and the reaction was allowed to warm to room temperature and stirred overnight. The reaction was poured into an ice cold 2N aqueous solution of hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give 1.2 g of a viscous oil. The crude product was purified via Biotage chromatography (FlasH40i, silica, 16% then 20% ethyl acetate/hexane) gave 200 mg (22%) of 1-[(1S,2S)-3-chloro-2-hydroxy-1-phenylpropyl]-7-fluoro-3,3-dimethyl-1,3-dihydro- 2H-indol-2-one. MS (ESI) m/z 348 $[(M+H)^+]$.

[0532] Step 8: A solution of 1-[(1S,2S)-3-chloro-2-hydroxy-1-phenylpropyl]-7-fluoro-3,3-dimethyl-1,3-dihydro- 2H-indol-2-one (300 mg, 0.86 mmol), sodium iodide (10 mg), and methylamine (8M solution in ethanol) was heated to 60ºC for 1h. The reaction was cooled to room temperature, concentrated *in vacuo* and pre-adsorbed onto Celite. The crude product was purified via Biotage chromatography (FlasH40i,

silica, 5%, 8% and 10% methanol with ammonia/dichloromethane) to give 187 mg of the free base. The free base was dissolved in a minimum amount of dichloromethane and treated with a 1M ethereal solution of hydrochloric acid until the pH=3 followed by diethyl ether. The product was crystallized by adding a minimum of hexane to afford the title compound 7-fluoro-1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3- dihydro-2H-indol-2-one hydrochloride as a white solid. MS (ESI) m/z 343 ($[M+H]^+$); HRMS: calcd for C20H23FN2O2 + H^+, 343.18163; found (ESI, $[M+H]^+$), 343.1804.

[0533] EXAMPLE 100: 1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro- 2H-indol-2-one hydrochloride

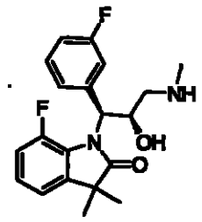


[0534] Step 1: In an analogous manner to EXAMPLE 99, step 6 1-[(1S,2S)-2,3-dihydroxy-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one was prepared from 3,3-dimethyl-1,3-dihydro-indol-2-one[10] and [(2R, 3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4). MS (ESI) m/z 311 ($[M+H]^+$).

[0535] Step 2: In an analogous manner to EXAMPLE 99, step 7 1-[(1S,2S)-3-chloro-2-hydroxy-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol- 2-one was prepared from 1-[(1S,2S)-2,3-dihydroxy-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one. MS (ESI) m/z 330 ($[M+H]^+$.

[0536] Step 3: In an analogous manner to EXAMPLE 99, step 8 1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one hydrochloride was prepared from 1-[(1S,2S)-3-chloro-2-hydroxy-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one. MS (ESI) m/z 325 ($[M+H)^+$], HRMS: calcd for C20H24N2O2 + H^+, 325.19105; found (ESI-FTMS, $[M+H]1^+$), 325.19093.

[0537] EXAMPLE 101: 7-fluoro-1-[(1S,2R)-1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-3,3- dimethyl-1,3-dihydro-2H-indol-2-one hydrochloride



[0538] Step 1: A mixture of 7-fluoro-3, 3-dimethyl-1,3-dihydro-2H-indol-2-one (EXAMPLE 99, step 5, 1.0 g; 5.58 mmol) and sodium *tert*-butoxide (1.0 g, 11.16 mmol) in dry dichloromethane (15 mL) was stirred at room temperature under nitrogen for 20 minutes. Titanium isopropoxide (2.0 mL, 6.70 mmol) was added to a solution of [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, step 3, 844 mg, 5.02 mmol) in dry dichloromethane (6 mL) and stirred for 20 minutes at room temperature. The epoxide complex was added drop-wise to the mixture of *tert*-butoxide and allowed to stir for 4 days. The reaction mixture was poured into a 2N aqueous solution of hydrochloric acid and diluted with ethyl acetate. The layers were separated, and the organic layer was washed with water and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give 2.0 g of crude product. The crude product was purified via Isco chromatography (RediSep, silica, gradient of 0% to 100% ethyl acetate in hexane) to yield 600 mg (31%) of (2S,3S)-7-Fluoro-1-[1-(3-fluoro-phenyl)-2,3-dihydroxy-propyl]-3,3-dimethyl-1,3-dihydro-indol-2-one as an oil. MS (ESI) m/z 348 ($[M+H]^+$).

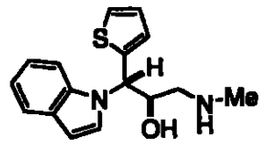
[0539] Step 2: In an analogous manner to EXAMPLE 1, step 2 (2S, 3S)-toluene-4-sulfonic acid 3-(7-fluoro-3,3-dimethyl-2-oxo-2,3-dihydro-indol-1-yl)-3-(3-fluoro-phenyl)-2-hydroxy-propyl ester was prepared from (2S,3S)-7-fluoro-1-[1-(3-fluoro-phenyl)-2,3-dihydroxy-propyl]-3,3-dimethyl-1,3-dihydro-indol-2-one. MS (ESI) m/z 502 ($[M+H]^+$).

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[10] A. Kende, *Synth. Comm.* 1: 12 (1982)

[0540] Step 3: In an analogous manner to EXAMPLE 5 7-fluoro-1-[(1S,2R)-1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-3,3- dimethyl-1,3-dihydro-2H-indol-2-one hydrochloride was prepared from (2S,3S)-toluene-4-sulfonic acid 3-(7-fluoro-3,3-dimethyl-2-oxo-2,3-dihydro-indol-1-yl)-3-(3-fluoro-phenyl)-2-hydroxy-propyl ester. MS (ESI) m/z 360 ([M+H]$^+$), HRMS: calcd for C20H22F2N2O2 + H$^+$, 361.17221; found (ESI, [M+H]$^+$), 361.1719.

[0541] EXAMPLE 102: (1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-(2-thienyl)propan-2-ol hydrochloride



[0542] Step 1: Thiophene (2.42 mL, 30.6 mmol) was dissolved in tetrahydrofuran (50 mL), cooled to –78°C, and treated with *n*-butyllithium (9.2 mL, 18.4 mmol) then warmed to 25°C. The mixture was stirred for 30 minutes then cooled to –78°C and a solution of 2,3-*O*-isopropylidene-D-glyceraldehyde[11] (2.00 g, 15.3 mmol) in tetrahydrofuran (15.3 mL) was added dropwise. Stirring was continued for 20 minutes then warmed to 0°C and quenched with a saturated aqueous solution of ammonium chloride. The mixture was diluted with ethyl acetate, washed with water, and saturated brine. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified via Biotage chromatography (FlasH40i, silica, 10% acetone/hexane) to afford the product 1.6 g (51%) as a 2:1 mixture of (R)-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl](2-thienyl)methanol and (S)-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl](2-thienyl)methanol as an oil. HRMS: calcd for $C_{16}H_{18}N_2OS$ + H+, 287.12126; found (ESI, [M+H]+), 287.1204.

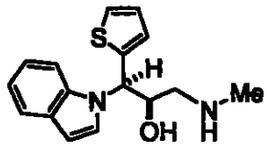
[11] Schmid, C. R.; Bryant, J. D.; Dowlatzedah, M.; Phillips, J. L.; Prather, D. E.; Schantz, R. D.; Sear, N. L.; Vianco, C. S. *J. Org. Chem.* 1991, *56*, 4056.

[0543] Step 2: A mixture of (R)-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl](2-thienyl)methanol and (S)-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl](2-thienyl)methanol (1.5 g, 7.0 mmol) was dissolved in tetrahydrofuran (28 mL) and sodium acetylide (2.1 g, 7.7 mmol; 18 wt% slurry in xylenes/light mineral oil) and the mixture was stirred for 2 hours. *para*-Toluenesulfonyl chloride (1.46 g, 7.7 mmol) was added and stirring was continued for 2 hours, then indoline (2.5 g, 21 mmol) was added followed by 2,6-lutidine (0.81 mL, 7.0 mmol). After 72 hours the mixture was quenched with a saturated aqueous solution of ammonium chloride, diluted with ethyl acetate, washed with water, and saturated brine. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified via Isco chromatography (Redisep, silica, gradient 1-10% ethyl acetate in hexane) to afford 590 mg that was immediately dissolved in dioxane (10 mL) and treated with dichlorodicyanobenzoquinone (552 mg, 2.4 mmol) and stirred for 30 minutes. The mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate, water, and saturated brine. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified via Isco chromatography (Redisep, silica, gradient 1-20% ethyl acetate in hexane) to afford 355 mg of 1-[(S)-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl](2-thienyl)methyl]-1H-indole. HRMS: calcd for $C_{18}H_{19}NO_2S$ + H+, 314.12092; found (ESI-FTMS, [M+H]1+), 314.12111.

[0544] Step 3: 1-[(S)-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl](2-thienyl)methyl]-1H-indole (350 mg, 1.12 mmol) was dissolved in methanol (20 mL) and benzenesulfonic acid (17 mg, 0.11 mmol) was added. The mixture was stirred for 6 hours then diluted with ethyl acetate and washed with a saturated aqueous solution of sodium bicarbonate, water, and saturated brine. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified via flash column chromatography (silica, 5% methanol/chloroform) to afford 260 mg (82%) of (2S,3S)-3-(1H-indol-1-yl)-3-thien-2-ylpropane-1,2-diol. HRMS: calcd for $C_{15}H_{15}NO_2S$ + H+, 274.08963; found (ESI, [M+H]+), 274.0892.

[0545] Step 4: (2S,3S)-3-(1H-indol-1-yl)-3-thien-2-ylpropane-1,2-diol (250 mg, 0.91 mmol) was dissolved in pyridine (3 mL), *para*-toluenesulfonyl chloride (216 mg, 1.13 mmol) was added and the mixture was stirred for 2 hours. The mixture was diluted with ethyl acetate and washed with water, a saturated aqueous solution of copper sulfate, and saturated brine. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified via Isco chromatography (Redisep, silica, gradient 0% - 100% ethyl acetate in hexane) to afford 360 mg that was immediately dissolved in methylamine (8M solution in ethanol, 15 mL) and stirred for 16 hours. The mixture was concentrated *in vacuo* and purified via flash column chromatography (silica, gradient 2% - 10% methanol saturated with ammonia in chloroform) to give 180 mg of (1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-(2-thienyl)propan-2-ol as a colorless oil. The freebase was dissolved in ether (5 mL) and treated with a 1N ethereal solution of hydrochloric acid (0.63 mL, 0.63 mmol, 1 equivalent). The white precipitate was collected and dried under vacuum to give 193 mg (60%) of (1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-(2-thienyl)propan-2-ol hydrochloride. HRMS: calcd for $C_{16}H_{18}N_2OS$ + H+, 287.12126; found (ESI, [M+H]+), 287.1204

[0546] EXAMPLE 103: (1R,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-(2-thienyl)propan-2-ol hydrochloride



[0547] Step 1: Thiophene (2.42 mL, 30.6 mmol) was dissolved in tetrahydrofuran (50 mL), cooled to –78°C, and treated with *n*-butyllithium (9.2 mL, 18.4 mmol) then warmed to 25°C. The mixture was stirred for 30 minutes then cooled to –78°C and a solution of 2,3-*O*-isopropylidene-D-glyceraldehyde[11] (2.00 g, 15.3 mmol) in tetrahydrofuran (15.3 mL) was added dropwise. Stirring was continued for 20 minutes then warmed to 0°C and quenched with a saturated aqueous solution of ammonium chloride. The mixture was diluted with ethyl acetate, washed with water, and saturated brine. The organic layer was separated, dried over anhydrous

magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified via Biotage chromatography (FlasH40i, silica, 10% acetone/hexane) to afford the product 1.6 g (51%) as a 2:1 mixture of (R)-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl](2-thienyl)methanol and (S)-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl](2-thienyl)methanol as an oil. HRMS: calcd for $C_{16}H18N_2OS$ + H+, 287.12126; found (ESI, [M+H]+), 287.1204.

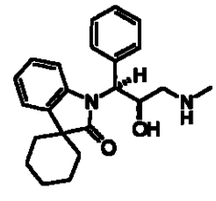
[0548] Step 2: A mixture of (R)-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl](2-thienyl)methanol and (S)-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl](2-thienyl)methanol (1.5 g, 7.0 mmol) was dissolved in tetrahydrofuran (28 mL) and sodium acetylide (2.1 g, 7.7 mmol; 18 wt% slurry in xylenes/light mineral oil) and the mixture was stirred for 2 hours. *para*-Toluenesulfonyl chloride (1.46 g, 7.7 mmol) was added, and stirring was continued for 2 hours, then indoline (2.5 g, 21 mmol) was added followed by 2,6-lutidine (0.81 mL, 7.0 mmol). After 72 hours the mixture was quenched with a saturated aqueous solution of ammonium chloride, diluted with ethyl acetate, washed with water, and saturated brine. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified via Isco chromatography (Redisep, silica, gradient 1-10% ethyl acetate in hexane) to afford 590 mg that was immediately dissolved in dioxane (10 mL) and treated with dichlorodicyanobenzoquinone (552 mg, 2.4 mmol) and stirred for 30 minutes. The mixture was diluted with ethyl acetate and washed with a saturated aqueous solution of sodium bicarbonate, water, and saturated brine. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified via Isco chromatography (Redisep, silica, gradient 1-20% ethyl acetate in hexane) to afford 160 mg of 1-[(R)-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl](2-thienyl)methyl]-1H-indole. HRMS: calcd for $C_{18}H_{19}NO_2S$ + H+, 314.12092; found (ESI-FTMS, [M+H]1+), 314.12089.

[0549] Step 3: 1-[(S)-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl](2-thienyl)methyl]-1H-indole (160 mg, 0.51 mmol) was dissolved in methanol (10 mL) and benzenesulfonic acid (10 mg, 0.06 mmol) was added. The mixture was stirred for 16 hours then diluted with ethyl acetate and washed with a saturated aqueous solution of sodium

bicarbonate, water, and saturated brine. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified via flash column chromatography (silica, 5% methanol/chloroform) to afford 102 mg (74%) of (2S,3R)-3-(1H-indol-1-yl)-3-thien-2-ylpropane-1,2-diol that was carried directly to the next step.

[0550] Step 4: (2S,3R)-3-(1H-indol-1-yl)-3-thien-2-ylpropane-1,2-diol (102 mg, 0.37 mmol) was dissolved in pyridine (1.5 mL), *para*-toluenesulfonyl chloride (88 mg, 0.46 mmol) was added and the mixture was stirred for 16 hours. The mixture was diluted with ethyl acetate and washed with water, a saturated aqueous solution of copper sulfate, and saturated brine. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified via Isco chromatography (Redisep, silica, gradient 0% - 100% ethyl acetate in hexane) to afford 140 mg that was immediately dissolved in methylamine (8M solution in ethanol, 15 mL) and stirred for 3 hours. The mixture was concentrated *in vacuo* and purified via flash column chromatography (silica, gradient 2% - 10% methanol saturated with ammonia in chloroform) to give 65 mg (71%) of (1R,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-(2-thienyl)propan-2-ol as a colorless oil. The freebase was dissolved in diethyl ether (5 mL) and treated with a 1N ethereal solution of hydrochloric acid (0.23 mL, 0.23 mmol, 1 equivalent). The white precipitate was collected and dried under vacuum to give (1R,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-(2-thienyl)propan-2-ol hydrochloride. HRMS: calcd for $C_{16}H_{18}N_2OS$ + H+, 287.12126; found (ESI, [M+H]+), 287.1209

[0551] EXAMPLE 104: 1'-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]spiro[cyclo-hexane-1,3'-indol]-2'(1'H)-one hydrochloride



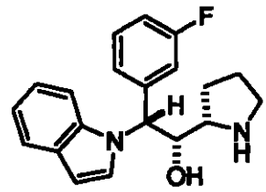
[0552] Step 1: Spiro[cyclohexane-1,3'-indol]-2'(1'H)-one[12] (0.82 g, 4.1 mmol) was dissolved in *N,N*-dimethylformamide (1 mL), and sodium hydride (168 mg, 4.4 mmol, 60% wt suspension in mineral oil) was added and the resulting mixture was stirred for 15 minutes. The mixture was warmed to 75°C and trans-3-phenylglycidol (306 mg, 2.04 mmol) was added in four portions. Stirring was continued for 2 hours, then the reaction mixture was cooled and quenched with a saturated aqueous solution of ammonium chloride. The mixture was diluted with ethyl acetate, washed with water, and saturated brine. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified via Isco chromatography (Redisep, silica, gradient 20% to 100% ethyl acetate in hexane) to afford 290 mg (41%) of 1'-[(1S,2S)-2,3-dihydroxy-1-phenyl-propyl]spiro[cyclohexane-1,3'-indol]-2'(1'H)-one as an oil. HPLC purity 100% at 210-370 nm, 9.4 min.; Xterra RP18, 3.5u, 150 x 4.6 mm column, 1.2 mL/minutes, 85/15-5/95 (Ammon. Form. Buff. Ph=3.5/ACN+MeOH) for 10minutes, hold 4min.

[0553] Step 2: 1'-[(1S,2S)-2,3-dihydroxy-1-phenyl-propyl]spiro[cyclohexane-1,3'-indol]-2'(1'H)-one (250 mg, 0.71 mmol) was dissolved in pyridine (2.5 mL) and *para*-toluenesulfonyl chloride (169 mg, 0.89 mmol) was added. The reaction was stirred for 5 hours, then the reaction mixture was diluted with ethyl acetate and washed with water, a saturated aqueous solution of copper sulfate, a 2N aqueous solution of hydrochloric acid, and saturated brine. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was immediately dissolved in methylamine (8M solution in ethanol, 15 mL) and stirred for 16 hours. The mixture was concentrated *in vacuo* and purified via flash column chromatography (silica, 5% methanol saturated with ammonia in chloroform) to give 85 mg (32%) 1'-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]spiro[cyclo-hexane-1,3'-indol]-2'(1'H)-one as a colorless oil. The freebase was dissolved in diethyl ether (5 mL) and treated with a 1N ethereal solution of hydrochloric acid (0.23 mL, 0.23 mmol, 1 equivalent). The white precipitate was collected and dried under vacuum to give 193 mg (60%) of 1'-

[12] Fensome, A.; Miller, L. L.; Ullrich, J. W.; Bender, R. H. W.; Zhang, P.; Wrobel, J. E.; Zhi, L.; Jones, T. K.; Marschke, K. B.; Tegley, C. M. PCT Int. PCT Int. Appl. 2000, 127 pp. WO2000068556

[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]spiro[cyclo-hexane-1,3'-indol]-2'(1'H)-one hydrochloride. HRMS: calcd for $C_{23}H_{28}N_2O_2$ + H+, 365.22235; found ([M+H]+), 365.2226;

[0554] EXAMPLE 105: (1S,2R)-2-(3-fluorophenyl)-2-(1H-indol-1-yl)-1-[(2S)-pyrrolidin-2-yl]ethanol hydrochloride



[0555] Step 1: To a suspension of 3-fluorobenzyltriphenylphosphonium bromide (6.8 g, 15 mmol) in tetrahydrofuran (50 mL) at 0°C was added sodium hydride (0.57 g, 15 mmol, 60% wt suspension in mineral oil), and the mixture was stirred for 1 hours. A solution of (S)-2-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester[13] (2.5 g, 12.5 mmol) in tetrahydrofuran (10 mL) was added and the mixture was stirred for 1 hour then warmed to 25°C and quenched with a saturated aqueous solution of ammonium chloride. The mixture was diluted with ethyl acetate, washed with water, and saturated brine. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified via Isco chromatography (Redisep, silica, 10% ethyl acetate/hexane) to afford 2.18 g (60%) of *tert*-butyl (2S)-2-[(E)-2-(3-fluorophenyl)vinyl]pyrrolidine-1-carboxylate as a colorless oil that crystallized on standing. HRMS: calcd for $C_{17}H_{22}FNO_2$ + H+, 292.17073; found (ESI, M+H), 292.1713.

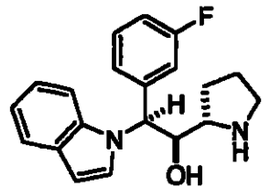
[0556] Step 2: *tert*-Butyl (2S)-2-[(E)-2-(3-fluorophenyl)vinyl]pyrrolidine-1-carboxylate (400 mg, 1.37 mmol) was dissolved in dichloromethane (50 mL). A saturated aqueous solution of sodium bicarbonate (50 mL) was added, followed by acetone (10 mL) and tetrabutylammonium hydrogen sulfate (46 mg, 0.14 mmol).

[13] Cook, G. R.; Stille, J. R. *Tetrahedron*, 1994, *50*(14), 4105.

With vigorous stirring Oxone (8.4 g, 13.7 mmol) was added over 2 hours in 8 portions (1.05 g every 15 minutes). The mixture was stirred an additional 16 hours then diluted with dichloromethane. The organic layer was separated and washed with water, and saturated brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified via Isco chromatography (Redisep, silica, 20% ethyl acetate/hexane) to give 240 mg that was immediately combined with indoline (0.14 g, 1.2 mmol) and heated to 90°C for 16 hours. The mixture was cooled and the crude orange oil was purified by Isco chromatography (Redisep, silica, gradient 0% to 25% ethyl acetate in hexane) to give 130 mg that was immediately dissolved in dichloromethane (20 mL). Manganese dioxide (0.86 g, 10 mmol) was added and the mixture was stirred for 5 hours, then diluted with dichloromethane and filtered through a pad of Celite and concentrated. The crude product was purified by Isco chromatography (Redisep, silica, gradient 0% to 50% ethyl acetate in hexane) to give 50 mg of (S)-2-[2-(R)-(3-fluoro-phenyl)-1-hydroxy-2-indol-1-yl-ethyl]-(S)-pyrrolidine-1-carboxylic acid tert-butyl ester.

[0557] Step 3:(S)-2-[2-(R)-(3-Fluoro-phenyl)-1-hydroxy-2-indol-1-yl-ethyl]-(S)-pyrrolidine-1-carboxylic acid tert-butyl ester (50 mg, 0.12 mmol) was dissolved in methanol (1 mL) and a 1N ethereal solution of hydrochloric acid (0.96 mL, 0.96 mmol) was added. After 6 hours the mixture was concentrated and purified via flash column chromatography (silica, 10% methanol saturated with ammonia in chloroform) to give 6 mg (15%) (1S,2R)-2-(3-fluorophenyl)-2-(1H-indol-1-yl)-1-[(2S)-pyrrolidin-2-yl]ethanol. The freebase was dissolved in diethyl ether (2 mL) and treated with a 1N ethereal solution of hydrochloric acid (0.02 mL, 0.02 mmol, 1 equivalent). The white precipitate was collected and dried under vacuum to give 4 mg of (1S,2R)-2-(3-fluorophenyl)-2-(1H-indol-1-yl)-1-[(2S)-pyrrolidin-2-yl]ethanol hydrochloride. HRMS: calcd for $C_{20}H_{21}FN_2O$ + H+, 325.17107; found (ESI, [M+H]+), 325.1712

[0558] EXAMPLE 106: (1R,2S)-2-(3-fluorophenyl)-2-(1H-indol-1-yl)-1-[(2S)-pyrrolidin-2-yl]ethanol hydrochloride



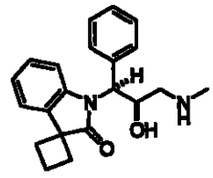
[0559] Step 1: To a suspension of 3-fluorobenzyltriphenylphosphonium bromide (6.8 g, 15 mmol) in tetrahydrofuran (50 mL) at 0°C was added sodium hydride (0.57 g, 15 mmol, 60% wt suspension in mineral oil) and the mixture was stirred for 1 hour at room temperature. A solution of (S)-2-formyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester[13] (2.5 g, 12.5 mmol) in tetrahydrofuran (10 mL) was added, and the mixture was stirred for 1 hour then warmed to 25°C and quenched with a saturated aqueous solution of ammonium chloride. The mixture was diluted with ethyl acetate, washed with water, and saturated brine. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified via Isco chromatography (Redisep, silica, 10% ethyl acetate/hexane) to afford 2.18 g (60%) of tert-butyl (2S)-2-[(E)-2-(3-fluorophenyl)vinyl]pyrrolidine-1-carboxylate as a colorless oil that crystallized on standing. HRMS: calcd for $C_{17}H_{22}FNO_2$ + H+, 292.17073; found (ESI, M+H), 292.1713.

[0560] Step 2: *tert*-Butyl (2S)-2-[(E)-2-(3-fluorophenyl)vinyl]pyrrolidine-1-carboxylate (400 mg, 1.37 mmol) was dissolved in dichloromethane (50 mL). A saturated aqueous solution of sodium bicarbonate (50 mL) was added, followed by acetone (10 mL) and tetrabutylammonium hydrogen sulfate (46 mg, 0.14 mmol). With vigorous stirring Oxone (8.4 g, 13.7 mmol) was added over 2 hours in 8 portions (1.05 g every 15 minutes). The mixture was stirred an additional 16 hours then diluted with dichloromethane. The organic layer was separated and washed with water, and saturated brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified via Isco chromatography (Redisep, silica, 20% ethyl acetate/hexane) to give 240 mg that was immediately combined with indoline (0.14 g, 1.2 mmol) and heated to 90°C for 16 hours. The mixture was cooled and the crude orange oil was purified by Isco chromatography (Redisep, silica, gradient 0% to 25% ethyl acetate in hexane) to give 130 mg that

was immediately dissolved in dichloromethane (20 mL). Manganese dioxide (0.86 g, 10 mmol) was added and the mixture was stirred for 5 hours then diluted with dichloromethane and filtered through a pad of Celite and concentrated. The crude product was purified by Isco chromatography (Redisep, silica, gradient 0% to 50% ethyl acetate in hexane) to give 50 mg of (R)-2-[2-(S)-(3-fluoro-phenyl)-1-hydroxy-2-indol-1-yl-ethyl]-(S)-pyrrolidine-1-carboxylic acid tert-butyl ester.

[0561] Step 3:(R)-2-[2-(S)-(3-Fluoro-phenyl)-1-hydroxy-2-indol-1-yl-ethyl]-(S)-pyrrolidine-1-carboxylic acid tert-butyl ester (50 mg, 0.12 mmol) was dissolved in methanol (1 mL) and a 1N ethereal solution hydrochloric acid (1.0 mL, 1.0 mmol) was added. After 16 hours the mixture was concentrated and purified via flash column chromatography (silica, 10% methanol saturated with ammonia in chloroform) to give 19 mg (50%) (1R,2S)-2-(3-fluorophenyl)-2-(1H-indol-1-yl)-1-[(2S)-pyrrolidin-2-yl]ethanol. The freebase was dissolved in diethyl ether (2 mL) and treated with 1N ethereal solution of hydrochloric acid (0.06 mL, 0.06 mmol, 1 equivalent). The white precipitate was collected and dried under vacuum to give 17 mg of (1R,2S)-2-(3-fluorophenyl)-2-(1H-indol-1-yl)-1-[(2S)-pyrrolidin-2-yl]ethanol hydrochloride. HRMS: calcd for $C_{20}H_{21}FN_2O$ + H+, 325.17107; found (ESI, [M+H]+), 325.1711

[0562] EXAMPLE 107: 1'-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]spiro[cyclo-butane-1,3'-indol]-2'(1'H)-one hydrochloride

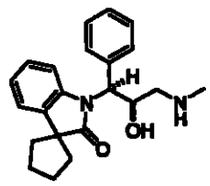


[0563] Step 1: In an analogous manner to EXAMPLE 104, step 1 1'-[(1S,2S)-2,3-dihydroxy-1-phenylpropyl]spiro[cyclobutane-1,3'-indol]-2'(1'H)-one was prepared from spiro[cyclobutane-1,3'-indol]-2'(1'H)-one[12] and trans-3-phenylglycidol. HPLC purity 100% at 210-370 nm, 8.4 min.; Xterra RP18, 3.5u, 150 x 4.6 mm column, 1.2

mL/minutes, 85/15-5/95 (Ammon. Form. Buff. Ph=3.5/ACN+MeOH) for 10minutes, hold 4min.

[0564] Step 2: In an analogous manner to EXAMPLE 104, step 2 1'-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]spiro[cyclo-butane-1,3'-indol]-2'(1'H)-one hydrochloride was prepared from 1'-[(1S,2S)-2,3-dihydroxy-1-phenylpropyl]spiro-[cyclobutane-1,3'-indol]-2'(1'H)-one. HRMS: calcd for $C_{21}H_{24}N_2O_2$ + H+, 337.19105; found (ESI, [M+H]+), 337.1917

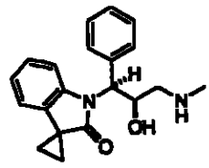
[0565] EXAMPLE 108: 1'-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]spiro-[cyclopentane-1,3'-indol]-2'(1'H)-one hydrochloride



[0566] Step 1: In an analogous manner to EXAMPLE 104, step 1 1'-[(1S,2S)-2,3-dihydroxy-1-phenylpropyl]spiro[cyclopentane-1,3'-indol]-2'(1'H)-one was prepared from spiro[cyclopentane-1,3'-indol]-2'(1'H)-one[12] and trans-3-phenylglycidol. HRMS: calcd for $C_{21}H_{23}NO_3$ + H+, 338.17507; found (ESI, [M+H]+), 338.1769

[0567] Step 2: In an analogous manner to EXAMPLE 104, step 2 1'-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]spiro-[cyclopentane-1,3'-indol]-2'(1'H)-one hydrochloride was prepared from 1'-[(1S,2S)-2,3-dihydroxy-1-phenylpropyl]spiro-[cyclopentane-1,3'-indol]-2'(1'H)-one. HRMS: calcd for $C_{22}H_{26}N_2O_2$ + H+, 351.20670; found (ESI, [M+H]+), 351.2061

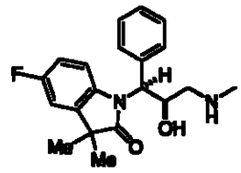
[0568] EXAMPLE 109: 1'-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]spiro-[cyclopropane-1,3'-indol]-2'(1'H)-one hydrochloride



[0569] Step 1: In an analogous manner to EXAMPLE 104, step 1 1'-[(1S,2S)-2,3-dihydroxy-1-phenylpropyl]spiro[cyclopropane-1,3'-indol]-2'(1'H)-one was pre-pared from spiro[cyclopropane-1,3'-indol]-2'(1'H)-one[14] and trans-3-phenylglycidol. HPLC purity 89.1% at 210-370 nm, 7.7 min.; Xterra RP18, 3.5u, 150 x 4.6 mm column, 1.2 mL/minutes, 85/15-5/95 (Ammon. Form. Buff. Ph=3.5/ACN+MeOH)
for 10minutes, hold 4min.

[0570] Step 2: In an analogous manner to EXAMPLE 104, step 2 1'-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]spiro-[cyclopropane-1,3'-indol]-2'(1'H)-one hydrochloride was prepared from 1'-[(1S,2S)-2,3-dihydroxy-1-phenylpropyl]-spiro[cyclopropane-1,3'-indol]-2'(1'H)-one. HRMS: calcd for $C_{20}H_{22}N_2O_2$ + H+, 323.17540; found (ESI, [M+H]+), 323.1744

[0571] EXAMPLE 110: 5-fluoro-1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one hydrochloride



[0572] Step 1: 5-Fluoro-1,3-dihydro-indol-2-one (2.0 g, 13.2 mmol) and lithium chloride (1.39 g, 33.0 mmol) were dissolved in tetrahydrofuran (40 mL) and cooled to 0°C. n-Butyllithium (10.6 mL, 26.4 mmol) was added dropwise and the mixture was stirred 20 minutes. Methyl iodide (1.63 mL, 26.4 mmol) was added slowly and stirring was continued for 2 hours at 0°C then warmed to 25°C. After 16 hours the

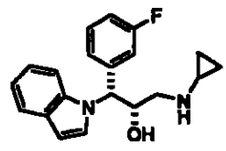
[14] Roberston, D. W.; Krushinski, J. H.; Pollock, G. D.; Wilson, H.; Kauffman, R. F.; Hayes, J. S. *J. Med. Chem.* **1987**, *30*, 824.

reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was diluted with ether, washed with water, and saturated brine. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified via Isco chromatography (Redisep, silica, gradient 10% to 50% ethyl acetate in hexane) to afford 1.18 g (50%) of 5-fluoro-3,3-dimethyl-1,3-dihydro-2H-indol-2-one as white crystals. HPLC purity 100% at 210-370 nm, 7.1 min.; Xterra RP18, 3.5u, 150 x 4.6 mm column, 1.2 mL/minutes, 85/15-5/95 (Ammon. Form. Buff. Ph=3.5/ACN+MeOH) for 10minutes, hold 4min.

[0573] Step 2: In an analogous manner to EXAMPLE 104, step 1-[(1S,2S)-2,3-dihydroxy-1-phenylpropyl]-5-fluoro-3,3-dimethyl-1,3-dihydro-2H-indol-2-one was prepared from 5-fluoro-3,3-dimethyl-1,3-dihydro-2H-indol-2-one and trans-3-phenylglycidol. HRMS: calcd for $C_{19}H_{20}FNO_3$ + H+, 330.15000; found (ESI, [M+H]+), 330.1485

[0574] Step 3: In an analogous manner to EXAMPLE 104, step 2 5-fluoro-1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one hydrochloride was prepared from 1-[(1S,2S)-2,3-dihydroxy-1-phenylpropyl]-5-fluoro-3,3-dimethyl-1,3-dihydro-2H-indol-2-one. HPLC purity 100% at 210-370 nm, 7.2 min.; Xterra RP18, 3.5u, 150 x 4.6 mm column, 1.2 mL/minutes, 85/15-5/95 (Ammon. Form. Buff. Ph=3.5/ACN+MeOH) for 10minutes, hold 4minutes. HRMS: calcd for $C_{20}H_{23}FN_2O_2$ + H+, 343.18163; found (ESI, [M+H]+), 343.184

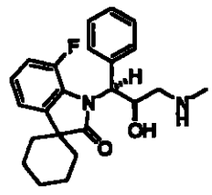
[0575] EXAMPLE 111: (1S,2R)-3-(cyclopropylamino)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)propan-2-ol hydrochloride



[0576] Step 1: (2S,3S)-3-(3-Fluorophenyl)-3-(1H-indol-1-yl)propane-1,2-diol (example 47, step 5) (0.6 g, 2.1 mmol) was dissolved in pyridine (5 mL) and *para*-

toluenesulfonyl chloride (0.44 g, 2.3 mmol) was added. The mixture was stirred for 3 hours then the reaction mixture was diluted with ethyl acetate and washed with water, followed by a saturated aqueous solution of copper sulfate, a 2N aqueous solution of hydrochloric acid, and saturated brine. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was immediately dissolved in methylamine (8M solution in ethanol, 25 mL) and stirred for 16 hours. The mixture was concentrated *in vacuo* and purified via flash column chromatography (silica, 5% methanol saturated with ammonia in chloroform) to give (1S,2R)-3-(cyclopropylamino)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)propan-2-ol as a colorless oil. The freebase was dissolved in diethyl ether (5 mL) and treated with a 1N ethereal solution of hydrochloric acid (1 equivalent). The white precipitate was collected and dried under vacuum to give 80 mg (12%) of (1S,2R)-3-(cyclopropylamino)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)propan-2-ol hydrochloride. HRMS: calcd for $C_{20}H_{21}FN_2O$ + H+, 325.17107; found (ESI, [M+H]+), 325.1728.

[0577] EXAMPLE 112: 7'-fluoro-1'-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-spiro[cyclohexane-1,3'-indol]-2'(1'H)-one hydrochloride



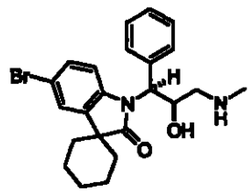
[0578] Step 1: 7-Fluoro-1,3-dihydro-indol-2-one (EXAMPLE 99, step 4) (1.16 g, 7.68 mmol) and lithium chloride (0.81 g, 19.2 mmol) were dissolved in tetrahydrofuran (50 mL) and cooled to 0°C. n-Butyllithium (6.14 mL, 15.4 mmol) was added dropwise and the mixture was stirred 15 minutes. 1,5-Dibromopentane (1.05 mL, 7.7 mmol) was added slowly and stirring was continued for 2 hours at 0°C then warmed to 25°C. After 16 hours the reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was diluted with ether, washed with water, and saturated brine. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude

product was purified via Isco chromatography (Redisep, silica, gradient 5% to 40% ethyl acetate in hexane) to afford 0.90 g (54%) of 7'-fluorospiro-[cyclohexane-1,3'-indol]-2'(1'H)-one. HPLC purity 95.9% at 210-370 nm, 19.2 min.; Xterra MSC18, 5u, 150 x 3.0 mm column, 0.5 mL/minutes, 95/5-5/95 (0.1% formic acid in H2O/MeOH) for 20minutes, hold 3 min.

[0579] Step 2: In an analogous manner to EXAMPLE 104, step 1 1'-[(1S,2S)-2,3-dihydroxy-1-phenylpropyl]-7'-fluorospiro[cyclohexane-1,3'-indol]-2'(1'H)-one was prepared from 7'-fluorospiro-[cyclohexane-1,3'-indol]-2'(1'H)-one and trans-3-phenylglycidol. HRMS: calcd for C22H24FNO3 + H+, 370.18130; found (ESI, [M+H]+), 370.1798

[0580] Step 3: In an analogous manner to EXAMPLE 104, step 2 7'-fluoro-1'-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-spiro[cyclohexane-1,3'-indol]-2'(1'H)-one hydrochloride was prepared from 1'-[(1S,2S)-2,3-dihydroxy-1-phenylpropyl]-7'-fluorospiro[cyclohexane-1,3'-indol]-2'(1'H)-one. HRMS: calcd for $C_{23}H_{27}FN_2O_2$ + H+, 383.21293; found (ESI, [M+H]+), 383.2109

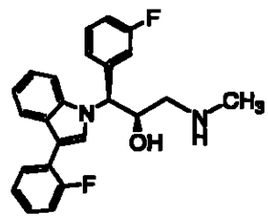
EXAMPLE 113: 5'-bromo-1'-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-spiro[cyclohexane-1,3'-indol]-2'(1'H)-one hydrochloride



[0581] Step 1: In an analogous manner to EXAMPLE 104, step 1 5'-bromo-1'-[(1S,2S)-2,3-dihydroxy-1-phenylpropyl]spiro[cyclohexane-1,3'-indol]-2'(1'H)-one was prepared from 5'-bromospiro[cyclohexane-1,3'-indol]-2'(1'H)-one[12] and trans-3-phenylglycidol. HRMS: calcd for C22H24BrNO3 + H+, 430.10123; found (ESI, [M+H]+), 430.1006

[0582] Step 2: In an analogous manner to EXAMPLE 104, step 2 5'-bromo-1'-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-spiro[cyclohexane-1,3'-indol]-2'(1'H)-one hydrochloride was prepared from 5'-bromo-1'-[(1S,2S)-2,3-dihydroxy-1-phenylpropyl]spiro[cyclohexane-1,3'-indol]-2'(1'H)-one. HRMS: calcd for C23H27BrN2O2 + H+, 443.13286; found (ESI, [M+H]+), 443.1333.

[0583] EXAMPLE 114: (1*S*,2*R*)-1-(3-fluorophenyl)-1-[3-(2-fluorophenyl)-1*H*-indol-1-yl]-3-(methylamino)propan-2-ol hydrochloride



[0584] Step 1: To a solution of (2S,3S)-3-indol-1-yl-3-(3-fluorophenyl)-propane-1,2-diol (EXAMPLE 47, Step 5, 1.34 g, 4.56 mmol) in N,N-dimethylformamide (20 mL) was added pulverized solid potassium hydroxide (0.76 g, 13.68 mmol). The mixture was stirred for 15 minutes under nitrogen at room temperature, whereupon iodine (1.21 g, 4.72 mmol) was added in one portion. The mixture was stirred for 30 minutes at room temperature, then poured into 100 mL of a 5% aqueous sodium thiosulfate solution. The solution was extracted 3 times with ethyl acetate and the combined extracts were washed 3 times with water. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified via Biotage chromatography (FlashH40i, silica, 40% ethyl acetate/hexane) to yield 0.91 g (48%) of (2*S*,3*S*)-3-(3-fluorophenyl)-3-(3-iodo-1*H*-indol-1-yl)propane-1,2-diol as a dark brown oil. MS (ES) *m/z* 411.9.

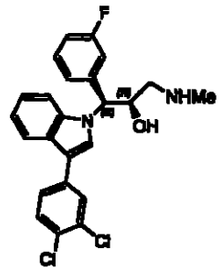
[0585] Step 2: A mixture of (2*S*,3*S*)-3-(3-fluorophenyl)-3-(3-iodo-1*H*-indol-1-yl)propane-1,2-diol (0.25 g, 0.61 mmol), 2-fluorobenzeneboronic acid (0.12 g, 0.85 mmol), and potassium phosphate (0.39 g, 1.83 mmol) in N,N-dimethylformamide (10

mL) was degassed with nitrogen for 5 minutes then a catalytic amount (0.02 g) of [1,4-bis-(diphenylphosphine)butane]palladium (II) dichloride was added. The solution was heated to 90°C for 3 hours then cooled and poured into 100 mL of water. The aqueous mixture was extracted 3 times with ethyl acetate and the combined extracts were then washed 2 times with water. The ethyl acetate was dried by filtration through a plug of silica gel then concentrated. The residue was purified by Biotage chromatography (FlasH40I, silica, 40% ethyl acetate/hexane) to yield 0.14 g of (2S,3S)-3-(3-fluorophenyl)-3-{3-[2-fluorophenyl]-1H-indol-1-yl}propane-1,2-diol as an oil, which was used in the next step without further purification.

[0586] Step 3: In an analogous manner to EXAMPLE 1, step 2 (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-3-[3-(2-fluorophenyl)-indol-1-yl]-2-hydroxy-propyl ester was prepared from (2S,3S)-3-(3-fluorophenyl)-3-{3-[2-fluorophenyl]-1H-indol-1-yl}propane-1,2-diol.

[0587] Step 4: In an analogous manner to EXAMPLE 5, (1*S*,2*R*)-1-(3-fluorophenyl)-1-[3-(2-fluorophenyl)-1*H*-indol-1-yl]-3-(methylamino)propan-2-ol hydrochloride was prepared from (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-fluoro-phenyl)-3-[3-(2-fluorophenyl)-indol-1-yl]-2-hydroxy-propyl ester and methylamine (2N solution in methanol). MS (ES) *m/z* 393.1.

[0588] EXAMPLE 115: (1*S*,2*R*)-1-[3-(3,4-dichlorophenyl)-1*H*-indol-1-yl]-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride



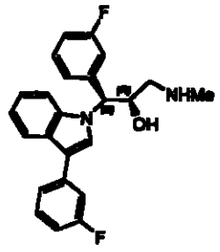
[0589] In an analogous manner to EXAMPLE 114, step 2, (2S,3S)-3-(3,4-dichlorophenyl)-3-{3-[2-fluorophenyl]-1H-indol-1-yl}propane-1,2-diol was prepared

from (2*S*,3*S*)-3-(3-fluorophenyl)-3-(3-iodo-1*H*-indol-1-yl)propane-1,2-diol (EXAMPLE 114, step 1) and 3,4-diclorobenzene boronic acid.

[0590] In an analogous manner to EXAMPLE 1, step 2 (2S,3S)-toluene-4-sulfonic acid 3-[3-(3,4-dichloro-phenyl)-indol-1-yl]-3-(3-fluorophenyl)-2-hydroxy-propyl ester was prepared from (2S,3S)-3-[3-(3,4-Dichloro-phenyl)-indol-1-yl]-3-(3-fluoro-phenyl)-propane-1,2-diol.

[0591] In an analogous manner to EXAMPLE 5, (1*S*,2*R*)-1-[3-(3,4-dichlorophenyl)-1*H*-indol-1-yl]-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride was prepared from (2S,3S)-toluene-4-sulfonic acid 3-[3-(3,4-dichloro-phenyl)-indol-1-yl]-3-(3-fluoro-phenyl)-2-hydroxy-propyl ester and methylamine (2N solution in methanol). MS (ES) *m/z* 443.0.

[0592] EXAMPLE 116: (1*S*,2*R*)-1-(3-fluorophenyl)-1-[3-(3-fluorophenyl)-1*H*-indol-1-yl]-3-(methylamino)propan-2-ol hydrochloride

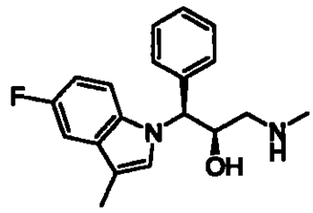


[0593] In an analogous manner to EXAMPLE 114, step 2, (2S,3S)-3-(3-fluorophenyl)-3-{3-[3-fluorophenyl]-1H-indol-1-yl}propane-1,2-diol was prepared from (2*S*,3*S*)-3-(3-fluorophenyl)-3-(3-iodo-1*H*-indol-1-yl)propane-1,2-diol (EXAMPLE 114, step 1) and 3-florobenzene boronic acid.

[0594] In an analogous manner to EXAMPLE 1, step 2 (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-3-[3-(3-fluorophenyl)-indol-1-yl]-2-hydroxy-propyl ester was prepared from (2S,3S)-3-(3-fluorophenyl)-3-{3-[3-fluorophenyl]-1H-indol-1-yl}propane-1,2-diol.

[0595] In an analogous manner to EXAMPLE 5, (1*S*,2*R*)-1-(3-fluorophenyl)-1-[3-(3-fluorophenyl)-1*H*-indol-1-yl]-3-(methylamino)propan-2-ol hydrochloride was prepared from (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-fluoro-phenyl)-3-[3-(3-fluorophenyl)-indol-1-yl]-2-hydroxy-propyl ester and methylamine (2N solution in methanol). MS (ESI) *m/z* 393.

[0596] EXAMPLE 117: (1*S*,2*R*)-1-(5-fluoro-3-methyl-1*H*-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride



[0597] Step 1: To a mixture of 4-fluoro-phenylamine (9 g, 81 mmol), concentrated hydrochloric acid (20.4 mL), and water (35.1 mL) was added sodium nitrite (6.3 g, 89.1 mmol) dissolved in water (7.8 mL). In a separate flask ethyl 2-ethylacetoacetate (14.4 g, 89.1 mmol) in ethanol (63.6 mL) at 0°C was treated with potassium hydroxide (5.1 g, 89.1 mmol) in water (7.5 mL) and ice and the above solution added. The pH of the reaction was adjusted to 5-6 and the reaction stirred at 0°C for 3 hours and then stored in the freezer overnight. The reaction was then extracted with ethyl acetate (100 mL) and the organics washed with saturated brine solution (100 mL), dried with anhydrous magnesium sulfate. Most of the solvent was removed *in vacuo* before it was added dropwise to a 14.5% ethanolic solution of hydrochloric acid (70 mL) at 78°C. Heating was continued for 2 hours. The solvent was removed *in vacuo* and the residue treated with dichloromethane (300 mL) and water (100 mL). The organic layer was washed with saturated sodium chloride (200 mL), dried over sodium sulfate and concentrated *in vacuo*. Purification on a short wash column (silica gel, 25% ethyl acetate/hexane) gave ethyl 5-fluoro-3-methyl-1H-indole-2-carboxylate as a white solid. MS (ES) *m/z* 220.0

[0598] Step 2: Ethyl 5-fluoro-3-methyl-1H-indole-2-carboxylate (8.3 g, 37.5 mmol) and potassium hydroxide (6.3 g, 112.5 mmol) in a mixture of ethanol (20 mL) and

water (15 mL) was heated at reflux for 1 hour . The volume was reduced to 10 mL under reduced pressure and the solution brought to an acidic pH with a 3N aqueous solution of hydrochloric acid. The resulting precipitate was filtered, washed with water (100 mL) and dried *in vacuo* at 80°C overnight to afford 5-fluoro-3-methyl-1H-indole-2-carboxylic acid as a white solid. MS (ES) *m/z* 192.0

[0599] Step 3; 5-fluoro-3-methyl-1H-indole-2-carboxylic acid (8.49 g, 43.9 mmol) and copper metal (0.35 g, 5.5 mmol) in distilled quinoline (22 mL) was heated to reflux for 3 hours. The copper powder was filtered off and the filtrate was brought to pH 3 at 0°C with a 6N aqueous solution of hydrochloric acid. The solution was extracted with ether (200 mL) and the organics washed with saturated sodium chloride (200 mL), dried over magnesium sulfate and concentrated *in vacuo* to give 5-fluoro-3-methyl-1H-indole as a brown solid. MS (ES) *m/z* 150.0.

[0600] Step 4: To a solution of diisopropyl D-tartrate (6 mL, 28 mmol) in methylene chloride (800 mL) at – 10°C under nitrogen was added 4A molecular sieves (15g), titanium isopropoxide (5.9 mL, 20 mmol), and cinnamyl alcohol (27g, 200 mmol). The mixture was allowed to age for 40 minutes at – 10°C, after which time it was cooled to –20°C, and treated in a dropwise fashion with a solution of *tert*-butyl hydroperoxide (TBHP, ~450 mmol) in isooctane. After 18 hours at –30 to -15°C, the reaction mixture was treated with a 30% aqueous solution of sodium hydroxide (5 mL) and diethyl ether (100 mL). The cold bath was removed and the mixture was allowed to warm to ~ 10°C. Magnesium sulfate (anhydrous, 15 g) was added and the mixture was stirred for 20 minutes. After the solids settled, the solution was filtered through a pad of silica gel, and washed with ether (50 mL). The filtrate was concentrated *in vacuo* and toluene was added to azeotropically remove the unreacted TBHP. The residue was then purified using a silica gel column (hexane:ethyl acetate/3:1) and the purified product was crystallized from hexane/ethyl acetate to yield [(2R,3R)-3-phenyloxiran-2-yl]methanol as white crystal (18g, 60%, 98.2%ee). MS (ESI) *m/z* 151.

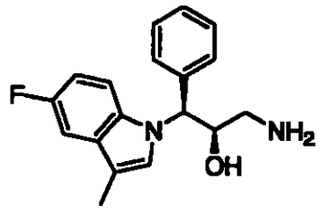
[0601] Step 5: A mixture of 5-fluoro-3-methyl-1H-indole (2.91 g, 19.5 mmol) and potassium hydride 50% dispersion in mineral oil (2.8 g, 35.1 mmol) in

dichloromethane (40 mL) was stirred for 10 minutes under nitrogen at room temperature. A solution of [(2R,3R)-3-phenyloxiran-2-yl]methanol (2.0 g, 13.0 mmol) and titanium isopropoxide (4.3 mL, 14.3 mmol) in dichloromethane (10 mL) was then added and the mixture was stirred at room temperature for 12 hours. After disappearance of the epoxide, the mixture was partitioned between a 1N aqueous solution of hydrochloric acid (50 mL) and ethyl acetate (50 mL). The organic layer was separated, washed with saturated sodium bicarbonate (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified via Biotage chromatography (FlasH40i, silica, 60% ethyl acetate/hexane) to give (2*S*,3*S*)-3-(5-fluoro-3-methyl-1*H*-indol-1-yl)-3-phenylpropane-1,2-diol. MS (ESI) *m/z* 300

[0602] Step 6: A solution of (2*S*,3*S*)-3-(5-fluoro-3-methyl-1*H*-indol-1-yl)-3-phenylpropane-1,2-diol (1.03 g, 3.4 mmol) and p-toluenesulfonyl chloride (0.78 g, 4.1 mmol) in anhydrous pyridine(11 ml) was stirred at room temperature under nitrogen for 12 hours. The reaction was poured into a 1N aqueous solution of hydrochloric acid (50 mL) and extracted with ethyl acetate (50 mL). The organics were dried over anhydrous sodium sulfate, filtered, and concentrated to give (2S,3S)-toluene-4-sulfonic acid 3-(5-fluoro-3-methyl-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester. The product was used in the next step without further purification. To a solution of toluene-4-sulfonic acid 3-(5-fluoro-3-methyl-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester (1.6 g, 3.4 mmol) in methanol (10 mL) was added a 2N solution of methylamine in methanol (8.6 mL, 17 mmol) and the reaction stirred for 12 hours. Upon completion, the reaction was partitioned between saturated sodium bicarbonate (50 mL) and ethyl acetate (50 mL). The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified via Biotage chromatography (FlasH40I, silica, 20% MeOH/dichloromethane) to give (1*S*,2*R*)-1-(5-fluoro-3-methyl-1*H*-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol as a clear oil. The free base was dissolved in a minimum amount of ethanol and treated with a 2N ethereal solution of hydrochloric acid and stirred for 1 hour . The ethanol was removed *in vacuo* and the clear oil was triturated with ether/dichloromethane to give (1*S*,2*R*)-1-(5-fluoro-3-methyl-1*H*-indol-

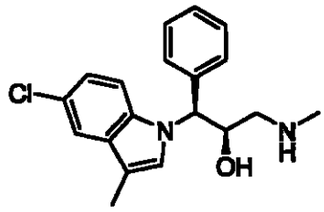
1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride as a white solid. MS (ESI) *m/z* 313

[0603] EXAMPLE 118: (1*S*R,2*R*S)-3-amino-1-(5-fluoro-3-methyl-1*H*-indol-1-yl)-1-phenylpropan-2-ol hydrochloride



[0604] To a solution of (2S,3S)-toluene-4-sulfonic acid 3-(5-fluoro-3-methyl-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester (Intermediate in EXAMPLE 117, step 6, 0.15 g, .33 mmol) in methanol (10 mL) was added concentrated ammonium hydroxide (20 mL), and the reaction was stirred for 12 hours. Upon completion, the reaction was partitioned between water (25 mL) and ethyl acetate (25 mL). The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified via Biotage chromatography (FlasH40i, silica, 25% MeOH/dichloromethane) to give (1*S*R,2*R*S)-3-amino-1-(5-fluoro-3-methyl-1*H*-indol-1-yl)-1-phenylpropan-2-ol as a clear oil. The free base was dissolved in a minimum amount of ethanol and treated with a 4N solution of hydrochloric acid in dioxane and stirred for 1 hour s. The ethanol was removed *in vacuo* and the clear oil was triturated with ether/dichloromethane to give (1*S*R,2*R*S)-3-amino-1-(5-fluoro-3-methyl-1*H*-indol-1-yl)-1-phenylpropan-2-ol hydrochloride as a white solid. MS (ES) *m/z* 299.0

EXAMPLE 119: (1*S*,2*R*)-1-(5-chloro-3-methyl-1*H*-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride



[0605] In an analogous manner to EXAMPLE 117, step 1 ethyl 5-chloro-3-methyl-1*H*-indole-2-carboxylate was prepared from 4-chloro-phenylamine. MS (ES) *m/z* 235.9

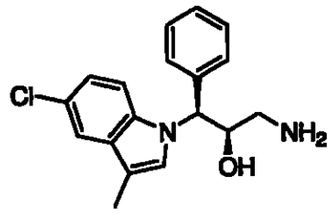
[0606] In an analogous manner to EXAMPLE 117, step 2 5-chloro-3-methyl-1*H*-indole-2-carboxylic acid was prepared from ethyl 5-chloro-3-methyl-1*H*-indole-2-carboxylate. MS (ESI) *m/z* 208

[0607] In an analogous manner to EXAMPLE 117, step 3 5-chloro-3-methyl-1*H*-indole was prepared from 5-chloro-3-methyl-1*H*-indole-2-carboxylic acid. MS (ESI) *m/z* 166.

[0608] In an analogous manner to EXAMPLE 117, step 5 (2*S*,3*S*)-3-(5-chloro-3-methyl-1*H*-indol-1-yl)-3-phenylpropane-1,2-diol was prepared from 5-chloro-3-methyl-1*H*-indole and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4). MS (ES) *m/z* 316.0

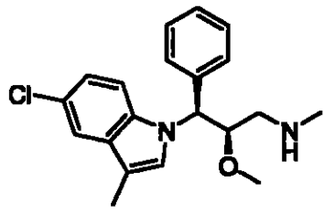
[0609] In an analogous manner to EXAMPLE 117, step 6 (1*S*,2*R*)-1-(5-chloro-3-methyl-1*H*-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2*S*,3*S*)-3-(5-chloro-3-methyl-1*H*-indol-1-yl)-3-phenylpropane-1,2-diol. MS (ES) *m/z* 329.0

[0610] EXAMPLE 120: (1*S*,2*R*)-3-amino-1-(5-chloro-3-methyl-1*H*-indol-1-yl)-1-phenylpropan-2-ol hydrochloride



[0611] In an analogous manner to EXAMPLE 118, (1*S*,2*R*)-3-amino-1-(5-chloro-3-methyl-1*H*-indol-1-yl)-1-phenylpropan-2-ol was prepared from (2*S*,3*S*)-3-(5-chloro-3-methyl-1*H*-indol-1-yl)-3-phenylpropane-1,2-diol (EXAMPLE 119, step 4). MS (ES) *m/z* 315.1

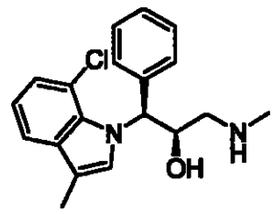
[0612] EXAMPLE 121: [(2*R*,3*S*)-3-(5-chloro-3-methyl-1*H*-indol-1-yl)-2-methoxy-3-phenylpropyl]methylamine



[0613] A mixture of (2S,3S)-toluene-4-sulfonic acid 3-(5-chloro-3-methyl-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester (Intermediate in EXAMPLE 119, step 6, 0.52 g, 1.1 mmol), trifluoro-methanesulfonic acid methyl ester (0.6 mL, 5.5 mmol), and 2,6-di-tert-butyl-4-methyl-pyridine (1.1 g, 5.5 mmol) was heated at reflux in dichloromethane (20 mL) for 2 hours. The reaction was partitioned between ethyl acetate (25 mL) and a 1N aqueous solution of hydrochloric acid (25 mL). The organics were separated and washed with a saturated aqueous solution of sodium bicarbonate (25 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude product was purified via flash column chromatography (silica, 20% ethyl acetate in hexane) to give (2S,3S)-toluene-4-sulfonic acid 3-(5-chloro-3-methyl-indol-1-yl)-2-methoxy-3-phenyl-propyl ester. To a solution of toluene-4-sulfonic acid 3-(5-chloro-3-methyl-indol-1-yl)-2-methoxy-3-phenyl-propyl ester (0.13 g, 0.27 mmol) in methanol (10 mL) was added a 2N solution of methylamine in methanol (1.4 mL, 2.7 mmol) and the reaction heated in a sealed tube for 12 hours. Upon completion, the reaction was partitioned between a saturated aqueous solution sodium bicarbonate (25 mL) and dichloromethane (25 mL). The organics were separated and removed *in vacuo*. The residue was taken up in diethyl ether (25 mL) and washed with a 1N aqueous solution of hydrochloric acid (25 mL). The aqueous layer was basified to pH 8 with a saturated aqueous solution of sodium bicarbonate (50 mL). The product was extracted with diethyl ether (25 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The free base was dissolved in a

minimum amount of ethanol and treated with a 4N solution of hydrochloric acid in dioxane and stirred for 1 hour s. The ethanol was removed *in vacuo* to give [(2*R*,3*S*)-3-(5-chloro-3-methyl-1*H*-indol-1-yl)-2-methoxy-3-phenylpropyl]methylamine as a yellow oil. MS (ESI) *m/z* 343

[0614] EXAMPLE 122: (1*S*,2*R*)-1-(7-chloro-3-methyl-1*H*-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride



[0615] In an analogous manner to EXAMPLE 117, step 1 ethyl 7-chloro-3-methyl-1*H*-indole-2-carboxylate was prepared from 2-chloro-phenylamine. MS (ESI) *m/z* 238

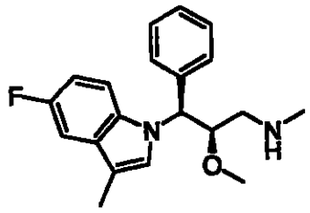
[0616] In an analogous manner to EXAMPLE 117, step 2 7-chloro-3-methyl-1*H*-indole-2-carboxylic acid was prepared from ethyl 7-chloro-3-methyl-1*H*-indole-2-carboxylate. MS (ES) *m/z* 208.0

[0617] In an analogous manner to EXAMPLE 117, step 3 7-chloro-3-methyl-1*H*-indole was prepared from 7-chloro-3-methyl-1*H*-indole-2-carboxylic acid.

[0618] In an analogous manner to EXAMPLE 117, step 5 (2*S*,3*S*)-3-(7-chloro-3-methyl-1*H*-indol-1-yl)-3-phenylpropane-1,2-diol was prepared from 7-chloro-3-methyl-1*H*-indole and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4). MS (ESI) *m/z* 316; MS (ESI) *m/z* 314.

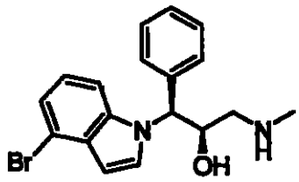
[0619] In an analogous manner to EXAMPLE 117, step 6 (1*S*,2*R*)-1-(7-chloro-3-methyl-1*H*-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2*S*,3*S*)-3-(7-chloro-3-methyl-1*H*-indol-1-yl)-3-phenylpropane-1,2-diol. MS (ESI) *m/z* 329

[0620] EXAMPLE 123: [(2*R*,3*S*)-3-(5-fluoro-3-methyl-1*H*-indol-1-yl)-2-methoxy-3-phenylpropyl]methylamine hydrochloride



[0621] In an analogous manner to EXAMPLE 121, [(2*R*,3*S*)-3-(5-fluoro-3-methyl-1*H*-indol-1-yl)-2-methoxy-3-phenylpropyl]methylamine hydrochloride was prepared (2S,3S)-toluene-4-sulfonic acid 3-(5-fluoro-3-methyl-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester (intermediate in EXAMPLE 117, step 6). MS (ESI) *m/z* 327.

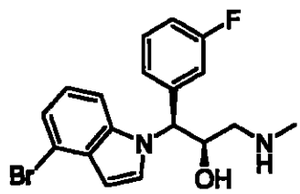
[0622] EXAMPLE 124: (1*S*,2*R*)-1-(4-bromo-1*H*-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride



[0623] In an analogous manner to EXAMPLE 117, step 5 (2*S*,3*S*)-3-(4-bromo-1*H*-indol-1-yl)-3-phenylpropane-1,2-diol was prepared from 4-bromo-1*H*-indole and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4). MS (ESI) *m/z* 346.

[0624] In an analogous manner to EXAMPLE 117, step 6 (1*S*,2*R*)-1-(4-bromo-1*H*-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2*S*,3*S*)-3-(4-bromo-1*H*-indol-1-yl)-3-phenylpropane-1,2-diol. MS (ESI) *m/z* 359.

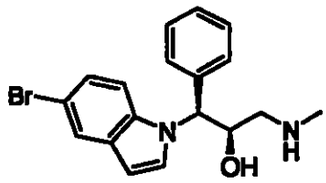
[0625] EXAMPLE 125: (1*S*,2*R*)-1-(4-bromo-1*H*-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride



[0626] In an analogous manner to EXAMPLE 117, step 5 (2*S*,3*S*)-3-(4-bromo-1*H*-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol was prepared from 4-bromo-1*H*-indole and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47 step 3). MS (ESI) *m/z* 364.

[0627] In an analogous manner to EXAMPLE 117, step 6 (1*S*,2*R*)-1-(4-bromo-1*H*-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride was prepared from (2*S*,3*S*)-3-(4-bromo-1*H*-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol. MS (ESI) *m/z* 377.

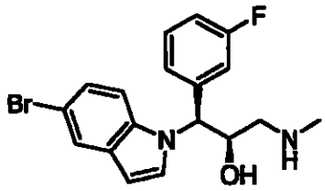
[0628] EXAMPLE 126: (1*S*,2*R*)-1-(5-bromo-1*H*-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride



[0629] In an analogous manner to EXAMPLE 117, step 5 (2*S*,3*S*)-3-(5-bromo-1*H*-indol-1-yl)-3-phenylpropane-1,2-diol was prepared from 5-bromo-1*H*-indole and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4). MS (ESI) *m/z* 346.

[0630] In an analogous manner to EXAMPLE 117, step 6 (1*S*,2*R*)-1-(5-bromo-1*H*-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2*S*,3*S*)-3-(5-bromo-1*H*-indol-1-yl)-3-phenylpropane-1,2-diol. MS (ESI) *m/z* 359.

[0631] EXAMPLE 127: (1*S*,2*R*)-1-(5-bromo-1*H*-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride

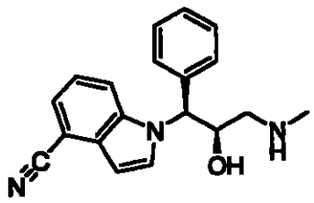


[0632] In an analogous manner to EXAMPLE 117, step 5 (2*S*,3*S*)-3-(5-bromo-1*H*-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol was prepared from 5-bromo-1*H*-indole

and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47 step 3). MS (ESI) *m/z* 364.

[0633] In an analogous manner to EXAMPLE 117, step 6 (1*S*,2*R*)-1-(5-bromo-1*H*-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride was prepared from (2*S*,3*S*)-3-(5-bromo-1*H*-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol. MS (ESI) *m/z* 377.

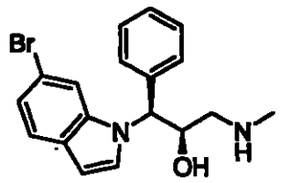
[0634] EXAMPLE 128: 1-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1*H*-indole-4-carbonitrile hydrochloride



[0635] In an analogous manner to EXAMPLE 117, step 5 1-(2,3-dihydroxy-1-phenyl-propyl)-1H-indole-4-carbonitrile was prepared from 1H-Indole-4-carbonitrile and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4).

[0636] In an analogous manner to EXAMPLE 117, step 6 1-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1*H*-indole-4-carbonitrile hydrochloride was prepared from 1-(2,3-dihydroxy-1-phenyl-propyl)-1H-indole-4-carbonitrile. MS (ESI) *m/z* 306.

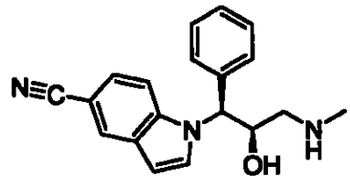
[0637] EXAMPLE 129: (1*S*,2*R*)-1-(6-bromo-1*H*-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride



[0638] In an analogous manner to EXAMPLE 117, step 5 3-(6-bromo-indol-1-yl)-3-phenyl-propane-1,2-diol was prepared from 6-bromo-1H-indole and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4).

[0639] In an analogous manner to EXAMPLE 117, step 6 (1*S*,2*R*)-1-(6-bromo-1*H*-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from 3-(6-bromo-indol-1-yl)-3-phenyl-propane-1,2-diol. MS (ESI) *m/z* 359

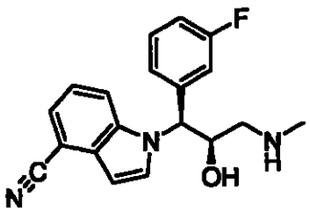
[0640] EXAMPLE 130: 1-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1*H*-indole-5-carbonitrile hydrochloride



[0641] In an analogous manner to EXAMPLE 117, step 5 1-[(1*S*,2*S*)-2,3-dihydroxy-1-phenylpropyl]-1*H*-indole-5-carbonitrile was prepared from 1H-Indole-5-carbonitrile and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4). MS (ESI) *m/z* 293

[0642] In an analogous manner to EXAMPLE 117, step 6 1-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1*H*-indole-5-carbonitrile hydrochloride was prepared from 1-[(1*S*,2*S*)-2,3-dihydroxy-1-phenylpropyl]-1*H*-indole-5-carbonitrile. MS (ES) *m/z* 306.1.

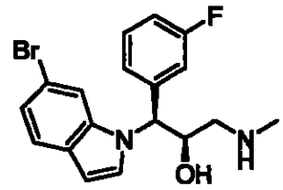
[0643] EXAMPLE 131: 1-[(1*S*,2*R*)-1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-1*H*-indole-4-carbonitrile hydrochloride



[0644] In an analogous manner to EXAMPLE 117, step 5 1-[1-(3-fluoro-phenyl)-2,3-dihydroxy-propyl]-1H-Indole-4-carbonitrile was prepared from 1H-Indole-4-carbonitrile and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47 step 3).

[0645] In an analogous manner to EXAMPLE 117, step 6 1-[(1*S*,2*R*)-1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-1*H*-indole-4-carbonitrile hydrochloride was prepared from 1-[1-(3-fluoro-phenyl)-2,3-dihydroxy-propyl]-1H-indole-4-carbonitrile. MS (ES) *m/z* 324.2.

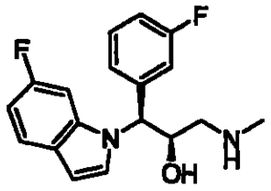
[0646] EXAMPLE 132: (1*S*,2*R*)-1-(6-bromo-1*H*-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride



[0647] In an analogous manner to EXAMPLE 117, step 5 3-(6-bromo-indol-1-yl)-3-(3-fluoro-phenyl)-propane-1,2-diol was prepared from 6-bromo-1H-Indole and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47 step 3).

[0648] In an analogous manner to EXAMPLE 117, step 6 (1*S*,2*R*)-1-(6-bromo-1*H*-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride was prepared from 3-(6-bromo-indol-1-yl)-3-(3-fluoro-phenyl)-propane-1,2-diol. MS (ES) *m/z* 377.1.

[0649] EXAMPLE 133: (1*S*,2*R*)-1-(6-fluoro-1*H*-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride

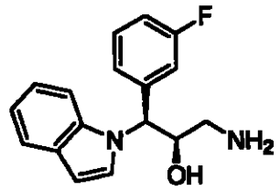


[0650] In an analogous manner to EXAMPLE 117, step 5 (2*S*,3*S*)-3-(6-fluoro-1*H*-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol was prepared from 6-fluoro-1H-indole and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47 step 3). MS (ESI) *m/z* 304.

[0651] In an analogous manner to EXAMPLE 117, step 6 (1*S*,2*R*)-1-(6-fluoro-1*H*-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride was

prepared from (2*S*,3*S*)-3-(6-fluoro-1*H*-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol. MS (ES) *m/z* 317.1.

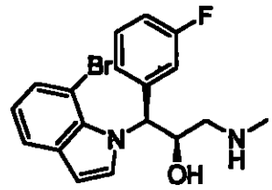
[0652] EXAMPLE 134: (1*S*,2*R*)-3-amino-1-(3-fluorophenyl)-1-(1*H*-indol-1-yl)propan-2-ol hydrochloride



[0653] In an analogous manner to EXAMPLE 117, step 5 3-(3-fluoro-phenyl)-3-indol-1-yl-propane-1,2-diol was prepared from 1H-indole and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, step 3).

[0654] In an analogous manner to EXAMPLE 117, step 6 (1*S*,2*R*)-3-amino-1-(3-fluorophenyl)-1-(1*H*-indol-1-yl)propan-2-ol hydrochloride was prepared from 3-(3-fluoro-phenyl)-3-indol-1-yl-propane-1,2-diol and *para*-toluenesulfonic acid followed by concentrated ammonium hydroxide. MS (ES) *m/z* 285.2.

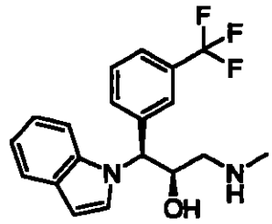
[0655] EXAMPLE 135: (1*S*,2*R*)-1-(7-bromo-1*H*-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride



[0656] In an analogous manner to EXAMPLE 117, step 5 3-(7-bromo-indol-1-yl)-3-(3-fluoro-phenyl)-propane-1,2-diol was prepared from 7-bromo-1H-indole and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47 step 3).

[0657] In an analogous manner to EXAMPLE 117, step 6 (1*S*,2*R*)-1-(7-bromo-1*H*-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride was prepared from 3-(7-bromo-indol-1-yl)-3-(3-fluoro-phenyl)-propane-1,2-diol. MS (ES) *m/z* 377.

[0658] EXAMPLE 136: (1*S*,2*R*)-1-(1*H*-indol-1-yl)-3-(methylamino)-1-[3-(trifluoromethyl)phenyl]propan-2-ol hydrochloride



[0659] In an analogous manner to EXAMPLE 47, step 1 cinnamic acid, m-(trifluoromethyl)-, methyl ester was prepared from 3-(3-trifluoromethyl-phenyl)-acrylic acid. MS (ES) *m/z* 231.1

[0660] In an analogous manner to EXAMPLE 47, step 2 (2E)-3-[3-[trifluoromethyl)phenyl]prop-2-en-1-ol was prepared from cinnamic acid, m-(trifluoromethyl)-, methyl ester. MS (ES) *m/z* 185.1

[0661] In an analogous manner to EXAMPLE 47, step 3 {(2*R*,3*R*)-3-[3-(trifluoromethyl)phenyl]oxiran-2-yl}methanol was prepared from (2E)-3-[3-[trifluoromethyl)phenyl]prop-2-en-1-ol. MS (ES) *m/z* 217.3

[0662] In an analogous manner to EXAMPLE 47, step 4 (2*S*,3*S*)-3-(2,3-dihydro-1*H*-indol-1-yl)-3-[3-(trifluoromethyl)phenyl]propane-1,2-diol was prepared from indoline and {(2*R*,3*R*)-3-[3-(trifluoromethyl)phenyl]oxiran-2-yl}methanol. MS (ESI) *m/z* 338.

[0663] In an analogous manner to EXAMPLE 47, step 5 (2*S*,3*S*)-3-(1*H*-indol-1-yl)-3-[3-(trifluoromethyl)phenyl]propane-1,2-diol was prepared from (2*S*,3*S*)-3-(2,3-dihydro-1*H*-indol-1-yl)-3-[3-(trifluoromethyl)phenyl]propane-1,2-diol. MS (ESI) *m/z* 336.

[0664] In an analogous manner to EXAMPLE 117, step 6 (1*S*,2*R*)-1-(1*H*-indol-1-yl)-3-(methylamino)-1-[3-(trifluoromethyl)phenyl]propan-2-ol hydrochloride was

prepared from (2*S*,3*S*)-3-(1*H*-indol-1-yl)-3-[3-(trifluoromethyl)ph nyl]propane-1,2-diol. MS (ES) *m/z* 349.1.

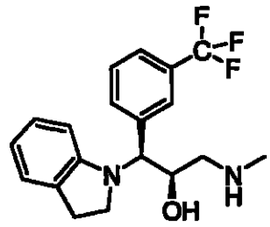
[0665] EXAMPLE 137: (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-spiro[cyclohexane-1,3'-indol]-1'(2'H)-ylpropan-2-ol hydrochloride



[0666] In an analogous manner to EXAMPLE 47, step 4, (2S,3S)-3-(3-fluorophenyl)-3-spiro[cyclohexane-1,3'-indol]-1'(2'H)-ylpropane-1,2-diol was prepared from 1',2'-dihydrospiro[cyclohexane-1,3'-indole][15] and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, step 3) as a white solid. MS (ES) *m/z* 356.2 ([M+H]$^+$); HRMS: calcd for $C_{22}H_{26}FNO_2$ + H^+, 356.2020; found (ESI, [M+H]$^+$), 356.2031.

[0667] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-spiro[cyclohexane-1,3'-indol]-1'(2'H)-ylpropan-2-ol hydrochloride was prepared from (2S,3S)-3-(3-fluorophenyl)-3-spiro[cyclohexane-1,3'-indol]-1'(2'H)-ylpropane-1,2-diol as a white powder. MS (ES) *m/z* 369.2 ([M+H]$^+$); HRMS: calcd for $C_{23}H_{29}FN_2O$ + H^+, 369.2337; found (ESI, [M+H]$^+$), 369.2332.

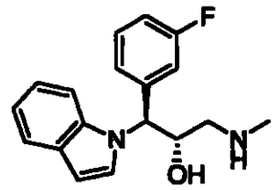
[0668] EXAMPLE 138: (1*S*,2*R*)-1-(2,3-dihydro-1*H*-indol-1-yl)-3-(methylamino)-1-[3-(trifluoromethyl)phenyl]propan-2-ol hydrochloride



[15]Kucerovy, A.; Hathaway, J. S.; Mattner, P. G.; Repic, O. *Synth. Commun.* 1992, 22, 729-733.

[0669] In an analogous manner to EXAMPLE 117, step 6 (1*S*,2*R*)-1-(2,3-dihydro-1*H*-indol-1-yl)-3-(methylamino)-1-[3-(trifluoromethyl)phenyl]propan-2-ol was prepared from (2*S*,3*S*)-3-(2,3-dihydro-1*H*-indol-1-yl)-3-[3-(trifluoromethyl)phenyl]propane-1,2-diol (EXAMPLE 136, step 4). MS (ES) *m/z* 351.1.

[0670] EXAMPLE 139: (1*S*,2*S*)-1-(3-fluorophenyl)-1-(1*H*-indol-1-yl)-3-(methylamino)propan-2-ol hydrochloride



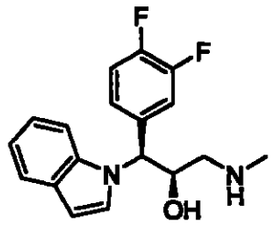
[0671] In an analogous manner to EXAMPLE 16, step 2 (2*S*,3*S*)-3-(3-fluorophenyl)-2-hydroxy-3-(1*H*-indol-1-yl)propyl 4-nitrobenzoate was prepared from 3-(3-fluoro-phenyl)-3-indol-1-yl-propane-1,2-diol (EXAMPLE 134, step 1). MS (ES) *m/z* 435.0.

[0672] In an analogous manner to EXAMPLE 16, step 3 4-nitro-benzoic acid 3-(3-fluoro-phenyl)-3-indol-1-yl-2-methanesulfonyloxy-propyl ester was prepared from (2*S*,3*S*)-3-(3-fluorophenyl)-2-hydroxy-3-(1*H*-indol-1-yl)propyl 4-nitrobenzoate.

[0673] In an analogous manner to EXAMPLE 16, step 4 1-{(*S*)-(3-fluorophenyl)[(2*R*)-oxiran-2-yl]methyl}-1*H*-indole was prepared from 4-nitro-benzoic acid 3-(3-fluoro-phenyl)-3-indol-1-yl-2-methanesulfonyloxy-propyl ester. MS (ESI) *m/z* 338.

[0674] In an analogous manner to EXAMPLE 16, step 5 (1*S*,2*S*)-1-(3-fluorophenyl)-1-(1*H*-indol-1-yl)-3-(methylamino)propan-2-ol hydrochloride was prepared from 1-{(*S*)-(3-fluorophenyl)[(2*R*)-oxiran-2-yl]methyl}-1*H*-indole. MS (ESI) *m/z* 299.

[0675] EXAMPLE 140: (1*S*,2*R*)-1-(3,4-difluorophenyl)-1-(1*H*-indol-1-yl)-3-(methylamino)propan-2-ol hydrochloride



[0676] In an analogous manner to EXAMPLE 47, step 1 cinnamic acid, 3,4-difluoro-, methyl ester, (E) was prepared from 3-(3,4-difluoro-phenyl)-acrylic acid. MS (ES) m/z 199.1

[0677] In an analogous manner to EXAMPLE 47, step 2 (2E)-3-(3,4-difluorophenyl)prop-2-en-1-ol was prepared from cinnamic acid, 3,4-difluoro-, methyl ester, (E). MS (ES) m/z 153.1

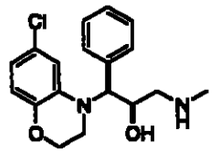
[0678] In an analogous manner to EXAMPLE 47, step 3 [(2R,3R)-3-(3,4-difluorophenyl)oxiran-2-yl]methanol was prepared from (2E)-3-(3,4-difluorophenyl)prop-2-en-1-ol. MS (ES) m/z 185.1

[0679] In an analogous manner to EXAMPLE 47, step 4 (2*S*,3*S*)-3-(3,4-difluorophenyl)-3-(2,3-dihydro-1*H*-indol-1-yl)propane-1,2-diol was prepared from indoline and [(2*R*,3*R*)-3-(3,4-difluorophenyl)oxiran-2-yl]methanol. MS (ES) *m/z* 306.1.

[0680] In an analogous manner to EXAMPLE 47, step 5 (2*S*,3*S*)-3-(3,4-difluorophenyl)-3-(1*H*-indol-1-yl)propane-1,2-diol was prepared from (2*S*,3*S*)-3-(3,4-difluorophenyl)-3-(2,3-dihydro-1*H*-indol-1-yl)propane-1,2-diol. MS (ESI) *m/z* 304.

[0681] In an analogous manner to EXAMPLE 117, step 6 (1*S*,2*R*)-1-(3,4-difluorophenyl)-1-(1*H*-indol-1-yl)-3-(methylamino)propan-2-ol hydrochloride was prepared from (2*S*,3*S*)-3-(3,4-difluorophenyl)-3-(1*H*-indol-1-yl)propane-1,2-diol. MS (ES) *m/z* 317.1.

[0682] EXAMPLE 141: (1RS,2SR)-1-(6-chloro-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride

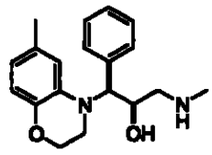


[0683] In an analogous manner to EXAMPLE 33, step 1, ethyl (2RS;3RS)-3-(6-chloro-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-2-hydroxy-3-phenylpropanoate was prepared from 6-chloro-3,4-dihydro-2H-1,4-benzoxazine (EXAMPLE 88, step 1) and *trans*-ethyl-3-phenylglycidate as a viscous, yellow liquid. MS (ESI) *m/z* 362.0 ($[M+H]^+$); HRMS: calcd for $C_{19}H_{20}ClNO_4$ + H^+, 362.1154; found (ESI, $[M+H]^+$), 362.1150.

[0684] In an analogous manner to EXAMPLE 33, step 2, (2RS,3RS)-3-(6-chloro-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-2-hydroxy-N-methyl-3-phenylpropanamide was prepared from ethyl (2RS,3RS)-3-(6-chloro-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-2-hydroxy-3-phenylpropanoate as white needles. MS (ESI) *m/z* 344.9 ($[M-H]^-$); HRMS: calcd for $C_{18}H_{19}ClN_2O_3$ + H^+, 347.1157; found (ESI, $[M+H]^+$), 347.1150.

[0685] In an analogous manner to EXAMPLE 33, step 3, (1RS,2SR)-1-(6-chloro-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2RS,3RS)-3-(6-chloro-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-2-hydroxy-N-methyl-3-phenylpropanamide as a white powder. MS (ESI) *m/z* 333.1 ($[M+H]^+$); HRMS: calcd for $C_{18}H_{21}ClN_2O_2$ + H^+, 333.1370; found (ESI, $[M+H]^+$), 333.1381.

[0686] EXAMPLE 142: (1RS,2SR)-3-(methylamino)-1-(6-methyl-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-1-phenylpropan-2-ol hydrochloride



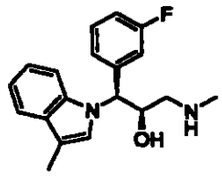
[0687] In an analogous manner to EXAMPLE 165, step 1, 6-methyl-3,4-dihydro-2H-1,4-benzoxazine was prepared from 6-methyl-2H-1,4-benzoxazin-3(4H)-one as a yellow oil. MS (ES) *m/z* 150.0 ($[M+H]^+$); HRMS: calcd for $C_9H_{11}NO + H^+$, 150.0919; found (ESI, $[M+H]^+$), 150.0924.

[0688] In an analogous manner to EXAMPLE 33, step 1, ethyl (2RS,3RS)-2-hydroxy-3-(6-methyl-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-phenylpropanoate was prepared from 6-methyl-3,4-dihydro-2H-1,4-benzoxazine and *trans*-ethyl-3-phenylglycidate as a viscous, yellow liquid. MS (ESI) *m/z* 342.0 ($[M+H]^+$); HRMS: calcd for $C_{20}H_{23}NO_4 + H^+$, 342.1700; found (ESI, $[M+H]^+$), 342.1683.

[0689] In an analogous manner to EXAMPLE 33, step 2, (2RS,3RS)-2-hydroxy-N-methyl-3-(6-methyl-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-phenylpropanamide was prepared from ethyl (2RS,3RS)-2-hydroxy-3-(6-methyl-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-phenylpropanoate as a white powder. MS (ESI) *m/z* 325.0 ($[M-H]^-$); HRMS: calcd for $C_{19}H_{22}N_2O_3 + H^+$, 327.1703; found (ESI, $[M+H]^+$), 327.1703.

[0690] In an analogous manner to EXAMPLE 33, step 3, (1RS,2SR)-3-(methylamino)-1-(6-methyl-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-1-phenylpropan-2-ol hydrochloride was prepared from (2RS,3RS)-2-hydroxy-N-methyl-3-(6-methyl-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-phenylpropanamide as a white powder. MS (ESI) *m/z* 313.0 ($[M+H]^+$); HRMS: calcd for $C_{19}H_{24}N_2O_2 + H^+$, 313.1911; found (ESI, $[M+H]^+$), 313.1908.

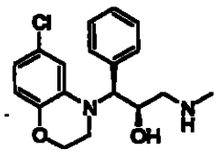
[0691] EXAMPLE 143: (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(3-methyl-1H-indol-1-yl)propan-2-ol hydrochloride



[0692] In an analogous manner to EXAMPLE 117, step 5, (2S,3S)-3-(3-fluorophenyl)-3-(3-methyl-1H-indol-1-yl)propane-1,2-diol was prepared from 3-methylindole and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, step 3) as a viscous, yellowish oil. MS (ES) *m/z* 300.0 ($[M+H]^+$); HRMS: calcd for $C_{18}H_{18}FNO_2 + H^+$, 300.1400; found (ESI, $[M+H]^+$), 300.1400.

[0693] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(3-methyl-1H-indol-1-yl)propan-2-ol hydrochloride was prepared from (2S,3S)-3-(3-fluorophenyl)-3-(3-methyl-1H-indol-1-yl)propane-1,2-diol as a white solid. MS (ES) *m/z* 313.0 ($[M+H]^+$); HRMS: calcd for $C_{19}H_{21}FN_2O + H^+$, 313.1711; found (ESI, $[M+H]^+$), 313.1713.

[0694] EXAMPLE 144: (1S,2R)-1-(6-chloro-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride

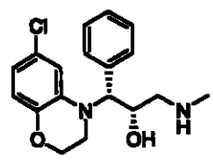


[0695] Step 1: Racemic (1RS,2SR)-1-(6-chloro-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-(methylamino)-1-phenylpropan-2-ol (EXAMPLE 141) was dissolved in methanol. The resulting solution was injected onto the Supercritical Fluid Chromatography instrument. The baseline resolved enantiomers, using the conditions described below, were collected. The enantiomeric purity of each enantiomer was determined under the same Supercritical Fluid Chromatography conditions using a Chiralpak AD-H 5u, 250 mm x 4.6 mm ID column at 2.0 mL/minutes flow rate using Analytical Supercritical Fluid Chromatography (Berger Instruments, Inc. Newark, DE USA).

SFC Instrument:	Berger MultiGram Prep SFC (Berger Instruments, Inc. Newark, DE 19702.
Column:	Chiralpak AD-H; 5u; 250mm L x 20mm ID (Chiral Technologies, Inc, Exton, PA, USA)
Column temperature:	35°C
SFC Modifier:	40% MeOH with 0.5% DEA
Flow rate:	50 mL/min
Outlet Pressure:	100 bar
Detector:	UV at 266 nm

[0696] Step 2: A solution of (1S,2R)-1-(6-chloro-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-(methylamino)-1-phenylpropan-2-ol, isolated as Peak 1, (58 mg, 0.17 mmol) in dichloromethane (3 mL) was treated with an ethereal solution of hydrochloric acid (1 M, 0.2 mL, 0.2 mmol). To the resulting solution was added hexane until white powder formed, which was collected, washed with hexane, and dried *in vacuo* to yield 62 mg (45%) of (1S,2R)-1-(6-chloro-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride. Chiral purity: > 99.9%. MS (ESI) *m/z* 333.0 ($[M+H]^+$); HRMS: calcd for $C_{18}H_{21}ClN_2O_2 + H^+$, 333.1370; found (ESI, $[M+H]^+$), 333.1372.

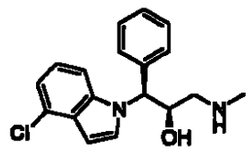
[0697] EXAMPLE 145: (1R,2S)-1-(6-chloro-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride



[0698] In an analogous manner to EXAMPLE 144, step 2, (1R,2S)-1-(6-chloro-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (1R,2S)-1-(6-chloro-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-(methylamino)-1-phenylpropan-2-ol which was isolated as Peak 2 of the chiral

separation (EXAMPLE 144, step 1). Chiral purity: > 99.9%. MS (ESI) *m/z* 333.0 ($[M+H]^+$); HRMS: calcd for $C_{18}H_{21}ClN_2O_2$ + H^+, 333.1370; found (ESI, $[M+H]^+$), 333.1374.

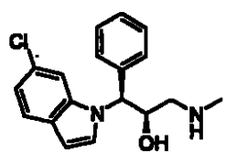
[0699] EXAMPLE 146: (1S,2R)-1-(4-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride



[0700] In an analogous manner to EXAMPLE 117, step 5, (2S,3S)-3-(4-chloro-1H-indol-1-yl)-3-phenylpropane-1,2-diol was prepared from 4-chloroindole and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4) as a viscous, yellowish oil. MS (ES) *m/z* 300.0 ($[M-H]^-$).

[0701] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(4-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2S,3S)-3-(4-chloro-1H-indol-1-yl)-3-phenylpropane-1,2-diol as a white powder. MS (ES) *m/z* 315.0 ($[M+H]^+$); HRMS: calcd for $C_{18}H_{19}ClN_2O$ + H^+, 315.1259; found (ESI, $[M+H]^+$), 315.1255.

[0702] EXAMPLE 147: (1S,2R)-1-(6-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride

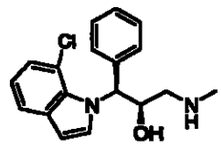


[0703] In an analogous manner to EXAMPLE 117, step 5, (2S,3S)-3-(6-chloro-1H-indol-1-yl)-3-phenylpropane-1,2-diol was prepared from 6-chloroindole and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4) as a viscous, colorless oil.

MS (ES) *m/z* 302.0 ([M+H]$^+$); HRMS: calcd for $C_{17}H_{16}ClNO_2$ + H^+, 302.0948; found (ESI, [M+H]$^+$), 302.0946.

[0704] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(6-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2S,3S)-3-(6-chloro-1H-indol-1-yl)-3-phenylpropane-1,2-diol as a white powder. MS (ES) *m/z* 315.0 ([M+H]$^+$); HRMS: calcd for $C_{18}H_{19}ClN_2O$ + H^+, 315.1259; found (ESI, [M+H]$^+$), 315.1263.

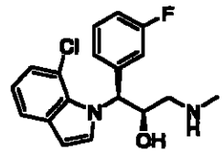
[0705] EXAMPLE 148: (1S,2R)-1-(7-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride



[0706] In an analogous manner to EXAMPLE 117, step 5, (2S,3S)-3-(7-chloro-1H-indol-1-yl)-3-phenylpropane-1,2-diol was prepared from 7-chloroindole and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4) as a viscous, colorless oil. MS (ES) *m/z* 302.0 ([M+H]$^+$); HRMS: calcd for $C_{17}H_{16}ClNO_2$ + H^+, 302.0948; found (ESI, [M+H]$^+$), 302.0949.

[0707] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(7-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2S,3S)-3-(7-chloro-1H-indol-1-yl)-3-phenylpropane-1,2-diol as a white powder. MS (ES) *m/z* 315.0 ([M+H]$^+$); HRMS: calcd for $C_{18}H_{19}ClN_2O$ + H^+, 315.1259; found (ESI, [M+H]$^+$), 315.1269.

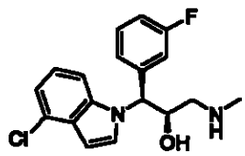
[0708] EXAMPLE 149: (1S,2R)-1-(7-chloro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride



[0709] In an analogous manner to EXAMPLE 117, step 5, (2S,3S)-3-(7-chloro-1H-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol was prepared from 7-chloroindole and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, step 3) as a viscous, colorless oil. MS (ES) *m/z* 320.0 ($[M+H]^+$); HRMS: calcd for $C_{17}H_{15}ClFNO_2$ + H^+, 320.0848; found (ESI, $[M+H]^+$), 320.0858.

[0710] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(7-chloro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride was prepared from (2S,3S)-3-(7-chloro-1H-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol as a white powder. MS (ES) *m/z* 333.0 ($[M+H]^+$); HRMS: calcd for $C_{18}H_{18}ClFN_2O$ + H^+, 333.1170; found (ESI, $[M+H]^+$), 333.1189.

[0711] EXAMPLE 150: (1S,2R)-1-(4-chloro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride

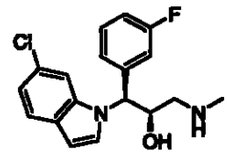


[0712] In an analogous manner to EXAMPLE 117, step 5, (2S,3S)-3-(4-chloro-1H-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol was prepared from 4-chloroindole and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, step 3) as a viscous, colorless oil. MS (ES) *m/z* 320.0 ($[M+H]^+$); HRMS: calcd for $C_{17}H_{15}ClFNO_2$ + H^+, 320.0848; found (ESI, $[M+H]^+$), 320.0856.

[0713] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(4-chloro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride was

prepared from (2S,3S)-3-(4-chloro-1H-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol as a white powder. MS (ES) *m/z* 333.2 ([M+H]$^+$); HRMS: calcd for $C_{18}H_{18}ClFN_2O$ + H^+, 333.1170; found (ESI, [M+H]$^+$), 333.1156.

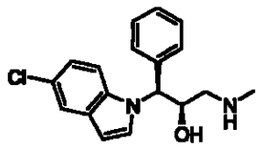
[0714] EXAMPLE 151: (1S,2R)-1-(6-chloro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride



[0715] In an analogous manner to EXAMPLE 117, step 5, (2S,3S)-3-(6-chloro-1H-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol was prepared from 6-chloroindole and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, step 3) as a viscous, colorless oil. MS (ES) *m/z* 320.0 ([M+H]$^+$); HRMS: calcd for $C_{17}H_{15}ClFNO_2$ + H^+, 320.0848; found (ESI, [M+H]$^+$), 320.0855.

[0716] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(6-chloro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride was prepared from (2S,3S)-3-(6-chloro-1H-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol as a white powder. MS (ES) *m/z* 333.2 ([M+H]$^+$); HRMS: calcd for $C_{18}H_{18}ClFN_2O$ + H^+, 333.1170; found (ESI, [M+H]$^+$), 333.1174.

[0717] EXAMPLE 152: (1S,2R)-1-(5-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride

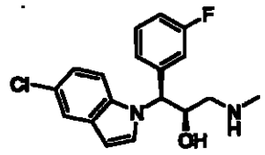


[0718] In an analogous manner to EXAMPLE 117, step 5, (2S,3S)-3-(5-chloro-1H-indol-1-yl)-3-phenylpropane-1,2-diol was prepared from 5-chloroindole and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4) as a viscous, colorless oil.

MS (ES) *m/z* 302.2 ([M+H]$^+$); HRMS: calcd for $C_{17}H_{16}ClNO_2$ + H^+, 302.0948; found (ESI, [M+H]$^+$), 302.0956.

[0719] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(5-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2S,3S)-3-(5-chloro-1H-indol-1-yl)-3-phenylpropane-1,2-diol as a white powder. MS (ES) *m/z* 315.1 ([M+H]$^+$); HRMS: calcd for $C_{18}H_{19}ClN_2O$ + H^+, 315.1259; found (ESI, [M+H]$^+$), 315.1247.

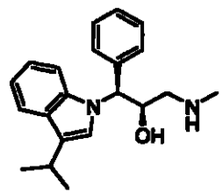
[0720] EXAMPLE 153: (1S,2R)-1-(5-chloro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride



[0721] In an analogous manner to EXAMPLE 117, step 5, (2S,3S)-3-(5-chloro-1H-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol was prepared from 5-chloroindole and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, step 3) as a viscous, colorless oil. MS (ES) *m/z* 320.1 ([M+H]$^+$); HRMS: calcd for $C_{17}H_{15}ClFNO_2$ + H^+, 320.0848; found (ESI, [M+H]$^+$), 320.0854.

[0722] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(5-chloro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride was prepared from 2S,3S)-3-(5-chloro-1H-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol as a white powder. MS (ES) *m/z* 333.1 ([M+H]$^+$); HRMS: calcd for $C_{18}H_{18}ClFN_2O$ + H^+, 333.1170; found (ESI, [M+H]$^+$), 333.1154.

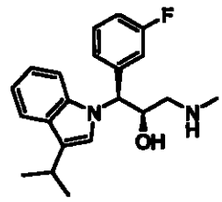
[0723] EXAMPLE 154: (1S,2R)-1-(3-isopropyl-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride



[0724] In an analogous manner to EXAMPLE 117, step 5, (2S,3S)-3-(3-isopropyl-1H-indol-1-yl)-3-phenylpropane-1,2-diol was prepared from 3-isopropylindole[16] and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4) as a viscous, yellowish oil. HRMS: calcd for $C_{20}H_{23}NO_2$ + H^+, 310.1802; found (ESI, $[M+H]^+$), 310.1793.

[0725] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(3-isopropyl-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2S,3S)-3-(3-isopropyl-1H-indol-1-yl)-3-phenylpropane-1,2-diol as a white powder. MS (ES) *m/z* 323.3 ($[M+H]^+$); HRMS: calcd for $C_{21}H_{26}N_2O$ + H^+, 323.2118; found (ESI, $[M+H]^+$), 323.2117.

[0726] EXAMPLE 155: (1S,2R)-1-(3-fluorophenyl)-1-(3-isopropyl-1H-indol-1-yl)-3-(methylamino)propan-2-ol hydrochloride



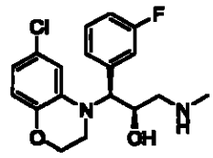
[0727] In an analogous manner to EXAMPLE 117, step 5, (2S,3S)-3-(3-fluorophenyl)-3-(3-isopropyl-1H-indol-1-yl)propane-1,2-diol was prepared from 3-isopropylindole[16] and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, step 3) as a viscous, yellowish oil. MS (ES) *m/z* 326.2 ($[M-H]^-$); HRMS: calcd for $C_{20}H_{22}FNO_2$ + H^+, 328.1707; found (ESI, $[M+H]^+$), 328.1709.

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[16]Odle, R.; Blevins, B.; Ratcliff, M.; Hegedus, L. S. *J. Org. Chem.* 1980, *45*, 2709-2710.

[0728] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(3-fluorophenyl)-1-(3-isopropyl-1H-indol-1-yl)-3-(methylamino)propan-2-ol hydrochloride was prepared from (2S,3S)-3-(3-fluorophenyl)-3-(3-isopropyl-1H-indol-1-yl)propane-1,2-diol as a white powder. MS (ES) *m/z* 341.3 ($[M+H]^+$); HRMS: calcd for $C_{21}H_{25}FN_2O + H^+$, 341.2024; found (ESI, $[M+H]^+$), 341.2025.

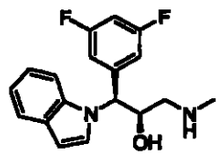
[0729] EXAMPLE 156: (1S,2R)-1-(6-chloro-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride



[0730] In an analogous manner to EXAMPLE 47, step 4, (2S,3S)-3-(6-chloro-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-(3-fluorophenyl)propane-1,2-diol was prepared from 6-chloro-3,4-dihydro-2H-1,4-benzoxazine (EXAMPLE 88, step 1) and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, step 3) as a viscous, yellowish liquid. MS (ES) *m/z* 335.8 ($[M-H]^-$); HRMS: calcd for $C_{20}H_{22}FNO_2 + H^+$, 338.0959; found (ESI, $[M+H]^+$), 338.0959.

[0731] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(6-chloro-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride was prepared from (2S,3S)-3-(6-chloro-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-(3-fluorophenyl)propane-1,2-diol as a white powder. MS (ES) *m/z* 351.0 ($[M+H]^+$); HRMS: calcd for $C_{18}H_{20}ClFN_2O_2 + H^+$, 351.1276; found (ESI, $[M+H]^+$), 351.1276.

[0732] EXAMPLE 157: (1S,2R)-1-(3,5-difluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol hydrochloride



[0733] Step 1: In an analogous manner to EXAMPLE 47, step 1, *trans*-3,5-difluorocinnamic acid methyl ester was prepared from *trans*-3,5-difluorocinnamic acid as a white solid. MS (ESI) *m/z* 198.0; HRMS: calcd for $C_{10}H_8F_2O_2$, 198.0492; found (ESI, $[M]^+$), 198.0489.

[0734] Step 2: In an analogous manner to EXAMPLE 47, step 2, *trans*-3,5-difluorocinnamyl alcohol was prepared from *trans*-3,5-difluorocinnamic acid methyl ester as a colorless oil.

[0735] Step 3: In an analogous manner to EXAMPLE 47, step 3, [(2R,3R)-3-(3,5-difluorophenyl)oxiran-2-yl]methanol was prepared from *trans*-3,5-difluorocinnamyl alcohol as a colorless liquid. Percent ee: 97.9%. MS (ESI) *m/z* 186.0; HRMS: calcd for $C_9H_8F_2O_2$, 186.0492; found (ESI, $[M]^+$), 186.0501.

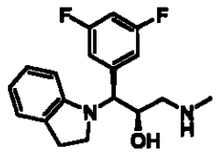
[0736] Step 4: In an analogous manner to EXAMPLE 47, step 4, (2S,3S)-3-(3,5-difluorophenyl)-3-(2,3-dihydro-1H-indol-1-yl)propane-1,2-diol was prepared from indoline and [(2R,3R)-3-(3,5-difluorophenyl)oxiran-2-yl]methanol as a viscous, yellowish oil. MS (ES) *m/z* 306.2 ($[M+H]^+$); HRMS: calcd for $C_{17}H_{17}F_2NO_2 + H^+$, 306.1300; found (ESI, $[M+H]^+$), 306.1299.

[0737] Step 5: In an analogous manner to EXAMPLE 47, step 5, (2S,3S)-3-(3,5-difluorophenyl)-3-(1H-indol-1-yl)propane-1,2-diol was prepared from (2S,3S)-3-(3,5-difluorophenyl)-3-(2,3-dihydro-1H-indol-1-yl)propane-1,2-diol as a viscous, yellowish oil. MS (ES) *m/z* 304.0 ($[M+H]^+$); HRMS: calcd for $C_{17}H_{15}F_2NO_2 + H^+$, 304.1144; found (ESI, $[M+H]^+$), 304.1146.

[0738] Step 6: In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(3,5-difluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol hydrochloride was prepared from (2S,3S)-3-(3,5-difluorophenyl)-3-(1H-indol-1-yl)propane-1,2-diol as a

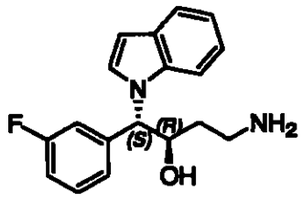
white powder. MS (ES) *m/z* 317.0 ([M+H]$^+$); HRMS: calcd for $C_{18}H_{18}F_2N_2O$ + H^+, 317.1465; found (ESI, [M+H]$^+$), 317.1465.

[0739] EXAMPLE 158: (1S,2R)-1-(3,5-difluorophenyl)-1-(2,3-dihydro-1H-indol-1-yl)-3-(methylamino)propan-2-ol hydrochloride



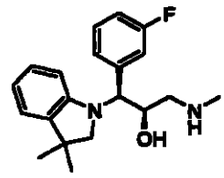
[0740] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(3,5-difluorophenyl)-1-(2,3-dihydro-1H-indol-1-yl)-3-(methylamino)propan-2-ol was prepared from (2S,3S)-3-(3,5-difluorophenyl)-3-(2,3-dihydro-1H-indol-1-yl)propane-1,2-diol as a white powder. MS (ES) *m/z* 319.0 ([M+H]$^+$); HRMS: calcd for $C_{18}H_{20}F_2N_2O$ + H^+, 319.1622; found (ESI, [M+H]$^+$), 319.1622.

[0741] EXAMPLE 159: (1S,2R)-4-amino-1-(3-fluorophenyl)-1-(1H-indol-1-yl)butan-2-ol
hydrochloride



[0742] In an analogous manner to Example 1, step 2 (2S,3S)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-2-hydroxy-3-indol-1-yl-propyl ester was prepared from (2S,3S)-3-(3-fluorophenyl)-3-(1H-indol-1-yl)propane-1,2-diol (Example 47, step 4). MS (ES) m/z 440 ([M+H]$^+$).

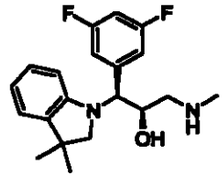
[0743] EXAMPLE 160: (1S,2R)-1-(3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride



[0744] In an analogous manner to EXAMPLE 47, step 4, (2S,3S)-3-(3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol was prepared from 3,3-dimethylindoline[15] and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, step 3) as a viscous, brown liquid. MS (ES) *m/z* 316.0 ([M+H]$^+$); HRMS: calcd for $C_{19}H_{22}FNO_2$ + H^+, 316.1713; found (ESI, [M+H]$^+$), 316.1713.

[0745] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride was prepared from (2S,3S)-3-(3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol as a white powder. MS (ES) *m/z* 329.0 ([M+H]$^+$).

[0746] EXAMPLE 161: (1S,2R)-1-(3,5-difluorophenyl)-1-(3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)propan-2-ol hydrochloride

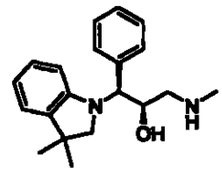


[0747] In an analogous manner to EXAMPLE 47, step 4, (2S,3S)-3-(3,5-difluorophenyl)-3-(3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)propane-1,2-diol was prepared from 3,3-dimethylindoline[15] and [(2R,3R)-3-(3,5-difluorophenyl)oxiran-2-yl]methanol (EXAMPLE 157, step 3) as a viscous, brown liquid. MS (ES) *m/z* 334.0 ([M+H]$^+$); HRMS: calcd for $C_{19}H_{21}F_2NO_2$ + H^+, 334.1619; found (ESI, [M+H]$^+$), 334.1619.

[0748] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(3,5-difluorophenyl)-1-(3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)propan-2-

ol hydrochloride was prepared from (2S,3S)-3-(3,5-difluorophenyl)-3-(3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)propane-1,2-diol as a white powder. MS (ES) *m/z* 347.0 ([M+H]$^+$); HRMS: calcd for $C_{20}H_{24}F_2N_2O$ + H$^+$, 347.1929; found (ESI, [M+H]$^+$), 347.1929.

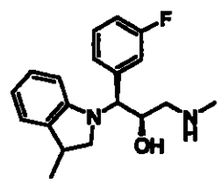
[0749] EXAMPLE 162: (1S,2R)-1-(3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride



[0750] In an analogous manner to EXAMPLE 47, step 4, (2S,3S)-3-(3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-3-phenylpropane-1,2-diol was prepared from 3,3-dimethylindoline[15] and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4) as a viscous, brown liquid. MS (ES) *m/z* 298.0 ([M+H]$^+$); HRMS: calcd for $C_{19}H_{23}NO_2$ + H$^+$, 298.1807; found (ESI, [M+H]$^+$), 298.1807.

[0751] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2S,3S)-3-(3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-3-phenylpropane-1,2-diol as a white powder. MS (ES) *m/z* 311.0 ([M+H]$^+$); HRMS: calcd for $C_{20}H_{26}N_2O$ + H$^+$, 311.2118; found (ESI, [M+H]$^+$), 311.2107.

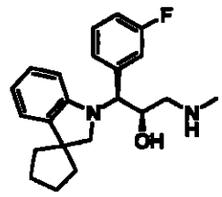
[0752] EXAMPLE 163: (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(3-methyl-2,3-dihydro-1H-indol-1-yl)propan-2-ol hydrochloride



[0753] In an analogous manner to EXAMPLE 47, step 4, (2S,3S)-3-(3-fluorophenyl)-3-(3-methyl-2,3-dihydro-1H-indol-1-yl)propane-1,2-diol was prepared from 3-methylindoline[4] and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, step 3) as a viscous, yellowish liquid. MS (ES) *m/z* 301.8 ($[M+H]^+$); HRMS: calcd for $C_{18}H_{20}FNO_2 + H^+$, 302.1551; found (ESI, $[M+H]^+$), 302.1539.

[0754] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(3-methyl-2,3-dihydro-1H-indol-1-yl)propan-2-ol hydrochloride was prepared from (2S,3S)-3-(3-fluorophenyl)-3-(3-methyl-2,3-dihydro-1H-indol-1-yl)propane-1,2-diol as a white powder. MS (ES) *m/z* 315.2 ($[M+H]^+$); HRMS: calcd for $C_{19}H_{23}FN_2O + H^+$, 315.1873; found (ESI, $[M+H]^+$), 315.1881.

[0755] EXAMPLE 164: (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-spiro[cyclopentane-1,3'-indol]-1'(2'H)-ylpropan-2-ol hydrochloride

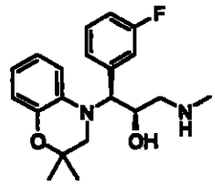


[0756] In an analogous manner to EXAMPLE 47, step 4, (2S,3S)-3-(3-fluorophenyl)-3-spiro[cyclopentane-1,3'-indol]-1'(2'H)-ylpropane-1,2-diol was prepared from 1',2'-dihydrospiro[cyclopentane-1,3'-indole][15] and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, step 3) as a viscous, yellowish liquid. MS (ES) *m/z* 342.2 ($[M+H]^+$).

[0757] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-spiro[cyclopentane-1,3'-indol]-1'(2'H)-ylpropan-2-ol hydrochloride was prepared from (2S,3S)-3-(3-fluorophenyl)-3-spiro[cyclopentane-1,3'-indol]-1'(2'H)-ylpropane-1,2-diol as a white powder. MS (ES) *m/z* 355.0

([M+H]$^+$); HRMS: calcd for $C_{22}H_{27}FN_2O$ + H^+, 355.2180; found (ESI, [M+H]$^+$), 355.2178.

[0758] EXAMPLE 165: (1S,2R)-1-(2,2-dimethyl-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride

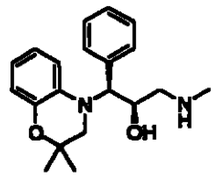


[0759] Step 1: To a solution of 2,2-dimethyl-2H-1,4-benzoxazin-3(4H)-one[17] (2.658 g, 15.0 mmol) in tetrahydrofuran (10 mL) under nitrogen was added slowly a solution of borane (1.0 M in tetrahydrofuran, 22.5 mL, 22.5 mmol) via a syringe. The resulting mixture was stirred at room temperature for 10 minutes and then at 70°C for 1 hour s. After cooling, the reaction mixture was quenched with methanol (3 mL) slowly. All volatiles were removed under reduced pressure. A 1 N aqueous solution of hydrochloric acid (10 mL) was added to the liquid residue and the mixture was warmed to 50°C for 10 minutes. After cooling, the reaction mixture was made alkaline using saturated sodium bicarbonate solution (15 mL), and extracted with ethyl acetate (25 mL). The organic layer was washed with water, brine, dried (anhydrous sodium sulfate), filtered through a pad of silica gel, and concentrated under reduced pressure to yield 2.310 g (94%) of 2,2-dimethyl-3,4-dihydro-2H-1,4-benzoxazine as a brown oil. MS (ES) *m/z* 164.0 ([M+H]$^+$).

[0760] Step 2: In an analogous manner to EXAMPLE 47, step 4, (2S,3S)-3-(2,2-dimethyl-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-(3-fluorophenyl)propane-1,2-diol was prepared from 2,2-dimethyl-3,4-dihydro-2H-1,4-benzoxazine and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, step 3) as a white solid. MS (ES) *m/z* 332.2 ([M+H]$^+$); HRMS: calcd for $C_{19}H_{22}FNO_3$ + H^+, 332.1657; found (ESI, [M+H]$^+$), 332.1648.

[0761] Step 3: In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(2,2-dimethyl-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride was prepared from (2S,3S)-3-(2,2-dimethyl-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-(3-fluorophenyl)propane-1,2-diol as a white powder. MS (ES) *m/z* 345.2 ($[M+H]^+$); HRMS: calcd for $C_{20}H_{25}FN_2O_2$ + H^+, 345.1978; found (ESI, $[M+H]^+$), 345.1981.

[0762] EXAMPLE 166: (1S,2R)-1-(2,2-dimethyl-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride



[0763] In an analogous manner to EXAMPLE 47, step 4, (2S,3S)-3-(2,2-dimethyl-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-phenylpropane-1,2-diol was prepared from 2,2-dimethyl-3,4-dihydro-2H-1,4-benzoxazine (EXAMPLE 165, step 1) and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4) as a white solid. MS (ES) *m/z* 314.1 ($[M+H]^+$).

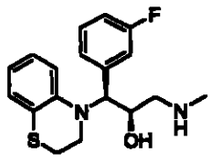
[0764] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(2,2-dimethyl-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2S,3S)-3-(2,2-dimethyl-2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-phenylpropane-1,2-diol as a white powder. MS (ES) *m/z* 327.2 ($[M+H]^+$); HRMS: calcd for $C_{20}H_{26}N_2O_2$ + H^+, 327.2073; found (ESI, $[M+H]^+$), 327.2082.

[0765] EXAMPLE 167: (1S,2R)-1-(2,3-dihydro-4H-1,4-benzothiazin-4-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride

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[17]Caliendo, G.; Perissutti, E.; Santagada, V.; Fiorino, F.; Severino, B.; Bianca, R.

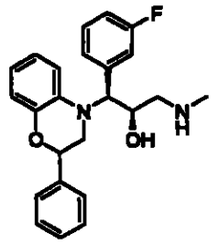
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[0766] In an analogous manner to EXAMPLE 47, step 4, (2S,3S)-3-(2,3-dihydro-4H-1,4-benzothiazin-4-yl)-3-(3-fluorophenyl)propane-1,2-diol was prepared from 3,4-dihydro-2H-1,4-benzothiazine[18] and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, step 3) as a viscous, yellowish liquid. MS (ES) *m/z* 320.1 ($[M+H]^+$); HRMS: calcd for $C_{17}H_{18}FNO_2S + H^+$, 320.1115; found (ESI, $[M+H]^+$), 320.1113.

[0767] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(2,3-dihydro-4H-1,4-benzothiazin-4-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride was prepared from (2S,3S)-3-(2,3-dihydro-4H-1,4-benzothiazin-4-yl)-3-(3-fluorophenyl)propane-1,2-diol as a white powder. MS (ES) *m/z* 333.1 ($[M+H]^+$); HRMS: calcd for $C_{18}H_{21}FN_2OS + H^+$, 333.1431; found (ESI, $[M+H]^+$), 333.1420.

[0768] EXAMPLE 168: (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(2-phenyl-2,3-dihydro-4H-1,4-benzoxazin-4-yl)propan-2-ol hydrochloride



[0769] In an analogous manner to EXAMPLE 47, step 4, (2S,3S)-3-(3-fluorophenyl)-3-(2-phenyl-2,3-dihydro-4H-1,4-benzoxazin-4-yl)propane-1,2-diol was prepared from 2-phenyl-3,4-dihydro-2H-1,4-benzoxazine[19] and [(2R,3R)-3-(3-

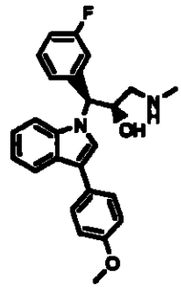
[18]El-Subbagh, H. I.; Abadi, A. H.; Al-Khawad, I. E.; Al-Rashood, K. A. *Arch. Pharm.* **1999**, *332*, 19-24.

[19]Olagbemiro, T. O.; Nyakutse, C. A.; Lajide, L.; Agho, M. O.; Chukwu, C. E. *Bull. Soc. Chim. Belg.* **1987**, *96*, 473-480.

fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, step 3) as a white solid. MS (ES) *m/z* 380.0 ([M+H]$^+$); HRMS: calcd for $C_{23}H_{22}FNO_3$ + H^+, 380.1662; found (ESI, [M+H]$^+$), 380.1661.

[0770] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(2-phenyl-2,3-dihydro-4H-1,4-benzoxazin-4-yl)propan-2-ol hydrochloride was prepared from (2S,3S)-3-(3-fluorophenyl)-3-(2-phenyl-2,3-dihydro-4H-1,4-benzoxazin-4-yl)propane-1,2-diol as a white powder. MS (ES) *m/z* 393.2 ([M+H]$^+$); HRMS: calcd for $C_{24}H_{25}FN_2O_2$ + H^+, 393.1978; found (ESI, [M+H]$^+$), 393.1986.

[0771] EXAMPLE 169: (1S,2R)-1-(3-fluorophenyl)-1-[3-(4-methoxyphenyl)-1H-indol-1-yl]-3-(methylamino)propan-2-ol hydrochloride



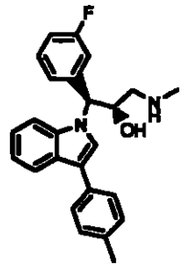
[0772] In an analogous manner to EXAMPLE 114, step 2, (2S,3S)-3-(3-fluorophenyl)-3-{3-[4-methoxyphenyl]-1H-indol-1-yl}propane-1,2-diol was prepared from (2*S*,3*S*)-3-(3-fluorophenyl)-3-(3-iodo-1*H*-indol-1-yl)propane-1,2-diol (EXAMPLE 114, step 1) and 4-methoxybenzeneboronic acid.

[0773] In an analogous manner to EXAMPLE 1, step 2, (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-3-[3-(4-methoxyphenyl)-indol-1-yl]-2-hydroxy-propyl ester was prepared from (2S,3S)-3-(3-fluorophenyl)-3-{3-[4-methoxyphenyl]-1H-indol-1-yl}propane-1,2-diol.

[0774] In an analogous manner to EXAMPLE 5, (1*S*,2*R*)-1-(3-fluorophenyl)-1-[3-(4-methoxyphenyl)-1*H*-indol-1-yl]-3-(methylamino)propan-2-ol hydrochloride was

prepared from (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-3-[3-(4-methoxyphenyl)-indol-1-yl]-2-hydroxy-propyl ester and methylamine (2N solution in methanol). MS (ESI) *m/z* 405.

[0775] EXAMPLE 170: (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-[3-(4-methylphenyl)-1H-indol-1-yl]propan-2-ol hydrochloride

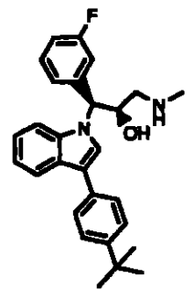


[0776] In an analogous manner to EXAMPLE 114, step 2, (2S,3S)-3-(3-fluorophenyl)-3-{3-[4-methylphenyl]-1H-indol-1-yl}propane-1,2-diol was prepared from (2*S*,3*S*)-3-(3-fluorophenyl)-3-(3-iodo-1*H*-indol-1-yl)propane-1,2-diol (EXAMPLE 114, step 1) and 4-methylbenzeneboronic acid.

[0777] In an analogous manner to EXAMPLE 1, step 2, (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-3-[3-(4-methylphenyl)-indol-1-yl]-2-hydroxy-propyl ester was prepared from (2S,3S)-3-(3-fluorophenyl)-3-{3-[4-methylphenyl]-1H-indol-1-yl}propane-1,2-diol.

[0778] In an analogous manner to EXAMPLE 5, (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-[3-(4-methylphenyl)-1H-indol-1-yl]propan-2-ol hydrochloride was prepared from (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-3-[3-(4-methylphenyl)-indol-1-yl]-2-hydroxy-propyl ester and methylamine (2N solution in methanol). MS (ESI) *m/z* 389.2.

[0779] EXAMPLE 171: (1S,2R)-1-[3-(4-tert-butylphenyl)-1H-indol-1-yl]-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride

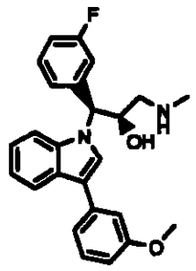


[0780] In an analogous manner to EXAMPLE 114, step 2, (2S,3S)-3-(3-fluorophenyl)-3-{3-[4-tert-butylphenyl]-1H-indol-1-yl}propane-1,2-diol was prepared from (2*S*,3*S*)-3-(3-fluorophenyl)-3-(3-iodo-1*H*-indol-1-yl)propane-1,2-diol (EXAMPLE 114, step 1) and 4-tert-butylphenylboronic acid.

[0781] In an analogous manner to EXAMPLE 1, step 2, (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-3-[3-(4-tert-butylphenyl)-indol-1-yl]-2-hydroxy-propyl ester was prepared from (2S,3S)-3-(3-fluorophenyl)-3-{3-[4-tert-butylphenyl]-1H-indol-1-yl}propane-1,2-diol.

[0782] In an analogous manner to EXAMPLE 5, (1S,2R)-1-[3-(4-tert-butylphenyl)-1H-indol-1-yl]-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride was prepared from (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-3-[3-(4-tert-butylphenyl)-indol-1-yl]-2-hydroxy-propyl ester and methylamine (2N solution in methanol). MS (ESI) *m/z* 430.9; HRMS: calcd for C28H31FN2O + H+, 431.24932; found (ESI, [M+H]+), 431.2516.

[0783] EXAMPLE 172: (1S,2R)-1-(3-fluorophenyl)-1-[3-(3-methoxyphenyl)-1H-indol-1-yl]-3-(methylamino)propan-2-ol hydrochloride

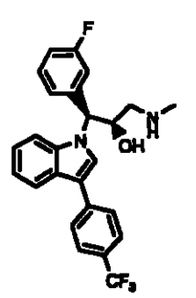


[0784] In an analogous manner to EXAMPLE 114, step 2, (2S,3S)-3-(3-fluorophenyl)-3-{3-[3-methoxyphenyl]-1H-indol-1-yl}propane-1,2-diol was prepared from (2*S*,3*S*)-3-(3-fluorophenyl)-3-(3-iodo-1*H*-indol-1-yl)propane-1,2-diol (EXAMPLE 114, step 1) and 3-methoxybenzeneboronic acid.

[0785] In an analogous manner to EXAMPLE 1, step 2, (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-3-[3-(3-methoxyphenyl)-indol-1-yl]-2-hydroxy-propyl ester was prepared from (2S,3S)-3-(3-fluorophenyl)-3-{3-[3-methoxyphenyl]-1H-indol-1-yl}propane-1,2-diol.

[0786] In an analogous manner to EXAMPLE 5, (1*S*,2*R*)-1-(3-fluorophenyl)-1-[3-(3-methoxyphenyl)-1*H*-indol-1-yl]-3-(methylamino)propan-2-ol hydrochloride was prepared from (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-3-[3-(3-methoxyphenyl)-indol-1-yl]-2-hydroxy-propyl ester and methylamine (2N solution in methanol). MS (ESI) *m/z* 405.1; HRMS: calcd for C25H25FN2O2 + H+, 405.19728; found (ESI, [M+H]+), 405.196.

[0787] EXAMPLE 173: (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-{3-[4-(trifluoromethyl)phenyl]-1H-indol-1-yl}propan-2-ol hydrochloride

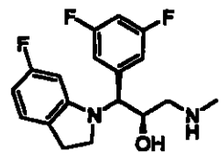


[0788] In an analogous manner to EXAMPLE 114, step 2, (2S,3S)-3-(3-fluorophenyl)-3-{3-[4-(trifluoromethyl)phenyl]-1H-indol-1-yl}propane-1,2-diol was prepared from (2*S*,3*S*)-3-(3-fluorophenyl)-3-(3-iodo-1*H*-indol-1-yl)propane-1,2-diol (EXAMPLE 114, step 1) and 4-(trifluoromethyl)benzeneboronic acid.

[0789] In an analogous manner to EXAMPLE 1, step 2 (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-3-[3-(4-(trifluoromethyl)phenyl)-indol-1-yl]-2-hydroxy-propyl ester was prepared from (2S,3S)-3-(3-fluorophenyl)-3-{3-[4-(trifluoromethyl)phenyl]-1H-indol-1-yl}propane-1,2-diol.

[0790] In an analogous manner to EXAMPLE 5 (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-{3-[4-(trifluoromethyl)phenyl]-1H-indol-1-yl}propan-2-ol hydrochloride was prepared from (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-fluoro-phenyl)-3-[3-(4-(trifluoromethyl)phenyl)-indol-1-yl]-2-hydroxy-propyl ester and methylamine (2N solution in methanol). MS (ESI) *m/z* 443.1.

[0791] EXAMPLE 174: (1S,2R)-1-(3,5-difluorophenyl)-1-(6-fluoro-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)propan-2-ol hydrochloride

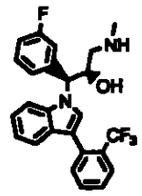


[0792] In an analogous manner to EXAMPLE 47, step 4, (2S,3S)-3-(3,5-difluorophenyl)-3-(6-fluoro-2,3-dihydro-1H-indol-1-yl)propane-1,2-diol was prepared from 6-fluoroindoline and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, step 3) as a viscous, yellowish liquid. MS (ES) *m/z* 324.1 ($[M+H]^+$); HRMS: calcd for $C_{17}H_{16}F_3NO_2 + H^+$, 324.1211; found (ESI, $[M+H]^+$), 324.1226.

[0793] In an analogous manner to EXAMPLE 47, step 6, (1S,2R)-1-(3,5-difluorophenyl)-1-(6-fluoro-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)propan-2-ol hydrochloride was prepared from (2S,3S)-3-(3,5-difluorophenyl)-3-(6-fluoro-2,3-

dihydro-1H-indol-1-yl)propane-1,2-diol as a white powder. MS (ES) *m/z* 337.3 ([M+H]$^+$); HRMS: calcd for $C_{18}H_{19}F_3N_2O$ + H$^+$, 337.1522; found (ESI, [M+H]$^+$), 337.1505.

[0794] EXAMPLE 175: (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-{3-[2-(trifluoromethyl)phenyl]-1H-indol-1-yl}propan-2-ol hydrochloride

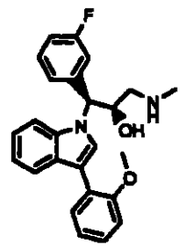


[0795] In an analogous manner to EXAMPLE 114, step 2, (2S,3S)-3-(3-fluorophenyl)-3-{3-[2-(trifluoromethyl)phenyl]-1H-indol-1-yl}propane-1,2-diol was prepared from (2*S*,3*S*)-3-(3-fluorophenyl)-3-(3-iodo-1*H*-indol-1-yl)propane-1,2-diol (EXAMPLE 114, step 1) and 2-(trifluoromethyl)boronic acid.

[0796] In an analogous manner to EXAMPLE 1, step 2, (2*S*,3*S*)- toluene-4-sulfonic acid 3-(3-fluorophenyl)-2-hydroxy-3-[3-(2-(trifluoromethyl)phenyl)-indol-1-yl]-propyl ester was prepared from (2S,3S)-3-(3-fluorophenyl)-3-{3-[2-(trifluoromethyl)phenyl]-1H-indol-1-yl}propane-1,2-diol.

[0797] In an analogous manner to EXAMPLE 5, (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-{3-[2-(trifluoromethyl)phenyl]-1H-indol-1-yl}propan-2-ol hydrochloride was prepared from (2*S*,3*S*)- toluene-4-sulfonic acid 3-(3-fluorophenyl)-2-hydroxy-3-[3-(2-(trifluoromethyl)phenyl)-indol-1-yl]-propyl ester and methylamine (2N solution in methanol). MS (ESI) *m/z* 443.1; HRMS: calcd for C25H22F4N2O + H+, 443.17410; found (ESI, [M+H]+), 443.172.

[0798] EXAMPLE 176: (1S,2R)-1-(3-fluorophenyl)-1-[3-(2-methoxyphenyl)-1H-indol-1-yl]-3-(methylamino)propan-2-ol hydrochloride

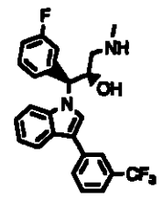


[0799] In an analogous manner to EXAMPLE 114, step 2, (2S,3S)-3-(3-fluorophenyl)-3-{3-[2-methoxyphenyl]-1H-indol-1-yl}propane-1,2-diol was prepared from (2*S*,3*S*)-3-(3-fluorophenyl)-3-(3-iodo-1*H*-indol-1-yl)propane-1,2-diol (EXAMPLE 114, step 1) and 2-methoxybenzeneboronic acid.

[0800] In an analogous manner to EXAMPLE 1, step 2, (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-3-[3-(2-methoxyphenyl)-indol-1-yl]-2-hydroxy-propyl ester was prepared from (2S,3S)-3-(3-fluorophenyl)-3-{3-[2-methoxyphenyl]-1H-indol-1-yl}propane-1,2-diol.

[0801] In an analogous manner to EXAMPLE 5, (1*S*,2*R*)-1-(3-fluorophenyl)-1-[3-(2-methoxyphenyl)-1*H*-indol-1-yl]-3-(methylamino)propan-2-ol hydrochloride was prepared from (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-3-[3-(2-methoxyphenyl)-indol-1-yl]-2-hydroxy-propyl ester and methylamine (2N solution in methanol). MS (ESI) *m/z* 405.1; HRMS: calcd for C25H25FN2O2 + H+, 405.19728; found (ESI, [M+H]+), 405.1984.

[0802] EXAMPLE 177: (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-{3-[3-(trifluoromethyl)phenyl]-1H-indol-1-yl}propan-2-ol hydrochloride



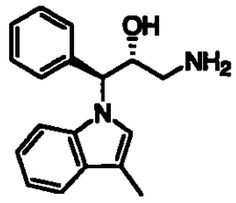
[0803] In an analogous manner to EXAMPLE 114, step 2, (2S,3S)-3-(3-fluorophenyl)-3-{3-[3-(trifluoromethyl)phenyl]-1H-indol-1-yl}propane-1,2-diol was

prepared from (2*S*,3*S*)-3-(3-fluorophenyl)-3-(3-iodo-1*H*-indol-1-yl)propane-1,2-diol (EXAMPLE 114, step 1) and 3-(trifluoromethyl)benzeneboronic acid.

[0804] In an analogous manner to EXAMPLE 1, step 2, (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-3-[3-(3-(trifluoromethyl)phenyl)-indol-1-yl]-2-hydroxy-propyl ester was prepared from (2S,3S)-3-(3-fluorophenyl)-3-{3-[3-(trifluoromethyl)phenyl]-1H-indol-1-yl}propane-1,2-diol.

[0805] In an analogous manner to EXAMPLE 5, (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-{3-[3-(trifluoromethyl)phenyl]-1H-indol-1-yl}propan-2-ol hydrochloride was prepared (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-3-[3-(3-(trifluoromethyl)phenyl)-indol-1-yl]-2-hydroxy-propyl ester and methylamine (2N solution in methanol). MS (ESI) *m/z* 443.1; HRMS: calcd for C25H22F4N2O + H+, 443.17410; found (ESI, [M+H]+), 443.1764.

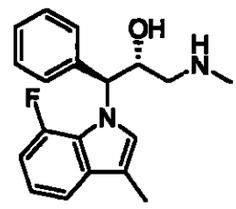
[0806] EXAMPLE 178: (1*S*,2*R*)-3-amino-1-(3-methyl-1*H*-indol-1-yl)-1-phenylpropan-2-ol hydrochloride



[0807] In an analogous manner to EXAMPLE 117, step 5 (2S,3S)-3-(3-methyl-indol-1-yl)-3-phenyl-propane-1,2-diol was prepared from 3-methylindole and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4) as an oil. MS (ESI) m/z 282 ([M+H]$^+$).

[0808] In an analogous manner to EXAMPLE 117, step 6 (1*S*,2*R*)-3-amino-1-(3-methyl-1*H*-indol-1-yl)-1-phenylpropan-2-ol hydrochloride was prepared from (2S,3S)-3-(3-methyl-indol-1-yl)-3-phenyl-propane-1,2-diol and *para*-toluenesulfonic acid followed by concentrated ammonium hydroxide as an off-white solid. MS (ESI) *m/z* 281.

[0809] EXAMPLE 179: (1*S*,2*R*)-1-(7-fluoro-3-methyl-1*H*-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride



[0810] In an analogous manner to EXAMPLE 117, step 1 ethyl 7-fluoro-3-methyl-1*H*-indole-2-carboxylate was prepared from 2-fluoroaniline as a brownish solid. MS (ESI) *m/z* 221.

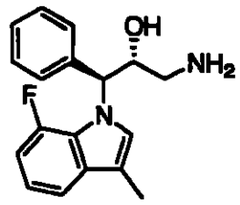
[0811] In an analogous manner to EXAMPLE 117, step 2 7-fluoro-3-methyl-1*H*-indole-2-carboxylic acid was prepared from ethyl 7-fluoro-3-methyl-1*H*-indole-2-carboxylate as a green solid. MS (ESI) *m/z* 192.

[0812] In an analogous manner to EXAMPLE 117, step 3 7-fluoro-3-methyl-1*H*-indole was prepared from 7-fluoro-3-methyl-1*H*-indole-2-carboxylic acid as a white solid. MS (ESI) *m/z* 150.

[0813] In an analogous manner to EXAMPLE 117, step 5 (2*S*,3*S*)-3-(7-fluoro-3-methyl-1*H*-indol-1-yl)-3-phenylpropane-1,2-diol was prepared from 7-fluoro-3-methyl-1*H*-indole and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, Step 4) as an oil. MS (ESI) *m/z* 300.

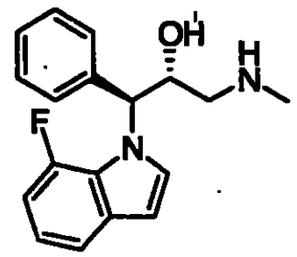
[0814] In an analogous manner to EXAMPLE 117, step 6 (1*S*,2*R*)-1-(7-fluoro-3-methyl-1*H*-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2*S*,3*S*)-3-(7-fluoro-3-methyl-1*H*-indol-1-yl)-3-phenylpropane-1,2-diol as a white solid. MS (ES) *m/z* 313.1.

[0815] EXAMPLE 180: (1*S*,2*R*)-3-amino-1-(7-fluoro-3-methyl-1*H*-indol-1-yl)-1-phenylpropan-2-ol hydrochloride



[0816] In an analogous manner to EXAMPLE 117, step 6 3-amino-1-(7-fluoro-3-methyl-1*H*-indol-1-yl)-1-phenylpropan-2-ol hydrochloride was prepared from (2*S*,3*S*)-3-(7-fluoro-3-methyl-1*H*-indol-1-yl)-3-phenylpropane-1,2-diol (EXAMPLE 179, step 4) and *para*-toluenesulfonic acid followed by ammonium hydroxide as a white solid. MS (ES) *m/z* 299.0.

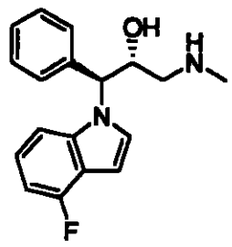
[0817] EXAMPLE 181: (1*S*,2*R*)-1-(7-fluoro-1*H*-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride



[0818] In an analogous manner to EXAMPLE 117, step 5 (2*S*,3*S*)-3-(7-fluoro-1*H*-indol-1-yl)-3-phenylpropane-1,2-diol was prepared from 7-fluoro-1*H*-indole and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, Step 4) as an oil. MS (ES) *m/z* 286.1.

[0819] In an analogous manner to EXAMPLE 117, step 6 (1*S*,2*R*)-1-(7-fluoro-1*H*-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2*S*,3*S*)-3-(7-fluoro-1*H*-indol-1-yl)-3-phenylpropane-1,2-diol as a pinkish solid. MS (ESI) *m/z* 299.

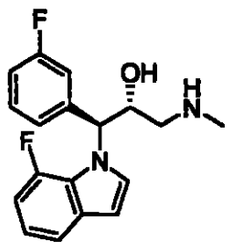
[0820] EXAMPLE 182: (1*S*,2*R*)-1-(4-fluoro-1*H*-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride



[0821] In an analogous manner to EXAMPLE 117, step 5 (2*S*,3*S*)-3-(4-fluoro-1*H*-indol-1-yl)-3-phenylpropane-1,2-diol was prepared from 4-fluoro-1*H*-indole and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, Step 4) as an oil. MS (ES) *m/z* 286.1.

[0822] In an analogous manner to EXAMPLE 117, step 6 (1*S*,2*R*)-1-(4-fluoro-1*H*-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2*S*,3*S*)-3-(4-fluoro-1*H*-indol-1-yl)-3-phenylpropane-1,2-diol as a white solid. MS (ESI) *m/z* 299.

[0823] EXAMPLE 183: (1*S*,2*R*)-1-(7-fluoro-1*H*-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride

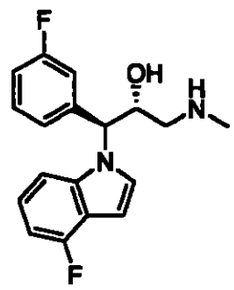


[0824] In an analogous manner to EXAMPLE 117, step 5 (2*S*,3*S*)-3-(7-fluoro-1*H*-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol was prepared from 7-fluoro-1*H*-indole and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, Step 3) as a brown oil. MS (ESI) *m/z* 304.

[0825] In an analogous manner to EXAMPLE 117, step 6 (1*S*,2*R*)-1-(7-fluoro-1*H*-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride was

prepared from (2*S*,3*S*)-3-(7-fluoro-1*H*-indol-1-yl)-3-(3-flu rophenyl)propane-1,2-diol as a pinkish solid. MS (ESI) *m/z* 317.

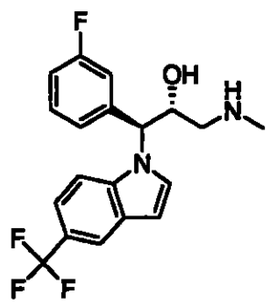
[0826] EXAMPLE 184: (1*S*,2*R*)-1-(4-fluoro-1*H*-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride



[0827] In an analogous manner to EXAMPLE 117, step 5 (2*S*,3*S*)-3-(4-fluoro-1*H*-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol was prepared from 4-fluoro-1*H*-indole and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, Step 3) as a brown oil. MS (ESI) *m/z* 304.

[0828] In an analogous manner to EXAMPLE 117, step 6 (1*S*,2*R*)-1-(4-fluoro-1*H*-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride was prepared from (2*S*,3*S*)-3-(4-fluoro-1*H*-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol as a white solid. MS (ESI) *m/z* 317.

[0829] EXAMPLE 185: (1*S*,2*R*)-1-(3-fluorophenyl)-3-(methylamino)-1-[5-(trifluoromethyl)-1*H*-indol-1-yl]propan-2-ol hydrochloride

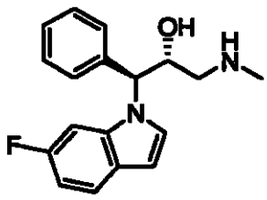


[0830] In an analogous manner to EXAMPLE 117, step 5 (2*S*,3*S*)- 3-(3-fluorophenyl)-3-(5-trifluoromethyl-1*H*-indol-1-yl)- propane-1,2-diol was prepared from

5-trifluoromethyl-1*H*-indole and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, Step 3).

[0831] In an analogous manner to EXAMPLE 117, step 6 (1*S*,2*R*)-1-(3-fluorophenyl)-3-(methylamino)-1-[5-(trifluoromethyl)-1*H*-indol-1-yl]propan-2-ol hydrochloride was prepared from (2*S*,3*S*)- 3-(3-fluorophenyl)-3-(5-trifluoromethyl-1*H*-indol-1-yl)- propane-1,2-diol as an off-white solid. MS (ESI) *m/z* 367.

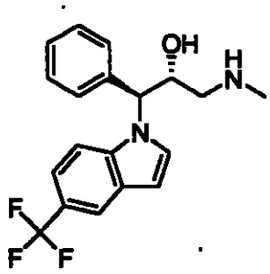
[0832] EXAMPLE 186: (1*S*,2*R*)-1-(6-fluoro-1*H*-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride



[0833] In an analogous manner to EXAMPLE 117, step 5 (2*S*,3*S*)-3-(6-fluoro-1*H*-indol-1-yl)-3-phenylpropane-1,2-diol was prepared from 6-fluoro-1*H*-Indole and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, Step 4) as a brown oil. MS (ES) *m/z* 286.1.

[0834] In an analogous manner to EXAMPLE 117, step 6 (1*S*,2*R*)-1-(6-fluoro-1*H*-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2*S*,3*S*)-3-(6-fluoro-1*H*-indol-1-yl)-3-phenylpropane-1,2-diol as a white solid. MS (ESI) *m/z* 299.

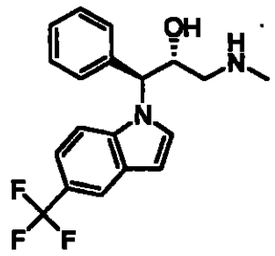
[0835] EXAMPLE 187: (1*S*,2*R*)-3-(methylamino)-1-phenyl-1-[6-(trifluoromethyl)-1*H*-indol-1-yl]propan-2-ol hydrochloride



[0836] In an analogous manner to EXAMPLE 117, step 5 (2*S*,3*S*)-3-phenyl-3-[6-(trifluoromethyl)-1*H*-indol-1-yl]propane-1,2-diol was prepared from 6-trifluoromethyl-1*H*-indole and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, Step 4) as a brown oil. MS (ES) *m/z* 336.

[0837] In an analogous manner to EXAMPLE 117, step 6 (1*S*,2*R*)-3-(methylamino)-1-phenyl-1-[6-(trifluoromethyl)-1*H*-indol-1-yl]propan-2-ol hydrochloride was prepared from (2*S*,3*S*)-3-phenyl-3-[6-(trifluoromethyl)-1*H*-indol-1-yl]propane-1,2-diol as a white solid. MS (ESI) *m/z* 349.

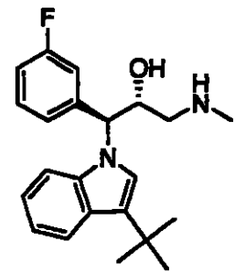
[0838] EXAMPLE 188: (1*S*,2*R*)-3-(methylamino)-1-phenyl-1-[5-(trifluoromethyl)-1*H*-indol-1-yl]propan-2-ol hydrochloride



[0839] In an analogous manner to EXAMPLE 117, step 5 (2*S*,3*S*)-3-phenyl-3-[5-(trifluoromethyl)-1*H*-indol-1-yl]propane-1,2-diol was prepared from 5-trifluoromethyl-1*H*-indole and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, Step 4) as a brown oil. MS (ES) *m/z* 336.

[0840] In an analogous manner to EXAMPLE 117, step 6 (1*S*,2*R*)-3-(methylamino)-1-phenyl-1-[5-(trifluoromethyl)-1*H*-indol-1-yl]propan-2-ol hydrochloride was prepared from (2*S*,3*S*)-3-phenyl-3-[5-(trifluoromethyl)-1*H*-indol-1-yl]propane-1,2-diol as an off-white solid. MS (ESI) *m/z* 349.2.

[0841] EXAMPLE 189: (1*S*,2*R*)-1-(3-*tert*-butyl-1*H*-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol

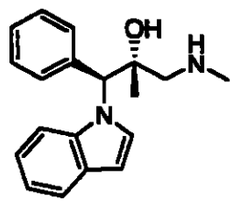


[0842] Step 1: To a mixture of indole (5g, 42.7 mmol), zinc triflate (9.3g, 25.6 mmol), and tetrabutylammonium iodide (7.9g, 21.4 mmol) in anhydrous toluene (120 mL) was added diisopropylethylamine (8.2 mL, 47 mmol) at room temperature under a blanket of nitrogen. After the reaction was stirred 15 minutes at room temperature, the reaction mixture was treated with *tert*-butyl bromide (2.5 mL, 21.7 mmol). The reaction solution was stirred at room temperature under nitrogen for 3 hours, then poured into a saturated aqueous solution of ammonium chloride (150 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3x50 mL). The combined organic layers were dried over magnesium sulfate, concentrated, and the residue was purified via flash column chromatography (silica, 10% ethyl acetate in hexane) to afford 3-*tert*-butyl-1*H*-indole as a white solid. MS (ES) *m/z* 174.2.

[0843] In an analogous manner to EXAMPLE 117, step 5 (2*S*,3*S*)-3-(3-*tert*-butyl-1*H*-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol was prepared from 3-*tert*-butyl-1*H*-indole and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, step 3).

[0844] In an analogous manner to EXAMPLE 117, step 6 (1*S*,2*R*)-1-(3-*tert*-butyl-1*H*-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol was prepared from (2*S*,3*S*)-3-(3-*tert*-butyl-1*H*-indol-1-yl)-3-(3-fluorophenyl)propane-1,2-diol as a clear oil. MS (ESI) *m/z* 355.3.

[0845] EXAMPLE 190: (1*S*,2*R*)-1-(1*H*-indol-1-yl)-2-methyl-3-(methylamino)-1-phenylpropan-2-ol hydrochloride

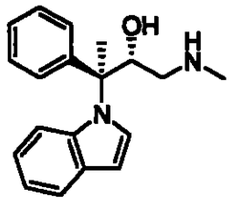


[0846] In an analogous manner to EXAMPLE 117, step 4 [(2*R*,3*R*)-2-methyl-3-phenyloxiran-2-yl]methanol was prepared from 2-methyl-3-phenylprop-2-en-1-ol as a white crystal. MS (ES) *m/z* 147.1.

[0847] In an analogous manner to EXAMPLE 117, step 5 (2*S*,3*S*)-2-methyl-3-phenyl-[1*H*-indol-1-yl]propane-1,2-diol was prepared from [(2*R*,3*R*)-2-methyl-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4) and indole

[0848] In an analogous manner to EXAMPLE 117, step 6 (1*S*,2*R*)-1-(1*H*-indol-1-yl)-2-methyl-3-(methylamino)-1-phenylpropan-2-ol hydrochloride was prepared from (2*S*,3*S*)-2-methyl-3-phenyl-[1*H*-indol-1-yl]propane-1,2-diol as a white solid. MS (ES) *m/z* 295.0.

[0849] EXAMPLE 191: (2*R*,3*S*)-3-(1*H*-indol-1-yl)-1-(methylamino)-3-phenylbutan-2-ol hydrochloride



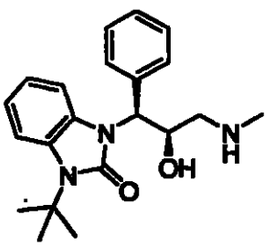
[0850] In an analogous manner to EXAMPLE 117, step 4 [(2*R*,3*R*)-3-methyl-3-phenyloxiran-2-yl]methanol was prepared from 3-methyl-3-phenylprop-2-en-1-ol as a white crystal. MS (ES) *m/z* 147.1.

[0851] In an analogous manner to EXAMPLE 47, step 4 (2*S*,3*S*)-3-(2,3-dihydro-1*H*-indol-1-yl)-3-phenylbutane-1,2-diol was prepared from [(2*R*,3*R*)-3-methyl-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4) and indoline as a brown solid. MS (ES) *m/z* 284.1.

[0852] In an analogous manner to EXAMPLE 47, step 5 (2*S*,3*S*)-3-(1*H*-indol-1-yl)-3-phenylbutane-1,2-diol was prepared from (2*S*,3*S*)-3-(2,3-dihydro-1*H*-indol-1-yl)-3-phenylbutane-1,2-diol as an off-white solid. MS (ESI) *m/z* 282.

[0853] In an analogous manner to EXAMPLE 117, step 6 (2*R*,3*S*)-3-(1*H*-indol-1-yl)-1-(methylamino)-3-phenylbutan-2-ol hydrochloride was prepared from (2*S*,3*S*)-3-(1*H*-indol-1-yl)-3-phenylbutane-1,2-diol as a white solid. MS (ES) *m/z* 295.1.

[0854] EXAMPLE 192: 1-tert-Butyl-3-(2-hydroxy-3-methylamino-1-phenyl-propyl)-1,3-dihydro-benzoimidazol-2-one hydrochloride



[0855] Step 1: To a solution of 1-fluoro-2-nitro-benzene (1g, 7.1 mmol) in dimethylformamide (15 mL) was added *tert*-butyl amine (0.82 mL, 7.81 mmol) at room temperature, and the reaction mixture stirred for 12 hours at room temperature under nitrogen. Upon completion, the reaction mixture was poured into a saturated aqueous solution of sodium chloride (50 mL) and extracted with ethyl acetate (50 mL). The organic layer was dried over anhydrous sodium sulfate, concentrated in *vacuo*, and the residue was purified via flash column chromatography (silica, 1% ethyl acetate in hexane) to give *tert*-butyl-(2-nitrophenyl)-amine as an orange oil. MS (ES) *m/z* 195.2

[0856] Step 2: To a solution of *tert*-butyl-(2-nitrophenyl)-amine (1.27 g, 6.5 mmol), 5% palladium on carbon (0.5 g), and sodium borohydride (0.49 g, 13.1 mmol) in tetrahydrofuran (20 mL) was added methanol (10 mL) in a dropwise manner. Upon completion of the reaction, it was filtered through a pad of Celite and the filtrate was poured into a saturated aqueous solution of ammonium chloride (50 mL), and

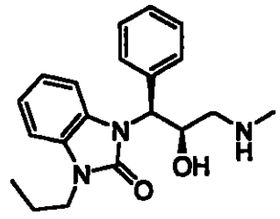
extracted with ethyl acetate (50 mL). The organic layer was dried over anhydrous magnesium sulfate, concentrated *in vacuo* to give *N-tert*-butyl-benzene-1,2-diamine which was used in the next step without further purification. A solution of *N-t*-butyl-benzene-1,2-diamine (1.1g, 6.7 mmol) and carbonyldiimidazole (1.63 g, 10 mmol) in anhydrous tetrahydrofuran (50 mL) was stirred at room temperature for 12 hours. Upon completion, the reaction was poured into a 1N aqueous solution of hydrochloric acid (50 mL) and extracted with ethyl acetate (50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified via flash column chromatography (silica, 50% ethyl acetate in hexane) to give 1-*tert*-butyl-1,3-dihydro-benzimidazol-2-one as an off-white solid. MS (ES) *m/z* 191.1.

[0857] Step 3: A mixture of 1-*tert*-butyl-1,3-dihydro-benzimidazol-2-one (0.66 g, 3.5 mmol) and sodium hydride (60% dispersion in mineral oil, 0.15 g, 3.8 mmol) in anhydrous dimethylformamide (4 mL) was stirred for 10 minutes under nitrogen at room temperature. A solution of [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4, 1.07 g, 7.1 mmol) and titanium isopropoxide (2.14 mL, 7.1 mmol) in dimethylformamide (4 mL) that was aged for 20 minutes was then added and the mixture was stirred at room temperature under nitrogen for 12 hours. After disappearance of the epoxide, the mixture was partitioned between a 1N aqueous solution of hydrochloric acid (50 mL) and ethyl acetate (50 mL). The organic layer was separated, washed with saturated sodium bicarbonate (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in *vacuo*. The residue was purified via silica gel column (60% ethyl acetate in hexane) to give 1-*tert*-butyl-3-[(*1S,2S*)-2,3-dihydroxy-1-phenyl-propyl]-1,3-dihydro-*2H*-benzimidazol-2-one as an oil. MS (ES) *m/z* 341.2.

[0858] Step 4: A solution of 1-*tert*-butyl-3-[(*1S,2S*)-2,3-dihydroxy-1-phenyl-propyl]-1,3-dihydro-*2H*-benzimidazol-2-one (0.55 g, 1.6 mmol) and *para*-toluenesulfonyl chloride (0.37 g, 1.9 mmol) in anhydrous pyridine (5 mL) was stirred at room temperature under nitrogen for 12 hours. The reaction was poured into a cold 1N aqueous solution of hydrochloric acid (50 mL) and extracted with ethyl acetate (50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and

concentrated to give (2S,3S)-toluene-4-sulfonic acid 3-(3-tert-butyl-2-oxo-2,3-dihydro-benzimidazol-1-yl)-2-hydroxy-3-phenyl-propyl ester. To a solution of (2S,3S)-toluene-4-sulfonic acid 3-(3-tert-butyl-2-oxo-2,3-dihydro-benzimidazol-1-yl)-2-hydroxy-3-phenyl-propyl ester (0.8 g, 1.6 mmol) in methanol (10 mL) was added a 2N solution of methylamine in methanol (4 mL, 8 mmol) and the reaction mixture stirred for 12 hours at room temperature in a sealed tube. Upon completion, the reaction was partitioned between a saturated aqueous solution of sodium bicarbonate (50 mL) and ethyl acetate (50 mL). The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified via flash column chromatography (silica, 20% MeOH in dichloromethane) to give 1-*tert*-butyl-3-[(1S,2R)-2-hydroxy-3-methylamino-1-phenylpropyl]-1,3-dihydro-*2H*-benzimidazol-2-one as a clear oil. The free base was dissolved in a minimum amount of ethanol and treated with a 2N ethereal solution of hydrochloric acid and stirred for 1 hour s. The ethanol was removed in *vacuo* and the clear oil was triturated with diethyl ether/dichloromethane to give 1-*tert*-butyl-3-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride as a white solid. HRMS: calcd for $C_{21}H_{27}N_3O_2$ + H+, 354.21760; found (ESI, $[M+H]^+$), 354.2179.

[0859] EXAMPLE 193: 1-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3-propyl-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride



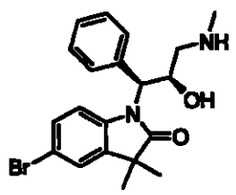
[0860] In an analogous manner to EXAMPLE 192, step 1 2-nitro-*N*-propylaniline was prepared from 1-fluoro-2-nitro-benzene and propyl amine. MS (ES) *m/z* 181.1.

[0861] In an analogous manner to EXAMPLE 192, step 2 1-propyl-1,3-dihydro-2*H*-benzimidazol-2-one was prepared from 2-nitro-*N*-propylaniline. MS (ES) *m/z* 177.1.

[0862] In an analogous manner to EXAMPLE 192, step 3 1-propyl-3-[(*1S,2S*)-2,3-dihydroxy-1-phenyl-propyl]-1,3-dihydro-*2H*-benzimidazol-2-one was prepared from 1-propyl-1,3-dihydro-2*H*-benzimidazol-2-one and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4).

[0863] In an analogous manner to EXAMPLE 192, step 4 1-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3-propyl-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride was prepared from 1-propyl-3-[(*1S,2S*)-2,3-dihydroxy-1-phenyl-propyl]-1,3-dihydro-*2H*-benzimidazol-2-one as a white solid. HRMS: calcd for $C_{20}H_{25}N_3O_2$ + H+, 340.20195; found (ESI, $[M+H]^+$), 340.2007

[0864] EXAMPLE 194: 5-bromo-1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one hydrochloride



[0865] Step 1: In an analogous manner to EXAMPLE 99, step 6 5-bromo-1-[(2S,3S)-2,3-dihydroxy-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one was prepared from 5-bromo-3,3-dimethyl-1,3-dihydro-indol-2-one[20] and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4). MS (ESI) m/z 391 ($[M+H]^+$).

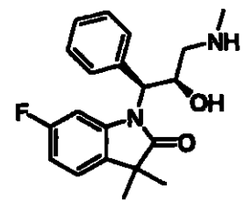
[0866] Step 2: In an analogous manner to EXAMPLE 1, step 2 (2S, 3S)-toluene-4-sulfonic acid 3-(5-bromo-3,3-dimethyl-2-oxo-2,3-dihydro-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester was prepared from (5-bromo-1-[(2S,3S)-2,3-dihydroxy-1-

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phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one). MS (ESI) m/z 545 ([M+H]$^+$).

[0867] Step 3: In an analogous manner to EXAMPLE 5 5-bromo-1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one hydrochloride was prepared from (2S, 3S)-toluene-4-sulfonic acid 3-(5-bromo-3,3-dimethyl-2-oxo-2,3-dihydro-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester. MS m/z 404 ([M+H]$^+$), HRMS: calcd for C20H23BrN2O2 + H$^+$, 403.10156; found (ESI, [M+H]$^+$), 403.0998.

[0868] EXAMPLE 195: 6-fluoro-1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one hydrochloride



[0869] Step 1: In an analogous manner to EXAMPLE 99, step 2 dimethyl (4-fluoro-2-nitrophenyl)malonate was prepared from 2,5-difluoronitrobenzene and dimethyl malonate. MS (ESI) m/z 272 ([M+H]$^+$).

[0870] Step 2: In an analogous manner to EXAMPLE 99, step 3 (4-fluoro-2-nitrophenyl)acetic acid was prepared from dimethyl (4-fluoro-2-nitrophenyl)malonate. MS (ESI) m/z 200 ([M+H]$^+$).

[0871] Step 3: In an analogous manner to EXAMPLE 99, step 4 6-fluoro-1,3-dihydro-2H-indol-2-one was prepared from (4-fluoro-2-nitrophenyl) acetic acid. MS (ESI) m/z 152 ([M+H]$^+$)

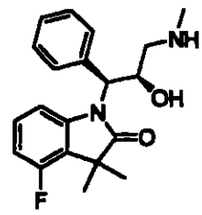
[0872] Step 4: In an analogous manner to EXAMPLE 99, step 5 6-fluoro-3,3-dimethyl-1,3-dihydro-2H-indol-2-one was prepared from 6-fluoro-1,3-dihydro-2H-indol-2-one. MS (ESI) m/z 180 ($[M+H]^+$.

[0873] Step 5: In an analogous manner to EXAMPLE 99, step 6 (2S, 3S)-1-(2,3-dihydroxy-1-phenyl-propyl)-6-fluoro-3,3-dimethyl-1,3-dihydro-indol-2-one was prepared from 6-fluoro-3,3-dimethyl-1,3-dihydro-2H-indol-2-one and [(2R, 3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4). MS (ESI) m/z 330 ($[M+H]^+$).

[0874] Step 6: In an analogous manner to EXAMPLE 1, step 2 (2S, 3S)-toluene-4-sulfonic acid 3-(6-fluoro-3,3-dimethyl-2-oxo-2,3-dihydro-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester was prepared from (2S,3S)-1-(2,3-dihydroxy-1-phenyl-propyl)-6-fluoro-3,3-dimethyl-1,3-dihydro-indol-2-one. MS (ESI) m/z 484 ($[M+H]^+$).

[0875] Step 7: A solution of (2S, 3S)-toluene-4-sulfonic acid 3-(6-fluoro-3,3-dimethyl-2-oxo-2,3-dihydro-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester (367 mg, 0.76 mmol) and methylamine (20 mL, 8M solution in ethanol) was stirred in a sealed tube for 16 hours. The solution was concentrated *in vacuo* to give 250 mg of the crude product. The crude product was purified via Biotage chromatography (FlasH40i, silica, 5%, 8% and 10% methanol with ammonia/dichloromethane) to give 77 mg of impure desired product. Final purification by reverse phase HPLC (X-terra MS C_{18} 19x150 mm, using an isocratic mixture of 60% methanol/water with 0.05% ammonium hydroxide at a rate of 20 mL/minute at 250 nm) gave 35 mg of desired product as the free base. The free base was treated with a 1 M ethereal solution of hydrochloric acid until the solution was pH=3 followed by diethyl ether. The product was crystallized by adding a minimum of hexane to afford the title compound 6-fluoro-1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one hydrochloride. MS (ESI) m/z 343 ($[M+H]^+$); HRMS: calcd for C20H23FN2O2 + H^+, 343.18163; found (ESI, $[M+H]^+$), 343.18.

[0876] EXAMPLE 196: 4-fluoro-1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one hydrochloride



[0877] Step 1: In an analogous manner to EXAMPLE 99, step1 1,2-difluoro-3-nitro-benzene was prepared from 2,3-Difluoro-phenylamine and a mixture of sodium perborate tetrahydrate . MS (ESI) m/z 160 ([M+H]$^+$).

[0878] Step 2: In an analogous manner to EXAMPLE 99, step 2 dimethyl (2-fluoro-6-nitrophenyl) malonate was prepared from 1,2-difluoro-3-nitro-benzene. MS (ESI) m/z 272.0576.

[0879] Step 3: In an analogous manner to EXAMPLE 99, step 3 (2-fluoro-6-nitrophenyl) acetic acid was prepared from dimethyl (2-fluoro-6-nitrophenyl)malonate. MS (ESI) m/z 200 ([M+H]$^+$).

[0880] Step 4: In an analogous manner to EXAMPLE 99, step 4 4-fluoro-1,3-dihydro-2H-indol-2-one was prepared from (2-fluoro-6-nitrophenyl)acetic acid. MS (ESI) m/z 152 ([M+H]$^+$).

[0881] Step 5: In an analogous manner to EXAMPLE 99, step 5 4-fluoro-3,3-dimethyl-1,3-dihydro-2H-indol-2-one was prepared from 4-fluoro-1,3-dihydro-2H-indol-2-one. MS (ESI) m/z 180 ([M+H]$^+$).

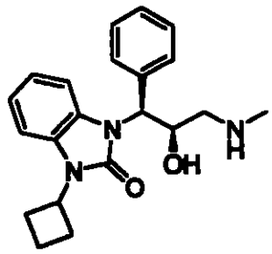
[0882] Step 6: In an analogous manner to EXAMPLE 99, step 6 1-[(2S,3S)-2,3-dihydroxy-1-phenylpropyl]-4-fluoro-3,3-dimethyl-1,3-dihydro-2H-indol-2-one was prepared from 4-fluoro-3,3-dimethyl-1,3-dihydro-2H-indol-2-one and [(2R, 3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4). MS (ESI) m/z 330 ([M+H]$^+$).

[0883] Step 7: In an analogous manner to EXAMPLE 1 step 2, (2S,3S)-toluene-4-sulfonic acid 3-(4-fluoro-3,3-dimethyl-2-oxo-2,3-dihydro-indol-1-yl)-2-hydroxy-3-

phenyl-propyl ester was prepared from 1-[(1S,2S)-2,3-dihydroxy-1-phenylpropyl]-4-fluoro-3,3-dimethyl-1,3-dihydro-2H-indol-2-one. MS (ESI) m/z 484 ([M+H]$^+$.

[0884] Step 8: In an analogous manner to EXAMPLE 195 step 7, 4-fluoro-1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one hydrochloride was prepared from (2S,3S)-toluene-4-sulfonic acid 3-(4-fluoro-3,3-dimethyl-2-oxo-2,3-dihydro-indol-1-yl)-2-hydroxy-3-phenyl-propyl ester. HRMS: calcd for C20H23FN2O2 + H$^+$, 343.18163; found (ESI, [M+H]$^+$), 343.1807.

[0885] EXAMPLE 197: 1-cyclobutyl-3-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride



[0886] In an analogous manner to EXAMPLE 192, step 1 *N*-cyclobutyl-2-nitroaniline was prepared from 1-fluoro-2-nitro-benzene and cyclobutyl amine. MS (ES) *m/z* 193.

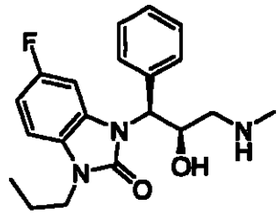
[0887] In an analogous manner to EXAMPLE 192, step 2 1-cyclobutyl-1,3-dihydro-2*H*-benzimidazol-2-one was prepared from *N*-cyclobutyl-2-nitroaniline. MS (ES) *m/z* 189.

[0888] In an analogous manner to EXAMPLE 192, step 3 1-cyclobutyl-3-[(*1S,2S*)-2,3-dihydroxy-1-phenyl-propyl]-1,3-dihydro-*2H*-benzimidazol-2-one was prepared from 1-cyclobutyl-1,3-dihydro-2*H*-benzimidazol-2-one and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4). MS (ES) *m/z* 339.2.

[0889] In an analogous manner to EXAMPLE 192, step 4 1-cyclobutyl-3-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2*H*-benzimidazol-2-one

hydrochloride was prepared from 1-cyclobutyl-3-[(*1S,2S*)-2,3-dihydroxy-1-phenyl-propyl]-1,3-dihydro-*2H*-benzimidazol-2-one as a white solid. MS (ES) *m/z* 352.2. HRMS: calcd for $C_{21}H_{25}N_3O_2$ + H+, 352.20195; found (ESI, $[M+H]^+$), 352.207

[0890] EXAMPLE 198: 5-fluoro-3-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1- propyl-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride



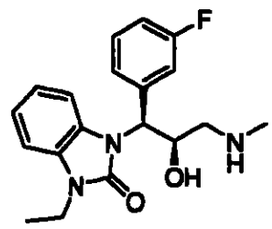
[0891] In an analogous manner to EXAMPLE 192, step 1 (4-fluoro-2-nitro-phenyl)-propyl-amine was prepared from 1,4-difluoro-2-nitro-benzene and propyl amine.

[0892] In an analogous manner to EXAMPLE 192, steps 1 and 2 5-fluoro-1-propyl-1,3-dihydro-benzimidazol-2-one was prepared from (4-fluoro-2-nitro-phenyl)-propyl-amine. MS (ES) *m/z* 195.2.

[0893] In an analogous manner to EXAMPLE 192, step 3 5-fluoro-3-[(*1S,2S*)-2,3-dihydroxy-1-phenyl-propyl]-1-propyl-1,3-dihydro-*2H*-benzimidazol-2-one was prepared from 5-fluoro-1-propyl-1,3-dihydro-benzimidazol-2-one and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4).

[0894] In an analogous manner to EXAMPLE 192, step 4 5-fluoro-3-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1-propyl-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride was prepared from 5-fluoro-3-[(*1S,2S*)-2,3-dihydroxy-1-phenyl-propyl]-1-propyl-1,3-dihydro-*2H*-benzimidazol-2-one as a white solid. MS (ES) *m/z* 358.2; HRMS: calcd for $C_{20}H_{24}FN_3O_2$ + H+, 358.19253; found (ESI, $[M+H]^+$), 358.1895

[0895] EXAMPLE 199: 1-Ethyl-3-[1-(3-fluoro-phenyl)-2-hydroxy-3-methylamino-propyl]-1,3-dihydro-benzimidazol-2-one hydrochloride



[0896] Step1: To a solution of ethylamine in methanol (2.0 M, 150 mL, 300 mmol) was added 1-fluoro-2-nitrobenzene (8 mL, 75.7 mmol). The reaction mixture was placed in a sealed vessel and heated to 55°C for 15 hours. The solvent was removed in *vacuo* and the residue was taken up in ethyl acetate (200 mL), washed with a saturated aqueous solution of sodium bicarbonate (80 mL), and dried over anhydrous sodium sulfate (50 g). After removal of solvent, ethyl-(2-nitro-phenyl)-amine (12.5g, 75 mmol) was obtained as a brown oil. MS (ES) *m/z* 167.1.

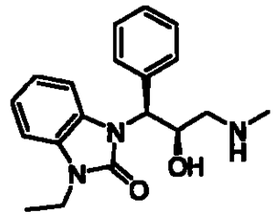
[0897] Step 2: To a solution of ethyl-(2-nitro-phenyl)-amine (12.5g, 75 mmol) in anhydrous tetrahydrofuran (150 mL) was added sodium borohydride (5.8g, 153 mmol), and 5% palladium on carbon (150 mg). Methanol (25 mL) was then added at room temperature under nitrogen in a dropwise manner. After addition, the reaction mixture was stirred at room temperature for about 30 minutes until the reaction was complete. The reaction mixture was then filtered through a pad of Celite. The filtrate was diluted with ethyl acetate (200 mL), washed with a saturated aqueous solution of ammonium chloride (80 mL), dried over sodium sulfite, and concentrated *in vacuo* to afford crude *N*-ethyl-benzene-1,2-diamine (8.4 g, 62 mmol) which was used in next step without further purification.

[0898] Step 3: To a solution of crude *N*-ethyl-benzene-1,2-diamine (8.4 g, 62 mmol) in anhydrous tetrahydrofuran (200 mL) was added 1,1'-carbonyldiimidazole (10g, 62 mmol). The mixture was stirred at room temperature under nitrogen for 12 hours and ethyl acetate (250 mL) followed by a cold 3N aqueous solution of hydrochloric acid (200 mL) were added. The organic layer was separated, dried over sodium sulfate and concentrated *in vacuo* to afford 1-ethyl-1,3-dihydro-benzimidazol-2-one as a white solid (8.5g, 69% for three steps). MS (ES) *m/z* 163.2.

[0899] Step 4: In an analogous manner to EXAMPLE 192, step 3 1-ethyl-3-[(*1S,2S*)-2,3-dihydroxy-1-(3-fluorophenyl)-propyl]-1,3-dihydro-*2H*-benzimidazol-2-one was prepared from 1-ethyl-1,3-dihydro-benzimidazol-2-one and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, step 3).

[0900] Step 5: In an analogous manner to EXAMPLE 192, step 4 1-ethyl-3-[(1S,2R)-1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-1,3- dihydro-2H-benzimidazol-2-one hydrochloride was prepared from 1-ethyl-3-[(*1S,2S*)-2,3-dihydroxy-1-(3-fluorophenyl)-propyl]-1,3-dihydro-*2H*-benzimidazol-2-one as a white solid. MS (ES) *m/z* 344.2

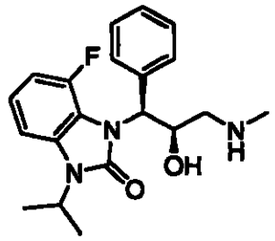
[0901] . EXAMPLE 200: 1-Ethyl-3-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride



[0902] In an analogous manner to EXAMPLE 192, step 3 1-ethyl-3-[(*1S,2S*)-2,3-dihydroxy-1-phenyl-propyl]-1,3-dihydro-*2H*-benzimidazol-2-one was prepared from 1-ethyl-1,3-dihydro-benzimidazol-2-one (EXAMPLE 199, step 2) and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4).

[0903] In an analogous manner to EXAMPLE 192, steps 4 and 5 1-ethyl-3-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride was prepared from 1-ethyl-3-[(*1S,2S*)-2,3-dihydroxy-1-phenyl-propyl]-1,3-dihydro-*2H*-benzimidazol-2-one as a white solid. MS (ES) *m/z* 326.2; HRMS: calcd for $C_{19}H_{23}N_3O_2$ + H+, 326.18630; found (ESI, $[M+H]^+$), 326.1845.

[0904] EXAMPLE 201: 4-Fluoro-3-(2-hydroxy-3-methylamino-1-phenyl-propyl)-1-isopropyl-1,3-dihydro-benzimidazol-2-one hydrochloride



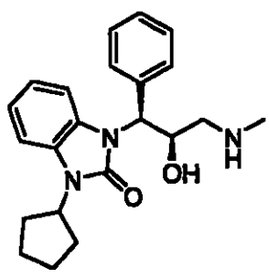
[0905] In an analogous manner to EXAMPLE 192, step 1 (3-fluoro-2-nitro-phenyl)-isopropyl-amine was prepared from 1,3-difluoro-2-nitro-benzene and *iso*-propylamine.

[0906] In an analogous manner to EXAMPLE 192, step 2 4-fluoro-1-isopropyl-1,3-dihydro-benzimidazol-2-one was prepared from (3-fluoro-2-nitro-phenyl)-isopropyl-amine. MS (ES) *m/z* 195.2.

[0907] In an analogous manner to EXAMPLE 192, step 3 4-fluoro-3-[(*1S,2S*)-2,3-dihydroxy-1-phenyl-propyl]-1-isopropyl-1,3-dihydro-*2H*-benzimidazol-2-one was prepared from 4-fluoro-1-isopropyl-1,3-dihydro-benzimidazol-2-one and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4).

[0908] In an analogous manner to EXAMPLE 192, step 4 4-fluoro-3-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1-isopropyl-1,3-dihydro-2H-benzimidazol-2-one hydrochloride was prepared from 4-fluoro-3-[(*1S,2S*)-2,3-dihydroxy-1-phenyl-propyl]-1-isopropyl-1,3-dihydro-*2H*-benzimidazol-2-one as a white solid. MS (ES) *m/z* 358.4.

[0909] EXAMPLE 202: 1-Cyclopentyl-3-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride



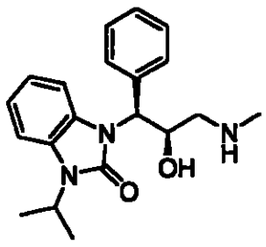
[0910] In an analogous manner to EXAMPLE 192, step 1 *N*-cyclopentyl-2-nitroaniline was prepared from 1-fluoro-2-nitro-benzene and cyclopentyl amine. MS (ESI) *m/z* 207.

[0911] In an analogous manner to EXAMPLE 192, step 2 1-cyclopentyl-1,3-dihydro-benzimidazol-2-one was prepared from *N*-cyclopentyl-2-nitroaniline. MS (ESI) *m/z* 203.

[0912] In an analogous manner to EXAMPLE 192, step 3 1-cyclopentyl-3-[(1*S*,2*S*)-2,3-dihydroxy-1-phenylpropyl]-1,3-dihydro-2*H*-benzimidazol-2-one was prepared from 1-cyclopentyl-1,3-dihydro-benzimidazol-2-one and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4) as a white solid. MS (ES) *m/z* 352.9.

[0913] In an analogous manner to EXAMPLE 192, step 4 1-cyclopentyl-3-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride was prepared from 1-cyclopentyl-3-[(1*S*,2*S*)-2,3-dihydroxy-1-phenylpropyl]-1,3-dihydro-2*H*-benzimidazol-2-one as a white solid. MS (ES) *m/z* MS (ESI) *m/z* 366.

[0914] EXAMPLE 203: 1-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3-isopropyl-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride



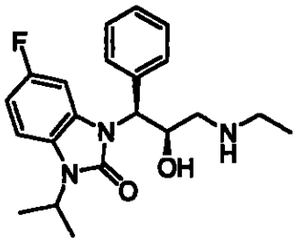
[0915] In an analogous manner to EXAMPLE 192, step 1 *N*-isopropyl-2-nitroanlline was prepared from 1-fluoro-2-nitro-benzene and isopropyl amine. MS (ES) *m/z* 181.2.

[0916] In an analogous manner to EXAMPLE 192, step 2 1-isopropyl-1,3-dihydro-2*H*-benzimidazol-2-one was prepared from *N*-isopropyl-2-nitroaniline. MS (ES) *m/z* 176.9.

[0917] In an analogous manner to EXAMPLE 192, step 3 1-[(1*S*,2*S*)-2,3-dihydroxy-1-phenylpropyl]-3-isopropyl-1,3-dihydro-2*H*-benzimidazol-2-one was prepared from 1-isopropyl-1,3-dihydro-2*H*-benzimidazol-2-one and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4) as a white solid.

[0918] In an analogous manner to EXAMPLE 192, step 4 1-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3-isopropyl-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride was prepared from 1-[(1*S*,2*S*)-2,3-dihydroxy-1-phenylpropyl]-3-isopropyl-1,3-dihydro-2*H*-benzimidazol-2-one as a white solid. MS (ES) *m/z* MS (ES) *m/z* 340.3; HRMS: calcd for $C_{20}H_{25}N_3O_2$ + H+, 340.20195; found (ESI, $[M+H]^+$), 340.2012.

[0919] EXAMPLE 204: 3-[(1*S*,2*R*)-3-(ethylamino)-2-hydroxy-1-phenylpropyl]-5-fluoro-1-isopropyl-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride



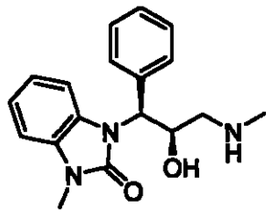
[0920] In an analogous manner to EXAMPLE 192, step 1 4-fluoro-*N*-isopropyl-2-nitroaniline was prepared from 1,4-difluoro-2-nitro-benzene and isopropyl amine. MS (ES) *m/z* 199.1.

[0921] In an analogous manner to EXAMPLE 192, step 2 5-fluoro-1-isopropyl-1,3-dihydro-2*H*-benzimidazol-2-one was prepared from 4-fluoro-*N*-isopropyl-2-nitroaniline. MS (ES) *m/z* 195.1.

[0922] In an analogous manner to EXAMPLE 192, step 3 5-fluoro-1-[(1*S*,2*S*)-2,3-dihydroxy-1-phenylpropyl]-3-isopropyl-1,3-dihydro-2*H*-benzimidazol-2-one was prepared from 5-fluoro-1-isopropyl-1,3-dihydro-2*H*-benzimidazol-2-one and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4) as a white solid.

[0923] In an analogous manner to EXAMPLE 192, step 4 3-[(1*S*,2*R*)-3-(ethylamino)-2-hydroxy-1-phenylpropyl]-5-fluoro-1-isopropyl-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride was prepared from 5-fluoro-1-[(1*S*,2*S*)-2,3-dihydroxy-1-phenylpropyl]-3-isopropyl-1,3-dihydro-2*H*-benzimidazol-2-one and *para*-toluenesulfonic acid followed by ethylamine as a white solid. MS (ESI) *m/z* 372.21; HRMS: calcd for $C_{21}H_{26}FN_3O_2$ + H+, 372.20818; found (ESI, $[M+H]^+$), 372.2099.

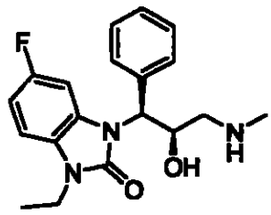
[0924] EXAMPLE 205: 1-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3-methyl-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride



[0925] In an analogous manner to EXAMPLE 192, step 3 1-[(1*S*,2*S*)-2,3-dihydroxy-1-phenylpropyl]-3-methyl-1,3-dihydro-2*H*-benzimidazol-2-one was prepared from 1-methyl-1,3-dihydro-benzimidazol-2-one and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4) as a white solid.

[0926] In an analogous manner to EXAMPLE 192, step 4 1-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3-methyl-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride was prepared from 1-[(1*S*,2*S*)-2,3-dihydroxy-1-phenylpropyl]-3-methyl-1,3-dihydro-2*H*-benzimidazol-2-one as a white solid. MS (ES) *m/z* 312.3; HRMS: calcd for $C_{18}H_{21}N_3O_2$ + H+, 312.17065; found (ESI, $[M+H]^+$), 312.17.

[0927] EXAMPLE 206: 1-Ethyl-5-fluoro-3-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride



[0928] In an analogous manner to EXAMPLE 199, step 1 ethyl-(4-fluoro-2-nitro-phenyl)-amine was prepared from 1,4-difluoro-2-nitroaniline and ethylamine.

[0929] In an analogous manner to EXAMPLE 199, step 2 *N*-ethyl-4-fluoro-benzene-1,2-diamine was prepared from ethyl-(4-fluoro-2-nitro-phenyl)-amine.

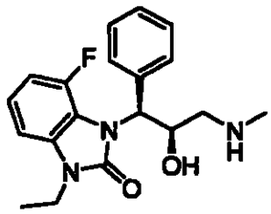
[0930] In an analogous manner to EXAMPLE 199, step 3 1-ethyl-5-fluoro-1,3-dihydro-2*H*-benzimidazol-2-one was prepared from *N*-ethyl-4-fluoro-benzene-1,2-diamine. MS (ES) *m/z* 181.2.

[0931] In an analogous manner to EXAMPLE 192, step 3 3-[(1*S*,2*S*)-2,3-dihydroxy-1-phenylpropyl]-1-ethyl-5-fluoro-1,3-dihydro-2*H*-benzimidazol-2-one was prepared from 1-ethyl-5-fluoro-1,3-dihydro-2*H*-benzimidazol-2-one and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4) as a white solid. MS (ES) *m/z* 331.1.

[0932] In an analogous manner to EXAMPLE 192, step 4 1-ethyl-5-fluoro-3-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2*H*-benzimidazol-

2-one hydrochloride was prepared from 3-[(1*S*,2*S*)-2,3-dihydroxy-1-phenylpropyl]-1-ethyl-5-fluoro-1,3-dihydro-2*H*-benzimidazol-2-one as a white solid. MS (ES) *m/z* 344.2; HRMS: calcd for $C_{19}H_{22}FN_3O_2$ + H+, 344.17688; found (ESI, $[M+H]^+$), 344.175.

[0933] EXAMPLE 207: 1-Ethyl-4-fluoro-3-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride



[0934] In an analogous manner to EXAMPLE 199, step 1 ethyl-(3-fluoro-2-nitro-phenyl)-amine was prepared from 1,3-difluoro-2-nitroaniline and ethylamine.

[0935] In an analogous manner to EXAMPLE 199, step 2 *N*-ethyl-3-fluoro-benzene-1,2-diamine was prepared from ethyl-(3-fluoro-2-nitro-phenyl)-amine.

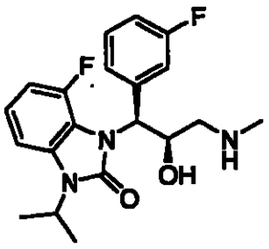
[0936] In an analogous manner to EXAMPLE 199, step 3 1-ethyl-4-fluoro-1,3-dihydro-2*H*-benzimidazol-2-one was prepared from *N*-ethyl-3-fluoro-benzene-1,2-diamine. MS (ES) *m/z* 181.2.

[0937] In an analogous manner to EXAMPLE 192, step 3 3-[(1*S*,2*S*)-2,3-dihydroxy-1-phenylpropyl]-1-ethyl-4-fluoro-1,3-dihydro-2*H*-benzimidazol-2-one was prepared from 1-ethyl-4-fluoro-1,3-dihydro-2*H*-benzimidazol-2-one and [(2R,3R)-3-phenyloxiran-2-yl]methanol (EXAMPLE 117, step 4) as a white solid. MS (ES) *m/z* 331.1.

[0938] In an analogous manner to EXAMPLE 192, step 4 1-ethyl-4-fluoro-3-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride was prepared from 3-[(1*S*,2*S*)-2,3-dihydroxy-1-phenylpropyl]-1-ethyl-4-fluoro-1,3-dihydro-2*H*-benzimidazol-2-one as a white solid. MS (ES) *m/z*

344.2; HRMS: calcd for $C_{19}H_{22}FN_3O_2$ + H+, 344.17688; found (ESI, $[M+H]^+$), 344.1768.

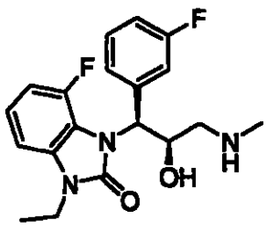
[0939] EXAMPLE 208: 4-fluoro-3-[(1S,2R)- 1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)-propyl]-1-isopropyl-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride



[0940] In an analogous manner to EXAMPLE 192, step 3 4-fluoro-3-[(1S,2S)- 1-(3-fluoro-phenyl)-2,3-dihydroxy-propyl]-1-isopropyl-1,3-dihydro-benzimidazol-2-one was prepared from 4-fluoro-1-isopropyl-1,3-dihydro-benzimidazol-2-one (EXAMPLE 201, step 2) and [(2R,3R)-3-(3-fluorophenyl)-oxiran-2-yl]methanol (EXAMPLE 47, step 3) as an oil.

[0941] In an analogous manner to EXAMPLE 192, step 4 4-fluoro-3-[(1S,2R)- 1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)-propyl]-1-isopropyl-1,3-dihydro-2H-benzimidazol-2-one hydrochloride was prepared from 4-fluoro-3-[(1S,2S)- 1-(3-fluorophenyl)-2,3-dihydroxy-propyl]-1-isopropyl-1,3-dihydro-benzimidazol-2-one as a white solid. MS (ES) *m/z* 376.2

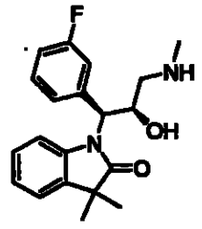
[0942] EXAMPLE 209: 1-Ethyl-4-fluoro-3-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-(3-fluorophenyl)-propyl]-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride



[0943] In an analogous manner to EXAMPLE 192, step 3 3-[(1*S*,2*S*)-2,3-dihydroxy-1-(3-fluorophenyl)-propyl]-1-ethyl-4-fluoro-1,3-dihydro-2*H*-benzimidazol-2-one was prepared from 1-ethyl-4-fluoro-1,3-dihydro-2*H*-benzimidazol-2-one (EXAMPLE 207, step 2) and [(2R,3R)-3-(3-fluorophenyl)-oxiran-2-yl]methanol (EXAMPLE 47, step 3) as clear oil. MS (ES) *m/z* 349.1.

[0944] In an analogous manner to EXAMPLE 192, step 4 1-ethyl-4-fluoro-3-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-(3-fluorophenyl)-propyl]-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride was prepared from 3-[(1*S*,2*S*)-2,3-dihydroxy-1-(3-fluorophenyl)-propyl]-1-ethyl-4-fluoro-1,3-dihydro-2*H*-benzimidazol-2-one as a white solid. MS (ES) *m/z* 362.1.

[0945] EXAMPLE 210 :1-[(1S,2R)-1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one hydrochloride

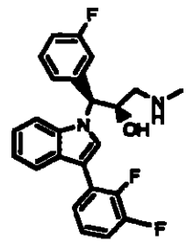


[0946] Step 1: In an analogous manner to EXAMPLE 101, step 1 (2S, 3S)-1-[1-(3-fluoro-phenyl)-2,3-dihydroxy-propyl]-3,3-dimethyl-1,3-dihydro-indol-2-one was prepared from 3,3-dimethyl-1,3-dihydro-indol-2-one[10] and [(2R,3R)-3-(3-fluorophenyl)oxiran-2-yl]methanol (EXAMPLE 47, step 3). MS (ESI) m/z 330 ([M+H]$^+$).

[0947] Step 2: In an analogous manner to EXAMPLE 1, step 2 (2S, 3S)-toluene-4-sulfonic acid 3-(3,3-dimethyl-2-oxo-2,3-dihydro-indol-1-yl)-3-(3-fluoro-phenyl)-2-hydroxy-propyl ester was prepared from (2S, 3S)-1-[1-(3-fluoro-phenyl)-2,3-dihydroxy-propyl]-3,3-dimethyl-1,3-dihydro-indol-2-one. MS (ESI) m/z 484 ([M+H]$^+$).

[0948] Step 3: In an analogous manner to EXAMPLE 5 1-[(1S,2R)-1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one hydrochloride was prepared from (2S,3S)-toluene-4-sulfonic acid 3-(3,3-dimethyl-2-oxo-2,3-dihydro-indol-1-yl)-3-(3-fluoro-phenyl)-2-hydroxy-propyl ester. MS (ESI) m/z 343 ([M+H]$^+$).

[0949] EXAMPLE 211: (1S,2R)-1-[3-(2,3-difluorophenyl)-1H-indol-1-yl]-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride

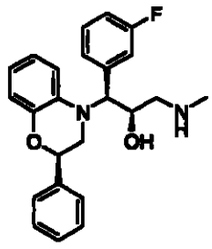


[0950] In an analogous manner to EXAMPLE 114, step 2, (2S,3S)-3-(3-fluorophenyl)-[3-(2, 3-difluorophenyl)-1H-indol-1-yl]propane-1,2-diol was prepared from (2*S*,3*S*)-3-(3-fluorophenyl)-3-(3-iodo-1*H*-indol-1-yl)propane-1,2-diol (EXAMPLE 114, step 1) and 2, 3-difluorobenzeneboronic acid.

[0951] In an analogous manner to EXAMPLE 1, step 2, (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-3-(2,3-difluorophenyl)-indol-1-yl]-2-hydroxy-propyl ester was prepared from (2S,3S)-3-(3-fluorophenyl)-3-[3-(2,3-difluorophenyl)-1H-indol-1-yl]propane-1,2-diol.

[0952] In an analogous manner to EXAMPLE 5, (1S,2R)-1-[3-(2,3-difluorophenyl)-1H-indol-1-yl]-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol was prepared from (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-3-(2,3-difluorophenyl)-indol-1-yl]-2-hydroxy-propyl ester. MS (ES) m/z 411.1; HRMS: calcd for C24H21F3N2O + H+, 411.16787; found (ESI, [M+H]+), 411.1675.

[0953] EXAMPLE 212: (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-[(2R)-2-phenyl-2,3-dihydro-4H-1,4-benzoxazin-4-yl]propan-2-ol hydrochloride

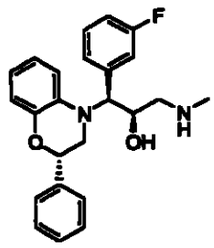


[0954] Step 1: Diastereomeric mixture of (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(2-phenyl-2,3-dihydro-4H-1,4-benzoxazin-4-yl)propan-2-ol (EXAMPLE 168) was dissolved in methanol. The resulting solution was injected onto the Supercritical Fluid Chromatography instrument. The baseline resolved diastereomers, using the conditions described below, were collected.

SFC Instrument: Berger MultiGram Prep SFC (Berger Instruments, Inc. Newark, DE 19702.
Column: Ethyl pyridine; 250mm L x 20mm ID (Princeton Chromatography Inc.)
Column temperature: 35°C
SFC Modifier: 15% MeOH with 85% CO_2
Flow rate: 50 mL/min
Outlet Pressure: 100 bar
Detector: UV at 220 nm

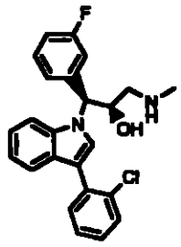
[0955] Step 2: (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-[(2R)-2-phenyl-2,3-dihydro-4H-1,4-benzoxazin-4-yl]propan-2-ol, isolated as peak 1, was subjected to hydrochloride salt formation in an analogous manner to EXAMPLE 144, step 2 to give (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-[(2R)-2-phenyl-2,3-dihydro-4H-1,4-benzoxazin-4-yl]propan-2-ol hydrochloride as a white powder. MS (ES) *m/z* 393.2 ($[M+H]^+$); HRMS: calcd for $C_{24}H_{25}FN_2O_2 + H^+$, 393.1973; found (ESI, $[M+H]^+$), 393.1992.

[0956] EXAMPLE 213: (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-[(2S)-2-phenyl-2,3-dihydro-4H-1,4-benzoxazin-4-yl]propan-2-ol hydrochloride



[0957] In an analogous manner to EXAMPLE 212, (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-[(2S)-2-phenyl-2,3-dihydro-4H-1,4-benzoxazin-4-yl]propan-2-ol hydrochloride was prepared as a white powder from (1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-[(2S)-2-phenyl-2,3-dihydro-4H-1,4-benzoxazin-4-yl]propan-2-ol, which was isolated as peak 2 of the diastereomeric separation (EXAMPLE 212, step1). MS (ES) *m/z* 393.2 ($[M+H]^+$); HRMS: calcd for $C_{24}H_{25}FN_2O_2$ + H^+, 393.1973; found (ESI, $[M+H]^+$), 393.1982.

[0958] EXAMPLE 214: (1S,2R)-1-[3-(2-chlorophenyl)-1H-indol-1-yl]-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride



[0959] In an analogous manner to EXAMPLE 114, step 2, (2S,3S)-3-(3-fluorophenyl)-3-{3-[2-chlorophenyl]-1H-indol-1-yl}propane-1,2-diol was prepared from (2*S*,3*S*)-3-(3-fluorophenyl)-3-(3-iodo-1*H*-indol-1-yl)propane-1,2-diol (EXAMPLE 114, step 1) and 2-chlorobenzeneboronic acid.

[0960] In an analogous manner to EXAMPLE 1, step 2, (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-fluorophenyl)-3-[3-(2-chlorophenyl)-indol-1-yl]-2-hydroxy-propyl ester was prepared from (2S,3S)-3-(3-fluorophenyl)-3-{3-[2-chlorophenyl]-1H-indol-1-yl}propane-1,2-diol.

[0961] In an analogous manner to EXAMPLE 5, (1S,2R)-1-[3-(2-chlorophenyl)-1H-indol-1-yl]-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol hydrochloride was prepared from (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-fluoro-phenyl)-3-[3-(2-chlorphenyl)-indol-1-yl]-2-hydroxy-propyl ester and methylamine (2N solution in methanol). MS (ESI) *m/z* 409.1; HRMS: calcd for C24H22ClFN2O + H+, 409.14774; found (ESI, [M+H]+), 409.146.

[0962] Cell Lines, Culture Reagents, and Assays

MDCK-Net6 cells, stably transfected with human hNET (Pacholczyk, T., R.D. Blakely, and S.G. Amara, *Nature*, **1991**, **350**(6316): p. 350-4) were cultured in growth medium containing high glucose DMEM (Gibco, Cat. No. 11995), 10% FBS (dialyzed, heat-inactivated, US Bio-Technologies, Lot FBD1129HI) and 500 □g/ml G418 (Gibco, Cat. No. 10131). Cells were plated at 300,000/ T75 flask and cells were split twice weekly. The JAR cell line (human placental choriocarcinoma) was purchased from ATCC (Cat. No. HTB-144). The cells were cultured in growth medium containing RPMI 1640 (Gibco, Cat. No. 72400), 10% FBS (Irvine, Cat. No. 3000), 1% sodium pyruvate (Gibco, Cat. No. 1136) and 0.25% glucose. Cells were plated at 250,000 cells/ T75 flask and split twice weekly. For all assays, cells were plated in Wallac 96-well sterile plates (PerkinElmer, Cat. No. 3983498).

[0963] Norepinephrine (NE) Uptake Assay

On day 1, cells were plated at 3,000 cells/well in growth medium and maintained in a cell incubator (37°C, 5% CO_2). On day 2, growth medium was replaced with 200 µl of assay buffer (25 mM HEPES; 120 mM NaCl; 5 mM KCl; 2.5 mM $CaCl_2$; 1.2 mM $MgSO_4$; 2 mg/ml glucose (pH 7.4, 37°C)) containing 0.2 mg/ml ascorbic acid and 10 µM pargyline. Plates containing cells with 200 µl of assay buffer were equilibrated for 10 minutes at 37°C prior to addition of compounds. A stock solution of desipramine was prepared in DMSO (10 mM) and delivered to triplicate wells containing cells for a final test concentration of 1 µM. Data from these wells were used to define non-specific NE uptake (minimum NE uptake). Test compounds were prepared in DMSO (10 mM) and diluted in assay buffer according

to test range (1 to 10,000 nM). Twenty-five microliters of assay buffer (maximum NE uptake) or test compound were added directly to triplicate wells containing cells in 200 µl of assay buffer. The cells in assay buffer with test compounds were incubated for 20 minutes at 37°C. To initiate the NE uptake, [^{3}H]NE diluted in assay buffer (120 nM final assay concentration) was delivered in 25 µl aliquots to each well and the plates were incubated for 5 minutes (37°C). The reaction was terminated by decanting the supernatant from the plate. The plates containing cells were washed twice with 200 µl assay buffer (37°C) to remove free radioligand. The plates were then inverted, left to dry for 2 minutes, then reinverted and air-dried for an additional 10 minutes. The cells were lysed in 25 µl of 0.25 N NaOH solution (4°C), placed on a shake table and vigorously shaken for 5 minutes. After cell lysis, 75 µl of scintillation cocktail was added to each well and the plates were sealed with film tape. The plates were returned to the shake table and vigorously shaken for a minimum of 10 minutes to ensure adequate partitioning of organic and aqueous solutions. The plates were counted in a Wallac Microbeta counter (PerkinElmer) to collect the raw cpm data.

[0964] Serotonin (5-HT) Uptake Assay

The methods for 5-HT functional reuptake using the JAR cell line were modified using a previous literature report (Prasad, *et al.*, *Placenta*, 1996. 17(4): 201-7). On day 1, cells were plated at 15,000 cells/well in 96-well plates containing growth medium (RPMI 1640 with 10% FBS) and maintained in a cell incubator (37°C, 5% CO_2). On day 2, cells were stimulated with staurosporine (40 nM) to increase the expression of the 5-HT transporter [17]. On day 3, cells were removed from the cell incubator two hours prior to assay and maintained at room temperature to equilibrate the growth medium to ambient oxygen concentration. Subsequently, the growth medium was replaced with 200 µl of assay buffer (25 mM HEPES; 120 mM NaCl; 5 mM KCl; 2.5 mM $CaCl_2$; 1.2 mM $MgSO_4$; 2 mg/ml glucose (pH 7.4, 37°C)) containing 0.2 mg/ml ascorbic acid and 10 µM pargyline. A stock solution of paroxetine (AHR-4389-1) was prepared in DMSO (10 mM) and delivered to triplicate wells containing cells for a final test concentration of 1 µM. Data from these wells

were used to define non-specific 5-HT uptake (minimum 5-HT uptake). Test compounds were prepared in DMSO (10 mM) and diluted in assay buffer according to test range (1 to 1,000 nM). Twenty-five microliters of assay buffer (maximum 5-HT uptake) or test compound were added directly to triplicate wells containing cells in 200 µl of assay buffer. The cells were incubated with the compound for 10 minutes (37°C). To initiate the reaction, [^{3}H]hydroxytryptamine creatinine sulfate diluted in assay buffer was delivered in 25 µl aliquots to each well for a final test concentration of 15 nM. The cells were incubated with the reaction mixture for 5 minutes at 37°C. The 5-HT uptake reaction was terminated by decanting the assay buffer. The cells were washed twice with 200 µl assay buffer (37°C) to remove free radioligand. The plates were inverted and left to dry for 2 minutes, then reinverted and air-dried for an additional 10 minutes. Subsequently, the cells were lysed in 25 µl of 0.25 N NaOH (4°C) then placed on a shaker table and shaken vigorously for 5 minutes. After cell lysis, 75 µl of scintillation cocktail was added to the wells, the plates were sealed with film tape and replaced on the shake table for a minimum of 10 minutes. The plates were counted in a Wallac Microbeta counter (PerkinElmer) to collect the raw cpm data.

[0965] Evaluation of Results

For each experiment, a data stream of cpm values collected from the Wallac Microbeta counter was downloaded to a Microsoft Excel statistical application program. Calculations of EC_{50} values were made using the transformed-both-sides logistic dose response program written by Wyeth Biometrics Department. The statistical program uses mean cpm values from wells representing maximum binding or uptake (assay buffer) and mean cpm values from wells representing minimum binding or uptake ((1 µM desipramine (hNET) or 1 µM paroxetine (hSERT)). Estimation of the EC_{50} value was completed on a log scale and the line was fit between the maximum and minimum binding or uptake values. All graphic data representation was generated by normalizing each data point to a mean percent based on the maximum and minimum binding or uptake values. The EC_{50} values reported from multiple experiments were calculated by pooling the raw data from

each experiment and analyzing the pooled data as one experiment. The results are reported in ***Table 1***.

Table 1

Example	% Inhibition @ 1 μM (hNET)
1	4.6
2	66.5 (@ 10 μM)
3	17.6
4	24.5
5	58.1
6	13.1
7	25.6
8	53.4
9	79.2 (@ 10 μM)
10	70.5 (@ 10 μM)
11	94.5
12	70.6
13	34.3
14	24.4
15	8.5
16	96.8
17	71.0
18	11.3
19	31.6
20	85.0
21	97.5
22	83.8
23	89.7
24	57.2
25	37.5
26	54.0
27	75.4

Example	% Inhibition 1 μM (hNET)
28	30.1
29	89.5
30	79.7
31	98.9
33	99.4
34	78.4
35	94.3
36	82.3
37	21.4
38	71.9
39	57.4
40	57.6
41	32.4
42	95.7
43	99
44	98.2
47	99.9
48	96.6
49	101.2
50	91.8
51	87.0
52	94.3
53	57.4
54	68.6
55	61.1
56	12.3
57	17.5
58	26.5
59	93.2
60	100

Example	% Inhibition 1 µM (hNET)
61	99.8
62	99.7
63	91.9
64	99.9
65	100
66	86.6
67	90.9
68	99.6
69	87.5
70	77.7
71	44.9
72	24
73	21.8
74	67
75	88.4
76	75.2
77	77.3
78	70.9
79	66
80	83.5
81	58.0
82	53.9
83	99.5
84	40.9
85	97.4
86	52.7
87	99.7
90	73.1
91	90.8
92	85.8

Example	% Inhibition 1 μM (hNET)
93	96.3
94	94.9
95	97.6
96	98.2
97	99.6
98	99.1
99	98.1
100	94.2
101	98.6
102	95.3
103	86.1
104	99.4
105	92.6
106	85.8
107	96.6
108	98.7
109	94.7
110	86.4
111	42.7
112	100.3
113	99.7
114	100
115	23.9
116	97.3
117	95.3
118	67.9
119	96.3
120	68.6
121	21.2
122	97.4

Example	% Inhibition 1 μM (hNET)
123	65
124	91.5
125	94.3
126	92.9
127	95.7
128	45.6
129	71.8
130	76
131	63.1
132	93
133	96.4
134	68.5
135	99.5
136	97
137	99.1
138	97.9
139	94.9
140	96.7
143	96.8
146	97.1
147	91.7
148	97.8
149	100.4
150	98.3
151	94.3
152	96.2
153	97.4
154	96.1
155	98.9
157	99.6

Example	% Inhibition @ 1 μM (hNET)
158	99.6
159	93.8
160	99.3
161	99.4
162	99.2
163	99.7
164	98.6
169	72
170	96.4
171	98.3
172	88
173	67.5
174	99.1
175	99.6
176	100
177	29.9
178	69.2
179	99.8
180	70.4
181	96.9
182	97.1
183	100.5
184	99.7
185	80.8
186	96.6
187	52
188	71.6
189	99.3
190	53.7
191	63.9

Example	% Inhibition @ 1 μM (hNET)
192	54.6
193	98.4
194	79
195	91
196	94.6
197	97
198	97.7
199	99.1
200	97.9
201	98.8
202	92.7
203	98.9
204	47.4
205	82.9
206	96.9
207	98.3
208	99.8
209	99.3
210	96.3
211	99.8
214	99.9

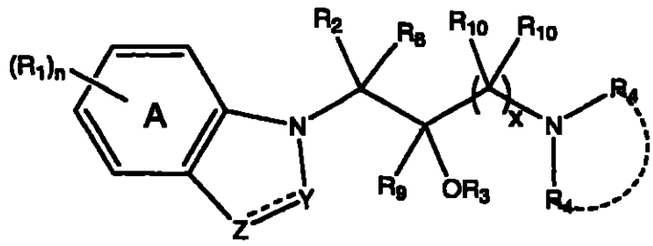
[0966] When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and subcombinations of ranges specific embodiments therein are intended to be included.

[0967] The disclosures of each patent, patent application and publication cited or described in this document are hereby incorporated herein by reference, in its entirety.

[0968] Those skilled in the art will appreciate that numerous changes and modifications can be made to the preferred embodiments of the invention and that such changes and modifications can be made without departing from the spirit of the invention. It is, therefore, intended that the appended claims cover all such equivalent variations as fall within the true spirit and scope of the invention.

What is claimed is:

1. A compound of formula I:



I

or a pharmaceutically acceptable salt thereof;

wherein:

the dotted line between Y and Z represents an optional double bond;

the dotted line between the two R_4 groups represents an optional heterocyclic ring of 4 to 6 ring atoms that may be formed between the two R_4 groups, together with the nitrogen through which they are attached;

Y is N, CR_6, or C=O;

Z is N, NR_7, CR_5, or $C(R_5)_2$;

R_1 is, independently at each occurrence, alkyl, alkoxy, halo, CF_3, OCF_3, arylalkyloxy substituted with 0-3 R_{11}, aryloxy substituted with 0-3 R_{11}, aryl substituted with 0-3 R_{11}, heteroaryl substituted with 0-3 R_{11}, hydroxy, alkanoyloxy, nitro, nitrile, alkenyl, alkynyl, alkylsulfoxide, phenylsulfoxide substituted with 0-3 R_{11}, alkylsulfone, phenylsulfone substituted with 0-3 R_{11}, alkylsulfonamide, phenylsulfonamide substituted with 0-3 R_{11}, heteroaryloxy substituted with 0-3 R_{11}, heteroarylmethyloxy substituted with 0-3 R_{11}, alkylamido, or arylamido substituted with 0-3 R_{11}; or two adjacent R_1 also represent methylenedioxy;

R_2 is aryl substituted with 0-3 R_1 or heteroaryl substituted with 0-3 R_1;

R_3 is H or C_1-C_4 alkyl;

R_4 is, independently at each occurrence, H, C_1-C_4 alkyl, arylalkyl, heteroarylmethyl, cycloheptylmethyl, cyclohexylmethyl, cyclopentylmethyl, or cyclobutylmethyl, or

both R_4 groups, together with the nitrogen through which they are attached, form a heterocyclic ring of 4 to 6 ring atoms, where one carbon may be optionally replaced with N, O, S, or SO_2, and where any carbon ring atom or additional N atom may be optionally substituted with C_1-C_4 alkyl, F, or CF_3;

R_5 is, independently at each occurrence, H, C_1-C_4 alkyl, aryl substituted with 0-3 R_1, or cyano; or when two R_5 are present, they form a carbocyclic ring of 3-7 carbons;

R_6 is H, C_1-C_4 alkyl, or cyano;

R_7 is H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or aryl substituted with 0-3 R_1;

R_8 is H, or C_1-C_4 alkyl;

R_9 is H, or C_1-C_4 alkyl;

R_{10} is, independently at each occurrence, H, or C_1-C_4 alkyl; or R_{10} and R_4 together with the nitrogen to which R_4 is attached form a nitrogen-containing ring containing 3-6 carbon atoms;

n is an integer from 0 to 4;

x is an integer from 1 to 2; and

R_{11} is alkyl, alkoxy, halo, CF_3, OCF_3, hydroxy, alkanoyloxy, nitro, nitrile, alkenyl, alkynyl, alkylsulfoxide, alkylsulfone, alkylsulfonamide, or alkylamido; or two adjacent R_{11} also represent methylenedioxy;

wherein 1-3 carbon atoms in ring A may optionally be replaced with N.

2. A compound according to claim 1, wherein:

Y is CR_6.

3. A compound according to claim 2, wherein:

Y is CH.

4. A compound according to any one of claims 1 to 3, wherein:

X is CR_5.

5. A compound according to any one of claims 1 to 4, wherein:

R_1 is halo.

6. A compound according to claim 5, wherein:

R_1 is fluoro or chloro.

7. A compound according to any one of claims 1 to 6, wherein:

R_2 is aryl substituted with 0-3 R_1.

8. A compound according to claim 6, wherein:

R_2 is phenyl.

9. A compound according to any one of claims 1 to 8, wherein:

R_3 is H or C_1 alkyl.

10. A compound according to any one of claims 1 to 9, wherein:

R_4 is H or C_1-C_4 alkyl.

11. A compound according to claim 10, wherein:

R_4 is H, methyl, ethyl, or isopropyl.

12. A compound according to any one of claims 1 to 9, wherein:

both R_4 groups, together with the nitrogen through which they are attached, form a pyridine, piperidine, piperazine, piperazine substituted with a methyl group, or morpholine ring.

13. A compound according to any one of claims 1 to 12, wherein:

R_5 is, independently at each occurrence, H, C_1 alkyl, or cyano.

14. A compound according to any one of claims 1 to 13, wherein:

R_6 is H, methyl, ethyl, or cyano.

15. A compound according to any one of claims 1 to 14, wherein:

R_7 is H, methyl, ethyl, isopropyl, cyclopentyl, cyclohexyl, phenyl, tolyl, or xylyl.

16. A compound according to any one of claims 1 to 15, wherein:

R_8 is H, methyl, or ethyl.

17. A compound according to any one of claims 1 to 16, wherein:

R_9 is H, methyl, or ethyl.

18. A compound according to any one of claims 1 to 17, wherein:

R_{10} is H or methyl.

19. A compound according to any one of claims 1 to 18, wherein:

n is 0 or 1.

20. A compound according to any one of claims 1 to 19, wherein:

x is 1.

21. A compound according to claim 1, wherein:

Y is N, CR_6, or C=O;

Z is N, NR_7, CR_6, or $C(R_5)_2$;

R_1 is, independently at each occurrence, alkyl, alkoxy, halo, CF_3, OCF_3, arylalkyloxy substituted with 0-3 R_{11}, aryloxy substituted with 0-3 R_{11}, aryl substituted with 0-3 R_{11}, heteroaryl substituted with 0-3 R_{11}, hydroxy, alkanoyloxy, nitro, nitrile, alkenyl, alkynyl, alkylsulfoxide, phenylsulfoxide substituted with 0-3 R_{11}, alkylsulfone, phenylsulfone substituted with 0-3 R_{11}, alkylsulfonamide, phenylsulfonamide substituted with 0-3 R_{11}, heteroaryloxy substituted with 0-3 R_{11}, heteroarylmethyloxy substituted with 0-3 R_{11}, alkylamido, or arylamido substituted with 0-3 R_{11}; or two adjacent R_1 also represent methylenedioxy;

R_2 is aryl substituted with 0-3 R_1 or heteroaryl substituted with 0-3 R_1;

R_3 is H

R_4 is, independently at each occurrence, H, or C_1-C_4 alkyl,

R_5 is, independently at each occurrence, H, C_1-C_4 alkyl, aryl substituted with 0-3 R_1, or cyano; or when two R_5 are present, they form a carbocyclic ring of 3-7 carbons;

R_8 is H, C_1-C_4 alkyl, or cyano;

R_7 is H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, aryl substituted with 0-3 R_1;

R_8 is H;

R_9 is H;

R_{10} is H;

n is an integer from 0 to 4;

x is 1;

R_{11} is alkyl, alkoxy, halo, CF_3, OCF_3, hydroxy, alkanoyloxy, nitro, nitrile, alkenyl, alkynyl, alkylsulfoxide, alkylsulfone, alkylsulfonamide, or alkylamido; or two adjacent R_{11} also represent methylenedioxy;

wherein 1-3 carbon atoms in ring A may optionally be replaced with N.

22. A compound according to claim 1, wherein:

Y is CR_6;

Z is CR_5;

R_1 is, independently at each occurrence, alkyl, alkoxy, halo, CF_3, OCF_3, arylalkyloxy substituted with 0-3 R_{11}, aryloxy substituted with 0-3 R_{11}, aryl substituted with 0-3 R_{11}, heteroaryl substituted with 0-3 R_{11}, hydroxy, alkanoyloxy, nitro, nitrile, alkenyl, alkynyl, alkylsulfoxide, phenylsulfoxide substituted with 0-3 R_{11}, alkylsulfone, phenylsulfone substituted with 0-3 R_{11}, alkylsulfonamide, phenylsulfonamide substituted with 0-3 R_{11}, heteroaryloxy substituted with 0-3 R_{11}, heteroarylmethyloxy substituted with 0-3 R_{11}, alkylamido, or arylamido substituted with 0-3 R_{11}; or two adjacent R_1 also represent methylenedioxy;

R_2 is aryl substituted with 0-3 R_1 or heteroaryl substituted with 0-3 R_1;

R_3 is H or C_1-C_4 alkyl;

R_4 is, independently at each occurrence, H, C_1-C_4 alkyl, arylalkyl, heteroarylmethyl, cycloheptylmethyl, cyclohexylmethyl, cyclopentylmethyl, or cyclobutylmethyl;

R_5 is, independently at each occurrence, H, C_1-C_4 alkyl, aryl substituted with 0-3 R_1, or cyano; or when two R_5 are present, they form a carbocyclic ring of 3-7 carbons;

R_6 is H, C_1-C_4 alkyl, or cyano;

R_7 is H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or aryl substituted with 0-3 R_1;

R_8 is H or C_1-C_4 alkyl;

R_9 is H or C_1-C_4 alkyl;

R_{10} is, independently at each occurrence, H or C_1-C_4 alkyl; or R_{10} and R_4, together with the nitrogen to which R_4 is attached, form a nitrogen-containing ring containing 3-6 carbon atoms;

n is an integer from 0 to 4;

x is an integer from 1 to 2; and

R_{11} is alkyl, alkoxy, halo, CF_3, OCF_3, hydroxy, alkanoyloxy, nitro, nitrile, alkenyl, alkynyl, alkylsulfoxide, alkylsulfone, alkylsulfonamide, or alkylamido; or two adjacent R_{11} also represent methylenedioxy;

wherein 1-3 carbon atoms in ring A may optionally be replaced with N.

23. A compound according to claim 1, wherein:

Y is CR_6;

Z is $C(R_5)_2$;

R_1 is, independently at each occurrence, alkyl, alkoxy, halo, CF_3, OCF_3, arylalkyloxy substituted with 0-3 R_{11}, aryloxy substituted with 0-3 R_{11}, aryl substituted with 0-3 R_{11}, heteroaryl substituted with 0-3 R_{11}, hydroxy, alkanoyloxy, nitro, nitrile, alkenyl, alkynyl, alkylsulfoxide, phenylsulfoxide substituted with 0-3 R_{11}, alkylsulfone, phenylsulfone substituted with 0-3 R_{11}, alkylsulfonamide, phenylsulfonamide substituted with 0-3 R_{11}, heteroaryloxy substituted with 0-3 R_{11}, heteroarylmethyloxy substituted with 0-3 R_{11}, alkylamido, or arylamido substituted with 0-3 R_{11}; or two adjacent R_1 also represent methylenedioxy;

R_2 is aryl substituted with 0-3 R_1 or heteroaryl substituted with 0-3 R_1;

R_3 is H or C_1-C_4 alkyl;

R_4 is, independently at each occurrence, H, C_1-C_4 alkyl, arylalkyl, heteroarylmethyl, cycloheptylmethyl, cyclohexylmethyl, cyclopentylmethyl, or cyclobutylmethyl;

R_5 is, independently at each occurrence, H, C_1-C_4 alkyl, aryl substituted with 0-3 R_1, or cyano; or when two R_5 are present, they form a carbocyclic ring of 3-7 carbons;

R_6 is H, C_1-C_4 alkyl, or cyano;

R_7 is H, C_1-C_8 alkyl, C_3-C_6 cycloalkyl, or aryl substituted with 0-3 R_1;

R_8 is H or C_1-C_4 alkyl;

R_9 is H or C_1-C_4 alkyl;

R_{10} is, independently at each occurrence, H or C_1-C_4 alkyl; or R_{10} and R_4, together with the nitrogen to which R_4 is attached, form a nitrogen-containing ring containing 3-6 carbon atoms;

n is an integer from 0 to 4;

x is an integer from 1 to 2; and

R_{11} is alkyl, alkoxy, halo, CF_3, OCF_3, hydroxy, alkanoyloxy, nitro, nitrile, alkenyl, alkynyl, alkylsulfoxide, alkylsulfone, alkylsulfonamide, or alkylamido; or two adjacent R_{11} also represent methylenedioxy;

wherein 1-3 carbon atoms in ring A may optionally be replaced with N.

24. A compound according to claim 1, wherein:

Y is C=O;

Z is $C(R_5)_2$;

R_1 is, independently at each occurrence, alkyl, alkoxy, halo, CF_3, OCF_3, arylalkyloxy substituted with 0-3 R_{11}, aryloxy substituted with 0-3 R_{11}, aryl substituted with 0-3 R_{11}, heteroaryl substituted with 0-3 R_{11}, hydroxy, alkanoyloxy, nitro, nitrile, alkenyl, alkynyl, alkylsulfoxide, phenylsulfoxide substituted with 0-3 R_{11}, alkylsulfone, phenylsulfone substituted with 0-3 R_{11}, alkylsulfonamide, phenylsulfonamide substituted with 0-3 R_{11}, heteroaryloxy substituted with 0-3 R_{11}, heteroarylmethyloxy substituted with 0-3 R_{11}, alkylamido, or arylamido substituted with 0-3 R_{11}; or two adjacent R_1 also represent methylenedioxy;

R_2 is aryl substituted with 0-3 R_1 or heteroaryl substituted with 0-3 R_1;

R_3 is H or C_1-C_4 alkyl;

R_4 is, independently at each occurrence, H, C_1-C_4 alkyl, arylalkyl, heteroarylmethyl, cycloheptylmethyl, cyclohexylmethyl, cyclopentylmethyl, or cyclobutylmethyl;

R_5 is, independently at each occurrence, H, C_1-C_4 alkyl, aryl substituted with 0-3 R_1, or cyano; or when two R_5 are present, they form a carbocyclic

ring of 3-7 carbons;

R_6 is H, C_1-C_4 alkyl, or cyano;

R_7 is H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or aryl substituted with 0-3 R_1;

R_8 is H or C_1-C_4 alkyl;

R_9 is H or C_1-C_4 alkyl;

R_{10} is, independently at each occurrence, H or C_1-C_4 alkyl; or R_{10} and R_4, together with the nitrogen to which R_4 is attached, form a nitrogen-containing ring containing 3-6 carbon atoms;

n is an integer from 0 to 4;

x is an integer from 1 to 2; and

R_{11} is alkyl, alkoxy, halo, CF_3, OCF_3, hydroxy, alkanoyloxy, nitro, nitrile, alkenyl, alkynyl, alkylsulfoxide, alkylsulfone, alkylsulfonamide, or alkylamido; or two adjacent R_{11} also represent methylenedioxy;

wherein 1-3 carbon atoms in ring A may optionally be replaced with N.

25. A compound according to claim 1, wherein:

Y is C=O;

Z is NR_7;

R_1 is, independently at each occurrence, alkyl, alkoxy, halo, CF_3, OCF_3, arylalkyloxy substituted with 0-3 R_{11}, aryloxy substituted with 0-3 R_{11}, aryl substituted with 0-3 R_{11}, heteroaryl substituted with 0-3 R_{11}, hydroxy, alkanoyloxy, nitro, nitrile, alkenyl, alkynyl, alkylsulfoxide, phenylsulfoxide substituted with 0-3 R_{11}, alkylsulfone, phenylsulfone substituted with 0-3 R_{11}, alkylsulfonamide, phenylsulfonamide substituted with 0-3 R_{11}, heteroaryloxy substituted with 0-3 R_{11}, heteroarylmethyloxy substituted with 0-3 R_{11}, alkylamido, or arylamido substituted with 0-3 R_{11}; or two adjacent R_1 also represent methylenedioxy;

R_2 is aryl substituted with 0-3 R_1 or heteroaryl substituted with 0-3 R_1;

R_3 is H or C_1-C_4 alkyl;

R_4 is, independently at each occurrence, H, C_1-C_4 alkyl, arylalkyl, heteroarylmethyl, cycloheptylmethyl, cyclohexylmethyl, cyclopentylmethyl, or cyclobutylmethyl;

R_5 is, independently at each occurrence, H, C_1-C_4 alkyl, aryl substituted

with 0-3 R_1, or cyano; or in the cases where two R_5 substitutions are present, they may form a carbocyclic ring of C_3-C_7;

R_6 is H, C_1-C_4 alkyl, or cyano;

R_7 is H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, or aryl substituted with 0-3 R_1;

R_8 is H or C_1-C_4 alkyl;

R_9 is H or C_1-C_4 alkyl;

R_{10} is, independently at each occurrence, H or C_1-C_4 alkyl; R_{10} is, independently at each occurrence, H or C_1-C_4 alkyl; or R_{10} and R_4, together with the nitrogen to which R_4 is attached, form a nitrogen-containing ring containing 3-6 carbon atoms;

n is an integer from 0 to 4;

x is an integer from 1 to 2; and

R_{11} is alkyl, alkoxy, halo, CF_3, OCF_3, hydroxy, alkanoyloxy, nitro, nitrile, alkenyl, alkynyl, alkylsulfoxide, alkylsulfone, alkylsulfonamide, or alkylamido; or two adjacent R_{11} also represent methylenedioxy;

wherein 1-3 carbon atoms in ring A may optionally be replaced with N.

26. A compound according to claim 1, wherein said compound is:

1-(1H-indol-1-yl)-3-(4-methylpiperazin-1-yl)-1-phenylpropan-2-ol;

1-(5-fluoro-1H-indol-1-yl)-3-(4-methylpiperazin-1-yl)-1-phenylpropan-2-ol;

1-(1H-indol-1-yl)-3-morpholin-4-yl-1-phenylpropan-2-ol;

3-(dimethylamino)-1-(1H-indol-1-yl)-1-phenylpropan-2-ol;

3-(ethylamino)-1-(1H-indol-1-yl)-1-phenylpropan-2-ol;

1-(1H-indol-1-yl)-3-(isopropylamino)-1-phenylpropan-2-ol;

3-(benzylamino)-1-(1H-indol-1-yl)-1-phenylpropan-2-ol;

3-[(cyclohexylmethyl)amino]-1-(1H-indol-1-yl)-1-phenylpropan-2-ol;

3-[(cyclohexylmethyl)amino]-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

3-(isopropylamino)-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

3-(ethylamino)-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

1-(1H-indol-1-yl)-1-phenyl-3-piperazin-1-ylpropan-2-ol di;

1-(1H-indol-1-yl)-1-phenyl-3-[(pyridin-4-ylmethyl) amino]propan-2-ol;

1-(5-chloro-1H-indol-1-yl)-1-phenyl-3-piperidin-1-ylpropan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

3-amino-1-(1H-indol-1-yl)-1-phenylpropan-2-ol;

3-(ethylamino)-1-(5-fluoro-1H-indol-1-yl)-1-phenylpropan-2-ol;

3-amino-1-(5-fluoro-1H-indol-1-yl)-1-phenylpropan-2-ol;

1-(5-fluoro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

3-(methylamino)-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

3-amino-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

3-[ethyl(methyl)amino]-1-(1H-indol-1-yl)-1-phenylpropan-2-ol;

1-(5-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(5-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-1-ol;

1-[2-hydroxy-3-(methylamino)-1-phenylpropyl]-1H-indole-3-carbonitrile;

1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

3-(methylamino)-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

1-(3-chlorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

1-(4-chlorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-[3-(trifluoromethoxy)phenyl]propan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-[2-(trifluoromethoxy)phenyl]propan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-[2-(trifluoromethoxy)phenyl]propan-2-ol;

1-(2-chlorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-[4-(trifluoromethoxy)phenyl]propan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-[4-(trifluoromethoxy)phenyl]propan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-[4-(trifluoromethoxy)phenyl]propan-2-ol;

4-amino-1-(3-chlorophenyl)-1-(1H-indol-1-yl)butan-2-ol

1-(3-bromophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

3-[2-hydroxy-1-(1H-indol-1-yl)-3-(methylamino)propyl]benzonitrile

1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-[3-(3-methylphenyl)-1H-indol-1-yl]propan-2-ol;

1-(4-fluorophenyl)-3-(methylamino)-1-(3-methyl-1H-indol-1-yl)propan-2-ol;

1-(2-fluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

1-(4-fluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-(3-methylphenyl)propan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-(2-methylphenyl)propan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-(2-methylphenyl)propan-2-ol;

3-(ethylamino)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)propan-2-ol;

1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-morpholin-4-ylpropan-2-ol;

1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-(propylamino)propan-2-ol;

1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-(4-methylpiperazin-1-yl)propan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-(4-methylphenyl)propan-2-ol;

1-(2,3-dihydro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(2,3-dihydro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-[3-(2-methylphenyl)-1H-indol-1-yl]propan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-(2-methyl-2,3-dihydro-1H-indol-1-yl)propan-2-ol;

1-(7-fluoro-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(7-fluoro-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

3-(methylamino)-1-(7-methyl-2,3-dihydro-1H-indol-1-yl)-1-phenylpropan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-(7-methyl-2,3-dihydro-1H-indol-1-yl)propan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-(5-methyl-2,3-dihydro-1H-indol-1-yl)propan-2-ol;

1-(1H-indol-1-yl)-1-(3-methoxyphenyl)-3-(methylamino)propan-2-ol;

1-(1H-indol-1-yl)-1-(4-methoxyphenyl)-3-(methylamino)propan-2-ol;

3-(methylamino)-1-(2-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

1-(1H-benzimidazol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

3-(methylamino)-1-(2-methyl-1H-benzimidazol-1-yl)-1-phenylpropan-2-ol;

1-(4-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(5-fluoro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(5-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(7-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(4-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(6-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(5-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(3-fluorophenyl)-1-(6-methoxy-1H-indol-1-yl)-3-(methylamino)propan-2-ol;

3-(methylamino)-1-phenyl-1-(1H-pyrrolo[2,3-b]pyridin-1-yl)propan-2-ol;

1-(5-chloro-2,3-dihydro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

3-(methylamino)-1-phenyl-1-(1H-pyrrolo[2,3-c]pyridin-1-yl)propan-2-ol;

1-(5-fluoro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

3-(methylamino)-1-(3-fluorophenyl)-1-(1H-pyrrolo[2,3-c]pyridin-1-yl)propan-2-ol;

1-(5-chloro-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

3-(methylamino)-1-(6-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

3-(methylamino)-1-(7-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-(5-methyl-1H-indol-1-yl)propan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-(7-methyl-1H-indol-1-yl)propan-2-ol;

3-(methylamino)-1-(4-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

3-(methylamino)-1-(5-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-(4-methyl-1H-indol-1-yl)propan-2-ol;

1-(3-ethyl-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-(3-phenyl-1H-indol-1-yl)propan-2-ol;

7-fluoro-1-[2hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3- dihydro-2H-indol-2-one;

1-[2hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one;

7-fluoro-1-[1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one;

1-(1H-indol-1-yl)-3-(methylamino)-1-(2-thienyl)propan-2-ol;

1(1H-indol-1-yl)-3-(methylamino)-1-(2-thienyl)propan-2-ol;

1'-[2-hydroxy-3-(methylamino)-1-phenylpropyl]spiro[cyclohexane-1,3'-indol]-2'(1'H)-one;

2-(3-fluorophenyl)-2-(1H-indol-1-yl)-1-[(2S)-pyrrolidin-2-yl]ethanol;

2-(3-fluorophenyl)-2-(1H-indol-1-yl)-1-[pyrrolidin-2-yl]ethanol;

1'-[2hydroxy-3-(methylamino)-1-phenylpropyl]spiro[cyclobutane-1,3'-indol]-2'(1'H)-one;

1'-[2hydroxy-3-(methylamino)-1-phenylpropyl]spiro[cyclopentane-1,3'-indol]-2'(1'H)-one;

1'-[2hydroxy-3-(methylamino)-1-phenylpropyl]spiro[cyclopropane-1,3'-indol]-2'(1'H)-one;

5-fluoro-1-[2hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one;

3-(cyclopropylamino)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)propan-2-ol;

7'-fluoro-1'-[2hydroxy-3-(methylamino)-1-phenylpropyl]spiro[cyclohexane-1,3'-indol]-2'(1'H)-one;

5'-bromo-1'-[2hydroxy-3-(methylamino)-1-phenylpropyl]spiro[cyclohexane-1,3'-indol]-2'(1'H)-one;

1-(3-fluorophenyl)-1-[3-(2-fluorophenyl)-1H-indol-1-yl]-3-(methylamino)propan-2-ol;

1-[3-(3,4-dichlorophenyl)-1H-indol-1-yl]-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(3-fluorophenyl)-1-[3-(3-fluorophenyl)-1H-indol-1-yl]-3-(methylamino)propan-2-ol;

1-(5-fluoro-3-methyl-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

3-amino-1-(5-fluoro-3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

1-(5-chloro-3-methyl-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

3amino-1-(5-chloro-3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

[3-(5-chloro-3-methyl-1H-indol-1-yl)-2-methoxy-3-phenylpropyl]methylamine;

1-(7-chloro-3-methyl-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

[3-(5-fluoro-3-methyl-1H-indol-1-yl)-2-methoxy-3-phenylpropyl]methylamine;

1-(4-bromo-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(4-bromo-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(5-bromo-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(5-bromo-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-[2-hydroxy-3-(methylamino)-1-phenylpropyl]-1H-indole-4-carbonitrile;

1-(6-bromo-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-[2-hydroxy-3-(methylamino)-1-phenylpropyl]-1H-indole-5-carbonitrile;

1-[1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-1H-indole-4-carbonitrile;

1-(6-bromo-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(6-fluoro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

3-amino-1-(3-fluorophenyl)-1-(1H-indol-1-yl)propan-2-ol;

1-(7-bromo-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(1H-indol-1-yl)-3-(methylamino)-1-[3-(trifluoromethyl)phenyl]propan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-spiro[cyclohexane-1,3'-indol]-1'(2'H)-ylpropan-2-ol;

1-(2,3-dihydro-1H-indol-1-yl)-3-(methylamino)-1-[3-(trifluoromethyl)phenyl]propan-2-ol;

1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

1-(3,4-difluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-(3-methyl-1H-indol-1-yl)propan-2-ol;

1-(4-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(6-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(7-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(7-chloro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(4-chloro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(6-chloro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(5-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(5-chloro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(3-isopropyl-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(3-fluorophenyl)-1-(3-isopropyl-1H-indol-1-yl)-3-(methylamino)propan-2-ol;

1-(3,5-difluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

1-(3,5-difluorophenyl)-1-(2,3-dihydro-1H-indol-1-yl)-3-(methylamino)propan-2-ol;

4-amino-1-(3-fluorophenyl)-1-(1H-indol-1-yl)butan-2-ol;

1-(3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(3,5-difluorophenyl)-1-(3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)propan-2-ol;

1-(3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-(3-methyl-2,3-dihydro-1H-indol-1-yl)propan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-spiro[cyclopentane-1,3'-indol]-1'(2'H)-ylpropan-2-ol;

1-(3-fluorophenyl)-1-[3-(4-methoxyphenyl)-1H-indol-1-yl]-3-(methylamino)propan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-[3-(4-methylphenyl)-1H-indol-1-yl]propan-2-ol;

1-[3-(4-tert-butylphenyl)-1H-indol-1-yl]-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(3-fluorophenyl)-1-[3-(3-methoxyphenyl)-1H-indol-1-yl]-3-(methylamino)propan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-{3-[4-(trifluoromethyl)phenyl]-1H-indol-1-yl}propan-2-ol;

1-(3,5-difluorophenyl)-1-(6-fluoro-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)propan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-{3-[2-(trifluoromethyl)phenyl]-1H-indol-1-yl}propan-2-ol;

1-(3-fluorophenyl)-1-[3-(2-methoxyphenyl)-1H-indol-1-yl]-3-(methylamino)propan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-{3-[3-(trifluoromethyl)phenyl]-1H-indol-1-yl}propan-2-ol;

3-amino-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

1-(7-fluoro-3-methyl-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

3-amino-1-(7-fluoro-3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

1-(7-fluoro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(4-fluoro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-(7-fluoro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(4-fluoro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(3-fluorophenyl)-3-(methylamino)-1-[5-(trifluoromethyl)-1H-indol-1-yl]propan-2-ol;

1-(6-fluoro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

3-(methylamino)-1-phenyl-1-[6-(trifluoromethyl)-1H-indol-1-yl]propan-2-ol;

3-(methylamino)-1-phenyl-1-[5-(trifluoromethyl)-1H-indol-1-yl]propan-2-ol;

1-(3-tert-butyl-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-(1H-indol-1-yl)-2-methyl-3-(methylamino)-1-phenylpropan-2-ol;

3-(1H-indol-1-yl)-1-(methylamino)-3-phenylbutan-2-ol;

1-tert-butyl-3-[2hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2H-benzimidazol-2-one;

1-[2-hydroxy-3-(methylamino)-1-phenylpropyl]-3-propyl-1,3-dihydro-2H-benzimidazol-2-one;

5-bromo-1-[2hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one;

6-fluoro-1-[2hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one;

4-fluoro-1-[2hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one;

1-cyclobutyl-3-[2hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2H-benzimidazol-2-one;

5-fluoro-3-[2hydroxy-3-(methylamino)-1-phenylpropyl]-1-propyl-1,3-dihydro-2H-benzimidazol-2-one;

1-ethyl-3-[1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-1,3-dihydro-2H-benzimidazol-2-one;

1-ethyl-3-[2hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2H-benzimidazol-2-one;

4-fluoro-3-[2hydroxy-3-(methylamino)-1-phenylpropyl]-1-isopropyl-1,3-dihydro-2H-benzimidazol-2-one;

1-cyclopentyl-3-[2hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2H-benzimidazol-2-one;

1-[2hydroxy-3-(methylamino)-1-phenylpropyl]-3-isopropyl-1,3-dihydro-2H-benzimidazol-2-one;

3-[3(ethylamino)-2-hydroxy-1-phenylpropyl]-5-fluoro-1-isopropyl-1,3-dihydro-2H-benzimidazol-2-one;

1-[2hydroxy-3-(methylamino)-1-phenylpropyl]-3-methyl-1,3-dihydro-2H-benzimidazol-2-one;

1-ethyl-5-fluoro-3-[2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2H-benzimidazol-2-one;

1-ethyl-4-fluoro-3-[2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2H-benzimidazol-2-one;

4-fluoro-3-[1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-1-isopropyl-1,3-dihydro-2H-benzimidazol-2-one;

1-ethyl-4-fluoro-3-[2hydroxy-3-(methylamino)-1-(3-fluorophenyl)-propyl]-1,3-dihydro-2H-benzimidazol-2-one;

1-[1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one;

1-[3-(2,3-difluorophenyl)-1H-indol-1-yl]-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-[3-(2-chlorophenyl)-1H-indol-1-yl]-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol; or

a pharmaceutically acceptable salt thereof.

27. A compound according to claim 1, wherein said compound is:

(1RS,2SR)-1-(1H-indol-1-yl)-3-(4-methylpiperazin-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-1-(5-fluoro-1H-indol-1-yl)-3-(4-methylpiperazin-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-1-(1H-indol-1-yl)-3-morpholin-4-yl-1-phenylpropan-2-ol;

(1RS,2SR)-3-(dimethylamino)-1-(1H-indol-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-3-(ethylamino)-1-(1H-indol-1-yl)-1-phenylpropan-2-ol ;

(1RS,2SR)-1-(1H-indol-1-yl)-3-(isopropylamino)-1-phenylpropan-2-ol;

(1RS,2SR)-3-(benzylamino)-1-(1H-indol-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-3-[(cyclohexylmethyl)amino]-1-(1H-indol-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-3-[(cyclohexylmethyl)amino]-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-3-(isopropylamino)-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1RS,2SR)-3-(ethylamino)-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-1-(1H-indol-1-yl)-1-phenyl-3-piperazin-1-ylpropan-2-ol;

(1RS,2SR)-1-(1H-indol-1-yl)-1-phenyl-3-[(pyridin-4-ylmethyl)amino]propan-2-ol;

(1RS,2SR)-1-(5-chloro-1H-indol-1-yl)-1-phenyl-3-piperidin-1-ylpropan-2-ol;

(1RS,2RS)-1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1RS,2SR)-3-amino-1-(1H-indol-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-3-(ethylamino)-1-(5-fluoro-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-3-amino-1-(5-fluoro-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-1-(5-fluoro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1RS,2SR)-3-(methylamino)-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1R,2S)-1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1RS,2SR)-3-amino-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-3-[ethyl(methyl)amino]-1-(1H-indol-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-1-(5-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1RS,2RS)-1-(5-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-1-ol;

1-[(1RS,2SR)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1H-indole-3-carbonitrile;

(1R,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2S)-1-(1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-3-(methylamino)-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1S,2R)-1-(3-chlorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(4-chlorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-[3-(trifluoromethoxy)phenyl]propan-2-ol;

(1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-[2-(trifluoromethoxy)phenyl]propan-2-ol;

(1R,2S)-1-(1H-indol-1-yl)-3-(methylamino)-1-[2-(trifluoromethoxy)phenyl]propan-2-ol;

(1S,2R)-1-(2-chlorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

(1SR,2RS)-1-(1H-indol-1-yl)-3-(methylamino)-1-[4-(trifluoromethoxy)phenyl]propan-2-ol;

(1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-[4-(trifluoromethoxy)phenyl]propan-2-ol;

(1R,2S)-1-(1H-indol-1-yl)-3-(methylamino)-1-[4-(trifluoromethoxy)phenyl]propan-2-ol;

(1S,2R)-4-amino-1-(3-chlorophenyl)-1-(1H-indol-1-yl)butan-2-ol

(1S,2R)-1-(3-bromophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

3-[(1S,2R)-2-hydroxy-1-(1H-indol-1-yl)-3-(methylamino)propyl]benzonitrile

(1S,2R)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-[3-(3-methylphenyl)-1H-indol-1-yl]propan-2-ol;

(1S,2R)-1-(4-fluorophenyl)-3-(methylamino)-1-(3-methyl-1H-indol-1-yl)propan-2-ol;

(1S,2R)-1-(2-fluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(4-fluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-(3-methylphenyl)propan-2-ol;

(1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-(2-methylphenyl)propan-2-ol;

(1R,2S)-1-(1H-indol-1-yl)-3-(methylamino)-1-(2-methylphenyl)propan-2-ol;

(1S,2R)-3-(ethylamino)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-morpholin-4-ylpropan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-(propylamino)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-(4-methylpiperazin-1-yl)propan-2-ol;

(1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-(4-methylphenyl)propan-2-ol;

(1S,2R)-1-(2,3-dihydro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(2,3-dihydro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-[3-(2-methylphenyl)-1H-indol-1-yl]propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(2-methyl-2,3-dihydro-1H-indol-1-yl)propan-2-ol;

(1S,2R)-1-(7-fluoro-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(7-fluoro-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-3-(methylamino)-1-(7-methyl-2,3-dihydro-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(7-methyl-2,3-dihydro-1H-indol-1-yl)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(5-methyl-2,3-dihydro-1H-indol-1-yl)propan-2-ol;

(1S,2R)-1-(1H-indol-1-yl)-1-(3-methoxyphenyl)-3-(methylamino)propan-2-ol;

(1SR,2RS)-1-(1H-indol-1-yl)-1-(4-methoxyphenyl)-3-(methylamino)propan-2-ol;

(1RS,2SR)-3-(methylamino)-1-(2-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-1-(1H-benzimidazol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1RS,2SR)-3-(methylamino)-1-(2-methyl-1H-benzimidazol-1-yl)-1-phenylpropan-2-ol;

(1RS,2SR)-1-(4-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(5-fluoro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(5-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(7-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(4-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(6-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1RS,2SR)-1-(5-methoxy-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-1-(6-methoxy-1H-indol-1-yl)-3-(methylamino)propan-2-ol;

(1S,2R)-3-(methylamino)-1-phenyl-1-(1H-pyrrolo[2,3-b]pyridin-1-yl)propan-2-ol;

(1S,2R)-1-(5-chloro-2,3-dihydro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-3-(methylamino)-1-phenyl-1-(1H-pyrrolo[2,3-c]pyridin-1-yl)propan-2-ol;

(1S,2R)-1-(5-fluoro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-3-(methylamino)-1-(3-fluorophenyl)-1-(1H-pyrrolo[2,3-c]pyridin-1-yl)propan-2-ol;

(1S,2R)-1-(5-chloro-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-3-(methylamino)-1-(6-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1S,2R)-3-(methylamino)-1-(7-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(5-methyl-1H-indol-1-yl)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(7-methyl-1H-indol-1-yl)propan-2-ol;

(1S,2R)-3-(methylamino)-1-(4-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1S,2R)-3-(methylamino)-1-(5-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(4-methyl-1H-indol-1-yl)propan-2-ol;

(1S,2R)-1-(3-ethyl-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(3-phenyl-1H-indol-1-yl)propan-2-ol;

7-fluoro-1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3- dihydro-2H-indol-2-one;

1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro- 2H-indol-2-one;

7-fluoro-1-[(1S,2R)-1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-3,3- dimethyl-1,3-dihydro-2H-indol-2-one;

(1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-(2-thienyl)propan-2-ol;

(1R,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-(2-thienyl)propan-2-ol;

1'-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]spiro[cyclohexane-1,3'-indol]-2'(1'H)-one;

(1S,2R)-2-(3-fluorophenyl)-2-(1H-indol-1-yl)-1-[(2S)-pyrrolidin-2-yl]ethanol;

(1R,2S)-2-(3-fluorophenyl)-2-(1H-indol-1-yl)-1-[(2S)-pyrrolidin-2-yl]ethanol;

1'-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]spiro[cyclobutane-1,3'-indol]-2'(1'H)-one;

1'-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]spiro[cyclopentane-1,3'-indol]-2'(1'H)-one;

1'-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]spiro[cyclopropane-1,3'-indol]-2'(1'H)-one;

5-fluoro-1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one;

(1S,2R)-3-(cyclopropylamino)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)propan-2-ol;

7'-fluoro-1'-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]spiro[cyclohexane-1,3'-indol]-2'(1'H)-one;

5'-bromo-1'-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]spiro[cyclohexane-1,3'-indol]-2'(1'H)-one;

(1S,2R)-1-(3-fluorophenyl)-1-[3-(2-fluorophenyl)-1H-indol-1-yl]-3-(methylamino)propan-2-ol;

(1S,2R)-1-[3-(3,4-dichlorophenyl)-1H-indol-1-yl]-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-1-[3-(3-fluorophenyl)-1H-indol-1-yl]-3-(methylamino)propan-2-ol;

(1S,2R)-1-(5-fluoro-3-methyl-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S*,2R*)-3-amino-1-(5-fluoro-3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1S,2R)-1-(5-chloro-3-methyl-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-3-amino-1-(5-chloro-3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

[(2R,3S)-3-(5-chloro-3-methyl-1H-indol-1-yl)-2-methoxy-3-phenylpropyl]methylamine;

(1S,2R)-1-(7-chloro-3-methyl-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

[(2R,3S)-3-(5-fluoro-3-methyl-1H-indol-1-yl)-2-methoxy-3-phenylpropyl]methylamine;

(1S,2R)-1-(4-bromo-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(4-bromo-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(5-bromo-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(5-bromo-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1H-indole-4-carbonitrile;

(1S,2R)-1-(6-bromo-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1H-indole-5-carbonitrile;

1-[(1S,2R)-1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-1H-indole-4-carbonitrile;

(1S,2R)-1-(6-bromo-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(6-fluoro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-3-amino-1-(3-fluorophenyl)-1-(1H-indol-1-yl)propan-2-ol;

(1S,2R)-1-(7-bromo-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(1H-indol-1-yl)-3-(methylamino)-1-[3-(trifluoromethyl)phenyl]propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-spiro[cyclohexane-1,3'-indol]-1'(2'H)-ylpropan-2-ol;

(1S,2R)-1-(2,3-dihydro-1H-indol-1-yl)-3-(methylamino)-1-[3-(trifluoromethyl)phenyl]propan-2-ol;

(1S,2S)-1-(3-fluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3,4-difluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(3-methyl-1H-indol-1-yl)propan-2-ol;

(1S,2R)-1-(4-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(6-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(7-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(7-chloro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(4-chloro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(6-chloro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(5-chloro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(5-chloro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3-isopropyl-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-1-(3-isopropyl-1H-indol-1-yl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3,5-difluorophenyl)-1-(1H-indol-1-yl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3,5-difluorophenyl)-1-(2,3-dihydro-1H-indol-1-yl)-3-(methylamino)propan-2-ol;

(1S,2R)-4-amino-1-(3-fluorophenyl)-1-(1H-indol-1-yl)butan-2-ol;

(1S,2R)-1-(3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3,5-difluorophenyl)-1-(3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-(3-methyl-2,3-dihydro-1H-indol-1-yl)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-spiro[cyclopentane-1,3'-indol]-1'(2'H)-ylpropan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-1-[3-(4-methoxyphenyl)-1H-indol-1-yl]-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-[3-(4-methylphenyl)-1H-indol-1-yl]propan-2-ol;

(1S,2R)-1-[3-(4-tert-butylphenyl)-1H-indol-1-yl]-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-1-[3-(3-methoxyphenyl)-1H-indol-1-yl]-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-{3-[4-(trifluoromethyl)phenyl]-1H-indol-1-yl}propan-2-ol;

(1S,2R)-1-(3,5-difluorophenyl)-1-(6-fluoro-2,3-dihydro-1H-indol-1-yl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-{3-[2-(trifluoromethyl)phenyl]-1H-indol-1-yl}propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-1-[3-(2-methoxyphenyl)-1H-indol-1-yl]-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-{3-[3-(trifluoromethyl)phenyl]-1H-indol-1-yl}propan-2-ol;

(1S,2R)-3-amino-1-(3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1S,2R)-1-(7-fluoro-3-methyl-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-3-amino-1-(7-fluoro-3-methyl-1H-indol-1-yl)-1-phenylpropan-2-ol;

(1S,2R)-1-(7-fluoro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(4-fluoro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-1-(7-fluoro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(4-fluoro-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(3-fluorophenyl)-3-(methylamino)-1-[5-(trifluoromethyl)-1H-indol-1-yl]propan-2-ol;

(1S,2R)-1-(6-fluoro-1H-indol-1-yl)-3-(methylamino)-1-phenylpropan-2-ol;

(1S,2R)-3-(methylamino)-1-phenyl-1-[6-(trifluoromethyl)-1H-indol-1-yl]propan-2-ol;

(1S,2R)-3-(methylamino)-1-phenyl-1-[5-(trifluoromethyl)-1H-indol-1-yl]propan-2-ol;

(1S,2R)-1-(3-tert-butyl-1H-indol-1-yl)-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-(1H-indol-1-yl)-2-methyl-3-(methylamino)-1-phenylpropan-2-ol;

(2R,3S)-3-(1H-indol-1-yl)-1-(methylamino)-3-phenylbutan-2-ol;

1-tert-butyl-3-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2H-benzimidazol-2-one;

1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3-propyl-1,3-dihydro-2H-benzimidazol-2-one;

5-bromo-1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one;

6-fluoro-1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one;

4-fluoro-1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one;

1-cyclobutyl-3-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2H-benzimidazol-2-one;

5-fluoro-3-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1-propyl-1,3-dihydro-2H-benzimidazol-2-one;

1-ethyl-3-[(1S,2R)-1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-1,3-dihydro-2H-benzimidazol-2-one;

1-ethyl-3-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2H-benzimidazol-2-one;

4-fluoro-3-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1-isopropyl-1,3-dihydro-2H-benzimidazol-2-one;

1-cyclopentyl-3-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2H-benzimidazol-2-one;

1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3-isopropyl-1,3-dihydro-2H-benzimidazol-2-one;

3-[(1S,2R)-3-(ethylamino)-2-hydroxy-1-phenylpropyl]-5-fluoro-1-isopropyl-1,3-dihydro-2H-benzimidazol-2-one;

1-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-3-methyl-1,3-dihydro-2H-benzimidazol-2-one;

1-ethyl-5-fluoro-3-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2H-benzimidazol-2-one;

1-ethyl-4-fluoro-3-[(1S,2R)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2H-benzimidazol-2-one;

4-fluoro-3-[(1S,2R)-1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-1-isopropyl-1,3-dihydro-2H-benzimidazol-2-one;

1-ethyl-4-fluoro-3-[(1S,2R)-2-hydroxy-3-(methylamino)-1-(3-fluorophenyl)-propyl]-1,3-dihydro-2H-benzimidazol-2-one;

1-[(1S,2R)-1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-3,3-dimethyl-1,3-dihydro-2H-indol-2-one;

(1S,2R)-1-[3-(2,3-difluorophenyl)-1H-indol-1-yl]-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol;

(1S,2R)-1-[3-(2-chlorophenyl)-1H-indol-1-yl]-1-(3-fluorophenyl)-3-(methylamino)propan-2-ol; or

a pharmaceutically acceptable salt thereof.

28. A composition, comprising:

a. at least one compound according to any one of claims 1 to 27; and

b. at least one pharmaceutically acceptable carrier.

29. A method for treating or preventing a condition ameliorated by monoamine reuptake in a subject in need thereof, comprising the step of:

administering to said subject an effective amount of a compound according to any one of claims 1 to 27 or pharmaceutically acceptable salt thereof or a composition according to claim 28.

30. A method according to claim 29,

wherein said condition ameliorated by monoamine reuptake is selected from the group consisting of vasomotor symptoms, sexual dysfunction, gastrointestinal and genitourinary disorders, chronic fatigue syndrome, fibromylagia syndrome, nervous system disorders, and combinations thereof.

31. A method according to claim 30,

wherein said condition ameliorated by monoamine reuptake is selected from the group consisting of major depressive disorder, vasomotor symptoms, stress and urge urinary incontinence, fibromyalgia, pain, diabetic neuropathy, and combinations thereof.

32. A method for treating or preventing at least one vasomotor symptom in a subject in need thereof, comprising the step of:

administering to said subject an effective amount of a compound according to any one of claims 1 to 27 or pharmaceutically acceptable salt thereof or a composition according to claim 28.

33. A method according to claim 32,

wherein said vasomotor symptom is hot flush.

34. A method according to claim 33,

wherein said subject is human.

35. A method according to claim 34,

wherein said human is a female.

36. A method according to claim 35,

wherein said female is pre-menopausal.

37. A method according to claim 35,

wherein said female is peri-menopausal.

38. A method according to claim 35,

wherein said female is post-menopausal.

39. A method according to claim 34,

wherein said human is a male.

40. A method according to claim 39,

wherein said male is naturally, chemically or surgically andropausal.

41. A method for treating or preventing at least one depression disorder in a subject in need thereof, comprising the step of:

administering to said subject an effective amount of a compound according to any one of claims 1 to 27 or pharmaceutically acceptable salt thereof or a composition according to claim 28.

42. A method according to claim 41,

wherein said depression disorder is major depressive disorder, anxiety, sleep disturbance, or social phobia.

43. A method according to claim 42,

wherein said subject is human.

44. A method for treating or preventing at least one sexual dysfunction in a subject in need thereof, comprising the step of:

administering to said subject an effective amount of a compound according to any one of claims 1 to 27 or pharmaceutically acceptable salt thereof or a composition according to claim 28.

45. A method according to claim 44,

wherein said sexual dysfunction is desire-related or arousal-related.

46. A method according to claim 45,

wherein said subject is human.

47. A method for treating or preventing pain in a subject in need thereof, comprising the step of:

administering to said subject an effective amount of a compound according to any one of claims 1 to 27 or pharmaceutically acceptable salt thereof or a composition according to claim 28.

48. A method according to claim 47,

wherein said pain is acute centralized pain, acute peripheral pain, or a combination thereof.

49. A method according to claim 47,

wherein said pain is chronic centralized pain, chronic peripheral pain, or a combination thereof.

50. A method according to claim 47,

wherein said pain is neuropathic pain, visceral pain, musculoskeletal pain, bony pain, cancer pain, inflammatory pain, or a combination thereof.

51. A method according to claim 50,

wherein said neuropathic pain is associated with diabetes, post traumatic pain of amputation, lower back pain, cancer, chemical injury, toxins, major surgery, peripheral nerve damage due to traumatic injury compression, post-herpetic neuralgia, trigeminal neuralgia, lumbar or cervical radiculopathies, fibromyalgia, glossopharyngeal neuralgia, reflex sympathetic dystrophy, casualgia, thalamic syndrome, nerve root avulsion, reflex sympathetic dystrophy or post thoracotomy pain, nutritional deficiencies, viral infection, bacterial infection, metastatic infiltration, adiposis dolorosa, burns, central pain conditions related to thalamic conditions, and combinations thereof.

52. A method according to claim 50,

wherein said visceral pain is associated with ulcerative colitis, irritable bowel syndrome, irritable bladder, Crohn's disease, rheumatologic (arthralgias), tumors, gastritis, pancreatitis, infections of the organs, biliary tract disorders, and combinations thereof.

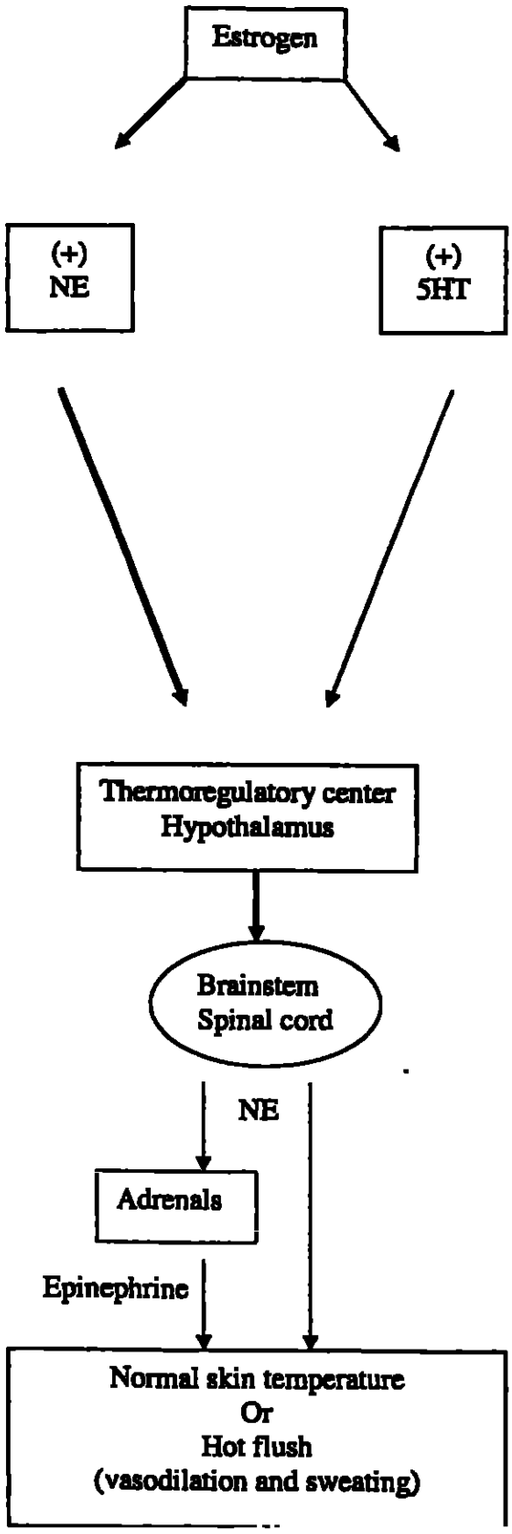
53. A method according to claim 47,

wherein said pain is female-specific pain.

54. A method according to claim 47,

wherein said subject is human.

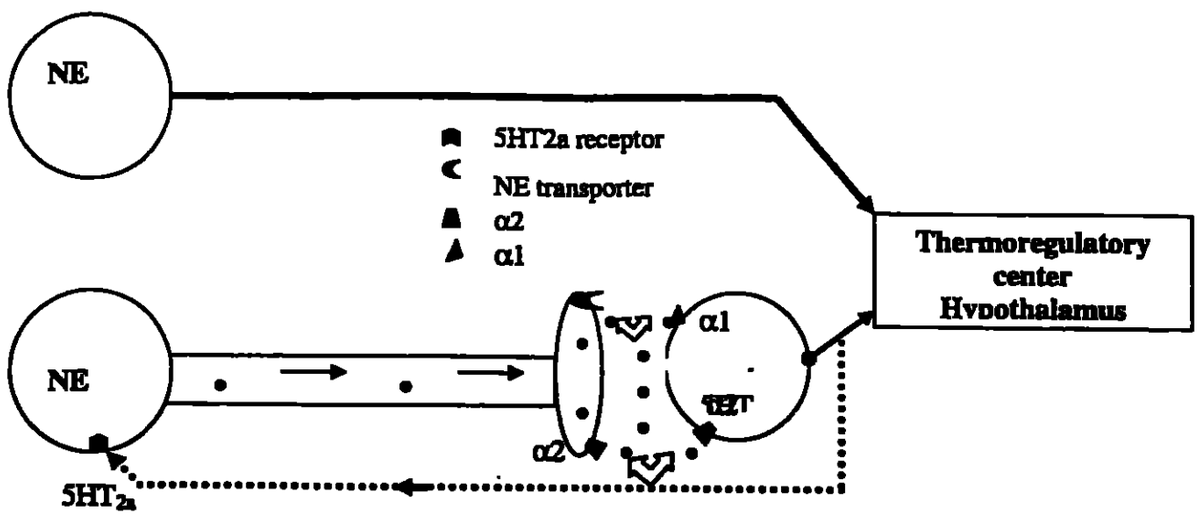
FIGURE 1


Estrogen
(+)
NE
(+)
5HT
Thermoregulatory center
Hypothalamus
Brainstem
Spinal cord
NE
Adrenals
Epinephrine
Normal skin temperature
Or
Hot flush
(vasodilation and sweating)

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FIGURE 2



DERIVADOS DE 1-(1H-INDOL-1-IL)-3-(4-METILPIPERAZINA-1-IL)-1-FENIL PROPANO-2-OL Y COMPUESTOS RELACIONADOS COMO MODULADORES DE LA ACTIVIDAD DE LA NOREPINEFRINA (NE) Y LA SEROTONINA (5-HT) Y LA RETOMA DE MONOAMINA PARA EL TRATAMIENTO DE SÍNTOMAS VASOMOTORES (VMS)

REFERENCIA CRUZADA SOLICITUD RELACIONADAS

[0001] Esta solicitud reivindica prioridad ante la solicitud U.S. No _____ presentada en Marzo 28, 2005, reivindica el beneficio de la solicitud U.S. No 60/557,651 presentada en Marzo 30, 2004, y la solicitud U.S. No 60/569,863 presentada en Mayo 11, 2004, cuyas descripciones completas se incorporan aquí como referencia.

CAMPO DE LA INVENCIÓN

[0002] La presente invención se relaciona con derivados de fenilaminopropanol, que composiciones que contienen estos derivados, y métodos de uso para la prevención de tratamientos de condiciones mejoradas por retoma de monoamina que incluye, *inter alia*, síntomas vasomotores(VMS), disfunción sexual, desórdenes gastrointestinales y genitourinario, síndrome de fatiga crónica, síndrome de fibromialgia, desórdenes del sistema nerviosos, y combinaciones de estos, particularmente aquellas condiciones seleccionadas del grupo que consiste del desorden depresivo principal o mayor, síntomas vasomotores, tensión e incontinencia urinaria apremiante, fibromialgia, dolor, neuropatía diabética, y combinaciones de estos.

ANTECEDENTES DE LA INVENCIÓN

[0003] Los síntomas vasomotores (VMS), referidos como flujos calientes o sudores nocturnos, son los síntomas más comunes asociados con la menopausia que ocurre en el 60 o 80% de todas las mujeres que siguen la menopausia natural o quirúrgicamente inducida. Los VMS son probablemente una respuesta adaptativa del sistema nervioso central (CNS) para declinar los esteroides del sexo. A la fecha, la mayoría de las partes efectivas para VMS solo se permiten basados en hormonas, que incluyen estrógenos y/o algunas progestinas. Los tratamientos hormonales son muy efectivos para aliviar los VMS, pero ellos no son apropiados para todas las mujeres. Es bien reconocido que los VMS son causados por fluctuaciones de los niveles esteroides de sexo y pueden ser disruptores y discapacitantes tanto en machos como en hembras. Un flujo caliente puede durar hasta 30 minutos y puede variar en su frecuencia de varios meses por semana a múltiples ocurrencias por día. el paciente experimenta un flujo caliente como una suita sensación de calor que se esparce rápidamente desde la cara al pecho y a la espalda y luego sobre el resto del cuerpo. Esta usualmente acompañado por emisiones de sudor profuso. Esto puede ocurrir varias veces en una hora, y a menudo puede ocurrir en la noche. Los flujos calientes y las erupciones de sudor que ocurren durante la noche pueden causar la privación del sueño. Los síntomas sicológicos y emocionales observados, tales como nerviosismo, fatiga, irritabilidad, insomnio, depresión, perdida de memoria, dolor de cabeza, ansiedad, nerviosismo o incapacidad para concentrarse son considerados la causa de la privación del sueño luego del flujo caliente y los sueños nocturnos (Kramer et

al., In: Murphy et al., 3rd Int'l Symposium on Rec ent Advances in Urological Cancer Diagnosis and Treatment- Proceedings, Paris, France: SCI: 3-7 (1992)).

[0004] Los flujos calientes pueden aún ser más severos en mujeres tratadas para cáncer de mama con varias razones: 1) Muchos sobrevivientes del cáncer de mama se les da tamoxifeno, el efecto colateral más covalente es el flujo caliente,: 2) muchas mujeres tratadas para cáncer de mama sufren de menopausia prematura por la quimioterapia, 3) las mujeres con historia de cáncer de mama se les ha denegado la terapia de estrógeno por ocupaciones a cerca del potencial de recurrencia de cáncer de mama (Loprinzi, et al., Lancet, 2000, 356(9247): 2059-2063).

[0005] Los hombres también experimentan flujos calientes luego del retiro de las hormonas esteroides (andrógenas). Esto es cierto en casos de declinación de andrógenos asociados con la edad (Katovich, et al., *Proceedings of the Society for Experimental Biology & Medicine*, 1990, 193(2): 129-35) así como también en casos extremos de privación de hormonas asociados con tratamientos para cáncer de próstata (Berendsen, et al., *European Journal of Pharmacology*, 2001 , 419(1): 47-54. tanto como un tercio de estos pacientes experimentaran síntomas persistentes y frecuentes suficientemente severos para originar una incomodidad e inconvenientes significativos.

[0006] El mecanismo preciso de estos síntomas es desconocido pero generalmente se cree que representa disturbios de los mecanismo homeostáticos normales que controlan la formo

regulación de la actividad vasomotora (Kronenberg et al., "Thermoregulatory Physiology of Menopausal Hot Flashes: A Review," Can. *J. Physiol. Pharmacol.*, 1987, 65:1312-1324).

[0007] El hecho de que el tratamiento con estrógeno (por ejemplo terapia de reemplazo de estrógeno) alivia los síntomas establece el enlace entre los síntomas y la eficiencia de estrógeno. Por ejemplo, la etapa de la menopausia de la vida está asociado por un alto rango de otros síntomas agudos como se describe anteriormente o estos síntomas generalmente responden al estrógeno.

[0008] Se ha sugerido que los estrógenos puedan estimular la actividad tanto de los sistemas de norepinefrina (NE) y/o serotonina (5-HT) (*J. Pharmacology & Experimental Therapeutics*, 1986, 236(3) 646-652). Se tiene la hipótesis de que los estrógenos modulan los niveles de NE y 5-HT suministrando homeostasis en el centro termorregulatorio del hipotálamo. Las sendas descendentes del hipotálamo por vía del tronco encefálico/con una vertebral y las adrenales a la piel están involucradas en mantener la temperatura de la piel normal. La acción de los inhibidores se retoma de NE y 5-HT es conocido por impactar tanto el CNS como sistema nervioso periférico (PNS). La patofisiología del VMS es mediada tanto por los mecanismos centrales como periféricos y, por lo tanto, el interjuego entre el CNS y PNS puede contar para la eficacia de la acción doble SRI/NRI en los tratamientos de la disfunción termorregulatoria. De hecho, los respectos fisiológicos y el involucramiento del CNS/PNS en el VMS se puede encontrar para las dosis inferiores

propuestas para tratar el VMS (Loprinzi, et al., Lancet, 2000, 356:2059-2063; Stearns et al., JAMA, 2003, 289:2827-2834). Comparado con las dosis utilizadas para tratar los respectos de comportamiento de la depresión. El interjuego del CNS/PNS en la patofisiología del VMS y los datos presentados dentro del documento fueron utilizados para sostener las reclamaciones de que el sistema de norepinefina podría ser blanco para tratar el VMS.

[0009] Aunque el VMS es más comúnmente tratado por la terapia de hormona (oralmente, transdermicamente, o por vía en implante) algunos pacientes no pueden tolerar el tratamiento de estrógeno (Berendsen, Maturitas, 2000, 36(3): 155-164, Fink et al., *Nature*, 1996, 383(6598): 306). Además, la terapia de reemplazo de hormonas usualmente no recomendada para mujeres u hombre con riesgo de cáncer hormonalmente sensible (por ejemplo de cáncer de mama o de próstata). Así, las terapias no hormonales (por ejemplo fluoxetina. Paroxetina [SRI] y clonidina) están siendo evaluadas clínicamente. La WO9944601 describe un método para disminuir los flujos calientes en hembras al administrar fluoxetina. Otras opciones se han estudiado para el tratamiento de los flujos calientes, que incluyen esteroides, agonistas alfa adrenérgicos, y beta bloqueadores, con grado variante de éxito (Waldinger et al., *Maturitas*, 2000, 36(3): 165-168).

[0010] Se ha reportado que los receptores o_2-adrenérgicos juegan un papel en las disfunciones termorregulatorias (Freedman et al., Fertility & Sterility, 2000, 74(1): 20- 3). Estos receptores estan localizados tanto pre como post-sinapticamente y median un

papel inhibitorio en el sistema nervioso central y periférico. Existen 4 subtipos distintos de receptores adrenérgicos$_{\alpha 2}$, es decir, son los α_{2A}, α_{2B}, α_{2B}, y α_{2D} (Mackinnon et al., TIPS, 1994, 15: 119; French, Pharmacol. Ther., 1995, 68: 175). Se ha reportado que el agonista α_2-adrenoreceptor no selectivo, yohimbina, induce un flujo y un agonista receptor α_2-adrenérgico, clonidina, alivia el efecto de la yohimbina (Katovich, et al., Proceedings of the Society for Experimental Biology & Medicine, 1990, 193(2): 129-35, Freedman et al., Fertility & Sterility, 2000, 74(1): 20-3). La clonidina se ha utilizado para tratar flujo cliente. sin embargo, el uso de tal tratamiento se asocia con un número de defectos colaterales no deseados originados por las altas dosis necesarias para abatir el flujo caliente descrito y conocido en las técnicas relacionadas.

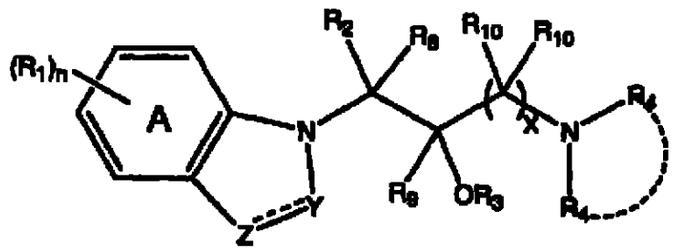
[0011] Dada la naturaleza multifaseta compleja de la termorregulación y el interjuego entre el CNS y PNS para mantener la homeostasis termorregulatoria, terapias múltiples y aproximaciones se pueden desarrollar para apuntar a los síntomas vasomotores. La presente invención se enfoca en compuestos y composiciones novedosas que contienen estos compuestos dirigidos a estas y a otros usos importantes.

RESUMEN DE LA INVENCIÓN

[0012] La presente invención está dirigida a los derivados de fenilaminopropanol, composiciones que contienen estos derivados, y métodos de su uso para la prevención y tratamientos de

condiciones mejoradas por la retoma de monoamina que incluye, *inter alia*, los síntomas vasomotores (VMS), la disfunción sexual, los desórdenes gastrointestinal y genitourinario, síndrome de fatiga crónica, síndrome de fibromialgia, desórdenes del sistema nerviosos, y combinaciones de estos, particularmente aquellas condiciones seleccionadas del grupo que consiste del desorden depresivo mayor, síntomas vasomotores, tensión e incontinencia urinaria apremiante, fibromialgia, dolor, neuropatía diabética, y combinaciones de estas.

[0013] En una modalidad, la presente invención está dirigida a compuestos de fórmula 1:



I

o una sal farmacéuticamente aceptable de estos;

en donde:

La línea punteada entre Y y Z representa un enlace doble opcional;

La línea punteada entre los dos grupos R_4 representa un anillo heterocíclico opcional de 4 a 6 átomos que se puede formar entre los dos grupos R_4, junto el nitrógeno a través del cual ellos están unidos;

Y es N, CR_6 o C=O;

Z es N, NR_7, CR_5, o $C(R_5)_2$;

R_1 es, independientemente a cada ocurrencia, alquilo, alcoxi, halo, CF_3, OCF_3, arilalquiloxi sustituido con 0-3 R_{11}, ariloxi sustituido con 0-3 R_{11}, arilo sustituido con 0-3 R_{11}, heteroarilo sustituido con 0-3 R_{11}, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo alquinilo, alquilsulfóxido, fenilsulfóxido sustituido con 0-3 R_{11}, alquilsulfona, fenilsulfona sustituido con 0-3 R_{11}, alquilsulfonamida, fenilsulfonamida sustituido con 0-3 R_{11}, heteroariloxi sustituido con 0-3 R_{11}, heteroarilmetoxi sustituido con 0-3 R_{11}, alquilamido, o arilamido sustituido con 0-3 R_{11}; o dos R_1 adyacentes también representan metilenodioxi;

R_2 es un arilo sustituido con 0-3 R_1 o heteroarilo sustituido con 0-3 R_1;

R_3 es H o alquilo C_1-C_4;

R_4 es, independientemente a cada ocurrencia, H, alquilo C_1-C_4, arilalquilo, heteroarilmetilo, cicloheptilmetilo, ciclohexilmetilo, ciclopentilmetilo, o ciclobutilmetilo, o

Ambos grupos R_4, junto con el nitrógeno a través del cual ellos están unidos, forman una anillo heterocíclico de 4 a 6 átomos por anillo, en donde un carbono puede ser opcionalmente reemplazado con N, O, S, o SO_2, y en donde el átomo del anillo de carbono o el átomo de N adicional puede ser opcionalmente sustituido con alquilo C_1-C_4 o CF_3;

R_5 es, independientemente a cada ocurrencia, H, alquilo C_1-C_4, arilo sustituido con 0-3 R_1 o ciano; o cuando dos R_5 están presentes, ellos forman un anillo carbocíclico de 3-7 carbonos;

R_6 es H, alquilo C_1-C_4, o ciano;

R_7 es H, alquilo C_1-C_6, cicloalquilo C_3-C_6, o arilo sustituido con 0-3 R_1;

R_8 es H, o alquilo C_1-C_4;

R_9 es H, o alquilo C_1-C_4;

R_{10} es, independientemente a cada ocurrencia, H, o alquilo C_1-C_4; o R_{10} y R_4 juntos con el átomo de nitrógeno al cual R_4 esta unido forma un anillo que contiene nitrógeno que contiene 3-6 átomos de carbono;

n es un entero de 0 a 4;

x es un entero de 1 a 2; y

R_{11} es alquilo, alcoxi, halo, CF_3, OCF_3, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo, alquinilo, alquilsulfóxido, alquilsulfona, alquilsulfonamida, o alquilamido; o dos R_{11} adyacentes también representan metilenodioxi;

En donde 1-3 átomos de carbono en el anillo A pueden opcionalmente ser reemplazados con N.

[0014] En aún otras modalidades, la presente invención está dirigida composiciones, que comprenden:

a) al menos un compuesto de fórmula 1; y

b) al menos un vehiculo farmacéuticamente aceptable.

[0015] En otra modalidad, la presente invención está dirigida a métodos para tratar a prevenir una condición mejorada por la retoma de monoamina en un sujeto necesitado de ello, que comprende la etapa de:

Administrar a dicho sujeto a una cantidad efectiva de un compuesto de fórmula 1 a una sal farmacéuticamente aceptable de esta.

Las condiciones mejoradas por la retoma de monoamina incluye aquellas seleccionadas del grupo que consiste de síntomas vasomotores, disfunción sexual, desórdenes gastrointestinal y genitourinario, síndrome de fatiga crónica, síndrome de fibromialgia, desórdenes del sistema nerviosos, y combinaciones de estos, particularmente aquellas condiciones seleccionadas del grupo que consiste del desorden depresivo mayor, síntomas vasomotores, tensión o incontinencia urinaria apremiante, fibromialgia, dolor, neuropatía diabética, y combinaciones de estos.

[0016] En otra modalidad, la presente invención está dirigida a métodos para tratar a prevenir los síntomas vasomotores en un sujeto necesitado de ello, que comprende la etapa de:

Administrar a dicho sujeto a una cantidad efectiva de al menos un compuesto de fórmula 1 o una sal farmacéuticamente aceptable de esta.

[0017] En otra modalidad, la presente invención está dirigida a métodos para tratar a prevenir el desorden de depresión en un sujeto necesitado de ello, que comprende la etapa de:

Administrar a dicho sujeto a una cantidad efectiva de al menos un compuesto de fórmula 1 o una sal farmacéuticamente aceptable de esta.

[0018] En otras modalidades, la presente invención está dirigida a métodos para tratar a prevenir la disfunción sexual en un sujeto necesitado de ello, que comprende las etapas de:

Administrar a dicho sujeto a una cantidad efectiva de al menos un compuesto de fórmula 1 o una sal farmacéuticamente aceptable de esta.

[0019] En modalidades adicionales, la presente invención está dirigida a métodos para tratar o prevenir el dolor en un sujeto necesitado de ello, que comprende las etapas de:

Administrar a dicho sujeto a una cantidad efectiva de al menos un compuesto de fórmula 1 o una sal farmacéuticamente aceptable de esta.

[0020] En otra modalidad, la presente invención está dirigida a métodos para tratar o prevenir el desorden gastrointestinal genitourinario, particularmente la incontinencia obtención o la

incontinencia urinaria apremiante, en un sujeto necesitado de ello, que comprende las etapas de:

Administrar a dicho sujeto una cantidad efectiva de al menos un compuesto de fórmula 1 o una sal farmacéuticamente aceptable de este.

[0021] En otra modalidad, la presente invención está dirigida a métodos para tratar o prevenir el síndrome de fatiga crónica en un sujeto necesitado de ello, que comprende las etapas de:

Administrar a dicho sujeto una cantidad efectiva de un compuesto de fórmula 1 o una sal farmacéuticamente aceptable de este.

[0022] En otra modalidad, la presente invención está dirigida a métodos para tratar o prevenir el síndrome fibromialgia en un sujeto necesitado de ello, que comprende las etapas de:

Administrar a dicho sujeto una cantidad efectiva de un compuesto de fórmula 1 o una sal farmacéuticamente aceptable de este.

BREVE DESCRIPCIÓN DE LOS DIBUJOS

[0023] La invención puede ser más completamente entendida de las siguiente descripción detallada y de los dibujos que la acompañan para que formen parte de esta solicitud

[0024] La figura 1 es una revisión de la acción del estrógeno o de la termorregulación mediada por norepinefrina/serotonina.

[0025] La figura 2 es una representación esquemática de las interacciones de la norepinefrina y la serotonina en su receptores respectivos (5-HT_{2a}, α_1 y α_2-adrenergico).

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

[0026] la presente invención está dirigida a derivados de fenilaminopropanol, composiciones que contienen estos derivados, y métodos de su uso para la prevención y tratamientos de condiciones mejoradas por la retoma de monoamina e incluyen, *inter alia*, síntomas vasomotores (VMS), disfunción sexual, desórdenes gastrointestinal y genitourinario, síndrome de fatiga crónica, síndrome de fibromialgia, desórdenes del sistema nerviosos, y combinaciones de estos, particularmente aquellas condiciones seleccionadas del grupo que consiste del desorden depresivo mayor, síntomas vasomotores, tensión e incontinencia urinaria apremiante, fibromialgia, dolor, neuropatía diabética, y combinaciones de estos.

[0027] Las siguientes definiciones se suministran para el entendimiento completo términos y abreviaturas utilizados en esta especificación.

[0028] Como se utilizan aquí y las reivindicaciones finales, las formas singulares "un", "una" y "el" incluyen las referencias plurales a menos que el contexto claramente indique otra cosa.

Así, por ejemplo, una referencia "un antagonista" incluye una pluralidad de tales antagonistas, y la referencia a "un compuesto" se refiere a uno o más compuestos y equivalentes de estos conocidos por aquellos expertos en la técnica, y así sucesivamente.

[0029] Las abreviaturas en la especificación corresponde a unidades de medida, técnicas, propiedades, o compuesto como seguidos: "min" significa minutos, "h" significa hora(s), "µl" significa micro litro(s), "mL" significa mililitro(s), "mM" significa mili molar, "M" significa molar, "m mol" significa mili mol(s), "cm" significa centímetros, "SEM" significa error de estándar de la media y "IU" significa unidades Internacionales. "Δ°C" y Δ "valor ED_{50}" significa dosis que resulta en un alivio del 50% de la condición o efecto observado (punto final máximo de la media del 50%).

[0030] "Transportador de norepinefrina " se abrevia NET.
"Transportador de norepinefrina humano " se abrevia hNET.
"Transportador de serotonina" se abrevia SERT.
"Transportador de serotonina humano" se abrevia hSERT.
"Inhibidor de retoma norepinefrina" se abrevia NRI.
"Inhibidor de retoma norepinefrina selectiva" se abrevia SNRI.
"Inhibidor de retoma serotonina" se abrevia SRI.
"Inhibidor de retoma serotonina selectiva" se abrevia SSRI.
"Norepinefrina " se abrevia NE.
"Serotonina" se abrevia 5-HT.
"Subcutáneos" se abrevia sc.
"Intraperitoneal" se abrevia ip.

"Oral" se abrevia po.

[0031] En el contexto de esta descripción, se deben utilizar un número de términos. El término "tratamiento" como se utiliza aquí incluye preventivo (por ejemplo, profilácticos) curativo o paliativo y "tratar" como se utiliza aquí incluye tratamiento preventivo, curativo o paliativo.

[0032] El término "cantidades efectivas", como se utiliza aquí, se refiere a una cantidad efectiva, en dosis, y durante el periodo de tiempos necesarios, para lograr el resultado deseado con respecto a la prevención o tratamiento de los síntomas vasomotores, los desórdenes de depresión la disfunción sexual o dolor. En particular, con respecto a los síntomas vasomotores, "cantidad efectiva" se refiere a la cantidad de compuesto o composición de compuestos e incrementaría los niveles de norepinefrina para compensar en parte o total la falta de disponibilidad de esteroide en sujetos afligidos con un síntoma vasomotor. Niveles de hormona variante se influenciaran la cantidad de compuestos requerido en la presente invención. Por ejemplo, el estado premenopáusico puede requerir un nivel inferior de compuesto hedido a niveles mayores de hormona que el estado perimenopáusico.

[0033] Se apreciara la cantidad efectiva de los componentes de la presente invención variara de paciente a apaciente no solamente con el compuesto particular, componente o composición seleccionada, la regla de administración, y la capacidad de los componentes (sola o en combinación con una o más drogas de

combinación) para elicitar la respuesta deseada del individuo, sino también con factores tales como, el estado o severidad de la enfermedad de la condición a ser aliviada, los niveles de hormona, edad, sexo, peso de los individuos, del estado de condición del paciente, y la severidad de la condición patológica a ser tratada, la medicación concurrente de dietas especiales , luego de ser seguida por un paciente particular, y otros factores que aquellos expertos en la técnica reconocerán, siendo las dosis apropiadas finalmente discreción del medico tratante. Los regimenes de dosis se pueden ajustar para suministrar las respuestas terapéuticas mejoradas. Una cantidad efectiva también es aquella en la cual cualquier efecto tóxico o detrimento de los componentes son sopesados por los efectos terapéuticos benéficos.

[0034] Preferiblemente, los compuestos de la presente invención se administran en una dosis y durante un tiempo tal que el número de flujos de calor se reduce comparado con el número de flujo de calor antes del inicio del tratamiento. Tal tratamiento puede ser benéfico para disminuir la distribución de severidad o intensidad total de cualquiera de los flujos de calor o un experimentado, comparados con la severidad de los flujos de calor antes del inicio de tratamiento. Con respecto a los desórdenes de depresión, la disfunción sexual, y el dolor, el compuesto de la siguiente presente invención se administra en una dosis y durante un tiempo tal que hay prevención, alivio, o eliminación del síntoma o condición.

[0035] Por ejemplo, para un paciente afligido, los compuestos de fórmula 1 o una sal farmacéuticamente aceptable de estos, se

puede administrar, preferiblemente en una dosis de aproximadamente 0.1 mg/día a aproximadamente 500 mg/día, dosificada una o dos veces diariamente, más que preferiblemente desde aproximadamente 1 mg/día a aproximadamente 200 mg/día y más preferiblemente de aproximadamente 1 mg/día a 100 mg/día durante un tiempo suficiente para reducir y/o eliminar sustancialmente el numero y/o la severidad de los flujos de calor o síntomas o condición del desorden depresión, la disfunción sexual, o dolor.

[0036] Los términos "componentes", "composición de compuestos", "compuestos", "drogas", o "agente farmacológicamente activo", o "agente activo", o "medicamentos", utilizados intercambiablemente aquí para referirse a un compuesto o compuestos o composición de material la cual, cuando se administra un sujeto (humano o animal) induce un efecto farmacológico y/o fisiológico deseado por la acción local y/o sistémica.

[0037] Los términos "componentes", "drogas", o "agente farmacológicamente activo", o "agente activo", o "medicamentos",se utilizan intercambiablemente aquí para referirse a un compuesto o compuestos o composición de material la cual, cuando se administra un sujeto (humano o animal) induce un efecto farmacológico y/o fisiológico por una acción local y/o sistémica.

[0038] el término "modulación" se refiere a la capacidad a mejorar o inhibir una propiedad funcional por una actividad proceso biológico, por ejemplo, la unión del receptor o la actividad de señal. El tal mejoramiento o inhibición puede ser

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contingente sobre la ocurrencia de un evento específico, tal como la activación de una senda de transducción de señal y/o puede ser manifiesta solamente en tipos de células particulares. El modulador esta destinado a comprender cualquier compuesto, por ejemplo, anticuerpo, molécula pequeña, péptido, oligopéptido, polipéptido o proteína, preferiblemente molécula pequeña, o péptido.

[0039] Como se utiliza aquí, el término "inhibidor" se refiere a cualquier agente que inhibe, suprime, reprime, disminuye una actividad especifica, tal como la actividad de retoma de serotonina o la actividad de retoma de norepinefrina.

[0040] El término "inhibidor" esta destinado a comprender cualquier compuesto, por ejemplo, anticuerpo, molécula pequeña, péptido, oligopéptido, polipéptido o proteína, preferiblemente molécula, o péptido pequeño, que exhiba un efecto parcial, completo, competitivo y/o inhibitorio sobre un mamífero preferiblemente la retoma de norepinefrina humana o tanto la retoma de serotonina como la retoma de norepinefrina, disminuyendo o bloqueando así, preferiblemente disminuyendo, algunos o todos los efectos biológicos de la retoma de norepinefrina endógena o tanto la retoma serotonina como la retoma de norepinefrina.

[0041] Dentro de la presente invención, los compuestos de fórmula 1 se pueden preparar en la forma de sales farmacéuticamente aceptables. Como se utiliza aquí, el término "sales farmacéuticamente aceptables" se refiere a las sales

preparadas de ácidos no tóxicos farmacéuticamente aceptables, que incluyen sales inorgánicas, y sales orgánicas. Las sales no orgánicas adecuadas incluyen ácidos inorgánicos y orgánicos tales como ácido acético, bencenosulfónico, benzoico, camforsulfónico, cítrico, etenosulfónico, fumárico, glucónico, glutámico, bromhídrico, clorhídrico, isetiónico, láctico, málico, maleico, mandélico, metanosulfónico, múcico, nítrico, pamóico, pantoténico, fosfórico, succínico, sulfúrico, ácido tartárico, p-toluenosulfónico y la similares. Particularmente preferidos son los ácidos clorhídrico, bromhídrico, fosfórico y sulfúrico, y más preferiblemente la sal de clorhidrato.

[0042] "Administrar", como se utiliza aquí, significa administrar directamente un compuesto o composición de la presente invención, o administrar una prodroga, derivado o análogo que formara una cantidad equivalente de compuesto activo o sustancia dentro del cuerpo.

[0043] El término "sujeto" o "paciente" se refiere a un animal que incluye las especies humana es tratable con las composiciones, y/o los métodos de la presente invención. Los términos "sujeto" o "sujetos" pretenden referirse tanto al género masculino como femenino a menos que un género este específicamente indicado. De acuerdo con esto, el término "pacientes" comprende un mamífero que puede beneficiarse del tratamiento o prevención de los síntomas vasomotores, los desórdenes de depresión. La disfunción sexual, o el dolor, tal como un humano, especialmente si el mamífero es hembra, en el periodo premenopáusico, perimenopáusico, o postmenopáusico.

Adicionalmente, el término paciente incluye animales hembra que incluyen humanos y, entre los humanos, no solamente mujeres de edad avanzada que han pasado a través de la menopausia si no también mujeres que han sufrido de histerectomía o por alguna otra razón si le han suprimido la producción de estrógeno. Tal como aquellas que han sufrido de administración de largo de plazo de corticosteroides, sufren de síndrome de Cushing obtienen disgénesis gonadal. Sin embargo, el término "paciente" no esta destinado a estar limitado a una mujer.

[0044] Los términos "menopausia prematura" o "menopausia artificial" se refieren a las fallas de ovarios de causa desconocida que pueda ocurrir antes de la edad de los 40. puede ser asociada con fumar, vivir a una altitud alta, o por un estado nutricional pobre. La menopausia artificial puede resultar de ooforectomía, quimioterapia, radiación de la pelvis, o cualquier proceso que dañe el suministro de sangre en los ovarios.

[0045] El término "premenopausia" significa antes de la menopausia, el término "perimenopausia" significa durante la menopausia y el término "postmenopausia" significa después de la menopausia. "ovariectomía" significa la eliminación de un ovario u ovarios y se puede afectar de acuerdo con Merchenthaler et al., Maturitas, 1998, 30(3): 307-316.

[0046] "Efectos colaterales" significa una consecuencia diferente de aquella o aquellas para las cuales un agente o medida se utiliza, como los efectos adversos producidos por una droga, especialmente sobre un tejido o sistemas de órganos

diferentes de aquel que se puede se va a beneficiar por su administración. El caso, por ejemplo, la falta de dosis de compuestos NRIs o NRI/SRI solos, el término "efectos colaterales" puede referirse a tales condiciones como, por ejemplo, vomito, nausea, sudoración, y flujos (Janowsky, et al., Journal of Clinical Psychiatry, 1984, 45(10 Pt 2): 3-9).

[0047] "Alquilo", como se utiliza aquí, se refiere a un hidrocarburo ramificado o cíclico saturado o insaturado opcionalmente sustituido que tiene desde aproximadamente 1 a aproximadamente 20 átomos de carbono (y todas las combinaciones y subcombinaciones de rangos y números específicos de átomos de carbono allí), donde aproximadamente 1 a aproximadamente 8 átomos de carbono siendo los preferidos, y donde aproximadamente 1 a aproximadamente 4 átomos de carbono, aquí denominados como "alquilo inferior", siendo los más preferidos los grupos alquilo incluye, pero no están limitados a, metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, t-butilo, n-pentilo, ciclopentilo, isopentilo, neopentilo, n-hexilo, isohexilo, ciclohexilo, ciclooctilo, adamantilo, 3-metilpentilo, 2,2-dimetilbutilo, y 2,3-dimetilbutilo.

[0048] "Alquilo perfluorinado", como se utiliza aquí, se refiere a un alquilo, como se definió anteriormente en el cual los hidrógenos se unen directamente a los de átomos de carbono son completamente reemplazados por flúor.

[0049] "Alquenilo", como se utiliza aquí, se refiere a un grupo alquilo de al menos dos átomos de carbono que tiene uno o más

dobles enlaces, en donde alquilo es como se definió aquí. Los grupos alquenilos pueden ser opcionalmente sustituidos.

[0050] "Alquinilo", como se utiliza aquí, se refiere a un grupo alquilo de al menos dos átomos de carbono que tiene uno o más triples enlaces, en donde alquilo es como se definió aquí. Los grupos alquinilos pueden ser opcionalmente sustituidos.

[0051] "Arilo", como se utiliza aquí, se refiere a un sistema de anillo aromático mono, di, tri, u otro multi cíclico opcionalmente sustituido que tiene de aproximadamente 5 a aproximadamente 50 átomos de carbono (y todas las combinaciones y subcombinaciones y de rangos y de números específicos de átomos de carbono allí), con desde aproximadamente 6 a aproximadamente 10 átomos de carbono siendo los preferidos. Ejemplo no limitantes, incluyen, por ejemplo, fenilo, naptilo, antracenilo, y fenantrenilo.

[0052] "Heteroarilo", como se utiliza aquí, se refiere a un sistema de anillo aromático mono, di, tri, u otro multi cíclico opcionalmente sustituido que incluye al menos 1, y preferiblemente de 1 a aproximadamente 4 miembros de anillo de heteroátomos flexionados de sulfuro, oxigeno, y nitrógeno. Los grupos heteroarilo pueden tener, por ejemplo, de aproximadamente 3 a aproximadamente 50 átomos de carbono (y todas las combinaciones y subcombinaciones y de rangos y de números específicos de átomos de carbono allí) cuando de aproximadamente 4 a aproximadamente 10 átomos de carbono siendo los preferidos. Ejemplos no limitantes de grupos heteroarilo incluyen, por

ejemplo, pirrilo, furilo, piridilo, 1,2,4-tiadiazolilo, pirimidilo, tienilo, isotiazolilo, imidazolilo, tetrazolilo, pirazinilo, pirimidilo, quinolilo, isoquinolilo, tiofenilo, benzotienilo, isobenzofurilo, pirazolilo, indolilo, purinilo, carbazolilo, benzimidazolilo, e isoxazolilo.

[0053] "Anillo heterocíclico", como se utiliza aquí, se refiere a un anillo heterocíclico monocíclico de 5 a 7 miembros o bicíclico de 7 a 10 miembros que es saturado, parcialmente insaturado o insaturado (aromático), y contiene átomos de carbono de 1 A 4 heteroátomos independientemente seleccionados del grupos que consiste en N, O y S y que incluye un bicíclico en el cual cualquiera de los anillos heterocíclicos anteriormente definidos se fusiona a una anillo de benceno. Los heteroátomos de nitrógeno y azufre pueden ser opcionalmente oxidados. El anillo heterocíclico se puede unir a su grupo dependiente o cualquier heteroátomo o átomo de carbón que resulte en una estructura estable. Los anillos heterocíclicos descritos aquí se pueden sustituir sobre un átomo de carbón o nitrógeno si el compuesto resultante es estable. Si la nota específicamente, un átomo de nitrógeno en el heterocíclico puede opcionalmente ser cuaternarizado. Se prefiere que cuando el numero total de átomos de S y O en heterociclo exceder uno, entonces estos heteroátomos no desean adyacentes uno al otro. Se refiere que el numero total de átomos de S y O en el heterociclo no sea más de uno. Ejemplos de heterociclos incluyen, pero no están limitados a, 1H-indazol, 2-pirrolidonilo, 2H, 6H-1,5,2-ditiazinilo, 2H-pirrolilo, 3H-indolilo, 4-piperidonilo, 4aH-carbazol, 4H-quinolizinilo, 6H-1,2,5-tiadiazinilo, acridinilo, azocinilo, benzimidazolilo,

benzofuranilo, benzotiofuranilo, benzotiofenilo, benzoxazolilo, benztiazolilo, benztriazolilo, benztetrazolilo, benzisoxazolilo, benzisotiazolilo, benzimidazalonilo, carbazolilo, 4H-carbazolilo, α-, β-, o γ-carbolinilo, cromanilo, cromenilo, cinnolinilo, decahidroquinolinilo, 2H, 6H-1,5,2-ditiazinilo, dihidrofuro[2,3-b] tetrahidrofurano, furanilo, furazanilo, imidazolidinilo, imidazolinilo, imidazolilo, 1H-indazolilo, indolenilo, indolinilo, indolizinilo, indolilo, isobenzofuranilo, isocromanilo, isoindazolilo, isoindolinilo, isoindolilo, isoquinolinilo, isotiazolilo, isoxazolilo, morfolinilo, naptiridinilo, octahidroisoquinolinilo, oxadiazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, oxazolidinilo., oxazolilo, oxazolidinilpirimidinilo, fenantridinilo, fenantrolinilo, fenoxazinilo, fenazinilo, fenotiazinilo, fenoxatiinilo, fenoxazinilo, ftalazinilo, piperazinilo, piperidinilo, pteridinilo, piperidonilo, 4-piperidonilo, pteridinilo, purinilo, piranilo, pirazinilo, pirazolidinilo, pirazolinilo, pirazolilo, piridazinilo, piridooxazol, piridoimidazol, piridotiazol, piridinilo, piridilo, pirimidinilo, pirrolidinilo, pirrolinilo, pirrolilo, quinazolinilo, quinolinilo, 4H-quinolizinilo, quinoxalinilo, quinuclidinilo, carbolinilo, tetrahidrofuranilo, tetrahidroisoquinolinilo, tetrahidroquinolinilo, 6H-1,2,5-tiadiazinilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, tiantrenilo, tiazolilo, tienilo, tienotiazolilo, tienooxazolilo, tienoimidazolilo, tiofenilo, triazinilo, 1,2,3-triazolilo, 1,2,4-triazolilo, 1,2,5-triazolilo, 1,3,4-triazolilo, xantenilo. Los heterociclos preferible se incluyen, pero no están limitados a, piridinilo,

furanilo, tienilo, pirrolilo, pirazolilo, imidazolilo, indolilo, benzimidazolilo, 1H-indazolilo, oxazolidinilo, benzotriazolilo, benzisoxazolilo, oxindolilo, benzoxazolinilo, o isatinilo. También incluidos están compuestos de anillo fusionado y espiro que contienen, por ejemplo, los heterociclos anteriores.

[0054] "Alcoxi", como se utiliza aquí, se refiere al grupo R-O en donde R es un grupo de alquilo, es definido aquí.

[0055] "Ariloxi", como se utiliza aquí, se refiere al grupo R-O en donde R es un grupo de arilo, como se definió aquí.

[0056] "Heteroariloxi", como se utiliza aquí, se refiere al grupo R-O en donde R es un grupo de heteroarilo, como se definió aquí.

[0057] "Alcanoiloxi", como se utiliza aquí, se refiere al grupo R-C(=O)-O- donde R es un grupo alquilo de 1 a 5 átomos de carbono.

[0058] "Alquilsulfóxido", como se utiliza aquí, se refiere al -S(=O)-R, en donde R es alquilo, como se definió anteriormente.

[0059] "Alquilsulfona", como se utiliza aquí, se refiere a $-S(=O)_2-R$, en donde R es alquilo, como se definió anteriormente.

[0060] "Alquilsulfonamida", como se utiliza aquí, se refiere a $-NR-S(=O)_2-R$, donde cada R es independientemente, alquilo, como se definió anteriormente o la parte NR también puede ser NH.

[0061] "Fenilsulfonamida", como se utiliza aquí, se refiere a -NR-S(=O)$_2$-fenilo, donde R es H o alquilo, como se definió anteriormente.

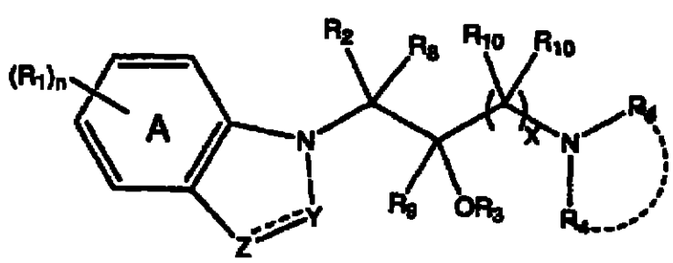
[0062] "Heteroarilmetiloxi", como se utiliza aquí, se refiere a -OCH$_2$-R, donde R es heteroarilo, como se definió anteriormente.

[0063] "Alquilamido", como se utiliza aquí, se refiere a -NR-C(=O)-R, donde cada R es independientemente, alquilo, como se definió anteriormente o la parte NR también puede ser NH.

[0064] Fenilamido", como se utiliza aquí, se refiere a -NR-C(=O)$_2$-fenilo, donde R es H o alquilo, como se definió anteriormente.

[0065] "Halo", como se utiliza aquí, se refiere a cloro, bromo, flúor, y yodo.

[0066] En una modalidad. la presente invención está dirigida a compuestos de la fórmula 1:



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O una sal farmacéuticamente aceptable de estos;

En donde:

La línea punteada entre Y y Z representa un enlace doble opcional;

La línea punteada entre los dos grupos R_4 representa un anillo heterocíclico opcional de 4 a 6 átomos por anillo que se puede formar entre los dos grupos R_4, junto con el nitrógeno a través del cual ellos están unidos;

Y es N, CR_6 o C=O;

Z es N, NR_7, CR_5, o $C(R_5)_2$;

R_1 es, independientemente a cada ocurrencia, alquilo, alcoxi, halo, CF_3, OCF_3, arilalquiloxi sustituido con 0-3 R_{11}, ariloxi sustituido con 0-3 R_{11}, arilo sustituido con 0-3 R_{11}, heteroarilo sustituido con 0-3 R_{11}, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo alquinilo, alquilsulfóxido, fenilsulfóxido sustituido con 0-3 R_{11}, alquilsulfona, fenilsulfona sustituido con 0-3 R_{11}, alquilsulfonamida, fenilsulfonamida sustituido con 0-3 R_{11}, heteroariloxi sustituido con 0-3 R_{11}, heteroarilmetoxi sustituido con 0-3 R_{11}, alquilamido, o arilamido sustituido con 0-3 R_{11}; o dos R_1 adyacentes también representan metilenodioxi;

R_2 es un arilo sustituido con 0-3 R_1 o heteroarilo sustituido con 0-3 R_1;

R_3 es H o alquilo C_1-C_4;

R_4 es, independientemente a cada ocurrencia, H, alquilo C_1-C_4, arilalquilo, heteroarilmetilo, cicloheptilmetilo, ciclohexilmetilo, ciclopentilmetilo, o ciclobutilmetilo, o

Ambos grupos R_4, junto con el nitrógeno a través del cual ellos están unidos, forman un anillo heterocíclico de 4 a 6 átomos por anillo, en donde un carbono puede ser opcionalmente reemplazado con N, O, S, o SO_2, y en donde el átomo del anillo de carbono o el átomo de N adicional puede ser opcionalmente sustituido con alquilo C_1-C_4 o CF_3;

R_5 es, independientemente a cada ocurrencia, H, alquilo C_1-C_4, arilo sustituido con 0-3 R_1 o ciano; o cuando dos R_5 están presentes, ellos forman un anillo carbocíclico de 3-7 carbonos;

R_6 es H, alquilo C_1-C_4, o ciano;

R_7 es H, alquilo C_1-C_6, cicloalquilo C_3-C_6, o arilo sustituido con 0-3 R_1;

R_8 es H, o alquilo C_1-C_4;
R_9 es H, o alquilo C_1-C_4;

R_{10} es, independientemente a cada ocurrencia, H, o alquilo C_1-C_4; o R_{10} y R_4 juntos con el átomo de nitrógeno al cual R_4 esta unido forma un anillo que contiene nitrógeno que contiene 3-6 átomos de carbono;

n es un entero de 0 a 4;

x es un entero de 1 a 2; y

R_{11} es alquilo, alcoxi, halo, CF_3, OCF_3, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo, alquinilo, alquilsulfóxido, alquilsulfona, alquilsulfonamida, o alquilamido; o dos R_{11} adyacentes también representan metilenodioxi;

En donde 1-3 átomos de carbono en el anillo A pueden opcionalmente ser reemplazados con N.

La línea punteada en el anillo fusionado al anillo A represente un doble enlace opcional entre Y y Z. la línea punteada entre los dos grupos R_4 representa un anillo heterocíclico opcional de 4 a 6 átomos por anillo que se puede formar entre los dos R_4, junto con el nitrógeno a través del cual ellos están unidos.

[0067] En ciertas modalidades preferidas de compuesto de fórmula 1, Y es N. En ciertas otras modalidades preferidas, Y es CR_6 preferiblemente CH. En ciertas otras modalidades preferidas, Y es C=O.

[0068] En ciertas modalidades más preferidas, Z es N. En ciertas modalidades preferidas de compuesto de fórmula 1, Z es NR_7. En ciertas otras modalidades más preferidas, Z es CR_5. En aún ciertas otras modalidades más preferidas, Z es $C(R_5)_2$. En aún ciertas otras modalidades más preferidas, Z es CH, $C(CH_3)$, o C(CN).

[0069] En ciertas modalidades preferidas de compuesto de fórmula 1, R_1 es, independiente a cada ocurrencia, alquilo, preferiblemente alquilo C_1-C_4, más preferiblemente metilo. En ciertas otras modalidades preferidas, R_1 es, independientemente de a cada ocurrencia alcoxi. En ciertas otras modalidades preferidas de compuestos, R_1 es, independientemente en cada ocurrencia, halo, preferiblemente F o Cl. En ciertas otras modalidades preferidas, R_1 es, independientemente en cada ocurrencia, CF_3. En ciertas otras modalidades preferidas, R_1 es, independientemente en cada ocurrencia, OCF_3. En ciertas otras modalidades preferidas, R_1 es, independientemente en cada ocurrencia, benciloxi sustituido con 0-3 R_1. En ciertas otras modalidades preferidas, R_1 es, independientemente en cada ocurrencia, ariloxi sustituido con 0-3 R^1. En ciertas otras modalidades preferidas, R_1 es, independientemente en cada ocurrencia, arilos sustituido con 0-3 R_1. En ciertas otras modalidades preferidas, R_1 es, independientemente en cada ocurrencia, heteroarilo sustituido con 0-3 R_1. En ciertas otras modalidades preferidas, R_1 es, independientemente en cada ocurrencia, hidróxido. En ciertas otras modalidades preferidas, R_1 es, independientemente en cada ocurrencia, alcanoiloxi. En ciertas otras modalidades preferidas, R_1 es, independientemente en cada ocurrencia, metilenodioxi. En ciertas otras modalidades preferidas, R_1 es, independientemente en cada ocurrencia, nitro. En ciertas otras modalidades preferidas, R_1 es, independientemente en cada ocurrencia, nitrilo. En ciertas otras modalidades preferidas, R_1 es, independientemente en cada ocurrencia, alquenilo. En ciertas otras modalidades preferidas, R_1 es, independientemente en cada ocurrencia, alquinilo. En

ciertas otras modalidades preferidas, R_1 es, independientemente en cada ocurrencia, alquilsufóxido. En ciertas otras modalidades preferidas, R_1 es, independientemente en cada ocurrencia, fenilsulfóxido sustituido con 0-3 R_1. En ciertas otras modalidades preferidas, R_1 es, independientemente en cada ocurrencia, alquilsufona. En ciertas otras modalidades preferidas, R_1 es, independientemente en cada ocurrencia, fenilsolfuna sustituido con 0-3 R_1. En ciertas otras modalidades preferidas, R_1 es, independientemente en cada ocurrencia, alquisulfonamida. En ciertas otras modalidades preferidas, R_1 es, independientemente en cada ocurrencia, fenilsulfonamida sustituido con 0-3 R_1. En ciertas otras modalidades preferidas, R_1 es, independientemente en cada ocurrencia, heteroariloxi sustituido con 0-3 R_1. En ciertas otras modalidades preferidas, R_1 es, independientemente en cada ocurrencia, heteroarilmetiloxi sustituido con 0-3 R_1. En ciertas otras modalidades preferidas, R_1 es, independientemente en cada ocurrencia, alquilamida. En ciertas otras modalidades preferidas, R_1 es, independientemente en cada ocurrencia, fenilamido sustituido con 0-3 R_1.

[0070] En ciertas modalidades preferidas de compuestos de fórmula 1, R_2 es arilo sustituido con 0-3 R_1, preferiblemente sustituido con no R_1, en ciertas modalidades preferidas, R_2 es naftilina sustituida con 0-3 R_1, preferiblemente sustituida con no R_1. En ciertas modalidades preferidas, R_2 es heteroarilo sustituido con 0-3 R_1, preferiblemente sustituido con no R_1.

[0071] En ciertas modalidades preferidas de compuestos de fórmula I, R_3 es H. En ciertas otras modalidades preferidas, R_3 es C_1 - C_4 alquilo, preferiblemente C_1 alquilo.

[0072] En otras modalidades preferidas de compuestos de fórmula I, R_4 es, independientemente en cada ocurrencia, H. En ciertas modalidades preferidas, R_4 es, independientemente en cada ocurrencia, C_1-C_4 alquilo más preferiblemente metilo, etilo, isopropilo. En ciertas modalidades preferidas de compuestos de fórmula I, R_4 es, independientemente de cada ocurrencia, bencilo. En ciertas modalidades preferidas, R_4 es, independientemente de cada ocurrencia heteroarilmetilo. En ciertas modalidades preferidas, R_4 es, independientemente en cada ocurrencia, cicloheptimetilo, ciclohexilmetilo, ciclopentimetilo, o ciclobutilmetilo.

[0073] En ciertas modalidades preferidas de compuestos de fórmula I, ambos grupos R_4, junto con el nitrógeno que forman un anillo heterocíclico de 4 a 6 átomos de anillo, en donde el carbón puede ser reemplazado opcionalmente con N, O, S o SO_2 y donde cualquier carbón de átomo de anillo o átomo de N adicional puede ser opcionalmente sustituido con C_1-C_4 alquilo, F o CF_3. En ciertas modalidades preferidas, ambos grupos R_4, junto con el nitrógeno, de forma de piridina, peperidina, piperacina, piperazina sustituida con un grupo metilo, o un anillo morfolino.

[0074] En ciertas modalidades preferidas de compuestos de fórmula 1, R_5 es, independientemente en cada ocurrencia, H. En ciertas modalidades preferidas de compuestos, R_5 es,

independientemente en cada ocurrencia, C_1-C_4 alquilo, preferiblemente metilo. En ciertas modalidades de preferidas de compuestos, R_5, es, independientemente en cada ocurrencia, arilo sustituido con 0-3 R_1, preferiblemente fenilo, tolilo, o xililo. En ciertas modalidades preferidas, R_5 es, independientemente en cada ocurrencia, ciano.

[0075] En ciertas modalidades preferidas de compuestos de fórmula I, cuando dos R_5 están presentes, forman un anillo carboxílico de 3-7 carbonos preferiblemente un ciclopentilo o ciclohexilo.

[0076] En ciertas modalidades preferidas de compuestos de fórmula I, R_6 es, independientemente en cada ocurrencia, H. En ciertas modalidades preferidas de compuestos R_6 es, independientemente en cada ocurrencia C_1-C_4 alquilo, preferiblemente metilo. En ciertas modalidades preferidas, R_6 es, independientemente en cada ocurrencia, ciano.

[0077] En ciertas modalidades preferidas de compuestos de fórmula I, R_7 es, independientemente en cada ocurrencia H. En ciertas modalidades preferidas de compuestos, R_7, es independientemente en cada ocurrencia, C_1-C_4 alquilo, preferiblemente C_1-C_4 alquilo, más preferiblemente metilo. En ciertas modalidades preferidas de compuestos, R_7 es, independientemente en cada ocurrencia C_3-C_6 cicloalquilo, preferiblemente, ciclopentilo o ciclohexilo. En ciertas modalidades preferidas, R_5 es, independientemente en cada

ocurrencia, arilo sustituido con 0-3 R_1, preferiblemente fenil, tolil, o xilil.

[0078] En ciertas modalidades preferidas de compuestos de fórmula 1, R_8 es independientemente en cada ocurrencia H. En ciertas modalidades preferidas de compuestos R_8 es, independientemente en cada ocurrencia, C_1-C_4 alquilo, preferiblemente metilo.

[0079] En ciertas modalidades preferidas de compuestos de fórmula I, R_9 es, independientemente en cada ocurrencia H. En ciertas modalidades preferidas de compuestos R_9 es, independientemente en cada ocurrencia, C_1-C_4 alquilo, preferiblemente metilo.

[0080] En ciertas modalidades preferidas de compuestos de fórmula I, R_9 es, independientemente en cada ocurrencia H. En ciertas modalidades preferidas de compuestos R_9 es, independientemente en cada ocurrencia, C_1-C_4 alquilo, preferiblemente metilo. En ciertas modalidades de preferencia de fórmula 1, R_{10} y R_4 son atacados con nitrógeno de anillo contenido en 3-6 átomos de carbono, especialmente pirrolidina, piperidilina, piridinila, azepanila, y azepinila.

[0081] En ciertas modalidades preferidas de compuestos de fórmula 1, n es un entero de 0 a 3. Más preferiblemente, n es 0 a 2. Incluso más preferiblemente, n es 0 a 1. Aún más preferiblemente, n es 0.

[0082] En ciertas modalidades preferidas de compuestos de fórmula 1, x es un entero de 1 a 2. Más preferiblemente, x es 1.

[0083] En ciertas modalidades preferidas de compuestos de fórmula 1, 1-2 átomos de carbono de anillo A pueden ser opcionalmente reemplazado con N. En ciertas modalidades preferidas de compuestos, un átomo de carbón en anillo A puede ser opcionalmente reemplazado con N. En ciertas modalidades preferidas, los átomos no carbonos en anillo A son reemplazados con N.

[0084] En ciertas modalidades preferidas de compuestos de fórmula I.

Y es N, CR_6, o C=O;

Z es N, NR7, CR5 o $C(R_5)_2$;

R_1 es, independientemente en cada ocurrencia, alquilo, alcoxi halo, CF_3, OCF_3, arilalquiloxi sustituido con 0-3 R_{11}, ariloxi sustituido con 0-3 R_{11}, arilo sustituido con 0-3 R_{11}, heteroarilo sustituido con 0-3 R_{11}, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo, alquinilo alquilsulfóxido, fenilsulfóxido sustituido con 0-3 R_{11}, alquilsulfona, fenilsulfona sustituida con 0-3 R_{11}, alquisulfonamida, fenilsulfonamida sustituido con 0-3 R_{11}, heteroariloxi sustituido con 0-3 R_{11}, heteroarilmetiloxi sustituido con 0-3 R_{11}, alquilamido, o arilamido sustituido con 0-3 R_{11}; o dos adyacentes R_1 que también representan metilenodioxi;

R_2 es arilo sustituido con 0-3 R-i o heteroaril sustituido con 0-3 R_1;

R_3 es H;

R_4 es, independientemente en cada ocurrencia, H, C_1-C_4 alquilo;

R_5 es, independientemente en cada ocurrencia, H, C_1-C_4 alquilo, arilo sustituido con 0-3 R_1, o ciano; o cuando dos R_5 están presentes, ellos forman un anillo carboxílico de 3-7 carbonos;

R_6 es H, C_1-C_4 alquilo, o ciano;

R_7 es H, C_1-C_6 alquilo, C_3-C_6 cicloalquilo, o arilo sustituido con 0-3 R_1;

R_8 es H;

R_9 es H;

R_{10} es H;

n es un entero de 0 a 4;

x es un entero de 1 a 2;

y R_{11} es alquilo, alcoxi, halo, CF_3, OCF_3, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo, alquinilo, alquilsulfoxido, alquilsulfona alquilsulfonamida, o alquilamido; o dos adyacentes R_{11} también representan metilenodioxi;

en donde 1-3 anillos de átomos de carbono A pueden ser reemplazados con N.

[0088] En ciertas modalidades preferidas de compuestos de fórmula I,

Y es C=O;

Z es NR_7

R_1 es independientemente en cada ocurrencia, alquilo, alkoxi, halo, CF_3, OCF_3, arilalquiloxi sustituido con 0-3 R_{11}, ariloxi sustituido con 0-3 R_{11}, arilo sustituido con 0-3 R_{11}, heteroarilo sustituido con 0-3 R_{11}, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo, alquinilo alquilsulfóxido, fenilsulfóxido sustituido con 0-3 R_{11}, alquilsulfona, fenilsulfona sustituida con 0-3 R_{11}, alquisulfonamida, fenilsulfonamida sustituido con 0-3 R_{11}, heteroariloxi sustituido con 0-3 R_{11}, heteroarilmetiloxi sustituido con 0-3 R_{11}, alquilamido, o arilamido sustituido con 0-3 R_{11}; o dos adyacentes R_1 que también representan metilenodioxi;

R_2 es arilo sustituido con 0-3 R-i o heteroarilo sustituido con 0-3 R_1;

R_3 es H o C_1-C_4 alquilo;

R_4 es, independientemente en cada ocurrencia, H, C_1-C_4 alquilo, arilalquilo, heteroarilmetilo, cicloheptilmetilo, ciclohexilmetilo, ciclopentilmetilo, o ciclobutilmetilo;

R_5 es, independientemente en cada ocurrencia, H, C_1-C_4 alquilo, arilo sustituido con 0-3 R_1, o ciano; o cuando dos R_5 están presentes, ellos forman un anillo carboxílico de 3-7 carbonos;

R_6 es H, C_1-C_4 alquilo, o ciano;

R_7 es H, C_1-C_6 alquilo, C_3-C_6 cicloalquilo, o arilo sustituido con 0-3 R_1;

R_8 es H o C_1-C_4 alquilo;

R_9 es H o C_1-C_4 alquilo;

R_{10} es H

n es un entero de 0 a 4;

x es 1;

y R_{11} es alquilo, alcoxi, halo, CF_3, OCF_3, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo, alquinilo, alquilsulfoxido, alquilsulfona alquilsulfonamida, o alquilamido; o dos adyacentes R_{11} también representan metilenodioxi;

en donde 1-3 anillos de átomos de carbono A pueden ser reemplazados con N.

[0085] En ciertas modalidades preferidas de compuestos de fórmula I,

Y es CR_6;

Z es CR_5;

R_1 es, independientemente en cada ocurrencia, alquilo, alcoxi halo, CF_3, OCF_3, arilalquiloxi sustituido con 0-3 R_{11}, ariloxi sustituido con 0-3 R_{11}, arilo sustituido con 0-3 R_{11}, heteroarilo sustituido con 0-3 R_{11}, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo, alquinilo alquilsulfóxido, fenilsulfóxido sustituido con 0-3 R_{11}, alquilsulfona, fenilsulfona sustituida con 0-3 R_{11}, alquisulfonamida, fenilsulfonamida sustituido con 0-3 R_{11}, heteroariloxi sustituido con 0-3 R_{11}, heteroarilmetiloxi sustituido con 0-3 R_{11}, alquilamido, o arilamido sustituido con 0-3 R_{11}; o dos adyacentes R_1 que también representan metilenodioxi;

R_2 es arilo sustituido con 0-3 R-i o heteroaril sustituido con 0-3 R_1;

R_3 es H;

R_4 es, independientemente en cada ocurrencia, H, C_1-C_4 alquilo;

R_5 es, independientemente en cada ocurrencia, H, C_1-C_4 alquilo, arilo sustituido con 0-3 R_1, o ciano; o cuando dos R_5 están presentes, ellos forman un anillo carboxílico de 3-7 carbonos;

R_6 es H, C_1-C_4 alquilo, o ciano;

R_7 es H, C_1-C_6 alquilo, C_3-C_6 cicloalquilo, o arilo sustituido con 0-3 R_1;

R_8 es H;

R_9 es H;

R_{10} es H;

n es un entero de 0 a 4;

x es un entero de 1 a 2;

y R_{11} es alquilo, alcoxi, halo, CF_3, OCF_3, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo, alquinilo, alquilsulfoxido, alquilsulfona alquilsulfonamida, o alquilamido; o dos adyacentes R_{11} también representan metilenodioxi;

en donde 1-3 anillos de átomos de carbono A pueden ser reemplazados con N.

[0088] En ciertas modalidades preferidas de compuestos de fórmula I,

Y es C=O;

Z es NR_7

R_1 es independientemente en cada ocurrencia, alquilo, alcoxi, halo, CF_3, OCF_3, arilalquiloxi sustituido con 0-3 R_{11}, ariloxi sustituido con 0-3 R_{11}, arilo sustituido con 0-3 R_{11}, heteroarilo sustituido con 0-3 R_{11}, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo, alquinilo alquilsulfóxido, fenilsulfóxido sustituido con 0-3 R_{11}, alquilsulfona, fenilsulfona sustituida con 0-3 R_{11}, alquisulfonamida, fenilsulfonamida sustituido con 0-

3 R_{11}, heteroariloxi sustituido con 0-3 R_{11}, heteroarilmetiloxi sustituido con 0-3 R_{11}, alquilamido, o arilamido sustituido con 0-3 R_{11}; o dos adyacentes R_1 que también representan metilenodioxi;

R_2 es arilo sustituido con 0-3 R-i o heteroarilo sustituido con 0-3 R_1;

R_3 es H o C_1-C_4 alquilo;

R_4 es, independientemente en cada ocurrencia, H, C_1-C_4 alquilo, arilalquilo, heteroarilmetilo, cicloheptilmetilo, ciclohexilmetilo, ciclopentilmetilo, o ciclobutilmetilo;

R_5 es, independientemente en cada ocurrencia, H, C_1-C_4 alquilo, arilo sustituido con 0-3 R_1, o ciano; o cuando dos R_5 están presentes, ellos forman un anillo carboxílico de 3-7 carbonos;

R_6 es H, C_1-C_4 alquilo, o ciano;

R_7 es H, C_1-C_6 alquilo, C_3-C_6 cicloalquilo, o arilo sustituido con 0-3 R_1;

R_8 es H o C_1-C_4 alquilo;

R_9 es H o C_1-C_4 alquilo;

R_{10} es H o C_1-C_4 alquilo; o R_{10} y R_4, juntos con el nitrógeno en el cual R_4 es atacado, de un anillo de nitrógeno que contiene de 3-6 átomos de carbono;

n es un entero de 0 a 4;

x es un entero de 1 a 2; y

y R_{11} es alquilo, alcoxi, halo, CF_3, OCF_3, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo, alquinilo, alquilsulfoxido, alquilsulfona alquilsulfonamida, o alquilamido; o dos adyacentes R_{11} también representan metilenodioxi;

en donde 1-3 anillos de átomos de carbono A pueden ser reemplazados con N.

[0086] En ciertas modalidades preferidas de compuestos de fórmula 1,

Y es CR_6;

Z es $C(R_5)_2$;

R_1 es, independientemente en cada ocurrencia, alquilo, alcoxi halo, CF_3, OCF_3, arilalquiloxi sustituido con 0-3 R_{11}, ariloxi sustituido con 0-3 R_{11}, arilo sustituido con 0-3 R_{11}, heteroarilo sustituido con 0-3 R_{11}, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo, alquinilo alquilsulfóxido, fenilsulfóxido sustituido con 0-3 R_{11}, alquilsulfona, fenilsulfona sustituida

con 0-3 R_{11}, alquisulfonamida, fenilsulfonamida sustituido con 0-3 R_{11}, heteroariloxi sustituido con 0-3 R_{11}, heteroarilmetiloxi sustituido con 0-3 R_{11}, alquilamido, o arilamido sustituido con 0-3 R_{11}; o dos adyacentes R_1 que también representan metilenodioxi;

R_2 es arilo sustituido con 0-3 R-i o heteroarilo sustituido con 0-3 R_1;

R_3 es H o C_1-C_4 alquilo;

R_4 es, independientemente en cada ocurrencia, H, C_1-C_4 alquilo;

R_5 es, independientemente en cada ocurrencia, H, C_1-C_4 alquilo, arilo sustituido con 0-3 R_1, o ciano; o cuando dos R_5 están presentes, ellos forman un anillo carboxílico de 3-7 carbonos;

R_6 es H, C_1-C_4 alquilo, o ciano;

R_7 es H, C_1-C_6 alquilo, C_3-C_6 cicloalquilo, o arilo sustituido con 0-3 R_1;

R_8 es H o C_1-C_4 alquilo;

R_9 es H o C_1-C_4 alquilo;

R_{10} es independientemente en cada ocurrencia, H o C_1-C_4 alquilo; o R_{10} y R_4, juntos con nitrógeno el cual R_4 es atacado, por un anillo de nitrógeno

Que contiene 3-6 átomos de carbono;

n es un entero de 0 a 4;

x es un entero de 1 a 2: y

R_{11} es alquilo, alcoxi, halo, CF_3, OCF_3, hidroxi, alcanoiloxi, nitro, nitrilo, alquilo, alquinilo, alquisulfóxido, alquisulfona, alquilsulfonamida, o alquilamido; o o dos R_{11} adyacentes también representan metilenodioxi:

En donde 1-3 átomos de carbono en anillo A pueden ser opcionalmente reemplazados con N.

[0087] En ciertas modalidades preferidas en los compuestos de fórmula 1:

Y es = O;

Z es $C(R_5)_2$;

R_1 es, independientemente en cada ocurrencia, alquilo, alcoxi halo, CF_3, OCF_3, arilalquiloxi sustituido con 0-3 R_{11}, ariloxi sustituido con 0-3 R_{11}, arilo sustituido con 0-3 R_{11}, heteroarilo sustituido con 0-3 R_{11}, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo, alquinilo alquilsulfóxido, fenilsulfóxido sustituido con 0-3 R_{11}, alquilsulfona, fenilsulfona sustituida con 0-3 R_{11}, alquisulfonamida, fenilsulfonamida sustituido con 0-3 R_{11}, heteroariloxi sustituido con 0-3 R_{11}, heteroarilmetiloxi sustituido con 0-3 R_{11}, alquilamido, o arilamido sustituido con 0-3 R_{11}; o dos adyacentes R_1 que también representan metilenodioxi;

R_2 es arilo sustituido con 0-3 R-i o heteroaril sustituido con 0-3 R_1;

R_3 es H o alquilo C_1-C_4;

R_4 es, independientemente en cada ocurrencia, H, alquilo C_1-C_4, arilalquilo, heteroarilmetilo, cicloheptilmetilo, ciclohexilmetilo, ciclopentilmetilo, o ciclobutilmetilo;

R_5 es, independientemente en cada ocurrencia, H, alquilo C_1-C_4, arilo sustituido con 0-3 R_1, o ciano; o cuando dos R_5 están presentes, ellos forman un anillo carboxílico de 3-7 carbonos;

R_6 es H, alquilo C_1-C_4, o ciano;

R_7 es H, C_1-C_6 alquilo, C_3-C_6 cicloalquilo, o arilo sustituido con 0-3 R_1;

R_8 es H o alquilo C_1-C_4;

R_9 es H o alquilo C_1-C_4;

R_{10} es, independientemente en cada ocurrencia, H o alquilo C_1-C_4; o R_{10} y R_4, junto con el nitrógeno al cual R_4 está unido, forma un anillo que contiene nitrógeno 3-6 átomos de carbono;

n es un entero de 0 a 4;

x es un entero de 1 a 2;

y R_{11} es alquilo, alcoxi, halo, CF_3, OCF_3, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo, alquinilo, alquilsulfoxido, alquilsulfona alquilsulfonamida, o alquilamido; o dos adyacentes R_{11} también representan metilenodioxi;

en donde 1-3 anillos de átomos de carbono A pueden ser reemplazados con N.

[0088] En ciertas modalidades preferidas de compuestos de fórmula I,

Y es C=O;

Z es NR_7

R_1 es independientemente en cada ocurrencia, alquilo, alcoxi, halo, CF_3, OCF_3, arilalquiloxi sustituido con 0-3 R_{11}, ariloxi sustituido con 0-3 R_{11}, arilo sustituido con 0-3 R_{11}, heteroarilo sustituido con 0-3 R_{11}, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo, alquinilo alquilsulfóxido, fenilsulfóxido sustituido con 0-3 R_{11}, alquilsulfona, fenilsulfona sustituida con 0-3 R_{11}, alquisulfonamida, fenilsulfonamida sustituido con 0-3 R_{11}, heteroariloxi sustituido con 0-3 R_{11}, heteroarilmetiloxi sustituido con 0-3 R_{11}, alquilamido, o arilamido sustituido con 0-3 R_{11}; o dos adyacentes R_1 que también representan metilenodioxi;

R_2 es arilo sustituido con 0-3 R-i o heteroarilo sustituido con 0-3 R_1;

R_3 es H o alquilo C_1-C_4;

R_4 es, independientemente en cada ocurrencia, H, alquilo C_1-C_4, arilalquilo, heteroarilmetilo, cicloheptilmetilo, ciclohexilmetilo, ciclopentilmetilo, o ciclobutilmetilo;

R_5 es, independientemente en cada ocurrencia, H, alquilo C_1-C_4, arilo sustituido con 0-3 R_1, o ciano; o cuando dos R_5 están presentes, ellos forman un anillo carboxílico de 3-7 carbonos;

R_6 es H, alquilo C_1-C_4, o ciano;

R_7 es H, C_1-C_6 alquilo, C_3-C_6 cicloalquilo, o arilo sustituido con 0-3 R_1;

R_8 es H o alquilo C_1-C_4;

R_9 es H o alquilo C_1-C_4;

R_{10} es, independientemente en cada ocurrencia, H o alquilo C_1-C_4; o R_{10} y R_4, junto con el nitrógeno al cual R_4 está unido, forma un anillo que contiene nitrógeno 3-6 átomos de carbono;

n es un entero de 0 a 4;

x es un entero de 1 a 2;

y R_{11} es alquilo, alcoxi, halo, CF_3, OCF_3, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo, alquinilo, alquilsulfoxido, alquilsulfona alquilsulfonamida, o alquilamido; o dos adyacentes R_{11} también representan metilenodioxi;

en donde 1-3 anillos de átomos de carbono A pueden ser reemplazados con N.

[0089] Los compuestos preferidos de fórmula I incluyen:

1-(1H-indol-1-il)-3-(4-metilpiperazin-1-il)-1-fenilpropan-2-ol;

1-(5-fluoro-1H-indol-1-il)-3-(4-metilpiperazin-1-il)-1-fenilpropan-2-ol;

1-(1H-indol-1-il)-3-morfolin-4-il-1-fenilpropan-2-ol;

3-(dimetilamino)-1-(1H-indol-1-il)-1-fenilpropan-2-ol;

3-(etilamino)-1-(1H-indol-1-il)-1-fenilpropan-2-ol;

1-(1H-indol-1-il)-3-(isopropilamino)-1-fenilpropan-2-ol;

3-(bencilamino)-1-(1H-indol-1-il)-1-fenilpropan-2-ol;

3-[(ciclohexilmetil)amino]-1-(1H-indol-1-il)-1-fenilpropan-2-ol;

3-[(ciclohexilmetil)amino]-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

3-(isopropilamino)-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

3-(etilamino)-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

1-(1H-indol-1-il)-1-fenil-3-piperazin-1-ilpropan-2-ol di;

1-(1H-indol-1-il)-1-fenil-3-[(piridin-4-ilmetil) amino]propan-2-ol;

1-(5-cloro-1H-indol-1-il)-1-fenil-3-piperidin-1-ilpropan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

3-amino-1-(1H-indol-1-il)-1-fenilpropan-2-ol;

3-(etilamino)-1-(5-fluoro-1H-indol-1-il)-1-fenilpropan-2-ol;

3-amino-1-(5-fluoro-1H-indol-1-il)-1-fenilpropan-2-ol;

1-(5-fluoro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

3-(metilamino)-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

3-amino-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

3-[etil(metil)amino]-1-(1H-indol-1-il)-1-fenilpropan-2-ol;

1-(5-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(5-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-1-ol;

1-[2-hidroxi-3-(metilamino)-1-fenilpropil]-1H-indol-3-carbonitrilo;

1-(1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

3-(metilamino)-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

1-(3-clorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

1-(4-clorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-[3-(trifluorometoxi)fenil]propan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-[2-(trifluorometoxi)fenil]propan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-[2-(trifluorometoxi)fenil]propan-2-ol;

1-(2-clorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-[4-(trifluorometoxi)fenil]propan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-[4-(trifluorometoxi)fenil]propan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-[4-(trifluorometoxi)fenil]propan-2-ol;

4-amino-1-(3-clorofenil)-1-(1H-indol-1-il)butan-2-ol

1-(3-bromofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

3-[2-hidroxi-1-(1H-indol-1-il)-3-(metilamino)propil]benzonitrilo

1-(3-fluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-[3-(3-metilfenil)-1H-indol-1-il]propan-2-ol;

1-(4-fluorofenil)-3-(metilamino)-1-(3-metil-1H-indol-1-il)propan-2-ol;

1-(2-fluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

1-(4-fluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-(3-metilfenil)propan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-(2-metilfenil)propan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-(2-metilfenil)propan-2-ol;

3-(etilamino)-1-(3-fluorofenil)-1-(1H-indol-1-il)propan-2-ol;

1-(3-fluorofenil)-1-(1H-indol-1-il)-3-morfolin-4-ilpropan-2-ol;

1-(3-fluorofenil)-1-(1H-indol-1-il)-3-(propilamino)propan-2-ol;

1-(3-fluorofenil)-1-(1H-indol-1-il)-3-(4-metilpiperazin-1-il)propan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-(4-metilfenil)propan-2-ol;

1-(2,3-dihidro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-[3-(2-metilfenil)-1H-indol-1-il]propan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-(2-metil-2,3-dihidro-1H-indol-1-il)propan-2-ol;

1-(7-fluoro-3,3-dimetil-2,3-dihidro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(7-fluoro-3,3-dimetil-2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

3-(metilamino)-1-(7-metil-2,3-dihidro-1H-indol-1-il)-1-fenilpropan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-(7-metil-2,3-dihidro-1H-indol-1-il)propan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-(5-metil-2,3-dihidro-1H-indol-1-il)propan-2-ol;

1-(1H-indol-1-il)-1-(3-metoxifenil)-3-(metilamino)propan-2-ol;

1-(1H-indol-1-il)-1-(4-metoxifenil)-3-(metilamino)propan-2-ol;

3-(metilamino)-1-(2-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

1-(1H-benzimidazol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

3-(metilamino)-1-(2-metil-1H-benzimidazol-1-il)-1-fenilpropan-2-ol;

1-(4-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(5-fluoro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(5-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(7-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(4-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(6-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(5-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(3-fluorofenil)-1-(6-metoxi-1H-indol-1-il)-3-(metilamino)propan-2-ol;

3-(metilamino)-1-fenil-1-(1H-pirrolo[2,3-b]piridin-1-il)propan-2-ol;

1-(5-cloro-2,3-dihidro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

3-(metilamino)-1-fenil-1-(1H-pirrolo[2,3-c]piridin-1-il)propan-2-ol;

1-(5-fluoro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

3-(metilamino)-1-(3-fluorofenil)-1-(1H-pirrolo[2,3-c]piridin-1-il)propan-2-ol;

1-(5-cloro-2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

3-(metilamino)-1-(6-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

3-(metilamino)-1-(7-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-(5-metil-1H-indol-1-il)propan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-(7-metil-1H-indol-1-il)propan-2-ol;

3-(metilamino)-1-(4-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

3-(metilamino)-1-(5-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-(4-metil-1H-indol-1-il)propan-2-ol;

1-(3-etil-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-(3-fenil-1H-indol-1-il)propan-2-ol;

7-fluoro-1-[2hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

1-[2hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

7-fluoro-1-[1-(3-fluorofenil)-2-hidroxi-3-(metilamino)propil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

1-(1H-indol-1-il)-3-(metilamino)-1-(2-tienil)propan-2-ol;

1(1H-indol-1-il)-3-(metilamino)-1-(2-tienil)propan-2-ol;

1'-[2-hidroxi-3-(metilamino)-1-fenilpropil]espiro[ciclohexano-1,3'-indol]-2'(1'H)-ona;

2-(3-fluorofenil)-2-(1H-indol-1-il)-1-[(2S)-pirrolidin-2-il]etanol;

2-(3-fluorofenil)-2-(1H-indol-1-il)-1-[pirrolidin-2-il]etanol;

1'-[2hidroxi-3-(metilamino)-1-fenilpropil]espiro[ciclobutano-1,3'-indol]-2'(1'H)-ona;

1'-[2hidroxi-3-(metilamino)-1-fenilpropil]espiro[ciclopentano-1,3'-indol]-2'(1H)-ona;

1'-[2hidroxi-3-(metilamino)-1-fenilpropil]espiro[ciclopropano-1,3'-indol]-2'(1H)-ona;

5-fluoro-1-[2hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

3-(ciclopropilamino)-1-(3-fluorofenil)-1-(1H-indol-1-il)propan-2-ol;

7'-fluoro-1'-[2hidroxi-3-(metilamino)-1-fenilpropil]espiro[ciclohexano-1,3'-indol]-2'(1'H)-ona;

5'-bromo-1'-[2hidroxi-3-(metilamino)-1-fenilpropil]espiro[ciclohexano-1,3'-indol]-2'(1'H)-ona;

1-(3-fluorofenil)-1-[3-(2-fluorofenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol;

1-[3-(3,4-diclorofenil)-1H-indol-1-il]-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(3-fluorofenil)-1-[3-(3-fluorofenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol;

1-(5-fluoro-3-metil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

3-amino-1-(5-fluoro-3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

1-(5-cloro-3-metil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

3amino-1-(5-cloro-3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

[3-(5-cloro-3-metil-1H-indol-1-il)-2-metoxi-3-fenilpropil]metilamina;

1-(7-cloro-3-metil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

[3-(5-fluoro-3-metil-1H-indol-1-il)-2-metoxi-3-fenilpropil]metilamina;

1-(4-bromo-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(4-bromo-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(5-bromo-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(5-bromo-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-[2-hidroxi-3-(metilamino)-1-fenilpropil]-1H-indol-4-carbonitrilo;

1-(6-bromo-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-[2-hidroxi-3-(metilamino)-1-fenilpropil]-1H-indol-5-carbonitrilo;

1-[1-(3-fluorofenil)-2-hidroxi-3-(metilamino)propil]-1H-indol-4-carbonitrilo;

1-(6-bromo-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(6-fluoro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

3-amino-1-(3-fluorofenil)-1-(1H-indol-1-il)propan-2-ol;

1-(7-bromo-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-[3-(trifluorometil)fenil]propan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-espiro[ciclohexano-1,3'-indol]-1'(2'H)-ilpropan-2-ol;

1-(2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-[3-(trifluorometil)fenil]propan-2-ol;

1-(3-fluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

1-(3,4-difluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-(3-metil-1H-indol-1-il)propan-2-ol;

1-(4-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(6-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(7-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(7-cloro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(4-cloro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(6-cloro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(5-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(5-cloro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(3-isopropil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(3-fluorofenil)-1-(3-isopropil-1H-indol-1-il)-3-(metilamino)propan-2-ol;

1-(3,5-difluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

1-(3,5-difluorofenil)-1-(2,3-dihidro-1H-indol-1-il)-3-(metilamino)propan-2-ol;

4-amino-1-(3-fluorofenil)-1-(1H-indol-1-il)butan-2-ol;

1-(3,3-dimetil-2,3-dihidro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(3,5-difluorofenil)-1-(3,3-dimetil-2,3-dihidro-1H-indol-1-il)-3-(metilamino)propan-2-ol;

1-(3,3-dimetil-2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-(3-metil-2,3-dihidro-1H-indol-1-il)propan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-espiro[ciclopentano-1,3'-indol]-1'(2'H)-ilpropan-2-ol;

1-(3-fluorofenil)-1-[3-(4-metoxifenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-[3-(4-metilfenil)-1H-indol-1-il]propan-2-ol;

1-[3-(4-terc-butilfenil)-1H-indol-1-il]-1-(3-fluorofenil)-3-(metilamino)propan-2-o!;

1-(3-fluorofenil)-1-[3-(3-metoxifenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-{3-[4-(trifluorometil)fenil]-1H-indol-1-il}propan-2-ol;

1-(3,5-difluorofenil)-1-(6-fluoro-2,3-dihidro-1H-indol-1-il)-3-(metilamino)propan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-{3-[2-(trifluorometil)fenil]-1H-indol-1-il}propan-2-ol;

1-(3-fluorofenil)-1-[3-(2-metoxifenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-{3-[3-(trifluorometil)fenil]-1H-indol-1-il}propan-2-ol;

3-amino-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

1-(7-fluoro-3-metil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

3-amino-1-(7-fluoro-3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

1-(7-fluoro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(4-fluoro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(7-fluoro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(4-fluoro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-[5-(trifluorometil)-1H-indol-1-il]propan-2-ol;

1-(6-fluoro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

3-(metilamino)-1-fenil-1-[6-(trifluorometil)-1H-indol-1-il]propan-2-ol;

3-(metilamino)-1-fenil-1-[5-(trifluorometil)-1H-indol-1-il]propan-2-ol;

1-(3-terc-butil-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(1H-indol-1-il)-2-metil-3-(metilamino)-1-fenilpropan-2-ol;

3-(1H-indol-1-il)-1-(metilamino)-3-fenilbutan-2-ol;

1-terc-butil-3-[2hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona;

1-[2-hidroxi-3-(metilamino)-1-fenilpropil]-3-propil-1,3-dihidro-2H-benzimidazol-2-ona;

5-bromo-1-[2hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

6-fluoro-1-[2hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

4-fluoro-1-[2hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

1-ciclobutil-3-[2hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona;

5-fluoro-3-[2hidroxi-3-(metilamino)-1-fenilpropil]-1-propil-1,3-dihidro-2H-benzimidazol-2-ona;

1-etil-3-[1-(3-fluorofenil)-2-hidroxi-3-(metilamino)propil]-1,3-dihidro-2H-benzimidazol-2-ona;

1-etil-3-[2hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona;

4-fluoro-3-[2hidroxi-3-(metilamino)-1-fenilpropil]-1-isopropil-1,3-dihidro-2H-benzimidazol-2-ona;

1-ciclopentil-3-[2hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona;

1-[2hidroxi-3-(metilamino)-1-fenilpropil]-3-isopropil-1,3-dihidro-2H-benzimidazol-2-ona;

3-[3(etilamino)-2-hidroxi-1-fenilpropil]-5-fluoro-1-isopropil-1,3-dihidro-2H-benzimidazol-2-ona;

1-[2hidroxi-3-(metilamino)-1-fenilpropil]-3-metil-1,3-dihidro-2H-benzimidazol-2-ona;

1-etil-5-fluoro-3-[2-hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona;

1-etil-4-fluoro-3-[2-hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona;

4-fluoro-3-[1-(3-fluorofenil)-2-hidroxi-3-(metilamino)propil]-1-isopropil-1,3-dihidro-2H-benzimidazol-2-ona;

1-etil-4-fluoro-3-[2hidroxi-3-(metilamino)-1-(3-fluorofenil)-propil]-1,3-dihidro-2H-benzimidazol-2-ona;

1-[1-(3-fluorofenil)-2-hidroxi-3-(metilamino)propil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

1-[3-(2,3-difluorofenil)-1H-indol-1-il]-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-[3-(2-clorofenil)-1H-indol-1-il]-1-(3-fluorofenil)-3-(metilamino)propan-2-ol; y

sales farmacéuticamente aceptable de estos, particularmente clorhidratos y sales de clorhidratos de estos.

[0090] Particularmente los compuestos preferidos de fórmula I incluyen:

(1RS,2SR)-1-(1H-indol-1-il)-3-(4-metilpiperazin-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-1-(5-fluoro-1H-indol-1-il)-3-(4-metilpiperazin-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-1-(1H-indol-1-il)-3-morfolin-4-il-1-fenilpropan-2-ol;

(1RS,2SR)-3-(dimetilamino)-1-(1H-indol-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-3-(etilamino)-1-(1H-indol-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-1-(1H-indol-1-il)-3-(isopropilamino)-1-fenilpropan-2-ol;

(1RS,2SR)-3-(bencilamino)-1-(1H-indol-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-3-[(ciclohexilmetil)amino]-1-(1H-indol-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-3-[(ciclohexilmetil)amino]-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-3-(isopropilamino)-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-1-(1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1RS,2SR)-3-(etilamino)-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-1-(1H-indol-1-il)-1-fenil-3-piperazin-1-ilpropan-2-ol;

(1RS,2SR)-1-(1H-indol-1-il)-1-fenil-3-[(piridin-4-ilmetil) amino]propan-2-ol;

(1RS,2SR)-1-(5-cloro-1H-indol-1-il)-1-fenil-3-piperidin-1-ilpropan-2-ol;

(1RS,2RS)-1-(1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1RS,2SR)-3-amino-1-(1H-indol-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-3-(etilamino)-1-(5-fluoro-1H-indol-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-3-amino-1-(5-fluoro-1H-indol-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-1-(5-fluoro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1RS,2SR)-3-(metilamino)-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

(1R,2S)-1-(1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1RS,2SR)-3-amino-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-3-[etil(metil)amino]-1-(1H-indol-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-1-(5-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1RS,2RS)-1-(5-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-1-ol;

1-[(1RS,2SR)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1H-indol-3-carbonitrilo;

(1R,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2S)-1-(1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-3-(metilamino)-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

(1S,2R)-1-(3-clorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(4-clorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-[3-(trifluorometoxi)fenil]propan-2-ol;

(1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-[2-(trifluorometoxi)fenil]propan-2-ol;

(1R,2S)-1-(1H-indol-1-il)-3-(metilamino)-1-[2-(trifluorometoxi)fenil]propan-2-ol;

(1S,2R)-1-(2-clorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

(1SR,2RS)-1-(1H-indol-1-il)-3-(metilamino)-1-[4-(trifluorometoxi)fenil]propan-2-ol;

(1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-[4-(trifluorometoxi)fenil]propan-2-ol;

(1R,2S)-1-(1H-indol-1-il)-3-(metilamino)-1-[4-(trifluorometoxi)fenil]propan-2-ol;

(1S,2R)-4-amino-1-(3-clorofenil)-1-(1H-indol-1-il)butan-2-ol

(1S,2R)-1-(3-bromofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

3-[(1S,2R)-2-hidroxi-1-(1H-indol-1-il)-3-(metilamino)propil]benzonitrilo

(1S,2R)-1-(3-fluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-[3-(3-metilfenil)-1H-indol-1-il]propan-2-ol;

(1S,2R)-1-(4-fluorofenil)-3-(metilamino)-1-(3-metil-1H-indol-1-il)propan-2-ol;

(1S,2R)-1-(2-fluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(4-fluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-(3-metilfenil)propan-2-ol;

(1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-(2-metilfenil)propan-2-ol;

(1R,2S)-1-(1H-indol-1-il)-3-(metilamino)-1-(2-metilfenil)propan-2-ol;

(1S,2R)-3-(etilamino)-1-(3-fluorofenil)-1-(1H-indol-1-il)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-1-(1H-indol-1-il)-3-morfolin-4-ilpropan-2-ol;

(1S,2R)-1-(3-fluorofenil)-1-(1H-indol-1-il)-3-(propilamino)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-1-(1H-indol-1-il)-3-(4-metilpiperazin-1-il)propan-2-ol;

(1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-(4-metilfenil)propan-2-ol;

(1S,2R)-1-(2,3-dihidro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-[3-(2-metilfenil)-1H-indol-1-il]propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(2-metil-2,3-dihidro-1H-indol-1-il)propan-2-ol;

(1S,2R)-1-(7-fluoro-3,3-dimetil-2,3-dihidro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(7-fluoro-3,3-dimetil-2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-3-(metilamino)-1-(7-metil-2,3-dihidro-1H-indol-1-il)-1-fenilpropan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(7-metil-2,3-dihidro-1H-indol-1-il)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(5-metil-2,3-dihidro-1H-indol-1-il)propan-2-ol;

(1S,2R)-1-(1H-indol-1-il)-1-(3-metoxifenil)-3-(metilamino)propan-2-ol;

(1SR,2RS)-1-(1H-indol-1-il)-1-(4-metoxifenil)-3-(metilamino)propan-2-ol;

(1RS,2SR)-3-(metilamino)-1-(2-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-1-(1H-benzimidazol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1RS,2SR)-3-(metilamino)-1-(2-metil-1H-benzimidazol-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-1-(4-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(5-fluoro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(5-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(7-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(4-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(6-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1RS,2SR)-1-(5-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(3-fluorofenil)-1-(6-metoxi-1H-indol-1-il)-3-(metilamino)propan-2-ol;

(1S,2R)-3-(metilamino)-1-fenil-1-(1H-pirrolo[2,3-b]piridin-1-il)propan-2-ol;

(1S,2R)-1-(5-cloro-2,3-dihidro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-3-(metilamino)-1-fenil-1-(1H-pirrolo[2,3-c]piridin-1-il)propan-2-ol;

(1S,2R)-1-(5-fluoro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-3-(metilamino)-1-(3-fluorofenil)-1-(1H-pirrolo[2,3-c]piridin-1-il)propan-2-ol;

(1S,2R)-1-(5-cloro-2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-3-(metilamino)-1-(6-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

(1S,2R)-3-(metilamino)-1-(7-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(5-metil-1H-indol-1-il)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(7-metil-1H-indol-1-il)propan-2-ol;

(1S,2R)-3-(metilamino)-1-(4-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

(1S,2R)-3-(metilamino)-1-(5-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(4-metil-1H-indol-1-il)propan-2-ol;

(1S,2R)-1-(3-etil-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(3-fenil-1H-indol-1-il)propan-2-ol;

7-fluoro-1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

7-fluoro-1-[(1S,2R)-1-(3-fluorofenil)-2-hidroxi-3-(metilamino)propil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

(1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-(2-tienil)propan-2-ol;

(1R,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-(2-tienil)propan-2-ol;

1'-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]espiro[ciclohexano-1,3'-indol]-2'(1H)-ona;

(1S,2R)-2-(3-fluorofenil)-2-(1H-indol-1-il)-1-[(2S)-pirrolidin-2-il]etanol;

(1R,2S)-2-(3-fluorofenil)-2-(1H-indol-1-il)-1-[(2S)-pirrolidin-2-il]etanol;

1'-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]espiro[ciclobutano-1,3'-indol]-2'(1'H)-ona;

1'-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]espiro[ciclopentano-1,3'-indol]-2'(1H)-ona;

1'-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]espiro[ciclopropano-1,3'-indol]-2'(1H)-ona;

5-fluoro-1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

(1S,2R)-3-(ciclopropilamino)-1-(3-fluorofenil)-1-(1H-indol-1-il)propan-2-ol;

7'-fluoro-1'-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]espiro[ciclohexano-1,3'-indol]-2'(1H)-ona;

5'-bromo-1'-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]espiro[ciclohexano-1,3'-indol]-2'(1H)-ona;

(1S,2R)-1-(3-fluorofenil)-1-[3-(2-fluorofenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol;

(1S,2R)-1-[3-(3,4-diclorofenil)-1H-indol-1-il]-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-1-[3-(3-fluorofenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol;

(1S,2R)-1-(5-fluoro-3-metil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol ;

(1S*,2R*)-3-amino-1-(5-fluoro-3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

(1S,2R)-1-(5-cloro-3-metil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-3-amino-1-(5-cloro-3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

[(2R,3S)-3-(5-cloro-3-metil-1H-indol-1-il)-2-metoxi-3-fenilpropil]metilamina;

(1S,2R)-1-(7-cloro-3-metil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

[(2R,3S)-3-(5-fluoro-3-metil-1H-indol-1-il)-2-metoxi-3-fenilpropil]metilamina;

(1S,2R)-1-(4-bromo-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(4-bromo-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(5-bromo-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(5-bromo-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1H-indol-4-carbonitrilo;

(1S,2R)-1-(6-bromo-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1H-indol-5-carbonitrilo;

1-[(1S,2R)-1-(3-fluorofenil)-2-hidroxi-3-(metilamino)propil]-1H-indol-4-carbonitrilo;

(1S,2R)-1-(6-bromo-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(6-fluoro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-3-amino-1-(3-fluorofenil)-1-(1H-indol-1-il)propan-2-ol;

(1S,2R)-1-(7-bromo-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-[3-(trifluorometil)fenil]propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-espiro[ciclohexano-1,3'-indol]-1'(2H)-ilpropan-2-ol;

(1S,2R)-1-(2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-[3-(trifluorometil)fenil]propan-2-ol;

(1S,2S)-1-(3-fluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3,4-difluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(3-metil-1H-indol-1-il)propan-2-ol;

(1S,2R)-1-(4-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(6-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(7-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(7-cloro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(4-cloro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(6-cloro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(5-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(5-cloro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3-isopropil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(3-fluorofenil)-1-(3-isopropil-1H-indol-1-il)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3,5-difluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3,5-difluorofenil)-1-(2,3-dihidro-1H-indol-1-il)-3-(metilamino)propan-2-ol;

(1S,2R)-4-amino-1-(3-fluorofenil)-1-(1H-indol-1-il)butan-2-ol;

(1S,2R)-1-(3,3-dimetil-2,3-dihidro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3,5-difluorofenil)-1-(3,3-dimetil-2,3-dihidro-1H-indol-1-il)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3,3-dimetil-2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(3-metil-2,3-dihidro-1H-indol-1-il)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-espiro[ciclopentano-1,3'-indol]-1'(2H)-ilpropan-2-ol;

(1S,2R)-1-(3-fluorofenil)-1-[3-(4-metoxifenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-[3-(4-metilfenil)-1H-indol-1-il]propan-2-ol;

(1S,2R)-1-[3-(4-terc-butilfenil)-1H-indol-1-il]-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-1-[3-(3-metoxifenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-{3-[4-(trifluorometil)fenil]-1H-indol-1-il}propan-2-ol;

(1S,2R)-1-(3,5-difluorofenil)-1-(6-fluoro-2,3-dihidro-1H-indol-1-il)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-{3-[2-(trifluorometil)fenil]-1H-indol-1-il}propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-1-[3-(2-metoxifenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-{3-[3-(trifluorometil)fenil]-1H-indol-1-il}propan-2-ol;

(1S,2R)-3-amino-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

(1S,2R)-1-(7-fluoro-3-metil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-3-amino-1-(7-fluoro-3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

(1S,2R)-1-(7-fluoro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(4-fluoro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(7-fluoro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(4-fluoro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-[5-(trifluorometil)-1H-indol-1-il]propan-2-ol;

(1S,2R)-1-(6-fluoro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-3-(metilamino)-1-fenil-1-[6-(trifluorometil)-1H-indol-1-il]propan-2-ol;

(1S,2R)-3-(metilamino)-1-fenil-1-[5-(trifluorometil)-1H-indol-1-il]propan-2-ol;

(1S,2R)-1-(3-terc-butil-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(1H-indol-1-il)-2-metil-3-(metilamino)-1-fenilpropan-2-ol;

(2R,3S)-3-(1H-indol-1-il)-1-(metilamino)-3-fenilbutan-2-ol;

1-terc-butil-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona;

1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3-propil-1,3-dihidro-2H-benzimidazol-2-ona;

5-bromo-1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

6-fluoro-1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

4-fluoro-1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

1-ciclobutil-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona;

5-fluoro-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1-propil-1,3-dihidro-2H-benzimidazol-2-ona;

1-etil-3-[(1S,2R)-1-(3-fluorofenil)-2-hidroxi-3-(metilamino)propil]-1,3-dihidro-2H-benzimidazol-2-ona;

1-etil-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona;

4-fluoro-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1-isopropil-1,3-dihidro-2H-benzimidazol-2-ona;

1-ciclopentil-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona;

1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3-isopropil-1,3-dihidro-2H-benzimidazol-2-ona;

3-[(1S,2R)-3-(etilamino)-2-hidroxi-1-fenilpropil]-5-fluoro-1-isopropil-1,3-dihidro-2H-benzimidazol-2-ona;

1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3-metil-1,3-dihidro-2H-benzimidazol-2-ona;

1-etil-5-fluoro-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona;

1-etil-4-fluoro-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona;

4-fluoro-3-[(1S,2R)-1-(3-fluorofenil)-2-hidroxi-3-(metilamino)propil]-1-isopropil-1,3-dihidro-2H-benzimidazol-2-ona;

1-etil-4-fluoro-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-(3-fluorofenil)-propil]-1,3-dihidro-2H-benzimidazol-2-ona;

1-[(1S,2R)-1-(3-fluorofenil)-2-hidroxi-3-(metilamino)propil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

(1S,2R)-1-[3-(2,3-difluorofenil)-1H-indol-1-il]-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-[3-(2-clorofenil)-1H-indol-1-il]-1-(3-fluorofenil)-3-(metilamino)propan-2-ol; y

sales farmacéuticamente aceptable de estos, particularmente clorhidratos y sales de clorhidratos de estos.

[0091] Algunos de los compuestos de la presente invención pueden contener centros quirales y tales compuestos pueden existir en la forma de estereoisómeros (es decir enantiómeros). La presente invención incluye todos los estereoisómeros y cualquiera mezclas de estos que incluyen mezclas racémicas. Las mezclas racémicas de los estereoisómeros así como también los estereoisómeros sustancialmente puros están dentro del alcance de la invención. El término "sustancialmente puro", como se utiliza aquí, se refiere al menos aproximadamente 90% moles, y más

preferiblemente al menos aproximadamente 95 moles %, y más preferiblemente al menos aproximadamente 98 moles % del estereoisómero deseado está presente en relación a otros posibles estereoisómeros. Los enantiómeros preferidos se pueden aislar de mezclas racémicas mediante cualquier método conocido por aquellos expertos en la técnica, que incluyen cromatografía líquida de alto desempeño (HPLC) y la formación y cristalización de sales quirales o preparados mediante los métodos descritos aquí. Ver, por ejemplo, (Wiley Interscience, New York, 1981); Wilen, S. H., et al., Tetrahedron, 33:2725 (1977); Eliel, E.L Stereochemistry of Carbon Compounds, (McGraw-Hill, NY, 1962); Wilen, S.H. Tables of Resolving Agents and Optical Resolutions, p. 268 (E.L. Eliel, Ed., University of Notre Dame Press, Notre Dame, IN 1972).

[0092] La presente invención incluye prodrogas de los compuestos de fórmula 1. "Prodrogas", como se utiliza aquí, significa un compuesto que es convertible in vivo mediante medios metabólicos (por ejemplo, mediante hidrólisis) a un compuesto de fórmula I. Varias formas de prodrogas son conocidas en la técnica, por ejemplo, como se discutió en Bundgaard, (ed.), Design of Prodrugs, Elsevier (1985); Widder, et al. (ed.), Methods in Enzymology, vol. 4, Academic Press (1985); Krogsgaard-Larsen, et al., (ed). "Design and Application of Prodrugs," Textbook of Drug Design and Development, Chapter 5, 113-191 (1991), Bundgaard, et al., Journal of Drug Deliver Reviews, 1992, 8:1-38, Bundgaard, J. of Pharmaceutical Sciences, 1988, 77:285 et seq/, and Higuchi and Stella (eds.) Prodrugs as Novel Drug Delivery Systems, American Chemical Society (1975).

[0093] Además, los compuestos de fórmula I pueden existir en formas no solvatadas así como también solvatadas con solventes farmacéuticamente aceptables tales como agua, etanol, y similares. En general, las formas solvatadas son consideradas equivalentes para las formas no solvatadas para el propósito de la presente invención.

[0094] Los compuestos de la presente invención se pueden preparar en un número de formas bien conocidas por aquellos expertos en la técnica. Los compuestos se pueden sintetizar, por ejemplo, mediante los métodos descritos adelante, o las variaciones de estos como se aprecia por la persona experta. Todos los procesos descritos en asocio con la presente invención se contemplan para ser practicados para cualquier escala, incluyendo miligramo, multigramo, gramo, kilogramo, multikilogramo o a escala comercial industrial.

[0095] Como se entenderá fácilmente, los grupos funcionales presentes pueden contener grupos protectores durante el curso de la síntesis. Los grupos protectores pueden ser conocidos per se como grupos funcionales químicos que pueden ser selectivamente anexados y removidos de las funcionalidades, tales como los grupos hidroxilo y grupos carboxilo. Estos grupos están presentes en un compuesto químico para ser tal funcionalidad inerte a las condiciones de reacción química a los cuales los compuestos están expuestos. Cualquier variedad de grupos protectores se puede emplear con la presente invención. Los grupos protectores que se pueden emplear con la presente invención se pueden describir en

Greene, T.W. and Wuts, P.G.M., Protective Groups in Organic Synthesis 2d. Ed., Wiley & Sons, 1991.

[0096] Los compuestos de la presente invención están adecuadamente preparados de acuerdo con la siguiente descripción general y los ejemplos específicos. Las variables utilizadas son como se definió para la fórmula I, al menos que se anote otra cosa. Los reactivos utilizados en la preparación de los compuestos de esta invención pueden ser comercialmente obtenidos o se pueden preparar mediante procedimientos estándar descritos en la literatura. De acuerdo con esta invención, los compuestos de fórmula I son producidos de acuerdo a los siguientes esquemas de invención **(esquema I-IV)**.

[0097] Los compuestos de esta invención contienen centros quirales, que suministran varias formas estereoisoméricas tales como mezclas enantioméricas así como también isómeros ópticos. Los isómeros ópticos individuales se pueden preparar directamente a través de síntesis asimétrica y/o esteroespecífica o mediante separación quiral convencional de los isómeros ópticos de la mezcla enantiomérica.

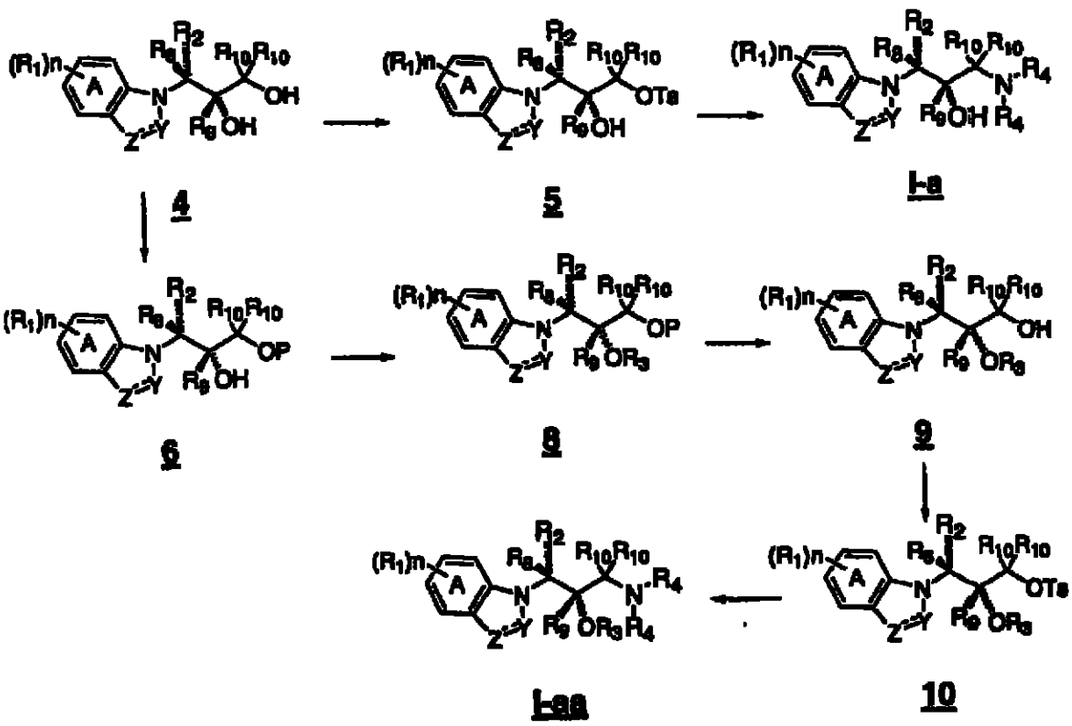
[0098] Los compuestos de la presente invención son adecuadamente preparados de acuerdo con la siguiente descripción general y ejemplos específicos. Las variables utilizadas son como se definió para la formula I, a menos que se anote otra cosa. Los reactivos utilizados en la preparación de los compuestos de esta invención pueden ser comercialmente obtenidos o se pueden preparar mediante procedimientos estándar descritos en la

literatura. De acuerdo con esta invención, los compuestos de fórmula I se producen por medio de los siguientes esquemas de reacción **(esquema I-IV)**.

[0099] Los compuestos de esta invención contienen centros quirales que suministran varias formas estereoisoméricas tales como mezclas enantioméricas así como también isómeros ópticos. Los isómeros ópticos individuales se pueden preparar directamente a través de síntesis asimétrica y/o estereoscópica o mediante separación quiral convencional de los isómeros ópticos proveniente de la mezcla enantiomérica.

[0100] De acuerdo con esta invención, los compuestos de la fórmula I se producen mediante los siguientes esquemas de reacción (esquemas I a IV). Dependiendo del diastereómero deseado, los compuestos se pueden preparar por vía de dos diferentes rutas sintéticas (A y B) esquemas (I y II). Si se desea sintetizar los compuestos de fórmula I- A a ellos se pueden preparar de los compuestos de fórmula 4 al convertir selectivamente el alcohol primario en un grupo saliente y desplazarlo con una amina deseada. (Ruta A, esquema I) cualquier método convencional para la conversión selectiva de un alcohol primario en un grupo saliente, y cualquier método convencional para desplazar un grupo saliente primario con una amina se puede utilizar para esta conversión. De acuerdo con la modalidad preferida de esta invención el diol de la fórmula 4 se trata con cloruro de paratoluenosulfonilo en piridina para formar el tosilato de fórmula 5, que es convertido al compuesto de fórmula I-a a través de tratamiento por un exceso de una solución de

amina alcohólica, o a temperatura ambiente o calentado a aproximadamente 40 grados a aproximadamente 80 grados en un tubo sellado. Los compuestos de fórmula I-a se pueden convertir a una sal farmacéuticamente aceptable utilizando cualquier método convencional.



en donde: A, Y, Z, R_1, n, R_2, R_4, R_8, R_9, R_{10} son como se describió anteriormente. R = C1-C4 P= grupo protector preferiblemente trimetisililo, terc- butildimetisililo, para- nitrobenzoilo; y Ots =grupo saliente paratoluenosulfonilato o cualquier grupo saliente convencional.

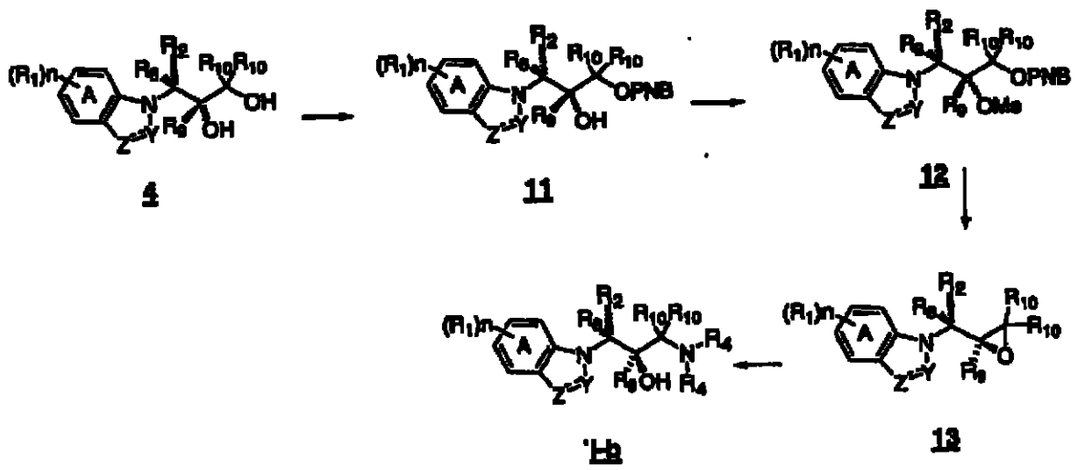
[0101] Si se desea formar compuestos de fórmula I-aa ellos se pueden preparar de los compuestos de fórmula 4 por via de protección selectiva del alcohol primario, seguido por

alquilación del alcohol secundario, y la desprotección del alcohol primario. Cualquier grupo protector de alcohol convencional se puede utilizar para esta conversión y cualquier método para la protección selectiva de un alcohol primario se puede emplear. De acuerdo con la modalidad preferida de esta invención, la reacción se lleva a cabo a temperatura baja en diclorometano con trimetilsilil cloruro y trietilamina como base para formar los compuestos de fórmula 6. La alquilación de un alcohol secundario se puede lograr por vía de cualquier método convencional de alquilatar un alcohol secundario encontrado en la literatura. De acuerdo con la modalidad preferida de esta invención, los compuestos de fórmula 6 reaccionan con el haluro de alquilo utilizando hidruro de sodio como base para formar los compuestos de fórmula 8, que se pueden desproteger para formar compuestos de fórmula 9 por vía de cualquier método convencional para la desprotección de un alcohol primario. De acuerdo con la modalidad preferida de esta invención, los compuestos de fórmula 8 son tratados con ácido clorhídrico acuoso diluido o ácido trifluoroacético en diclorometano para formar los compuestos de fórmula 9. La conversión del alcohol primario en los compuestos de fórmula 9 para contemplar la síntesis de los compuestos de fórmula I-aa se pueden desarrollar como se describió previamente para la síntesis de los compuestos de fórmula I-aa. Los compuestos de fórmula I-a Los compuestos de fórmula I-aa se pueden convertir a una sal farmacéuticamente aceptable utilizando cualquier método convencional.

[0102] Alternativamente, los compuestos de fórmula 10 se pueden preparar directamente de los compuestos de fórmula 5. Cualquier método de alquilatar de un grupo hidroxilo en la presencia de un grupo toxilo se puede emplear para esta conversión. De acuerdo con la modalidad preferida de esta invención, los compuestos de fórmula 5 son tratados con un alquil trifluorometalsulfonato, por ejemplo, metil metilfluorometanosulfonato, en la presencia de una base impedida, por ejemplo, 6-di-terc-butil-4-metilpiridina. La reacción se puede desarrollar a temperatura ambiente o calentada a aproximadamente 40°C a aproximadamente 80°C. Los compuestos de fórmula 10 se pueden convertir a compuestos de fórmula I-aa, como se describió previamente para las síntesis de los compuestos de fórmula I-a. Los compuestos de fórmula I-aa se pueden convertir a una sal farmacéuticamente aceptable utilizando cualquier método convencional.

[0103] Si se desea formar compuestos de 1-b, ellos también se pueden preparar de los compuestos de fórmula 4 por vía de la ruta b (esquema II). Esta ruta involucra la protección selectiva del alcohol primario seguida por la conversión del alcohol secundario a un grupo saliente. Cualquier método convencional para la protección selectiva de un alcohol primario, y cualquier método convencional para convertir de un alcohol secundario a un grupo saliente se puede utilizar para esta conversión. De acuerdo con la modalidad preferida de esta invención, los compuestos de fórmula 4 son tratados con cloruro de paranitrobenzoilo en piridina a baja temperatura (preferiblemente por debajo de

aproximadamente 0°C) Para formar compuestos de fórmula 11. Los compuestos de fórmula 11 se pueden convertir a un mesilato secundario de fórmula 12 por vía de la reacción concluida de la metanosulfonilo en diclorometano utilizando trietilamina como base. La reacción se lleva preferiblemente a cabo a temperaturas entre aproximadamente -15°C y aproximadamente 10°C. La desprotección del alcohol primario en los compuestos de fórmula 12 permite una formación de un epóxido primario a través de una reacción S_N2 que resulta en una inversión del estereocentro. Cualquier método convencional para la desprotección de un alcohol primario, y cualquier método convencional para la formación de óxido sobre un grupo saliente alfa se puede emplear para esta conversión. De acuerdo con la modalidad preferida de esta invención, los compuestos de fórmula, son tratados con una solución acuosa de una base adecuada en solvente orgánico, preferiblemente, hidróxido de sodio acuoso en dioxano. El epóxido resultante de fórmula 13 puede ser de anillo abierto selectivamente con una amina para producir el amino alcohol deseado de fórmula I-b. Cualquier método convencional para la apertura del anillo regio selectivo del epóxido primario se puede emplear para esta conversión. De acuerdo con la modalidad preferida de esta invención, los compuestos de fórmula 13 son tratados con un exceso de una solución de amina alcohólica en recipiente sellado, o a temperatura ambiente o calentado a aproximadamente 40°C a aproximadamente 90°. Los compuestos de fórmula I-b se pueden convertir en una sal farmacéuticamente aceptable utilizando los métodos convencionales.



Donde: A, Y, Z, R_1, n, R_2, y R_4, R_8, R_{10} son como se describió previamente R_9 es H.

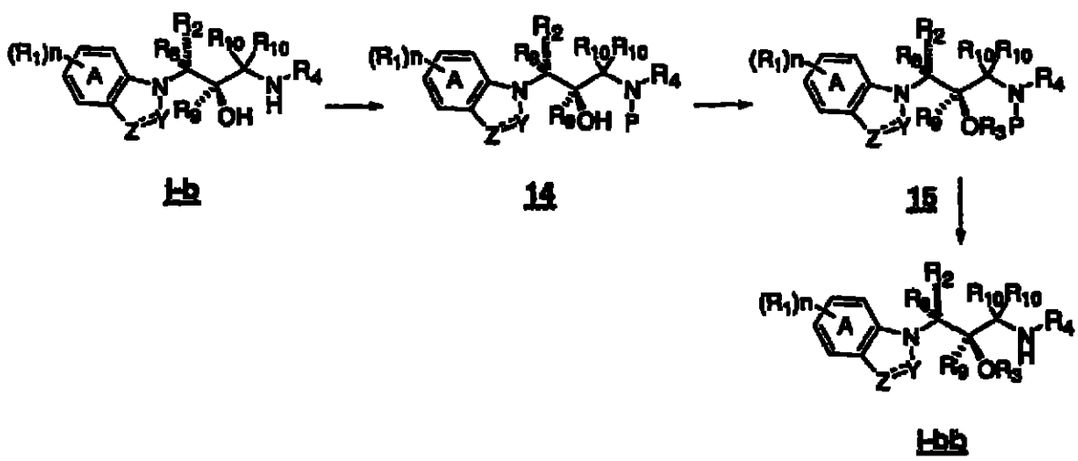
PNB= para nitrobenzoilo y cualquier grupo protector convencional; y

Oms = grupo metanosulfonato o cualquier grupo saliente convencional.

[00104] Si se desea formar compuestos de fórmula 1-b ellos se pueden hacer de compuestos de fórmula I-b por vía de protección de la amina, alquilación del alcohol secundario y desprotección de la amina (esquema III). Cualquier método convencional para la protección de una amina, alquilación de un alcohol secundario, y desprotección de una amina se puede utilizar para esta conversión. De acuerdo con la modalidad preferida de esta invención, los compuestos de fórmula I-b se tratan con anhídrido boc donde boc= terc-butoxicarbnilo, para formar los compuestos de fórmula 14 que se pueden alquilatar con un hidruro de sodio como base para formar los compuestos de fórmula 15. La desprotección se logra utilizando un ácido, preferiblemente ácido trifluoroacético en diclorometano para formar los compuestos de

fórmula 1-bb que se pueden convertir en una sal farmacéuticamente aceptable utilizando los métodos convencionales.

Esquema III



Donde: A, Y, Z, R_1, n, R_2 y R_4, R_8, R_{10} son como se describió previamente R_9 es H

R_3= alquilo inferior C_1-C_3, P= grupo protector, preferiblemente terc- butoxicarbonilo.

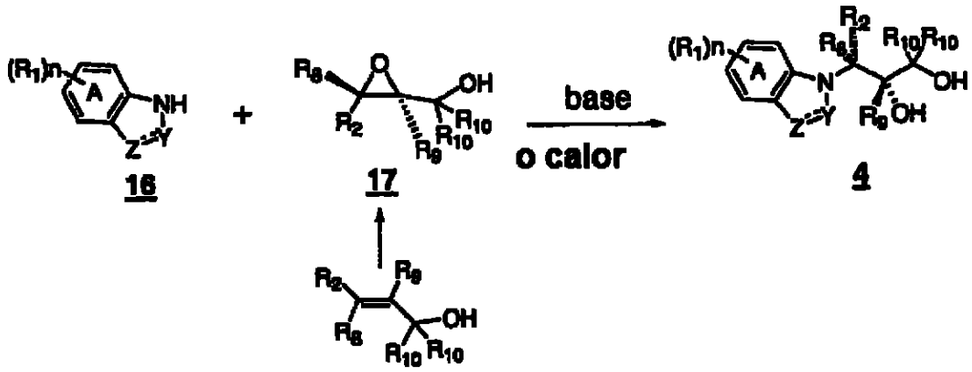
[0105] Los compuestos de fórmula 4 se forman por vía de la abertura del anillo regio y estereoselectivo de un epóxido apropiadamente sustituido de fórmula 17 (formado por vía de una epoxidación de un alcohol alhílico apropiadamente sustituido) con un compuesto apropiadamente sustituido de fórmula 16 (esquema IV). Cualquier método convencional para la abertura del anillo regio y estereoselectivo de un epóxido se puede emplear para esta conversión. De acuerdo con la modalidad preferida de esta invención, los compuestos de fórmula 16 se tratan como una base,

por ejemplo, hidróxido de sodio, terc-butóxido de sodio, hidróxido de potasio, terc-butóxido de potasio o hidróxido de potasio, luego se tratan con el epóxido de la fórmula 17. El epóxido de la fórmula 17 se puede pretatar con un ácido Lewis, por ejemplo, iso-propóxido de titanio, trifloruro de boro, etc. para asegurar la abertura regio selectiva del anillo. La reacción ocurre a temperatura ambiente con una duración de aproximadamente 2 horas a aproximadamente 72. Alternativamente, los compuestos de fórmula 16 que son adecuadamente nucleofílicos, por ejemplo, indolino, se puede calentar con el epóxido de la fórmula 17 a temperaturas desde aproximadamente 50°C a aproximadamente 170°C para formar los compuestos de fórmula 4.

[0106] La epoxidación de los alcoholes trans-alilico se pude desarrollar racémicamente o asimétricamente utilizando los métodos descritos en la literatura. De acuerdo con la modalidad preferida de esta invención, la epoxidación racémica se conduce con ácido paracético o ácido meta- cloroperbenzoico. Si se desea producir un enantiómero simple de los compuestos de fórmula I subrayado, la epoxidación asimétrica de un alcohol alílico se puede desarrollar con terc- butilhidroperóxido o hidroperóxido de cumeno en la presencia de éster de tartrato apropiado, isoproóxido de titaneo (IV), y tamices moleculares. Este método está bien establecido en la literatura (por ejemplo, K.B. Sharpless, et. al., J. Organismo. Chem. 1986, 51, 3710). Los compuestos de fórmula 16 y los alcoholes alílicos de partida están disponibles de fuentes comerciales o son accesibles a través de métodos bien establecidos en la literatura.

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Esquema IV



Donde: A, Y, Z, R_1, n, R_8, R_9, R_{10} y R_2, son como se describió previamente.

[0107] En otras modalidades, la invención está dirigida a las composiciones farmacéuticas que comprenden:

a. Al menos un compuesto de fórmula I, o una sal farmacéuticamente aceptable de este; y

b. Al menos un vehículo farmacéuticamente aceptable.

Generalmente, el compuesto de fórmula I, o la sal farmacéuticamente aceptable de este, estará presente a un nivel aproximadamente 0.1% en peso, a aproximadamente 90% en peso, con base en el peso total de la composición farmacéutica, basado en el peso total de la composición farmacéutica. Preferiblemente, el

compuesto de fórmula I, o una sal farmacéuticamente aceptable de este, estará presente a un nivel de al menos aproximadamente 1% en peso, con base en el peso total de la composición farmacéutica. Más preferiblemente, el compuesto de fórmula I, a una sal farmacéuticamente aceptable de este, estará presente de un nivel de al menos aproximadamente del 5%, en peso, con base en el peso total de la composición farmacéutica. Aún más preferiblemente, el inhibidor de norepinefrina o una sal farmacéuticamente aceptable de este estará presente a un nivel de al menos aproximadamente 10%, en peso, con base en el peso total de la composición farmacéutica. Aún más preferiblemente, el compuesto de fórmula I a una sal farmacéuticamente aceptable de este, estará presente a un nivel de al menos aproximadamente 25% en peso, con base en el peso total de la composición farmacéutica.

[0108] Tales composiciones están preparadas de acuerdo con procedimientos farmacéuticos aceptables, tales como se describió en Remignton's Farmaceuticals Sciences, 17h edition, ed. Alfonoso R. Gennaro, Mack Publishing Company, Easton, PA (1985). Los vehículos farmacéuticamente aceptables son aquellos que son compatibles con los otros ingredientes en la formulación y biológicamente aceptables.

[0109] Los compuestos de esta invención se pueden administrar oralmente o parenteralmente, puro o en recombinación con vehículos farmacéuticos convencionales. Los vehículos sólidos aplicables se pueden incluir una o más sustancias que también

pueden actuar como agentes saborizantes, lubricantes, solubrizadores, agentes de suspensión. Glidantes, deslizantes, ayudas de compresión, ligadores o agentes desintegrantes de tableta o un material encapsulante. Los polvos, el vehículo, es un sólido finamente dividido que es una mezcla con el ingrediente activo finamente dividido. En las tabletas, el ingrediente activo se mezcla con un vehículo que tiene las propiedades de compresión necesarias en la proporción adecuada y compactado en la forma y tamaño deseados. Los polvos y las tabletas preferiblemente contienen hasta el 99% del ingrediente activo. Los vehículos sólidos adecuados incluyen, por ejemplo, fosfato de calcio, estearato de magnesio, talco, azucares, lactosa, dextrina, almidón, gelatina, celulosa, metilcelulosa, carboxímetilcelulosa de sodio, polivinilpirrolidina, ceras de baja fusión y resinas de intercambiadores de ión.

[0110] Los vehículos líquidos se pueden utilizar para preparar soluciones, suspensiones, emulsiones, melazas, y elíxires. El ingrediente activo de esta invención se puede disolver suspender en un vehículo líquido farmacéuticamente aceptable tal como agua, un solvente orgánico, una mezcla de ambos o aceites farmacéuticamente aceptables o grasas. El vehículo líquido puede contener otros aditivos farmacéuticos adecuados tales como solubilizadores, emulsificadores, amortiguadores, preservativos, endulzantes, agentes saborizantes, agentes de suspensión, agentes espesantes, colores, reguladores de la viscosidad, estabilizadores, u osmoreguladores. Los ejemplos adecuados de los vehículos líquidos para la administración oral y parenteral

incluyen agua (contiene particularmente aditivos como los anteriores, por ejemplo, derivados de celulosa preferiblemente solución de carboximetil celulosa de sodio), alcoholes (que incluyen alcoholes monohídricos y alcoholes polihídricos (por ejemplo, glicoles) y sus derivados y aceites. Para la administración parenteral, el vehículo también pude ser un éster aceitoso. Los vehículos líquidos estériles son utilizados en forma líquida en composiciones con forma líquida estéril para la administración parenteral.

[0111] Las composiciones farmacéuticas líquidas, son soluciones estériles o suspensiones, se pueden administrar por, por ejemplo, inyección intramuscular, intraperitoneal o subcutánea. Las soluciones estériles también se pueden administrar intravenosamente. La administración oral puede ser una forma de composición líquida o sólida.

[0112] Preferiblemente la composición farmacéutica es una forma de dosis unitaria por ejemplo, como tabletas, cápsulas, polvos, soluciones, suspensiones, emulsiones, gránulos, o supositorios. En tal forma, la composición se subdivide en dosis unitaria que contiene cantidades apropiadas del ingrediente activo; las formas de dosis unitaria pueden ser en composiciones empacadas, por ejemplo polvos empacados, frascos, ollas, jeringas prellenadas o sacos que contienen líquidos. La forma de dosis unitaria puede ser, por ejemplo, una cápsula o tableta en si misma, o esta puede ser el número apropiado de cualquiera de tales composiciones en forma de paquete.

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[0113] En otra modalidad de la presente invención, los compuestos útiles en la presente invención se pueden administrar a un mamífero con uno o más de otros agentes farmacéuticos activos tales como aquellos agentes que son utilizados para tratar cualquier otra condición médica presente en el mamífero. Ejemplos de tales farmacéuticos activos incluyen agentes de alivio de dolor, agentes antiangiogénicos, agentes antineoclásicos, agentes antidiabéticos, agentes antidiabéticos, agentes anti infecciosos, agentes gastrointestinales, o combinaciones de esto.

[0114] El uno o más de los otros agentes farmacéuticos activos se puede administrar en una cantidad terapéuticamente efectiva simultáneamente (tal como individualmente al mismo tiempo, o junto en una composición farmacéutica), y/o sucesivamente con uno o más compuestos de la presente invención.

[0115] El término "terapia de combinación" se refiere a la administración de dos o más agentes terapéuticos o compuestos para tratar una condición terapéutica o desorden descrito en la presente descripción, por ejemplo, fluido caliente, sudoración, condición termoreguladora relacionada, o desorden, u otro. La administración incluye el uso de cada tipo de agente terapéutico de manera concurrente. En cualquier caso, el régimen de tratamiento suministrará efectos benéficos de la combinación de droga para tratar las condiciones o los desórdenes descritos aquí.

[0116] La ruta de administración puede ser cualquier ruta, que transporte efectivamente el compuesto activo de fórmula I, o una sal farmacéuticamente aceptable de este, al sitio de acción apropiado o deseado tal como suministro oral, nasal, pulmonar, transdérmico, tal como suministro pasivo y/o iotoforético, o parenteral, por ejemplo, rectal, depósito, subcutáneo, intravenoso, intrauretral, intramuscular, intranasal, solución oftálmica o en ungüento. Además, la administración del compuesto de fórmula 1 o la sal farmacéuticamente aceptable de este, con otros ingredientes activos puede ser concurrente o simultánea.

[0117] Se cree que la presente invención descrita presenta un hallazgo sustancial en el campo de tratamiento, alivio, inhibición y/o prevención de la condición mejorada por la retoma de monoamina que incluye, inter alia, los síntomas vasomotores (VMS), la disfunción sexual, los desórdenes gastrointestinales y genitourinarios, el síndrome de fatiga crónica, el síndrome de filoamialgia, desórdenes del sistema nervioso, y combinaciones de esto, particularmente aquellas condiciones seleccionadas del grupo que consiste de un desorden depresivo mayor, síntomas vasomotores, incontinencia urinaria apremiante, fibromialgia, dolor, neuropatía diabética, y combinaciones de estos.

[0118] De acuerdo a esto, en una modalidad de la presente invención está dirigida a los métodos para tratar o prevenir una condición mejorada por la retoma de monoamina en un sujeto necesitado de ella, que comprende las etapas de: administrar a dicho sujeto una cantidad efectiva de un compuesto de fórmula I o una sal farmacéuticamente aceptable de este.

Las condiciones mejoradas mediante la retoma de monoamina incluyen aquellas seleccionadas del grupo que consiste de síntomas vasomotores, disfunción sexual, los desórdenes gastrointestinales y genitourinarios, el síndrome de fatiga crónica, el síndrome de fibromialgia, desórdenes del sistema nervioso, y combinaciones de esto, particularmente aquellas condiciones seleccionadas del grupo que consiste de un desorden depresivo mayor, síntomas vasomotores, incontinencia urinaria apremiante, fibromialgia, dolor, neuropatía diabética, y combinaciones de estos.

[0119] "Síntomas vasomotores", "síntomas de inestabilidad vasomotora" y "disturbios vasomotores" incluye, pero no está limitado a, flujos de calor (destellos), insomnio, perturbación del sueño, desórdenes de modo, irritabilidad, transpiración excesiva, sudoración nocturna, fatiga, y similares originados, por inter alia, disfunción termoreguladora.

[0120] El término "flujo caliente" es un término reconocido en la técnica que se refiere a un disturbio episódico en la temperatura del cuerpo típicamente que consiste en un flujo repentino en la piel usualmente acompañado por transpiración en un sujeto.

[0121] El término "disfunción sexual" incluye, pero no está limitado a, condición que se relaciona con el deseo y/o excitación.

[0122] Como se utiliza aquí, "desórdenes gastrointestinales y genitourinarios" incluye síndrome de intestino irritable, GERD sintomático, esófago hipertensivo, dispepsia, dolor de pecho no cardíaco, disquinesia biliar, esfínter de disfunción oddi, incontinencia (es decir, incontinencia apremiante, incontinencia por tensión, incontinencia por tensión genuina, y incontinencia mezcla ácida (que incluye el vaciamiento involuntario de heces u orina, y regateo o chorreadura de heces u orina que se puede deber a una o más causas incluyendo pero no estando limitada a patología del control de esfínter alterante, pérdida de función cognitiva, sobre distensión de la vejiga, hiperreflexia y/o relajación uretral involuntaria, debilidad de los músculos asociada con la vejiga o anormalidades neurológica), cistitis intercistial (vejiga irritable), y dolor pélvico crónico (que incluye, pero no está limitado a vulvodinia, prostatodinia y proctalgia).

[0123] Como se utiliza aquí, "síndrome de fatiga crónica" (CFS) es una condición caracterizada por síntomas fisiológicos seleccionados de debilidad, dolores y neuralgias musculares, sueño excesivo, malaria, fiebre, dolor de garganta, nudos linfáticos, memoria afectada y/o concentración mental, insomnio, sueño desordenado, suavidad localizada, dolor y fatiga difusa, y combinaciones de estos.

[0124] Como se utiliza aquí "síndrome de fibromialgia" (FMS) incluye FMS y otros desórdenes de somatoforma, que incluyen FMS asociado con depresión, desorden de somatización, desorden de conversión, desorden de dolor, hipocondriasis, desorden

dismórfica de cuerpo, desorden de somatoforma no diferenciada, y NOS de somatoforma. El FMS y otros desórdenes de somatoforma están acompañados por síntomas fisiológicos seleccionados de una percepción elevada generalizada de estímulos sensoriales, anormalidades en percepción de dolor en la forma de alodinia (dolor con estimulación inocua), anormalidades en la percepción del dolor en la forma de hiperalgesia (sensibilidad creciente en los estímulos de dolor), y combinaciones de estos.

[0125] Como se utiliza aquí, "desórdenes del sistema de reunión social", incluye desórdenes adictivos (que incluyen aquellos debidos a alcohol, nicotina y otras sustancias sicoactivas) y retiro del síndrome, aprendizaje asociado con la edad y desórdenes mentales (que incluyen enfermedad de Alzheimer), anorexia nerviosa, bulimia nerviosa, desorden por déficit de atención con o sin, desorden de hiperactividad, desorden bipolar, dolor, desorden ciclotímico, desorden por depresión (que incluye desorden depresivo mayor, depresión refractaria, depresión de adolescente y depresión menor), desorden distímico, desorden por ansiedad generalizada (GAD), obesidad (es decir, reducir el peso de pacientes obesos a sobrepeso (desórdenes obsesivos compulsivos y desórdenes relacionados con el espectro, desorden desafiante o posicional, desorden por pánico, desorden por estrés post traumático, desorden disfórico premenstrual (es decir, síndrome premenstrual y desorden disfórico de fase luteal tardía), desórdenes sicóticos (que incluyen esquizofrenia, desórdenes psicoafectivos y esquizofreniformes), desorden afectivo estacional, desorden de sueño, tal como la narcolepsia y enuresis), fobia social (que

incluye desorden por ansiedad social), inhibición de la retoma de serotonina (SSRI) síndrome "poop out" (es decir, en donde un paciente falla en mantener una respuestas satisfactoria a una terapia SSRI después de un período de respuesta inicial satisfactorio).

[0126] Como se utiliza aquí, "dolor", incluye tanto dolor agudo como dolor crónico, que puede ser dolor centralizado, dolor periférico, o combinaciones de estos. El termino incluye muchos tipos diferentes de dolores que incluyen, pero no están limitados a, dolor neuropático, dolor visceral, dolor músculo esqueletal, dolor de huesos, dolor de cáncer, dolor inflamatorio, o combinaciones de estos tales como dolor de la espalda inferior, dolor atípico del pecho, dolor de cabeza tal como dolor de cabeza "cluster" migraña, neuralgia por herpes, dolor de limbo fantasma, dolor pélvico, dolor por fase facial, dolor abdominal, dolor del cuello, dolor central, dolor dental, dolor resistente a opioides, dolor visceral, dolor quirúrgico, dolor por daño de hueso, dolor durante trabajo y entrega, dolor que resulta de quemaduras, dolor post parto, dolor por angina, dolor neuropático tal como neuropatía periférica y neropatía diabética, dolor post operativo, y dolor que es como los desórdenes del sistema nervioso descritos.

[0127] Como se utiliza aquí, el término "dolor agudo" se refiere a un dolor centralizado o periférico que es intenso, localizado, agudo, punzonado y/o apagado, que se asoció difuso o de naturaleza quemante y que ocurre durante cortos períodos de tiempo.

[0128] Como se utiliza el término "dolor crónico" se refiere a dolor centralizado o periférico que es intenso, localizado, agudo, o punzante y/o sordo, desasosiego, difuso, o de naturaleza quemante y que ocurre durante períodos extendidos de tiempo (es decir, resisten y/o regularmente recurrentes) que incluye, para el propósito de la presente invención, dolor neuropático y dolor de cáncer. El dolor crónico incluye dolor neuropático, hiperalgesia, y/o alodinia.

[0129] Como se utiliza aquí, el término "dolor neuropático" se refiere al dolor crónico causado por el daño o los cambios patológicos en el sistema periférico o el sistema nervioso central. Ejemplos de cambios patológicos relacionados con el dolor neuropático incluyen sensación periférica prolongada o neuronal central, sensación central relacionada con daño a las funciones inhibitoria y/o exhibitoria del sistema nervioso o interacciones anormales entre el sistema nervioso parasimpático y simpático. Un rango rápido de condiciones quirales se pueden asociar como la base para el dolor neuropático que incluye, por ejemplo, diabetes, dolor post traumático de amputación, sensibilización periférica y/o central tal como dolor de limbo fantasma, dolor de espalda inferior, cáncer, daño químico, toxinas u otras cirugías mayores, daño nervioso periférico debido a compresión post daño traumático, neuralgia post herpética, neuralgia trigeminal, radiculopatias lumbares, fibromialgia, glosoafaringea, distrofia simpática de reflejo, causalgia, síndrome talámico, e ablución de raíz nerviosa, distrofia simpática refleja o dolor post toracotomía, deficiencias

nutricionales, o infecciones virales o bacteriales tales como herpes zoster o virus de la inmunodeficiencia humana (VIH), y combinaciones de estos. También incluidos en la definición del dolor neuropático está una condición secundaria de infiltración metastásica, adiposis dolorosa, quemaduras, condiciones de dolor central relacionadas con condiciones talámicas, y combinaciones de estos.

[0130] Como se utiliza aquí, el término "hiperalgesia" se refiere al dolor donde existe un incremento en la sensibilidad a un estímulo típicamente nocivo.

[0131] Como se utiliza aquí el término "alodinia" se refiere a un incremento en la sensibilidad hasta un estímulo típicamente no nocivo.

[0132] Como se utiliza aquí el término "dolor visceral" se refiere a un dolor asociado o resultante de enfermedades de los órganos internos, tales como, colitis ulcero activa, síndrome de intestino irritable, vejiga irritable, enfermad de Crohn, reumatológica, tumores, gastritis, pancreatitis, infecciones de los órganos, infecciones del tracto biliar, y combinaciones de estos.

[0133] Como se utiliza aquí el término "dolor específico de hembra" se refiere a un dolor que puede ser agudo y/o crónico asociados con condiciones femeninas. Tales grupos de dolor incluyen aquellas que se encuentran solamente o terminantemente en hembras, que incluyen dolor asociado con menstruación,

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ovulación, embarazo, nacimiento de niños, aborto espontáneo, embarazo ectópico, menstruación retrógrada, ruptura de un quiste folicular o un quiste del cortus luteum, irritación de la víscera pélvica, tiroides uterina, adenoamidosis, endometriosis, infección e inflamación e isquemia, isquemia de órgano pélvico, obstrucción, adhesiones intraabdominales, distorsión anatómica de la víscera pélvica, absceso de ovarios, pérdida del soporte pélvico, tumores, congestión pélvica o dolor referido de causas no ginecológicas y combinaciones de estos.

[0134] En una modalidad, la presente invención está dirigida a métodos para tratar o prevenir los síntomas vasomotores en un sujeto necesitado de ello, que comprende las etapas de:

Administrar a dicho sujeto una cantidad efectiva de al menos un compuesto de fórmula I o una sal farmacéuticamente aceptable.

[0135] Cuando los niveles de estrógeno son bajos o el estrógeno está ausente, los niveles normales están entre n y 5-HT se alteran y este cambio alterado en los niveles de neurotransmisor pueden resultar en cambios de la sensibilidad del centro termorregulador. Los niveles químicos alterados se pueden trasladar o se pueden traducir en el centro termorregulador como una sensación de calor y como una respuesta, el hipotálamo puede activar las celdas autonómicas descendentes y que resultan en una excitación del calor por vía de la vaso dilatación y sudoración (flujo caliente) (Figura 1). De acuerdo con esto, la privación de estrógeno puede resultar en una actividad de norepinefrina alterada.

[0136] La norepinefrina sintetizada en pericaria del vástago del cerebro es liberado como los terminales nerviosos en el hipotálamo y el vástago del cerebro. En el hipotálamo, el NR regula la actividad de las neuronas que residen en el centro termoreguladora. El vástago del cerebro, el NE inervatos neuronas serotoninérgicas (5HT), y actúan por vía de los receptores adrenpergicos$_{\alpha 1}$ y adrenérgicos$_{\alpha 2}$ post sinápticos, este estimula la actividad del sistema serotoninérgico. En respuesta, las neuronas 5-HT también modulan la actividad del centro termoregulador y retroalimenta las neuronas NE. Por vía de esta conexión de retroalimentación, 5-HT, actúa por vía de los receptores 5-HT inhibe la actividad de las neuronas NE. La norepinefrina en la fisura sináptica es también tomada por el transportador NE (NET) localizados en las neuronas NE. El transportador recicla el NE y lo hace disponible para neurotransmisión múltiple (Figura 2).

[0137] La presente invención suministra un tratamiento para los síntomas vasomotores mediante métodos de recuperación de la actividad reducida de la norepinefrina. La actividad de la norepinefrina en el hipotálamo o en el vástago del cerebro puede ser elevada mediante (i) el bloqueo de la actividad del transportador NE, (ii) bloqueo de la actividad del receptor adrenérgico α_2 precináotico como un antagonista, o (iii) bloqueo de la actividad 5-HT de las neuronas NE con un antagonista 5-HTα_2.

[0138] En otra modalidad, la presenta invención está dirigida a métodos para tratar o prevenir un desorden por depresión en un sujeto necesitado de ello que comprende las etapas de:

Administrar una cantidad efectiva de al menos un compuesto de la fórmula I a una sal farmacéuticamente aceptable de este.

[0139] En aún otras modalidades, la presente invención está dirigida a métodos para tratar o prevenir la disfunción sexual en un sujeto necesitado de ello que comprende las etapas:

Administrar una cantidad efectiva de al menos un compuesto de la fórmula I a una sal farmacéuticamente aceptable de este.

[0140] En otra modalidad, la presente invención está dirigida a métodos para tratar o prevenir el desorden gastrointestinal o genitourinario, particularmente la incontinencia por tensión o la incontinencia urinaria apremiante, en un sujeto necesitado de ello, que comprende las etapas de:

Administrar una cantidad efectiva de al menos un compuesto de la fórmula I a una sal farmacéuticamente aceptable de este.

[0141] En otra modalidad, la presente invención está dirigida a métodos para tratar o prevenir el síndrome de fatiga crónica en un sujeto necesitado de ello que comprende las etapas de:

Administrar una cantidad efectiva de al menos un compuesto de la fórmula I a una sal farmacéuticamente aceptable de este.

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[0142] En otra modalidad, la presente invención está dirigida a métodos para tratar o prevenir el síndrome de fibromialgia en un sujeto necesitado de ello que comprende las etapas de:

Administrar a dicho sujeto una cantidad efectiva de al menos un compuesto de la fórmula I a una sal farmacéuticamente aceptable de este.

[0143] En modalidades adicionales, la presente invención está dirigida a métodos para tratar o prevenir el dolor en un sujeto necesitado de ello que comprende las etapas de:

Administrar a dicho sujeto una cantidad efectiva de al menos un compuesto de la fórmula I a una sal farmacéuticamente aceptable de este.

[0144] El dolor puede ser por ejemplo, dolor agudo (duración corta), o dolor crónico (regularmente recurrente o persistente). El dolor también puede ser centralizado o periférico.

[0145] Ejemplos de dolor que pueden ser agudos o crónicos y que se pueden tratar de acuerdo con los métodos de la presente invención incluyen dolor inflamatorio, dolor músculo esqueletal dolor de huesos, dolor lumbosacro, dolor de cuello o la espalda superior, dolor visceral, dolor somático, dolor neuropático, dolor por cáncer, dolor causado por daño o cirugía tal como dolor por quemadura o dolor dental o dolores de cabeza tales como migraña, o dolores por tensión o combinaciones de estos dolores. Un experto en la técnica reconocerá que estos dolores se pueden

uno con el otro. Por ejemplo, un dolor causado por inflamación también puede ser de naturaleza visceral o músculo esqueletal.

[0146] En una modalidad preferida de la presente invención los compuestos útiles en la presente invención son administrados en mamíferos para tratar el dolor crónico tal como el dolor neuropático asociado por ejemplo con el daño a los cambios patológicos en el sistema nervioso periférico o central. Dolor de cáncer, dolor visceral asociado como por ejemplo el dolor abdominal, pélvico, y/o las regiones perineales o pancreatitis; dolor músculo esqueletal asociado como por ejemplo la espalda inferior o superior, columna, fibromialgia, articulación temporomandibular o síndrome de dolor de huesos asociado como por ejemplo desórdenes de degeneración de huesos o articulaciones tal como osteoartritis u osteoartritis reumatoide, o estenosis espinal, dolores de cabeza tales como migraña o dolores de cabeza por tensión; o dolores asociados con infecciones tales como VIH, anemia de célula calciforme, desórdenes autoinmunes, esclerosis múltiple, o inflamación tal como osteoartritis o artritis reumatoide.

[0147] En una modalidad más preferida, los compuestos útiles en esta invención son utilizados para tratar dolor crónico que es neuropático, dolor visceral, dolor músculo esqueletal, dolor de huesos, dolor de cáncer o dolor inflamatorio o combinaciones de estos, de acuerdo con los métodos descritos aquí. El dolor inflamatorio se pude asociar con una variedad de condiciones médicas tales como osteoartritis, artitritis reumatoide, cirugía, o daño. El dolor neuropático se puede asociar con por ejemplo,

neuropatía diabética, neuropatía periférica, neuralgia post herpética, neuralgia trigeminal, radiculopatía lumbar o cervical, fibromialgia, neuralgia glosofaríngea, distrofia simpática refleja, casualgia, síndrome talámico, ablución de la raíz del nervio, o daño nervioso causado por daño resultante en la sensibilización periférica y/o central tal como dolor de limbo fantasma, distrofia simpática refleja o dolor post toracotomía, cáncer, daño químico, toxinas, deficiencias nutricionales, o infecciones virales o bacteriales tales como herpes zoster o VIH, o combinaciones de estos. Los métodos de uso de los compuestos de esta invención incluyen además tratamientos en los cuales el dolor neuropático es una condición secundaria a la infiltración metastásica, adiposis dolorosa, quemaduras, o condiciones de dolor central relacionadas con condiciones talámicas.

[0148] Como se mencionó previamente, los métodos de la presente invención se pueden utilizar para tratar dolor que es somático y/o visceral de naturaleza. Por ejemplo, el dolor somático que se puede tratar de acuerdo con los métodos de la presente invención incluyen dolores asociados con daño estructural o de tejido suave experimentado durante la cirugía, procedimientos dentales, quemaduras o daños de cuerpo traumático. Ejemplos de dolor visceral que se pueden tratar con los métodos de la presente invención incluyen aquellos tipos de dolor asociado con o que resultan de las enfermedades de los órganos internos tales como la colitis ulcerativa, el síndrome de intestino irritable vejiga irritable, enfermedad de Crohn, reumatológicas (artrálgias), tumores, gastritis, pancreatitis,

infecciones de los órganos o desórdenes del tracto biliar o combinaciones de estos. Un experto en la técnica también reconocerá que el dolor tratado de acuerdo con los métodos de la presente invención se pueden relacionar con condiciones de hiperalgesia, alodinia o ambos. Adicionalmente, el dolor crónico puede ser con o sin sensibilización periférica o central.

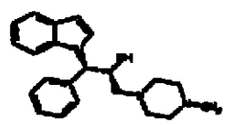
[0149] Los compuestos útiles en esta invención también se pueden utilizar para tratar dolores agudos y/o crónicos asociados con condiciones femeninas, que también se pueden denominar como con dolores específicos femeninos. Tales grupos de dolores incluye aquellos que son encontrados solamente en hembras, que incluyen dolor asociado con la menstruación, ovulación, embarazo o nacimiento de niños, aborto espontáneo, embarazo ectópico, menstruación retrógrada, ruptura de un quiste folicular o de corpes luteum, irritación de la úlcera pélvica, fibroides uterinos, adenomiosis, endometriosis, infección e inflamación, isquemia del órgano pélvico, obstrucción, adhesiones intraabdominales, distorsión anatómica de la víscera pélvica, abscesos del ovario, pérdida de soporte pélvico, tumores, congestión pélvica o dolor requerido de causas no ginecológicas.

[0150] La presente invención está definida adicionalmente en los siguientes ejemplos, en los cuales todas las partes y porcentajes son el peso equilibrad y los grados Celsius, a menos que se establezca otra cosa. Se debe entender que estos ejemplos, aunque indican las modalidades preferidas de la invención, son dados por vía solamente de ilustración. En la discusión anterior

y estos ejemplos, un experto en la técnica puede establecer las características esenciales de esta invención, y sin apartarse del espíritu y alcance de este, pueden hacer varios cambios y modificaciones de la invención para adaptarlo a varios usos y condiciones.

EJEMPLOS

[0151] EJEMPLO 1: clorhidrato de (1RS,2SR)-1-(1H-indol-1-il)-3-(4-metilpiperazin-1-il)-1-fenill propan-2-ol



[0152] Etapa 1: Una mezcla de indol (2.34 g, 20 mmol) e hidróxido de potasio sólido pulverizado (1.12 g, 20 mmol) se agita durante 30 minutos bajo nitrógeno a temperatura ambiente. *Trans*-3-fenilglicidol (3.0 g, 20 mmol) en dimetilsulfóxido (1 mL) entonces se agrega y la mezcla se agita a 70° C durante 2 horas hasta que no permanece epóxido. La mezcla entonces se enfría y se particiona entre agua y diclorometano. La capa orgánica se separa, se lava con agua varias veces, se seca sobre sulfato de sodio anhidro, se filtra, y se concentra en vacío. El producto crudo se purifica por vía de Cromatografía Biotage (FlasH40i, sílice, 10%, 20%, 30% de acetato de etilo/hexano) para proporcionar 1.92 g (36%) de (2RS,3RS)-3-indol-1-il-3-fenil-propano-1,2-diol como un aceite. ^{1}H RMN (DMSO): δ3.27 (m, 2H,

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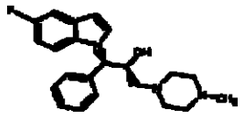
CH_2OH), δ4.45 (m, 1 H, CHOH), δ4.80 (t, 1 H, CH_2OH), δ5.20 (d, 1 H, CHOH), δ5.60 (d, 1 H, CHPh); MS (ESI) *m/z* 268 ($[M+H]^+$).

[0153] Etapa 2: Una solución de (2RS,3RS)-3-indol-1-il-3-fenil-propano-1,2-diol (1.83 g, 6.8 mmol) y cloruro de p-toluenosulfonilo (1.31 g, 6.8 mmol) en piridina anhidra (10 mL) se agita a temperatura ambiente bajo nitrógeno durante 15 horas. La mezcla entonces se diluye con agua (10 mL), se apaga con una solución de ácido clorhídrico 2 N acuosa en un baño de hielo/agua hasta la solución es de pH = 3, y se extrae con diclorometano. La capa orgánica se lava con agua de nuevo, se seca sobre sulfato de sodio anhidro, se filtra, y se concentra. El residuo se purifica por vía de Cromatografía Biotage (FlasH40i, sílice, 10%, 25% de EtOAc/hexano) para proporcionar 1.98 g (69%) de 2-hidroxi-3-indol-1-il-3-fenil-propil éster de ácido (2RS,3RS)-tolueno-4-sulfónico como un sólido blanco. ^1H RMN (DMSO): δ3.70 y δ3.85 (dd y dd, 2H, CH_2OTs), δ4.80 (m, 1 H, CHOH), δ5.52 (d, 1 H, CHPh), δ5.82 (d, 1 H, CHOH); MS (ESI) *m/z* 422 ($[M+H]^+$).

[0154] Etapa 3: Una mezcla de 2-hidroxi-3-indol-1-il-3-fenil-propil éster de ácido (2RS,3RS)-tolueno-4-sulfónico (0.185 g, 0.4 mmol), 1-metil piperazina (0.05 mL, 0.4 mmol) y carbonato de potasio (0.07 g, 0.44 mmol) en acetonitrilo (10 mL) se agita a reflujo bajo nitrógeno durante 24 horas. Después de enfriamiento, la mezcla se filtra y el filtrado se concentra y se purifica vía de Cromatografía Biotage (5% metanol/diclorometano) para dar un sólido blanco de (1RS,2SR)-1-(1H-indol-1-il)-3-(4-metilpiperazin-1-il)-1-fenilpropan-2-ol. La base libre se disuelve en una

cantidad mínima de etanol y se trata con una solución etérea 1 N de ácido clorhídrico hasta que la solución tenga un pH = 3 seguido por dietil éter. El producto luego se cristaliza para agregar una cantidad mínima de hexano para lograr el compuesto del título, diclorhidrato de (1RS,2SR)-1-(1H-indol-1-il)-3-(4-metilpiperazin-1-il)-1-fenilpropan-2-ol como un sólido blanco apagado. MS *m/z* 350 ($[M+H]^+$); HRMS: calculado para $C_{22}H_{27}N_3O$+ H+, 350.22269; encontrado (ESI, $[M+H]^+$), 350.2228.

[0155] EJEMPLO 2: diclorhidrato de (1RS,2SR)-1-(5-fluoro-1H-indol-1-il)-3-(4-metilpiperazin-1-il)-1-fenilpropan-2-ol



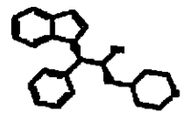
[0156] De forma análoga al EJEMPLO 1, etapa 1 (2RS,3RS)-3-(5-fluoro-indol-1-il)-3-fenil-propano-1,2-diol se prepara de 5-fluoroindol y *trans*-3-fenilglicidol como un aceite. MS (ESI) *m/z* 286 ($[M+H]^+$).

[0157] De forma análoga al EJEMPLO 1, etapa 2 3-(5-fluoro-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2RS,3RS)-tolueno-4-sulfónico se prepara de (2RS,3RS)-3-(5-fluoro-indol-1-il)-3-fenil-propano-1,2-diol. MS (ESI) *m/z* 440 ($[M+H]^+$).

[0158] De forma análoga al EJEMPLO 1, etapa 3 diclorhidrato de (1RS,2SR)-1-(5-fluoro-1H-indol-1-il)-3-(4-metilpiperazin-1-il)-1-fenilpropan-2-ol se prepara de 3-(5-fluoro-indol-1-il)-2-hidroxi-

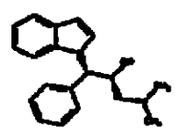
3-fenil-propil éster de ácido (2RS,3RS)-tolueno-4-sulfónico. MS *m/z* 368 ($[M+H]^+$); HRMS: calculado para $C_{22}H_{26}FN_3O$ + H+, 368.21327; encontrado (ESI, $[M+H]^+$), 368.213.

[0159] EJEMPLO 3: clorhidrato de (1RS,2SR)-1-(1H-indol-1-il)-3-morfolin-4-il-1-fenilpropan-2-ol



[0160] De forma análoga al EJEMPLO 1, etapa 3 se prepara clorhidrato de (1RS,2SR)-1-(1H-indol-1-il)-3-(4-metilpiperazin-1-il)-1-fenilpropan-2-ol de 2-hidroxi-3-indol-1-il-3-fenil-propil éster de ácido (2RS,3RS)-tolueno-4-sulfónico (EJEMPLO 1, etapa 3) y morfolina. MS (ESI) *m/z* 337 ($[M+H]^+$); HRMS: calculado para $C_{21}H_{24}N_2O_2$ + H+, 337.19105; encontrado (ESI, $[M+H]^+$), 337.1909.

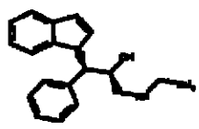
[0161] EJEMPLO 4: clorhidrato de (1RS,2SR)-3-(dimetilamino)-1-(1H-indol-1-il)-1-fenilpropan-2-ol



[0162] De forma análoga al EJEMPLO 1, etapa 3 se prepara clorhidrato de (1RS,2SR)-3-(dimetilamino)-1-(1H-indol-1-il)-1-fenilpropan-2-ol de 2-hidroxi-3-indol-1-il-3-fenil-propil éster de ácido (2RS,3RS)-tolueno-4-sulfónico (EJEMPLO 1, etapa 3) y

clorhidrato de dimetilamina. MS (ES) *m/z* 295.2 ($[M+H]^+$); HRMS: calculado para $C_{19}H_{22}N_2O$ + H+, 295.18049; encontrado (ESI, $[M+H]^+$), 295.1829.

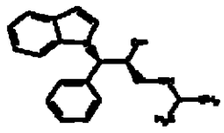
[0163] EJEMPLO 5: clorhidrato de (1RS,2SR)-3-(etilamino)-1-(1H-indol-1-il)-1-fenilpropan-2-ol



[0164] De forma análoga al EJEMPLO 1, etapa 3, una solución de 2-hidroxi-3-indol-1-il-3-fenil-propil éster de ácido (2RS.3RS)-tolueno-4-sulfónico (EJEMPLO 1, etapa 3, 0.42 g, 1.0 mmol) y etilamina (solución en metanol 2N, 5 mL) se agita en un frasco sellado a temperatura ambiente durante 15 horas. Después de dilución con una solución acuosa saturada de bicarbonato de sodio, la mezcla se extrae con una solución de diclorometano/alcohol isopropílico (3/1). El extracto se lava con agua, se seca sobre sulfato de sodio anhidro, se filtra y se concentra en vacío. El producto crudo se purifica sobre vía de Cromatografía Biotage (FlasH40i, sílice, diclorometano, 5% metanol/diclorometano) para dar un aceite como una base libre del producto previsto. La base libre se disuelve en una cantidad mínima de etanol y se trata con una solución etérea 1 N de ácido clorhídrico hasta que la solución tenga un pH = 3 seguido por dietil éter. El producto luego se cristaliza por adición de una cantidad mínima de acetato de etilo para proporcionar el compuesto del título, clorhidrato de (1RS,2SR)-3-(etilamino)-1-

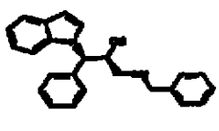
(1H-indol-1-il)-1-fenilpropan-2-ol como un sólido ámbar. MS (ES) *m/z* 295.2 ($[M+H]^+$); HRMS: calculado para $C_{19}H_{22}N_2O$ + H+, 295.18049; encontrado (ESI, $[M+H]^+$), 295.1797.

[0165] EJEMPLO 6: clorhidrato de (1RS,2SR)-1-(1H-indol-1-il)-3-(isopropilamino)-1-fenilpropan-2-ol



[0166] De forma análoga al EJEMPLO 1, etapa 3 se prepara clorhidrato de (1RS,2SR)-1-(1H-indol-1-il)-3-(isopropilamino)-1-fenilpropan-2-ol de 2-hidroxi-3-indol-1-il-3-fenil-propil éster de ácido (2RS,3RS)-tolueno-4-sulfónico (EJEMPLO 1, etapa 3) e isopropilamina. MS (ES) *m/z* 309.2 ($[M+H]^+$); HRMS: calculado para $C_{20}H_{24}N_2O$ + H+, 309.19614; encontrado (ESI, $[M+H]^+$), 309.1971.

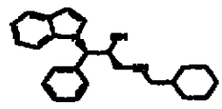
[0167] EJEMPLO 7: clorhidrato de (1RS,2SR)-3-(bencilamino)-1-(1H-indol-1-il)-1-fenilpropan-2-ol



[0168] De forma análoga al EJEMPLO 1, etapa 3 se prepara clorhidrato de (1RS,2SR)-3-(bencilamino)-1-(1H-indol-1-il)-1-fenilpropan-2-ol de 2-hidroxi-3-indol-1-il-3-fenil-propil éster de ácido (2RS,3RS)-tolueno-4-sulfónico (EJEMPLO 1, etapa 3) y

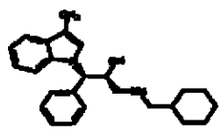
bencilamina. MS (ES) *m/z* 357.2 ($[M+H]^+$); HRMS: calculado para $C_{24}H_{24}N_2O$ + H+, 357.19614; encontrado (ESI, $[M+H]^+$), 357.1962.

[0169] EJEMPLO 8: clorhidrato de (1RS,2SR)-3-[(ciclohexilmetil)amino]-1-(1H-indol-1-il)-1-fenilpropan-2-ol



[0170] De forma análoga al EJEMPLO 1, etapa 3 se prepara clorhidrato de (1RS,2SR)-3-[(ciclohexilmetil)amino]-1-(1H-indol-1-il)-1-fenilpropan-2-ol de 2-hidroxi-3-indol-1-il-3-fenil-propil éster de ácido (2RS,3RS)-tolueno-4-sulfónico (EJEMPLO 1, etapa 3) y ciclohexil metilamina. MS (ES) *m/z* 363.3 ($[M+H]^+$); HRMS: calculado para $C_{24}H_{30}N_{20}$ + H+, 363.24309; encontrado (ESI, $[M+H]^+$), 363.2421.

[0171] EJEMPLO 9: clorhidrato de (1RS,2SR)-3-[(ciclohexilmetil)amino]-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol



[0172] De forma análoga al EJEMPLO 1, etapa 1 se prepara (2RS,3RS)-3-(3-metil-indol-1-il)-3-fenil-propano-1,2-diol de 3-metilindol y *trans*-3-fenilglicidol como un sólido amarillo. MS (ESI) *m/z* 282 ($[M+H]^+$).

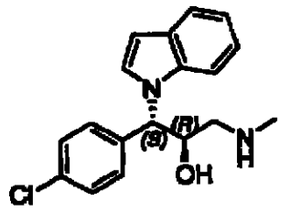
[0245] Etapa 4a (Método B): [(2R,R)-3-(3-clorofenil)oxiran-2-il]metanol (4.8 g, 26 mmol) e indolina (de 1.063, 2.9 mL, 26 mmol) se calientan puros a 135° C en un frasco sellado. Después de 1.5 horas, la mezcla enfriada se preadsorbe sobre gel de sílice (25 g). Cromatografía de columna flash (sílice 375 g, 20%, 40%, 80% de acetato de etilo/hexanos) suministra (2S,3S)-3-(3-clorofenil)-3-(2,3-dihidro-1H-indol-1-il)propano-1,2-diol (5.8 g, 73%) como un sólido blanco. MS (ES) *m/z* 304 ($[M+H]^+$).

[0246] Etapa 4b (Método B): Una solución de (2S,3S)-3-(3-clorofenil)-3-(2,3-dihidro-1H-indol-1-il)propano-1,2-diol (5.8 g, 19 mmol) en ca. 1:1(v/v) se trata tolueno-diclorometano (200 mL) con una solución de 2,3-dicloro-5,6-diciano-1,4-benzoquinona (4.4 g, 19 mmol) en tolueno (100 mL) a 0° C. Después de 30 minutos, la mezcla se diluye con acetato de etilo (1 L) y se lava con 5% de carbonato de sodio acuoso (4 x 1 L), agua (1 L) y solución salina (1 L), se seca (sulfato de magnesio) y se concentra bajo vacío para dar un aceite oscuro (5.4 g) este se preadsorbe sobre gel de sílice (15 g). Cromatografía de columna flash (sílice 235 g, 20%, 40% de acetato de etilo/hexanos) suministra (2S,3S)-3-(3-clorofenil)-3-(1H-indol-1-il)propano-1,2-diol, (4.7 g, 82%) como un aceite amarillo nublado. MS (ES) *m/z* 302 ($[M+H]^+$).

[0247] Etapa 5: De forma análoga al EJEMPLO 1, etapa 3-(3-clorofenil)-2-hidroxi-3-indol-1-il-propil éster de ácido 2, (2S,3S)-tolueno-4-sulfónico se prepara de (2S,3S)-3-(3-clorofenil)-3-(1H-indol-1-il)propano-1,2-diol. MS (ES) *m/z* 456 ($[M+H]^+$).

[0248] Etapa 6: 3-(3-clorofenil)-2-hidroxi-3-indol-1-il-propil éster de ácido (2S,3S)-tolueno-4-sulfónico (0.60 g, 1.2 mmol) se trata con una solución de metilamina en metanol (2.0 M, 3 mL, 6 mmol) y la solución se agita a 23° C durante 18 horas. En este tiempo, la solución se concentra bajo vacío y se disuelve en dietil éter (50 mL). La solución orgánica se lava con una solución de hidróxido de sodio acuosa 1N (50 mL), agua (50 mL) y solución salina (50 mL), se seca (sulfato de sodio) y se concentra bajo vacío para suministrar una espuma naranja (0.30 g) esta se purifica por HPLC de fase inversa (90:10 agua-acetonitrilo a 50:50 agua-acetonitrilo que contiene 0.1% de ácido trifluoroacético @ 20 mL/min). Los productos fraccionados se concentran bajo vacío para remover acetonitrilo y la solución acuosa se basifica con una solución de hidróxido de amonio acuosa 2N. La suspensión lechosa resultante se extrae con acetato de etilo (200 mL) y la fase orgánica se lava con agua (200 mL) y solución salina (100 mL), se seca (sulfato de sodio) y se concentra bajo vacío. El residuo se disuelve en etanol absoluto (4 mL), se trata con a ácido clorhídrico 4 M en 1,4-dioxano (1.3 eq) y se agita durante 10 minutos. La solución se concentra bajo vacío, luego se disuelve en etanol absoluto (3 mL) y se deja en reposo a 23° C durante toda la noche. La filtración por vacío suministra clorhidrato de (1S,2R)-1-(3-clorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol (62 mg, 5% durante 3 etapas) como un sólido blanco cristalino. HRMS calculado para $C_{18}H_{19}ClN_2O$ + H+, 315.12587; encontrado (ESI) 315.1267 ($[M+H]^+$).

[0249] EJEMPLO 34: clorhidrato de (1S,2R)-1-(4-clorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol



[0250] De forma análoga al EJEMPLO 33, etapa 1 etil éster de ácido (2E)-3-(4-clorofenil)-acrílico se prepara de dietil etoxicarbonilmetilfosfonato y 4-clorobenzaldehído. MS (ESI) *m/z* 210 ($[M+H]^+$).

[0251] De forma análoga al EJEMPLO 33, etapa 2 (2E)-3-(4-clorofenil)prop-2-en-1-ol se prepara de etil éster de ácido (2E)-3-(4-clorofenil)-acrílico. MS (ESI) *m/z* 151($[M+H-H_2O]^+$).

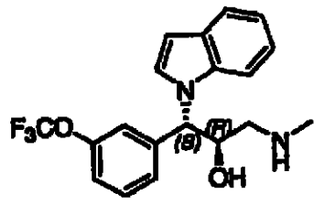
[0252] De forma análoga al EJEMPLO 117, etapa 4, [-3-(4-clorofenil)oxiran-2-il]metanol se prepara de (2E)-3-(4-clorofenil)prop-2-en-1-ol. MS (ESI) *m/z* 167 ($[M+H-H_2O]^+$); [DD0 +41(c 0.0121 g/mL, DMSO); 99.2% ee.

[0253] De forma análoga al EJEMPLO 117, etapa 5, (2S,3S)-3-(4-clorofenil)-3-(1H-indol-1-il)propano-1,2-diol se prepara de 1 H-indol y [(2R,3R)-3-(4-clorofenil)oxiran-2-il]metanol. MS (ES) *m/z* 302 ($[M+H]^+$).

[0254] De forma análoga al EJEMPLO 1, etapa 2, 3-(4-clorofenil)-2-hidroxi-3-indol-1-il-propil éster de ácido (2S,3S)-tolueno-4-sulfónico se prepara de (2S,3S)-3-(4-clorofenil)-3-(1H-indol-1-il)propano-1,2-diol. MS (ES) *m/z* 456 ($[M+H]^+$).

[0255] De forma análoga al EJEMPLO 33, etapa 6 clorhidrato de (1S,2R)-1-(4-clorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol se prepara de 3-(4-clorofenil)-2-hidroxi-3-indol-1-il-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina (solución en metanol 2N). HRMS: calculado para $C_{18}H_{19}ClN_2O$ + H+, 315.12587; encontrado (ESI) 315.124 ($[M+H]^+$).

[0256] **EJEMPLO 35: clorhidrato de (1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-[3-(trifluorometoxi)fenil]propan-2-ol**



[0257] De forma análoga al EJEMPLO 33, etapa 1, etil éster deácido (2E)-3-(3-trifluorometoxi-fenil)-acrílico se prepara de dietil etoxicarbonilmetilfosfonato y 3-(trifluorometoxi)benzaldehído. MS (ES)

[0258] De forma análoga al EJEMPLO 33, etapa 2, (2E)-3-[3-(trifluorometoxi)fenil]prop-2-en-1-ol se prepara de etil éster de ácido (2E)-3-(3-trifluorometoxi-fenil)-acrílico. MS (ES) *m/z* 201($[MH-H-H_2O]^+$).

[0259] De forma análoga al EJEMPLO 117, etapa 4, {(2R,3R)-3-[3-(trifluorometoxi)fenil]oxiran-2-il}metanol se prepara de (2E)-

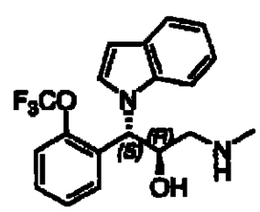
3-[3-(trifluorometoxi)fenil]prop-2-en-1-ol. MS (ES) *m/z* 217 ([MH-H-H_2O]$^+$); [□]$_D^{25}$ = +30° (c = 0.0118 g/mL, DMSO); 84.4% ee.

[0260] De forma análoga al EJEMPLO 117, etapa 5, (2S,3S)-3-(1H-indol-1-il)-3-[3-(trifluorometoxi)fenil]propano-1,2-diol se prepara de 1*H*-indol y {(2R,3R)-3-[3-(trifluorometoxi)fenil]oxiran-2-il}metanol. MS (ES) *m/z* 352 ([M+H]$^+$).

[0261] De forma análoga al EJEMPLO 1, etapa 2 2-hidroxi-3-indol-1-il-3-(3-trifluorometoxi-fenil)-propil éster de ácido (2S,3S)-tolueno-4-sulfónico se prepara de (2S,3S)-3-(1H-indol-1-il)-3-[3-(trifluorometoxi)fenil]propano-1,2-diol. MS (ES) *m/z* 506 ([M+H]$^+$).

[0262] De forma análoga al EJEMPLO 33, etapa 6 clorhidrato de (1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-[3-(trifluorometoxi)fenil]propan-2-ol se prepara de 2-hidroxi-3-indol-1-il-3-(3-trifluorometoxi-fenil)-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina (2 N en metanol). MS (ES) *m/z* 365 ([M+H]$^+$).

[0263] EJEMPLO 36: clorhidrato de (1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-[2-(trifluorometoxi)fenil]propan-2-ol



[0264] Etapa 1: De forma análoga al EJEMPLO 33, etapa 1, etil éster de ácido (2E)-3-(2-trifluorometoxi-fenil)-acrílico se prepara de dietil etoxicarbonilmetilfosfonato y 2-(trifluorometoxi)benzaldehído. MS (ES) *m/z* 261($[M+H]^+$).

[0265] Etapa 2: De forma análoga al EJEMPLO 33, etapa 2, (2E)-3-[2-(trifluorometoxi)fenil]prop-2-en-1-ol se prepara de etil éster de ácido (2E)-3-(2-trifluorometoxi-fenil)-acrílico. MS (ES) *m/z* 201($[M+H-H_2O]^+$).

[0266] Etapa 3: Una solución de (2E)-3-[2-(trifluorometoxi)fenil]prop-2-en-1-ol (3.9 g, 18 mmol) en diclorometano (90 mL) se trata con ácido meta-cloroperoxibenzóico (77%, 8.0 g, 36 mmol) a 23° C. Después de 5 horas, la reacción se apaga con una solución de hidróxido de sodio acuosa 1N (200 mL) con agitación vigorosa y las fases se separan. La fase acuosa se extrae con dietil éter (2 x 100 mL). Las fases orgánicas combinadas se lavan con agua (3 x 100 mL), se secan (sulfato de sodio) y se concentran bajo vacío para suministrar un aceite incoloro, claro (3.8 g) este se preadsorbe sobre gel de sílice (6 g). Cromatografía de columna flash (sílice 60 g, 10%, 20% de acetato de etilo/hexanos) suministra ((2RS,3SRS)-3-[2-(trifluorometoxi)fenil]oxiran-2-il}metanol (2.4 g, 57%) como un sólido blanco. MS (ES) *m/z* 217 ($[MH-H-H_2O]^+$).

[0267] Se disuelve {(2RS,3RS)-3-[2-(trifluorometoxi)fenil]oxiran-2-il}metanol en metanol. La solución resultante se inyecta en el instrumento de Cromatografía de Fluido Supercrítico, y los

enantiómeros resueltos en Línea de base se recolectan utilizando las condiciones descritas adelante. Se determina la pureza enantiomérica de cada enantiómero bajo las mismas condiciones de Cromatografía de Fluido Supercrítico utilizando una columna Chiralpak AS-H 5u, 250 mm x 4.6 mm ID a un índice de flujo de 2.0 mL/minutos utilizando Cromatografía de Fluido Supercrítico Analítico (Berger Instruments, Inc. Newark, DE USA).

Instrumento SFC: Berger MultiGram Prep SFC (Berger Instruments, Inc. Newark, DE 19702.

Columna: Chiralpak AS-H; 5u; 250mm L x 20mm ID (Chiral Technologies, Inc, Exton, PA, USA)

Temperatura de columna: 35° C

Modificador SFC: 5% I PA/95% CO2

Índice de flujo: 35 mL/min

Presión de Salida: 100 bar

Detector: UV a 220 nm [

0268] Se aísla {(2R,3R)-3-[2-(trifluorometoxi)fenil]oxiran-2-il}metanol como pico 1. MS (ES) *m/z* 217 ($[M+H-H_2O]^+$); $[\square]_D^{25}$ = +19.4° (c = 0.0102 g/mL, DMSO); > 99.9% ee.

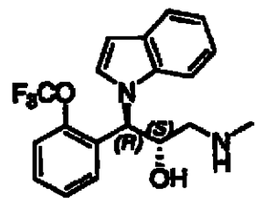
[0269] se aísla {(2S,3S)-3-[2-(trifluorometoxi)fenil]oxiran-2-il}metanol como pico 2. MS (ES) *m/z* 217 ($[M+H-H_2O]^+$); $[\square]_D^{25}$ = -15.7° (c = 0.0125 g/mL, DMSO); 95.8% ee.

[0270] Etapa 4: De forma análoga al EJEMPLO 117, etapa 5, (2S,3S)-3-(1H-indol-1-il)-3-[2-(trifluorometoxi)fenil]propano-1,2-diol se prepara de 1 H-indol y {(2R,3R)-3-[2-(trifluorometoxi)fenil]oxiran-2-il}metanol, sustituir *terc*-butóxido de sodio en lugar de hidruro de potasio. MS (ES) *m/z* 352 ($[M+H]^+$).

[0271] Etapa 5: De forma análoga al EJEMPLO 1, etapa 2, 2-hidroxi-3-indol-1-il-3-(2-trifluorometoxi-fenil)-propil éster de ácido (2S,3S)-tolueno-4-sulfónico se prepara de (2S,3S)-3-(1H-indol-1-il)-3-[2-(trifluorometoxi)fenil]propano-1,2-diol. MS (ES) *m/z* 506 ($[M+H]^+$).

[0272] Etapa 6: De forma análoga al EJEMPLO 33, etapa 6 se prepara clorhidrato de (1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-[2-(trifluorometoxi)fenil]propan-2-ol de 2-hidroxi-3-indol-1-il-3-(2-trifluorometoxi-fenil)-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina (2 N en metanol). MS (ES) *m/z* 365 ($[M+H]^+$).

[0273] EJEMPLO 37: clorhidrato de (1R,2S)-1-(1H-indol-1-il)-3-(metilamino)-1-[2-(trifluorometoxi)fenil]propan-2-ol

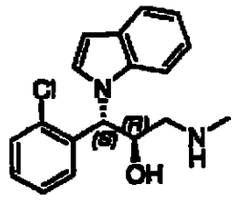


[0274] De forma análoga al EJEMPLO 117, etapa 5, (2R,3R)-3-(1H-indol-1-il)-3-[2-(trifluorometoxi)fenil]propano-1,2-diol se prepara de 1 H-indol y {(2S,3S)-3-[2-(trifluorometoxi)fenil]oxiran-2-il}metanol (EJEMPLO 36, etapa 3) sustituir *terc*-butóxido de sodio en lugar de hidruro de potasioe. MS (ES) *m/z* 352 ($[M+H]^+$).

[0275] De forma análoga al EJEMPLO 1, etapa se prepara 2-hidroxi-3-indol-1-il-3-(2-trifluorometoxi-fenil)-propil éster de ácido 2, (2R,3R)-tolueno-4-sulfónico de {2R,3R)-3-(1H-indol-1-il)-3-[2-(trifluorometoxi)fenil]propano-1,2-diol. MS (ES) *m/z* 506 ($[M+H]^+$).

[0276] De forma análoga al EJEMPLO 33, etapa 6 clorhidrato de (1R,2S)-1-(1H-indol-1-il)-3-(metilamino)-1-[2-(trifluorometoxi)fenil]propan-2-ol se prepara de 2-hidroxi-3-indol-1-il-3-(2-trifluorometoxi-fenil)-propil éster de ácido (2R,3R)-tolueno-4-sulfónico y metilamina (2 N en metanol). MS (ES) *m/z* 365 ($[M+H]^+$).

[0277] EJEMPLO 38: clorhidrato de (1S,2R)-1-(2-clorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol



[0278] De forma análoga al EJEMPLO 33, etapa 1, etil éster de (2E)-3-(2-clorofenil)-acrílico se prepara de dietil etoxicarbonilmetilfosfonato y 2-clorobenzaldehído. MS (ESI) *m/z* 210 ($[M+H]^+$).

[0279] De forma análoga al EJEMPLO 33, etapa 2, (2E)-3-(2-clorofenil)prop-2-en-1-ol se prepara de etil éster de (2E)-3-(2-clorofenil)-acrílico. MS (ESI) *m/z* 151($[MH-H-H_2O]^+$).

[0280] De forma análoga al EJEMPLO 36, etapa 3, [(2RS,3RS)-3-(2-clorofenil)oxiran-2-il]metanol se prepara de (2E)-3-(2-clorofenil)prop-2-en-1-ol.

[0281] Se disuelve [(2RS,3RS)-3-(2-clorofenil)oxiran-2-il]metanol en metanol. La solución resultante se inyecta (50 mg/inyección) en el instrumento de Cromatografía de Fluido Supercrítico, y los enantiómeros resueltos en Línea de base se recolectan utilizando las condiciones descritas adelante. Se determina la pureza enantiomérica de cada enantiómero bajo las mismas condiciones de Cromatografía de Fluido Supercrítico utilizando una columna Chiralpak AD-H 5u, 250 mm x 4.6 mm ID a un índice de flujo de 2.0 mL/minutos utilizando Cromatografía de Fluido Supercrítico Analítico (Berger Instruments, Inc. Newark, DE USA).

Instrumento SFC: Berger MultiGram Prep SFC (Berger Instruments, Inc. Newark, DE 19702.

Columna: Chiralpak AD-H; 5u; 250mm L x 20mm ID (Chiral Technologies, Inc, Exton, PA, USA)

Temperatura de columna: 35° C

Modificador SFC: 20% de MeOH/80% CO2

Índice de flujo: 50 mL/min

Presión de Salida: 100 bar

Detector: UV a 220 nm

[0282] Se aísla [(2S,3S)-3-(2-clorofenil)oxiran-2-il]metanol como pico 1. MS (ES) *m/z* 167 ($[MH-H-H_2O]^+$); $[\square]_D^{25}$ = +2.6° (c = 0.0153 g/mL, DMSO); >99.8% ee.

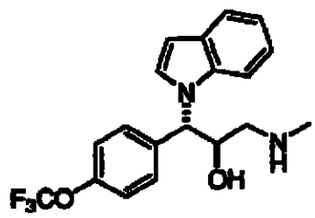
[0283] Se aísla [(2R,3R)-3-(2-clorofenil)oxiran-2-il]metanol como pico 2. MS (ES) *m/z* 167 ($[MH-H-H_2O]^+$); $[\square]_D^{25}$ =-2.5° (c = 0.0139 g/mL, DMSO); >99.8% ee.

[0284] De forma análoga al EJEMPLO 117, etapa 5, se prepara (2S,3S)-3-(2-clorofenil)-3-(1H-indol-1-il)propano-1,2-diol de 1H-indol y [(2R,3R)-3-(2-clorofenil)oxiran-2-il]metanol) se sustituye *terc*-butóxido de sodio en lugar de hidruro de potasio. MS (ES) *m/z* 302 ($[M+H]^+$).

[0285] De forma análoga al EJEMPLO 1, etapa 2, 3-(2-clorofenil)-2-hidroxi-3-indol-1-il-propil éster de ácido (2S,3S)-tolueno-4-sulfónico se prepara de (2S,3S)-3-(2-clorofenil)-3-(1H-indol-1-il)propano-1,2-diol. MS (ES) *m/z* 456 ($[M+H]^+$).

[0286] De forma análoga al EJEMPLO 33, etapa 6 se prepara clorhidrato de (1S,2R)-1-(2-clorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol de 3-(2-clorofenil)-2-hidroxi-3-indol-1-il-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina (2 N en metanol). MS (ES) *m/z* 315 ($[M+H]^+$).

[0287] EJEMPLO 39: clorhidrato de (1RS,2SR)-1-(1H-indol-1-il)-3-(metilamino)-1-[4-(trifluorometoxi)fenil]propan-2-ol



[0288] Etapa 1: De forma análoga al EJEMPLO 33, etapa 1, se prepara etil éster de ácido (2E)-3-(4-trifluorometoxi-fenil)-acrílico de dietil etoxicarbonilmetilfosfonato y 4-(trifluorometoxi)benzaldehído. MS (ES) *m/z* 261($[M+H]^+$).

[0289] Etapa 2: De forma análoga al EJEMPLO 33, etapa 2, se prepara (2E)-3-[4-(trifluorometoxi)fenil]prop-2-en-1-ol de etil éster de ácido (2E)-3-(4-trifluorometoxi-fenil)-acrílico. MS (ES) *m/z* 201($[M+H-H_2O]^+$).

[0290] Etapa 3: De forma análoga al EJEMPLO 36, etapa 3, se prepara {(2RS,3RS)-3-[4-(trifluorometoxi)fenil]oxiran-2-il}metanol de (2E)-3-[4-(trifluorometoxi)fenil]prop-2-en-1-ol. MS (ES) *m/z* 217 ($[M+H-H_2O]^+$).

[0291] Etapa 4: De forma análoga al EJEMPLO 33, etapa 4a (Método B), se prepara (2RS,3RS)-3-(2,3-dihidro-1H-indol-1-il)-3-[4-(trifluorometoxi)fenil]propano-1,2-diol de indolina y {(2RS,3RS)-3-[4-(trifluorometoxi)fenil]oxiran-2-il}metanol. MS (ES) *m/z* 354 ($[M+H]^+$).

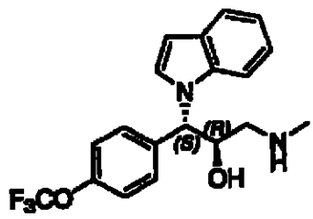
[0292] Etapa 5: De forma análoga al EJEMPLO 33, etapa 4b (Método B), se prepara (2RS1SRS)-S-(1H-indol-1-il)-3-[4-(trifluorometoxi)fenil]propano -1,2-diol de (2RS,3RS)-3-(2,3-dihidro-1H-indol-1-il)-3-[4-(trifluorometoxi)fenil]propano-1,2-diol. MS (ES) *m/z* 352 ($[M+H]^+$).

[0293] Etapa 6: De forma análoga al EJEMPLO 1, etapa 2, se prepara 2-hidroxi-3-indol-1-il-3-(4-trifluorometoxi-fenil)-propil éster de ácido (2RS,3RS)-tolueno-4-sulfónico de (2RS1SRS)-S-(1H-indol-1-il)-3-[4-(trifluorometoxi)fenil]propano-1,2-diol. MS (ES) *m/z* 506 ($[M+H]^+$).

[0294] Etapa 7: De forma análoga al EJEMPLO 33, etapa 6 (Método B), se prepara clorhidrato de (1RS,2SR)-1-(1H-indol-1-il)-3-(metilamino)-1-[4-(trifluorometoxi)fenil]propan-2-ol de 2-hidroxi-3-indol-1-il-3-(4-trifluorometoxi-fenil)-propil éster de

ácido (2RS,3RS)-tolueno-4-sulfónico y metilamina (2 N en metanol). MS (ES) *m/z* 365 ($[M+H]^+$).

[0295] EJEMPLO 40: clorhidrato de (1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-[4-(trifluorometoxi)fenil]propan-2-ol



[0296] Etapa 1: clorhidrato de (1RS,2Sr)-1-(1H-indol-1-il)-3-(metilamino)-1-[4-(trifluorometoxi)fenil]propan-2-ol (EJEMPLO 39, etapa 7) se disuelve en metanol. La solución resultante se inyecta (35 mg/inyección) en el instrumento de Cromatografía de Fluido Supercrítico, y los enantiómeros resueltos en Línea de base se recolectan utilizando las condiciones descritas adelante. Se determina la pureza enantiomérica de cada enantiómero bajo las mismas condiciones de Cromatografía de Fluido Supercrítico utilizando una columna Chiralpak AD-H 5u, 250 mm x 4.6 mm ID a un índice de flujo de 2.0 mL/minutos utilizando Cromatografía de Fluido Supercrítico Analítico (Berger Instruments, Inc. Newark, DE USA).

Instrumento SFC: Berger MultiGram Prep SFC (Berger Instruments, Inc. Newark, DE 19702.

Columna: Chiralpak AD-H; 5u; 250mm L x 20mm ID (Chiral Technologies, Inc, Exton, PA, USA)

Temperatura de columna: 35° C

Modificador SFC: 25% de MeOH w/ 1.0%DEA/75% CO_2

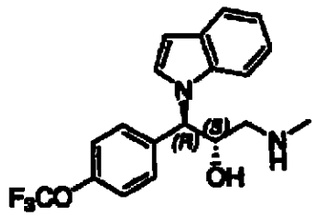
Índice de flujo: 50 mL/min

Presión de Salida: 100 bar

Detector: UV a 220 nm

[0297] se aísla clorhidrato de (1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-[4-(trifluorometoxi)fenil]propan-2-ol como pico 1 después de neutralización y conversión de la base libre a la sal de clorhidrato de acuerdo con el EJEMPLO 33, etapa 6. MS (ES) *m/z* 365 ($[M+H]^+$); 98.4% ee.

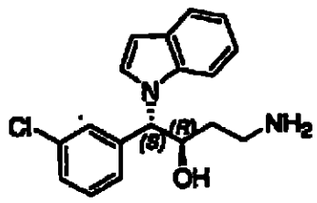
[0298] EJEMPLO 41: clorhidrato de (1R,2S)-1-(1H-indol-1-il)-3-(metilamino)-1-[4-(trifluorometoxi)fenil]propan-2-ol



[0299] Se aísla clorhidrato de (1R,2S)-1-(1H-indol-1-il)-3-(metilamino)-1-[4-(trifluorometoxi)fenil]propan-2-ol (EJEMPLO 40, etapa 1) como pico 2 después de neutralización y conversión de la

base libre a la sal de clorhidrato de acuerdo con el EJEMPLO 33, etapa 6. MS (ES) *m/z* 365 ($[M+H]^+$); >99.9% ee.

[0300] EJEMPLO 42: clorhidrato de (1S,2R)-4-amino-1-(3-clorofenil)-1-(1H-indol-1-il)butan-2-ol



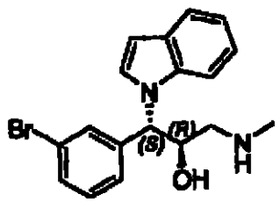
[0301] Etapa 1: Una mezcla de 3-(3-clorofenil)-2-hidroxi-3-indol-1-il-propil éster de ácido (2S,3S)-tolueno-4-sulfónico (EJEMPLO 33, etapa 5, 1.9 g, 4.2 mmol) y cianuro de sodio (0.23 g, 4.7 mmol) en dimetilsulfóxido seco (20 mL) se calienta a 100° C (microondas). Después de 15 minutos, la solución fría se retira en acetato de etilo (200 mL), se lava con agua (3 x 200 mL), se seca (sulfato de sodio) y se concentra bajo vacío para dar una espuma ámbar (1.3 g) este se preadsorbe sobre gel de sílice (3 g). Cromatografía de columna flash (sílice 30 g, 10%, 20%, 40% de acetato de etilo/hexanos) suministra (3R,4S)-4-(3-clorofenil)-3-hidroxi-4-indol-1-il-butironitrilo (1.2 g, 92%) como una espuma ámbar. MS (ES) *m/z* 311($[M+H]^+$).

[0302] Etapa 2: Una solución de (3R,4S)-4-(3-clorofenil)-3-hidroxi-4-indol-1-il-butironitrilo (1.2 g, 3.9 mmol) en tetrahidrofurano (20 mL) se trata con solución de tetrahidrofurano-borano (1.0 M, 20 mL, 20 mmol) a 23° C. Después

420

de 16 horas, la reacción se apaga con metanol (7 mL) a 23° C y la solución se concentra bajo vacío para dar una espuma blanca que se particiona entre dietil éter (200 mL) y una solución de hidróxido de sodio acuosa 1N (200 mL). La fase orgánica se separa, se lava con solución salina (200 mL), se seca (sulfato de sodio) y se concentra bajo vacío para dar una espuma amarilla (1.2 g)que se purifica por vía de Cromatografía Biotage [Columna de sílice AnaLogix, 2 x 40 g en series, diclorometano a 5% de amonio saturado en metanol/diclorometano] para suministrar (1S,2R)-4-amino-1-(3-clorofenil)-1-(1H-indol-1-il)butan-2-ol (0.43 g, 36%). La base libre se convierte a la sal de clorhidrato como se describe en el EJEMPLO 33, etapa 6, para suministrar clorhidrato de (1S,2R)-4-amino-1-(3-clorofenil)-1-(1H-indol-1-il)butan-2-ol (0.47 g, 34%) como una espuma. MS (ES) *m/z* 315 ($[M+H]^+$).

[0303] EJEMPLO 43: clorhidrato de (1S,2R)-1-(3-bromofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol



[0304] Etapa 1: De forma análoga al EJEMPLO 33, etapa 1, se prepara etil éster de ácido (2E)-3-(3-bromofenil)-acrílico de dietil etoxicarbonilmetilfosfonato y 3-bromobenzaldehído. MS (ES) *m/z* 255 ($[M+H]^+$).

[0305] Etapa 2: De forma análoga al EJEMPLO 33, etapa 2, se prepara (2E)-3-(3-bromofenil)prop-2-en-1-ol de etil éster de ácido (2E)-3-(3-bromofenil)-acrílico. MS (ES) *m/z* 195 ([M+H-H_2O]$^+$).

[0306] Etapa 3: De forma análoga al EJEMPLO 117, etapa 4, se prepara [(2R,3R)-3-(3-bromofenil)oxiran-2-il]metanol de (2E)-3-(3-brorriofenil)prop-2-en-1-ol. MS (ES) *m/z* 211([M+H-H_2O]$^+$); 95% ee.

[0307] Etapa 4: De forma análoga al EJEMPLO 33, etapa 4a (Método B), se prepara (2S,3S)-3-(3-bromofenil)-3-(2,3-dihidro-1H-indol-1-il)propano-1,2-diol de indolina y [(2R,3R)-3-(3-bromofenil)oxiran-2-il]metanol. MS (ES) *m/z* 348 ([M+H]$^+$).

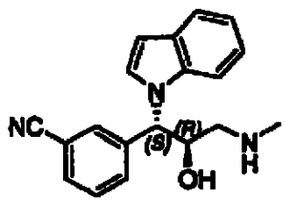
[0308] Etapa 5: De forma análoga al EJEMPLO 33, etapa 4b (Método B), se prepara (2S,3S)-3-(3-bromofenil)-3-(1H-indol-1-il)propano-1,2-diol de (2S,3S)-3-(3-bromofenil)-3-(2,3-dihidro-1H-indol-1-il)propano-1,2-diol. MS (ES) *m/z* 346 ([M+H]$^+$).

[0309] Etapa 6: De forma análoga al EJEMPLO 1, etapa 2, se prepara 3-(3-bromofenil)-2-hidroxi-3-indol-1-il-propil éster de ácido (2S,3S)-tolueno-4-sulfónico de (2S,3S)-3-(3-bromofenil)-3-(1H-indol-1-il)propano-1,2-diol. MS (ES) *m/z* 500 ([M+H]$^+$).

[0310] Etapa 7: De forma análoga al EJEMPLO 33, etapa 6 se prepara clorhidrato de (1S,2R)-1-(3-bromofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol de 3-(3-bromofenil)-2-hidroxi-3-

indol-1-il-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina (solución en metanol 2N). MS (ES) *m/z* 359 ($[M+H]^+$).

[0311] EJEMPLO 44: clorhidrato de 3-[(1S,2R)-2-hidroxi-1-(1H-indol-1-il)-3-(metilamino)propil]benzonitrilo



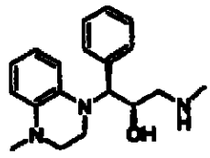
[0312] Una mezcla de (2S,3S)-3-(3-bromofenil)-(1H-indol-1-il)propano-1,2-diol (EJEMPLO 43, etapa 5, 1.4 g, 4.0 mmol), cianuro de zinc (II) (4.7 g, 40 mmol) y tetraquis(trifenilfosfina)paladio (0) (0.46 g, 0.40 mmol) en 1-metil-2-pirrolidona desgasificada (25 mL) se calienta a 150° C en un frasco sellado. Después de 3.5 horas, la mezcla fría café se diluye con acetato de etilo (250 mL) y se filtra a través de Celita. El filtrado se lava con agua (5 x 250 mL) y solución salina (1 x 250 mL), se seca (sulfato de sodio), y se concentra bajo vacío para dar un aceite ámbar (1.6 g) este se preadsorbe sobre gel de sílice (6 g). Cromatografía de columna flash (sílice 70 g, 30%, 60% de acetato de etilo/hexanos) suministra 3-[(1S,2S)-2,3-dihidroxi-1-(1H-indol-1-il)propil]benzonitrilo (1.0 g, 83%) como una espuma amarilla pálida. MS (ES) *m/z* 293 ($[M+H]^+$).

[0313] De forma análoga al EJEMPLO 1, etapa 2, se prepara 3-(3-ciano-fenil)-2-hidroxi-3-indol-1-il-propil éster de ácido

(2S,3S)-tolueno-4-sulfónico de 3-[(1S,2S)-2,3-dihidroxi-1-(1H-indol-1-il)propil]benzonitrilo. MS (ES) *m/z* 447 ($[M+H]^+$).

[0314] De forma análoga al EJEMPLO 33, etapa 6 se prepara clorhidrato de 3-[(1S,2R)-2-hidroxi-1-(1H-indol-1-il)-3-(metilamino)propil]benzonitrilo de 3-(3-ciano-fenil)-2-hidroxi-3-indol-1-il-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina (solución en metanol 2N). MS (ESI) *m/z* 306 ($[M+H]^+$).

[0315] EJEMPLO 45: clorhidrato de (1SR,2RS)-3-(metilamino)-1-(4-metil-3,4-dihidroquinoxalin-1(2H)-il)-1-fenilpropan-2-ol



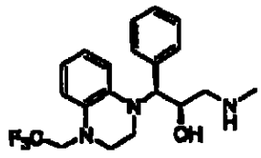
[0316] Etapa 1: De forma análoga al EJEMPLO 53, etapa 3, se prepara 3-fenilglicidol de alcohol cinamilo como un sólido blanco. MS (ES) *m/z* 151.1 ($[M+H]^+$).

[0317] Etapa 2: De forma análoga al EJEMPLO 47, etapa 4, se prepara (2SR,3SR)-3-(4-metil-3,4-dihidroquinoxalin-1(2H)-il)-3-fenilpropano-1,2-diol de 1-metil-1,2,3,4-tetrahidroquinoxalina[1] y 3-fenilglicidol como un aceite viscoso incoloro. MS (ES) *m/z* 299.0 ($[M+H]^+$); HRMS: calculado para $C_{18}H_{22}N_2O_2$ + H+, 299.1760; encontrado (ESI, $[M+H]^+$), 299.1739.

[1] Cavagnol, J. C; Wiselogle, F. Y. J. *Am. Chem. Soc.* 1947, 69, 795-799

[0318] Etapa 3: De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1SR,2RS)-3-(metilamino)-1-(4-metil-3,4-dihidroquinoxalin-1(2H)-il)-1-fenilpropan-2-ol de (2SR,3SR)-3-(4-metil-3,4-dihidroquinoxalin-1(2H)-il)-3-fenilpropano-1,2-diol como un polvo blanco. MS (ES) *m/z* 312.0 ($[M+H]^+$); HRMS: calculado para $C_{19}H_{25}N_3O$ + H+, 312.2076; encontrado (ESI, $[M+H]^+$), 312.2065.

[0319] EJEMPLO 46: clorhidrato de (1SR,2RS)-3-(metilamino)-1-fenil-1-[4-(2,2,2-trifluoroetil)-3,4-dihidroquinoxalin-1(2H)-il]propan-2-ol



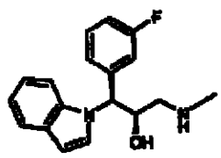
[0320] Se obtiene el compuesto 1-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidroquinoxalina como un subproducto de polvo blanco de la reacción de reducción de quinoxalina a 1,2,3,4-tetrahidroquinoxalina[2] utilizando borohidruro de sodio en ácido trifluoroacético. MS (ES) *m/z* 217.1 ($[M+H]^+$).

[0321] De forma análoga al EJEMPLO 47, etapa 4, se prepara (2SR,3SR)-3-(4-(2,2,2-trifluoroetil)-3,4-dihidroquinoxalin-1(2H)-il)-3-fenilpropano-1,2-diol de 1-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidroquinoxalina y 3-fenilglicidol (EJEMPLO 45, etapa 1) como un aceite viscoso incoloro.

[2] Bugle, R. C; Osteryoung, R. A. J. Org. Chem. 1979, 44, 1719-1720.

[0322] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1SR,2RS)-3-(metilamino)-1-fenil-1-[4-(2,2,2-trifluoroetil)-3,4-dihidroquinoxalin-1(2H)-il]propan-2-ol de (2SR,3SR)-3-(4-(2,2,2-trifluoroetil)-3,4-dihidroquinoxalin-1(2H)-il)-3-fenilpropano-1,2-diol como un polvo blanco. MS (ES) *m/z* 380.0 ($[M+H]^+$); HRMS: calculado para $C_{20}H_{24}F_3N_3O$ + H^+, 380.1950; encontrado (ESI, $[M+H]^+$) 380.1934.

[0323] EJEMPLO 47: clorhidrato de (1S,2R)-1-(3-fluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol



[0324] Etapa 1: A una mezcla de ácido *trans*-3-fluorocinámico (50 g, 300 mmol) y yodometano (300 mL) en acetona (1 L) se agrega enn forma de porción carbonato de cesio (147 g, 450 mmol, 1.5 equivalente), y la mezcla se calienta a 65° C durante 1.5 horas en un vaso de reacción sellado. Luego de enfriar a temperatura ambiente, la mezcla de reacción se diluye con acetato de etilo (1 L), se filtra a través de almohadilla de gel de sílice, y se concentra para dar 47.33 g (87%) de metil éster de ácido *trans*-3-fluorocinámico como un aceite incoloro. MS (ES) *m/z* 180.0 (M+).

[0325] Etapa 2: A una solución de metil éster de ácido *trans*-3-fluorocinámico (69.61 g, 386 mmol) en diclorometano seco (1 L) a -78° C bajo nitrógeno se agrega en forma de gota hidruro de diisobutilaluminio (neto, 172 mL, 965 mmol, 2.5 equivalente) por

vía de un túnel de adición. Después la adición se completa, la mezcla de reacción se le permite calentarse a -30° C y se agita adicionalmente durante 1 hora, entonces se apaga con metanol (150 mL). Luego de calentar a temperatura ambiente, la mezcla de reacción se trata con solución de tartrato de potasio/sodio saturada acuosa (300 mL) y se agita durante 30 minutos. La capa orgánica se lava secuencialmente con solución de ácido clorhídrico acuosa 1 N, solución de bicarbonato de sodio acuosa saturada, solución salina, y se seca (sulfato de sodio anhidro). El aceite crudo se purifica por cromatografía de gel de sílice (0-50% de acetato de etilo:hexano) para dar 53.07 g (90%) de alcohol *trans*-3-fluorocinamilo como un aceite incoloro. MS (ES) *m/z* 152.1 (M^+).

[0326] Etapa 3: Un frasco de fondo redondo 2L, de 3 cuellos secado al horno ajustado con dos túneles adicionales de secado al horno y un septo de caucho se carga con D-tartrato de diisopropilo (11.55 g, 49.3 mmol, 0.30 equivalente), tamices moleculares activados para pulverizado a 4 Å (40 g) y diclorometano seco (800 mL) bajo nitrógeno. Después se enfría a -25° C, a la mezcla de reacción se agrega isopropóxido de titanio (9.6 mL, 33 mmol, 0.20 equivalente) lentamente por vía de una jeringa hipodérmica. Después de agitación durante 10 minutos, se agrega hidroperóxido de t-butilo anhidro (5.5 M en decano, 75.0 mL, 413 mmol, 2.5 equivalente) a una velocidad por vía de un túnel de adición. La mezcla resultante se agita a -25° C durante 30 minutos. Se agrega alcohol *trans*-3-fluorocinamilo (25.0 g, 164 mmol) en diclorometano seco (50 mL) en forma de gota por vía de un túnel de adición mientras que se mantiene la temperatura a -

25° C. Después de la adición, la mezcla de reacción se agita a -25° C durante 1 hora y a -20° C durante otras 3 horas. Después la reacción se completa, solución de hidróxido de sodio acuosa fría (30%, 20 mL) saturada con cloruro de sodio se agrega lentamente a -20° C. Después se agrega dietil éter (150 mL), el baño frío se remueve y se le permite a la mezcla calentarse a ~ 5° C y se agita durante 1 hora. Se agrega sulfato de magnesio (anhidro, 50 g) y la mezcla se agita durante 20 minutos, entonces se filtra a través de almohadilla de gel de sílice, y se lava con éter (300 mL). El filtrado se concentra y se utiliza tolueno para remover azeotrópicamente el exceso de hidroperóxido de t-butilo. El aceite residual se purifica sobre gel de sílice (0-30% de acetato de etilo:hexano) para dar 24.80 g (90%) de [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol como un aceite incoloro, viscoso. Por ciento ee: > 96.5%. MS (ESI) *m/z* 169.1 ($[M+H]^+$).

[0327] Etapa 4: Una mezcla de indolina (1.42 g, 11.89 mmol) y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (2.0 g, 11.89 mmol) se calienta a 125° C durante 5 horas en un frasco de reacción sellado. Luego de enfriarse, el producto crudo se disuelve en acetato de etilo, se absorbe sobre Fluorocilo, y se purifica por Cromatografía Biotage (FlasH40i, sílice, 0-55% de EtOAc/hexano) para dar 2.55 g (75%) de (2S,3S)-3-(2,3-dihidro-1H-indol-1-il)-3-(3-fluorofenil)propano-1,2-diol como un aceite incoloro. MS (ESI) *m/z* 288.1 ($[M+H]^+$).

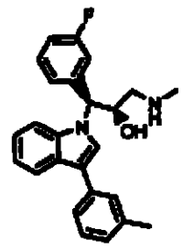
[0328] Etapa 5: Una mezcla de (2S,3S)-3-(2,3-dihidro-1H-indol-1-il)-3-(3-fluorofenil)propano-1,2-diol (2.00 g, 6.96 mmol) y dióxido de manganeso activado (20.0 g, 230 mmol) en diclorometano

(30 mL) se agita a 20° C durante 3 horas. La mezcla se diluye con acetato de etilo (15 mL), se filtra a través de almohadilla de gel de sílice, y se concentra. El producto crudo se purifica por Cromatografía Biotage (FlasH40i, sílice, 0-70% de EtOAc/hexano) para dar 1.40 g (71%) de (2S,3S)-3-(3-fluorofenil)-3-(1H-indol-1-il)propano-1,2-diol como un aceite incoloro. MS (ESI) *m/z* 286.0 ($[M+H]^+$). HRMS: calculado para $C_{17}H_{16}FNO_2 + H^+$, 286.1238; encontrado (ESI, $[M+H]^+$), 286.1239.

[0329] Etapa 6: A una solución de (2S,3S)-3-(2,3-dihidro-1H-indol-1-il)-3-(3-fluorofenil)propano-1,2-diol (452 mg, 1.586 mmol) en diclorometano (3 mL) bajo nitrógeno se agrega trietilamina (1.1 mL, 7.93 mmol). La mezcla se enfría a 0° C, y se agrega cloruro de *para*-toluenosulfonilo (423 mg, 2.22 mmol) en forma de porción. La mezcla de reacción se agita a 0° C durante 1 hora y se almacena a 0° C durante toda la noche. Se agrega metilamina en etanol absoluto (8 M, 5 mL, 40 mmol) y la mezcla de reacción se sella, y se agita durante toda la noche mientras que se calienta a temperatura ambiente. Se remueven todos los volátiles bajo presión reducida. El residuo de aceite se disuelve en diclorometano (20 mL), se lava sobre carbonato de sodio acuoso (5 mL), se seca (sulfato de sodio anhidro), y se concentra. La purificación por Cromatografía Biotage (FlasH12i, sílice, 0-15% de MeOH/diclorometano/0.5% de trietilamina) da (1S,2R)-1-(3-fluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol, que se disuelve en diclorometano (5 mL) y se trata con una solución etérea 1 M de ácido clorhídrico (1.9 mL, 1.9 mmol). Se agrega a la solución resultante hexano hasta que se forma el polvo blanco, que se recolecta, se lava con hexano, y se seca en vacío para

proporcionar 209 mg (44%) de clorhidrato de (1S,2R)-1-(3-fluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol como un polvo blanco. MS (ES) *m/z* 299.0 ($[M+H]^+$); HRMS: calculado para $C_{18}H_{19}FN_2O$ + H^+, 299.1554; encontrado (ESI, $[M+H]^+$), 299.1553.

[0330] EJEMPLO 48: clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-[3-(3-metilfenil)-1H-indol-1-il]propan-2-ol



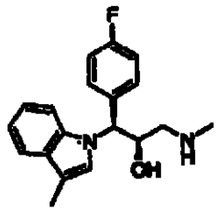
[0331] De forma análoga al EJEMPLO 114, etapa 2, se prepara (2S,3S)-3-(3-fluorofenil)-3-{3-[3-metilfenil]-1H-indol-1-il}propano-1,2-diol de (2S,3S)-3-(3-fluorofenil)-3-(3-yodo-1H-indol-1-il)propano-1,2-diol (EJEMPLO 114, etapa 1) y ácido 3-metilbencenoborónico.

[0332] De forma análoga al EJEMPLO 1, etapa 2, se prepara 3-(3-fluorofenil)-3-[3-(2-clorofenil)-indol-1-il]-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico de (2S,3S)-3-(3-fluorofenil)-3-{3-[3-metilfenil]-1H-indol-1-il}propano-1,2-diol.

[0333] De forma análoga al EJEMPLO 5, se prepara clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-[3-(3-metilfenil)-1H-indol-1-il]propan-2-ol de 3-(3-fluoro-fenil)-3-[3-(3-metilfenil)-indol-1-il]-2-hidroxi-propil éster de ácido (2S,3S)-

tolueno-4-sulfónico y metilamina (solución en metanol 2N). MS (ESI) *m/z* 389.2; HRMS: calculado para $C_{25}H_{25}FN_2O$ + H+, 389.20237; encontrado (ESI, $[M+H]^+$), 389.2005.

[0334] EJEMPLO 49: clorhidrato de (1S,2R)-1-(4-fluorofenil)-3-(metilamino)-1-(3-metil-1H-indol-1-il)propan-2-ol



[0335] Etapa 1: De forma análoga al EJEMPLO 47, etapa 3, [(2R,3R)-3-(4-fluorofenil)oxiran-2-il]metanol se prepara de alcohol *trans*-4-fluorocinamilo[3] como un sólido blanco. Por ciento ee: > 97%. MS (ES) *m/z* 167.0 ([M-H]").

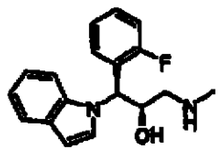
[0336] Etapa 2: De forma análoga al EJEMPLO 117, etapa 5, se prepara (2S,3S)-3-(4-fluorofenil)-3-(3-metil-1H-indol-1-il)propano-1,2-diol de 3-metilindol y [(2R,3R)-3-(4-fluorofenil)oxiran-2-il]metanol como un aceite incoloro, viscoso. MS (ES) *m/z* 300.1 ($[M+H]^+$); HRMS: calculado para $C_{18}H_{18}FNO_2$ + H^+, 300.1400; encontrado (ESI, $[M+H]^+$), 300.1406.

[0337] Etapa 3: De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(4-fluorofenil)-3-(metilamino)-1-(3-metil-1H-indol-1-il)propan-2-ol de (2S,3S)-3-(4-fluorofenil)-3-(3-metil-1H-indol-1-il)propano-1,2-diol como un

[3] Takeuchi, R.; Ue, N.; Tanabe, K.; Yamashita, K.; Shiga, N. *J. Am. Chem. Soc*, 2001, 123, 9525-9534.

polvo blanco. MS (ESI) *m/z* 313.1 ($[M+H]^+$); HRMS: calculado para $C_{19}H_{21}FN_2O + H^+$, 313.1711; encontrado (ESI, $[M+H]^+$), 313.1727.

[0338] EJEMPLO 50: clorhidrato de (1S,2R)-1-(2-fluorofenil)-1,(1H-indol-1-il)-3-(metilamino)propan-2-ol



[0339] De forma análoga al EJEMPLO 47, etapa 1, metil éster ácido *trans*-2-fluorocinnámico se prepara de ácido *trans*-2-fluorocinnámico como un sólido blanco. MS *m/z* 180.9 ($[M+H]^+$).

[0340] De forma análoga al EJEMPLO 47, etapa 2, se prepara alcohol *trans*-2-fluorocinamilo de metil éster de ácido *trans*-2-fluorocinnámico como un aceite incoloro. MS (ESI) *m/z* 152.0 $[M]^+$; HRMS: calculado para C_9H_9FO, 152.0637; encontrado (ESI, $[M]^+$), 152.0640.

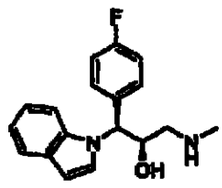
[0341] De forma análoga al EJEMPLO 47, etapas 3, se prepara [(2R,3R)-3-(2-fluorofenil)oxiran-2-il]metanol de alcohol *trans*-2-.fluorocinamilo como un sólido blanco. MS *m/z* 169.0 ($[M+H]^+$).

[0342] De forma análoga al EJEMPLO 117, etapa 5, se prepara (2S,3S)-3-(2-fluorofenil)-3-(1H-indol-1-il)propano-1,2-diol de indol y [(2R,3R)-3-(2-fluorofenil)oxiran-2-il]metanol como un aceite incoloro, viscoso. MS (ES) *m/z* 286.2 ($[M+H]^+$); HRMS:

calculado para $C_{17}H_{16}FNO_2$ + H^+, 286.1238; encontrado (ESI, $[M+H]^+$), 286.1231.

[0343] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(2-fluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol de (2S,3S)-3-(2-fluorofenil)-3-(3-metil-1H-indol-1-il)propano-1,2-diol como un polvo blanco. MS (ES) *m/z* 299.1 ($[M+H]^+$); HRMS: calculado para $C_{18}H_{19}FN_2O$ + H^+, 299.1554; encontrado (ESI, $[M+H]^+$), 299.1557.

[0344] EJEMPLO 51: clorhidrato de (1S,2R)-1-(4-fluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol

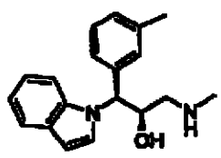


[0345] De forma análoga al EJEMPLO 117, etapa 5, se prepara (2S,3S)-3-(4-fluorofenil)-3-(1H-indol-1-il)propano-1,2-diol de indol y [3-(4-fluorofenil)oxiran-2-il]metanol (EJEMPLO 49, etapa 1) como un aceite incoloro, viscoso. MS (ES) *m/z* 286.1 ($[M+H]^+$); HRMS: calculado para $C_{17}H_{16}FNO_2$ + H^+, 286.1238; encontrado (ESI, $[M+H]^+$), 286.1230.

[0346] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(4-fluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol de (2S,3S)-3-(4-fluorofenil)-3-(1H-indol-

1-il)propano-1,2-diol como un polvo blanco. MS (ES) *m/z* 299.1 ($[M+H]^+$).

[0347] EJEMPLO 52: clorhidrato de (1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-(3-metilfenil)propan-2-ol



[0348] De forma análoga al EJEMPLO 47, etapa 1, se prepara metil éster de ácido *trans*-3-metilcinnámico de ácido *trans*-3-metilcinnámico.

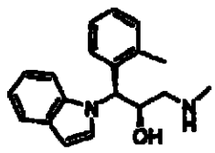
[0349] De forma análoga al EJEMPLO 47, etapa 2, se prepara alcohol *trans*-3-metilcinamilo de metil éster de ácido *trans*-3-metilcinnámico como un aceite incoloro.

[0350] De forma análoga al EJEMPLO 47, etapas 3, se prepara [(2R,3R)-3-(3-metilfenil)oxiran-2-il]metanol de alcohol *trans*-3-metilcinamilo como un aceite incoloro. HRMS: calculado para $C_{10}H_{12}O_2 + H^+$, 165.0916; encontrado (ESI, $[M+H]^+$), 165.0926.

[0351] De forma análoga al EJEMPLO 117, etapa 5, se prepara (2S,3S)-3-(1H-indol-1-il)-3-(3-metilfenil)propano-1,2-diol de indol y [(2R,3R)-3-(3-metilfenil)oxiran-2-il]metanol como un líquido incoloro, viscoso. MS (ES) *m/z* 282.1 ($[M+H]^+$); HRMS: calculado para $C_{18}H_{19}NO_2 + H^+$, 282.1494; encontrado (ESI, $[M+H]^+$), 282.1488.

[0352] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(1H-indol-1-il)-3-metilamino)-1-(3-metilfenil)propan-2-ol de (2S,3S)-3-(1H-indol-1-il)-3-(3-metilfenil)propano-1,2-diol como un polvo blanco. MS (ES) *m/z* 295.3 ($[M+H]^+$); HRMS: calculado para $C_{19}H_{20}N_2O$ + H^+, 295.1805; encontrado (ESI, $[M+H]^+$), 295.1799.

[0353] EJEMPLO 53: clorhidrato de (1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-(2-metilfenil)propan-2-ol



[0354] Etapa 1: De forma análoga al EJEMPLO 47, etapa 1, metil éster de ácido *trans*-2-metilcinnámico se prepara de ácido *trans*-2-metilcinnámico.

[0355] Etapa 2: De forma análoga al EJEMPLO 47, etapa 2, se prepara alcohol *trans*-2-metilcinamilo de metil éster de ácido *trans*-2-metilcinnámico como un aceite incoloro. MS (ES) *m/z* 146.9 ($[M-H]^-$).

[0356] Etapa 3: A una solución de alcohol *trans*-2-metilcinamilo (1.50 g, 10.14 mmol) en diclorometano (30 mL) se agrega carbonato de sodio (1.50 g, 14.19 mmol). La mezcla se enfría a 10° C y se agrega ácido peracético (32 p %, 2.56 mL, 12.16 mmol) en forma de gota por vía de un túnel de adición. La mezcla de reacción se

agita durante 3 horas mientras que se calienta a temperatura ambiente, y se apaga con solución de sulfito de sodio acuosa saturada (15 mL) lentamente. Se agrega más diclorometano (30 mL) y la mezcla se extrae. La capa orgánica se lava con solución salina, se seca (sulfato de sodio anhidro), y se concentra. El residuo de aceite se purifica por cromatografía de gel de sílice (10-30% de EtOAc/hexano) para dar 920 mg (55%) de 3-(2-metilfenil)glicidol como un aceite incoloro. HRMS: calculado para $C_{10}H_{12}O_2 + H^+$, 165.0916; encontrado (ESI, $[M+H]^+$), 165.0936.

[0357] Etapa 4: De forma análoga al EJEMPLO 117, etapa 5, se prepara (2SR,3SR)-3-(1H-indol-1-il)-3-(2-metilfenil)propano-1,2-diol de indol y 3-(2-metilfenil)glicidol como un líquido incoloro, viscoso. MS (ES) *m/z* 282.2 ($[M+H]^+$); HRMS: calculado para $C_{18}H_{19}NO_2 + H^+$, 282.1494; encontrado (ESI, $[M+H]^+$), 282.1499.

[0358] Etapa 5: De forma análoga al EJEMPLO 47, etapa 6, se prepara (1SR,2RS)-1-(1H-indol-1-il)-3-(metilamino)-1-(2-metilfenil)propan-2-ol de (2SR,3SR)-3-(1H-indol-1-il)-3-(2-metilfenil)propano-1,2-diol como un aceite.

[0359] Etapa 6: Se disuelve (1SR,2RS)1-(1H-indol-1-il)-3-(metilamino)-1-(2-metilfenil)propan-2-ol racémico en etanol (20 mg/mL). La solución resultante se almacena inyectando en el instrumento de Cromatografía de Fluido Supercrítico a 1 mL de incrementos. Se recolectan los enantiómeros resueltos en Línea de base, que utilizan las condiciones descritas adelante. Se determina la pureza enantiomérica de cada enantiómero bajo condiciones similares de Cromatografía de Fluido Supercrítico

utilizando una columna Chiralcel OJ-H 5u, 250 mm L x 4.6 mm ID a un índice de flujo de 1.2 mL/minutos utilizando Cromatografía de Fluido Supercrítico Analítico (Berger Instruments, Inc. Newark, DE USA).

Instrumento SFC: Berger MultiGram Prep SFC (Berger Instruments, Inc. Newark, DE 19702.

Columna: Chiralcel OJ-H; 5u; 250mm L x 20mm ID (Chiral Technologies, Inc., Exton, PA, USA)

Temperatura de columna: 35° C

Modificador SFC: 15% de MeOH con 1.0% DEA / 85% CO_2

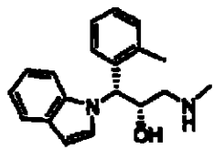
Índice de flujo: 50 mL/min

Presión de Salida: 100 bar

Detector: UV a 220 nm

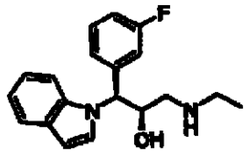
[0360] Etapa 7: De forma análoga al EJEMPLO 144, etapa 2, clorhidrato de (1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-(2-metilfenil)propan-2-ol se prepara como un sólido blanco, de (1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-(2-metilfenil)propan-2-ol, que se aísla como pico 1 de la separación quiral (etapa 6). Pureza quiral: 100%. MS (ESI) *m/z* 295.3 ($[M+H]^+$); HRMS: calculado para $C_{19}H_{22}N_2O + H^+$, 295.1805; encontrado (ESI, $[M+H]^+$), 295.1795.

[0361] EJEMPLO 54: clorhidrato de (1R,2S)-1-(1H-indol-1-il)-3-(metilamino)-1-(2-metilfenil)propan-2-ol



[0362] De forma análoga al EJEMPLO 53, etapa 7, clorhidrato de (1R,2S)-1-(1H-indol-1-il)-3-(metilamino)-1-(2-metilfenil)propan-2-ol se prepara como un sólido blanco, de (1R,2S)-1-(1H-indol-1-il)-3-(metilamino)-1-(2-metilfenil)propan-2-ol, que se aísla como pico 2 de la separación quiral (EJEMPLO 53, etapa 6). Pureza quiral: 100%. MS (ESI) *m/z* 295.3 ($[M+H]^+$); HRMS: calculado para $C_{19}H_{22}N_2O$ + H^+, 295.1805; encontrado (ESI, $[M+H]^+$), 295.1805.

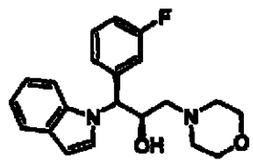
[0363] EJEMPLO 55: clorhidrato de (1S,2R)-3-(etilamino)-1-(3-fluorofenil)-1-(1H-indol-1-il)propan-2-ol



[0364] Etapa 1: De forma análoga al EJEMPLO 1, etapa 2, se prepara 4-metilbencenosulfonato de (2S,3S)-3-(3-fluorofenil)-2-hidroxi-3-(1H-indol-1-il)propilo de (2S,3S)-3-(3-fluorofenil)-3-(1H-indol-1-il)propano-1,2-diol (EJEMPLO 47, etapa 5) como un sólido marfilo. HRMS: calculado para $C_{24}H_{22}FN_2O_4S$ + H^+, 440.1326; encontrado (ESI, $[M+H]^+$), 440.1345.

[0365] Etapa 2: 4-metilbencenosulfonato de (2S,3S)-3-(3-fluorofenil)-2-hidroxi-3-(1H-indol-1-il)propilo (200 mg, 0.456 mmol) se disuelve en una solución de etilamina en metanol (2.0 M, 10 mL) y se agita durante 12 horas en un vaso de reacción sellado. Se remueven todos los volátiles bajo presión reducida, y el residuo líquido se disuelve en diclorometano (15 mL), se lava con una solución acuosa saturada de carbonato de potasio, se seca (sulfato de sodio anhidro), y se concentra. La purificación del residuo líquido por Cromatografía Biotage (FlasH12i, sílice, 0-15% de MeOH/diclorometano/0.5% de trietilamina) da (1S,2R)-1-(3-fluorofenil)-1-(1H-indol-1-il)-3-(etilamino)propan-2-ol, que se utiliza para preparar clorhidrato de (1S,2R)-3-(etilamino)-1-(3-fluorofenil)-1-(1H-indol-1-il)propan-2-ol como un polvo blanco en una forma análoga al EJEMPLO 144, etapa 2. Producción: 99 mg (70%). MS (ES) *m/z* 313.1 ($[M+H]^+$); HRMS: calculado para $C_{19}H_{21}FN_2O$ + H^+, 313.1716; encontrado (ESI, $[M+H]^+$), 313.1716.

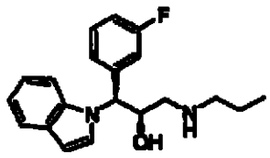
[0366] EJEMPLO 56: clorhidrato de (1S,2R)-1-(3-fluorofenil)-1-(1H-indol-1-il)-3-morfolin-4-ilpropan-2-ol



[0367] De forma análoga al EJEMPLO 55, etapa 2, se prepara clorhidrato de (1S,2R)-1-(3-fluorofenil)-1-(1H-indol-1-il)-3-morfolin-4-ilpropan-2-ol de morfolina y 4-metilbencenosulfonato de (2S,3S)-3-(3-fluorofenil)-2-hidroxi-3-(1H-indol-1-il)propilo (EJEMPLO 55, etapa 1) como un polvo blanco. MS (ES) *m/z* 355.1

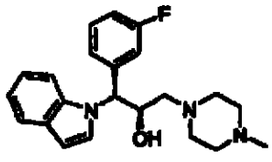
([M+H]$^+$); HRMS: calculado para $C_{2123}FN_2O_2$ + H^+, 355.1816; encontrado (ESI, [M+H]$^+$), 355.1822.

[0368] EJEMPLO 57: clorhidrato de (1S,2R)-1-(3-fluorofenil)-1-(1H-indol-1-il)-3-(propilamino)propan-2-ol



[0369] De forma análoga al EJEMPLO 55, etapa 2, se prepara clorhidrato de (1S,2R)-1-(3-fluorofenil)-1-(1H-indol-1-il)-3-(propilamino)propan-2-ol de propilamina y 4-metilbencenosulfonato de (2S,3S)-3-(3-fluorofenil)-2-hidroxi-3-(1H-indol-1-il)propilo (EJEMPLO 55, etapa 1) como un polvo blanco. MS (ES) *m/z* 327.1 ([M+H]$^+$); HRMS: calculado para $C_{2023}FN_2O$ + H^+, 327.1867; encontrado (ESI, [M+H]$^+$), 327.1873.

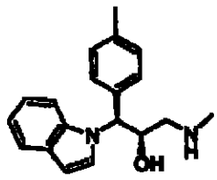
[0370] EJEMPLO 58: diclorhidrato de (1S,2R)-1-(3-fluorofenil)-1-(1H-indol-1-il)-3-(4-metilpiperazin-1-il)propan-2-ol



[0371] De forma análoga al EJEMPLO 55, etapa 2, se prepara diclorhidrato de (1S,2R)-1-(3-fluorofenil)-1-(1H-indol-1-il)-3-(4-metilpiperazin-1-il)propan-2-ol de 1-metilpiperazina y 4-metilbencenosulfonato de (2S,3S)-3-(3-fluorofenil)-2-hidroxi-3-

(1H-indol-1-il)propilo (EJEMPLO 55, etapa 1) como un polvo blanco. MS (ES) *m/z* 368.1 ($[M+H]^+$); HRMS: calculado para $C_{22}H_{26}FN_3O$ + H^+, 368.2133; encontrado (ESI, $[M+H]^+$), 368.2138.

[0372] EJEMPLO 59: clorhidrato de (1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-(4-metilfenil)propan-2-ol



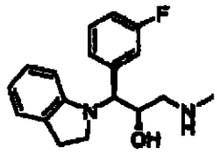
[0373] De forma análoga al EJEMPLO 47, etapas 3, se prepara [(2R,3R)-3-(4-metilfenil)oxiran-2-il]metanol de alcohol *trans*-4-metilcinamilo[3] como un aceite incoloro. MS (ES) *m/z* 165.1 ($[M+H]^+$); HRMS: calculado para $C_{10}H_{12}O_2$ + H^+, 165.0916; encontrado (ESI, $[M+H]^+$), 165.0937.

[0374] De forma análoga al EJEMPLO 117, etapa 5, se prepara (2S,3S)-3-(1H-indol-1-il)-3-(4-metilfenil)propano-1,2-diol de indol y [(2R,3R)-3-(4-metilfenil)oxiran-2-il]metanol como un líquido viscoso incoloro. MS (ES) *m/z* 282.1 ($[M+H]^+$); HRMS: calculado para $C_{18}H_{19}NO_2$ + H^+, 282.1494; encontrado (ESI, $[M+H]^+$), 282.1492.

[0375] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-(4-metilfenil)propan-2-ol de (2S,3S)-3-(1H-indol-1-il)-3-(4-metilfenil)propano-1,2-diol como un polvo blanco. MS (ES) *m/z*

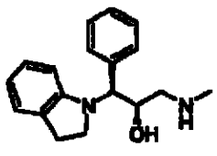
295.1 ([M+H]$^+$); HRMS: calculado para $C_{19}H_{22}N_2O$ + H^+, 295.1805; encontrado (ESI, [M+H]$^+$), 295.1810.

[0376] EJEMPLO 60: clorhidrato de (1S,2R)-1-(2,3-dihidro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol



[0377] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(2,3-dihidro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol de (2S,3S)-3-(2,3-dihidro-1H-indol-1-il)-3-(3-fluorofenil)propano-1,2-diol (EJEMPLO 47, etapa 4) como un sólido blanco. MS (ES) *m/z* 301.1 ([M+H]$^+$); HRMS: calculado para $C_{18}H_{21}FN_2O$ + H^+, 301.1711; encontrado (ESI, [M+H]$^+$), 301.1716.

[0378] EJEMPLO 61: clorhidrato de (1S,2R)-1-(2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol

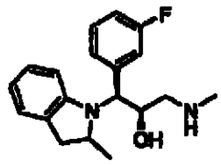


[0379] De forma análoga al EJEMPLO 47, etapa 4, se prepara (2S,3S)-3-(2,3-dihidro-1H-indol-1-il)-3-fenilpropano-1,2-diol de indolina y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un aceite incoloro, viscoso. MS (ES) *m/z* 270.2

([M+H]$^+$); HRMS: calculado para $C_{17}H_{20}NO_2$ + H^+, 270.1494; encontrado (ESI, [M+H]$^+$), 270.1493.

[0380] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol de (2S,3S)-3-(2,3-dihidro-1H-indol-1-il)-3-fenilpropano-1,2-diol como un sólido blanco. MS (ES) *m/z* 283.1 ([M+H]$^+$); HRMS: calculado para $C_{18}H_{21}N_2O$ + H^+, 283.1805; encontrado (ESI, [M+H]$^+$), 283.1810.

[0381] EJEMPLO 63: clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(2-metil-2,3-dihidro-1H-indol-1-il)propan-2-ol

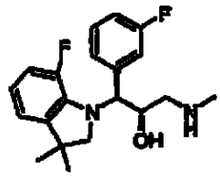


[0382] De forma análoga al EJEMPLO 47, etapa 4, se prepara (2S,3S)-3-(3-fluorofenil)-3-(2-metil-2,3-dihidro-1H-indol-1-il)propano-1,2-diol de 2-metilindolina y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3) como un aceite incoloro, viscoso. MS (ES) *m/z* 302.1 ([M+H]$^+$); HRMS: calculado para $C_{18}H_{20}FNO_2$ + H^+, 302.1551; encontrado (ESI, [M+H]$^+$), 302.1556.

[0383] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(2-metil-2,3-dihidro-1H-indol-1-il)propan-2-ol de (2S,3S)-3-(3-fluorofenil)-3-(2-metil-2,3-dihidro-1H-indol-1-il)propano-1,2-

diol como un sólido blanco. MS (ES) *m/z* 315.0 ($[M+H]^+$); HRMS: calculado para $C_{1923}FN_2O + H^+$, 315.1867; encontrado (ESI, $[M+H]^+$), 315.1850.

[0384] EJEMPLO 64: clorhidrato de (1S(2R)-1-(7-fluoro-3,3-dimetil-2,3-dihidro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol

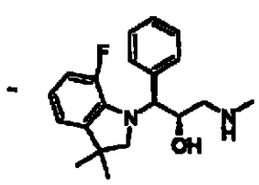


[0385] Etapa 1: Una mezcla de 7-fluoro-3,3-dimetiloxindol (EJEMPLO 99, etapa 5, 2.24 g 12.5 mmol) en tolueno (15 mL) bajo nitrógeno se calienta a 80° C. Se agrega Vitride (65% en peso en tolueno, 6 mL, 19.3 mmol) en forma de gota por vía de un túnel de adición. La solución resultante se agita a 80° C adicionalmente durante 1.5 horas, luego se enfría en un baño frío. Se agrega solución de hidróxido de sodio acuoso (1 N, 15 mL) lentamente para apagar la reacción. Se agrega agua (15 mL) y la mezcla de reacción se extrae con acetato de etilo (20 mL). La capa orgánica se lava con solución salina, se seca (sulfato de sodio anhidro), se filtra a través de almohadilla de gel de sílice, y se concentra bajo presión reducida para proporcionar 1.68 g (82%) de 7-fluoro-3,3-dimetilindolina como un aceite incoloro. MS (ES) *m/z* 166.1 ($[M+H]^+$); HRMS: calculado para $C_{10}H_{12}FN + H^+$, 166.1032; encontrado (ESI, $[M+H]^+$), 166.1040.

[0386] Etapa 2: De forma análoga al EJEMPLO 47, etapa 4, se prepara (2S,3S)-3-(7-fluoro-3,3-dimetil-2,3-dihidro-1H-indol-1-il)-3-(3-fluorofenil)propano-1,2-diol de 7-fluoro-3,3-dimetilindolina y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3) como un aceite incoloro, viscoso. MS (ES) *m/z* 334.1 ($[M+H]^+$); HRMS: calculado para $C_{19}H_{21}F_2NO_2$ + H^+, 334.1613; encontrado (ESI, $[M+H]^+$), 334.1616.

[0387] Etapa 3: De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(7-fluoro-3,3-dimetil-2,3-dihidro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol de (2S,3S)-3-(7-fluoro-3,3-dimetil-2,3-dihidro-1H-indol-1-il)-3-(3-fluorofenil)propano-1,2-diol como un sólido blanco. MS (ES) *m/z* 347 ($[M+H]^+$); HRMS: calculado para $C_{20}H_{24}F_2N_2O$ + H^+, 347.1929; encontrado (ESI, $[M+H]^+$), 347.1935.

[0388] EJEMPLO 65: clorhidrato de (1S,2R)-1-(7-fluoro-3,3-dimetil-2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol

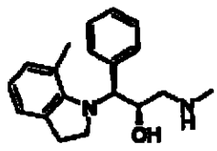


[0389] De forma análoga al EJEMPLO 47, etapa 4, se prepara (2S,3S)-3-(7-fluoro-3,3-dimetil-2,3-dihidro-1H-inclol-1-il)-3-fenilpropano-1,2-diol de 7-fluoro-3,3-dimetilindolina (EJEMPLO 64, etapa 1) y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un aceite incoloro, viscoso. MS (ES) *m/z* 316.1

([M+H]$^+$); HRMS: calculado para $C_{19}H_{22}FNO_2$ + H^+, 316.1707; encontrado (ESI, [M+H]$^+$), 316.1690.

[0390] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(7-fluoro-3,3-dimetil-2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol de (2S,3S)-3-(7-fluoro-3,3-dimetil-2,3-dihidro-1H-indol-1-il)-3-fenilpropano-1,2-diol como un sólido blanco. HRMS: calculado para $C_{20}H_{25}FN_2O$ + H^+, 329.2029; encontrado (ESI, [M+H]$^+$), 329.2041.

[0391] EJEMPLO 66: clorhidrato de (1S,2R)-3-(metilamino)-1-(7-metil-2,3-dihidro-1H-indol-1-il)-1-fenilpropan-2-ol



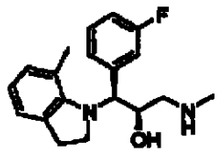
[0392] De forma análoga al EJEMPLO 47, etapa 4, se prepara (2S,3S)-3-(7-metil-2,3-dihidro-1H-indol-1-il)-3-fenilpropano-1,2-diol de 7-metilindolina[4] y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un aceite incoloro, viscoso. MS (ES) *m/z* 284.2 ([M+H]$^+$); HRMS: calculado para $C_{18}H_{21}NO_2$ + H^+, 284.1651; encontrado (ESI, [M+H]$^+$), 284.1650.

[0393] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-3-(metilamino)-1-(7-metil-2,3-dihidro-1H-indol-1-il)-1-fenilpropan-2-ol de (2S,3S)-3-(7-metil-2,3-dihidro-1H-indol-1-il)-3-fenilpropano-1,2-diol como un sólido blanco. MS

[4] Gribble, G. W.; Hoffman, J. H. *Synthesis* 1977, 12, 859-860.

(ES) *m/z* 297.0 ($[M+H]^+$); HRMS: calculado para $C_{19}H_{24}N_2O$ + H^+, 297.1961; encontrado (ESI, $[M+H]^+$), 297.1957.

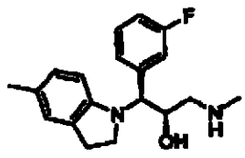
[0394] EJEMPLO 67: clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(7-metil-2,3-dihidro-1H-indol-1-il)propan-2-ol



[0395] De forma análoga al EJEMPLO 47, etapa 4, se prepara (2S,3S)-3-(3-fluorofenil)-3-(7-metil-2,3-dihidro-1H-indol-1-il)propano-1,2-diol de 7-metilindolina[4] y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3) como un aceite incoloro, viscoso. MS (ES) *m/z* 302.1 ($[M+H]^+$); HRMS: calculado para $C_{18}H_{20}FNO_2$ + H^+, 302.1551; encontrado (ESI, [M+Hf), 302.1551.

[0396] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(7-metil-2,3-dihidro-1H-indol-1-il)propan-2-ol de (2S,3S)-3-(3-fluorofenil)-3-(7-metil-2,3-dihidro-1H-indol-1-il)propano-1,2-diol como un sólido blanco. MS (ES) *m/z* 315.0 ($[M+H]^+$); HRMS: calculado para $C_{1923}FN_2O$ + H^+, 315.1873; encontrado (ESI, $[M+H]^+$), 315.1862.

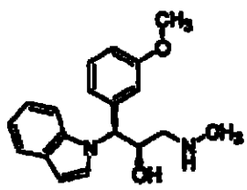
[0397] EJEMPLO 68: clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(5-metil-2,3-dihidro-1H-indol-1-il)propan-2-ol



[0398] De forma análoga al EJEMPLO 47, etapa 4, se prepara (2S,3S)-3-(3-fluorofenil)-3-(5-metil-2,3-dihidro-1H-indol-1-il)propano-1,2-diol de 5-metilindolina y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3) como un aceite incoloro, viscoso. MS (ES) *m/z* 302.1 ($[M+H]^+$); HRMS: calculado para $C_{18}H_{20}FNO_2$, 302.1551; encontrado (ESI, $[M+H]^+$), 302.1551.

[0399] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(5-metil-2,3-dihidro-1H-indol-1-il)propan-2-ol de (2S,3S)-3-(3-fluorofenil)-3-(5-metil-2,3-dihidro-1H-indol-1-il)propano-1,2-diol como un sólido blanco. MS (ES) *m/z* 315.0 ($[M+H]^+$); HRMS: calculado para $C_{1923}FN_2O + H^+$, 315.1873; encontrado (ESI, $[M+H]^+$), 315.1896.

[0400] EJEMPLO 69: clorhidrato de (1S,2R)-1-(1H-indol-1-il)-1-(3-metoxifenil)-3-(metilamino)propan-2-ol



[0401] De forma análoga al EJEMPLO 33, etapa 1, se prepara etil (2E)-3-(3-metoxifenil)acrilato de 3-metoxibenzaldehído y

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dietil etoxicarbonilmetilfosfonato. ^{1}H RMN (DMSO): □1.26 (t, 3H, OCH_2CH_3), □3.79 (s, 3H, OCH_3), □4.19 (q, 2H, OCH_2CH_3), □6.66 (d, 1 H, CH=CHC(O)), □6.99 (m, 1 H1 CH=CH(CO)), □7.31(m, 3H, ArH) y □7.62 (d, 1 H, ArH).

[0402] De forma análoga al EJEMPLO 33, etapa 2, se prepara (2E)-3-(3-metoxifenil)prop-2-en-1-ol de etil (2E)-3-(3-metoxifenil)acrilato. MS (ES) *m/z* 147.2 ([M + H-H_2O]$^+$).

[0403] De forma análoga al EJEMPLO 117, etapa 4, se prepara [(2R,3R)-3-(3-metoxifenil)oxiran-2-il]metanol de (2E)-3-(3-metoxifenil)prop-2-en-1-ol. MS (ES) *m/z* 222 ([M+H + CH_3CN]+); 93.2% ee.

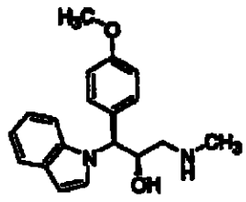
[0404] De forma análoga al EJEMPLO 117, etapa 5, (2S,3S)-3-(1H-indol-1-il)-3-(3-metoxifenil)propano-1,2-diol se prepara de 1 H-indol y [(2R,3R)-3-(3-metoxifenil)oxiran-2-il]metanol. MS (ES) *m/z* 298.2 ([M+H]$^+$).

[0405] De forma análoga al EJEMPLO 1, etapa 2, se prepara 2-hidroxi-3-(1H-indol-1-il)-3-(3-metoxifenil)-propil éster de ácido (2S,3S)-tolueno-4-sulfónico de (2S,3S)-3-(1H-indol-1-il)-3-(3-metoxifenil)propano-1,2-diol. MS (ES) *m/z* 452.2 ([M+H]$^+$).

[0406] De forma análoga al EJEMPLO 33, etapa 6 se prepara clorhidrato de (1S,2R)-1-(1H-indol-1-il)-1-(3-metoxifenil)-3-(metilamino)propan-2-ol de 2-hidroxi-3-(1H-indol-1-il)-3-(3-metoxifenil)-propil éster de ácido (2S,3S)-tolueno-4-sulfónico.

MS (ES) *m/z* 311.3 ($[M+H]^+$); HRMS: calculado para $C_{19}H_{22}N_2O_2 + H^+$, 311.17540; encontrado (ESI, $[M+H]^+$), 311.1758.

[0407] EJEMPLO 70: clorhidrato de (1SR,2RS)-1-(1H-indol-1-il)-1-(4-metoxifenil)-3-(metilamino)propan-2-ol



[0408] Una mezcla de metil *trans*-3-(4-metoxifenil)glicidato (2.11 g, 10.1 mmol) e indolina (1.14 mL, 10.1 mmol) se calientan a 135° C en un tubo sellado durante 16 horas. La mezcla de reacción fría entonces se purifica directamente por cromatografía flash (sílice, 20%, 30% de acetato de etilo/hexano) para proporcionar 2.94 g (89%) de (2SR,3SR)-3-(2,3-dihidro-1H-indol-1-il)-2-hidroxi-3-(4-metoxifenil) propanoato metilo como un sólido amarillo. MS (ES) *m/z* 328.2 ($[M+H]^+$); HRMS: calculado para $C_{19}H_{21}NO_4 + H^+$, 328.15434; encontrado (ESI, $[M+H]^+$), 328.1536.

[0409] A una solución de (2SR,3SR)-3-(2,3-dihidro-1H-indol-1-il)-2-hidroxi-3-(4-metoxifenil)propanoato de metilo (2.63 g, 8.0 mmol) en tolueno anhidro (50 mL) a 0° C bajo nitrógeno se agrega una solución de 2,3-dicloro-5,6-diciano-1,4-benzoquinona (1.87 g, 8.2 mmol) en tolueno anhidro (50 mL) durante 5 minutos. La mezcla de reacción se agita 0° C a temperatura ambiente durante 1.5 horas entonces se apaga por la adición de 7% p/v de solución acuosa de carbonato de sodio (100 mL). La mezcla bifásica

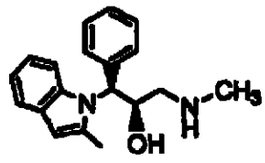
resultante se agita vigorosamente durante 5 minutos entonces se particiona entre acetato de etilo (300 mL) y 7% p/v de carbonato de sodio acuoso (250 mL). La fase orgánica se separa, se lava con 7% p/v de solución acuosa de carbonato de sodio (3 x 250 mL), agua (250 mL) y solución salina saturada (250 mL), se seca sobre sulfato de magnesio anhidro, se filtra y se concentra bajo presión reducida para dar un sólido lila. La purificación por cromatografía flash (sílice, 20%, 30% de acetato de etilo/hexano) produce 2.5 g (96%) de (2SR,3SR)-2-hidroxi-3-(1H-indol-1-il)-3-(4-metoxifenil)propanoato de metilo como un sólido crema. MS (ES) *m/z* 326.3 ($[M+H]^+$); HRMS: calculado para $C_{19}H_{19}NO_4 + H^+$, 326.13869; encontrado (ESI, $[M+H]^+$), 326.1378.

[0410] Una solución de (2SR,3SR)-2-hidroxi-3-(1H-indol-1-il)-3-(4-metoxifenil)propanoato de metilo (2.43 g, 7.5 mmol) en solución de metilamina (33% p. en etanol absoluto, 40 mL) se calienta a 75° C en un tubo sellado durante 1 hora. La mezcla de reacción fría entonces se concentra bajo presión reducida para proporcionar un jarabe amarillo. La purificación por cristalización de 80% de cloroformo/hexano (50 mL) produce 1.93 g (80%) de (2SR,3SR)-2-hidroxi-3-(1H-indol-1-il)-3-(4-metoxifenil)-N-metilpropanamida como un sólido blanco cristalino. MS (ES) m/z 323.2 ($[M-H]^-$); HRMS: calculado para $C_{19}H_{20}N_2O_3 + H^+$, 325.15467; encontrado (ESI, $[M+H]^+$), 325.1562.

[0411] A una solución de (2SR,3SR)-2-hidroxi-3-(1H-indol-1-il)-3-(4-metoxifenil)-N-metilpropanamida (900 mg, 2.8 mmol) en tetrahidrofurano anhidro (50 mL) a temperatura ambiente bajo nitrógeno se agrega en forma de gota una solución de complejo

tetrahidrofurano-borano (1.0 M en tetrahidrofurano, 13.9 mL, 13.9 mmol) y la mezcla se calienta hasta reflujo durante 3 horas. La mezcla de reacción luego se enfría a 50° C, se agrega metanol (20 mL), y la mezcla se agita a 50° C durante 1 hora. La mezcla de reacción fría entonces se concentra bajo presión reducida para proporcionar un sólido blanco. La purificación por cromatografía flash (sílice, 15% metanol/diclorometano) produce 272 mg (32%). de (1SR,2RS)-1-(1H-indol-1-il)-1-(4-metoxifenil)-3-(metilamino)propan-2-ol como un jarabe amarillo. El producto se disuelve en etanol absoluto (4 mL), se agrega una solución de cloruro de hidrógeno (4 M en 1,4-dioxano, 0.28 mL, 1.12 mmol), la solución se agita durante 10 minutos luego se concentran bajo presión reducida para proporcionar una espuma blanca. Cristalización de 1: 1: 1 v/v etanol absoluto: dietil éter: hexano (12 mL) a -35° C produce 81.3 mg (8%) de clorhidrato de (1SR,2RS)-1-(1H-indol-1-il)-1-(4-metoxifenil)-3-(metilamino)propan-2-ol como un sólido blanco higroscópico. MS (ES) *m/z* 311.3 ($[M+H]^+$); HRMS: calculado para $C_{19}H_{22}N_2O_2 + H^+$, 311.17540; encontrado (ESI, $[M+H]^+$), 311.176.

[0412] EJEMPLO 71: clorhidrato de (1RS,2SR)-3-(metilamino)-1-(2-metil-1H-indol-1-il)-1-fenilpropan-2-ol



[0413] Etapa 1: Una mezcla de hidruro de sodio (60% en aceite mineral, 0.40 g, 10 mmol) y (5 mL) se agita durante 15 minutos

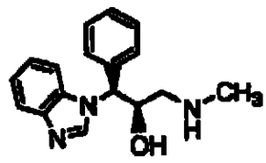
bajo nitrógeno a temperatura ambiente. Entonces se agrega 2-metilindol (1.31 g, 10 mmol) en cloruro de metileno (2 mL) y la mezcla se agita adicionalmente durante 30 minutos, a temperatura ambiente. Una solución premezclada de isopropóxido de titanio (3.55 mL, 12 mmol) y *trans*-3-fenilglicidol (1.5g, 10 mmol) en cloruro de metileno (2 mL) se agrega, y la mezcla de reacción se agita a temperatura ambiente durante 15 horas hasta que no permanece epóxido como se determina por tlc. La mezcla se filtra a través de almohadilla de Celita, y el filtrado entonces se trata con una solución de ácido clorhídrico 2 N acuosa (50 mL) con agitación durante 30 minutos. La capa orgánica se separa y la capa acuosa se extrae con cloruro de metileno varias veces. Los extractos combinados se lavan con agua, se secan sobre sulfato de sodio anhidro, se filtran, y se concentran en vacío. El producto crudo se purifica por vía de Biotage Horizon (Flash 40 M, sílice, gradiente de 10% de acetato de etilo/hexano a 65% de acetato de etilo/hexano) para proporcionar (2RS,3RS)-3-(2-metil-indol-1-il)-3-fenil-propano-1,2-diol como un sólido blanco. MS (ESI) *m/z* 282 ($[M+H]^+$).

[0414] De forma análoga al EJEMPLO 1, etapa 2 se prepara 3-(2-metil-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2RS,3RS)-tolueno-4-sulfónico de (2RS,3RS)-3-(2-metil-indol-1-il)-3-fenil-propano-1,2-diol como un aceite. MS (ESI) *m/z* 436 ($[M+H]^+$).

[0415] De forma análoga al EJEMPLO 5, se prepara clorhidrato de (1RS,2SR)-3-metilamino)-1-(2-metil-1H-indol-1-il)-1-fenilpropan-2-ol de 3-(2-metil-indol-1-il)-2-hidroxi-3-fenil-

propil éster de ácido (2RS,3RS)-tolueno-4-sulfónico y metilamina (solución en metanol 2N) como un sólido ámbar. MS (ES) *m/z* 295.0; HRMS: calculado para C19H22N2O + H^+, 295.18049; encontrado (ESI, $[M+H]^+$), 295.1818.

[0416] EJEMPLO 72: clorhidrato de (1RS,2SR)-1-(1H-benzimidazol-1-il)-3-(metilamino)-1-fenil propan-2-ol



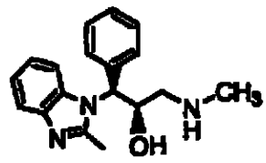
[0417] De forma análoga al EJEMPLO 17, etapa se prepara 1(2RS,3RS)-3-(1H-benzimidazol-1-il)-3-fenil-propano-1,2-diol de benzimidazol y *trans*-3-fenilglicidol como un sólido aceitoso. MS (ESI) *m/z* 269 ($[M+H]^+$).

[0418] De forma análoga al EJEMPLO 1, etapa 2 se prepara 3-benzoimidazol-1-il-2-hidroxi-3-fenil-propil éster de ácido (2RS,3RS)-tolueno-4-sulfónico de (2RS,3RS)-1-(1H-benzimidazol-1-il)-3-fenil-propano-1,2-diol como un sólido blanco. MS (ESI) *m/z* 423 ($[M+H]^+$).

[0419] De forma análoga al EJEMPLO 5, se prepara clorhidrato de (1RS,2SR)-1-(1H-bencimidazo-1-il)-3-(metilamino)-1-fenilpropan-2-ol de 3-benzoimidazol-1-il-2-hidroxi-3-fenil-propil éster de ácido (2RS,3RS)-tolueno-4-sulfónico y metilamina (solución en metanol 2N) como un sólido blanco. MS (ES) *m/z*

282.1; HRMS: calculado para C17H19N3O + H^+, 282.16009; encontrado (ESI, $[M+H]^+$), 282.1617.

[0420] EJEMPLO 73: clorhidrato de (1RS,2SR)-3-(metilamino)-1-(2-metil-1H-benzimidazol-1-il)-1-fenilpropan-2-ol

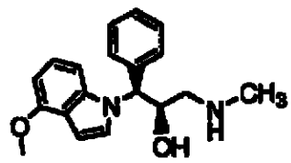


[0421] De forma análoga al EJEMPLO 17, etapa 1 (2RS,3RS)-3-(2-metil-1H-benzimidazol-1-il)-3-fenil-propano-1,2-diol se prepara de 2-metilbenzimidazol y *trans*-3-fenilglicidol como un sólido amarillo. MS (ESI) *m/z* 283 ($[M+H]^+$).

[0422] De forma análoga al EJEMPLO 1, etapa 2 se prepara 2-hidroxi-3-(2-metil-benzoimidazol-1-il)-3-fenil-propil éster de ácido (2RS,3RS)-tolueno-4-sulfónico de (2RS,3RS)-3-(2-metil-1H-benzimidazol-1-il)-3-fenil-propano-1,2-diol como un sólido blanco. MS (ESI) *m/z* 437 ($[M+H]^+$).

[0423] De forma análoga al EJEMPLO 5, se prepara clorhidrato de (1RS,2SR)-1-(2-metil-1H-bencimidazo-1-il)-3-(metilamino)-1-fenilpropan-2-ol de 2-hidroxi-3-(2-metil-benzoimidazol-1-il)-3-fenil-propil éster de ácido (2RS,3RS)-tolueno-4-sulfónico y metilamina como un sólido blanco. MS (ES) *m/z* 296.1; SHRMS: calculado para C18H21N3O + H^+, 296.17574; encontrado (ESI, $[M+H]^+$), 296.1752.

[0424] EJEMPLO 74: clorhidrato de (1RS,2SR)-1-(4-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenil propan-2-ol

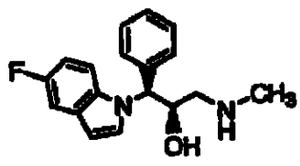


[0425] De forma análoga al EJEMPLO 17, etapa 1 (2RS,3RS)-3-(4-metoxi-1H-indol-1-il)-3-fenil-propano-1,2-diol se prepara de 4-metoxiindol y *trans*-3-fenilglicidol como un aceite. MS (ESI) *m/z* 298 ($[M+H]^+$).

[0426] De forma análoga al EJEMPLO 1, etapa 2 se prepara 2-hidroxi-3-(4-metoxi-indol-1-il)-3-fenil-propil éster de ácido (2RS,3RS)-tolueno-4-sulfónico de (2RS,3RS)-3-(4-metoxi-1H-indol-1-il)-3-fenil-propano-1,2-diol como un sólido blanco. MS (ESI) *m/z* 452 ($[M+H]^+$).

[0427] De forma análoga al EJEMPLO 5, se prepara clorhidrato de (1RS,2SR)-3-(4-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol de 2-hidroxi-3-(4-metoxi-indol-1-il)-3-fenil-propil éster de ácido (2RS,3RS)-tolueno-4-sulfónico y metilamina como un sólido blanco. MS (ESI) *m/z* 311; HRMS: calculado para C19H22N2O2 + H^+, 311.17540; encontrado (ESI, $[M+H]^+$), 311.1772.

[0428] EJEMPLO 75: clorhidrato de (1S,2R)-1-(5-fluoro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol

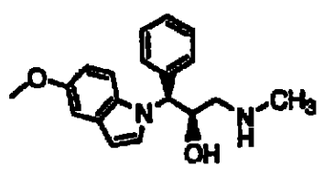


[0429] De forma análoga al EJEMPLO 17, etapa 1 (2S,3S)-3-(5-fluoro-1H-indol-1-il)-3-fenil-propano-1,2-diol se prepara de 5-fluoroindol y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un aceite. MS (ESI) *m/z* 286 ($[M+H]^+$).

[0430] De forma análoga al EJEMPLO 1, etapa 2 se prepara 3-(5-fluoro-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S,3S)-tolueno-4-sulfónico de (2S,3S)-3-(5-fluoro-1H-indol-1-il)-3-fenil-propano-1,2-diol como un aceite. MS (ESI) *m/z* 438 ($[M+H]^+$).

[0431] De forma análoga al EJEMPLO 5, se prepara clorhidrato de (1S,2R)-1-(5-fluoro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol de 3-(5-fluoro-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina como un sólido blanco. MS (ES) *m/z* 299.1; HRMS: calculado para C18H19FN2O + H^+, 299.15542; encontrado (ESI, $[M+H]^+$), 299.1556.

[0432] EJEMPLO 76: clorhidrato de (1S,2R)-1-(5-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol

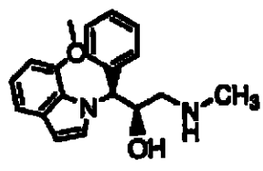


[0433] De forma análoga al EJEMPLO 17, etapa 1 (2S,3S)-3-(5-metoxi-1H-indol-1-il)-3-fenil-propano-1,2-diol se prepara de 5-metoxiindol y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un aceite. MS (ESI) *m/z* 298 ($[M+H]^+$).

[0434] De forma análoga al EJEMPLO 1, etapa 2 se prepara 3-(5-metoxi-indol-1-il)-2-hidroxi-3-fenil-propil éster de 4 ácido (2S,3S)-tolueno-4-sulfónico de (2S,3S)-3-(5-metoxi-1H-indol-1-il)-3-fenil-propano-1,2-diol como un aceite. MS (ESI) *m/z* 452 ($[M+H]^+$).

[0435] De forma análoga al EJEMPLO 5, se prepara clorhidrato de (1S,2R)-1-(5-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol de 3-(5-metoxi-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S.3S)-tolueno-4-sulfónico y metilamina como un sólido blanco. MS (ES) *m/z* 311.1; HRMS: calculado para $C19H22N2O_2 + H^+$, 311.17540; encontrado (ESI, $[M+H]^+$), 311.1745.

[0436] EJEMPLO 77: clorhidrato de (1S,2R)-1-(7-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol

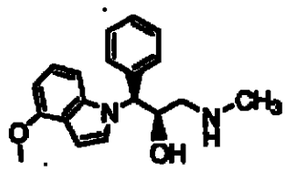


[0437] De forma análoga al EJEMPLO 17, etapa 1 (2S,3S)-3-(7-metoxi-1H-indol-1-il)-3-fenil-propano-1,2-diol se prepara de 7-metoxiindol y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un aceite. MS (ESI) *m/z* 298 ($[M+H]^+$).

[0438] De forma análoga al EJEMPLO 1, etapa 2 se prepara 3-(7-metoxi-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S,3S)-tolueno-4-sulfónico de (2S,3S)-3-(7-metoxi-1H-indol-1-il)-3-fenil-propano-1,2-diol como un aceite. MS (ESI) *m/z* 452 ($[M+H]^+$).

[0439] De forma análoga al EJEMPLO 5, clorhidrato de (1S,2R)-1-(7-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol se prepara de 3-(7-metoxi-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina como un sólido blanco. MS (ES) *m/z* 311.1; HRMS: calculado para $C_{19}H_{22}N_2O_2 + H^+$, 311.17540; encontrado (ESI, $[M+H]^+$), 311.1753.

[0440] EJEMPLO 78: clorhidrato de (1S,2R)-1-(4-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenil propan-2-ol



[0441] De forma análoga al EJEMPLO 17, etapa 1 (2S,3S)-3-(4-metoxi-1H-indol-1-il)-3-fenil-propano-1,2-diol se prepara de 4-metoxiindol y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un aceite. MS (ESI) *m/z* 298 ($[M+H]^+$).

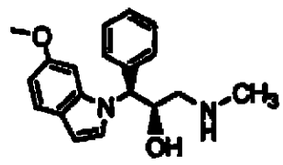
[0442] De forma análoga al EJEMPLO 1, etapa 2 se prepara 3-(4-metoxi-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S,3S)-tolueno-4-sulfónico de (2S,3S)-3-(4-metoxi-1H-indol-1-

459

il)-3-fenil-propano-1,2-diol como un aceite. MS (ESI) *m/z* 452 ($[M+H]^+$).

[0443] De forma análoga al EJEMPLO 5, se prepara clorhidrato de (1S,2R)-1-(4-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol de 3-(4-metoxi-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S.3S)-tolueno-4-sulfónico y metilamina como un sólido blanco. MS (ESI) *m/z* 311; HRMS: calculado para $C19H22N2O_2 + H^+$, 311.17540; encontrado (ESI, $[M+H]^+$), 311.175.

[0444] EJEMPLO 79: clorhidrato de (1S,2R)-1-(6-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenil propan-2-ol

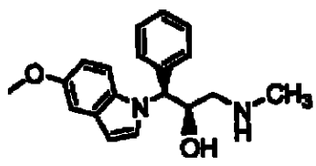


[0445] De forma análoga al EJEMPLO 17, etapa 1 (2S,3S)-3-(6-metoxi-1H-indol-1-il)-3-fenil-propano-1,2-diol se prepara de 6-metoxiindol y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un aceite. MS (ESI) *m/z* 298 ($[M+H]^+$).

[0446] De forma análoga al EJEMPLO 1, etapa 2 se prepara 3-(6-metoxi-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S,3S)-tolueno-4-sulfónico de (2S,3S)-3-(6-metoxi-1H-indol-1-il)-3-fenil-propano-1,2-diol como un aceite. MS (ESI) *m/z* 452 ($[M+H]^+$).

[0447] De forma análoga al EJEMPLO 5, se prepara clorhidrato de (1S,2R)-1-(6-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol de 3-(6-metoxi-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina como un sólido blanco. MS (ESI) *m/z* 311; HRMS: calculado para $C_{19}H_{22}N_2O_2 + H^+$, 311.17540; encontrado (ESI, $[M+H]^+$), 311.1757.

[0448] EJEMPLO 80: clorhidrato de (1RS,2SR)-1-(5-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenil propan-2-ol



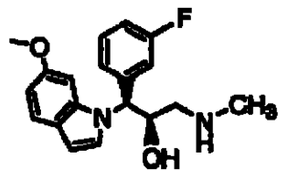
[0449] De forma análoga al EJEMPLO 17, etapa 1 (2RS,3RS)-3-(5-metoxi-1H-indol-1-il)-3-fenil-propano-1,2-diol se prepara de 5-metoxiindol y *trans*-3-fenilglicidol como un aceite. MS (ESI) *m/z* 298 ($[M+H]^+$).

[0450] De forma análoga al EJEMPLO 1, etapa 2 se prepara 3-(5-metoxi-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2RS.3RS)-tolueno-4-sulfónico de (2RS,3RS)-3-(5-metoxi-1H-indol-1-il)-3-fenil-propano-1,2-diol como un aceite. MS (ESI) *m/z* 452 ($[M+H]^+$).

[0451] De forma análoga al EJEMPLO 5, clorhidrato de (1RS,2SR)-1-(5-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol se prepara de 3-(5-metoxi-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2RS,3RS)-tolueno-4-sulfónico y

metilamina como un sólido blanco. MS (ESI) *m/z* 311; HRMS: calculado para $C_{19}H_{22}N_2O_2$ + H^+, 311.17540; encontrado (ESI, $[M+H]^+$), 311.1756.

[0452] EJEMPLO 81: clorhidrato de (1S,2R)-1-(3-fluorofenil)-1-(6-metoxi-1H-indol-1-il)-3-(metil-amino)propan-2-ol



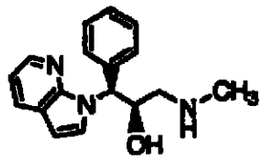
[0453] De forma análoga al EJEMPLO 17, etapa 1 (2S,3S)-3-(6-metoxi-1H-indol-1-il)-3-(3-fluorofenil)-propano-1,2-diol se prepara de 6-metoxiindol y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3) como un aceite. MS (ESI) *m/z* 316 ($[M+H]^+$).

[0454] De forma análoga al EJEMPLO 1, etapa 2 3-(6-metoxi-indol-1-il)-2-hidroxi-3-(3-fluorofenil)-propil éster de ácido (2S,3S)-tolueno-4-sulfónico se prepara de (2S,3S)-3-(6-metoxi-1H-indol-1-il)-3-(3-fluorofenil)-propano-1,2-diol como un aceite. MS (ESI) *m/z* 470 ($[M+H]^+$).

[0455] De forma análoga al EJEMPLO 5, se prepara clorhidrato de (1S,2R)-1-(3-fluorofenil)-1-(6-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol de 3-(6-metoxi-indol-1-il)-2-hidroxi-3-(3-fluorofenil)-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina como un sólido blanco. MS (ES) *m/z*

329.2; HRMS: calculado para $C_{19}H_{21}FN_2O_2$ + H^+, 329.16598; encontrado (ESI, $[M+H]^+$), 329.1663.

[0456] EJEMPLO 82: (1S,2R)-3-(metilamino)-1-fenil-1-(1H-pirrol[2,3-b]piridin-1-il)propan-2-ol



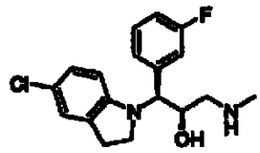
[0457] De forma análoga al EJEMPLO 17, etapa 1 (2S,3S)-3-fenil-3-(1H-pirrol[2,3-b]piridin-1-il)propano-1,2-diol se prepara de 7-azaindol y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un sólido blanco. MS (ES) *m/z* 269.2; HRMS: calculado para C16H16N2O2 + H^+, 269.12845; encontrado (ESI, $[M+H]^+$), 269.13.

[0458] De forma análoga al EJEMPLO 1, etapa 2 se prepara 2-hidroxi-3-fenil-3-pirrol[2,3-b]piridin-1-il-propil éster de ácido (2S,3S)-tolueno-4-sulfónico de (2S,3S)-3-fenil-3-(1H-pirrol[2,3-b]piridin-1-il)propano-1,2-diol como un aceite. MS (ESI) *m/z* 423 ($[M+H]^+$).

[0459] De forma análoga al EJEMPLO 5, (1S,2R)-3-(metilamino)-1-fenil-1-(1H-pirrol[2,3-b]piridin-1-il)propan-2-ol se prepara de 2-hidroxi-3-fenil-3-pirrol[2,3-b]piridin-1-il-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina como un sólido blanco. MS (ES) *m/z* 282.3; HRMS: calculado para C17H19N3O + H^+, 282.16009; encontrado (ESI, $[M+H]^+$), 282.16.

463

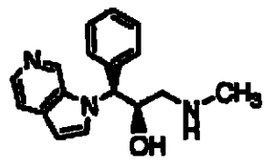
[0460] EJEMPLO 83: clorhidrato de (1S,2R)-1-(5-cloro-2,3-dihidro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol



[0461] De forma análoga al EJEMPLO 47, etapa 4, (2S,3S)-3-(5-cloro-2,3-dihidro-1H-indol-1-il)-3-(3-fluorofenil)propano-1,2-diol se prepara de 5-cloroindolina y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3) como un aceite incoloro, viscoso. MS (ES) *m/z* 322.1 ($[M+H]^+$); HRMS: calculado para C17H17CIFNO2 + H^+, 322.1005; encontrado (ESI, $[M+H]^+$), 322.1005.

[0462] De forma análoga al EJEMPLO 47, etapa 6, clorhidrato de (1S,2R)-1-(5-cloro-2,3-dihidro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol se prepara de (2S,3S)-3-(5-cloro-2,3-dihidro-1H-indol-1-il)-3-(3-fluorofenil)propano-1,2-diol como un sólido blanco. MS (ES) *m/z* 335.1 ($[M+H]^+$); HRMS: calculado para C18H20CIFN2O H^+ +, 335.1326; encontrado (ESI, $[M+H]^+$), 335.1349.

[0463] EJEMPLO 84: clorhidrato de (1S,2R)-3-metilamino-1-fenil-1-(1H-pirrol[2,3-c]piridin-1-il) propan-2-ol



[0464] De forma análoga al EJEMPLO 17, etapa 1 (2S,3S)-3-(7-cloro-1H-pirrol[2,3-c]piridin-1-il)-3-fenilpropano-1,2-diol se prepara de 7-cloro-1H-pirrol[2,3-c]piridina[5] y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un aceite. MS (ES) *m/z* 303 ($[M+H]^+$).

[0465] De forma análoga al EJEMPLO 1, etapa 2 se prepara 3-(7-cloro-pirrol[2,3-c]piridin-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S,3S)-tolueno-4-sulfónico de (2S,3S)-3-(7-cloro-pirrol[2,3-c]piridin-1-il)-3-fenil-propano-1,2-diol como un aceite. MS (ESI) *m/z* 457 ($[M+H]^+$).

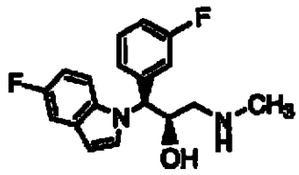
[0466] De forma análoga al EJEMPLO 5, (1S,2R)-1-(7-cloro-pirrol[2,3-c]piridina-1-il)-3-metilamino-1-fenil-propan-2-ol se prepara de 3-(7-cloro-pirrol[2,3-c]piridin-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S.3S)-tolueno-4-sulfónico y metilamina como un sólido blanco. MS (ES) *m/z* 316.1 ($[M+H]^+$).

[0467] Etapa 4: (1S,2R)-1-(7-cloro-pirrol[2,3-c]piridina-1-il)-3-metilamino-1-fenil-propan-2-ol (0.12 g, 0.38 mmol) se disuelve en etanol (20 mL) y se trata con 10% de paladio sobre carbón. La mezcla de reacción se coloca bajo 50 psi de hidrógeno sobre un agitador Parr durante 15 horas. La mezcla de reacción se filtra a través de almohadilla de Celita y el filtrado se concentra en

[5] Zhang, Z., et al., *J. Org. Chem.* 2002, 67, 2345-2347

vacío. El producto crudo se purifica por vía de Biotage Horizon (Flash 25 S, sílice, gradiente de 30% a 100% de 0.9% de hidróxido de amonio en 10% metanol-cloruro de metileno/cloruro de metileno) para dar un sólido blanco como la base libre del producto previsto. La base libre se disuelve en una cantidad mínima de etanol y se trata con una solución etérea 1 N de ácido clorhídrico hasta que la solución tenga un pH = 3 seguido por dietil éter. El producto luego se cristaliza por adición de una cantidad mínima de acetato de etilo para proporcionar el compuesto del título, clorhidrato de (1S,2R)-3-metilamino-1-fenil-1-(1H-pirrol[2,3-c]piridin-1-il)-propan-2-ol como un sólido blanco. MS (ES) *m/z* 282.1.

[0468] EJEMPLO 85: clorhidrato de (1S,2R)-1-(5-fluoro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metil-amino)propan-2-ol



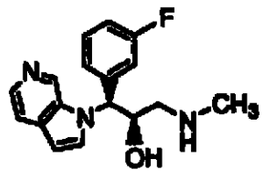
[0469] De forma análoga al EJEMPLO 17, etapa 1 (2S,3S)-3-(5-fluoro-1H-indol-1-il)-3-(3-fluorofenil)-propano-1,2-diol se prepara de 5-fluoroindol y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3) como un aceite. MS (ESI) *m/z* 304 ($[M+H]^+$).

[0470] De forma análoga al EJEMPLO 1, etapa 2 se prepara 3-(5-fluoro-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S,3S)-tolueno-4-sulfónico de (2S,3S)-3-(5-fluoro-1H-indol-1-

il)-3-(3-fluorofenil)-propano-1,2-diol como un aceite. MS (ESI) *m/z* 458 ($[M+H]^+$).

[0471] De forma análoga al EJEMPLO 5, se prepara clorhidrato de (1S,2R)-1-(5-fluoro-1H-indol-3-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol de 3-(5-fluoro-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina como un sólido ámbar claro. MS (ES) *m/z* 317.2; HRMS: calculado para C18H18F2N2O + H^+, 317.14599; encontrado (ESI, $[M+H]^+$), 317.1472.

[0472] EJEMPLO 86: diclorhidrato de (1S,2R)-3-metilamino-1-(3-fluorofenil)-1-(1H-pirrol[2,3-c]piridin-1-il) propan-2-ol



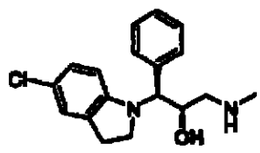
[0473] De forma análoga al EJEMPLO 17, etapa 1 (2S,3S)-3-(7-cloro-pirrol[2,3-c]piridin-1-il)-3-(3-fluorofenil)-propano-1,2-diol se prepara de 7-cloro-1H-pirrol[2,3-c]piridina[5] y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3) como un aceite. MS (ESI) *m/z* 321($[M+H]^+$).

[0474] De forma análoga al EJEMPLO 1, etapa 2 se prepara 3-(7-cloro-pirrol[2,3-c]piridin-1-il)-2-hidroxi-3-(3-fluorofenil)-propil éster de ácido (2S,3S)-tolueno-4-sulfónico de (2S,3S)-3-(7-cloro-pirrol[2,3-c]piridin-1-il)-3-(3-fluorofenil)-propano-1,2-diol como un aceite. MS (ESI) *m/z* 475 ($[M+H]^+$).

[0475] De forma análoga al EJEMPLO 5, (1S,2R)-1-(7-cloro-pirrol[2,3-c]piridina-1-il)-3-metilamino-1-(3-fluorofenil)-propan-2-ol se prepara de 3-(7-cloro-pirrol[2,3-c]piridin-1-il)-2-hidroxi-3-(3-fluorofenil)-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina como un sólido blanco. MS (ESI) *m/z* 334 ($[M+H]^+$).

[0476] De forma análoga al EJEMPLO 84, etapa 4 se prepara clorhidrato de (1S,2R)-3-metilamino-1-(3-fluorofenil)-1-(1H-pirrol[2,3-c]piridin-1-il)-propan-2-ol de (1S,2R)-1-(7-cloro-pirrol[2,3-c]piridina-1-il)-3-metilamino-1-(3-fluorofenil)-propan-2-ol como un sólido blanco. MS (ESI) *m/z* 282.1 ($[M+H]^+$).

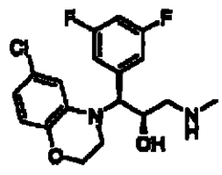
[0477] EJEMPLO 87: clorhidrato de (1S,2R)-1-(5-cloro-2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol



[0478] De forma análoga al EJEMPLO 47, etapa 4, (2S,3S)-3-(5-chloro-2,3-dihidro-1H-indol-1-il)-3-fenilpropano-1,2-diol se prepara de 5-cloroindolina y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un aceite incoloro, viscoso. MS (ES) *m/z* 304.1 ($[M+H]^+$); HRMS: calculado para $C_{17}H_{18}ClNO_2 + H^+$, 304.1099; encontrado (ESI, $[M+H]^+$), 304.1081.

[0479] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(5-cloro-2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol de 2S,3S)-3-(5-cloro-2,3-dihidro-1H-indol-1-il)-3-fenilpropano-1,2-diol como un polvo blanco. MS (ES) *m/z* 317.1 ($[M+H]^+$); HRMS: calculado para $C_{18}H_{21}ClN_2O + H^+$, 317.1421; encontrado (ESI, $[M+H]^+$), 317.1431.

[0480] EJEMPLO 88: clorhidrato de (1S,2R)-1-(6-cloro-2,3-dihidro-4H-1,4-benzoxazin-4-il)-1-(3,5-difluorofenil)-3-(metilamino)propan-2-ol

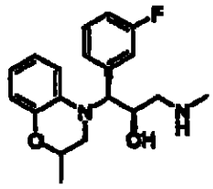


[0481] Etapa 1: De forma análoga al EJEMPLO 165, etapa 1, 6-cloro-3,4-dihidro-2H-1,4-benzoxazina se prepara de 6-cloro-2H-1,4-benzoxazin-3(4H)-ona como un sólido amarillo. MS (ES) *m/z* 170.0 ($[M+H]^+$); HRMS: calculado para $C_8H_8ClNO + H^+$, 170.0367; encontrado (ESI, $[M+H]^+$), 170.0365.

[0482] Etapa 2: De forma análoga al EJEMPLO 47, etapa 4, (2S,3S)-3-(6-cloro-2,3-dihidro-4H-1,4-benzoxazin-4-il)-3-(3,5-difluorofenil)propano-1,2-diol se prepara de 6-cloro-3,4-dihidro-2H-1,4-benzoxazina y [(2R,3R)-3-(3,5-difluorofenil)oxiran-2-il]metanol (EJEMPLO 157, etapa 3) como un líquido amarillento, viscoso. MS (ES) *m/z* 356.1 ($[M+H]^+$); HRMS: calculado para $C_{17}H_{16}ClF_2NO_3 + H^+$, 356.0860; encontrado (ESI, $[M+H]^+$), 356.0869.

[0483] Etapa 3: De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(6-cloro-2,3-dihidro-4H-1,4-benzoxazin-4-il)-1-(3,5-difluorofenil)-3-(metilamino)propan-2-ol de (2S,3S)-3-(6-cloro-2,3-dihidro-4H-1,4-benzoxazin-4-il)-3-(3,5-difluorofenil)propano-1,2-diol como un polvo blanco. MS (ES) *m/z* 369.1 ($[M+H]^+$); HRMS: calculado para $C_{18}H_{19}ClF_2N_2O_2$ + H^+, 369.1176; encontrado (ESI, $[M+H]^+$), 369.1178.

[0484] EJEMPLO 89: clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(2-metil-2,3-dihidro-4H-1,4-benzoxazin-4-il)propan-2-ol



[0485] De forma análoga al EJEMPLO 165, etapa 1, se prepara 2-metil-3,4-dihidro-2H-1,4-benzoxazina de 2-metil-2H-1,4-benzoxazin-3(4H)-ona[6] como un aceite café. MS (ES) *m/z* 149.9 ($[M+H]^+$).

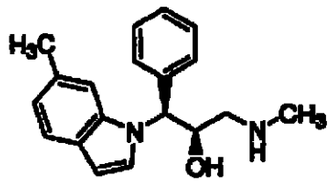
[0486] De forma análoga al EJEMPLO 47, etapa 4, (2S,3S)-3-(3-fluorofenil)-3-(2-metil-2,3-dihidro-4H-1,4-benzoxazin-4-il)propano-1,2-diol se prepara de 2-metil-3,4-dihidro-2H-1,4-benzoxazina y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3) como un líquido café, viscoso. MS (ES) *m/z*

[6] Wheeler, K. W. *J. Med. Pharm. Chem.* **1962**, 5, 1378-1383.

318.2 ([M+H]$^+$); HRMS: calculado para $C_{18}H_{20}FNO_3$ + H^+, 318.1500; encontrado (ESI, [M+H]$^+$), 318.1513.

[0487] De forma análoga al EJEMPLO 47, etapa 6, clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(2-metil-2,3-dihidro-4H-1,4-benzoxazin-4-il)propan-2-ol se prepara de (2S,3S)-3-(3-fluorofenil)-3-(2-metil-2,3-dihidro-4H-1,4-benzoxazin-4-il)propano-1,2-diol como un polvo blanco. MS (ES) *m/z* 331.0 ([M+H]$^+$); HRMS: calculado para $C_{1923}FN_2O_2$ + H^+, 331.1816; encontrado (ESI, [M+H]$^+$), 331.1804.

[0488] EJEMPLO 90: clorhidrato de (1S,2R)-3-(metilamino)-1-(6-metil-1H-indol-1-il)-1-fenilpropan-2-ol

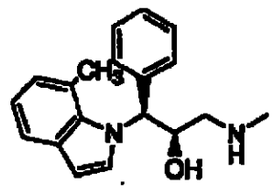


[0489] De forma análoga al EJEMPLO 117, etapa 5 se prepara (2S,3S)-3-(6-metil-1H-indol-1-il)-3-fenilpropano-1,2-diol de 6-metilindol y 2R,3R-(+)-3-fenilglicidol como un aceite. MS (ESI) *m/z* 282 ([M+H]$^+$).

[0490] De forma análoga al EJEMPLO 1, etapa 2 se prepara 3-(6-metil-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S,3S)-tolueno-4-sulfónico de (2S,3S)-3-(6-metil-1H-indol-1-il)-3-fenilpropano-1,2-diol MS (ESI) *m/z* 436 ([M+H]$^+$).

[0491] De forma análoga al EJEMPLO 5 se prepara clorhidrato de (1S,2R)-3-(metilamino)-1-(6-metil-1H-indol-1-il)-1-fenilpropan-2-ol de 3-(6-metil-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina (solución en metanol 2N); MS (ESI) *m/z* 295 ($[M+H]^+$); HRMS: calculado para C19H22N2O + H+, 295.18049; encontrado (ESI-FT/MS, [M+H]1+), 295.1809.

[0492] EJEMPLO 91: clorhidrato de (1S,2R)-3-(metilamino)-1-(7-metil-1H-indol-1-il)-1-fenilpropan-2-ol



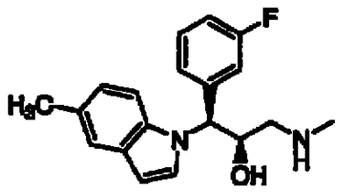
[0493] De forma análoga al EJEMPLO 117, etapa 5 se prepara (2S,3S)-3-(7-metil-1H-indol-1-il)-3-fenilpropano-1,2-diol de 7-metilindol y 2R,3R-(+)-3-fenilglicidol como un aceite. MS (ESI) *m/z* 282 ($[M+H]^+$).

[0494] De forma análoga al EJEMPLO 1, etapa 2 se prepara 3-(7-metil-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S,3S)-tolueno-4-sulfónico de (2S,3S)-3-(7-metil-1H-indol-1-il)-3-fenilpropano-1,2-diol MS (ESI) *m/z* 436 ($[M+H]^+$).

[0495] De forma análoga al EJEMPLO 5 clorhidrato de (1S,2R)-3-(metilamino)-1-(7-metil-1H-indol-1-il)-1-fenilpropan-2-ol se prepara de 3-(7-metil-indol-1-il)-2-hidroxi-3-fenil-propil éster

de ácido (2S,3S)-tolueno-4-sulfónico y metilamina (solución en metanol 2N); MS (ESI) *m/z* 295 ($[M+H]^+$); HRMS: calculado para C19H22N2O + H+, 295.18049; encontrado (ESI-FT/MS, [M+H]1+), 295.1809.

[0496] EJEMPLO 92: clorhidrato de ((1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(5-metil-1H-indol-1-il)propan-2-ol



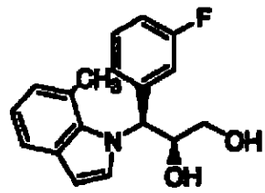
[0497] De forma análoga al EJEMPLO 117, etapa 5 se prepara (2S,3S)-3-(3-fluorofenil)-3-(5-metil-1H-indol-1-il)propano-1,2-diol de 5-metilindol y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (ver EJEMPLO 47, etapa 3) como un aceite. MS (ESI) *m/z* 300 ($[M+H]^+$).

[0498] De forma análoga al EJEMPLO 1, etapa 2 se prepara 3-(3-fluorofenil)-3-(5-metil-indol-1-il)-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico de (2S,3S)-3-(3-fluorofenil)-3-(5-metil-1H-indol-1-il)propano-1,2-diol MS (ESI) m/z 454 ($[M+H]^+$).

[0499] De forma análoga al EJEMPLO 5 clorhidrato de ((1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(5-metil-1H-indol-1-il)propan-2-ol se prepara de 3-(3-fluorofenil)-3-(5-metil-indol-1-il)-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y

metilamina (solución en metanol 2N); MS (ESI) *m/z* 313 ($[M+H]^+$); HRMS: calculado para C19H21FN2O + H+, 313.17107; encontrado (ESI-FTMS, [M+H]1+), 313.17163.

[0500] EJEMPLO 93: clorhidrato de ((1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(7-metil-1H-indol-1-il)propan-2-ol



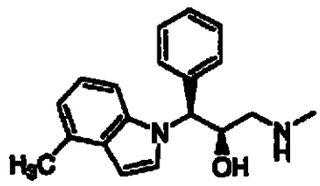
[0501] De forma análoga al EJEMPLO 117, etapa 5 se prepara (2S,3S)-3-(3-fluorofenil)-3-(7-metil-1H-indol-1-il)propano-1,2-diol de 7-metilindol y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (ver EJEMPLO 47, etapa 3) como un aceite. MS (ESI) *m/z* 300 ($[M+H]^+$).

[0502] De forma análoga al EJEMPLO 1, etapa 2 se prepara 3-(3-fluorofenil)-3-(7-metil-indol-1-il)-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico de (2S,3S)-3-(3-fluorofenil)-3-(7-metil-1H-indol-1-il)propano-1,2-diol MS (ESI) *m/z* 454 ($[M+H]^+$).

[0503] De forma análoga al EJEMPLO 5 clorhidrato de ((1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(7-metil-1H-indol-1-il)propan-2-ol se prepara de 3-(3-fluorofenil)-3-(7-metil-indol-1-il)-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina (solución en metanol 2N); MS (ESI) *m/z* 313 ($[M+H]^+$);

HRMS: calculado para C19H21FN2O + H+, 313.17107; encontrado (ESI-FTMS, [M+H]1+), 313.17141.

[0504] EJEMPLO 94: clorhidrato de (1S,2R)-3-(metilamino)-1-(4-metil-1H-indol-1-il)-1-fenilpropan-2-ol



[0505] De forma análoga al EJEMPLO 117, etapa 5 se prepara (2S,3S)-3-(4-metil-1H-indol-1-il)-3-fenilpropano-1,2-diol de 4-metilindol[7] y 2R,3R-(+)-3-fenilglicidol como un aceite. MS (ESI) *m/z* 282 ($[M+H]^+$).

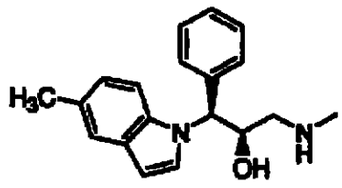
[0506] De forma análoga al EJEMPLO 1, etapa 2 se prepara 3-(4-metil-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S,3S)-tolueno-4-sulfónico de (2S,3S)-3-(4-metil-1H-indol-1-il)-3-fenilpropano-1,2-diol MS (ESI) *m/z* 436 ($[M+H]^+$).

[0507] De forma análoga al EJEMPLO 5 clorhidrato de (1S,2R)-3-(metilamino)-1-(4-metil-1H-indol-1-il)-1-fenilpropan-2-ol se prepara de 3-(4-metil-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina (solución en metanol 2N); MS (ESI) *m/z* 295 ($[M+H]^+$); HRMS: calculado para C19H22N2O + H+, 295.18049; encontrado (ESI-FT/MS, [M+H]1+), 295.1811.

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[7] Raucher, Stanley; Koolpe, Gary A. *J. Org. Chem.* 1983, 48(12), 2066-9

[0508] EJEMPLO 95: clorhidrato de (1S,2R)-3-(metilamino)-1-(5-metil-1H-indol-1-il)-1-fenilpropan-2-ol

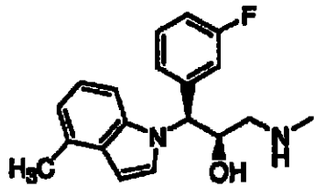


[0509] De forma análoga al EJEMPLO 117, etapa 5 (2S,3S)-3-(5-metil-1H-indol-1-il)-3-fenilpropano-1,2-diol se prepara de 5-metilindol y 2R,3R-(+)-3-fenilglicidol como un aceite. MS (ESI) *m/z* 282 ($[M+H]^+$).

[0510] De forma análoga al EJEMPLO 1, etapa 2 se prepara 3-(5-metil-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S,3S)-tolueno-4-sulfónico de (2S,3S)-3-(5-metil-1H-indol-1-il)-3-fenilpropano-1,2-diol MS (ESI) *m/z* 436 ($[M+H]^+$).

[0511] De forma análoga al EJEMPLO 5 clorhidrato de (1S,2R)-3-(metilamino)-1-(5-metil-1H-indol-1-il)-1-fenilpropan-2-ol se prepara de 3-(5-metil-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina (solución en metanol 2N); MS (ESI) *m/z* 295 ($[M+H]^+$); HRMS: calculado para C19H22N2O + H+, 295.18049; encontrado (ESI-FT/MS, [M+H]I+), 295.1812.

[0512] EJEMPLO 96: clorhidrato de ((1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(4-metil-1H-indol-1-il)propan-2-ol

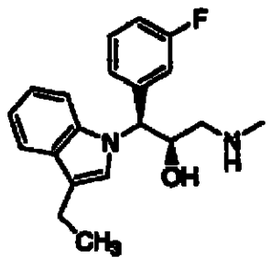


[0513] De forma análoga al EJEMPLO 117, etapa 5 se prepara (2S,3S)-3-(3-fluorofenil)-3-(4-metil-1H-indol-1-il)propano-1,2-diol de 4-metilindol[7] y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (ver EJEMPLO 47, etapa 3) como un aceite. MS (ESI) *m/z* 300 ($[M+H]^+$).

[0514] De forma análoga al EJEMPLO 1, etapa 2 se prepara 3-(3-fluorofenil)-3-(4-metil-indol-1-il)-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico de (2S,3S)-3-(3-fluorofenil)-3-(4-metil-1H-indol-1-il)propano-1,2-diol MS (ESI) *m/z* 454 ($[M+H]^+$).

[0515] De forma análoga al EJEMPLO 5 clorhidrato de ((1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(4-metil-1H-indol-1-il)propan-2-ol se prepara de 3-(3-fluorofenil)-3-(4-metil-indol-1-il)-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina (solución en metanol 2N); MS (ESI) *m/z* 313 ($[M+H]^+$); HRMS: calculado para C19H21FN2O + H+, 313.17107; encontrado (ESI-FT/MS, [M+H]1+), 313.171.

[0516] EJEMPLO 97: clorhidrato de ((1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(3-etil-1H-indol-1-il)propan-2-ol



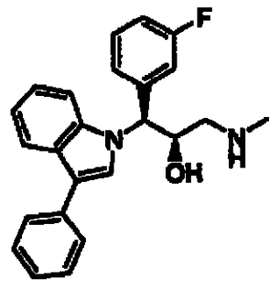
[0517] De forma análoga al EJEMPLO 117, etapa 5 se prepara (2S,3S)-3-(3-fluorofenil)-3-(3-etil-1H-indol-1-il)propano-1,2-diol de 3-etilindol[8] y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (ver EJEMPLO 47, etapa 3) como un aceite. MS (ESI) *m/z* 314 ($[M+H]^+$).

[0518] De forma análoga al EJEMPLO 1, etapa 2 se prepara 3-(3-fluorofenil)-3-(3-etil-indol-1-il)-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico de (2S,3S)-3-(3-fluorofenil)-3-(3-etil-1H-indol-1-il)propano-1,2-diol MS (ESI) *m/z* 468 ($[M+H]^+$).

[0519] De forma análoga al EJEMPLO 5 clorhidrato de ((1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(3-etil-1H-indol-1-il)propan-2-ol se prepara de 3-(3-fluorofenil)-3-(3-etil-indol-1-il)-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina (solución en metanol 2N); MS (ESI) *m/z* 327 ($[M+H]^+$); HRMS: calculado para $C20_{23}FN2O$ + H+, 327.18672; encontrado (ESI, $[M+H]^+$), 327.1871.

[0520] EJEMPLO 98: clorhidrato de ((1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(3-fenil-1H-indol-1-il)propan-2-ol

[8] Ainsworth, D. P.; Suschitzky, Hans *J. Chem Soc. [Section] C: Organic* 1967, (4), 315-19



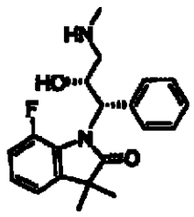
[0521] De forma análoga al EJEMPLO 117, etapa 5 se prepara (2S,3S)-3-(3-fluorofenil)-3-(3-fenil-1H-indol-1-il)propano-1,2-diol de 3-fenilindol[9] y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (ver EJEMPLO 47, etapa 3) como un aceite; MS (ESI) *m/z* 362 ($[M+H]^+$).

[0522] De forma análoga al EJEMPLO 1, etapa 2 se prepara 3-(3-fluorofenil)-3-(3-fenil-indol-1-il)-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico de (2S,3S)-3-(3-fluorofenil)-3-(3-fenil-1H-indol-1-il)propano-1,2-diol MS (ESI) *m/z* 516 ($[M+H]^+$).

[0523] De forma análoga al EJEMPLO 5 clorhidrato de ((1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(3-fenil-1H-indol-1-il)propan-2-ol se prepara de 3-(3-fluorofenil)-3-(3-fenil-indol-1-il)-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina (solución en metanol 2N); MS (ESI) *m/z* 375 ($[M+H]^+$); HRMS: calculado para $C24_{23}FN_2O$ + H+, 375.18672; encontrado (ESI, $[M+H]^+$), 375.1886.

[9] Cacchi, Sandro; Fabrizi, Giancarlo; Marinelli, Fabio; Moro, Leonardo; Pace, Paola *Synlett* 1997, (12), 1363-1366.

[0524] EJEMPLO 99: clorhidrato de 7-fluoro-1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona



[0525] Etapa 1: Una mezcla de tetrahidrato de perborato de sodio (65 g, 422 mmol) en ácido acético glacial (250 mL) se agita a 80° C. Se agrega 2,6-Difluoroanilina (11.0 g, 85 mmol) en ácido acético glacial (50 mL) lentamente a la mezcla. La temperatura se mantiene entre 80-90° C durante 1 hora. La mezcla de reacción fría se vierte en agua y se extrae dos veces con dietil éter. Las capas orgánicas combinadas se lavan con una solución diluida de bicarbonato de sodio, se secan sobre sulfato de magnesio anhidro y se evaporan. El residuo se purifica por vía de Cromatografía Biotage (FlasH90i, sílice, 10% de THF/hexano) y el producto se lava con hexano para proporcionar 2,6-difluoronitrobenceno (7.0 g) (52%). MS (ESI) *m/z* 160 ($[M+H]^+$).

[0526] Etapa 2: A una solución de 2,6-difluoronitrobenceno (5.0 g, 31.44 mmol) en n,N-dimetilformamida seca (50 mL) se agrega carbonato de potasio (4.41 g, 32 mmol) y dimetilmalonato (3.6 mL, 31.44 mmol). La mezcla de reacción se calienta a 65° C y se agita durante 24 horas. Después de enfriamiento a temperatura ambiente, la mezcla se neutraliza con una solución acuosa diluida de ácido clorhídrico y se extrae con dietil éter. La capa etérea se seca

sobre sulfato de magnesio anhidro, y se concentra en vacío. La cristalización de 5% de acetato de etilo/hexano da 4.6 g (54%) dimetil éster de ácido 2-(6-fluoro-2-nitro-fenil)-malónico. MS (ESI) *m/z* 272 $[M+H]^+$).

[0527] Etapa 3: dimetil éster de ácido 2-(6-fluoro-2-nitro-fenil)-malónico (12 g, 44 mmol) en una solución acuosa 6N de ácido clorhídrico (200 mL) se calienta a reflujo durante 4 horas. La mezcla se enfría, se diluye con 250 mL de agua y se extrae con dietil éter. La capa etérea se seca sobre sulfato de magnesio anhidro, y se concentra en vacío. Cristalización de 5% de acetato de etilo/hexano da 7.6 g de ácido (6-fluoro-2-nitro-fenil)-acético (54%). MS (ESI) *m/z* 200 ($[M+H]^+$).

[0528] Etapa 4: Una mezcla de ácido (6-fluoro-2-nitro-fenil)-acético (9.6 g, 48 mmol) y 10% de paladio sobre carbón (1.3 g) en ácido acético (100 ml) se hidrogena a 50 psi durante 24 horas. El catalizador se remueve por filtración a través de Celita y el solvente se evapora. El residuo entonces se disuelve en etanol (100 mL) y se agrega *para*-toluenosulfonato de piridinio (50 mg) y la mezcla se calienta hasta reflujo durante 1 hora. La mezcla se enfría, se vierte en agua, se extrae con acetato de etilo y se seca sobre sulfato de magnesio anhidro. El solvente se filtra y se concentra en vacío. El sólido se tritura con 5% de acetato de etilo/hexano para dar 6.0 g (83%) 7-fluoro-1,3-dihidro-indol-2-ona. MS (ESI) *m/z* 152, $[M+H]^+$).

[0529] Etapa 5: 7-Fluoro-1,3-dihidro-indol-2-ona (7.3 g, 48 mmol) y cloruro de litio (6.67 g, 158 mmol) se disuelven en

tetrahidrofurano (200 mL). La solución se enfría a -78° C y se agrega n-butillitio (40 mL, 100 mmol) lentamente durante un periodo de 15 minutos. Después de 20 minutos a -78° C, se agrega yoduro de metilo (6 mL, 96 mmol) y se le permite a la mezcla calentarse a temperatura ambiente. Después de 24 horas, la mezcla se vierte en agua y se extrae con acetato de etilo. La capa orgánica se seca sobre sulfato de magnesio anhidro, y se concentra en vacío. El producto crudo se purifica por vía de Cromatografía Biotage (Flash40i, sílice, 10% luego 20% de acetato de etilo/hexano) da 4.1 g (48%) 7-fluoro-3,3-dimetil-1,3-dihidro-2H-indol-2-ona. MS (ESI) *m/z* 180, $[M+H]^+$).

[0530] Etapa 6: Una mezcla de hidruro de sodio (244 mg, 6.1 mmol, 60% en aceite mineral) y 7-fluoro-3,3-dimetil-1,3-dihidro-2H-indol-2-ona (1.1 g, 6.1 mmol) en N,N-dimetilformamida seca (3.5 mL) se agita a temperatura ambiente durante 20 minutos. Se agrega [(2R, 3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4, 460 mg, 3.0 mmol) y la mezcla se calienta a 60° C bajo nitrógeno. Después de 20 minutos, adicionales se agrega [(2R, 3R)-3-feniloxiran-2-il]metanol (230 mg) seguido por otra adición de [(2R, 3R)-3-feniloxiran-2-il]metanol (230 mg) 30 minutos después. La reacción se monitorea por tlc (hexano: acetato de etilo 1:1) durante la desaparición epóxido de partida. La mezcla de reacción se vierte en una solución de ácido clorhídrico 2 N acuosa y se diluye con acetato de etilo. Las capas se separan y la capa orgánica se lava con agua y solución salina. La capa orgánica se seca sobre sulfato de sodio anhidro, se filtra y se concentra en vacío para dar 1.8 g de un aceite amarillo como producto crudo. El producto crudo se purifica por vía de Cromatografía Biotage

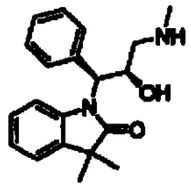
(FlasH40i, sílice, 6:1 a 1:1 hexano: acetato de etilo) para proporcionar 450 mg (23%) de 1-[(1S,2S)-2,3-dihidroxi-1-fenilpropil]-7-fluoro-3,3-dimetil-1,3-dihidro-2H-indol-2-ona como un aceite amarillo. MS (ESI) *m/z* 330 [(MH-H)+].

[0531] Etapa 7: Una solución de 1-[(1S,2S)-2,3-dihidroxi-1-fenilpropil]-7-fluoro-3,3-dimetil-1,3-dihidro-2H-indol-2-ona (870 mg, 2:6 mmol) en piridina seca (7.5 mL) se enfría a 0° C. Se agregan cloruro de *para*-toluenosulfonilo (524 mg, 2.75 mmol) y 4-dimetilaminopiridina (50 mg) y a la reacción se le permite calentarse a temperatura ambiente y se agita durante toda la noche. La reacción se vierte en una solución acuosa enfriada en hielo de ácido clorhídrico 2N y se extrae con acetato de etilo. La capa orgánica se lava con agua y solución salina. La capa orgánica se seca sobre sulfato de sodio anhidro, se filtra y se concentra en vacío para dar 1.2 g de un aceite viscoso. El producto crudo se purifica por vía de Cromatografía Biotage (FlasH40i, sílice, 16% luego 20% de acetato de etilo/hexano) da 200 mg (22%) de 1-[(1S,2S)-3-cloro-2-hidroxi-1-fenilpropil]-7-fluoro-3,3-dimetil-1,3-dihidro-2H-indol-2-ona. MS (ESI) *m/z* 348 $[(M+H)^+]$.

[0532] Etapa 8: Una solución de 1-[(1S,2S)-3-cloro-2-hidroxi-1-fenilpropil]-7-fluoro-3,3-dimetil-1,3-dihidro-2H-indol-2-ona (300 mg, 0.86 mmol), yoduro de sodio (10 mg), y metilamina (solución en etanol al 8M) se calientan a 60° C durante 1h. La reacción se enfría a temperatura ambiente, se concentra en vacío y se preadsorbe en Celita. El producto crudo se purifica por vía de Cromatografía Biotage (FlasH40i, sílice, 5%, 8% y 10% metanol con

amonio/diclorometano) para dar 187 mg de la base libre. La base libre se disuelve en una cantidad mínima de diclorometano y se trata con una solución etérea 1 M de ácido clorhídrico hasta pH=3 seguido por dietil éter. El producto se cristaliza por adicionar un mínimo de hexano para proporcionar el compuesto del título clorhidrato de 7-fluoro-1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona como un sólido blanco. MS (ESI) *m/z* 343 ($[M+H]^+$); HRMS: calculado para $C20_{23}FN2O2$ + H+, 343.18163; encontrado (ESI, $[M+H]^+$), 343.1804.

[0533] EJEMPLO 100: clorhidrato de 1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona



[0534] Etapa 1: De forma análoga al EJEMPLO 99, etapa 6 se prepara 1-[(1S,2S)-2,3-dihidroxi-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona de 3,3-dimetil-1,3-dihidro-indol-2-ona[10] y [(2R, 3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4). MS (ESI) *m/z* 311($[M+H]^+$).

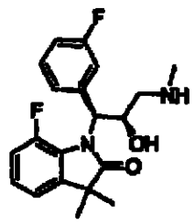
[0535] Etapa 2: De forma análoga al EJEMPLO 99, etapa 7 se prepara 1-[(1S,2S)-3-cloro-2-hidroxi-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona de 1-[(1S,2S)-2,3-dihidroxi-1-

[10] A. Kende, *Synth. Comm.* 1: 12 (1982)

fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona. MS (ESI) *m/z* 330 ([M+H]$^+$.

[0536] Etapa 3: De forma análoga al EJEMPLO 99, etapa 8 clorhidrato de 1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona se prepara de 1-[(1S,2S)-3-cloro-2-hidroxi-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona. MS (ESI) *m/z* 325 ([M+H)$^+$], HRMS: calculado para C20H24N2O2 + H+, 325.19105; encontrado (ESI-FTMS, [M+H]1+), 325.19093.

[0537] EJEMPLO 101: clorhidrato de 7-fluoro-1-[(1S,2R)-1-(3-fluorofenil)-2-hidroxi-3-(metilamino)propil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona



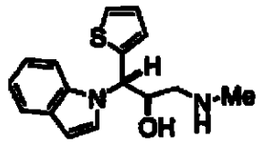
[0538] Etapa 1: Una mezcla de 7-fluoro-3, 3-dimetil-1,3-dihidro-2H-indol-2-ona (EJEMPLO 99, etapa 5, 1.0 g; 5.58 mmol) y *terc*-butóxido de sodio (1.0 g, 11.16 mmol) en diclorometano seco (15 mL) se agita a temperatura ambiente bajo nitrógeno durante 20 minutos. Se agrega isopropóxido de titanio (2.0 mL, 6.70 mmol) a una solución de [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3, 844 mg, 5.02 mmol) en diclorometano seco (6 mL) y se agita durante 20 minutos a temperatura ambiente. El complejo epóxido se agrega en forma de gota a la mezcla de terc-

butóxido y se le permite agitar durante 4 días. La mezcla de reacción se vierte en una solución de ácido clorhídrico 2 N acuosa y se diluye con acetato de etilo. Las capas se separan, y la capa orgánica se lava con agua y solución salina. La capa orgánica se seca sobre sulfato de sodio anhidro, se filtra y se concentra en vacío para dar 2.0 g de producto crudo. El producto crudo se purifica por vía de cromatografía Isco (RediSep, sílice, gradiente de 0% a 100% de acetato de etilo en hexano) para proporcionar 600 mg (31%) de (2S,3S)-7-Fluoro-1-[1-(3-fluoro-fenil)-2,3-dihidroxi-propil]-3,3-dimetil-1,3-dihidro-indol-2-ona como un aceite. MS (ESI) *m/z* 348 ($[M+H]^+$).

[0539] Etapa 2: De forma análoga al EJEMPLO 1, etapa 2 se prepara 3-(7-fluoro-3,3-dimetil-2-oxo-2,3-dihidro-indol-1-il)-3-(3-fluoro-fenil)-2-hidroxi-propil éster de ácido (2S, 3S)-tolueno-4-sulfónico de (2S,3S)-7-fluoro-1-[1-(3-fluoro-fenil)-2,3-dihidroxi-propil]-3,3-dimetil-1,3-dihidro-indol-2-ona. MS (ESI) *m/z* 502 ($[M+H]^+$).

[0540] Etapa 3: De forma análoga al EJEMPLO 5 se prepara clorhidrato de 7-fluoro-1-[(1S,2R)-1-(3-fluorofenil)-2-hidroxi-3-(metilamino)propil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona a partir de 3-(7-fluoro-3,3-dimetil-2-oxo-2,3-dihidro-indol-1-il)-3-(3-fluoro-fenil)-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico. MS (ESI) *m/z* 360 ($[M+H]^+$), HRMS: calculado para C20H22F2N2O2 + H^+, 361.17221; encontrado (ESI, [M+HD, 361.1719.

[0541] EJEMPLO 102: clorhidrato de (1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-(2-tienil)propan-2-ol



[0542] Etapa 1: se disuelve tiofeno (2.42 mL, 30.6 mmol) en tetrahidrofurano (50 mL), se enfría a -78° C, y se trata con n-butillitio (9.2 mL, 18.4 mmol) luego se calienta a 25° C. La mezcla se agita durante 30 minutos luego se enfría a -78° C y se agrega gota a gota una solución de 2,3-O-isopropilideno-D-gliceraldehído[11] (2.00 g, 15.3 mmol) en tetrahidrofurano (15.3 mL). La agitación se continúa durante 20 minutos luego se calienta a 0° C y se calma con una solución acuosa saturada de cloruro de amonio. La mezcla se diluye con acetato de etilo, se lava con agua, y solución salina saturada. La capa orgánica se separa, se seca sobre sulfato de magnesio anhidro, se filtra, y se concentra en vacío. El producto crudo se purifica por vía de Cromatografía Biotage (FlasH40i, sílice, 10% acetona/hexano) para proporcionar el producto 1.6 g (51%) como una mezcla 2:1 de (R)-[(4R)-2,2-dimetil-1,3-dioxolan-4-il](2-tienil)metanol y (S)-[(4R)-2,2-dimetil-1,3-dioxolan-4-il](2-tienil)metanol como un aceite. HRMS: calculado para C16H18N2OS + H^+, 287.12126; encontrado (ESI, $[M+H]^+$), 287.1204.

[11] Schmid, C. R.; Bryant, J. D.; Dowlatzedah, M.; Phillips, J. L; Prather, D. E.; Schantz, R. D.; Sear, N. L; Vianco, C. S. *J. Org. Chem.* 1991, 56, 4056.

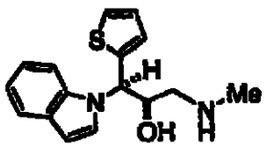
[0543] Etapa 2: Una mezcla de (R)-[(4R)-2,2-dimetil-1,3-dioxolan-4-il](2-tienil)metanol y (S)-[(4R)-2,2-dimetil-1,3-dioxolan-4-il](2-tienil)metanol (1.5 g, 7.0 mmol) se disuelve en tetrahidrofurano (28 mL) y acetiluro de sodio (2.1 g, 7.7 mmol; 18% en peso de lodos en xilenos/aceite mineral claro) y la mezcla se agita durante 2 horas. Se agrega cloruro de *para*-toluenosulfonilo (1.46 g, 7.7 mmol) y la agitación se continúa durante 2 horas, entonces se agrega indolina (2.5 g, 21 mmol) seguido por 2,6-lutidina (0.81 mL, 7.0 mmol). Después de 72 horas la mezcla se apaga con una solución acuosa saturada de cloruro de amonio, se diluye con acetato de etilo, se lava con agua, y solución salina saturada. La capa orgánica se separa, se seca sobre sulfato de magnesio anhidro, se filtra, y se concentra en vacío. El producto crudo se purifica por vía de cromatografía Isco (Redisep, sílice, gradiente 1-10% de acetato de etilo en hexano) para proporcionar 590 mg que inmediatamente se disuelve en dioxano (10 mL) y se trata con diclorodicianobenzoquinona (552 mg, 2.4 mmol) y se agita durante 30 minutos. La mezcla se diluye con acetato de etilo y se lava con bicarbonato de sodio saturado, agua, y solución salina saturada. La capa orgánica se separa, se seca sobre sulfato de magnesio anhidro, se filtra, y se concentra en vacío. El producto crudo se purifica por vía de cromatografía Isco (Redisep, sílice, gradiente 1-20% de acetato de etilo en hexano) para proporcionar 355 mg de 1-[(S)-[(4S)-2,2-dimetil-1,3-dioxolan-4-il](2-tienil)metil]-1H-indol. HRMS: calculado para $C_{18}H_{19}NO_2S + H^+$, 314.12092; encontrado (ESI-FTMS, [M+H]1+), 314.12111.

[0544] Etapa 3: 1-[(S)-[(4S)-2,2-dimetil-1,3-dioxolan-4-il](2-tienil)metil]-1H-indol (350 mg, 1.12 mmol) se disuelve en metanol (20 mL) y se agrega ácido bencenosulfónico (17 mg, 0.11 mmol). La mezcla se agita durante 6 horas luego se diluye con acetato de etilo y se lava con una solución acuosa saturada de bicarbonato de sodio, agua, y solución salina saturada. La capa orgánica se separa, se seca sobre sulfato de magnesio anhidro, se filtra, y se concentra en vacío. El producto crudo se purifica vía cromatografía de columna flash (sílice, 5% metanol/cloroformo) para proporcionar 260 mg (82%) de (2S,3S)-3-(1H-indol-1-il)-3-tien-2-ilpropano-1,2-diol. HRMS: calculado para $C_{15}H_{15}NO_2S + H^+$, 274.08963; encontrado (ESI, $[M+H]^+$), 274.0892.

[0545] Etapa 4: (2S,3S)-3-(1H-indol-1-il)-3-tien-2-ilpropano-1,2-diol (250 mg, 0.91 mmol) se disuelve en piridina (3 mL), se agrega cloruro de *para*-toluenosulfonilo (216 mg, 1.13 mmol) y la mezcla se agita durante 2 horas. La mezcla se diluye con acetato de etilo y se lava con agua, una solución acuosa saturada de sulfato de cobre, y solución salina saturada. La capa orgánica se separa, se seca sobre sulfato de magnesio anhidro, se filtra, y se concentra en vacío. El producto crudo se purifica por vía de cromatografía Isco (Redisep, sílice, gradiente 0%-100% de acetato de etilo en hexano) para proporcionar 360 mg que inmediatamente se disuelve en metilamina (solución en etanol al 8M, 15 mL) y se agita durante 16 horas. La mezcla se concentra en vacío y se purifica vía cromatografía de columna flash (sílice, gradiente 2%-10% metanol saturado con amonio en cloroformo) para dar 180 mg de (1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-(2-tienil)propan-2-

ol como un aceite incoloro. La base libre se disuelve en éter (5 mL) y se trata con una solución etérea de ácido clorhídrico 1 N (0.63 mL, 0.63 mmol, 1 equivalente). El precipitado blanco se recolecta y se seca bajo vacío para dar 193 mg (60%) de clorhidrato de (1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-(2-tienil)propan-2-ol. HRMS: calculado para $C_{16}H_{18}N_2OS + H^+$, 287.12126; encontrado (ESI, $[M+H]^+$), 287.1204

[0546] EJEMPLO 103: clorhidrato de (1R,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-(2-tienil)propan-2-ol



[0547] Etapa 1: Tiofeno (2.42 mL, 30.6 mmol) se disuelve en tetrahidrofurano (50 mL), se enfría a -78° C, y se trata con n-butillitio (9.2 mL, 18.4 mmol) luego se calienta a 25° C. La mezcla se agita durante 30 minutos luego se enfría a -780C y una solución de 2,3-O-isopropilideno-D-gliceraldehído[11](2.00 g, 15.3 mmol) en tetrahidrofurano (15.3 mL) se agrega en forma de gota. La agitación se continúa durante 20 minutos luego se calienta a 0° C y se apaga con una solución acuosa saturada de cloruro de amonio. La mezcla se diluye con acetato de etilo, se lava con agua, y solución salina saturada. La capa orgánica se separa, se seca sobre sulfato de magnesio anhidro, se filtra, y se concentra en vacío. El producto crudo se purifica por vía de Cromatografía Biotage (FlasH40i, sílice, 10% acetona/hexano) para proporcionar el producto 1.6 g (51%) como una mezcla 2:1 de (R)-[(4R)-2,2-dimetil-1,3-dioxolan-4-il](2-tienil)metanol y (S)-[(4R)-2,2-dimetil-1,3-dioxolan-4-il](2-tienil)metanol como un aceite. HRMS:

calculado para $C_{16}H_{18}N_2OS + H^+$, 287.12126; encontrado (ESI, $[M+H]^+$), 287.1204.

[0548] Etapa 2: Una mezcla de (R)-[(4R)-2,2-dimetil-1,3-dioxolan-4-il](2-tienil)metanol y (S)-[(4R)-2,2-dimetil-1,3-dioxolan-4-il](2-tienil)metanol (1.5 g, 7.0 mmol) se disuelve en tetrahidrofurano (28 mL) y acetiluro de sodio (2.1 g, 7.7 mmol; 18% en peso de lodos en xilenos/aceite mineral claro) y la mezcla se agita durante 2 horas. Se agrega cloruro de *para*-toluenosulfonilo (1.46 g, 7.7 mmol), y la agitación se continúa durante 2 horas, luego se agrega indolina (2.5 g, 21 mmol) seguido por 2,6-lutidina (0.81 mL, 7.0 mmol). Después de 72 horas la mezcla se apaga con una solución acuosa saturada de cloruro de amonio, se diluye con acetato de etilo, se lava con agua, y solución salina saturada. La capa orgánica se separa, se seca sobre sulfato de magnesio anhidro, se filtra, y se concentra en vacío. El producto crudo se purifica por vía de cromatografía Isco (Redisep, sílice, gradiente 1-10% de acetato de etilo en hexano) para proporcionar 590 mg que inmediatamente se disuelve en dioxano (10 mL) y se trata con diclorodicianobenzoquinona (552 mg, 2.4 mmol) y se agita durante 30 minutos. La mezcla se diluye con acetato de etilo y se lava con una solución acuosa saturada de bicarbonato de sodio, agua, y solución salina saturada. La capa orgánica se separa, se seca sobre sulfato de magnesio anhidro, se filtra, y se concentra en vacío. El producto crudo se purifica por vía de cromatografía Isco (Redisep, sílice, gradiente 1-20% de acetato de etilo en hexano) para proporcionar 160 mg de 1-[(R)-[(4S)-2,2-dimetil-1,3-dioxolan-4-il](2-

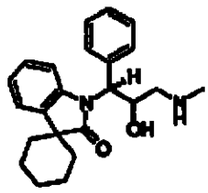
tienil)metil]-1H-indol. HRMS: calculado para $C_{18}H_{19}NO_2S + H^+$, 314.12092; encontrado (ESI-FTMS, [M+H]1+), 314.12089.

[0549] Etapa 3: se disuelve 1-[(S)-[(4S)-2,2-dimetil-1,3-dioxolan-4-il](2-tienil)metil]-1H-indol (160 mg, 0.51 mmol) en metanol (10 mL) y se agrega ácido bencenosulfónico (10 mg, 0.06 mmol). La mezcla se agita durante 16 horas luego se diluye con acetato de etilo y se lava con una solución acuosa saturada de bicarbonato de sodio, agua, y solución salina saturada. La capa orgánica se separa, se seca sobre sulfato de magnesio anhidro, se filtra, y se concentra en vacío. El producto crudo se purifica vía cromatografía de columna flash (sílice, 5% metanol/cloroformo) para proporcionar 102 mg (74%) de (2S,3R)-3-(1H-indol-1-il)-3-tien-2-ilpropano-1,2-diol que se lleva directamente a la siguiente etapa.

[0550] Etapa 4: se disuelve (2S,3R)-3-(1H-indol-1-il)-3-tien-2-ilpropano-1,2-diol (102 mg, 0.37 mmol) en piridina (1.5 mL), se agrega cloruro de *para*-toluenosulfonilo (88 mg, 0.46 mmol) y la mezcla se agita durante 16 horas. La mezcla se diluye con acetato de etilo y se lava con agua, una solución acuosa saturada de sulfato de cobre, y solución salina saturada. La capa orgánica se separa, se seca sobre sulfato de magnesio anhidro, se filtra, y se concentra en vacío. El producto crudo se purifica por vía de cromatografía Isco (Redisep, sílice, gradiente 0%-100% de acetato de etilo en hexano) para proporcionar 140 mg que inmediatamente se disuelve en metilamina (solución en etanol al 8M, 15 mL) y se agita durante 3 horas. La mezcla se concentra en vacío y se purifica vía cromatografía de columna flash (sílice, gradiente

2%-10% metanol saturado con amonio en cloroformo) para dar 65 mg (71%) de (1R,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-(2-tienil)propan-2-ol como un aceite incoloro. La base libre se disuelve en dietil éter (5 mL) y se trata con una solución etérea de ácido clorhídrico 1 N (0.23 mL, 0.23 mmol, 1 equivalente). El precipitado blanco se recolecta y se seca bajo vacío para dar clorhidrato de (1R,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-(2-tienil)propan-2-ol. HRMS: calculado para $C_{16}H_{18}N_2OS$ + H^+, 287.12126; encontrado (ESI, $[M+H]^+$), 287.1209

[0551] EJEMPLO 104: clorhidrato de 1'-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]espiro[ciclo-hexano-1,3'-indol]-2'(1H)-ona



[0552] Etapa 1: espiro[ciclohexano-1,3'-indol]-2'(1H)-ona[12] (0.82 g, 4.1 mmol) se disuelve en N,N-dimetilformamida (1 mL), e hidruro de sodio (168 mg, 4.4 mmol, 60% peso en suspensión en aceite mineral) se agrega y la mezcla resultante se agita durante 15 minutos. La mezcla se calienta a 75° C y se agrega *trans*-3-fenilglicidol (306 mg, 2.04 mmol) en cuatro porciones. La agitación se continúa durante 2 horas, luego la mezcla de reacción se enfría y se apaga con una solución acuosa saturada de

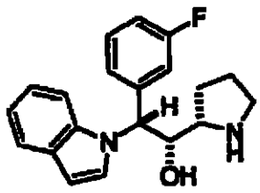
[12] Fensome, A.; Miller, L L.; Ullrich, J. W.; Bender, R. H. W.; Zhang, P.; Wrobel, J. E.; Zhi, L; Jones, T. K.; Marschke, K. B.; Tegley, C. M. PCT Int. PCT Int. Appl. 2000, 127 pp. WO2000066556

cloruro de amonio. La mezcla se diluye con acetato de etilo, se lava con agua, y solución salina saturada. La capa orgánica se separa, se seca sobre sulfato de magnesio anhidro, se filtra, y se concentra en vacío. El producto crudo se purifica por vía de cromatografía Isco (Redisep, sílice, gradiente 20% a 100% de acetato de etilo en hexano) para proporcionar 290 mg (41%) de 1'-[(1S,2S)-2,3-dihidroxi-1-fenil-propil]espiro[ciclohexano-1,3'-indol]-2'(1H)-ona como un aceite. Pureza HPLC de % a 210-370 nm, 9.4 min.; columna Xterra RP18, 3.5u, 150 x 4.6 mm, 1.2 mL/minutos, 85/15-5/95 (Ammon. Form. Buff. Ph=3.5/ACN+MeOH) durante 10 minutos se mantiene 4 minutos.

[0553] Etapa 2: se disuelve 1'[(1S,2S)-2,3-dihidroxi-1-fenil-propil]espiro[ciclohexano-1,31-indol]-2'(1H)-ona (250 mg, 0.71 mmol) en piridina (2.5 mL) y se agrega cloruro de *para*-toluenosulfonilo (169 mg, 0.89 mmol). La reacción se agita durante 5 horas, luego la mezcla de reacción se diluye con acetato de etilo y se lava con agua, una solución acuosa saturada de sulfato de cobre, una solución de ácido clorhídrico 2 N acuosa, y solución salina saturada. La capa orgánica se separa, se seca sobre sulfato de magnesio anhidro, se filtra, y se concentra en vacío. El producto crudo se disuelve inmediatamente en metilamina (solución en etanol al 8M, 15 mL) y se agita durante 16 horas. La mezcla se concentra en vacío y se purifica vía cromatografía de columna flash (sílice, 5% metanol saturado con amonio en cloroformo) para dar 85 mg (32%) de 1'-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]espiro[ciclo-hexano-1,3'-indol]-2'(1'H)-ona como un aceite incoloro. La base libre se disuelve en dietil éter (5 mL) y se trata con una solución etérea

de ácido clorhídrico 1 N (0.23 mL, 0.23 mmol, 1 equivalente). El precipitado blanco se recolecta y se secan bajo vacío para dar 193 mg (60%) de clorhidrato de [(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropiljspiro[ciclo-hexano-i,3'-indol]-2'(1'H)-ona. HRMS: calculado para $C_{23}H_{28}N_2O_2$ + H^+, 365.22235; encontrado ($[M+H]^+$), 365.2226;

[0554] EJEMPLO 105: clorhidrato de (1S,2R)-2-(3-fluorofenil)-2-(1H-indol-1-il)-1-[(2S)-pirrolidin-2-il]etanol



[0555] Etapa 1: A una suspensión de bromuro de 3-fluorobenciltrifenilfosfonio (6.8 g, 15 mmol) en tetrahidrofurano (50 mL) a 0° C se agrega hidruro de sodio (0.57 g, 15 mmol, 60% peso en suspensión en aceite mineral), y la mezcla se agita durante 1 hora. Una solución de terc-butil éster de ácido (S)-2-formil-pirrolidin-1-carboxílico[13] (2.5 g, 12.5 mmol) en tetrahidrofurano (10 mL) se agrega y la mezcla se agita durante 1 hora luego se calienta a 25° C y se apaga con una solución acuosa saturada de cloruro de amonio. La mezcla se diluye con acetato de etilo, se lava con agua, y solución salina saturada. La capa orgánica se separa, se seca sobre sulfato de magnesio anhidro, se filtra, y se concentra en vacío. El producto crudo se purifica por vía de cromatografía Isco (Redisep, sílice, 10% de acetato de

[13] Cook, G. R.; StHIe, J. R. *Tetrahedron*, 1994, 50(14), 4105.

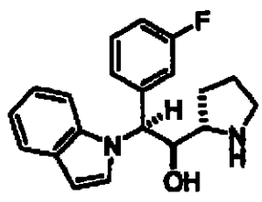
etilo/hexano) para proporcionar 2.18 g (60%) de (2S)-2-[(E)-2-(3-fluorofenil)vinil]pirrolidin-1-carboxilato de terc-butilo como un aceite incoloro que se cristaliza en reposo. HRMS: calculado para $C_{17}H_{22}FNO_2 + H^+$, 292.17073; encontrado (ESI, M+H), 292.1713.

[0556] Etapa 2: (2S)-2-[(E)-2-(3-fluorofenil)vinil]pirrolidin-1-carboxilato terc-butilo (400 mg, 1.37 mmol) se disuelve en diclorometano (50 mL). Una solución acuosa saturada de bicarbonato de sodio (50 mL) se agrega, seguido por acetona (10 mL) y hidrogen sulfato de tetrabutilamonio (46 mg, 0.14 mmol). Con agitación vigorosa se agrega Ozono (8.4 g, 13.7 mmol) durante 2 horas en 8 porciones (1.05 g cada 15 minutos). La mezcla se agita durante 16 horas adicionales luego se diluye con diclorometano. La capa orgánica se separa y se lava con agua, y solución salina saturada, se seca sobre sulfato de magnesio anhidro, se filtra, y se concentra en vacío. El producto crudo se purifica por vía de cromatografía Isco (Redisep, sílice, 20% de acetato de etilo/hexano) para dar 240 mg que inmediatamente se combina con indolina (0.14 g, 1.2 mmol) y se calienta a 90° C durante 16 horas. La mezcla se enfría y el aceite naranja crudo se purifica por cromatografía Isco (Redisep, sílice, gradiente 0% a 25% de acetato de etilo en hexano) para dar 130 mg que inmediatamente se disuelve en diclorometano (20 mL). Se agrega dióxido de manganeso (0.86 g, 10 mmol) y la mezcla se agita durante 5 horas, luego se diluye con diclorometano y se filtra a través de almohadilla de Celita y se concentra. El producto crudo se purifica por cromatografía Isco (Redisep, sílice, gradiente 0% a 50% de acetato de etilo en hexano) para dar 50 mg de terc-butil

éster de ácido (S)-2-[2-(R)-(3-fluoro-fenil)-1-hidroxi-2-indol-1-il-etil]-(S)-pirrolidin-1-carboxílico.

[0557] Etapa 3: terc-butil éster de ácido (S)-2-[2-(R)-(3-fluoro-fenil)-1-hidroxi-2-indol-1-il-etil]-(S)-pirrolidin-1-carboxílico (50 mg, 0.12 mmol) se disuelve en metanol (1 mL) y una solución etérea de ácido clorhídrico 1 N (0.96 mL, 0.96 mmol) se agrega. Después 6 horas la mezcla se concentra y se purifica vía cromatografía de columna flash (sílice, 10% metanol saturado con amonio en cloroformo) para dar 6 mg (15%) de (1S,2R)-2-(3-fluorofenil)-2-(1H-indol-1-il)-1-[(2S)-pirrolidin-2-il]etanol. La base libre se disuelve en dietil éter (2 mL) y se trata con una solución etérea de ácido clorhídrico 1 N (0.02 mL, 0.02 mmol, 1 equivalente). El precipitado blanco se recolecta y se secan bajo vacío para dar 4 mg de clorhidrato de (1S,2R)-2-(3-fluorofenil)-2-(1H-indol-1-il)-1-[(2S)-pirrolidin-2-il]etanol. HRMS: calculado para $C_{20}H_{21}FN_{20}$ + H^+, 325.17107; encontrado (ESI, $[M+H]^+$), 325.1712.

[0558] EJEMPLO 106: clorhidrato de (1R,2S)-2-(3-fluorofenil)-2-(1H-indol-1-il)-1-[(2S)-pirrolidin-2-il]etanol



[0559] Etapa 1: A una suspensión de bromuro de 3-fluorobenciltrifenilfosfonio (6.8 g, 15 mmol) en tetrahidrofurano

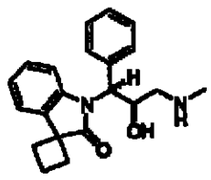
(50 mL) a 0° C se agrega hidruro de sodio (0.57 g, 15 mmol, 60% peso en suspensión en aceite mineral) y la mezcla se agita durante 1 hora a temperatura ambiente. Una solución de terc-butil éster de ácido (S)-2-formil-pirrolidin-1-carboxílico[13] (2.5 g, 12.5 mmol) en tetrahidrofurano (10 mL) se agrega, y la mezcla se agita durante 1 hora luego se calienta a 25° C y se apaga con una solución acuosa saturada de cloruro de amonio. La mezcla se diluye con acetato de etilo, se lava con agua, y solución salina saturada. La capa orgánica se separa, se seca sobre sulfato de magnesio anhidro, se filtra, y se concentra en vacío. El producto crudo se purifica por vía de cromatografía Isco (Redisep, sílice, 10% de acetato de etilo/hexano) para proporcionar 2.18 g (60%) de (2S)-2-[(E)-2-(3-fluorofenil)vinil]pirrolidin-1-carboxilato de terc-butilo como un aceite incoloro que se cristaliza en reposo. HRMS: calculado para $C_{17}H_{22}FNO_2$ + H^+, 292.17073; encontrado (ESI, M+H), 292.1713.

[0560] Etapa 2: (2S)-2-[(E)-2-(3-fluorofenil)vinil]pirrolidin-1-carboxilato de terc-butilo (400 mg, 1.37 mmol) se disuelve en diclorometano (50 mL). Una solución acuosa saturada de bicarbonato de sodio (50 mL) se agrega, seguido por acetona (10 mL) e hidrogen sulfato de tetrabutilamonio (46 mg, 0.14 mmol). Se agrega con agitación vigorosa Ozono (8.4 g, 13.7 mmol) durante 2 horas en 8 porciones (1.05 g cada 15 minutos). La mezcla se agita durante 16 horas adicionales luego se diluye con diclorometano. La capa orgánica se separa y se lava con agua, y solución salina saturada, se seca sobre sulfato de magnesio anhidro, se filtra, y se concentra en vacío. El producto crudo se purifica por vía de cromatografía Isco (Redisep, sílice, 20% de acetato de

etilo/hexano) para dar 240 mg que inmediatamente se combina con indolina (0.14 g, 1.2 mmol) y se calienta a 90° C durante 16 horas. La mezcla se enfría y el aceite naranja crudo se purifica por cromatografía Isco (Redisep, sílice, gradiente 0% a 25% de acetato de etilo en hexano) para dar 130 mg que inmediatamente se disuelve en diclorometano (20 mL). Se agrega dióxido de manganeso (0.86 g, 10 mmol) y la mezcla se agita durante 5 horas luego se diluye con diclorometano y se filtra a través de almohadilla de Celita y se concentra. El producto crudo se purifica por cromatografía Isco (Redisep, sílice, gradiente 0% a 50% de acetato de etilo en hexano) para dar 50 mg de terc-butil éster de ácido (R)-2-[2-(S)-(3-fluoro-fenil)-1-hidroxi-2-indol-1-il-etil]-(S)-pirrolidin-1-carboxílico.

[0561] Etapa 3:terc-butil éster de ácido (R)-2-[2-(S)-(3-fluoro-fenil)-1-hidroxi-2-indol-1-il-etil]-(S)-pirrolidin-1-carboxílico (50 mg, 0.12 mmol) se disuelve en metanol (1 mL) y se agrega una solución etérea de ácido clorhídrico 1 N (1.0 mL, 1.0 mmol). Después de 16 horas la mezcla se concentra y se purifica vía cromatografía de columna flash (sílice, 10% metanol saturado con amonio en cloroformo) para dar 19 mg (50%) de (1R,2S)-2-(3-fluorofenil)-2-(1H-indol-1-il)-1-[(2S)-pirrolidin-2-il]etanol. La base libre se disuelve en dietil éter (2 mL) y se trata con una solución etérea de ácido clorhídrico 1 N (0.06 mL, 0.06 mmol, 1 equivalente). El precipitado blanco se recolecta y se seca bajo vacío para dar 17 mg de clorhidrato de (1R,2S)-2-(3-fluorofenil)-2-(1H-indol-1-il)-1-[(2S)-pirrolidin-2-il]etanol. HRMS: calculado para $C_{20}H_{21}FN_2O + H^+$, 325.17107; encontrado (ESI, $[M+H]^+$), 325.1711

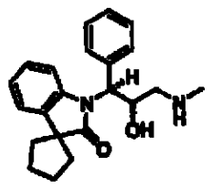
[0562] EJEMPLO 107: clorhidrato de 1'-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]espiro[ciclo-butano-1,3'-indol]-2'(1H)-ona



[0563] Etapa 1: De forma análoga al EJEMPLO 104, etapa 1 se prepara 1'-[(1S,2S)-2,3-dihidroxi-1-fenilpropil]espiro[ciclobutano-1,3'-indol]-2'(1'H)-ona a partir de espiro[ciclobutano-1,3'-indol]-2'(1'H)-ona[12] y *trans*-3-fenilglicidol. Pureza HPLC 100% a 210-370 nm, 8.4 min.; Columna Xterra RP18, 3.5u, 150 x 4.6 mm, 1.2 mL/minutos, 85/15-5/95 (Ammon. Form. Buff. Ph=3.5/ACN+MeOH) durante 10 minutos, manteniendo a 4 minutos.

[0564] Etapa 2: De forma análoga al EJEMPLO 104, etapa 2 se prepara clorhidrato de 1'-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]espiro[ciclo-butano-1,3'-indol]-2'(1H)-ona a partir de 1'-[(1S,2S)-2,3-dihidroxi-1-fenilpropil]espiro-[ciclobutano-1,3'-indol]-2'(1H)-ona. HRMS: calculado para $C_{21}H_{24}N_2O_2 + H^+$, 337.19105; encontrado (ESI, $[M+H]^+$), 337.1917

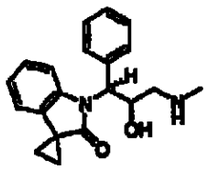
[0565] EJEMPLO 108: clorhidrato de 1'-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]espiro-[ciclopentano-1,3'-indol]-2'(1H)-ona



[0566] Etapa 1: De forma análoga al EJEMPLO 104, etapa 1 se prepara 1'-[(1S,2S)-2,3-dihidroxi-1-fenilpropil]espiro[ciclopentano-1,3'-indol]-2'(1H)-ona a partir de espiro[ciclopentano-1,3'-indol]-21(1'H)-ona[12] y *trans*-3-fenilglicidol. HRMS: calculado para $C_{2123}NO_3$ + H^+, 338.17507; encontrado (ESI, $[M+H]^+$), 338.1769.

[0567] Etapa 2: De forma análoga al EJEMPLO 104, etapa 2 se prepara clorhidrato de 1'-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]espiro-[ciclopentano-1,3'-indol]-2'(1'H)-ona a partir de 1'-[(1S,2S)-2,3-dihidroxi-1-fenilpropil]espiro-[ciclopentano-1,3'-indol]-2'(1'H)-ona. HRMS: calculado para $C_{22}H_{26}N_2O_2$ + H^+, 351.20670; encontrado (ESI, $[M+H]^+$), 351.2061

[0568] EJEMPLO 109: clorhidrato de 1'-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]espiro-[ciclopropano-1,3'-indol]-2'(1H)-ona

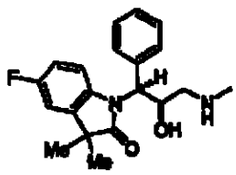


[0569] Etapa 1: De forma análoga al EJEMPLO 104, etapa 1 se prepara 1'-[(1S,2S)-2,3-dihidroxi-1-

fenilpropil]espiro[ciclopropano-1,3'-indol]-2'(1H)-ona a partir de espiro[ciclopropano-1,3'-indol]-2'(1H)-ona[14] y *trans*-3-fenilglicidol. Pureza HPLC 89.1% a 210-370 nm, 7.7 min.; Columna Xterra RP18, 3.5u, 150 x 4.6 mm, 1.2 mL/minutos, 85/15-5/95 (Ammon. Form. Buff. Ph=3.5/ACN+MeOH) durante 10 minutos, manteniendo a 4 minutos.

[0570] Etapa 2: De forma análoga al EJEMPLO 104, etapa 2 se prepara clorhidrato de 1'-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]espiro-[ciclopropano-1,3'-indol]-2'(1H)-ona a partir de 1'-[(1S,2S)-2,3-dihidroxi-1-fenilpropil]-espiro[ciclopropano-1,3'-indol]-2'(1H)-ona. HRMS: calculado para $C_{20}H_{22}N_2O_2$ + H^+, 323.17540; encontrado (ESI, $[M+H]^+$), 323.1744.

[0571] EJEMPLO 110: clorhidrato de 5-fluoro-1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona



[0572] Etapa 1: 5-Fluoro-1,3-dihidro-indol-2-ona (2.0 g, 13.2 mmol) y cloruro de litio (1.39 g, 33.0 mmol) se disuelven en tetrahidrofurano (40 mL) y se enfrían a 0° C. se agrega n-Butillitio (10.6 mL, 26.4 mmol) en forma de gota y la mezcla se agita 20 minutos. Se agrega yoduro de metilo (1.63 mL, 26.4 mmol)

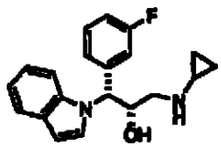
[14] Roberston, D. W.; Krushinski, J. H.; Pollock, G. D.; Wilson, H.; Kauffman, R. F.; Hayes, J. S. *J. Med. Chem.* 1987, 30, 824.

lentamente y la agitación se continúa durante 2 horas a 0° C luego se calienta a 25° C. Después de 16 horas la reacción se apaga con una solución acuosa saturada de cloruro de amonio. La mezcla se diluye con éter, se lava con agua, y solución salina saturada. La capa orgánica se separa, se seca sobre sulfato de magnesio anhidro, se filtra, y se concentra en vacío. El producto crudo se purifica por vía de cromatografía Isco (Redisep, sílice, gradiente 10% a 50% de acetato de etilo en hexano) para proporcionar 1.18 g (50%) de 5-fluoro-3,3-dimetil-1,3-dihidro-2H-indol-2-ona como cristales blancos. Pureza HPLC 100% a 210-370 nm, 7.1 min.; Columna Xterra RP18, 3.5u, 150 x 4.6 mm, 1.2 mL/minutos, 85/15-5/95 (Ammon. Form. Buff. Ph=3.5/ACN+MeOH) durante 10 minutos, manteniendo a 4 minutos.

[0573] Etapa 2: De forma análoga al EJEMPLO 104, etapa se prepara 1-[(1S,2S)-2,3-dihidroxi-1-fenilpropil]-5-fluoro-3,3-dimetil-1,3-dihidro-2H-indol-2-ona a partir de 5-fluoro-3,3-dimetil-1,3-dihidro-2H-indol-2-ona y *trans*-3-fenilglicidol. HRMS: calculado para $C_{19}H_{20}FNO_3 + H^+$, 330.15000; encontrado (ESI, $[M+H]^+$), 330.1495

[0574] Etapa 3: De forma análoga al EJEMPLO 104, etapa 2 se prepara clorhidrato de 5-fluoro-1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona a partir de 1-[(1S,2S)-2,3-dihidroxi-1-fenilpropil]-5-fluoro-3,3-dimetil-1,3-dihidro-2H-indol-2-ona. Pureza HPLC 100% a 210-370 nm, 7.2 min.; Columna Xterra RP18, 3.5u, 150 x 4.6 mm, 1.2 mL/minutos, 85/15-5/95 (Ammon. Form. Buff. Ph=3.5/ACN+MeOH) durante 10 minutos, manteniendo a 4 minutos. HRMS: calculado para $C_{2023}FN_2O_2 + H^+$, 343.18163; encontrado (ESI, $[M+H]^+$), 343.184

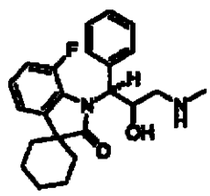
[0575] EJEMPLO 111: clorhidrato de (1S,2R)-3-(ciclopropilamino)-1-(3-fluorofenil)-1-(1H-indol-1-il)propan-2-ol



[0576] Etapa 1: (2S,3S)-3-(3-Fluorofenil)-3-(1H-indol-1-il)propano-1,2-diol (EJEMPLO 47, etapa 5) (0.6 g, 2.1 mmol) se disuelve en piridina (5 mL) y se agrega cloruro de *para*-toluenosulfonilo (0.44 g, 2.3 mmol). La mezcla se agita durante 3 horas luego la mezcla de reacción se diluye con acetato de etilo y se lava con agua, seguido por una solución acuosa saturada de sulfato de cobre, una solución de ácido clorhídrico 2 N acuosa, y solución salina saturada. La capa orgánica se separa, se seca sobre sulfato de magnesio anhidro, se filtra, y se concentra en vacío. El producto crudo se disuelve inmediatamente en metilamina (solución en etanol al 8M, 25 mL) y se agita durante 16 horas. La mezcla se concentra en vacio y se purifica vía cromatografía de columna flash (sílice, 5% metanol saturado con amonio en cloroformo) para dar (1S,2R)-3-(ciclopropilamino)-1-(3-fluorofenil)-1-(1H-indol-1-il)propan-2-ol como un aceite incoloro. La base libre se disuelve en dietil éter (5 mL) y se trata con una solución etérea de ácido clorhídrico 1 N (1 equivalente). El precipitado blanco se recolecta y se seca bajo vacio para dar 80 mg (12%) de clorhidrato de (1S,2R)-3-(ciclopropilamino)-1-(3-fluorofenil)-1-(1H-indol-1-il)propan-2-

ol. HRMS: calculado para $C_{20}H_{21}FN_2O$ + H^+, 325.17107; encontrado (ESI, $[M+H]^+$), 325.1728.

[0577] EJEMPLO 112: clorhidrato de 7'-fluoro-1'-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-espiro[ciclohexano-1,3'-indol]-2'(1H)-ona



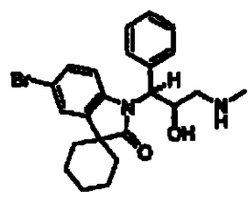
[0578] Etapa 1: 7-Fluoro-1,3-dihidro-indol-2-ona (EJEMPLO 99, etapa 4) (1.16 g, 7.68 mmol) y cloruro de litio (0.81 g, 19.2 mmol) se disuelven en tetrahidrofurano (50 mL) y se enfría a 0° C. Se agrega n-Butillitio (6.14 mL, 15.4 mmol) en forma de gota y la mezcla se agita 15 minutos. Se agrega lentamente 1,5-dibromopentano (1.05 mL, 7.7 mmol) y la agitación se continúa durante 2 horas a 0° C luego se calienta a 25° C. Después de 16 horas la reacción se apaga con una solución acuosa saturada de cloruro de amonio. La mezcla se diluye con éter, se lava con agua, y solución salina saturada. La capa orgánica se separa, se seca sobre sulfato de magnesio anhidro, se filtra, y se concentra en vacío. El producto crudo se purifica por vía de cromatografía Isco (Redisep, sílice, gradiente 5% a 40% de acetato de etilo en hexano) para proporcionar 0.90 g (54%) de 7'-fluorospiro-[ciclohexano-1,3'-indol]-2'(1'H)-ona. Pureza HPLC 95.9% a 210-370 nm, 19.2 min.; Columna Xterra MSC18, 5u, 150 x 3.0 mm, 0.5

mL/minutos, 95/5-5/95 (0.1% de ácido fórmico en H_2O/MeOH) durante 20 minutos, mantenido 3 min.

[0579] Etapa 2: De forma análoga al EJEMPLO 104, etapa 1 se prepara 1'-[(1S,2S)-2,3-dihidroxi-1-fenilpropil]-7'-fluoroespiro[ciclohexano-1,3'-indol]-2'(1H)-ona a partir de 7'-fluorospiro-[ciclohexano-1,3'-indol]-2'(1H)-ona y *trans*-3-fenilglicidol. HRMS: calculado para $C_{22}H_{24}FNO_3$ + H^+, 370.18130; encontrado (ESI, $[M+H]^+$), 370.1798

[0580] Etapa 3: De forma análoga al EJEMPLO 104, etapa 2 se prepara clorhidrato de 7'-fluoro-1'-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-espiro[ciclohexano-1,3'-indol]-2'(1'H)-ona a partir de 1'-[(1S,2S)-2,3-dihidroxi-1-fenilpropil-7'fluroespiro[ciclohexano-1,3'-indol]-2'(1'H)-ona HRMS: calculado para $C_{23}H_{27}FN_2O_2$ + H^+, 383.21293; encontrado (ESI, $[M+H]^+$), 383.2109

EJEMPLO 113: clorhidrato de 5'-bromo-1'-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-espiro[ciclohexano-1,3'-indol]-2'(1H)-ona

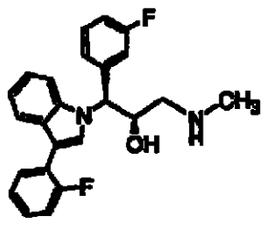


[0581] Etapa 1: De forma análoga al EJEMPLO 104, etapa 1 se prepara 5'-bromo-1'-[(1S,2S)-2,3-dihidroxi-1-

fenilpropil]espiro[ciclohexano-1,3'-indol]-2'(1H)-ona a partir de 5'-bromoespiro[ciclohexano-1,3'-indol]-2'(1'H)-ona[12] y *trans*-3-fenilglicidol. HRMS: calculado para $C_{22}H_{24}BrNO_3$ + H^+, 430.10123; encontrado (ESI, $[M+H]^+$), 430.1006

[0582] Etapa 2: De forma análoga al EJEMPLO 104, etapa 2 se prepara clorhidrato de 5'-bromo-1'-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-espiro[ciclohexano-1,3'-indol]-2'(1'H)-ona a partir de 5'-bromo-1'-[(1S,2S)-2,3-dihidroxi-1-fenilpropil]espiro[ciclohexano-1,3'-indol]-2'(1'H)-ona. HRMS: calculado para $C_{23}H_{27}BrN_2O_2$ + H^+, 443.13286; encontrado (ESI, $[M+H]^+$), 443.1333.

[0583] EJEMPLO 114: clorhidrato de (1S,2R)-1-(3-fluorofenil)-1-[3-(2-fluorofenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol



[0584] Etapa 1: A una solución de (2S,3S)-3-indol-1-il-3-(3-fluorofenil)-propano-1,2-diol (EJEMPLO 47, etapa 5, 1.34 g, 4.56 mmol) en N,N-dimetilformamida (20 mL) se agrega hidróxido de potasio sólido pulverizado (0.76 g, 13.68 mmol). La mezcla se agita durante 15 minutos bajo nitrógeno a temperatura ambiente, después de lo cual se agrega yodo (1.21 g, 4.72 mmol) en una porción. La mezcla se agita durante 30 minutos a temperatura ambiente, luego se vierte en 100 mL de a 5% de solución de

tiosulfato de sodio acuosa. La solución se extrae 3 veces con acetato de etilo y los extractos combinados se lavan 3 veces con agua. La capa orgánica se seca sobre sulfato de sodio anhidro, se filtra, y se concentra en vacío. El producto crudo se purifica por vía de Cromatografía Biotage (FlasH40i, sílice, 40% de acetato de etilo/hexano) para proporcionar 0.91 g (48%) de (2S,3S)-3-(3-fluorofenil)-3-(3-yodo-1H-indol-1-il)propano-1,2-diol como un aceite café oscuro. MS (ES) *m/z* 411.9.

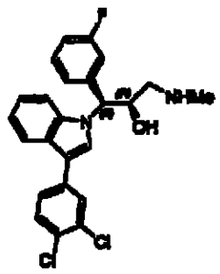
[0585] Etapa 2: Una mezcla de (2S,3S)-3-(3-fluorofenil)-3-(3-yodo-1H-indol-1-il)propano-1,2-diol (0.25 g, 0.61 mmol), ácido 2-fluorobencenoborónico (0.12 g, 0.85 mmol), y fosfato de potasio (0.39 g, 1.83 mmol) en N,N-dimetilformamida (10 mL) se desgasifica con nitrógeno durante 5 minutos luego se agrega una cantidad catalítica (0.02 g) de [1,4-bis-dicloruro de (difenilfosfina)butano]paladio (II). La solución se calienta a 90° C durante 3 horas luego se enfría y se vierte en 100 mL de agua. La mezcla acuosa se extrae 3 veces con acetato de etilo y los extractos combinados luego se lavan 2 veces con agua. El acetato de etilo se seca por filtración a través de un tapón de gel de sílice luego se concentra. El residuo se purifica por Cromatografía Biotage (FlasH40i, sílice, 40% de acetato de etilo/hexano) para proporcionar 0.14 g de (2S,3S)-3-(3-fluorofenil)-3-{3-[2-fluorofenil]-1H-indol-1-il}propano-1,2-diol como un aceite, el cual se usa en la siguiente etapa sin purificación adicional.

[0586] Etapa 3: De forma análoga al EJEMPLO 1, etapa 2 se prepara 3-(3-fluorofenil)-3-[3-(2-fluorofenil)-indol-1-il]-2-hidroxi-

propil éster de ácido (2S,3S)-tolueno-4-sulfónico a partir de (2S,3S)-3-(3-fluorofenil)-3-{3-[2-fluorofenil]-1H-indol-1-il}propano-1,2-diol.

[0587] Etapa 4: De forma análoga al EJEMPLO 5, se prepara clorhidrato de (1S,2R)-1-(3-fluorofenil)-1-[3-(2-fluorofenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol a partir de 3-(3-fluorofenil)-3-[3-(2-fluorofenil)-indol-1-il]-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina (solución en metanol 2N). MS (ES) *m/z* 393.1.

[0588] EJEMPLO 115: clorhidrato de (1S,2R)-1-[3-(3,4-diclorofenil)-1H-indol-1-il]-1-(3-fluorofenil)-3-(metilamino)propan-2-ol



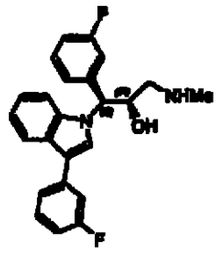
[0589] De forma análoga al EJEMPLO 114, etapa 2, se prepara (2S,3S)-3-(3,4-diclorofenil)-3-{3-[2-fluorofenil]-1H-indol-1-il}propano-1,2-diol a partir de (2S,3S)-3-(3-fluorofenil)-3-(3-yodo-1H-indol-1-il)propano-1,2-diol (EJEMPLO 114, etapa 1) y ácido 3,4-diclorobenceno borónico.

[0590] De forma análoga al EJEMPLO 1, etapa 2 se prepara 3-[3-(3,4-dicloro-fenil)-indol-1-il]-3-(3-fluorofenil)-2-hidroxi-

propil éster de ácido (2S,3S)-tolueno-4-sulfónico a partir de (2S,3S)-3-[3-(3,4-Dicloro-fenil)-indol-1-il]-3-(3-fluoro-fenil)-propano-1,2-diol.

[0591] De forma análoga al EJEMPLO 5, se prepara clorhidrato de (1S,2R)-1-[3-(3,4-diclorofenil)-1H-indol-1-il]-1-(3-fluorofenil)-3-(metilamino)propan-2-ol a partir de 3-[3-(3,4-dicloro-fenil)-indol-1-il]-3-(3-fluoro-fenil)-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina (solución en metanol 2N). MS (ES) *m/z* 443.0.

[0592] EJEMPLO 116: clorhidrato de (1S,2R)-1-(3-fluorofenil)-1-[3-(3-fluorofenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol



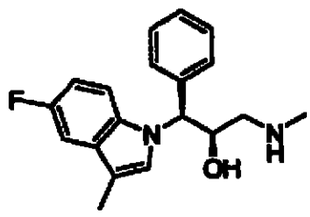
[0593] De forma análoga al EJEMPLO 114, etapa 2, se prepara (2S,3S)-3-(3-fluorofenil)-3-{3-[3-fluorofenil]-1H-indol-1-il}propano-1,2-diol a partir de (2S,3S)-3-(3-fluorofenil)-3-(3-yodo-1H-indol-1-il)propano-1,2-diol (EJEMPLO 114, etapa 1) y ácido 3-fluorobenceno borónico.

[0594] De forma análoga al EJEMPLO 1, etapa 2 se prepara 3-(3-fluorofenil)-3-[3-(3-fluorofenil)-indol-1-il]-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico a partir de (2S,3S)-3-

(3-fluorofenil)-3-{3-[3-fluorofenil]-1H-indol-1-il}propano-1,2-diol.

[0595] De forma análoga al EJEMPLO 5, se prepara clorhidrato de (1S,2R)-1-(3-fluorofenil)-1-[3-(3-fluorofenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol a partir de 3-(3-fluoro-fenil)-3-[3-(3-fluorofenil)-indol-1-il]-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina (solución en metanol 2N). MS (ESI) *m/z* 393.

[0596] EJEMPLO 117: clorhidrato de (1S,2R)-1-(5-fluoro-3-metil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol



[0597] Etapa 1: a una mezcla de 4-fluoro-fenilamina (9 g, 81 mmol), ácido clorhídrico concentrado (20.4 mL), y agua (35.1 mL) se agrega nitrito de sodio (6.3 g, 89.1 mmol) se disuelve en agua (7.8 mL). En un frasco separado 2-etilacetoacetato de etilo (14.4 g, 89.1 mmol) en etanol (63.6 mL) a 0° C se trata con hidróxido de potasio (5.1 g, 89.1 mmol) en agua (7.5 mL) y hielo y se agrega la solución anterior. El pH de la reacción se ajusta a 5-6 y la reacción se agita a 0° C durante 3 horas y luego se almacena en el congelador durante toda la noche. La reacción entonces se extrae con acetato de etilo (100 mL) y los orgánicos se lavan con solución salina saturada (100 mL), se secan con sulfato de

magnesio anhidro. La mayor parte de el solvente se remueve en vacío antes de que se agrega en forma de gota a 14.5% de Una solución etanólica de ácido clorhídrico (70 mL) a 78° C. El calentamiento se continúa durante 2 horas. El solvente se remueve en vacío y el residuo se trata con diclorometano (300 mL) y agua (100 mL). La capa orgánica se lava con cloruro de sodio saturado (200 mL), se seca sobre sulfato de sodio y se concentra en vacío. La purificación sobre una columna de lavado corta (gel de sílice, 25% de acetato de etilo/hexano) da 5-fluoro-3-metil-1H-indol-2-carboxilato de etilo como un sólido blanco. MS (ES) *m/z* 220.0

[0598] Etapa 2: 5-fluoro-3-metil-1H-indol-2-carboxilato de etilo (8.3 g, 37.5 mmol) y hidróxido de potasio (6.3 g, 112.5 mmol) en una mezcla de etanol (20 mL) y agua (15 mL) se calienta a reflujo durante 1 hora. El volumen se reduce a 10 mL bajo presión reducida y la solución se lleva a un pH acídico con una solución acuosa de ácido clorhídrico 3N. El precipitado resultante se filtra, se lava con agua (100 mL) y se seca en vacío a 80° C durante toda la noche para proporcionar ácido 5-fluoro-3-metil-1H-indol-2-carboxílico como un sólido blanco. MS (ES) *m/z* 192.0

[0599] Etapa 3: ácido 5-fluoro-3-metil-1H-indol-2-carboxílico (8.49 g, 43.9 mmol) y metal de cobre (0.35 g, 5.5 mmol) en quinolina destilada (22 mL) se calienta a reflujo durante 3 horas. El polvo de cobre se filtra y retira y el filtrado se lleva a un pH 3 a 0° C con una solución acuosa de ácido clorhídrico 6N. La solución se extrae con éter (200 mL) y los orgánicos se lava con cloruro de sodio saturado (200 mL), se seca

sobre sulfato de magnesio y se concentra en vacío para dar 5-fluoro-3-metil-1H-indol como un sólido café. MS (ES) *m/z* 150.0.

[0600] Etapa 4: A una solución de D-tartrato de diisopropilo (6 mL, 28 mmol) en cloruro de metileno (800 mL) a -10° C bajo nitrógeno se agrega tamices moleculares 4A (15g), isopropóxido de titanio (5.9 mL, 20 mmol), y alcohol de cinamilo (27g, 200 mmol). La mezcla se le permite envejecer durante 40 minutos a -10° C, después de lo cual se enfría a -20° C, y se trata en a en forma de gota con una solución de hidroperóxido de terc-butilo (TBHP, ~450 mmol) en isooctano. Después de 18 horas a -30 hasta -15° C, la mezcla de reacción se trata con una solución acuosa de hidróxido de sodio al 30% (5 mL) y dietil éter (100 mL). El baño frío se remueve y se le permite a la mezcla calentarse a ~ 10° C. Se agrega sulfato de magnesio (anhidro, 15 g) y la mezcla se agita durante 20 minutos. Después los sólidos se asentaron, la solución se filtra a través de almohadilla de gel de sílice, y se lava con éter (50 mL). El filtrado se concentra en vacío y se agrega tolueno para remover azeotrópicamente el TBPH que no reacciona. El residuo luego se purifica utilizando una columna de gel de sílice (hexano:acetato de etilo/3: 1) y el producto purificado se cristaliza de hexano/acetato de etilo para proporcionar [(2R,3R)-3-feniloxiran-2-il]metanol como cristal blanco (18g, 60%, 98.2% ee). MS (ESI) *m/z* 15

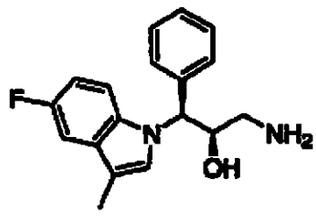
[0601] Etapa 5: Una mezcla de 5-fluoro-3-metil-1H-indol (2.91 g, 19.5 mmol) e hidruro de potasio en dispersión al 50% en aceite mineral (2.8 g, 35.1 mmol) en diclorometano (40 mL) se agita durante 10 minutos bajo nitrógeno a temperatura ambiente. Una

solución de [(2R,3R)-3-feniloxiran-2-il]metanol (2.0 g, 13.0 mmol) e isopropóxido de titanio (4.3 mL, 14.3 mmol) en diclorometano (10 mL) entonces se agrega y la mezcla se agita a temperatura ambiente durante 12 horas. Después de la desaparición del epóxido, la mezcla se particiona entre una solución acuosa de ácido clorhídrico 1 N (50 mL) y acetato de etilo (50 mL). La capa orgánica se separa, se lava con bicarbonato de sodio saturado (50 mL), se seca sobre sulfato de sodio anhidro, se filtra, y se concentra en vacío. El producto crudo se purifica por vía de Cromatografía Biotage (FlasH40i, sílice, 60% de acetato de etilo/hexano) para dar (2S,3S)-3-(5-fluoro-3-metil-1H-indol-1-il)-3-fenilpropano-1,2-diol. MS (ESI) *m/z* 300.

[0602] Etapa 6: Una solución de (2S,3S)-3-(5-fluoro-3-metil-1H-indol-1-il)-3-fenilpropano-1,2-diol (1.03 g, 3.4 mmol) y cloruro de p-toluenosulfonilo (0.78 g, 4.1 mmol) en piridina anhidra (11 ml) se agita a temperatura ambiente bajo nitrógeno durante 12 horas. La reacción se vierte en una solución acuosa de ácido clorhídrico 1 N (50 mL) y se extrae con acetato de etilo (50 mL). Los orgánicos se secan sobre sulfato de sodio anhidro, se filtra, y se concentra para dar 3-(5-fluoro-3-metil-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S,3S)-tolueno-4-sulfónico. El producto se utiliza en la siguiente etapa sin purificación adicional. A una solución de 3-(5-fluoro-3-metil-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido tolueno-4-sulfónico (1.6 g, 3.4 mmol) en metanol (10 mL) se agrega una solución de metilamina 2N en metanol (8.6 mL, 17 mmol) y la reacción se agita durante 12 horas. Luego de que se completa, la reacción se particiona entre bicarbonato de sodio saturado (50

mL) y acetato de etilo (50 mL). La capa orgánica se separa, se seca sobre sulfato de sodio anhidro, se filtra, y se concentra en vacío. El producto crudo se purifica por vía de Cromatografía Biotage (FlasH40i, sílice, 20% de MeOH/diclorometano) para dar (1S,2R)-1-(5-fluoro-3-metil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol como un aceite claro. La base libre se disuelve en una cantidad mínima de etanol y se trata con a una solución etérea de ácido clorhídrico 2N y se agita durante 1 hora. El etanol se remueve en vacío y el aceite claro se tritura con éter/diclorometano para dar clorhidrato de (1S,2R)-1-(5-fluoro-3-metil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol como un sólido blanco. MS (ESI) *m/z* 313.

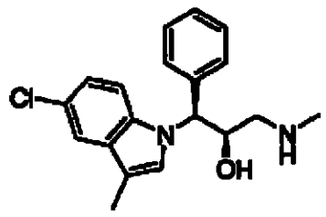
[0603] EJEMPLO 118: clorhidrato de (1SR,2RS)-3-amino-1-(5-fluoro-3-metil-1H-indol-1-il)-1-fenilpropan-2-ol



[0604] A una solución de 3-(5-fluoro-3-metil-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S,3S)-tolueno-4-sulfónico (Intermedio en el EJEMPLO 117, etapa 6, 0.15 g,.33 mmol) en metanol (10 mL) se agrega hidróxido de amonio concentrado (20 mL), y la reacción se agita durante 12 horas. Luego de que se completa, la reacción se particiona entre agua (25 mL) y acetato de etilo (25 mL). La capa orgánica se separa, se seca sobre sulfato de sodio anhidro, se filtra, y se concentra en vacío. El

producto crudo se purifica por vía de Cromatografía Biotage (FlasH40i, sílice, 25% de MeOH/diclorometano) para dar (1SR,2RS)-3-amino-1-(5-fluoro-3-metil-1H-indol-1-il)-1-fenilpropan-2-ol como un aceite claro. La base libre se disuelve en una cantidad mínima de etanol y se trata con una solución de ácido clorhídrico 4N en dioxano y se agita durante 1 hora. El etanol se remueve en vacío y el aceite claro se tritura con éter/diclorometano para dar clorhidrato de (1SR,2RS)-3-amino-1-(5-fluoro-3-metil-1H-indol-1-il)-1-fenilpropan-2-ol como un sólido blanco. MS (ES) *m/z* 299.0

EJEMPLO 119: clorhidrato de (1S,2R)-1-(5-cloro-3-metil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol



[0605] De forma análoga al EJEMPLO 117, etapa 1 se prepara 5-cloro-3-metil-1H-indol-2-carboxilato de etilo a partir de 4-cloro-fenilamina. MS (ES) *m/z* 235.9

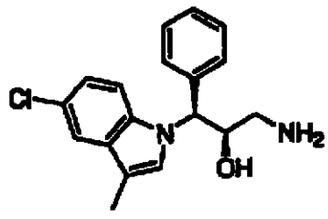
[0606] De forma análoga al EJEMPLO 117, etapa 2 se prepara ácido 5-cloro-3-metil-1H-indol-2-carboxílico a partir de 5-cloro-3-metil-1H-indol-2-carboxilato de etilo. MS (ESI) *m/z* 208.

[0607] De forma análoga al EJEMPLO 117, etapa 3 5-cloro-3-metil-1H-indol se prepara a partir de ácido 5-cloro-3-metil-1H-indol-2-carboxílico. MS (ESI) *m/z* 166.

[0608] De forma análoga al EJEMPLO 117, etapa 5 se prepara (2S,3S)-3-(5-cloro-3-metil-1H-indol-1-il)-3-fenilpropano-1,2-diol a partir de 5-cloro-3-metil-1H-indol y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4). MS (ES) *m/z* 316.0.

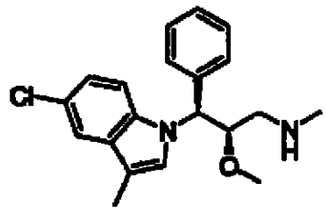
[0609] De forma análoga al EJEMPLO 117, etapa 6 se prepara clorhidrato de (1S,2R)-1-(5-cloro-3-metil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol a partir de (2S,3S)-3-(5-cloro-3-metil-1H-indol-1-il)-3-fenilpropano-1,2-diol. MS (ES) *m/z* 329.0.

[0610] EJEMPLO 120: clorhidrato de (1S,2R)-3-amino-1-(5-cloro-3-metil-1H-indol-1-il)-1-fenilpropan-2-ol



[0611] De forma análoga al EJEMPLO 118, se prepara (1S,2R)-3-amino-1-(5-cloro-3-metil-1H-indol-1-il)-1-fenilpropan-2-ol a partir de (2S,3S)-3-(5-cloro-3-metil-1H-indol-1-il)-3-fenilpropano-1,2-diol (EJEMPLO 119, etapa 4). MS (ES) *m/z* 315.1.

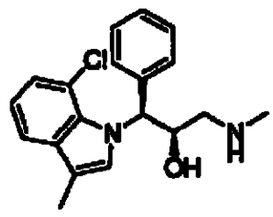
[0612] EJEMPLO 121: [(2R,3S)-3-(5-cloro-3-metil-1H-indol-1-il)-2-metoxi-3-fenilpropil]metilamina



[0613] Una mezcla de 3-(5-cloro-3-metil-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S,3S)-tolueno-4-sulfónico (Intermedio en el EJEMPLO 119, etapa 6, 0.52 g, 1.1 mmol), metil éster de ácido trifluoro-metanosulfónico (0.6 mL, 5.5 mmol), y 2,6-di-terc-butil-4-metil-piridina (1.1 g, 5.5 mmol) se calienta a reflujo en diclorometano (20 mL) durante 2 horas. La reacción se particiona entre acetato de etilo (25 mL) y una solución acuosa de ácido clorhídrico 1 N (25 mL). Los orgánicos se separan y se lavan con una solución acuosa saturada de bicarbonato de sodio (25 mL), se secan sobre sulfato de sodio anhidro, y se concentran en vacío. El producto crudo se purifica vía cromatografía de columna flash (sílice, 20% de acetato de etilo en hexano) para dar 3-(5-cloro-3-metil-indol-1-il)-2-metoxi-3-fenil-propil éster de ácido (2S,3S)-tolueno-4-sulfónico. A una solución de 3-(5-cloro-3-metil-indol-1-il)-2-metoxi-3-fenil-propil éster de ácido tolueno-4-sulfónico (0.13 g, 0.27 mmol) en metanol (10 mL) se agrega una solución de metilamina 2N en metanol (1.4 mL, 2.7 mmol) y la reacción se calienta en un tubo sellado durante 12 horas. Luego de que se completa, la reacción se particiona entre una solución acuosa saturada bicarbonato de sodio (25 mL) y diclorometano (25 mL). Los orgánicos se separan y

se remueven en vacío. El residuo se retira en dietil éter (25 mL) y se lava con una solución acuosa de ácido clorhídrico 1 N (25 mL). La capa acuosa se basifica a un pH 8 con una solución acuosa saturada de bicarbonato de sodio (50 mL). El producto se extrae con dietil éter (25 mL), se seca sobre sulfato de sodio anhidro, y se concentra en vacío. La base libre se disuelve en una cantidad mínima de etanol y se trata con una solución de ácido clorhídrico 4N en dioxano y se agita durante 1 hora. El etanol se remueve en vacío para dar [(2R,3S)-3-(5-cloro-3-metil-1H-indol-1-il)-2-metoxi-3-fenilpropil]metilamina como un aceite amarillo. MS (ESI) *m/z* 343

[0614] EJEMPLO 122: clorhidrato de (1S,2R)-1-(7-cloro-3-metil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol



[0615] De forma análoga al EJEMPLO 117, etapa 1 se prepara 7-cloro-3-metil-1H-indol-2-carboxilato de etilo a partir de 2-cloro-fenilamina. MS (ESI) *m/z* 238.

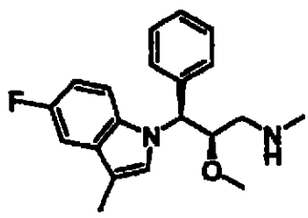
[0616] De forma análoga al EJEMPLO 117, etapa 2 se prepara ácido 7-cloro-3-metil-1H-indol-2-carboxílico a partir de 7-cloro-3-metil-1H-indol-2-carboxilato de etilo. MS (ES) *m/z* 208.0.

[0617] De forma análoga al EJEMPLO 117, etapa 3 se prepara 7-cloro-3-metil-1H-indol a partir de ácido 7-cloro-3-metil-1H-indol-2-carboxílico.

[0618] De forma análoga al EJEMPLO 117, etapa 5 se prepara (2S,3S)-3-(7-cloro-3-metil-1H-indol-1-il)-3-fenilpropano-1,2-diol a partir de 7-cloro-3-metil-1H-indol y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4). MS (ESI) m/z 316; MS (ESI) *m/z* 314.

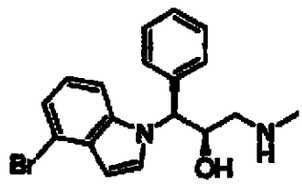
[0619] De forma análoga al EJEMPLO 117, etapa 6 se prepara clorhidrato de (1S,2R)-1-(7-cloro-3-metil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol a partir de (2S,3S)-3-(7-cloro-3-metil-1H-indol-1-il)-3-fenilpropano-1,2-diol. MS (ESI) *m/z* 329.

[0620] EJEMPLO 123: clorhidrato de [(2R,3S)-3-(5-fluoro-3-metil-1H-indol-1-il)-2-metoxi-3-fenilpropil]metilamina



[0621] De forma análoga al EJEMPLO 121, se prepara clorhidrato de [(2R,3S)-3-(5-fluoro-3-metil-1H-indol-1-il)-2-metoxi-3-fenilpropil]metilamina de 3-(5-fluoro-3-metil-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S,3S)-tolueno-4-sulfónico (Intermedio en el EJEMPLO 117, etapa 6). MS (ESI) *m/z* 327.

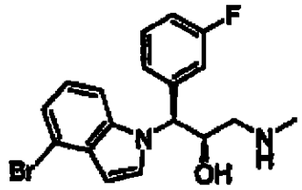
[0622] EJEMPLO 124: clorhidrato de (1S,2R)-1-(4-bromo-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol



[0623] De forma análoga al EJEMPLO 117, etapa 5 se prepara (2S,3S)-3-(4-bromo-1H-indol-1-il)-3-fenilpropano-1,2-diol a partir de 4-bromo-1H-indol y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4). MS (ESI) *m/z* 346.

[0624] De forma análoga al EJEMPLO 117, etapa 6 se prepara clorhidrato de (1S,2R)-1-(4-bromo-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol a partir de (2S,3S)-3-(4-bromo-1H-indol-1-il)-3-fenilpropano-1,2-diol. MS (ESI) *m/z* 359.

[0625] EJEMPLO 125: clorhidrato de (1S,2R)-1-(4-bromo-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol

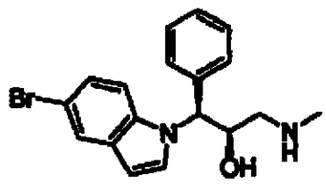


[0626] De forma análoga al EJEMPLO 117, etapa 5 se prepara (2S,3S)-3-(4-bromo-1H-indol-1-il)-3-(3-fluorofenil)propano-1,2-diol a partir de 4-bromo-1H-indol y [(2R,3R)-3-(3-

fluorofenil)oxiran-2-il]metanol (EJEMPLO 47 etapa 3). MS (ESI) *m/z* 364.

[0627] De forma análoga al EJEMPLO 117, etapa 6 se prepara clorhidrato de (1S,2R)-1-(4-bromo-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol a partir de (2S,3S)-3-(4-bromo-1H-indol-1-il)-3-(3-fluorofenil)propano-1,2-diol. MS (ESI) *m/z* 377.

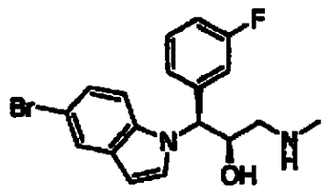
[0628] EJEMPLO 126: clorhidrato de (1S,2R)-1-(5-bromo-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol



[0629] De forma análoga al EJEMPLO 117, etapa 5 se prepara (2S,3S)-3-(5-bromo-1H-indol-1-il)-3-fenilpropano-1,2-diol a partir de 5-bromo-1H-indol y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4). MS (ESI) m/z346.

[0630] De forma análoga al EJEMPLO 117, etapa 6 se prepara clorhidrato de (1S,2R)-1-(5-bromo-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol a partir de (2S,3S)-3-(5-bromo-1H-indol-1-il)-3-fenilpropano-1,2-diol. MS (ESI) *m/z* 359.

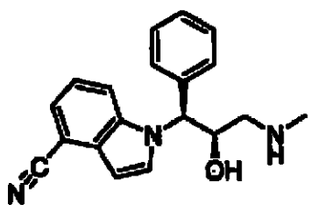
[0631] EJEMPLO 127: clohidrato de (1S,2R)-1-(5-bromo-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol



[0632] De forma análoga al EJEMPLO 117, etapa 5 se prepara (2S,3S)-3-(5-bromo-1H-indol-1-il)-3-(3-fluorofenil)propano-1,2-diol a partir de 5-bromo-1H-indol y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47 etapa 3). MS (ESI) *m/z* 364.

[0633] De forma análoga al EJEMPLO 117, etapa 6 se prepara clorhidrato de (1S,2R)-1-(5-bromo-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol a partir de (2S,3S)-3-(5-bromo-1H-indol-1-il)-3-(3-fluorofenil)propano-1,2-diol. MS (ESI) *m/z* 377.

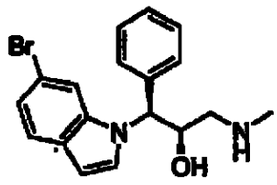
[0634] EJEMPLO 128: clorhidrato de 1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1H-indol-4-carbonitrilo



[0635] De forma análoga al EJEMPLO 117, etapa 5 se prepara 1-(2,3-dihidroxi-1-fenil-propil)-1H-indol-4-carbonitrilo a partir de 1 H-indol-4-carbonitrilo y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4).

[0636] De forma análoga al EJEMPLO 117, etapa 6 se prepara clorhidrato de 1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1H-indol-4-carbonitrilo a partir de 1-(2,3-dihidroxi-1-fenil-propil)-1H-indol-4-carbonitrilo. MS (ESI) *m/z* 306.

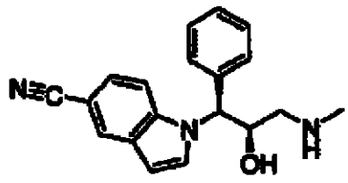
[0637] EJEMPLO 129: clorhidrato de (1S,2R)-1-(6-bromo-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol



[0638] De forma análoga al EJEMPLO 117, etapa 5 se prepara 3-(6-bromo-indol-1-il)-3-fenil-propano-1,2-diol a partir de 6-bromo-1H-indol y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4).

[0639] De forma análoga al EJEMPLO 117, etapa 6 se prepara clorhidrato de (1S,2R)-1-(6-bromo-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol a partir de 3-(6-bromo-indol-1-il)-3-fenil-propano-1,2-diol. MS (ESI) *m/z* 359.

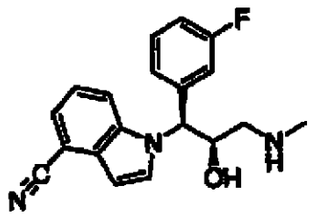
[0640] EJEMPLO 130: clorhidrato de 1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1H-indol-5-carbonitrilo



[0641] De forma análoga al EJEMPLO 117, etapa 5 se prepara 1-[(1S,2S)-2,3-dihidroxi-1-fenilpropil]-1H-indol-5-carbonitrilo a partir de 1 H-indol-5-carbonitrilo y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4). MS (ESI) *m/z* 293.

[0642] De forma análoga al EJEMPLO 117, etapa 6 se prepara clorhidrato de 1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1H-indol-5-carbonitrilo a partir de 1-[(1S,2S)-2,3-dihidroxi-1-fenilpropil]-1H-indol-5-carbonitrilo. MS (ES) *m/z* 306.1.

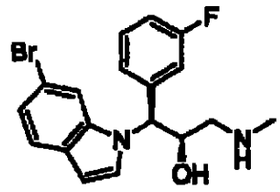
[0643] EJEMPLO 131: clorhidrato de 1-[(1S,2R)-1-(3-fluorofenil)-2-hidroxi-3-(metilamino)propil]-1H-indol-4-carbonitrilo



[0644] De forma análoga al EJEMPLO 117, etapa 5 se prepara 1-[1-(3-fluoro-fenil)-2,3-dihidroxi-propil]-1H-indol-4-carbonitrilo a partir de 1 H-indol-4-carbonitrilo y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47 etapa 3).

[0645] De forma análoga al EJEMPLO 117, etapa se prepara 6 clorhidrato de 1-[(1S,2R)-1-(3-fluorofenil)-2-hidroxi-3-(metilamino)propil]-1H-indol-4-carbonitrilo a partir de 1-[1-(3-fluoro-fenil)-2,3-dihidroxi-propil]-1H-indol-4-carbonitrilo. MS (ES) *m/z* 324.2.

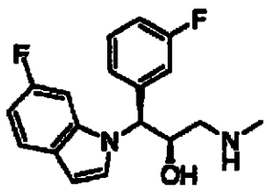
[0646] EJEMPLO 132: Clorhidrato de (1S, 2R)-1-(6-bromo-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol



[0647] De una manera análoga al EJEMPLO 117, etapa 5 se prepara 3-(6-bromo-indol-1-il)-3-(3-fluoro-fenil)-propano-1,2-diol a partir de 6-bromo-1H-indol y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47 etapa 3).

[0648] De una manera análoga al EJEMPLO 117, etapa 6 se prepara el Clorhidrato de (1S, 2R)-1-(6-bromo-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol a partir de 3-(6-bromo-indol-1-il)-3-(3-fluoro-fenil)-propano-1,2-diol. MS (ES) m/z 377.1.

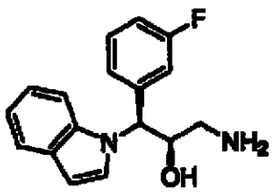
[0649] EJEMPLO 133: Clorhidrato de (1S, 2R)-1-(6-fluoro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol



[0650] De una manera análoga al EJEMPLO 117, etapa 5 se prepara (2S,3s)-3-(6-flouro-1H-indol-1-il)-3-(3-fluorofenil)-propano-1,2-diol a partir de 6-fluoro-1H-indol y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47 etapa 3). MS (ESI) m/z 304.

[0651] De una manera análoga al EJEMPLO 117, etapa 6 se prepara el Clorhidrato de (1S, 2R)-1-(6-fluoro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol a partir de (2S,3S)-3-(6-fluoro-indol-1-il)-3-(3-fluorofenil)-propano-1,2-diol. MS (ES) m/z 317.1.

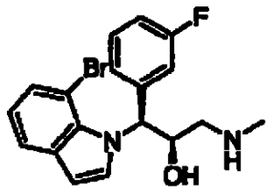
[0652] EJEMPLO 134: Clorhidrato de (1S, 2R)-3-amino-1- (3-fluorofenil)-1-(1H-indol-1-il)propan-2-ol



[0653] De una manera análoga al EJEMPLO 117, etapa 5 se prepara 3- (3-fluoro-fenil)-3-indol-1-il-propano-1,2-diol a partir de 1H-indol y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47 etapa 3).

[0654] De una manera análoga al EJEMPLO 117, etapa 6 se prepara Clorhidrato de (1S, 2R)-3-amino-1- (3-fluorofenil)-1-(1H-indol-1-il)propan-2-ol el a partir de 3- (3-fluoro-fenil)-3-indol-1-il-propano-1,2-diol y ácido *para*-toluenosulfónico. MS (ES) m/z 377.1.

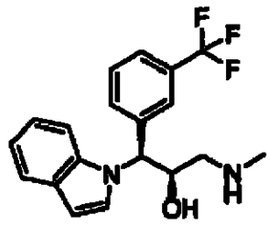
[0655] EJEMPLO 135: Clorhidrato de (1S, 2R)-1-(7-bromo-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol



[0656] De una manera análoga al EJEMPLO 117, etapa 5 se prepara 3-(7-bromo-indol-1-il)-3-(3-fluoro-fenil)-propano-1,2-diol a partir de 7-bromo-1H-indol y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47 etapa 3).

[0657] De una manera análoga al EJEMPLO 117, etapa 6 se prepara el Clorhidrato de (1S, 2R)-1-(7-bromo-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol a partir de 3-(7-bromo-indol-1-il)-3-(3-fluoro-fenil)-propano-1,2-diol. MS (ES) m/z 377.

[0658] EJEMPLO 136: Clorhidrato de (1S, 2R)-1-(1H-indol-1-il)-3-(metilamino)-1-[3-(trifluorometil)fenil]propan-2-ol



[0659] De una manera análoga al EJEMPLO 47, etapa 1 se prepara m-(trifluorometil)-, metil éster de ácido cinámico a partir de ácido 3-(3-trifluorometil-fenil)-acrílico. MS (ES) m/z 231.1.

[0660] De una manera análoga al EJEMPLO 47, etapa 2 se prepara (2E)-3-[3-(trifluorometil)fenil]prop-2-en-1-ol a partir de m-(trifluorometil)-, metil éster de ácido cinámico. MS (ES) m/z 185.1.

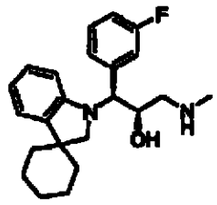
[0661] De una manera análoga al EJEMPLO 47, etapa 3 se prepara {(2R,3R)-3-[3-(trifluorometil)oxiran-2-il}metanol a partir de (2E)-3-[3-(trifluorometil)fenil]prop-2-en-1-ol. MS (ES) m/z 217.3.

[0662] De una manera análoga al EJEMPLO 47, etapa 4 se prepara (2S, 3S)-3-(2,3-dihidro-1H-indol-1-il) -3-[3-(trifluorometil)fenil]propano-1,2-diol a partir de {(2R,3R)-3-[3-(trifluorometil)oxiran-2-il}metanol. MS (ES) m/z 338.

[0663] De una manera análoga al EJEMPLO 47, etapa 5 se prepara (2S, 3S)-3-(1H-indol-1-il) -3-[3-(trifluorometil)fenil]propano-1,2-diol a partir de (2S, 3S)-3-(2,3-dihidro-1H-indol-1-il) -3-[3-(trifluorometil)fenil]propano-1,2-diol . MS (ESI) m/z 336.

[0664] De una manera análoga al EJEMPLO 117, etapa 6 se prepara Clorhidrato de (1S, 2R)-1-(1H-indol-1-il) -3-(metilamino)-1-[3-(trifluorometil)fenil]propan-2-ol a partir de (2S, 3S)-3-(1H-indol-1-il) -3-[3-(trifluorometil)fenil]propano-1,2-diol. MS (ESI) m/z 349.1.

[0665] EJEMPLO 137: Clorhidrato de (1S, 2R)-1-(3-fluorofenil) -3-(metilamino)-1-espiro[ciclohexano-1-3'-indol]-1'(2'H)-ilpropan-2-ol



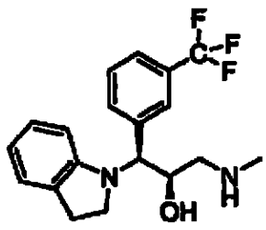
[0666] De una manera análoga al EJEMPLO 47, etapa 4 se prepara (2S, 3S)-3-(3-fluorofenil) -3-espiro[ciclohexano-1-3'-indol]-1'(2'H)-ilpropano-1,2-diol a partir de 1',2'-dihidroespiro[ciclohexano-1-3'-indol][15] y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47 etapa 3) como un sólido blanco. MS (ES) m/z 356.2 ($[M+H]^+$); HRMS: Calc. Para $C_{22}H_{26}FNO_2 + H^+$, 356.2020; se encuentra (ESI, $[M+H]^+$, 356.2031.

[0667] De una manera análoga al EJEMPLO 47, etapa 6, se prepara el Clorhidrato de (1S, 2R)-1-(3-fluorofenil) -3-(metilamino)-1-espiro[ciclohexano-1-3'-indol]-1'(2'H)-ilpropan-2-ol a partir de (2S, 3S)-3-(3-fluorofenil) -3-espiro[ciclohexano-

[15] Kucerovy, A.; Hathaway, J. S.; Mattner, P. G.; Repic, O. *Synth. Commun.* 1992, 22, 729-733.

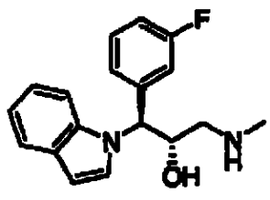
1-3'-indol]-1'(2'H)-ilpropano-1,2-diol como un polvo blanco.. MS (ES) m/z 369.2 ($[M+H]^+$); HRMS: Calc. Para $C_{23}H_{29}FN_2O$ + H^+, 369.2337; se encuentra (ESI, $[M+H]^+$, 369.2332.

[0668] EJEMPLO 138: clorhidrato de (1S,2R)-1-(2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-[3-(trifluorometil)fenil]propan-2-ol



[0669] De forma análoga al EJEMPLO 117, etapa 6 se prepara (1S,2R)-1-(2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-[3-(trifluorometil)fenil]propan-2-ol a partir de (2S,3S)-3-(2,3-dihidro-1H-indol-1-il)-3-[3-(trifluorometil)feniljpropano-1,2-diol (EJEMPLO 136, etapa 4). MS (ES) *m/z* 351.1.

[0670] EJEMPLO 139: clorhidrato de (1S,2S)-1-(3-fluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol



[0671] De forma análoga al EJEMPLO 16, etapa 2 se prepara 4-nitrobenzoato de (2S,3S)-3-(3-fluorofenil)-2-hidroxi-3-(1H-indol-

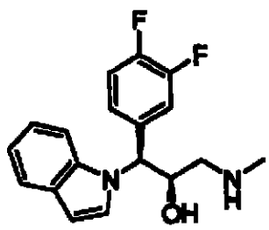
1-il)propilo a partir de 3-(3-fluoro-fenil)-3-indol-1-il-propano-1,2-diol (EJEMPLO 134, etapa 1). MS (ES) *m/z* 435.0.

[0672] De forma análoga al EJEMPLO 16, etapa 3 se prepara a 3-(3-fluoro-fenil)-3-indol-1-il-2-metanosulfoniloxi-propil éster de ácido 4-nitro-benzóico partir de 4-nitrobenzoato de (2S,3S)-3-(3-fluorofenil)-2-hidroxi-3-(1H-indol-1-il)propilo.

[0673] De forma análoga al EJEMPLO 16, etapa 4 se prepara 1-{(S)-(3-fluorofenil)[(2R)-oxiran-2-il]metil}-1H-indol a partir de 3-(3-fluoro-fenil)-3-indol-1-il-2-metanosulfoniloxi-propil éster de ácido 4-nitro-benzóico . MS (ESI) *m/z* 338.

[0674] De forma análoga al EJEMPLO 16, etapa 5 se prepara clorhidrato de (1S,2S)-1-(3-fluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol a partir de 1-{(S)-(3-fluorofenil) [(2R)-oxiran-2-il]metil}-1H-indol. MS (ESI) *m/z* 299.

[0675] EJEMPLO 140: clorhidrato de (1S,2R)-1-(3,4-difluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol



[0676] De forma análoga al EJEMPLO 47, etapa 1 3,4-difluoro-, metil éster, de ácido cinámico (E) se prepara a partir de ácido 3-(3,4-difluoro-fenil)-acrílico. MS (ES) *m/z* 199.1.

[0677] De forma análoga al EJEMPLO 47, etapa 2 se prepara (2E)-3-(3,4-difluorofenil)prop-2-en-1-ol a partir de 3,4-difluoro-, metil éster, de ácido cinámico (E). MS (ES) *m/z* 153.1.

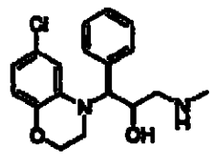
[0678] De forma análoga al EJEMPLO 47, etapa 3 se prepara [(2R,3R)-3-(3,4-difluorofenil)oxiran-2-il]metanol a partir de (2E)-3-(3,4-difluorofenil)prop-2-en-1-ol. MS (ES) *m/z* 185.1.

[0679] De forma análoga al EJEMPLO 47, etapa 4 se prepara (2S,3S)-3-(3,4-difluorofenil)-3-(2,3-dihidro-1H-indol-1-il)propano-1,2-diol a partir de indolina y [(2R,3R)-3-(3)4-difluorofenil)oxiran-2-il]metanol. MS (ES) *m/z* 306.1.

[0680] De forma análoga al EJEMPLO 47, etapa 5 se prepara (2S,3S)-3-(3,4-difluorofenil)-3-(1H-indol-1-il)propano-1,2-diol a partir de (2S,3S)-3-(3,4-difluorofenil)-3-(2,3-dihidro-1H-indol-1-il)propano-1,2-diol. MS (ESI) *m/z* 304.

[0681] De forma análoga al EJEMPLO 117, etapa 6 se prepara clorhidrato de (1S,2R)-1-(3,4-difluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol a partir de (2S,3S)-3-(3,4-difluorofenil)-3-(1H-indol-1-il)propano-1,2-diol. MS (ES) *m/z* 317.1.

[0682] EJEMPLO 141: clorhidrato de (1RS,2SR)-1-(6-cloro-2,3-dihidro-4H-1,4-benzoxazin-4-il)-3-(metilamino)-1-fenilpropan-2-ol

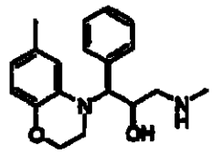


[0683] De forma análoga al EJEMPLO 33, etapa 1, se prepara (2RS,3RS)-3-(6-cloro-2,3-dihidro-4H-1,4-benzoxazin-4-il)-2-hidroxi-3-fenilpropanoato de etilo a partir de 6-cloro-3,4-dihidro-2H-1,4-benzoxazina (EJEMPLO 88, etapa 1) y *trans*-etil-3-fenilglicidato como un líquido amarillo, viscoso. MS (ESI) *m/z* 362.0 ($[M+H]^+$); HRMS: calculado para $C_{19}H_{20}ClNO_4$ + H^+, 362.1154; encontrado (ESI, $[M+H]^+$), 362.1150.

[0684] De forma análoga al EJEMPLO 33, etapa 2, se prepara (2RS,3RS)-3-(6-cloro-2,3-dihidro-4H-1,4-benzoxazin-4-il)-2-hidroxi-N-metil-3-fenilpropanamida a partir de (2RS,3RS)-3-(6-cloro-2,3-dihidro-4H-1,4-benzoxazin-4-il)-2-hidroxi-3-fenilpropanoato de etilo como agujas blancas. MS (ESI) *m/z* 344.9 ($[M-H^-]$); HRMS: calculado para $C_{18}H_{19}ClN_2O_3$ + H^+, 347.1157; encontrado (ESI, $[M+H]^+$), 347.1150.

[0685] De forma análoga al EJEMPLO 33, etapa 3, se prepara clorhidrato de (1RS,2SR)-1-(6-cloro-2,3-dihidro-4H-1,4-benzoxazin-4-il)-3-(metilamino)-1-fenilpropan-2-ol a partir de (2RS,3RS)-3-(6-cloro-2,3-dihidro-4H-1,4-benzoxazin-4-il)-2-hidroxi-N-metil-3-fenilpropanamida como un polvo blanco. MS (ESI) *m/z* 333.1 ($[M+H]^+$); HRMS: calculado para $C_{18}H_{21}ClN_2O_2$ + H^+, 333.1370; encontrado (ESI, $[M+H]^+$), 333.1381.

[0686] EJEMPLO 142: clorhidrato de (1RS,2SR)-3-(metilamino)-1-(6-metil-2,3-dihidro-4H-1,4-benzoxazin-4-il)-1-fenilpropan-2-ol



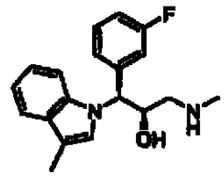
[0687] De forma análoga al EJEMPLO 165, etapa 1, se prepara 6-metil-3,4-dihidro-2H-1,4-benzoxazina a partir de 6-metil-2H-1,4-benzoxazin-3(4H)-ona como un aceite amarillo. MS (ES) *m/z* 150.0 ($[M+H]^+$); HRMS: calculado para $C_9H_{11}NO + H^+$, 150.0919; encontrado (ESI, $[M+H]^+$), 150.0924.

[0688] De forma análoga al EJEMPLO 33, etapa 1, se prepara (2RS,3RS)-2-hidroxi-3-(6-metil-2,3-dihidro-4H-1,4-benzoxazin-4-il)-3-fenilpropanoato de etilo a partir de 6-metil-3,4-dihidro-2H-1,4-benzoxazina y *trans*-etil-3-fenilglicidato como un líquido amarillo, viscoso. MS (ESI) *m/z* 342.0 ($[M+H]^+$); HRMS: calculado para $C_{2023}NO_4+ H^+$, 342.1700; encontrado (ESI, $[M+H]^+$), 342.1683.

[0689] De forma análoga al EJEMPLO 33, etapa 2, se prepara (2RS,3RS)-2-hidroxi-N-metil-3-(6-metil-2,3-dihidro-4H-1,4-benzoxazin-4-il)-3-fenilpropanamida a partir de (2RS,3RS)-2-hidroxi-3-(6-metil-2,3-dihidro-4H-1,4-benzoxazin-4-il)-3-fenilpropanoato de etilo como un polvo blanco. MS (ESI) *m/z* 325.0 ($[M-H]^-$); HRMS: calculado para $C_{19}H_{22}N_2O_3 + H^+$, 327.1703; encontrado (ESI, $[M+H]^+$), 327.1703.

[0690] De forma análoga al EJEMPLO 33, etapa 3, se prepara clorhidrato de (1RS,2SR)-3-(metilamino)-1-(6-metil-2,3-dihidro-4H-1,4-benzoxazin-4-il)-1-fenilpropan-2-ol a partir de (2RS,3RS)-2-hidroxi-N-metil-3-(6-metil-2,3-dihidro-4H-1,4-benzoxazin-4-il)-3-fenilpropanamida como un polvo blanco. MS (ESI) *m/z* 313.0 ($[M+H]^+$); HRMS: calculado para $C_{19}H_{24}N_2O_2$ + H^+, 313.1911; encontrado (ESI, $[M+H]^+$), 313.1908.

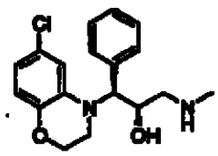
[0691] EJEMPLO 143: clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(3-metil-1H-indol-1-il)propan-2-ol



[0692] De forma análoga al EJEMPLO 117, etapa 5, se prepara (2S,3S)-3-(3-fluorofenil)-3-(3-metil-1H-indol-1-il)propano-1,2-diol a partir de 3-metilindol y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3) como un aceite amarilloso, viscoso. MS (ES) *m/z* 300.0 ($[M+H]^+$); HRMS: calculado para $C_{18}H_{18}FNO_2$ + H^+, 300.1400; encontrado (ESI, $[M+H]^+$), 300.1400.

[0693] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(3-metil-1H-indol-1-il)propan-2-ol a partir de (2S,3S)-3-(3-fluorofenil)-3-(3-metil-1H-indol-1-il)propano-1,2-diol como un sólido blanco. MS (ES) *m/z* 313.0 ($[M+H]^+$); HRMS: calculado para $C_{19}H_{21}FN_2O$ + H^+, 313.1711; encontrado (ESI, $[M+H]^+$), 313.1713.

[0694] EJEMPLO 144: clorhidrato de (1S,2R)-1-(6-cloro-2,3-dihidro-4H-1,4-benzoxazin-4-il)-3-(metilamino)-1-fenilpropan-2-ol



[0695] Etapa 1: (1RS,2SR)-1-(6-cloro-2,3-dihidro-4H-1,4-benzoxazin-4-il)-3-(metilamino)-1-fenilpropan-2-ol racémico (EJEMPLO 141) se disuelve en metanol. La solución resultante se inyecta en el instrumento de Cromatografía de Fluido Supercrítico. Se recolectan los enantiómeros resueltos en Línea de base, que utilizan las condiciones descritas adelante. Se determina la pureza enantiomérica de cada enantiómero bajo las mismas condiciones de Cromatografía de Fluido Supercrítico utilizando una columna Chiralpak AD-H 5u, 250 mm x 4.6 mm ID a un índice de flujo de 2.0 mL/minutos utilizando Cromatografía de Fluido Supercrítico Analítico (Berger Instruments, Inc. Newark, DE USA).

Instrumento SFC: Berger MultiGram Prep SFC (Berger Instruments, Inc. Newark, DE 19702.

Columna: Chiralpak AD-H; 5u; 250mm L x 20mm ID (Chiral Technologies, Inc, Exton, PA, USA)

Temperatura de columna: 35° C

Modificador SFC: 40% de MeOH con 0.5% DEA

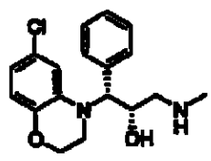
Índice de flujo: 50 mL/min

Presión de Salida: 100 bar

Detector: UV a 266 nm

[0696] Etapa 2: Una solución de (1S,2R)-1-(6-cloro-2,3-dihidro-4H-1,4-benzoxazin-4-il)-3-(metilamino)-1-fenilpropan-2-ol, aislada como pico 1, (58 mg, 0.17 mmol) en diclorometano (3 mL) se trata con una solución etérea de ácido clorhídrico (1 M, 0.2 mL, 0.2 mmol). A la solución resultante se agrega hexano hasta que se forma el polvo blanco, que se recolecta, se lava con hexano, y se seca en vacío para proporcionar 62 mg (45%) de clorhidrato de (1S,2R)-1-(6-cloro-2,3-dihidro-4H-1,4-benzoxazin-4-il)-3-(metilamino)-1-fenilpropan-2-ol. Pureza quiral: > 99.9%. MS (ESI) *m/z* 333.0 ($[M+H]^+$); HRMS: calculado para $C_{18}H_{21}ClN_2O_2$ + H^+, 333.1370; encontrado (ESI, $[M+H]^+$), 333.1372.

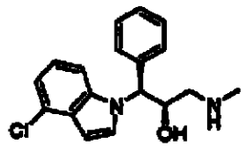
[0697] EJEMPLO 145: clorhidrato de (1R,2S)-1-(6-cloro-2,3-dihidro-4H-1,4-benzoxazin-4-il)-3-(metilamino)-1-fenilpropan-2-ol



[0698] De forma análoga al EJEMPLO 144, etapa 2, se prepara clorhidrato de (1R,2S)-1-(6-cloro-2,3-dihidro-4H-1,4-benzoxazin-

4-il)-3-(metilamino)-1-fenilpropan-2-ol a partir de (1R,2S)-1-(6-cloro-2,3-dihidro-4H-1,4-benzoxazin-4-il)-3-(metilamino)-1-fenilpropan-2-ol que se aísla como pico 2 de la separación quiral (EJEMPLO 144, etapa 1). Pureza quiral: > 99.9%. MS (ESI) *m/z* 333.0 ($[M+H]^+$); HRMS: calculado para $C_{18}H_{21}ClN_2O_2$ + H^+, 333.1370; encontrado (ESI, $[M+H]^+$), 333.1374.

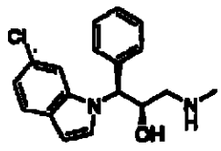
[0699] EJEMPLO 146: clorhidrato de (1S,2R)-1-(4-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol



[0700] De forma análoga al EJEMPLO 117, etapa 5, se prepara (2S,3S)-3-(4-cloro-1H-indol-1-il)-3-fenilpropano-1,2-diol a partir de 4-cloroindol y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un aceite amarilloso, viscoso. MS (ES) m/z 300.0 ($[M-H]^-$).

[0701] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(4-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol a partir de (2S,3S)-3-(4-cloro-1H-indol-1-il)-3-fenilpropano-1,2-diol como un polvo blanco. MS (ES) *m/z* 315.0 ($[M+H]^+$); HRMS: calculado para $C_{18}H_{19}ClN_2O$ + H^+, 315.1259; encontrado (ESI, $[M+H]^+$), 315.1255.

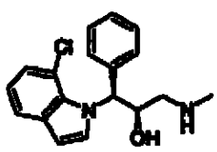
[0702] EJEMPLO 147: clorhidrato de (1S,2R)-1-(6-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol



[0703] De forma análoga al EJEMPLO 117, etapa 5, se prepara (2S,3S)-3-(6-cloro-1H-indol-1-il)-3-fenilpropano-1,2-diol a partir de 6-cloroindol y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un aceite incoloro, viscoso. MS (ES) *m/z* 302.0 ($[M+H]^+$); HRMS: calculado para $C_{17}H_{16}ClNO_2 + H^+$, 302.0948; encontrado (ESI, $[M+H]^+$), 302.0946.

[0704] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(6-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol a partir de (2S,3S)-3-(6-cloro-1H-indol-1-il)-3-fenilpropano-1,2-diol como un polvo blanco. MS (ES) *m/z* 315.0 ($[M+H]^+$); HRMS: calculado para $C_{18}H_{19}ClN_2O + H^+$, 315.1259; encontrado (ESI, $[M+H]^+$), 315.1263.

[0705] EJEMPLO 148: clorhidrato de (1S,2R)-1-(7-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol

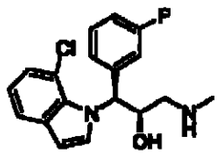


[0706] De forma análoga al EJEMPLO 117, etapa 5, se prepara (2S,3S)-3-(7-cloro-1H-indol-1-il)-3-fenilpropano-1,2-diol a partir de 7-cloroindol y [(2R,3R)-3-feniloxiran-2-il]metanol

(EJEMPLO 117, etapa 4) como un aceite incoloro, viscoso. MS (ES) *m/z* 302.0 ($[M+H]^+$); HRMS: calculado para $C_{17}H_{16}ClNO_2$ + H^+, 302.0948; encontrado (ESI, $[M+H]^+$), 302.0949.

[0707] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(7-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol a partir de (2S,3S)-3-(7-cloro-1H-indol-1-il)-3-fenilpropano-1,2-diol como un polvo blanco. MS (ES) *m/z* 315.0 ($[M+H]^+$); HRMS: calculado para $C_{18}H_{19}ClN_2O$ + H^+, 315.1259; encontrado (ESI, $[M+H]^+$), 315.1269.

[0708] EJEMPLO 149: clorhidrato de (1S,2R)-1-(7-cloro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol

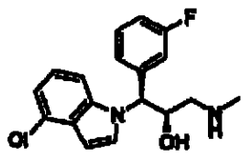


[0709] De forma análoga al EJEMPLO 117, etapa 5, se prepara (2S,3S)-3-(7-cloro-1H-indol-1-il)-3-(3-fluorofenil)propano-1,2-diol a partir de 7-cloroindol y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3) como un aceite incoloro, viscoso. MS (ES) *m/z* 320.0 ($[M+H]^+$); HRMS: calculado para $C_{17}H_{15}ClFNO_2$ + H^+, 320.0848; encontrado (ESI, $[M+H]^+$), 320.0858.

[0710] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(7-cloro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol a partir de (2S,3S)-3-(7-cloro-1H-indol-1-il)-3-(3-fluorofenil)propano-1,2-diol como un

polvo blanco. MS (ES) *m/z* 333.0 ($[M+H]^+$); HRMS: calculado para $C_{18}H_{18}ClFN_2O$ + H^+, 333.1170; encontrado (ESI, $[M+H]^+$), 333.1189.

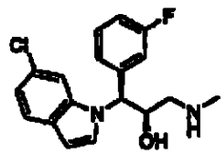
[0711] EJEMPLO 150: clorhidrato de (1S,2R)-1-(4-cloro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol



[0712] De forma análoga al EJEMPLO 117, etapa 5, se prepara (2S,3S)-3-(4-cloro-1H-indol-1-il)-3-(3-fluorofenil)propano-1,2-diol a partir de 4-cloroindol y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3) como un aceite incoloro, viscoso. MS (ES) *m/z* 320.0 ($[M+H]^+$); HRMS: calculado para $C_{17}H_{15}ClFNO_2$ + H^+, 320.0848; encontrado (ESI, $[M+H]^+$), 320.0856.

[0713] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(4-cloro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol a partir de (2S,3S)-3-(4-cloro-1H-indol-1-il)-3-(3-fluorofenil)propano-1,2-diol como un polvo blanco. MS (ES) *m/z* 333.2 ($[M+H]^+$); HRMS: calculado para $C_{18}H_{18}ClFN_2O$ + H^+, 333.1170; encontrado (ESI, $[M+H]^+$), 333.1156.

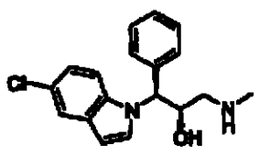
[0714] EJEMPLO 151: clorhidrato de (1S,2R)-1-(6-cloro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol



[0715] De forma análoga al EJEMPLO 117, etapa 5, se prepara (2S,3S)-3-(6-cloro-1H-indol-1-il)-3-(3-fluorofenil)propano-1,2-diol a partir de 6-cloroindol y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3) como un aceite incoloro, viscoso. MS (ES) *m/z* 320.0 ($[M+H]^+$); HRMS: calculado para $C_{17}H_{15}ClFNO_2 + H^+$, 320.0848; encontrado (ESI, $[M+H]^+$), 320.0855.

[0716] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(6-cloro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol a partir de (2S,3S)-3-(6-cloro-1H-indol-1-il)-3-(3-fluorofenil)propano-1,2-diol como un polvo blanco. MS (ES) *m/z* 333.2 ($[M+H]^+$); HRMS: calculado para $C_{18}H_{18}ClFN_2O + H^+$, 333.1170; encontrado (ESI, $[M+H]^+$), 333.1174.

[0717] EJEMPLO 152: clorhidrato de (1S,2R)-1-(5-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol

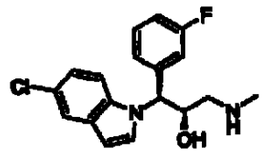


[0718] De forma análoga al EJEMPLO 117, etapa 5, se prepara (2S,3S)-3-(5-cloro-1H-indol-1-il)-3-fenilpropano-1,2-diol a partir de 5-cloroindol y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un aceite incoloro, viscoso. MS (ES)

m/z 302.2 ($[M+H]^+$); HRMS: calculado para $C_{17}H_{16}ClNO_2$ + H^+, 302.0948; encontrado (ESI, $[M+H]^+$), 302.0956.

[0719] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(5-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol a partir de (2S,3S)-3-(5-cloro-1H-indol-1-il)-3-fenilpropano-1,2-diol como un polvo blanco. MS (ES) *m/z* 315.1 ($[M+H]^+$); HRMS: calculado para $C_{18}H_{19}ClN_2O$ + H^+, 315.1259; encontrado (ESI, [M+KT), 315.1247.

[0720] EJEMPLO 153: clorhidrato de (1S,2R)-1-(5-cloro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol

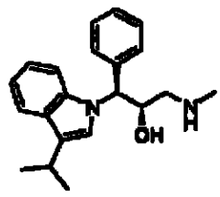


[0721] De forma análoga al EJEMPLO 117, etapa 5, se prepara (2S,3S)-3-(5-cloro-1H-indol-1-il)-3-(3-fluorofenil)propano-1,2-diol a partir de 5-cloroindol y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3) como un aceite incoloro, viscoso. MS (ES) *m/z* 320.1 ($[M+H]^+$); HRMS: calculado para $C_{17}H_{15}ClFNO_2$ + H^+, 320.0848; encontrado (ESI, $[M+H]^+$), 320.0854.

[0722] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(5-cloro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol a partir de 2S,3S)-3-(5-cloro-1H-indol-1-il)-3-(3-fluorofenil)propano-1,2-diol como un

polvo blanco. MS (ES) *m/z* 333.1 ($[M+H]^+$); HRMS: calculado para $C_{18}H_{18}ClFN_2O$ + H^+, 333.1170; encontrado (ESI, $[M+H]^+$), 333.1154.

[0723] EJEMPLO 154: clorhidrato de (1S,2R)-1-(3-isopropil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol

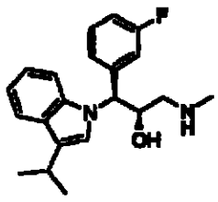


[0724] De forma análoga al EJEMPLO 117, etapa 5, se prepara (2S,3S)-3-(3-isopropil-1H-indol-1-il)-3-fenilpropano-1,2-diol a partir de 3-isopropilindol[16] y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un aceite amarilloso, viscoso. HRMS: calculado para $C_{2023}NO_2$ + H^+, 310.1802; encontrado (ESI, $[M+H]^+$), 310.1793.

[0725] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(3-isopropil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol a partir de (2S,3S)-3-(3-isopropil-1H-indol-1-il)-3-fenilpropano-1,2-diol como un polvo blanco. MS (ES) *m/z* 323.3 ($[M+H]^+$); HRMS: calculado para $C_{21}H_{26}N_2O$ + H^+, 323.2118; encontrado (ESI, $[M+H]^+$), 323.2117.

[0726] EJEMPLO 155: clorhidrato de (1S,2R)-1-(3-fluorofenil)-1-(3-isopropil-1H-indol-1-il)-3-(metilamino)propan-2-ol

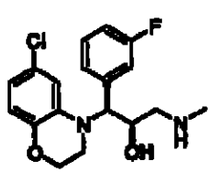
[16] Odle, R.; Blevins, B.; Ratcliff, M.; Hegedus, L. S. *J. Org. Chem.* 1980, 45, 2709-2710.



[0727] De forma análoga al EJEMPLO 117, etapa 5, se prepara (2S,3S)-3-(3-fluorofenil)-3-(3-isopropil-1H-indol-1-il)propano-1,2-diol a partir de 3-isopropilindol[16] y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3) como un aceite amarilloso, viscoso. MS (ES) *m/z* 326.2 ($[M-H]^-$); HRMS: calculado para $C_{20}H_{22}FNO_2$ + H^+, 328.1707; encontrado (ESI, $[M+H]^+$), 328.1709.

[0728] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(3-fluorofenil)-1-(3-isopropil-1H-indol-1-il)-3-(metilamino)propan-2-ol a partir de (2S,3S)-3-(3-fluorofenil)-3-(3-isopropil-1H-indol-1-il)propano-1,2-diol como un polvo blanco. MS (ES) *m/z* 341.3 ($[M+H]^+$); HRMS: calculado para $C_{21}H_{25}FN_2O$ + H^+, 341.2024; encontrado (ESI, $[M+H]^+$), 341.2025.

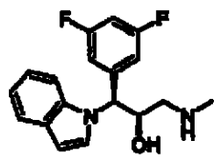
[0729] EJEMPLO 156: clorhidrato de (1S,2R)-1-(6-cloro-2,3-dihidro-4H-1,4-benzoxazin-4-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol



[0730] De forma análoga al EJEMPLO 47, etapa 4, se prepara (2S,3S)-3-(6-cloro-2,3-dihidro-4H-1,4-benzoxazin-4-il)-3-(3-fluorofenil)propano-1,2-diol a partir de 6-cloro-3,4-dihidro-2H-1,4-benzoxazina (EJEMPLO 88, etapa 1) y [(2R.3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3) como un líquido amarillento, viscoso. MS (ES) *m/z* 335.8 ([M-H]"); HRMS: calculado para $C_{20}H_{22}FNO_2$ + H^+, 338.0959; encontrado (ESI, $[M+H]^+$), 338.0959.

[0731] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(6-cloro-2,3-dihidro-4H-1,4-benzoxazin-4-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol a partir de (2S,3S)-3-(6-cloro-2,3-dihidro-4H-1,4-benzoxazin-4-il)-3-(3-fluorofenil)propano-1,2-diol como un polvo blanco. MS (ES) *m/z* 351.0 ([M+HD; HRMS: calculado para $C_{18}H_{20}ClFN_2O_2$ + H^+, 351.1276; encontrado (ESI, $[M+H]^+$), 351.1276.

[0732] EJEMPLO 157: clorhidrato de (1S,2R)-1-(3,5-difluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol



[0733] Etapa 1: De forma análoga al EJEMPLO 47, etapa 1, se prepara metil éster de ácido *trans*-3,5-difluorocinámico a partir de ácido trans-3,5-difluorocinámico como un sólido blanco. MS (ESI) *m/z* 198.0; HRMS: calculado para $C_{10}H_8F_2O_2$, 198.0492; encontrado (ESI, [M]+), 198.0489.

[0734] Etapa 2: De forma análoga al EJEMPLO 47, etapa 2, se prepara alcohol trans-3,5-difluorocinamilo a partir del metil éster de ácido trans-3,5-difluorocinámico como un aceite incoloro.

[0735] Etapa 3: De forma análoga al EJEMPLO 47, etapa 3, se prepara [(2R,3R)-3-(3,5-difluorofenil)oxiran-2-il]metanol a partir de alcohol *trans*-3,5-difluorocinamilo como un líquido sin color. Por ciento ee: 97.9%. MS (ESI) *m/z* 186.0; HRMS: calculado para $C_9H_8F_2O_2$, 186.0492; encontrado (ESI, [M]+), 186.0501.

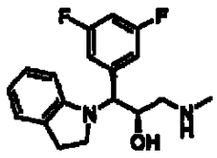
[0736] Etapa 4: De forma análoga al EJEMPLO 47, etapa 4, se prepara (2S,3S)-3-(3,5-difluorofenil)-3-(2,3-dihidro-1H-indol-1-il)propano-1,2-diol a partir de indolina y [(2R,3R)-3-(3,5-difluorofenil)oxiran-2-il]metanol como un aceite amarilloso, viscoso. MS (ES) *m/z* 306.2 ($[M+H]^+$); HRMS: calculado para $C_{17}H_{17}F_2NO_2 + H^+$, 306.1300; encontrado (ESI, $[M+H]^+$), 306.1299.

[0737] Etapa 5: De forma análoga al EJEMPLO 47, etapa 5, se prepara (2S,3S)-3-(3,5-difluorofenil)-3-(1H-indol-1-il)propano-1,2-diol a partir de (2S,3S)-3-(3,5-difluorofenil)-3-(2,3-dihidro-1H-indol-1-il)propano-1,2-diol como un aceite amarilloso, viscoso. MS (ES) *m/z* 304.0 ($[M+H]^+$); HRMS: calculado para $C_{17}H_{15}F_2NO_2 + H^+$, 304.1144; encontrado (ESI, $[M+H]^+$), 304.1146.

[0738] Etapa 6: De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(3,5-difluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol a partir de (2S,3S)-3-(3,5-

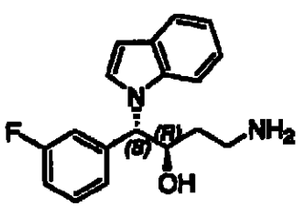
difluorofenil)-3-(1H-indol-1-il)propano-1,2-diol como un polvo blanco. MS (ES) *m/z* 317.0 ([M+H]$^+$); HRMS: calculado para $C_{18}H_{18}F_2N_2O$ + H^+, 317.1465; encontrado (ESI, [M+H]$^+$), 317.1465.

[0739] EJEMPLO 158: clorhidrato de (1S,2R)-1-(3,5-difluorofenil)-1-(2,3-dihidro-1H-indol-1-il)-3-(metilamino)propan-2-ol



[0740] De forma análoga al EJEMPLO 47, etapa 6, se prepara (1S,2R)-1-(3,5-difluorofenil)-1-(2,3-dihidro-1H-indol-1-il)-3-(metilamino)propan-2-ol a partir de (2S,3S)-3-(3,5-difluorofenil)-3-(2,3-dihidro-1H-indol-1-il)propano-1,2-diol como un polvo blanco. MS (ES) *m/z* 319.0 ([M+H3+); HRMS: calculado para $C_{18}H_{20}F_2N_2O$ + H^+, 319.1622; encontrado (ESI, [M+H]$^+$), 319.1622.

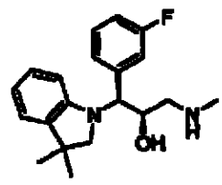
[0741] EJEMPLO 159: clorhidrato de (1S,2R)-4-amino-1-(3-fluorofenil)-1-(1H-indol-1-il)butan-2-ol



[0742] De forma análoga al EJEMPLO 1, etapa 2 se prepara 3-(3-fluorofenil)-2-hidroxi-3-indol-1-il-propil éster de ácido

(2S,3S)-tolueno-4-sulfónico a partir de (2S,3S)-3-(3-fluorofenil)-3-(1H-indol-1-il)propano-1,2-diol (EJEMPLO 47, etapa 4). MS (ES) *m/z* 440 ($[M+H]^+$).

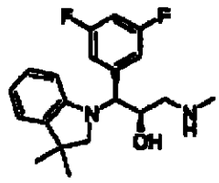
[0743] EJEMPLO 160: clorhidrato de (1S,2R)-1-(3,3-dimetil-2,3-dihidro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol



[0744] De forma análoga al EJEMPLO 47, etapa 4, se prepara (2S,3S)-3-(3,3-dimetil-2,3-dihidro-1H-indol-1-il)-3-(3-fluorofenil)propano-1,2-diol a partir de 3,3-dimetilindolina[15] y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3) como un líquido café, viscoso. MS (ES) *m/z* 316.0 ($[M+H]^+$); HRMS: calculado para $C_{19}H_{22}FNO_2 + H^+$, 316.1713; encontrado (ESI, $[M+H]^+$), 316.1713.

[0745] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(3,3-dimetil-2,3-dihidro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol a partir de (2S,3S)-3-(3,3-dimetil-2,3-dihidro-1H-indol-1-il)-3-(3-fluorofenil)propano-1,2-diol como un polvo blanco. MS (ES) *m/z* 329.0 ($[M+H]^+$).

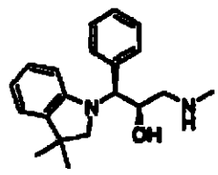
[0746] EJEMPLO 161: clorhidrato de (1S,2R)-1-(3,5-difluorofenil)-1-(3,3-dimetil-2,3-dihidro-1H-indol-1-il)-3-(metilamino)propan-2-ol



[0747] De forma análoga al EJEMPLO 47, etapa 4, se prepara (2S,3S)-3-(3,5-difluorofenil)-3-(3,3-dimetil-2,3-dihidro-1H-indol-1-il)propano-1,2-diol a partir de 3,3-dimetilindolina[15] y [(2R,3R)-3-(3,5-difluorofenil)oxiran-2-il]metanol (EJEMPLO 157, etapa 3) como un líquido café, viscoso. MS (ES) *m/z* 334.0 ($[M+H]^+$); HRMS: calculado para $C_{19}H_{21}F_2NO_2$ + H^+, 334.1619; encontrado (ESI, $[M+H]^+$), 334.1619.

[0748] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(3,5-difluorofenil)-1-(3,3-dimetil-2,3-dihidro-1H-indol-1-il)-3-(metilamino)propan-2-ol a partir de (2S,3S)-3-(3,5-difluorofenil)-3-(3,3-dimetil-2,3-dihidro-1H-indol-1-il)propano-1,2-diol como un polvo blanco. MS (ES) *m/z* 347.0 ($[M+H]^+$); HRMS: calculado para $C_{20}H_{24}F_2N_2O$ + H^+, 347.1929; encontrado (ESI, $[M+H]^+$), 347.1929.

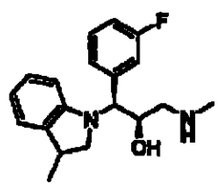
[0749] EJEMPLO 162: clorhidrato de (1S,2R)-1-(3,3-dimetil-2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol



[0750] De forma análoga al EJEMPLO 47, etapa 4, se prepara (2S,3S)-3-(3,3-dimetil-2,3-dihidro-1H-indol-1-il)-3-fenilpropano-1,2-diol a partir de 3,3-dimetilindolina[15] y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un líquido café, viscoso. MS (ES) *m/z* 298.0 ($[M+H]^+$); HRMS: calculado para $C_{1923}NO_2$ + H^+, 298.1807; encontrado (ESI, $[M+H]^+$), 298.1807.

[0751] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(3,3-dimetil-2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol a partir de (2S,3S)-3-(3,3-dimetil-2,3-dihidro-1H-indol-1-il)-3-fenilpropano-1,2-diol como un polvo blanco. MS (ES) *m/z* 311.0 ($[M+H]^+$); HRMS: calculado para $C_{20}H_{26}N_2O$ + H^+, 311.2118; encontrado (ESI, $[M+H]^+$), 311.2107.

[0752] EJEMPLO 163: clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(3-metil-2,3-dihidro-1H-indol-1-il)propan-2-ol

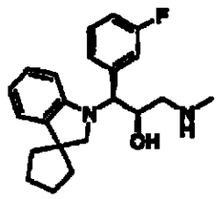


[0753] De forma análoga al EJEMPLO 47, etapa 4, se prepara (2S,3S)-3-(3-fluorofenil)-3-(3-metil-2,3-dihidro-1H-indol-1-il)propano-1,2-diol a partir de 3-metilindolina[4] y [(2R,3R)-3-(3-

fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3) como un líquido amarillento, viscoso. MS (ES) *m/z* 301.8 ($[M+H]^+$); HRMS: calculado para $C_{18}H_{20}FNO_2$ + H^+, 302.1551; encontrado (ESI, $[M+H]^+$), 302.1539.

[0754] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(3-metil-2,3-dihidro-1H-indol-1-il)propan-2-ol a partir de (2S,3S)-3-(3-fluorofenil)-3-(3-metil-2,3-dihidro-1H-indol-1-il)propano-1,2-diol como un polvo blanco. MS (ES) *m/z* 315.2 ([M+HD; HRMS: calculado para $C_{1923}FN_2O$ + H^+, 315.1873; encontrado (ESI, $[M+H]^+$), 315.1881.

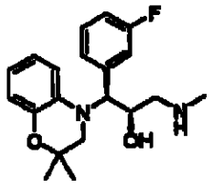
[0755] EJEMPLO 164: clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-espiro[ciclopentano-1,3'-indol]-1'(2H)-ilpropan-2-ol



[0756] De forma análoga al EJEMPLO 47, etapa 4, se prepara (2S,3S)-3-(3-fluorofenil)-3-espiro[ciclopentano-1,3'-indol]-1'(2'H)-ilpropano-1,2-diol a partir de 1',2'-dihidroespiro[ciclopentano-1,3'-indol][15] y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3) como un líquido amarillento, viscoso. MS (ES) *m/z* 342.2 ($[M+H]^+$).

[0757] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-espiro[ciclopentano-1,3'-indol]-1'(2'H)-ilpropan-2-ol a partir de (2S,3S)-3-(3-fluorofenil)-3-espiro[ciclopentano-1,3'-indol]-1'(2'H)-ilpropano-1,2-diol como un polvo blanco. MS (ES) *m/z* 355.0 ($[M+H]^+$); HRMS: calculado para $C_{22}H_{27}FN_2O + H^+$, 355.2180; encontrado (ESI, $[M+H]^+$), 355.2178.

[0758] EJEMPLO 165: clorhidrato de (1S,2R)-1-(2,2-dimetil-2,3-dihidro-4H-1,4-benzoxazin-4-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol



[0759] Etapa 1: A una solución de 2,2-dimetil-2H-1,4-benzoxazin-3(4H)-ona[17] (2.658 g, 15.0 mmol) en tetrahidrofurano (10 ml) bajo nitrógeno se agrega lentamente una solución de borano (1.0 M en tetrahidrofurano, 22.5 mL, 22.5 mmol) por medio de una jeringa. La mezcla resultante se agita a temperatura ambiente durante 10 minutos y luego a 70° C durante 1 hora. Después de enfriamiento, la mezcla de reacción se apaga con metanol (3 mL) lentamente. Se remueven todos los volátiles bajo presión reducida. Una solución acuosa de ácido clorhídrico 1 N (10 mL) se agrega al residuo líquido y la mezcla se calienta a 50° C durante 10 minutos.

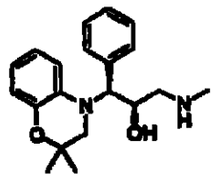
[17] Caliendo, G.; Perissutti, E.; Santagada, V.; Fiorino, F.; Severino, B.; Bianca, R.

Después de enfriamiento, la mezcla de reacción se hace alcalina utilizando solución de bicarbonato de sodio saturada (15 mL), y se extrae con acetato de etilo (25 mL). La capa orgánica se lava con agua, solución salina, se seca (sulfato de sodio anhidro), se filtra a través de almohadilla de gel de sílice, y se concentra bajo presión reducida para proporcionar 2.310 g (94%) de 2,2-dimetil-3,4-dihidro-2H-1,4-benzoxazina como un aceite café. MS (ES) *m/z* 164.0 ($[M+H]^+$).

[0760] Etapa 2: De forma análoga al EJEMPLO 47, etapa 4, se prepara (2S,3S)-3-(2,2-dimetil-2,3-dihidro-4H-1,4-benzoxazin-4-il)-3-(3-fluorofenil)propano-1,2-diol a partir de 2,2-dimetil-3,4-dihidro-2H-1,4-benzoxazina y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3) como un sólido blanco. MS (ES) *m/z* 332.2 ($[M+H]^+$); HRMS: calculado para $C_{19}H_{22}FNO_3 + H^+$, 332.1657; encontrado (ESI, $[M+H]^+$), 332.1648.

[0761] Etapa 3: De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(2,2-dimetil-2,3-dihidro-4H-1,4-benzoxazin-4-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol a partir de (2S,3S)-3-(2,2-dimetil-2,3-dihidro-4H-1,4-benzoxazin-4-il)-3-(3-fluorofenil)propano-1,2-diol como un polvo blanco. MS (ES) *m/z* 345.2 ($[M+H]^+$); HRMS: calculado para $C_{20}H_{25}FN_2O_2 + H^+$, 345.1978; encontrado (ESI, $[M+H]^+$), 345.1981.

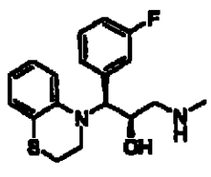
[0762] EJEMPLO 166: clorhidrato de (1S,2R)-1-(2,2-dimetil-2,3-dihidro-4H-1,4-benzoxazin-4-il)-3-(metilamino)-1-fenilpropan-2-ol



[0763] De forma análoga al EJEMPLO 47, etapa 4, se prepara (2S,3S)-3-(2,2-dimetil-2,3-dihidro-4H-1,4-benzoxazin-4-il)-3-fenilpropano-1,2-diol a partir de 2,2-dimetil-3,4-dihidro-2H-1,4-benzoxazina (EJEMPLO 165, etapa 1) y [(2R.3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un sólido blanco. MS (ES) m/z 314.1 ($[M+H]^+$)

[0764] De forma análoga al EJEMPLO 47, etapa 6, se prepara a clorhidrato de (1S,2R)-1-(2,2-dimetil-2,3-dihidro-4H-1,4-benzoxazin-4-il)-3-(metilamino)-1-fenilpropan-2-ol partir de (2S,3S)-3-(2,2-dimetil-2,3-dihidro-4H-1,4-benzoxazin-4-il)-3-fenilpropano-1,2-diol como un polvo blanco. MS (ES) *m/z* 327.2 ($[M+H]^+$); HRMS: calculado para $C_{20}H_{26}N_2O_2$ + H^+, 327.2073; encontrado (ESI, $[M+H]^+$), 327.2082.

[0765] EJEMPLO 167: clorhidrato de (1S,2R)-1-(2,3-dihidro-4H-1,4-benzotiazin-4-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol

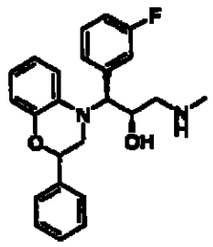


[0766] De forma análoga al EJEMPLO 47, etapa 4, se prepara (2S,3S)-3-(2,3-dihidro-4H-1,4-benzotiazin-4-il)-3-(3-fluorofenil)propano-1,2-diol a partir de 3,4-dihidro-2H-1,4-

benzotiazina[18] y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3) como un líquido amarillento, viscoso. MS (ES) *m/z* 320.1 ($[M+H]^+$); HRMS: calculado para $C_{17}H_{18}FNO_2S + H^+$, 320.1115; encontrado (ESI, [M+Hf), 320.1113.

[0767] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(2,3-dihidro-4H-1,4-benzotiazin-4-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol a partir de (2S,3S)-3-(2,3-dihidro-4H-1,4-benzotiazin-4-il)-3-(3-fluorofenil)propano-1,2-diol como un polvo blanco. MS (ES) *m/z* 333.1 ($[M+H]^+$); HRMS: calculado para $C_{18}H_{21}FN_2OS + H^+$, 333.1431; encontrado (ESI, $[M+H]^+$) 333.1420.

[0768] EJEMPLO 168: clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(2-fenil-2,3-dihidro-4H-1,4-benzoxazin-4-il)propan-2-ol



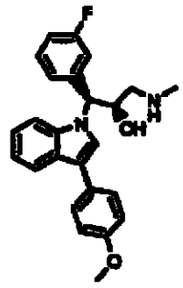
[0769] De forma análoga al EJEMPLO 47, etapa 4, se prepara (2S,3S)-3-(3-fluorofenil)-3-(2-fenil-2,3-dihidro-4H-1,4-benzoxazin-4-il)propano-1,2-diol a partir de 2-fenil-3,4-dihidro-

[18] El-Subbagh, H. I.; Abadi, A. H.; Al-Khawad, I. E.; Al-Rashood, K. A. Arch. *Pharm.* 1999, 332, 19-24.

2H-1,4-benzoxazina[19] y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3) como un sólido blanco. MS (ES) *m/z* 380.0 ($[M+H]^+$); HRMS: calculado para $C_{23}H_{22}FNO_3$ + H^+, 380.1662; encontrado (ESI, $[M+H]^+$), 380.1661.

[0770] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(2-fenil-2,3-dihidro-4H-1,4-benzoxazin-4-il)propan-2-ol a partir de (2S,3S)-3-(3-fluorofenil)-3-(2-fenil-2,3-dihidro-4H-1,4-benzoxazin-4-il)propano-1,2-diol como un polvo blanco. MS (ES) *m/z* 393.2 ($[M+H]^+$); HRMS: calculado para $C_{24}H_{25}FN_2O_2$ + H^+, 393.1978; encontrado (ESI, $[M+H]^+$), 393.1986.

[0771] EJEMPLO 169: clorhidrato de (1S,2R)-1-(3-fluorofenil)-1-[3-(4-metoxifenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol



[0772] De forma análoga al EJEMPLO 114, etapa 2, se prepara (2S,3S)-3-(3-fluorofenil)-3-{3-[4-metoxifenil]-1H-indol-1-il}propano-1,2-diol a partir de (2S,3S)-3-(3-fluorofenil)-3-(3-yodo-1H-indol-1-il)propano-1,2-diol (EJEMPLO 114, etapa 1) y ácido 4-metoxibencenobóronico.

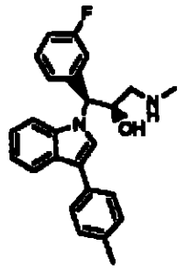
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[19] Olagbemiro, T. O.; Nyakutse, C. A.; Lajide, L.; Agho, M. O.; Chukwu, C. E. *Bull. Soc. CMm. Belg.* 1987, 96, 473-480.

[0773] De forma análoga al EJEMPLO 1, etapa 2, se prepara 3-(3-fluorofenil)-3-[3-(4-metoxifenil)-indol-1-il]-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico a partir de (2S,3S)-3-(3-fluorofenil)-3-{3-[4-metoxifenil]-1H-indol-1-il}propano-1,2-diol.

[0774] De forma análoga al EJEMPLO 5, se prepara clorhidrato de (1S,2R)-1-(3-fluorofenil)-1-[3-(4-metoxifenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol a partir de 3-(3-fluorofenil)-3-[3-(4-metoxifenil)-indol-1-il]-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina (solución en metanol 2N). MS (ESI) *m/z* 405.

[0775] EJEMPLO 170: clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-[3-(4-metilfenil)-1H-indol-1-il]propan-2-ol

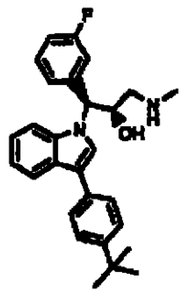


[0776] De forma análoga al EJEMPLO 114, etapa 2, se prepara (2S,3S)-3-(3-fluorofenil)-3-{3-[4-metilfenil]-1H-indol-1-il}propano-1,2-diol a partir de (2S,3S)-3-(3-fluorofenil)-3-(3-yodo-1H-indol-1-il)propano-1,2-diol (EJEMPLO 114, etapa 1) y ácido 4-metilbencenoborónico.

[0777] De forma análoga al EJEMPLO 1, etapa 2, se prepara 3-(3-fluorofenil)-3-[3-(4-metilfenil)-indol-1-il]-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico a partir de (2S,3S)-3-(3-fluorofenil)-3-{3-[4-metilfenil]-1H-indol-1-il}propano-1,2-diol.

[0778] De forma análoga al EJEMPLO 5, se prepara clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-[3-(4-metilfenil)-1H-indol-1-il]propan-2-ol a partir de 3-(3-fluorofenil)-3-[3-(4-metilfenil)-indol-1-il]-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina (solución en metanol 2N). MS (ESI) *m/z* 389.2.

[0779] EJEMPLO 171: clorhidrato de (1S,2R)-1-[3-(4-terc-butilfenil)-1H-indol-1-il]-1-(3-fluorofenil)-3-(metilamino)propan-2-ol

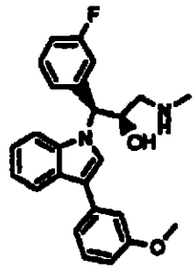


[0780] De forma análoga al EJEMPLO 114, etapa 2, se prepara (2S,3S)-3-(3-fluorofenil)-3-{3-[4-terc-butilfenil]-1H-indol-1-il}propano-1,2-diol a partir de (2S,3S)-3-(3-fluorofenil)-3-(3-yodo-1H-indol-1-il)propano-1,2-diol (EJEMPLO 114, etapa 1) y ácido 4-terc-butilfenilborónico.

[0781] De forma análoga al EJEMPLO 1, etapa 2, 3-(3-fluorofenil)-3-[3-(4-terc-butilfenil)-indol-1-il]-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico se prepara a partir de (2S,3S)-3-(3-fluorofenil)-3-{3-[4-terc-butilfenil]-1H-indol-1-il}propano-1,2-diol.

[0782] De forma análoga al EJEMPLO 5, clorhidrato de (1S,2R)-1-[3-(4-terc-butilfenil)-1H-indol-1-il]-1-(3-fluorofenil)-3-(metilamino)propan-2-ol se prepara a partir de 3-(3-fluorofenil)-3-[3-(4-terc-butilfenil)-indol-1-il]-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina (solución en metanol 2N). MS (ESI) *m/z* 430.9; HRMS: calculado para $C_{28}H_{31}FN_2O$ + H^+, 431.24932; encontrado (ESI, $[M+H]^+$), 431.2516.

[0783] EJEMPLO 172: clorhidrato de (1S,2R)-1-(3-fluorofenil)-1-[3-(3-metoxifenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol

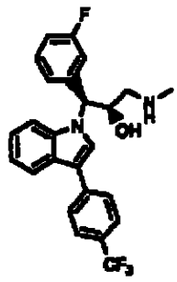


[0784] De forma análoga al EJEMPLO 114, etapa 2, se prepara (2S,3S)-3-(3-fluorofenil)-3-{3-[3-metoxifenil]-1H-indol-1-il}propano-1,2-diol a partir de (2S,3S)-3-(3-fluorofenil)-3-(3-yodo-1H-indol-1-il)propano-1,2-diol (EJEMPLO 114, etapa 1) y ácido 3-metoxibencenoborónico.

[0785] De forma análoga al EJEMPLO 1, etapa 2, se prepara 3-(3-fluorofenil)-3-[3-(3-metoxifenil)-indol-1-il]-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico a partir de (2S,3S)-3-(3-fluorofenil)-3-{3-[3-metoxifenil]-1H-indol-1-il}propano-1,2-diol.

[0786] De forma análoga al EJEMPLO 5, se prepara clorhidrato de (1S,2R)-1-(3-fluorofenil)-1-[3-(3-metoxifenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol a partir de 3-(3-fluorofenil)-3-[3-(3-metoxifenil)-indol-1-il]-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina (solución en metanol 2N). MS (ESI) *m/z* 405.1; HRMS: calculado para $C_{25}H_{25}FN2O_2$ + H^+, 405.19728; encontrado (ESI, $[M+H]^+$), 405.196.

[0787] EJEMPLO 173: clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-{3-[4-(trifluorometil)fenil]-1H-indol-1-il}propan-2-ol

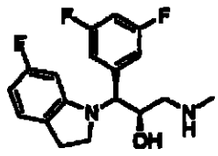


[0788] De forma análoga al EJEMPLO 114, etapa 2, se prepara (2S,3S)-3-(3-fluorofenil)-3-{3-[4-(trifluorometil)fenil]-1H-indol-1-il}propano-1,2-diol a partir de (2S,3S)-3-(3-fluorofenil)-3-(3-yodo-1H-indol-1-il)propano-1,2-diol (EJEMPLO 114, etapa 1) y ácido 4-(trifluorometil)bencenoborónico.

[0789] De forma análoga al EJEMPLO 1, etapa 2 se prepara 3-(3-fluorofenil)-3-[3-(4-(trifluorometil)fenil)-indol-1-il]-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico a partir de (2S,3S)-3-(3-fluorofenil)-3-{3-[4-(trifluorometil)fenil]-1H-indol-1-il}propano-1,2-diol.

[0790] De forma análoga al EJEMPLO 5 se prepara clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-{3-[4-(trifluorometil)fenil]-1H-indol-1-il}propan-2-ol a partir de 3-(3-fluoro-fenil)-3-[3-(4-(trifluorometil)fenil)-indol-1-il]-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina (solución en metanol 2N). MS (ESI) *m/z* 443.1.

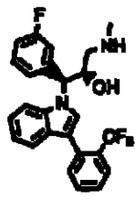
[0791] EJEMPLO 174: clorhidrato de (1S,2R)-1-(3,5-difluorofenil)-1-(6-fluoro-2,3-dihidro-1H-indol-1-il)-3-(metilamino)propan-2-ol



[0792] De forma análoga al EJEMPLO 47, etapa 4, se prepara (2S,3S)-3-(3,5-difluorofenil)-3-(6-fluoro-2,3-dihidro-1H-indol-1-il)propano-1,2-diol a partir de 6-fluoroindolina y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3) como un líquido amarillento, viscoso. MS (ES) *m/z* 324.1 ($[M+H]^+$); HRMS: calculado para $C_{17}H_{16}F_3NO_2$ + H^+, 324.1211; encontrado (ESI, $[M+H]^+$), 324.1226.

[0793] De forma análoga al EJEMPLO 47, etapa 6, se prepara clorhidrato de (1S,2R)-1-(3,5-difluorofenil)-1-(6-fluoro-2,3-dihidro-1H-indol-1-il)-3-(metilamino)propan-2-ol a partir de (2S,3S)-3-(3,5-difluorofenil)-3-(6-fluoro-2,3-dihidro-1H-indol-1-il)propano-1,2-diol como un polvo blanco. MS (ES) *m/z* 337.3 ($[M+H]^+$); HRMS: calculado para $C_{18}H_{19}F_3N_2O$ + H^+, 337.1522; encontrado (ESI, $[M+H]^+$), 337.1505.

[0794] EJEMPLO 175: clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-{3-[2-(trifluorometil)fenil]-1H-indol-1-il}propan-2-ol

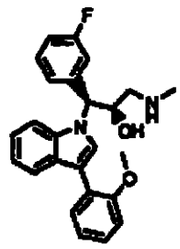


[0795] De forma análoga al EJEMPLO 114, etapa 2, se prepara (2S,3S)-3-(3-fluorofenil)-3-{3-[2-(trifluorometil)fenil]-1H-indol-1-il}propano-1,2-diol a partir de (2S,3S)-3-(3-fluorofenil)-3-(3-yodo-1H-indol-1-il)propano-1,2-diol (EJEMPLO 114, etapa 1) y ácido 2-(trifluorometil)borónico.

[0796] De forma análoga al EJEMPLO 1, etapa 2, se prepara 3-(3-fluorofenil)-2-hidroxi-3-[3-(2-(trifluorometil)fenil)-indol-1-il]-propil éster de ácido (2S,3S)-tolueno-4-sulfónico a partir de (2S,3S)-3-(3-fluorofenil)-3-{3-[2-(trifluorometil)fenil]-1H-indol-1-il}propano-1,2-diol.

[0797] De forma análoga al EJEMPLO 5, se prepara clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-{3-[2-(trifluorometil)fenil]-1H-indol-1-il}propan-2-ol a partir de 3-(3-fluorofenil)-2-hidroxi-3-[3-(2-(trifluorometil)fenil)-indol-1-il]-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina (solución en metanol 2N). MS (ESI) *m/z* 443.1; HRMS: calculado para $C_{25}H_{22}F_4N_2O$ + H^+, 443.17410; encontrado (ESI, $[M+H]^+$), 443.172.

[0798] EJEMPLO 176: clorhidrato dr (1S,2R)-1-(3-fluorofenil)-1-[3-(2-metoxifenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol



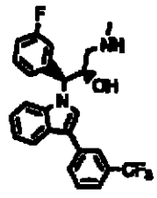
[0799] De forma análoga al EJEMPLO 114, etapa 2, se prepara (2S,3S)-3-(3-fluorofenil)-3-{3-[2-metoxifenil]-1H-indol-1-il}propano-1,2-diol a partir de (2S,3S)-3-(3-fluorofenil)-3-(3-yodo-1H-indol-1-il)propano-1,2-diol (EJEMPLO 114, etapa 1) y ácido 2-metoxibencenoborónico.

[0800] De forma análoga al EJEMPLO 1, etapa 2, se prepara 3-(3-fluorofenil)-3-[3-(2-metoxifenil)-indol-1-il]-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico a partir de (2S,3S)-3-

(3-fluorofenil)-3-{3-[2-metoxifenil]-1H-indol-1-il}propano-1,2-diol.

[0801] De forma análoga al EJEMPLO 5, se prepara clorhidrato de (1S,2R)-1-(3-fluoroFenil)-1-[3-(2-metoxifenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol a partir de 3-(3-fluorofenil)-3-[3-(2-metoxifenil)-indol-1-il]-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina (solución en metanol 2N). MS (ESI) *m/z* 405.1; HRMS: calculado para $C_{25}H_{25}FN_2O_2$ + H^+, 405.19728; encontrado (ESI, $[M+H]^+$), 405.1984.

[0802] EJEMPLO 177: clorhidrato (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-{3-[3-(trifluorometil)fenil]-1H-indol-1-il}propan-2-ol



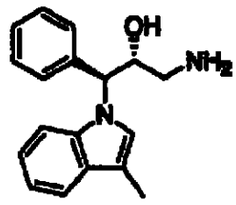
[0803] De forma análoga al EJEMPLO 114, etapa 2, se prepara (2S,3S)-3-(3-fluorofenil)-3-{3-[3-(trifluorometil)fenil]-1H-indol-1-il}propano-1,2-diol a partir de (2S,3S)-3-(3-fluorofenil)-3-(3-yodo-1H-indol-1-il)propano-1,2-diol (EJEMPLO 114, etapa 1) y ácido 3-(trifluorometil)bencenoborónico.

[0804] De forma análoga al EJEMPLO 1, etapa 2, se prepara 3-(3-fluorofenil)-3-[3-(3-(trifluorometil)fenil)-indol-1-il]-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico a

partir de (2S,3S)-3-(3-fluorofenil)-3-(3-[3-(trifluorometil)fenil]-1H-indol-1-il}propano-1,2-diol.

[0805] De forma análoga al EJEMPLO 5, clorhidrato se prepara (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-{3-[3-(trifluorometil)fenil]-1H-indol-1-il}propan-2-ol de 3-(3-fluorofenil)-3-[3-(3-(trifluorometil)fenil)-indol-1-il]-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina (solución en metanol 2N). MS (ESI) *m/z* 443.1; HRMS: calculado para $C_{25}H_{22}F_4N_2O$ + H^+, 443.17410; encontrado (ESI, $[M+H]^+$), 443.1764.

[0806] EJEMPLO 178: clorhidrato de (1S,2R)-3-amino-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol

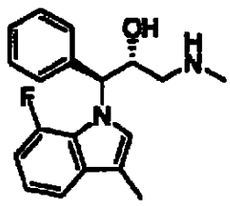


[0807] De forma análoga al EJEMPLO 117, etapa 5 se prepara (2S,3S)-3-(3-metil-indol-1-il)-3-fenil-propano-1,2-diol a partir de 3-metilindol y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un aceite. MS (ESI) *m/z* 282 ($[M+H]^+$).

[0808] De forma análoga al EJEMPLO 117, etapa 6 se prepara clorhidrato de (1S,2R)-3-amino-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol a partir de (2S,3S)-3-(3-metil-indol-1-il)-3-fenil-propano-1,2-diol y ácido *para*-toluenosulfónico seguido por

hidróxido de amonio concentrado como un sólido muy blanco. MS (ESI) *m/z* 281.

[0809] EJEMPLO 179: clorhidrato de (1S,2R)-1-(7-fluoro-3-metil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol



[0810] De forma análoga al EJEMPLO 117, etapa 1 se prepara 7-fluoro-3-metil-1H-indol-2-carboxilato de etilo a partir de 2-fluoroanilina como un sólido café. MS (ESI) *m/z* 221.

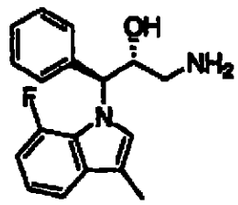
[0811] De forma análoga al EJEMPLO 117, etapa 2 se prepara ácido 7-fluoro-3-metil-1H-indol-2-carboxílico a partir de 7-fluoro-3-metil-1H-indol-2-carboxilato de etilo como un sólido verde. MS (ESI) *m/z* 192.

[0812] De forma análoga al EJEMPLO 117, etapa 3 se prepara 7-fluoro-3-metil-1H-indol a partir de ácido 7-fluoro-3-metil-1H-indol-2-carboxílico como un sólido blanco. MS (ESI) *m/z* 150.

[0813] De forma análoga al EJEMPLO 117, etapa 5 se prepara (2S,3S)-3-(7-fluoro-3-metil-1H-indol-1-il)-3-fenilpropano-1,2-diol a partir de 7-fluoro-3-metil-1H-indol y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un aceite. MS (ESI) *m/z* 300.

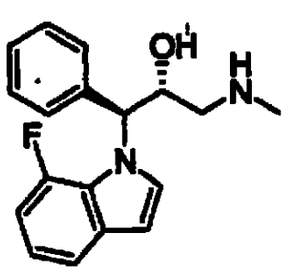
[0814] De forma análoga al EJEMPLO 117, etapa 6 se prepara clorhidrato de (1S,2R)-1-(7-fluoro-3-metil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol a partir de (2S,3S)-3-(7-fluoro-3-metil-1H-indol-1-il)-3-fenilpropano-1,2-diol como un sólido blanco. MS (ES) *m/z* 313.1.

[0815] EJEMPLO 180: clorhidrato de (1S,2R)-3-amino-1-(7-fluoro-3-metil-1H-indol-1-il)-1-fenilpropan-2-ol



[0816] De forma análoga al EJEMPLO 117, etapa 6 se prepara clorhidrato de 3-amino-1-(7-fluoro-3-metil-1H-indol-1-il)-1-fenilpropan-2-ol a partir de (2S,3S)-3-(7-fluoro-3-metil-1H-indol-1-il)-3-fenilpropano-1,2-diol (EJEMPLO 179, etapa 4) y ácido *para*-toluenosulfónico seguido por hidróxido de amonio como un sólido blanco. MS (ES) *m/z* 299.0.

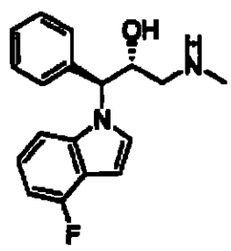
[0817] EJEMPLO 181: clorhidrato de (1S,2R)-1-(7-fluoro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol



[0818] De forma análoga al EJEMPLO 117, etapa 5 se prepara (2S,3S)-3-(7-fluoro-1H-indol-1-il)-3-fenilpropano-1,2-diol a partir de 7-fluoro-1H-indol y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un aceite. MS (ES) *m/z* 286.1.

[0819] De forma análoga al EJEMPLO 117, etapa 6 se prepara clorhidrato de (1S,2R)-1-(7-fluoro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol a partir de (2S,3S)-3-(7-fluoro-1H-indol-1-il)-3-fenilpropano-1,2-diol como un sólido rosado. MS (ESI) *m/z* 299.

[0820] EJEMPLO 182: clorhidrato de (1S,2R)-1-(4-fluoro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol

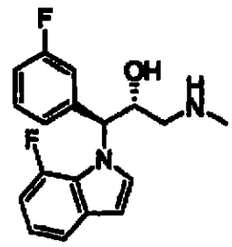


[0821] De forma análoga al EJEMPLO 117, etapa 5 se prepara (2S,3S)-3-(4-fluoro-1H-indol-1-il)-3-fenilpropano-1,2-diol a partir de 4-fluoro-1H-indol y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un aceite. MS (ES) *m/z* 286.1.

[0822] De forma análoga al EJEMPLO 117, etapa 6 se prepara clorhidrato de (1S,2R)-1-(4-fluoro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol a partir de (2S,3S)-3-(4-fluoro-1H-indol-1-

il)-3-fenilpropano-1,2-diol como un sólido blanco. MS (ESI) *m/z* 299.

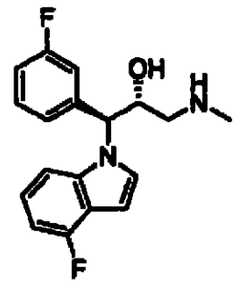
[0823] EJEMPLO 183: clorhidrato de (1S,2R)-1-(7-fluoro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol



[0824] De forma análoga al EJEMPLO 117, etapa 5 se prepara (2S,3S)-3-(7-fluoro-1H-indol-1-il)-3-(3-fluorofenil)propano-1,2-diol a partir de 7-fluoro-1H-indol y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3) como un aceite café. MS (ESI) *m/z* 304.

[0825] De forma análoga al EJEMPLO 117, etapa 6 se prepara clorhidrato de (1S,2R)-1-(7-fluoro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol a partir de (2S,3S)-3-(7-fluoro-1H-indol-1-il)-3-(3-fluorofenil)propano-1,2-diol como un sólido rosado. MS (ESI) *m/z* 317.

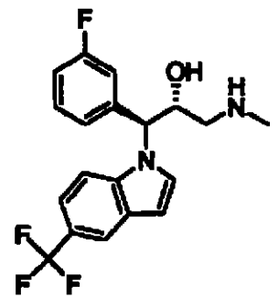
[0826] EJEMPLO 184: clorhidrato de (1S,2R)-1-(4-fluoro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol



[0827] De forma análoga al EJEMPLO 117, etapa 5 se prepara (2S,3S)-3-(4-fluoro-1H-indol-1-il)-3-(3-fluorofenil)propano-1,2-diol a partir de 4-fluoro-1H-indol y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3) como un aceite café. MS (ESI) *m/z* 304.

[0828] De forma análoga al EJEMPLO 117, etapa 6 se prepara clorhidrato de (1S,2/7)-1-(4-fluoro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol a partir de (2S,3S)-3-(4-fluoro-1H-indol-1-il)-3-(3-fluorofenil)propano-1,2-diol como un sólido blanco. MS (ESI) *m/z* 317.

[0829] EJEMPLO 185: clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-[5-(trifluorometil)-1H-indol-1-il]propan-2-ol

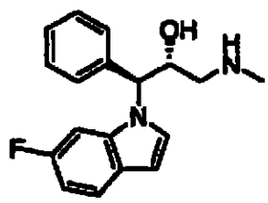


[0830] De forma análoga al EJEMPLO 117, etapa 5 se prepara (2S,3S)-3-(3-fluorofenil)-3-(5-trifluorometil-1H-indol-1-il)-

propano-1,2-diol a partir de 5-trifluorometil-1H-indol y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3).

[0831] De forma análoga al EJEMPLO 117, etapa 6 se prepara clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-[5-(trifluorometil)-1H-indol-1-il]propan-2-ol a partir de (2S,3S)-3-(3-fluorofenil)-3-(5-trifluorometil-1H-indol-1-il)-propano-1,2-diol como un sólido muy blanco. MS (ESI) *m/z* 367.

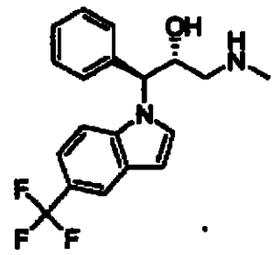
[0832] EJEMPLO 186: clorhidrato de (1S,2R)-1-(6-fluoro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol



[0833] De forma análoga al EJEMPLO 117, etapa 5 se prepara (2S,3S)-3-(6-fluoro-1H-indol-1-il)-3-fenilpropano-1,2-diol a partir de 6-fluoro-1H-indol y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un aceite café. MS (ES) *m/z* 286.1.

[0834] De forma análoga al EJEMPLO 117, etapa 6 se prepara clorhidrato de (1S,2R)-1-(6-fluoro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol a partir de (2S,3S)-3-(6-fluoro-1H-indol-1-il)-3-fenilpropano-1,2-diol como un sólido blanco. MS (ESI) *m/z* 299.

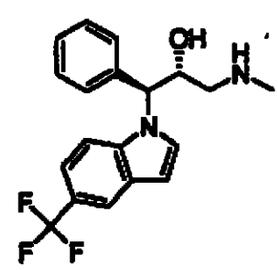
[0835] EJEMPLO 187: clorhidrato de (1S,2R)-3-(metilamino)-1-fenil-1-[6-(trifluorometil)-1H-indol-1-il]propan-2-ol



[0836] De forma análoga al EJEMPLO 117, etapa 5 se prepara (2S,3S)-3-fenil-3-[6-(trifluorometil)-1H-indol-1-il]propano-1,2-diol a partir de 6-trifluorometil-1H-indol y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un aceite café. MS (ES) *m/z* 336.

[0837] De forma análoga al EJEMPLO 117, etapa 6 se prepara clorhidrato de (1S,2H)-3-(metilamino)-1-fenil-1-[6-(trifluorometil)-1H-indol-1-il]propan-2-ol a partir de (2S,3S)-3-fenil-3-[6-(trifluorometil)-1H-indol-1-il]propano-1,2-diol como un sólido blanco. MS (ESI) *m/z* 349.

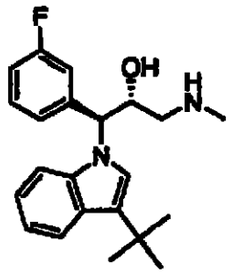
[0838] EJEMPLO 188: clorhidrato de (1S,2R)-3-(metilamino)-1-fenil-1-[5-(trifluorometil)-1H-indol-1-il]propan-2-ol



[0839] De forma análoga al EJEMPLO 117, etapa 5 se prepara (2S,3S)-3-fenil-3-[5-(trifluorometil)-1H-indol-1-il]propano-1,2-diol a partir de 5-trifluorometil-1H-indol y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un aceite café. MS (ES) *m/z* 336.

[0840] De forma análoga al EJEMPLO 117, etapa 6 se prepara clorhidrato de (1S,2R)-3-(metilamino)-1-fenil-1-[5-(trifluorometil)-1H-indol-1-il]propan-2-ol a partir de (2S,3S)-3-fenil-3-[5-(trifluorometil)-1H-indol-1-il]propano-1,2-diol como un sólido muy blanco. MS (ESI) *m/z* 349.2.

[0841] EJEMPLO 189: (1S,2R)-1-(3-terc-butil-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol



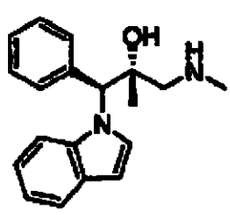
[0842] Etapa 1: a una mezcla de indol (5g, 42.7 mmol), triflato de zinc (9.3 g, 25.6 mmol), y yoduro de tetrabutilamonio (7.9 g, 21.4 mmol) en tolueno anhidro (120 mL) se agrega diisopropiletilamina (8.2 mL, 47 mmol) a temperatura ambiente bajo un manto de nitrógeno. Después la reacción se agita 15 minutos a temperatura ambiente, la mezcla de reacción se trata con bromuro de terc-butilo (2.5 mL, 21.7 mmol). La solución de reacción se agita a temperatura ambiente bajo nitrógeno durante 3

horas, luego se vierte en una solución acuosa saturada de cloruro de amonio (150 mL). La capa orgánica se separa y la capa acuosa se extrae con acetato de etilo (3x50 mL). Las capas orgánicas combinadas se secan sobre sulfato de magnesio, se concentran, y el residuo se purifica vía cromatografía de columna flash (sílice, 10% de acetato de etilo en hexano) para proporcionar 3-terc-butil-1H-indol como un sólido blanco. MS (ES) *m/z* 174.2.

[0843] De forma análoga al EJEMPLO 117, etapa 5 se prepara (2S,3S)-3-(3-terc-butil-1H-indol-1-il)-3-(3-fluorofenil)propano-1,2-diol a partir de 3-terc-butil-1H-indol y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3).

[0844] De forma análoga al EJEMPLO 117, etapa 6 se prepara (1S,2R)-1-(3-terc-butil-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol a partir de (2S,3S)-3-(3-terc-butil-1H-indol-1-il)-3-(3-fluorofenil)propano-1,2-diol como un aceite claro. MS (ESI) *m/z* 355.3.

[0845] EJEMPLO 190: clorhidrato de (1S,2R)-1-(1H-indol-1-il)-2-metil-3-(metilamino)-1-fenilpropan-2-ol

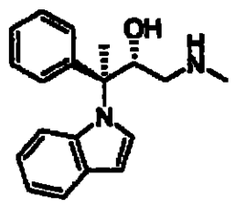


[0846] De forma análoga al EJEMPLO 117, etapa 4 se prepara [(2R,3R)-2-metil-3-feniloxiran-2-il]metanol a partir de 2-metil-3-fenilprop-2-en-1-ol como un cristal blanco. MS (ES) *m/z* 147.1.

[0847] De forma análoga al EJEMPLO 117, etapa 5 se prepara (2S,3S)-2-metil-3-fenil-[1H-indol-1-il]propano-1,2-diol a partir de [(2R,3R)-2-metil-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) e indol.

[0848] De forma análoga al EJEMPLO 117, etapa 6 se prepara clorhidrato de (1S,2R)-1-(1H-indol-1-il)-2-metil-3-(metilamino)-1-fenilpropan-2-ol a partir de (2S,3S)-2-metil-3-fenil-[1 H-indol-1-il]propano-1,2-diol como un sólido blanco. MS (ES) *m/z* 295.0.

[0849] EJEMPLO 191: clorhidrato de (2R,3S)-3-(1H-indol-1-il)-1-(metilamino)-3-fenilbutan-2-ol



[0850] De forma análoga al EJEMPLO 117, etapa 4 se prepara [(2R,3R)-3-metil-3-feniloxiran-2-il]metanol a partir de 3-metil-3-fenilprop-2-en-1-ol como un cristal blanco. MS (ES) *m/z* 147.1.

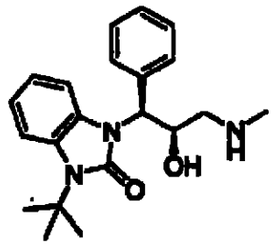
[0851] De forma análoga al EJEMPLO 47, etapa 4 se prepara (2S,3S)-3-(2,3-dihidro-1H-indol-1-il)-3-fenilbutano-1,2-diol a

partir de [(2R,3R)-3-metil-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) e indolina como un sólido café. MS (ES) *m/z* 284.1.

[0852] De forma análoga al EJEMPLO 47, etapa 5 se prepara (2S,3S)-3-(1H-indol-1-il)-3-fenilbutano-1,2-diol a partir de (2S,3S)-3-(2,3-dihidro-1H-indol-1-il)-3-fenilbutano-1,2-diol como un sólido muy blanco. MS (ESI) *m/z* 282.

[0853] De forma análoga al EJEMPLO 117, etapa 6 se prepara clorhidrato de (2R,3S)-3-(1H-indol-1-il)-1-(metilamino)-3-fenilbutan-2-ol a partir de (2S,3S)-3-(1H-indol-1-il)-3-fenilbutano-1,2-diol como un sólido blanco. MS (ES) *m/z* 295.1.

[0854] EJEMPLO 192: clorhidrato de 1-terc-Butil-3-(2-hidroxi-3-metilamino-1-fenil-propil)-1,3-dihidro-benzoimidazol-2-ona



[0855] Etapa 1: A una solución de 1-fluoro-2-nitro-benceno (1 g, 7.1 mmol) en dimetilformamida (15 mL) se agrega terc-butilamina (0.82 mL, 7.81 mmol) a temperatura ambiente, y la mezcla de reacción se agita durante 12 horas a temperatura ambiente bajo nitrógeno. Luego de que se completa, la mezcla de reacción se vierte en una solución acuosa saturada de cloruro de sodio (50 mL) y se extrae con acetato de etilo (50 mL). La capa orgánica se

seca sobre sulfato de sodio anhidro, se concentra en vacío, y el residuo se purifica vía cromatografía de columna flash (sílice, 1% de acetato de etilo en hexano) para dar terc-butil-(2-nitrofenil)-amina como un aceite naranja. MS (ES) *m/z* 195.2

[0856] Etapa 2: A una solución de terc-butil-(2-nitrofenil)-amina (1.27 g, 6.5 mmol), 5% de paladio sobre carbón (0.5 g), y borohidruro de sodio (0.49 g, 13.1 mmol) en tetrahidrofurano (20 mL) se agrega metanol (10 mL) en una manera en forma de gota. Luego de que se completa de la reacción, esta se filtra a través de almohadilla de Celita y el filtrado se vierte en una solución acuosa saturada de cloruro de amonio (50 mL), y se extrae con acetato de etilo (50 mL). La capa orgánica se seca sobre sulfato de magnesio anhidro, se concentra en vacío para dar N-terc-butil-benceno-1,2-diamina la cual se usa en la siguiente etapa sin purificación adicional. Una solución de N-t-butil-benceno-1,2-diamina (1.1 g, 6.7 mmol) y carbonildiimidazol (1.63 g, 10 mmol) en tetrahidrofurano anhidro (50 mL) se agita a temperatura ambiente durante 12 horas. Luego de que se completa, la reacción se vierte en una solución acuosa de ácido clorhídrico 1 N (50 mL) y se extrae con acetato de etilo (50 mL). La capa orgánica se seca sobre sulfato de sodio anhidro y se concentra en vacío. El producto crudo se purifica vía cromatografía de columna flash (sílice, 50% de acetato de etilo en hexano) para dar, 3-dihidro-benzimidazol-2-ona como un sólido muy blanco. MS (ES) *m/z* 191.1.

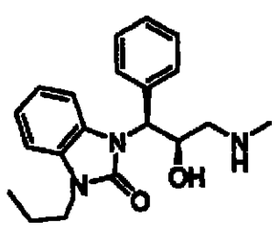
[0857] Etapa 3: Una mezcla de 1-terc-butil-1,3-dihidro-benzimidazol-2-ona (0.66 g, 3.5 mmol) e hidruro de sodio (60% en dispersión en aceite mineral, 0.15 g, 3.8 mmol) en

dimetilformamida anhidra (4 mL) se agita durante 10 minutos bajo nitrógeno a temperatura ambiente. Una solución de [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4, 1.07 g, 7.1 mmol) e isopropóxido de titanio (2.14 mL, 7.1 mmol) en dimetilformamida (4 mL) que se envejece durante 2 0 minutos entonces se agrega y la mezcla se agita a temperatura ambiente bajo nitrógeno durante 12 horas. Después la desaparición del epóxido, la mezcla se particiona entre una solución acuosa de ácido clorhídrico 1 N (50 mL) y acetato de etilo (50 mL). La capa orgánica se separa, se lava con bicarbonato de sodio saturado (50 mL), se seca sobre sulfato de sodio anhidro, se filtra, y se concentra en vacío. El residuo se purifica vía columna de gel de sílice (60% de acetato de etilo en hexano) para dar 1-terc-butil-3-[(1S,2S)-2,3-dihidroxi-1-fenil-propil]-1,3-dihidro-2H-benzimidazol-2-ona como un aceite. MS (ES) *m/z* 341.2.

[0858] Etapa 4: Una solución de 1-terc-butil-3-[(7S,2S)-2,3-dihidroxi-1-fenil-propil]-1,3-dihidro-2H-benzimidazol-2-ona (0.55 g, 1.6 mmol) y cloruro de *para*-toluenosulfonilo (0.37 g, 1.9 mmol) en piridina anhidra (5 mL) se agita a temperatura ambiente bajo nitrógeno durante 12 horas. La reacción se vierte en a cold 1 N solución acuosa de ácido clorhídrico (50 mL) y se extrae con acetato de etilo (50 mL). La capa orgánica se seca sobre sulfato de sodio anhidro, se filtra, y se concentra para dar 3-(3-terc-butil-2-oxo-2,3-dihidro-benzimidazol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S,3S)-tolueno-4-sulfónico . A una solución de 3-(3-terc-butil-2-oxo-2,3-dihidro-benzimidazol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S,3S)-tolueno-4-sulfónico (0.8 g, 1.6 mmol) en metanol (10 mL) se agrega una

solución de metilamina en metanol 2N (4 mL, 8 mmol) y la mezcla de reacción se agita durante 12 horas a temperatura ambiente en un tubo sellado. Luego de que se completa, la reacción se particiona entre una solución acuosa saturada de bicarbonato de sodio (50 mL) y acetato de etilo (50 mL). La capa orgánica se separa, se seca sobre sulfato de sodio anhidro, se filtra, y se concentra en vacío. El residuo se purifica vía cromatografía de columna flash (sílice, 20% de MeOH en diclorometano) para dar 1-terc-butil-3-[(1S,2R)-2-hidroxi-3-metilamino-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona como un aceite claro. La base libre se disuelve en una cantidad mínima de etanol y se trata con a una solución etérea de ácido clorhídrico 2N y se agita durante 1 hora. El etanol se remueve en vacío y el aceite claro se tritura con dietil éter/diclorometano para dar clorhidrato de 1-terc-butil-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona como un sólido blanco. HRMS: calculado para $C_{21}H_{27}N_3O_2$ + H^+, 354.21760; encontrado (ESI, $[M+H]^+$), 354.2179.

[0859] EJEMPLO 193: clorhidrato de 1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3-propil-1,3-dihidro-2H-benzimidazol-2-ona



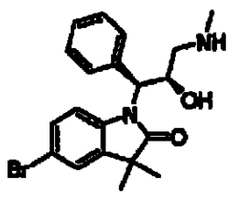
[0860] De forma análoga al EJEMPLO 192, etapa 1 se prepara 2-nitro-N-propilanilina a partir de 1-fluoro-2-nitro-benceno y propil amina. MS (ES) *m/z* 181.1.

[0861] De forma análoga al EJEMPLO 192, etapa 2 se prepara 1-propil-1,3-dihidro-2H-benzimidazol-2-ona a partir de 2-nitro-N-propilanilina. MS (ES) *m/z* 177.1.

[0862] De forma análoga al EJEMPLO 192, etapa 3 se prepara 1-propil-3-[(1,2S)-2,3-dihidroxi-1-fenil-propil]-1,3-dihidro-2H-benzimidazol-2-ona a partir de 1-propil-1,3-dihidro-2H-benzimidazol-2-ona y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4).

[0863] De forma análoga al EJEMPLO 192, etapa 4 se prepara clorhidrato de 1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3-propil-1,3-dihidro-2H-benzimidazol-2-ona a partir de 1-propil-3-[(1S,2S)-2,3-dihidroxi-1-fenil-propil]-2,3-dihidro-2H-benzimidazol-2-ona como un sólido blanco. HRMS: calculado para $C_{20}H_{25}N_3O_2$ + H^+, 340.20195; encontrado (ESI, $[M+H]^+$), 340.2007.

[0864] EJEMPLO 194:clorhidrato de 5-bromo 1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona



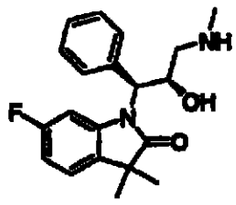
[0865] Etapa 1: De forma análoga al EJEMPLO 99, etapa 6 se prepara 5-bromo-1-[(2S,3S)-2,3-dihidroxi-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona a partir de 5-bromo-3,3-dimetil-1,3-dihidro-indol-2-ona[20] y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4). MS (ESI) *m/z* 391($[M+H]^+$).

[0866] Etapa 2: De forma análoga al EJEMPLO 1, etapa 2 se prepara a 3-(5-bromo-3,3-dimetil-2-oxo-2,3-dihidro-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S, 3S)-tolueno-4-sulfónico partir de (5-bromo-1-[(2S,3S)-2,3-dihidroxi-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona). MS (ESI) *m/z* 545 ($[M+H]^+$).

[0867] Etapa 3: De forma análoga al EJEMPLO 5 se prepara clorhidrato de 5-bromo-1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona a partir de 3-(5-bromo-3,3-dimetil-2-oxo-2,3-dihidro-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S, 3S)-tolueno-4-sulfónico . MS *m/z* 404 ($[M+H]^+$), HRMS: calculado para C20H23BrN2O2 + H^+, 403.10156; encontrado (ESI, $[M+H]^+$), 403.0998.

[0868] EJEMPLO 195: clorhidrato de 6-fluoro-1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona

[20] WO 00/66166



[0869] Etapa 1: De forma análoga al EJEMPLO 99, se prepara etapa (4-fluoro-2-nitrofenil)malonato de 2 dimetilo a partir de 2,5-difluoronitrobenceno y malonato de dimetilo. MS (ESI) *m/z* 272 ($[M+H]^+$).

[0870] Etapa 2: De forma análoga al EJEMPLO 99, etapa 3 se prepara ácido (4-fluoro-2-nitrofenil)acético a partir de (4-fluoro-2-nitrofenil)malonato de dimetilo. MS (ESI) *m/z* 200 ($[M+H]^+$).

[0871] Etapa 3: De forma análoga al EJEMPLO 99, etapa 4 se prepara 6-fluoro-1,3-dihidro-2H-indol-2-ona a partir de ácido (4-fluoro-2-nitrofenil) acético. MS (ESI) *m/z* 152 ($[M+H]^+$).

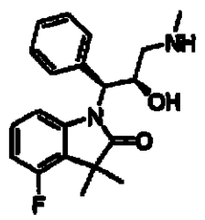
[0872] Etapa 4: De forma análoga al EJEMPLO 99, etapa 5 se prepara 6-fluoro-3,3-dimetil-1,3-dihidro-2H-indol-2-ona a partir de 6-fluoro-1,3-dihidro-2H-indol-2-ona. MS (ESI) *m/z* 180 ($[M+H]^+$.

[0873] Etapa 5: De forma análoga al EJEMPLO 99, etapa 6 se prepara (2S, 3S)-1-(2,3-dihidroxi-1-fenil-propil)-6-fluoro-3,3-dimetil-1,3-dihidro-indol-2-ona a partir de 6-fluoro-3,3-dimetil-1,3-dihidro-2H-indol-2-ona y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4). MS (ESI) *m/z* 330 ($[M+H]^+$).

[0874] Etapa 6: De forma análoga al EJEMPLO 1, etapa 2 se prepara 3-(6-fluoro-3,3-dimetil-2-oxo-2,3-dihidro-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S, 3S)-tolueno-4-sulfónico a partir de (2S,3S)-1-(2,3-dihidroxi-1-fenil-propil)-6-fluoro-3,3-dimetil-1,3-dihidro-indol-2-ona. MS (ESI) *m/z* 484 ($[M+H]^+$).

[0875] Etapa 7: Una solución de 3-(6-fluoro-3,3-dimetil-2-oxo-2,3-dihidro-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S, 3S)-tolueno-4-sulfónico (367 mg, 0.76 mmol) y metilamina (20 mL, solución en etanol al 8M) se agita en un tubo sellado durante 16 horas. La solución se concentra en vacío para dar 250 mg del producto crudo. El producto crudo se purifica por vía de Cromatografía Biotage (FlasH40i, sílice, 5%, 8% y 10% metanol con amonio/diclorometano) para dar 77 mg de producto deseado impuro. La purificación final por HPLC de fase inversa (X-terra MS C18 19x150 mm, utilizando una mezcla isocrática de 60% metanol/agua con 0.05% hidróxido de amonio a una velocidad de 20 mL/minuto a 250 nm) da 35 mg del producto deseado como la base libre. La base libre se trata con una solución etérea de ácido clorhídrico 1 M hasta la solución tiene un pH=3 seguido por dietil éter. El producto se cristaliza por adicionar un mínimo de hexano para proporcionar el compuesto del título clorhidrato de 6-fluoro-1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona. MS (ESI) *m/z* 343 ($[M+H]^+$); HRMS: calculado para C20H23FN2O2 + H^+, 343.18163; encontrado (ESI, $[M+H]^+$), 343.18.

[0876] EJEMPLO 196: clorhidrato de 4-fluoro-1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona



[0877] Etapa 1: De forma análoga al EJEMPLO 99, etapa 1 se prepara 1,2-difluoro-3-nitro-benceno a partir de 2,3-Difluoro-fenilamina y una mezcla de tetrahidrato de perborato de sodio. MS (ESI) *m/z* 160 ($[M+H]^+$).

[0878] Etapa 2: De forma análoga al EJEMPLO 99, etapa 2 se prepara (2-fluoro-6-nitrofenil) malonato de dimetilo a partir de 1,2-difluoro-3-nitro-benceno. MS (ESI) *m/z* 272.0576.

[0879] Etapa 3: De forma análoga al EJEMPLO 99, etapa se prepara 3 ácido (2-fluoro-6-nitrofenil) acético a partir de (2-fluoro-6-nitrofenil)malonato de dimetilo . MS (ESI) *m/z* 200 ($[M+H]^+$).

[0880] Etapa 4: De forma análoga al EJEMPLO 99, etapa se prepara 4 4-fluoro-1,3-dihidro-2H-indol-2-ona de ácido (2-fluoro-6-nitrofenil) acético. MS (ESI) *m/z* 152 ($[M+H]^+$).

[0881] Etapa 5: De forma análoga al EJEMPLO 99, etapa 5 se prepara 4-fluoro-3,3-dimetil-1,3-dihidro-2H-indol-2-ona a partir

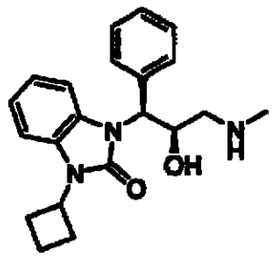
de 4-fluoro-1,3-dihidro-2H-indol-2-ona. MS (ESI) *m/z* 180 ([M+H]$^+$).

[0882] Etapa 6: De forma análoga al EJEMPLO 99, etapa 6 se prepara 1-[(2S,3S)-2,3-dihidroxi-1-fenilpropil]-4-fluoro-3,3-dimetil-1,3-dihidro-2H-indol-2-ona a partir de 4-fluoro-3,3-dimetil-1,3-dihidro-2H-indol-2-ona y [(2R, 3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4). MS (ESI) *m/z* 330 ([M+H]$^+$).

[0883] Etapa 7: De forma análoga al EJEMPLO 1 etapa 2, se prepara 3-(4-fluoro-3,3-dimetil-2-oxo-2,3-dihidro-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S,3S)-tolueno-4-sulfónico a partir de 1-[(1S,2S)-2,3-dihidroxi-1-fenilpropil]-4-fluoro-3,3-dimetil-1,3-dihidro-2H-indol-2-ona. MS (ESI) *m/z* 484 ([M+H]$^+$.

[0884] Etapa 8: De forma análoga al EJEMPLO 195 etapa 7, se prepara clorhidrato de 4-fluoro-1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona a partir de 3-(4-fluoro-3,3-dimetil-2-oxo-2,3-dihidro-indol-1-il)-2-hidroxi-3-fenil-propil éster de ácido (2S,3S)-tolueno-4-sulfónico . HRMS: calculado para C20H23FN2O2 + H$^+$, 343.18163; encontrado (ESI, [M+H]$^+$), 343.1807.

[0885] EJEMPLO 197: clorhidrato de 1-ciclobutil-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona



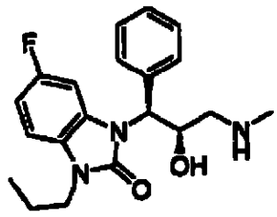
[0886] De forma análoga al EJEMPLO 192, etapa 1 se prepara N-ciclobutil-2-nitroanilina a partir de 1-fluoro-2-nitro-benceno y ciclobutil amina. MS (ES) *m/z* 193.

[0887] De forma análoga al EJEMPLO 192, etapa 2 se prepara 1-ciclobutil-1,3-dihidro-2H-benzimidazol-2-ona a partir de N-ciclobutil-2-nitroanilina. MS (ES) *m/z* 189.

[0888] De forma análoga al EJEMPLO 192, etapa 3 se prepara 1-ciclobutil-3-[(1S,2S)-2,3-dihidroxi-1-fenil-propil]-1,3-dihidro-2H-benzimidazol-2-ona a partir de 1-ciclobutil-1,3-dihidro-2H-benzimidazol-2-ona y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4). MS (ES) *m/z* 339.2.

[0889] De forma análoga al EJEMPLO 192, etapa 4 se prepara clorhidrato de 1-ciclobutil-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona a partir de 1-ciclobutil-3-[(1S,2S)-2,3-dihidroxi-1-fenil-propil]-1,3-dihidro-2H-benzimidazol-2-ona como un sólido blanco. MS (ES) *m/z* 352.2. HRMS: calculado para $C_{21}H_{25}N_3O_2$ + H^+, 352.20195; encontrado (ESI, $[M+H]^+$), 352.207

[0890] EJEMPLO 198: clorhidrato de 5-fluoro-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1-propil-1,3-dihidro-2H-benzimidazol-2-ona



[0891] De forma análoga al EJEMPLO 192, etapa 1 se prepara (4-fluoro-2-nitro-fenil)-propil-amina a partir de 1,4-difluoro-2-nitro-benceno y propil amina.

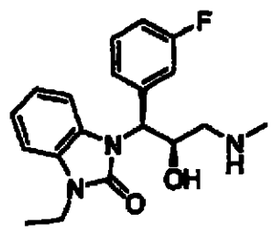
[0892] De forma análoga al EJEMPLO 192, etapas 1 y 2 se prepara 5-fluoro-1-propil-1,3-dihidro-benzimidazol-2-ona a partir de (4-fluoro-2-nitro-fenil)-propil-amina. MS (ES) *m/z* 195.2.

[0893] De forma análoga al EJEMPLO 192, etapa 3 se prepara 5-fluoro-3-[(7S,2S)-2,3-dihidroxi-1-fenil-propil]-1-propil-1,3-dihidro-2H-benzimidazol-2-ona a partir de 5-fluoro-1-propil-1,3-dihidro-benzimidazol-2-ona y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4).

[0894] De forma análoga al EJEMPLO 192, etapa 4 se prepara clorhidrato de 5-fluoro-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1-propil-1,3-dihidro-2H-benzimidazol-2-ona a partir de 5-fluoro-3-[(1S,2S)-2,3-dihidroxi-1-fenil-propil]-1-propil-1,3-dihidro-2H-benzimidazol-2-ona como un sólido blanco. MS (ES)

m/z 358.2; HRMS: calculado para $C_{20}H_{24}FN_3O_2$ + H^+, 358.19253; encontrado (ESI, $[M+H]^+$), 358.1895

[0895] EJEMPLO 199: clorhidrato de 1-Etil-3-[1-(3-fluoro-fenil)-2-hidroxi-3-metilamino-propil]-1,3-dihidro-benzimidazol-2-ona



[0896] Etapa 1: A una solución de etilamina en metanol (2.0 M, 150 mL, 300 mmol) se agrega 1-fluoro-2-nitrobenceno (8 mL, 75.7 mmol). La mezcla de reacción se coloca en una vasija sellada y se calienta a 55° C durante 15 horas. El solvente se remueve en vacío y el residuo se retira en acetato de etilo (200 mL), se lava con una solución acuosa saturada de bicarbonato de sodio (80 mL), y se seca sobre sulfato de sodio anhidro (50 g). Después de remover el solvente, se obtiene etil-(2-nitro-fenil)-amina (12.5g, 75 mmol) como un aceite café. MS (ES) *m/z* 167.1.

[0897] Etapa 2: A una solución de etil-(2-nitro-fenil)-amina (12.5 g, 75 mmol) en tetrahidrofurano anhidro (150 mL) se agrega borohidruro de sodio (5.8g, 153 mmol), y 5% de paladio sobre carbón (150 mg). Entonces se agrega metanol (25 mL) a temperatura ambiente bajo nitrógeno en una forma de gota a gota. Después de la adición, la mezcla de reacción se agita a temperatura ambiente durante cerca de 30 minutos hasta que la reacción se completa. La

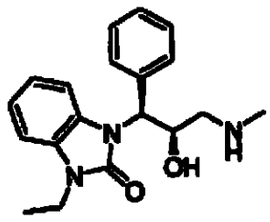
mezcla de reacción entonces se filtra a través de almohadilla de Celita. El filtrado se diluye con acetato de etilo (200 mL), se lava con una solución acuosa saturada de cloruro de amonio (80 mL), se seca sobre sulfito de sodio, y se concentra en vacío para proporcionar N-etil-benceno-1,2-diamina cruda (8.4 g, 62 mmol) que se utiliza en la siguiente etapa sin purificación adicional.

[0898] Etapa 3: A una solución de N-etil-benceno-1,2-diamina cruda (8.4 g, 62 mmol) en tetrahidrofurano anhidro (200 mL) se agrega 1,1'-carbonildiimidazol (10g, 62 mmol). La mezcla se agita a temperatura ambiente bajo nitrógeno durante 12 horas y seguida por acetato de etilo (250 mL) se agrega una solución acuosa de ácido clorhídrico 3N fría (200 mL). La capa orgánica se separa, se seca sobre sulfato de sodio y se concentra en vacío para proporcionar 1-etil-1,3-dihidro-benzimidazol-2-ona como un sólido blanco (8.5g, 69% durante tres etapas). MS (ES) *m/z* 163.2.

[0899] Etapa 4: De forma análoga al EJEMPLO 192, etapa 3 se prepara 1-etil-3-[(1S,2S)-2,3-dihidroxi-1-(3-fluorofenil)-propil]-1,3-dihidro-2H-benzimidazol-2-ona a partir de 1-etil-1,3-dihidro-benzimidazol-2-ona y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3).

[0900] Etapa 5: De forma análoga al EJEMPLO 192, etapa 4 se prepara clorhidrato de 1-etil-3-[(1S,2R)-1-(3-fluorofenil)-2-hidroxi-3-(metilamino)propil]-1,3-dihidro-2H-benzimidazol-2-ona a partir de 1-etil-3-[(1S,2S)-2,3-dihidroxi-1-(3-fluorofenil)-propil]-1,3-dihidro-2H-benzimidazol-2-ona como un sólido blanco. MS (ES) *m/z* 344.2

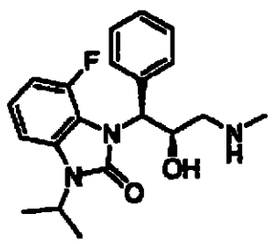
[0901] EJEMPLO 200: clorhidrato de 1-Etil-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona



[0902] De forma análoga al EJEMPLO 192, etapa 3 se prepara 1-etil-3-[(7S,2S)-2,3-dihidroxi-1-fenil-propil]-1,3-dihidro-2H-benzimidazol-2-ona a partir de 1-etil-1,3-dihidro-benzimidazol-2-ona (EJEMPLO 199, etapa 2) y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4).

[0903] De forma análoga al EJEMPLO 192, etapas 4 y 5 se prepara clorhidrato de 1-Etil-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona a partir de 1-etil-3-[(1S,2S)-2,3-dihidroxi-1-fenil-propil]-1,3-dihidro-2H-benzimidazol-2-ona como un sólido blanco. MS (ES) *m/z* 326.2; HRMS: calculado para $C_{1923}N_3O_2$ + H^+, 326.18630; encontrado (ESI, $[M+H]^+$), 326.1845.

[0904] EJEMPLO 201: clorhidrato de 4-Fluoro-3-(2-hidroxi-3-metilamino-1-fenil-propil)-1-isopropil-1,3-dihidro-benzimidazol-2-ona



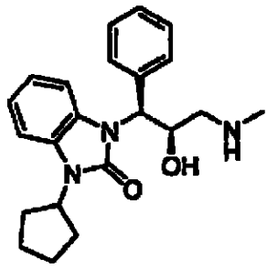
[0905] De forma análoga al EJEMPLO 192, etapa 1 se prepara (3-fluoro-2-nitro-fenil)-isopropil-amina a partir de 1,3-difluoro-2-nitro-benceno e iso-propilamina.

[0906] De forma análoga al EJEMPLO 192, etapa 2 se prepara 4-fluoro-1-isopropil-1,3-dihidro-benzimidazol-2-ona a partir de (3-fluoro-2-nitro-fenil)-isopropil-amina. MS (ES) *m/z* 195.2.

[0907] De forma análoga al EJEMPLO 192, etapa 3 se prepara 4-fluoro-3-[(1S,2S)-2,3-dihidroxi-1-fenil-propil]-1-isopropil-1,3-dihidro-2H-benzimidazol-2-ona a partir de 4-fluoro-1-isopropil-1,3-dihidro-benzimidazol-2-ona y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4).

[0908] De forma análoga al EJEMPLO 192, etapa 4 se prepara clorhidrato de 4-fluoro-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1-isopropil-1,3-dihidro-2H-benzimidazol-2-ona a partir de 4-fluoro-3-[(1S,2S)-2,3-dihidroxi-1-fenil-propil]-1-isopropil-1,3-dihidro-2H-benzimidazol-2-ona como un sólido blanco. MS (ES) *m/z* 358.4.

[0909] EJEMPLO 202: clorhidrato de 1-Ciclopentil-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona



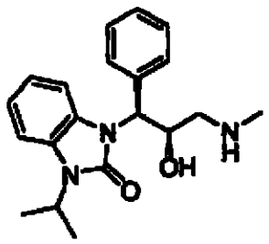
[0910] De forma análoga al EJEMPLO 192, etapa 1 se prepara N-ciclopentil-2-nitroanilina a partir de 1-fluoro-2-nitro-benceno y ciclopentil amina. MS (ESI) *m/z* 207.

[0911] De forma análoga al EJEMPLO 192, etapa 2 se prepara 1-ciclopentil-1,3-dihidro-benzimidazol-2-ona a partir de N-ciclopentil-2-nitroanilina. MS (ESI) *m/z* 203.

[0912] De forma análoga al EJEMPLO 192, etapa 3 se prepara 1-ciclopentil-3-[(1S,2S)-2,3-dihidroxi-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona a partir de 1-ciclopentil-1,3-dihidro-benzimidazol-2-ona y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un sólido blanco. MS (ES) *m/z* 352.9.

[0913] De forma análoga al EJEMPLO 192, etapa 4 se prepara clorhidrato de 1-ciclopentil-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona a partir de 1-ciclopentil-3-[(1S,2S)-2,3-dihidroxi-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona como un sólido blanco. MS (ES) *m/z* MS (ESI) *m/z* 366.

[0914] EJEMPLO 203: clorhidrato de 1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3-isopropil-1,3-dihidro-2H-benzimidazol-2-ona



[0915] De forma análoga al EJEMPLO 192, etapa 1 se prepara N-isopropil-2-nitroanilina a partir de 1-fluoro-2-nitro-benceno e isopropil amina. MS (ES) *m/z* 181.2.

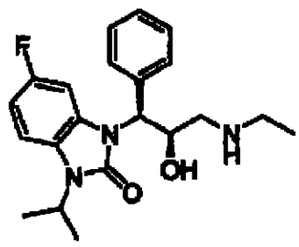
[0916] De forma análoga al EJEMPLO 192, etapa 2 se prepara 1-isopropil-1,3-dihidro-2H-benzimidazol-2-ona a partir de N-isopropil-2-nitroanilina. MS (ES) *m/z* 176.9.

[0917] De forma análoga al EJEMPLO 192, etapa 3 se prepara 1-[(1S,2S)-2,3-dihidroxi-1-fenilpropil]-3-isopropil-1,3-dihidro-2H-benzimidazol-2-ona a partir de 1-isopropil-1,3-dihidro-2H-benzimidazol-2-ona y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un sólido blanco.

[0918] De forma análoga al EJEMPLO 192, etapa 4 se prepara clorhidrato de 1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3-isopropil-1,3-dihidro-2H-benzimidazol-2-ona a partir de 1-[(1S,2S)-2,3-dihidroxi-1-fenilpropil]-3-isopropil-1,3-dihidro-2H-benzimidazol-2-ona como un sólido blanco. MS (ES)

m/z MS (ES) *m/z* 340.3; HRMS: calculado para $C_{20}H_{25}N_3O_2$ + H^+, 340.20195; encontrado (ESI, $[M+H]^+$), 340.2012.

[0919] EJEMPLO 204: clorhidrato de 3-[(1S,2H)-3-(etilamino)-2-hidroxi-1-fenilpropil]-5-fluoro-1-isopropil-1,3-dihidro-2H-benzimidazol-2-ona



[0920] De forma análoga al EJEMPLO 192, etapa 1 se prepara 4-fluoro-N-isopropil-2-nitroanilina a partir de 1,4-difluoro-2-nitro-benceno e isopropil amina. MS (ES) *m/z* 199.1.

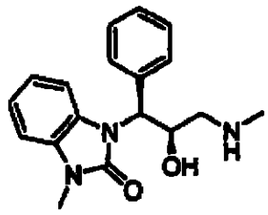
[0921] De forma análoga al EJEMPLO 192, etapa 2 se prepara 5-fluoro-1-isopropil-1,3-dihidro-2H-benzimidazol-2-ona a partir de 4-fluoro-N-isopropil-2-nitroanilina. MS (ES) *m/z* 195.1.

[0922] De forma análoga al EJEMPLO 192, etapa 3 se prepara 5-fluoro-1-[(1S,2S)-2,3-dihidroxi-1-fenilpropil]-3-isopropil-1,3-dihidro-2H-benzimidazol-2-ona a partir de 5-fluoro-1-isopropil-1,3-dihidro-2H-benzimidazol-2-ona y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un sólido blanco.

[0923] De forma análoga al EJEMPLO 192, etapa 4 se prepara clorhidrato de 3-[(1S,2R)-3-(etilamino)-2-hidroxi-1-fenilpropil]-5-fluoro-1-isopropil-1,3-dihidro-2H-benzimidazol-2-ona a partir

de 5-fluoro-1-[(1S,2S)-2,3-dihidroxi-1-fenilpropil]-3-isopropil-1,3-dihidro-2H-benzimidazol-2-ona y ácido *para*-toluenosulfónico seguido por etilamina como un sólido blanco. MS (ESI) *m/z* 372.21; HRMS: calculado para $C_{21}H_{26}FN_3O_2$ + H^+, 372.20818; encontrado (ESI, $[M+H]^+$), 372.2099.

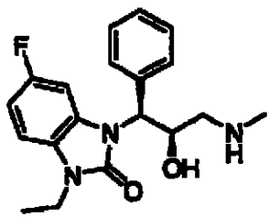
[0924] EJEMPLO 205: clorhidrato de 1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3-metil-1,3-dihidro-2H-benzimidazol-2-ona



[0925] De forma análoga al EJEMPLO 192, etapa 3 se prepara 1-[(1S,2S)-2,3-dihidroxi-1-fenilpropil]-3-metil-1,3-dihidro-2H-benzimidazol-2-ona a partir de 1-metil-1,3-dihidro-benzimidazol-2-ona y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un sólido blanco.

[0926] De forma análoga al EJEMPLO 192, etapa 4 se prepara Clorhidrato de 1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil-3-metil-1,3-dihidro-2H-benzimidazol-a-ona a partir de 1-[(1S,2S)-2,3-dihidroxi-1-fenilpropil]-3-metil-1,3-dihidro-2H-benzimidazol-2-ona como un sólido blanco. MS (ES) *m/z* 312.3; HRMS: calculado para $C_{18}H_{21}N_3O_2$ + H^+, 312.17065; encontrado (ESI, $[M+H]^+$), 312.17.

[0927] EJEMPLO 206: clorhidrato de 1-Etil-5-fluoro-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona



[0928] De forma análoga al EJEMPLO 199, etapa 1 se prepara etil-(4-fluoro-2-nitro-fenil)-amina a partir de 1,4-difluoro-2-nitroanilina y etilamina.

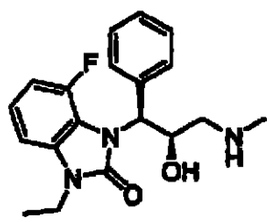
[0929] De forma análoga al EJEMPLO 199, etapa 2 se prepara N-etil-4-fluoro-benceno-1,2-diamina a partir de etil-(4-fluoro-2-nitro-fenil)-amina.

[0930] De forma análoga al EJEMPLO 199, etapa 3 se prepara 1-etil-5-fluoro-1,3-dihidro-2H-benzimidazol-2-ona a partir de N-etil-4-fluoro-benceno-1,2-diamina. MS (ES) *m/z* 181.2.

[0931] De forma análoga al EJEMPLO 192, etapa 3 se prepara 3-[(1S,2S)-2,3-dihidroxi-1-fenilpropil]-1-etil-5-fluoro-1,3-dihidro-2H-benzimidazol-2-ona a partir de 1-etil-5-fluoro-1,3-dihidro-2H-benzimidazol-2-ona y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un sólido blanco. MS (ES) *m/z* 331.1.

[0932] De forma análoga al EJEMPLO 192, etapa 4 se prepara clorhidrato de 1-etil-5-fluoro-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona a partir de 3-[(1S,2S)-2,3-dihidroxi-1-fenilpropil]-1-etil-5-fluoro-1,3-dihidro-2H-benzimidazol-2-ona como un sólido blanco. MS (ES) *m/z* 344.2; HRMS: calculado para $C_{19}H_{22}FN_3O_2$ + H^+, 344.17688; encontrado (ESI, $[M+H]^+$), 344.175.

[0933] EJEMPLO 207: clorhidrato de 1-Etil-4-fluoro-3-[(1S,2/7)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona



[0934] De forma análoga al EJEMPLO 199, etapa 1 se prepara etil-(3-fluoro-2-nitro-fenil)-amina a partir de 1,3-difluoro-2-nitroanilina y etilamina.

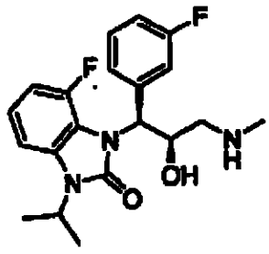
[0935] De forma análoga al EJEMPLO 199, etapa 2 se prepara N-etil-3-fluoro-benceno-1,2-diamina a partir de etil-(3-fluoro-2-nitro-fenil)-amina.

[0936] De forma análoga al EJEMPLO 199, etapa 3 se prepara 1-etil-4-fluoro-1,3-dihidro-2H-benzimidazol-2-ona a partir de N-etil-3-fluoro-benceno-1,2-diamina. MS (ES) *m/z* 181.2.

[0937] De forma análoga al EJEMPLO 192, etapa 3 se prepara 3-[(1S,2S)-2,3-dihidroxi-1-fenilpropil]-1-etil-4-fluoro-1,3-dihidro-2H-benzimidazol-2-ona a partir de 1-etil-4-fluoro-1,3-dihidro-2H-benzimidazol-2-ona y [(2R,3R)-3-feniloxiran-2-il]metanol (EJEMPLO 117, etapa 4) como un sólido blanco. MS (ES) *m/z* 331.1.

[0938] De forma análoga al EJEMPLO 192, etapa 4 se prepara clorhidrato de 1-etil-4-fluoro-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona a partir de 3-[(1S,2S)-2,3-dihidroxi-1-fenilpropil]-1-etil-4-fluoro-1,3-dihidro-2H-benzimidazol-2-ona como un sólido blanco. MS (ES) *m/z* 344.2; HRMS: calculado para $C_{19}H_{22}FN_3O_2$ + H^+, 344.17688; encontrado (ESI, $[M+H]^+$), 344.1768.

[0939] EJEMPLO 208: clorhidrato de 4-fluoro-3-[(1S,2R)-1-(3-fluorofenil)-2-hidroxi-3-(metilamino)-propil]-1-isopropil-1,3-dihidro-2H-benzimidazol-2-ona

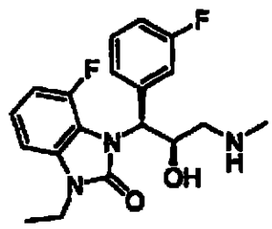


[0940] De forma análoga al EJEMPLO 192, etapa 3 se prepara 4-fluoro-3-[(1S,2S)-1-(3-fluoro-fenil)-2,3-dihidroxi-propil]-1-isopropil-1,3-dihidro-benzimidazol-2-ona a partir de 4-fluoro-1-isopropil-1,3-dihidro-benzimidazol-2-ona (EJEMPLO 201, etapa 2) y

[(2R,3R)-3-(3-fluorofenil)-oxiran-2-il]metanol (EJEMPLO 47, etapa 3) como un aceite.

[0941] De forma análoga al EJEMPLO 192, etapa 4 se prepara clorhidrato de 4-fluoro-3-[(1S,2R)-1-(3-fluorofenil)-2-hidroxi-3-(metilamino)-propil]-1-isopropil-1,3-dihidro-2H-benzimidazol-2-ona a partir de 4-fluoro-3-[(1S,2S)-1-(3-fluorofenil)-2,3-dihidroxi-propil]-1-isopropil-1,3-dihidro-benzimidazol-2-ona como un sólido blanco. MS (ES) *m/z* 376.2

[0942] EJEMPLO 209: clorhidrato de 1-Etil-4-fluoro-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-(3-fluorofenil)-propil]-1,3-dihidro-2H-benzimidazol-2-ona

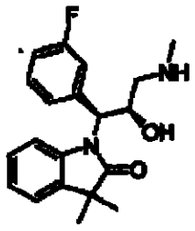


[0943] De forma análoga al EJEMPLO 192, etapa 3 se prepara 3-[(1S,2S)-2,3-dihidroxi-1-(3-fluorofenil)-propil]-1-etil-4-fluoro-1,3-dihidro-2H-benzimidazol-2-ona a partir de 1-etil-4-fluoro-1,3-dihidro-2H-benzimidazol-2-ona (EJEMPLO 207, etapa 2) y [(2R,3R)-3-(3-fluorofenil)-oxiran-2-il]metanol (EJEMPLO 47, etapa 3) como un aceite claro. MS (ES) *m/z* 349.1.

[0944] De forma análoga al EJEMPLO 192, etapa 4 se prepara clorhidrato de 1-Etil-4-fluoro-3-[(1S,2R)-2-hidroxi-3-

(metilamino)-1-(3-fluorofenil)-propil]-1,3-dihidro-2H-benzimidazol-2-ona a partir de 3-[(1S,2S)-2,3-dihidroxi-1-(3-fluorofenil)-propil]-1-etil-4-fluoro-1,3-dihidro-2H-benzimidazol-2-ona como un sólido blanco. MS (ES) *m/z* 362.1.

[0945] EJEMPLO 210: clorhidrato de 1-[(1S,2R)-1-(3-fluorofenil)-2-hidroxi-3-(metilamino)propil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona



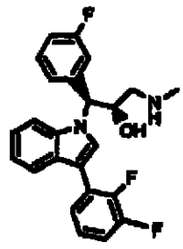
[0946] Etapa 1: De forma análoga al EJEMPLO 101, etapa 1 se prepara (2S, 3S)-1-[1-(3-fluoro-fenil)-2,3-dihidroxi-propil]-3,3-dimetil-1,3-dihidro-indol-2-ona a partir de 3,3-dimetil-1,3-dihidro-indol-2-ona[10] y [(2R,3R)-3-(3-fluorofenil)oxiran-2-il]metanol (EJEMPLO 47, etapa 3). MS (ESI) *m/z* 330 ($[M+H]^+$).

[0947] Etapa 2: De forma análoga al EJEMPLO 1, etapa 2 se prepara 3-(3,3-dimetil-2-oxo-2,3-dihidro-indol-1-il)-3-(3-fluoro-fenil)-2-hidroxi-propil éster de ácido (2S, 3S)-tolueno-4-sulfónico a partir de (2S, 3S)-1-[1-(3-fluoro-fenil)-2,3-dihidroxi-propil]-3,3-dimetil-1,3-dihidro-indol-2-ona. MS (ESI) *m/z* 484 ($[M+H]^+$).

[0948] Etapa 3: De forma análoga al EJEMPLO 5 se prepara clorhidrato de 1-[(1S,2R)-1-(3-fluorofenil)-2-hidroxi-3-(metilamino)propil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona a

partir de 3-(3,3-dimetil-2-oxo-2,3-dihidro-indol-1-il)-3-(3-fluoro-fenil)-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico. MS (ESI) *m/z* 343 ($[M+H]^+$).

[0949] EJEMPLO 211: clorhidrato de (1S,2R)-1-[3-(2,3-difluorofenil)-1H-indol-1-il]-1-(3-fluorofenil)-3-(metilamino)propan-2-ol



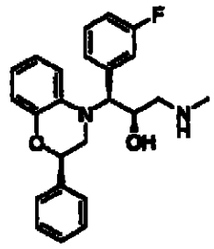
[0950] De forma análoga al EJEMPLO 114, etapa 2, se prepara (2S,3S)-3-(3-fluorofenil)-[3-(2,3-difluorofenil)-1H-indol-1-il]propano-1,2-diol a partir de (2S,3S)-3-(3-fluorofenil)-3-(3-yodo-1H-indol-1-il)propano-1,2-diol (EJEMPLO 114, etapa 1) y ácido 2, 3-difluorobencenoborónico.

[0951] De forma análoga al EJEMPLO 1, etapa 2, se prepara 3-(3-fluorofenil)-3-(2,3-difluorofenil)-indol-1-il]-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico a partir de (2S,3S)-3-(3-fluorofenil)-3-[3-(2,3-difluorofenil)-1H-indol-1-il]propano-1,2-diol.

[0952] De forma análoga al EJEMPLO 5, se prepara (1S,2R)-1-[3-(2,3-difluorofenil)-1H-indol-1-il]-1-(3-fluorofenil)-3-(metilamino)propan-2-ol a partir de 3-(3-fluorofenil)-3-(2,3-

difluorofenil)-indol-1-il]-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico. MS (ES) *m/z* 411.1; HRMS: calculado para $C_{24}H_{21}F_3N_2O$ + H^+, 411.16787; encontrado (ESI, $[M+H]^+$), 411.1675.

[0953] EJEMPLO 212: clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-[(2R)-2-fenil-2,3-dihidro-4H-1,4-benzoxazin-4-il]propan-2-ol



[0954] Etapa 1: La mezcla diastereomérica de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(2-fenil-2,3-dihidro-4H-1,4-benzoxazin-4-il)propan-2-ol (EJEMPLO 168) se disuelve en metanol. La solución resultante se inyecta en el instrumento de Cromatografía de Fluido Supercrítico. La línea base resuelve los diastereómeros, que utilizan las condiciones descritas adelante, se recolectan.

Instrumento SFC: Berger MultiGram Prep SFC (Berger Instruments, Inc. Newark, DE 19702.

Columna: Etil piridina; 250mm L x 20mm ID (Princeton Chromatography Inc.)

Temperatura de columna: 350C

Modificador SFC: 15% de MeOH con 85% CO_2

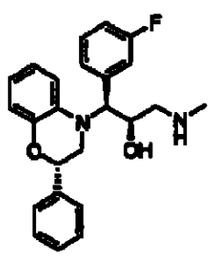
Índice de flujo: 50 mL/min

Presión de Salida: 100 bar

Detector: UV a 220 nm

[0955] Etapa 2: (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-[(2R)-2-fenil-2,3-dihidro-4H-1,4-benzoxazin-4-il]propan-2-ol, se aísla como pico 1, se somete a la formación de sal de clorhidrato De forma análoga al EJEMPLO 144, etapa 2 para dar clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-[(2R)-2-fenil-2,3-dihidro-4H-1,4-benzoxazin-4-il]propan-2-ol como un polvo blanco. MS (ES) *m/z* 393.2 ($[M+H]^+$); HRMS: calculado para $C_{24}H_{25}FN_2O_2$ + H^+, 393.1973; encontrado (ESI, [M+Hj+), 393.1992.

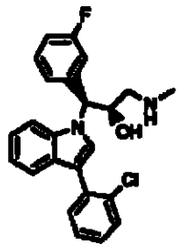
[0956] EJEMPLO 213: clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-[(2S)-2-fenil-2,3-dihidro-4H-1,4-benzoxazin-4-il]propan-2-ol



[0957] De forma análoga al EJEMPLO 212, se prepara clorhidrato de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-[(2S)-2-fenil-2,3-

dihidro-4H-1,4-benzoxazin-4-il]propan-2-ol como un polvo blanco a partir de (1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-[(2S)-2-fenil-2,3-dihidro-4H-1,4-benzoxazin-4-il]propan-2-ol, que se aísla como pico 2 de la separación diastereomérica (EJEMPLO 212, etapa 1). MS (ES) *m/z* 393.2 ($[M+H]^+$); HRMS: calculado para $C_{24}H_{25}FN_2O_2$ + H^+, 393.1973; encontrado (ESI, $[M+H]^+$), 393.1982.

[0958] EJEMPLO 214: clorhidrato de (1S,2R)-1-[3-(2-clorofenil)-1H-indol-1-il]-1-(3-fluorofenil)-3-(metilamino)propan-2-ol



[0959] De forma análoga al EJEMPLO 114, etapa 2, se prepara (2S,3S)-3-(3-fluorofenil)-3-{3-[2-clorofenil]-1H-indol-1-il}propano-1,2-diol a partir de (2S,3S)-3-(3-fluorofenil)-3-(3-yodo-1H-indol-1-il)propano-1,2-diol (EJEMPLO 114, etapa 1) y ácido 2-clorobencenoborónico.

[0960] De forma análoga al EJEMPLO 1, etapa 2, se prepara 3-(3-fluorofenil)-3-[3-(2-clorofenil)-indol-1-il]-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico a partir de (2S,3S)-3-(3-fluorofenil)-3-{3-[2-clorofenil]-1H-indol-1-il}propano-1,2-diol.

[0961] De forma análoga al EJEMPLO 5, se prepara clorhidrato de (1S,2R)-1-[3-(2-clorofenil)-1H-indol-1-il]-1-(3-fluorofenil)-3-(metilamino)propan-2-ol a partir de 3-(3-fluoro-fenil)-3-[3-(2-clorofenil)-indol-1-il]-2-hidroxi-propil éster de ácido (2S,3S)-tolueno-4-sulfónico y metilamina (solución en metanol 2N). MS (ESI) *m/z* 409.1; HRMS: calculado para $C_{24}H_{22}ClFN_2O$ + H^+, 409.14774; encontrado (ESI, $[M+H]^+$), 409.146.

[0962] Líneas celulares, Reactivos de Cultivo y Ensayos

Células MDCK-Net6 transfectadas establemente con hNET humano (Pacholczyk, T., R.D. Blakely, and S.G. Amara, *Nature*, **1991**, 350(6316): p. 350-4) se cultivan en un medio de cultivo que contiene DMEM de alta glucosa (Gibco, Cat. No. 11995), 10% de FBS (dializado, inactivado por calor, US Bio-Technologies, Lote FBD1129HI) y 500 µg/ml de G418 (Gibco, Cat. No. 10131). Las células se colocan en placas a 300,000/frasco T75 y las células se dividen dos veces por semana. La línea celular JAR (coriocarcinoma placental humano) se compra de ATCC (Cat. No. HTB-144). Las células se cultivan en medio de cultivo que contiene RPMI 1640 (Gibco, Cat. No. 72400), 10% de FBS (Irvine, Cat. No. 3000), 1% de piruvato de sodio (Gibco, Cat. No. 1136) y 0.25% de glucosa. Las células se colocan en placas a razón de 250,000 células/frasco T75 y se dividen dos veces por semana. Para todos los ensayos las células se colocan en placas estériles Wallac de 96 pozos (PerkinElmer, Cat. No. 3983498).

[0963] Ensayos de toma de Norepinefrina (NE)

En el día 1, las células se colocan en placas a razón de 3,000 células/pozo el medio de crecimiento y se mantienen en una incubadora de células (37SC, 5% de CO2). En el día 2, el medio de crecimiento se reemplaza con 200 µl de amortiguador de ensayo (25 mM de HEPES; 120 mM de NaCl; 5 mM de KCl; 2.5 mM de $CaCl_2$; 1.2 de mM $MgSO_4$; 2 mg/ml de glucosa (pH 7.4, 37° C)) que contiene 0.2 mg/ml de ácido ascórbico y 10 µM de pargilina. Las placas que contienen las células con 200 µl del amortiguador de ensayo se equilibran 10 minutos a 37° C antes de la adición de los compuestos. Una solución de base de desipramina se prepara en DMSO (10 mM) y se suministran a los pozos triplicados que contienen células para un ensayo de concentración final de 1 µM. Los datos de estos pozos se utilizan para definir la toma de NE no específica (toma mínima de NE). Los compuestos de ensayo se preparan en DMSO (10 mM) y se diluyen en el amortiguador de ensayo de acuerdo al rango de ensayo (1 a 10,000 nM). Veinticinco microlitros de amortiguador de ensayo (toma máxima de NE) o el compuesto de ensayo se agrega directamente a los pozos triplicados que contienen las células en 200 µl de amortiguador de ensayo. Las células en amortiguador de ensayo con los compuestos de ensayo se incuban durante 20 minutos a 37° C. Para iniciar la Toma de NE, se suministra [^{3}H]NE diluido en amortiguador de ensayo (120 nM de concentración de ensayo final) en alícuotas de 25 µl a cada pozo y las placas se incuban durante 5 minutos (37° C). La reacción se termina por medio de decantar el supernadante de la placa. Las placas que contienen las células se lavan dos veces con 200 µl amortiguador de ensayo (37° C) para remover el radio ligando libre. Las placas entonces se invierten, izquierda para secar durante 2 minutos, luego reinvertidas y

secadas por aire durante 10 minutos adicionales. Las células se lisan en 25 µl de una solución de NaOH 0.25 N (4° C), se colocan sobre una tabla de agitación y se agitan vigorosamente durante 5 minutos. Después de la lisis celular, 75 µl del cóctel de cintilación se agrega a cada pozo y las placas se sellan con cinta de película. Las placas regresan a la mesa agitadora y se agitan vigorosamente durante un mínimo de 10 minutos para asegurar una partición adecuada de las y soluciones orgánicas y acuosas. Las placas se cuentan en un contador Wallac Microbeta (PerkinElmer) para recolectar los datos brutos cpm.

[0964] Ensayo de Toma de Serotonina (5-HT)

Los métodos para la retoma funcional de 5-HT que usan la línea celular JAR se modifican utilizando un informe de literatura previo (Prasad, *et al.*, *Placenta*, 1996. 17(4): 201-7). En el día 1, las células se colocan en placas a razón de 15,000 células/pozo en placas de 96 pozos que contienen el medio de crecimiento (RPM1 1640 con 10% de FBS) y se mantienen en una incubadora para células (37SC, 5% de CO_2). En el día 2, las células se estimulan con estaurosporina (40 nM) para incrementar la expresión del transportador 5-HT [17]. En el día 3, las células se remueven de la incubadora de células dos días antes del ensayo y mantenidas a temperatura ambiente para equilibrar el medio de crecimiento a la concentración de oxígeno del ambiente. Subsecuentemente, el medio de crecimiento se reemplaza con 200 µl del amortiguador de ensayo (25 mM de HEPES; 120 mM de NaCl; 5 mM de KCl; 2.5 mM de $CaCl_2$; 1.2 de mM $MgSO_4$; 2 mg/ml de glucosa (pH 7.4, 37° C)) que contiene 0.2 mg/ml de ácido ascórbico y 10 µM de

pargilina. Una solución de partida de paroxetina (AHR-4389-1) se prepara en DMSO (10 mM) y se suministra los pozos triplicados que contienen las células para una concentración de ensayo final de 1 µM. Los datos de estos pozos utilizan para definir la toma no específica 5-HT (toma mínima de 5-HT). Los compuestos de ensayo se preparan en DMSO (10 mM) y se diluyen en el amortiguador de ensayo de acuerdo con el rango de ensayo (1 a 1,000 nM). Veinticinco microlitros de amortiguador de ensayo (toma máxima de 5-HT) o del compuesto de ensayo se agrega directamente a los pozos triplicados que contienen las células en 200 µl de amortiguador de ensayo. Las células se incuban con el compuesto durante 10 minutos a 37° C. Para iniciar la reacción, se suministra sulfato de [^{3}H]hidroxitriptamina creatinina diluido en el amortiguador de ensayo en alícuotas de 25 µl a cada pozo para una concentración final de ensayo de 15 nM. Las células se incuban con la mezcla de reacción durante 5 minutos a 37° C. La reacción de toma de 5-HT se termina por medio de decantar el amortiguador de ensayo. Las células se lavan dos veces con 200 µl amortiguador de ensayo (37° C) para remover el radio ligando libre. Las placas se invierten, y se dejan para secar durante 2 minutos, luego se reinvierten y se secan al aire durante 10 minutos adicionales. Subsecuentemente las células se lisan en 25 µl de NaOH 0.25 N (4° C), luego se colocan sobre una tabla agitadora y se agitan vigorosamente durante 5 minutos. Después de la lisis celular, se agrega un cóctel de cintilación de 75 µl a los pozos, las placas se sellan con cinta de película y se recolocan sobre la tabla agitadora y durante un mínimo de 10 minutos. Las placas se cuentan en un contador Wallac Microbeta (PerkinElmer) para recolectar los datos brutos cpm.

[0965] Evaluación de los Resultados

Para cada experimento, un flujo de datos de valores cpm se recolectan del contador nWallac Microbeta se bajan a un programa de aplicación estadística Excel de Microsoft. Los cálculos de los valores EC_{50} se hacen utilizando el programa de respuesta de dosis logística de transformación de ambos lados escrito por Wyeth Biometrics Department. El programa estadístico usa valores medios cpm de los pozos que representan un ligado o toma máxima (amortiguador de ensayo) y valores medios cpm de los pozos que representan el ligado mínimo o toma mínima ((1 μM de desipramina (hNET) o 1 μM de paroxetina (hSERT)). La estimación del valor EC_{50} se completa en una escala logarítmica y la línea se ajusta entre los valores de ligado o toma máxima y mínima. Toda la representación de datos gráficos se genera por medio de normalizar cada punto de datos a un porcentaje medio con base en los valores de ligado o toma máximo o mínimo. Los valores EC_{50} reportados para los múltiples experimentos se calculan por medio de agrupar los datos brutos de cada experimento y analizar los datos agrupados como un experimento. Los resultados se reportan en la Tabla 1.

[0966] Cuando los rangos se utilizan aquí para las propiedades físicas tales como peso molecular o propiedades químicas tales como fórmulas químicas, todas las combinaciones y subcombinaciones de rango, modalidades específicas de rangos allí tienen el propósito de estar incluidas.

[0967] Las divulgaciones de cada patente, solicitud de patente y publicaciones citadas o descritas en este documento se incorporan aquí como referencia en su totalidad.

[0968] Aquellos versados en la técnica podrán aprecia que numerosos cambios y modificaciones pueden ser hechos a las modalidades preferidas de la invención y que tales cambios y modificaciones pueden hacerse sin salirse del espíritu de la invención. Por lo tanto, es el propósito de que las reivindicaciones adjuntas cubran todas aquellas variaciones equivalentes que caen dentro del espíritu y alcance verdadero de la invención.

Ejemplo	% de Inhibición @ µM (hNET)
1	4.6
2	66.5 (@ 10 µM)
3	17.6
4	24.5
5	58.1
6	13.1
7	25.6
8	53.4
9	79.2 (@ 10 µM)
10	70.5 (@ 10 µM)
11	94.5
12	70.6
13	34.3
14	24.4
15	8.5
16	96.8
17	71.0
18	11.3
19	31.6
20	85.0
21	97.5
22	83.8
23	89.7
24	57.2
25	37.5
26	54.0
27	75.4

Ejemplo	% de Inhibición @ 1 μM (hNET)
28	30.1
29	89.5
30	79.7
31	98.9
33	99.4
34	78.4
35	94.3
36	82.3
37	21.4
38	71.9
39	57.4
40	57.6
41	32.4
42	95.7
43	99
44	98.2
47	99.9
48	96.6
49	101.2
50	91.8
51	87.0
52	94.3
53	57.4
54	68.6
55	61.1
56	12.3
57	17.5
58	26.5
59	93.2
60	100

Ejemplo	% de Inhibición @ 1 μM (hNET)
61	99.8
62	99.7
63	91.9
64	99.9
65	100
66	86.6
67	90.9
68	99.6
69	87.5
70	77.7
71	44.9
72	24
73	21.8
74	67
75	88.4
76	75.2
77	77.3
78	70.9
79	66
80	83.5
81	58.0
82	53.9
83	99.5
84	40.9
85	97.4
86	52.7
87	99.7
90	73.1
91	90.8
92	85.8

Ejemplo	% de Inhibición @ µM (hNET)
93	96.3
94	94.9
95	97.6
96	98.2
97	99.6
98	99.1
99	98.1
100	94.2
101	98.6
102	95.3
103	86.1
104	99.4
105	92.6
106	85.8
107	96.6
108	98.7
109	94.7
110	86.4
111	42.7
112	100.3
113	99.7
114	100
115	23.9
116	97.3
117	95.3
118	67.9
119	96.3
120	68.6
121	21.2
122	97.4

Ejemplo	% de Inhibición @ µM (hNET)
123	65
124	91.5
125	94.3
126	92.9
127	95.7
128	45.6
129	71.8
130	76
131	63.1
132	93
133	96.4
134	68.5
135	99.5
136	97
137	99.1
138	97.9
139	94.9
140	96.7
143	96.8
146	97.1
147	91.7
148	97.8
149	100.4
150	98.3
151	94.3
152	96.2
153	97.4
154	96.1
155	98.9
157	99.6

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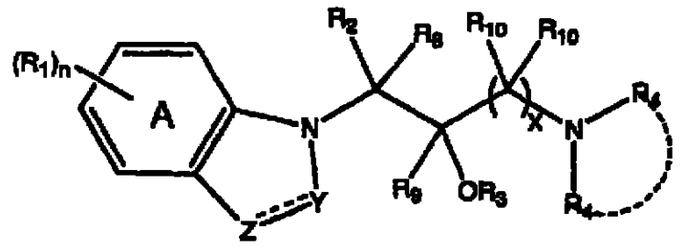
Ejemplo	% de Inhibición @ μM (hNET)
158	99.6
159	93.8
160	99.3
161	99.4
162	99.2
163	99.7
164	98.6
169	72
170	96.4
171	98.3
172	88
173	67.5
174	99.1
175	99.6
176	100
177	29.9
178	69.2
179	99.8
180	70.4
181	96.9
182	97.1
183	100.5
184	99.7
185	80.8
186	96.6
187	52
188	71.6
189	99.3
190	53.7
191	63.9

Ejemplo	% de Inhibición @ µM (hNET)
192	54.6
193	98.4
194	79
195	91
196	94.6
197	97
198	97.7
199	99.1
200	97.9
201	98.8
202	92.7
203	98.9
204	47.4
205	82.9
206	96.9
207	98.3
208	99.8
209	99.3
210	96.3
211	99.8
214	99.9

REIVINDICACIONES

Lo que se reivindica es:

1. Un compuesto de fórmula I:



I

O una sal farmacéuticamente aceptable de estos;

En donde:

La líneas punteadas entre Y y Z representa un enlace doble opcional;

La línea punteada entre los dos grupos R_4 representa un anillo heterocíclico opcional de 4 a 6 átomos de anillo y se puede formar entre los dos grupos R_4, junto con el nitrógeno al cual ellos están unidos;

Y es N, CR_6 O C=O;

Z es N, NR_7, CR_5, o $C(R_5)_2$;

R1 es, independientemente a cada ocurrencia, alquilo, alcoxi, halo, CF_3, OCF_3, arilalquiloxi sustituido con 0-3 R_{11}, ariloxi sustituido con 0-3 R_{11}, arilo sustituido con 0-3 R_{11}, heteroarilo sustituido con 0-3 R_{11}, hidroxi, alcanoiloxi,

nitro, nitrilo, alquenilo alquinilo, alquilsulfóxido, fenilsulfóxido sustituido con 0-3 R_{11}, alquilsulfona, fenilsulfona sustituido con 0-3 R_{11}, alquilsulfonamida, fenilsulfonamida sustituido con 0-3 R_{11}, heteroariloxi sustituido con 0-3 R_{11}, heteroarilmetoxi sustituido con 0-3 R_{11}, alquilamida, o arilamida sustituido con 0-3 R_{11}; o dos R_1 adyacentes también representan metilenodioxi;

R_2 es un arilo sustituido con 0-3 R_1 o heteroarilo sustituido con 0-3 R_1;

R_3 es H o alquilo C_1-C_4;

R_4 es, independientemente a cada ocurrencia, H, alquilo C_1-C_4, arilalquilo, heteroarilmetilo, cicloheptilmetilo, ciclohexilmetilo, ciclopentilmetilo, o ciclobutilmetilo; o

Ambos grupos R_4, junto con el nitrógeno al cual ellos están unidos, forman una anillo heterocíclico de 4 a 6 átomos por anillo, en donde un carbono puede ser opcionalmente reemplazado con N, O, S, o SO_2, y en donde cualquier átomo del anillo de carbono o el átomo de N adicional puede ser opcionalmente sustituido con alquilo C_1-C_4 o CF_3;

R_5 es, independientemente a cada ocurrencia, H, alquilo C_1-C_4, arilo sustituido con 0-3 R_1 o ciano; o cuando dos R_5 están presentes, ellos forman un anillo carbocíclico de 3-7 carbonos;

R_6 es H, alquilo C_1-C_4, o ciano;

R_7 es H, alquilo C_1-C_4, cicloalquilo C_3-C_6, o arilo sustituido con 0-3 R_1;

R_8 es H, o alquilo C_1-C_4;

R_9 es H, o alquilo C_1-C_4;

R_{10} es, independientemente de cada ocurrencia, H, o alquilo C_1-C_4; o R_{10} y R_4 juntos con el nitrógeno al cual R_4 esta unido forma un anillo que contiene nitrógeno que contiene 3-6 átomos de carbono;

n es un entero de 0 a 4;

x es un entero de 1 a 2; y

R_{11} es alquilo, alcoxi, halo, CF_3, OCF_3, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo, alquinilo, alquilsulfóxido, alquilsulfona, alquilsulfonamida, o alquilamida;

o dos R_{11} adyacentes también representan metilenodioxi;

En donde 1-3 átomos de carbono en el anillo A pueden opcionalmente ser reemplazados con N.

2. Un compuesto de acuerdo a la reivindicación 1, en donde:

Y es CR_5.

3. Un compuesto de acuerdo a la reivindicación 2, en donde:

Y es CH.

4. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 3, en donde:

X es CR_5.

5. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 4, en donde:

R_1 es halo. 6.

6. Un compuesto de acuerdo a la reivindicación 5, en donde: R_1 es fluor o cloro.

7. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 6, en donde:

R_2 es arilo sustituido con 0-3 R_1.

8. Un compuesto de acuerdo a la reivindicación 6, en donde: R_2 es fenilo.

9. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 8, en donde:

R_3 es H o alquilo C_1.

10. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 9, en donde:

R4 es H o alquilo C_1-C_4.

11. Un compuesto de acuerdo a la reivindicación 10, en donde:

R_4 es H, metilo, etilo, o isopropilo.

12. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 9, en donde:

ambos grupos R_4, juntos con el nitrógeno al cual ellos están sujetos, forman una piridina, piperidina, piperazina, piperazina sustituida con un grupo metilo, o anillo morfolino.

13. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 12, en donde:

R5 es, independientemente de cada ocurrencia, H, alquilo C_1, o ciano.

14. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 13, en donde:

R_6 es H, metilo, etilo, o ciano.

15. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 14, en donde:

R_7 es H, metilo, etilo, isopropilo, ciclopentilo, ciclohexilo, fenilo, tolilo, o xililo.

16. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 15, en donde:

R_8 es H, metilo, o etilo.

17. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 16, en donde:

R_9 es H, metilo, o etilo.

18. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 17, en donde:

R_{10} es H o metilo.

19. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 18, en donde:

n es 0 o 1.

20. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 19, en donde:

x es 1.

21. Un compuesto de acuerdo a la reivindicación 1, en donde:

Y es N, CR_6 O C=O;

Z es N, NR_7, CR_5, o $C(R_5)_2$;

R_1 es, independientemente a cada ocurrencia, alquilo, alcoxi, halo, CF_3, OCF_3, arilalquiloxi sustituido con 0-3 R_{11}, ariloxi sustituido con 0-3 R_{11}, arilo sustituido con 0-3 R_{11}, heteroarilo sustituido con 0-3 R_{11}, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo alquinilo, alquilsulfóxido, fenilsulfóxido sustituido con 0-3 R_{11}, alquilsulfona, fenilsulfona sustituido con 0-3 R_{11}, alquilsulfonamida, fenilsulfonamida sustituido con 0-3 R_{11}, heteroariloxi sustituido con 0-3 R_{11}, heteroarilmetiloxi sustituido con 0-3

R_{11}, alquilamida, o arilamida sustituido con 0-3 R_{11}; o dos R_1 adyacentes también representan metilenodioxi;

R_2 es un arilo sustituido con 0-3 R_1 o heteroarilo sustituido con 0-3 R_1;

R_3 es H

R_4 es, independientemente a cada ocurrencia, H, alquilo C_1-C_4;

R_5 es, independientemente a cada ocurrencia, H, alquilo C_1-C_4, arilo sustituido con 0-3 R_1 o ciano; o cuando dos R_5 están presentes, ellos forman un anillo carbocíclico de 3-7 carbonos;

R_6 es H, alquilo C_1-C_4, o ciano;

R_7 es H, alquilo C_1-C_4, cicloalquilo C_3-C_6, o arilo sustituido con 0-3 R_1;

R_8 es H;

R_9 es H;

R_{10} es H;

n es un entero de 0 a 4;

x es 1;

R_{11} es alquilo, alcoxi, halo, CF_3, OCF_3, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo, alquinilo, alquilsulfóxido, alquilsulfona, alquilsulfonamida, o alquilamida;

o dos R_{11} adyacentes también representan metilenodioxi;

En donde 1-3 átomos de carbono en el anillo A pueden opcionalmente ser reemplazados con N.

22. Un compuesto de acuerdo a la reivindicación 1, en donde:

Y es CR_6;

Z es CR_5;

R_1 es, independientemente a cada ocurrencia, alquilo, alcoxi, halo, CF_3, OCF_3, arilalquiloxi sustituido con 0-3 R_{11}, ariloxi sustituido con 0-3 R_{11}, arilo sustituido con 0-3 R_{11}, heteroarilo sustituido con 0-3 R_{11}, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo alquinilo, alquilsulfóxido, fenilsulfóxido sustituido con 0-3 R_{11}, alquilsulfona, fenilsulfona sustituido con 0-3 R_{11}, alquilsulfonamida, fenilsulfonamida sustituido con 0-3 R_{11}, heteroariloxi sustituido con 0-3 R_{11}, heteroarilmetoxi sustituido con 0-3 R_{11}, alquilamida, o arilamida sustituido con 0-3 R_{11}; o dos R_1 adyacentes también representan metilenodioxi;

R_2 es un arilo sustituido con 0-3 R_1 o heteroarilo sustituido con 0-3 R_1;

R_3 es H o alquilo C_1-C_4;

R_4 es, independientemente a cada ocurrencia, H, alquilo C_1-C_4, arilalquilo, heteroarilmetilo, cicloheptilmetilo, ciclohexilmetilo, ciclopentilmetilo, o ciclobutilmetilo;

R_5 es, independientemente a cada ocurrencia, H, alquilo C_1-C_4, arilo sustituido con 0-3 R_1 o ciano; o cuando dos R_5 están presentes, ellos forman un anillo carbocíclico de 3-7 carbonos;

R_6 es H, alquilo C_1-C_4, o ciano;

R_7 es H, alquilo C_1-C_4, cicloalquilo C_3-C_6, o arilo sustituido con 0-3 R_1;

R_8 es H, o alquilo C_1-C_4;

R_9 es H, o alquilo C_1-C_4;

R_{10} es, independientemente de cada ocurrencia, H, o alquilo C_1-C_4; o R_{10} y R_4 juntos con el nitrógeno al cual R_4 esta unido forma un anillo que contiene nitrógeno que contiene 3-6 átomos de carbono;

n es un entero de 0 a 4;

x es un entero de 1 a 2; y

R_{11} es alquilo, alcoxi, halo, CF_3, OCF_3, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo, alquinilo, alquilsulfóxido, alquilsulfona, alquilsulfonamida, o alquilamida;

o dos R_{11} adyacentes también representan metilenodioxi;

En donde 1-3 átomos de carbono en el anillo A pueden opcionalmente ser reemplazados con N.

23. Un compuesto de acuerdo con la reivindicación 1 en donde:

Y es CR_6;

Z es CR_5;

R_1 es, independientemente a cada ocurrencia, alquilo, alcoxi, halo, CF_3, OCF_3, arilalquiloxi sustituido con 0-3 R_{11}, ariloxi sustituido con 0-3 R_{11}, arilo sustituido con 0-3 R_{11}, heteroarilo sustituido con 0-3 R_{11}, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo alquinilo, alquilsulfóxido, fenilsulfóxido sustituido con 0-3 R_{11}, alquilsulfona, fenilsulfona sustituido con 0-3 R_{11}, alquilsulfonamida, fenilsulfonamida sustituido con 0-3 R_{11}, heteroariloxi sustituido con 0-3 R_{11}, heteroarilmetoxi sustituido con 0-3 R_{11}, alquilamida, o arilamida sustituido con 0-3 R_{11}; o dos R_1 adyacentes también representan metilenodioxi;

R_2 es un arilo sustituido con 0-3 R_1 o heteroarilo sustituido con 0-3 R_1;

R_3 es H o alquilo C_1-C_4;

R_4 es, independientemente a cada ocurrencia, H, alquilo C_1-C_4, arilalquilo, heteroarilmetilo, cicloheptilmetilo, ciclohexilmetilo, ciclopentilmetilo, o ciclobutilmetilo;

R_5 es, independientemente a cada ocurrencia, H, alquilo C_1-C_4, arilo sustituido con 0-3 R_1 o ciano; o cuando dos R_5 están presentes, ellos forman un anillo carbocíclico de 3-7 carbonos;

R_6 es H, alquilo C_1-C_4, o ciano;

R_7 es H, alquilo C_1-C_6, cicloalquilo C_3-C_6, o arilo sustituido con 0-3 R_1;

R_8 es H, o alquilo C_1-C_4;

R_9 es H, o alquilo C_1-C_4;

R_{10} es, independientemente de cada ocurrencia, H, o alquilo C_1-C_4; o R_{10} y R_4 juntos con el nitrógeno al cual R_4 esta unido forma un anillo que contiene nitrógeno que contiene 3-6 átomos de carbono;

n es un entero de 0 a 4;

x es un entero de 1 a 2; y

R_{11} es alquilo, alcoxi, halo, CF_3, OCF_3, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo, alquinilo, alquilsulfóxido, alquilsulfona, alquilsulfonamida, o alquilamida;

o dos R_{11} adyacentes también representan metilenodioxi;

En donde 1-3 átomos de carbono en el anillo A pueden opcionalmente ser reemplazados con N.

24. Un compuesto de acuerdo a la reivindicación 1, en donde:

Y es C=O;

Z es $C(R_5)_2$;

R1 es, independientemente a cada ocurrencia, alquilo, alcoxi, halo, CF_3, OCF_3, arilalquiloxi sustituido con 0-3 R_{11}, ariloxi sustituido con 0-3 R_{11}, arilo sustituido con 0-3 R_{11}, heteroarilo sustituido con 0-3 R_{11}, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo alquinilo, alquilsulfóxido, fenilsulfóxido sustituido con 0-3 R_{11}, alquilsulfona, fenilsulfona sustituido con 0-3 R_{11}, alquilsulfonamida, fenilsulfonamida sustituido con 0-3 R_{11}, heteroariloxi sustituido con 0-3 R_{11}, heteroarilmetiloxi sustituido con 0-3 R_{11}, alquilamida, o arilamida sustituido con 0-3 R_{11}; o dos R_1 adyacentes también representan metilenodioxi;

R_2 es un arilo sustituido con 0-3 R_1 o heteroarilo sustituido con 0-3 R_1;

R_3 es H o alquilo C_1-C_4;

R_4 es, independientemente a cada ocurrencia, H, alquilo C_1-C_4, arilalquilo, heteroarilmetilo, cicloheptilmetilo, ciclohexilmetilo, ciclopentilmetilo, o ciclobutilmetilo;

R_5 es, independientemente a cada ocurrencia, H, alquilo C_1-C_4, arilo sustituido con 0-3 R_1 o ciano; o cuando dos R_5 están

presentes, ellos forman un anillo carbocíclico de 3-7 carbonos;

R_6 es H, alquilo C_1-C_4, o ciano;

R_7 es H, alquilo C_1-C_6, cicloalquilo C_3-C_6, o arilo sustituido con 0-3 R_1;

R_8 es H, o alquilo C_1-C_4;

R_9 es H, o alquilo C_1-C_4;

R_{10} es, independientemente de cada ocurrencia, H, o alquilo C_1-C_4; o R_{10} y R_4 juntos con el nitrógeno al cual R_4 esta unido forma un anillo que contiene nitrógeno que contiene 3-6 átomos de carbono;

n es un entero de 0 a 4;

x es un entero de 1 a 2; y

R_{11} es alquilo, alcoxi, halo, CF_3, OCF_3, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo, alquinilo, alquilsulfóxido, alquilsulfona, alquilsulfonamida, o alquilamida;

o dos R_{11} adyacentes también representan metilenodioxi;

En donde 1-3 átomos de carbono en el anillo A pueden opcionalmente ser reemplazados con N.

25. Un compuesto de acuerdo a la reivindicación 1, en donde:

Y es C=O;

Z es $C(R_5)_2$;

R1 es, independientemente a cada ocurrencia, alquilo, alcoxi, halo, CF_3, OCF_3, arilalquiloxi sustituido con 0-3 R_{11}, ariloxi sustituido con 0-3 R_{11}, arilo sustituido con 0-3 R_{11}, heteroarilo sustituido con 0-3 R_{11}, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo alquinilo, alquilsulfóxido, fenilsulfóxido sustituido con 0-3 R_{11}, alquilsulfona, fenilsulfona sustituido con 0-3 R_{11}, alquilsulfonamida, fenilsulfonamida sustituido con 0-3 R_{11}, heteroariloxi sustituido con 0-3 R_{11}, heteroarilmetiloxi sustituido con 0-3 R_{11}, alquilamida, o arilamida sustituido con 0-3 R_{11}; o dos R_1 adyacentes también representan metilenodioxi;

R_2 es un arilo sustituido con 0-3 R_1 o heteroarilo sustituido con 0-3 R_1;

R_3 es H o alquilo C_1-C_4;

R_4 es, independientemente a cada ocurrencia, H, alquilo C_1-C_4, arilalquilo, heteroarilmetilo, cicloheptilmetilo, ciclohexilmetilo, ciclopentilmetilo, o ciclobutilmetilo;

R_5 es, independientemente a cada ocurrencia, H, alquilo C_1-C_4, arilo sustituido con 0-3 R_1 o ciano; o cuando dos R_5 están presentes, ellos forman un anillo carbocíclico de 3-7 carbonos;

R_6 es H, alquilo C_1-C_4, o ciano;

R_7 es H, alquilo C_1-C_6, cicloalquilo C_3-C_6, o arilo sustituido con 0-3 R_1;

R_8 es H, o alquilo C_1-C_4;

R_9 es H, o alquilo C_1-C_4;

R_{10} es, independientemente de cada ocurrencia, H, o alquilo C_1-C_4; o R_{10} y R_4 juntos con el nitrógeno al cual R_4 esta unido forma un anillo que contiene nitrógeno que contiene 3-6 átomos de carbono;

n es un entero de 0 a 4;

x es un entero de 1 a 2; y

R_{11} es alquilo, alcoxi, halo, CF_3, OCF_3, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo, alquinilo, alquilsulfóxido, alquilsulfona, alquilsulfonamida, o alquilamida;

o dos R_{11} adyacentes también representan metilenodioxi;

En donde 1-3 átomos de carbono en el anillo A pueden opcionalmente ser reemplazados con N.

26. Un compuesto de acuerdo a la reivindicación 1, en donde dicho compuesto es:

1-(1H-indol-1-il)-3-(4-metilpiperazin-1-il)-1-fenilpropan-2-ol;

1-(5-fluoro-1H-indol-1-il)-3-(4-metilpiperazin-1-il)-1-fenilpropan-2-ol;

1-(1H-indol-1-il)-3-morfolin-4-il-1-fenilpropan-2-ol;

3-(dimetilamino)-1-(1H-indol-1-il)-1-fenilpropan-2-ol;

3-(etilamino)-1-(1H-indol-1-il)-1-fenilpropan-2-ol;

1-(1H-indol-1-il)-3-(isopropilamino)-1-fenilpropan-2-ol;

3-(bencilamino)-1-(1H-indol-1-il)-1-fenilpropan-2-ol;

3-[(ciclohexilmetil)amino]-1-(1H-indol-1-il)-1-fenilpropan-2-ol;

3-[(ciclohexilmetil)amino]-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

3-(isopropilamino)-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

3-(etilamino)-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

1-(1H-indol-1-il)-1-fenil-3-piperazin-1-ilpropan-2-ol di;

1-(1H-indol-1-il)-1-fenil-3-[(piridin-4-ilmetil) amino]propan-2-ol;

1-(5-cloro-1H-indol-1-il)-1-fenil-3-piperidin-1-ilpropan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

3-amino-1-(1H-indol-1-il)-1-fenilpropan-2-ol;

3-(etilamino)-1-(5-fluoro-1H-indol-1-il)-1-fenilpropan-2-ol;

3-amino-1-(5-fluoro-1H-indol-1-il)-1-fenilpropan-2-ol;

1-(5-fluoro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

3-(metilamino)-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

3-amino-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

3-[etil(metil)amino]-1-(1H-indol-1-il)-1-fenilpropan-2-ol;

1-(5-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(5-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-1-ol;

1-[2-hidroxi-3-(metilamino)-1-fenilpropil]-1H-indol-3-carbonitrilo;

1-(1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

3-(metilamino)-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

1-(3-clorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

1-(4-clorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-[3-(trifluorometoxi)fenil]propan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-[2-(trifluorometoxi)fenil]propan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-[2-(trifluorometoxi)fenil]propan-2-ol;

1-(2-clorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-[4-(trifluorometoxi)fenil]propan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-[4-(trifluorometoxi)fenil]propan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-[4-(trifluorometoxi)fenil]propan-2-ol;

4-amino-1-(3-clorofenil)-1-(1H-indol-1-il)butan-2-ol

1-(3-bromofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

3-[2-hidroxi-1-(1H-indol-1-il)-3-(metilamino)propil]benzonitrilo

1-(3-fluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-[3-(3-metilfenil)-1H-indol-1-il]propan-2-ol;

1-(4-fluorofenil)-3-(metilamino)-1-(3-metil-1H-indol-1-il)propan-2-ol;

1-(2-fluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

1-(4-fluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-(3-metilfenil)propan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-(2-metilfenil)propan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-(2-metilfenil)propan-2-ol;

3-(etilamino)-1-(3-fluorofenil)-1-(1H-indol-1-il)propan-2-ol;

1-(3-fluorofenil)-1-(1H-indol-1-il)-3-morfolin-4-ilpropan-2-ol;

1-(3-fluorofenil)-1-(1H-indol-1-il)-3-(propilamino)propan-2-ol;

1-(3-fluorofenil)-1-(1H-indol-1-il)-3-(4-metilpiperazin-1-il)propan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-(4-metilfenil)propan-2-ol;

1-(2,3-dihidro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-[3-(2-metilfenil)-1H-indol-1-il]propan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-(2-metil-2,3-dihidro-1H-indol-1-il)propan-2-ol;

1-(7-fluoro-3,3-dimetil-2,3-dihidro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(7-fluoro-3,3-dimetil-2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

3-(metilamino)-1-(7-metil-2,3-dihidro-1H-indol-1-il)-1-fenilpropan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-(7-metil-2,3-dihidro-1H-indol-1-il)propan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-(5-metil-2,3-dihidro-1H-indol-1-il)propan-2-ol;

1-(1H-indol-1-il)-1-(3-metoxifenil)-3-(metilamino)propan-2-ol;

1-(1H-indol-1-il)-1-(4-metoxifenil)-3-(metilamino)propan-2-ol;

3-(metilamino)-1-(2-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

1-(1H-benzimidazol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

3-(metilamino)-1-(2-metil-1H-benzimidazol-1-il)-1-fenilpropan-2-ol;

1-(4-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(5-fluoro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(5-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(7-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(4-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(6-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(5-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(3-fluorofenil)-1-(6-metoxi-1H-indol-1-il)-3-(metilamino)propan-2-ol;

3-(metilamino)-1-fenil-1-(1H-pirrolo[2,3-b]piridin-1-il)propan-2-ol;

1-(5-cloro-2,3-dihidro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

3-(metilamino)-1-fenil-1-(1H-pirrolo[2,3-c]piridin-1-il)propan-2-ol;

1-(5-fluoro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

3-(metilamino)-1-(3-fluorofenil)-1-(1H-pirrolo[2,3-c]piridin-1-il)propan-2-ol;

1-(5-cloro-2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

3-(metilamino)-1-(6-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

3-(metilamino)-1-(7-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-(5-metil-1H-indol-1-il)propan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-(7-metil-1H-indol-1-il)propan-2-ol;

3-(metilamino)-1-(4-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

3-(metilamino)-1-(5-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-(4-metil-1H-indol-1-il)propan-2-ol;

1-(3-etil-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-(3-fenil-1H-indol-1-il)propan-2-ol;

7-fluoro-1-[2hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

1-[2hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

7-fluoro-1-[1-(3-fluorofenil)-2-hidroxi-3-(metilamino)propil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

1-(1H-indol-1-il)-3-(metilamino)-1-(2-tienil)propan-2-ol;

1(1H-indol-1-il)-3-(metilamino)-1-(2-tienil)propan-2-ol;

1'-[2-hidroxi-3-(metilamino)-1-fenilpropil]espiro[ciclohexano-1,3'-indol]-2'(1'H)-ona;

2-(3-fluorofenil)-2-(1H-indol-1-il)-1-[(2S)-pirrolidin-2-il]etanol;

2-(3-fluorofenil)-2-(1H-indol-1-il)-1-[pirrolidin-2-il]etanol;

1'-[2hidroxi-3-(metilamino)-1-fenilpropil]espiro[ciclobutano-1,3'-indol]-2'(1'H)-ona;

1'-[2hidroxi-3-(metilamino)-1-fenilpropil]espiro[ciclopentano-1,3'-indol]-2'(1H)-ona;

1'-[2hidroxi-3-(metilamino)-1-fenilpropil]espiro[ciclopropano-1,3'-indol]-2'(1H)-ona;

5-fluoro-1-[2hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

3-(ciclopropilamino)-1-(3-fluorofenil)-1-(1H-indol-1-il)propan-2-ol;

7'-fluoro-1'-[2hidroxi-3-(metilamino)-1-fenilpropil]espirofciclohexano-1,3'-indol]-2'(1'H)-ona;

5'-bromo-1'-[2hidroxi-3-(metilamino)-1-fenilpropil]espiro[ciclohexano-1,3'-indol]-2'(1'H)-ona;

1-(3-fluorofenil)-1-[3-(2-fluorofenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol;

1-[3-(3,4-diclorofenil)-1H-indol-1-il]-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(3-fluorofenil)-1-[3-(3-fluorofenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol;

1-(5-fluoro-3-metil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

3-amino-1-(5-fluoro-3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

1-(5-cloro-3-metil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

3amino-1-(5-cloro-3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

[3-(5-cloro-3-metil-1H-indol-1-il)-2-metoxi-3-fenilpropil]metilamina;

1-(7-cloro-3-metil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

[3-(5-fluoro-3-metil-1H-indol-1-il)-2-metoxi-3-fenilpropil]metilamina;

1-(4-bromo-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(4-bromo-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(5-bromo-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(5-bromo-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-[2-hidroxi-3-(metilamino)-1-fenilpropil]-1H-indol-4-carbonitrilo;

1-(6-bromo-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-[2-hidroxi-3-(metilamino)-1-fenilpropil]-1H-indol-5-carbonitrilo;

1-[1-(3-fluorofenil)-2-hidroxi-3-(metilamino)propil]-1H-indol-4-carbonitrilo;

1-(6-bromo-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(6-fluoro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

3-amino-1-(3-fluorofenil)-1-(1H-indol-1-il)propan-2-ol;

1-(7-bromo-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(1H-indol-1-il)-3-(metilamino)-1-[3-(trifluorometil)fenil]propan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-espiro[ciclohexano-1,3'-indol]-1'(2'H)-ilpropan-2-ol;

1-(2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-[3-(trifluorometil)fenil]propan-2-ol;

1-(3-fluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

1-(3,4-difluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-(3-metil-1H-indol-1-il)propan-2-ol;

1-(4-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(6-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(7-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(7-cloro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(4-cloro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(6-cloro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(5-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(5-cloro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(3-isopropil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(3-fluorofenil)-1-(3-isopropil-1H-indol-1-il)-3-(metilamino)propan-2-ol;

1-(3,5-difluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

1-(3,5-difluorofenil)-1-(2,3-dihidro-1H-indol-1-il)-3-(metilamino)propan-2-ol;

4-amino-1-(3-fluorofenil)-1-(1H-indol-1-il)butan-2-ol;

1-(3,3-dimetil-2,3-dihidro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(3,5-difluorofenil)-1-(3,3-dimetil-2,3-dihidro-1H-indol-1-il)-3-(metilamino)propan-2-ol;

1-(3,3-dimetil-2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-(3-metil-2,3-dihidro-1H-indol-1-il)propan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-espiro[ciclopentano-1,3'-indol]-1'(2'H)-ilpropan-2-ol;

1-(3-fluorofenil)-1-[3-(4-metoxifenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-[3-(4-metilfenil)-1H-indol-1-il]propan-2-ol;

1-[3-(4-terc-butilfenil)-1H-indol-1-il]-1-(3-fluorofenil)-3-(metilamino)propan-2-o!;

1-(3-fluorofenil)-1-[3-(3-metoxifenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-{3-[4-(trifluorometil)fenil]-1H-indol-1-il}propan-2-ol;

1-(3,5-difluorofenil)-1-(6-fluoro-2,3-dihidro-1H-indol-1-il)-3-(metilamino)propan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-{3-[2-(trifluorometil)fenil]-1H-indol-1-il}propan-2-ol;

1-(3-fluorofenil)-1-[3-(2-metoxifenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-{3-[3-(trifluorometil)fenil]-1H-indol-1-il}propan-2-ol;

3-amino-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

1-(7-fluoro-3-metil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

3-amino-1-(7-fluoro-3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

1-(7-fluoro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(4-fluoro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-(7-fluoro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(4-fluoro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(3-fluorofenil)-3-(metilamino)-1-[5-(trifluorometil)-1H-indol-1-il]propan-2-ol;

1-(6-fluoro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

3-(metilamino)-1-fenil-1-[6-(trifluorometil)-1H-indol-1-il]propan-2-ol;

3-(metilamino)-1-fenil-1-[5-(trifluorometil)-1H-indol-1-il]propan-2-ol;

1-(3-terc-butil-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-(1H-indol-1-il)-2-metil-3-(metilamino)-1-fenilpropan-2-ol;

3-(1H-indol-1-il)-1-(metilamino)-3-fenilbutan-2-ol;

1-terc-butil-3-[2hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona;

1-[2-hidroxi-3-(metilamino)-1-fenilpropil]-3-propil-1,3-dihidro-2H-benzimidazol-2-ona;

5-bromo-1-[2hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

6-fluoro-1-[2hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

4-fluoro-1-[2hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

1-ciclobutil-3-[2hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona;

5-fluoro-3-[2hidroxi-3-(metilamino)-1-fenilpropil]-1-propil-1,3-dihidro-2H-benzimidazol-2-ona;

1-etil-3-[1-(3-fluorofenil)-2-hidroxi-3-(metilamino)propil]-1,3-dihidro-2H-benzimidazol-2-ona;

1-etil-3-[2hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona;

4-fluoro-3-[2hidroxi-3-(metilamino)-1-fenilpropil]-1-isopropil-1,3-dihidro-2H-benzimidazol-2-ona;

1-ciclopentil-3-[2hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona;

1-[2hidroxi-3-(metilamino)-1-fenilpropil]-3-isopropil-1,3-dihidro-2H-benzimidazol-2-ona;

3-[3(etilamino)-2-hidroxi-1-fenilpropil]-5-fluoro-1-isopropil-1,3-dihidro-2H-benzimidazol-2-ona;

1-[2hidroxi-3-(metilamino)-1-fenilpropil]-3-metil-1,3-dihidro-2H-benzimidazol-2-ona;

1-etil-5-fluoro-3-[2-hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona;

1-etil-4-fluoro-3-[2-hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona;

4-fluoro-3-[1-(3-fluorofenil)-2-hidroxi-3-(metilamino)propil]-1-isopropil-1,3-dihidro-2H-benzimidazol-2-ona;

1-etil-4-fluoro-3-[2hidroxi-3-(metilamino)-1-(3-fluorofenil)-propil]-1,3-dihidro-2H-benzimidazol-2-ona;

1-[1-(3-fluorofenil)-2-hidroxi-3-(metilamino)propil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

1-[3-(2,3-difluorofenil)-1H-indol-1-il]-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-[3-(2-clorofenil)-1H-indol-1-il]-1-(3-fluorofenil)-3-(metilamino)propan-2-ol; y

sales farmacéuticamente aceptable de estos, particularmente clorhidratos y sales de clorhidratos de estos.

27. Un compuesto de acuerdo a la reivindicación 1, dicho compuesto es:

(1RS,2SR)-1-(1H-indol-1-il)-3-(4-metilpiperazin-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-1-(5-fluoro-1H-indol-1-il)-3-(4-metilpiperazin-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-1-(1H-indol-1-il)-3-morfolin-4-il-1-fenilpropan-2-ol;

(1RS,2SR)-3-(dimetilamino)-1-(1H-indol-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-3-(etilamino)-1-(1H-indol-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-1-(1H-indol-1-il)-3-(isopropilamino)-1-fenilpropan-2-ol;

(1RS,2SR)-3-(bencilamino)-1-(1H-indol-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-3-[(ciclohexilmetil)amino]-1-(1H-indol-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-3-[(ciclohexilmetil)amino]-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-3-(isopropilamino)-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-1-(1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1RS,2SR)-3-(etilamino)-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-1-(1H-indol-1-il)-1-fenil-3-piperazin-1-ilpropan-2-ol;

(1RS,2SR)-1-(1H-indol-1-il)-1-fenil-3-[(piridin-4-ilmetil)amino]propan-2-ol;

(1RS,2SR)-1-(5-cloro-1H-indol-1-il)-1-fenil-3-piperidin-1-ilpropan-2-ol;

(1RS,2RS)-1-(1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1RS,2SR)-3-amino-1-(1H-indol-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-3-(etilamino)-1-(5-fluoro-1H-indol-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-3-amino-1-(5-fluoro-1H-indol-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-1-(5-fluoro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1RS,2SR)-3-(metilamino)-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

(1R,2S)-1-(1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1RS,2SR)-3-amino-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-3-[etil(metil)amino]-1-(1H-indol-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-1-(5-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1RS,2RS)-1-(5-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-1-ol;

1-[(1RS,2SR)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1H-indol-3-carbonitrilo;

(1R,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2S)-1-(1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-3-(metilamino)-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

(1S,2R)-1-(3-clorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(4-clorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-[3-(trifluorometoxi)fenil]propan-2-ol;

(1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-[2-(trifluorometoxi)fenil]propan-2-ol;

(1R,2S)-1-(1H-indol-1-il)-3-(metilamino)-1-[2-(trifluorometoxi)fenil]propan-2-ol;

(1S,2R)-1-(2-clorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

(1SR,2RS)-1-(1H-indol-1-il)-3-(metilamino)-1-[4-(trifluorometoxi)fenil]propan-2-ol;

(1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-[4-(trifluorometoxi)fenil]propan-2-ol;

(1R,2S)-1-(1H-indol-1-il)-3-(metilamino)-1-[4-(trifluorometoxi)fenil]propan-2-ol;

(1S,2R)-4-amino-1-(3-clorofenil)-1-(1H-indol-1-il)butan-2-ol

(1S,2R)-1-(3-bromofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

3-[(1S,2R)-2-hidroxi-1-(1H-indol-1-il)-3-(metilamino)propil]benzonitrilo

(1S,2R)-1-(3-fluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-[3-(3-metilfenil)-1H-indol-1-il]propan-2-ol;

(1S,2R)-1-(4-fluorofenil)-3-(metilamino)-1-(3-metil-1H-indol-1-il)propan-2-ol;

(1S,2R)-1-(2-fluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(4-fluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-(3-metilfenil)propan-2-ol;

(1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-(2-metilfenil)propan-2-ol;

(1R,2S)-1-(1H-indol-1-il)-3-(metilamino)-1-(2-metilfenil)propan-2-ol;

(1S,2R)-3-(etilamino)-1-(3-fluorofenil)-1-(1H-indol-1-il)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-1-(1H-indol-1-il)-3-morfolin-4-ilpropan-2-ol;

(1S,2R)-1-(3-fluorofenil)-1-(1H-indol-1-il)-3-(propilamino)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-1-(1H-indol-1-il)-3-(4-metilpiperazin-1-il)propan-2-ol;

(1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-(4-metilfenil)propan-2-ol;

(1S,2R)-1-(2,3-dihidro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-[3-(2-metilfenil)-1H-indol-1-il]propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(2-metil-2,3-dihidro-1H-indol-1-il)propan-2-ol;

(1S,2R)-1-(7-fluoro-3,3-dimetil-2,3-dihidro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(7-fluoro-3,3-dimetil-2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-3-(metilamino)-1-(7-metil-2,3-dihidro-1H-indol-1-il)-1-fenilpropan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(7-metil-2,3-dihidro-1H-indol-1-il)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(5-metil-2,3-dihidro-1H-indol-1-il)propan-2-ol;

(1S,2R)-1-(1H-indol-1-il)-1-(3-metoxifenil)-3-(metilamino)propan-2-ol;

(1SR,2RS)-1-(1H-indol-1-il)-1-(4-metoxifenil)-3-(metilamino)propan-2-ol;

(1RS,2SR)-3-(metilamino)-1-(2-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-1-(1H-benzimidazol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1RS,2SR)-3-(metilamino)-1-(2-metil-1H-benzimidazol-1-il)-1-fenilpropan-2-ol;

(1RS,2SR)-1-(4-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(5-fluoro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(5-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(7-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(4-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(6-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1RS,2SR)-1-(5-metoxi-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(3-fluorofenil)-1-(6-metoxi-1H-indol-1-il)-3-(metilamino)propan-2-ol;

(1S,2R)-3-(metilamino)-1-fenil-1-(1H-pirrolo[2,3-b]piridin-1-il)propan-2-ol;

(1S,2R)-1-(5-cloro-2,3-dihidro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-3-(metilamino)-1-fenil-1-(1H-pirrolo[2,3-c]piridin-1-il)propan-2-ol;

(1S,2R)-1-(5-fluoro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-3-(metilamino)-1-(3-fluorofenil)-1-(1H-pirrolo[2,3-c]piridin-1-il)propan-2-ol;

(1S,2R)-1-(5-cloro-2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-3-(metilamino)-1-(6-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

(1S,2R)-3-(metilamino)-1-(7-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(5-metil-1H-indol-1-il)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(7-metil-1H-indol-1-il)propan-2-ol;

(1S,2R)-3-(metilamino)-1-(4-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

(1S,2R)-3-(metilamino)-1-(5-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(4-metil-1H-indol-1-il)propan-2-ol;

(1S,2R)-1-(3-etil-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(3-fenil-1H-indol-1-il)propan-2-ol;

7-fluoro-1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

7-fluoro-1-[(1S,2R)-1-(3-fluorofenil)-2-hidroxi-3-(metilamino)propil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

(1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-(2-tienil)propan-2-ol;

(1R,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-(2-tienil)propan-2-ol;

1'-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]espiro[ciclohexano-1,3'-indol]-2'(1H)-ona;

(1S,2R)-2-(3-fluorofenil)-2-(1H-indol-1-il)-1-[(2S)-pirrolidin-2-il]etanol;

(1R,2S)-2-(3-fluorofenil)-2-(1H-indol-1-il)-1-[(2S)-pirrolidin-2-il]etanol;

1'-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]espiro[ciclobutano-1,3'-indol]-2'(1'H)-ona;

1'-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]espiro[ciclopentano-1,3'-indol]-2'(1H)-ona;

1'-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]espiro[ciclopropano-1,3'-indol]-2'(1H)-ona;

5-fluoro-1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

(1S,2R)-3-(ciclopropilamino)-1-(3-fluorofenil)-1-(1H-indol-1-il)propan-2-ol;

7'-fluoro-1'-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]espiro[ciclohexano-1,3'-indol]-2'(1H)-ona;

5'-bromo-1'-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]espiro[ciclohexano-1,3'-indol]-2'(1H)-ona;

(1S,2R)-1-(3-fluorofenil)-1-[3-(2-fluorofenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol;

(1S,2R)-1-[3-(3,4-diclorofenil)-1H-indol-1-il]-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-1-[3-(3-fluorofenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol;

(1S,2R)-1-(5-fluoro-3-metil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol ;

(1S*,2R*)-3-amino-1-(5-fluoro-3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

(1S,2R)-1-(5-cloro-3-metil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-3-amino-1-(5-cloro-3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

[(2R,3S)-3-(5-cloro-3-metil-1H-indol-1-il)-2-metoxi-3-fenilpropil]metilamina;

(1S,2R)-1-(7-cloro-3-metil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

[(2R,3S)-3-(5-fluoro-3-metil-1H-indol-1-il)-2-metoxi-3-fenilpropil]metilamina;

(1S,2R)-1-(4-bromo-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(4-bromo-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(5-bromo-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(5-bromo-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1H-indol-4-carbonitrilo;

(1S,2R)-1-(6-bromo-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1H-indol-5-carbonitrilo;

1-[(1S,2R)-1-(3-fluorofenil)-2-hidroxi-3-(metilamino)propil]-1H-indol-4-carbonitrilo;

(1S,2R)-1-(6-bromo-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(6-fluoro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-3-amino-1-(3-fluorofenil)-1-(1H-indol-1-il)propan-2-ol;

(1S,2R)-1-(7-bromo-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(1H-indol-1-il)-3-(metilamino)-1-[3-(trifluorometil)fenil]propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-espiro[ciclohexano-1,3'-indol]-1'(2H)-ilpropan-2-ol;

(1S,2R)-1-(2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-[3-(trifluorometil)fenil]propan-2-ol;

(1S,2S)-1-(3-fluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3,4-difluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(3-metil-1H-indol-1-il)propan-2-ol;

(1S,2R)-1-(4-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(6-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(7-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(7-cloro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(4-cloro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(6-cloro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(5-cloro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(5-cloro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3-isopropil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(3-fluorofenil)-1-(3-isopropil-1H-indol-1-il)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3,5-difluorofenil)-1-(1H-indol-1-il)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3,5-difluorofenil)-1-(2,3-dihidro-1H-indol-1-il)-3-(metilamino)propan-2-ol;

(1S,2R)-4-amino-1-(3-fluorofenil)-1-(1H-indol-1-il)butan-2-ol;

(1S,2R)-1-(3,3-dimetil-2,3-dihidro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3,5-difluorofenil)-1-(3,3-dimetil-2,3-dihidro-1H-indol-1-il)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3,3-dimetil-2,3-dihidro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-(3-metil-2,3-dihidro-1H-indol-1-il)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-espiro[ciclopentano-1,3'-indol]-1'(2H)-ilpropan-2-ol;

(1S,2R)-1-(3-fluorofenil)-1-[3-(4-metoxifenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-[3-(4-metilfenil)-1H-indol-1-il]propan-2-ol;

(1S,2R)-1-[3-(4-terc-butilfenil)-1H-indol-1-il]-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-1-[3-(3-metoxifenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-{3-[4-(trifluorometil)fenil]-1H-indol-1-il}propan-2-ol;

(1S,2R)-1-(3,5-difluorofenil)-1-(6-fluoro-2,3-dihidro-1H-indol-1-il)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-{3-[2-(trifluorometil)fenil]-1H-indol-1-il}propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-1-[3-(2-metoxifenil)-1H-indol-1-il]-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-{3-[3-(trifluorometil)fenil]-1H-indol-1-il}propan-2-ol;

(1S,2R)-3-amino-1-(3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

(1S,2R)-1-(7-fluoro-3-metil-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-3-amino-1-(7-fluoro-3-metil-1H-indol-1-il)-1-fenilpropan-2-ol;

(1S,2R)-1-(7-fluoro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(4-fluoro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-1-(7-fluoro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(4-fluoro-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(3-fluorofenil)-3-(metilamino)-1-[5-(trifluorometil)-1H-indol-1-il]propan-2-ol;

(1S,2R)-1-(6-fluoro-1H-indol-1-il)-3-(metilamino)-1-fenilpropan-2-ol;

(1S,2R)-3-(metilamino)-1-fenil-1-[6-(trifluorometil)-1H-indol-1-il]propan-2-ol;

(1S,2R)-3-(metilamino)-1-fenil-1-[5-(trifluorometil)-1H-indol-1-il]propan-2-ol;

(1S,2R)-1-(3-terc-butil-1H-indol-1-il)-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-(1H-indol-1-il)-2-metil-3-(metilamino)-1-fenilpropan-2-ol;

(2R,3S)-3-(1H-indol-1-il)-1-(metilamino)-3-fenilbutan-2-ol;

1-terc-butil-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona;

1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3-propil-1,3-dihidro-2H-benzimidazol-2-ona;

5-bromo-1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

6-fluoro-1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

4-fluoro-1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

1-ciclobutil-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona;

5-fluoro-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1-propil-1,3-dihidro-2H-benzimidazol-2-ona;

1-etil-3-[(1S,2R)-1-(3-fluorofenil)-2-hidroxi-3-(metilamino)propil]-1,3-dihidro-2H-benzimidazol-2-ona;

1-etil-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona;

4-fluoro-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1-isopropil-1,3-dihidro-2H-benzimidazol-2-ona;

1-ciclopentil-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona;

1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3-isopropil-1,3-dihidro-2H-benzimidazol-2-ona;

3-[(1S,2R)-3-(etilamino)-2-hidroxi-1-fenilpropil]-5-fluoro-1-isopropil-1,3-dihidro-2H-benzimidazol-2-ona;

1-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-3-metil-1,3-dihidro-2H-benzimidazol-2-ona;

1-etil-5-fluoro-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona;

1-etil-4-fluoro-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-fenilpropil]-1,3-dihidro-2H-benzimidazol-2-ona;

4-fluoro-3-[(1S,2R)-1-(3-fluorofenil)-2-hidroxi-3-(metilamino)propil]-1-isopropil-1,3-dihidro-2H-benzimidazol-2-ona;

1-etil-4-fluoro-3-[(1S,2R)-2-hidroxi-3-(metilamino)-1-(3-fluorofenil)-propil]-1,3-dihidro-2H-benzimidazol-2-ona;

1-[(1S,2R)-1-(3-fluorofenil)-2-hidroxi-3-(metilamino)propil]-3,3-dimetil-1,3-dihidro-2H-indol-2-ona;

(1S,2R)-1-[3-(2,3-difluorofenil)-1H-indol-1-il]-1-(3-fluorofenil)-3-(metilamino)propan-2-ol;

(1S,2R)-1-[3-(2-clorofenil)-1H-indol-1-il]-1-(3-fluorofenil)-3-(metilamino)propan-2-ol; y

sales farmacéuticamente aceptable de estos, particularmente clorhidratos y sales de clorhidratos de estos

28. Una composición, que comprende:

a. por lo menos un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 27; y

b. por lo menos un portador farmacéuticamente aceptable.

29. Un método para tratar o prevenir una condición mejorada por la retoma de monoamina en un sujeto que lo necesita, comprende la etapa de:
administrar a dicho sujeto una cantidad efectiva de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 27 una sal farmacéuticamente aceptable de estas o una composición de acuerdo con la reivindicación 28.

30. Un método de acuerdo a la reivindicación 29, en donde dicha condición mejorada por retoma de monoamina se selecciona del grupo que consiste de síntomas vasomotores, disfunción sexual, los desórdenes gastrointestinales y genitourinarios, el síndrome de fatiga crónica, el síndrome de fibroamialgia, desórdenes del sistema nervioso, y combinaciones de estos.

31. Un método de acuerdo a la reivindicación 30, en donde dicha condición mejorada por la retoma de monoamina se selecciona del grupo que consiste de: desorden depresivo mayor, síntomas vasomotores, estrés, incontinencia urinaria

apremiante, fibromialgia, dolor, neuropatía diabética, y combinaciones de estos.

32. Un método para tratar o prevenir por lo menos un síntoma vasomotor en un sujeto que lo necesita, que comprende la etapa de:

administrar a dicho sujeto una cantidad efectiva de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 27 o una sal farmacéuticamente aceptable de estas o una composición de acuerdo con la reivindicación 28.

33. Un método de acuerdo a la reivindicación 32, en donde dicho síntoma vasomotor es sudor caliente.

34. Un método de acuerdo a la reivindicación 33, en donde dicho sujeto es humano.

35. Un método de acuerdo a la reivindicación 34, en donde dicho humano es una hembra.

36. Un método de acuerdo a la reivindicación 35, en donde dicha hembra es preparación-menopausal.

37. Un método de acuerdo a la reivindicación 35, en donde dicha hembra es peri-menopausal.

38. Un método de acuerdo a la reivindicación 35, en donde dicha hembra es post-monopausal.

39. Un método de acuerdo a la reivindicación 34, en donde dicho humano es un macho.

40. Un método de acuerdo a la reivindicación 39, en donde es naturalmente, químicamente o quirúrgicamente andropausal.

41. Un método para tratar o impedir por lo menos un desorden de depresión en un sujeto que lo necesita, que comprende la etapa de:

administrar a dicho sujeto una cantidad efectiva de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 27 una sal farmacéuticamente aceptable de estas o una composición de acuerdo con la reivindicación 28.

42. Un método de acuerdo a la reivindicación 41, en donde dicho desorden de depresión es un desorden depresivo mayor, ansiedad, disturbio del sueño o fobia social.

43. Un método de acuerdo a la reivindicación 42, en donde dicho sujeto es un humano.

44. Un método para tratar o impedir por lo menos una disfunción sexual en un sujeto que lo requiere, que comprende la etapa de:

administrar a dicho sujeto una cantidad efectiva de un compuesto de acuerdo con una cualquiera de las

reivindicaciones 1 a 27 una sal farmacéuticamente aceptable de estas o una composición de acuerdo con la reivindicación 28.

45. Un método de acuerdo a la reivindicación 44, en donde dicha disfunción sexual está relacionada con el deseo o relacionada con excitación.

46. Un método de acuerdo a la reivindicación 45, en donde dicho sujeto es un humano.

47. Un método para tratar o prevenir el dolor en un sujeto que lo requiere, que comprende la etapa de:
administrar a dicho sujeto una cantidad efectiva de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 27 una sal farmacéuticamente aceptable de estas o una composición de acuerdo con la reivindicación 28.

48. Un método de acuerdo a la reivindicación 47, en donde dicho dolor centralizado agudo, dolor periférico agudo, o una combinación de ellos.

49. Un método de acuerdo a la reivindicación 47, en donde dicho dolor es dolor centralizado Crónico, dolor periférico Crónico o una combinación de ellos.

50. Un método de acuerdo a la reivindicación 47, en donde dicho dolor es dolor neuropático, dolor visceral, dolor

músculo esquelético, dolor óseo, dolor de cáncer, dolor inflamatorio, o combinaciones de estos.

51. Un método de acuerdo a la reivindicación 50, en donde dicho dolor neuropático está asociado con diabetes, dolor post traumático por amputación, dolor de espalda inferior, cáncer, daño químico, toxinas, cirugía mayor, daño del nervio periférico debido a compresión post daño traumático, neuralgia post herpética, neuralgia trigeminal, radiculopatias lumbares o cervicales, fibromialgia, neuralgia glosoafaringeal, distrofia del reflejo simpático, casualgia, síndrome talámico, ablución de la raíz del nervios, distrofia simpática refleja o dolor post toracotomía, deficiencias nutricionales, o infección viral o infección bacteriana, infiltración metastásica, adiposis dolorosa, quemaduras, condiciones de dolor central relacionadas con condiciones talámicas, y combinaciones de estos.

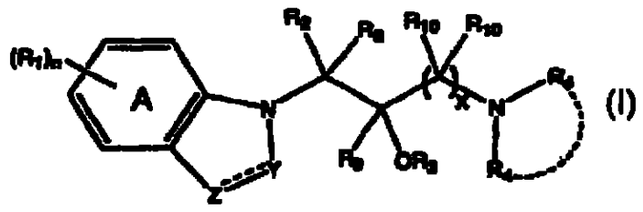
52. Un método de acuerdo a la reivindicación 50, en donde dicho dolor visceral está asociado con colitis ulcero activa, síndrome de intestino irritable, vejiga irritable, enfermedad de Crohn, (antralgías) reumatológicas, tumores, gastritis, pancreatitis, infecciones de los órganos, desórdenes del tracto biliar, y combinaciones de estos.

53. Un método de acuerdo a la reivindicación 47, en donde dicho dolor es un dolor específico a las mujeres.

54. Un método de acuerdo a la reivindicación 47, en donde dicho sujeto es un humano.

DERIVADOS DE 1-(1H-INDOL-1-IL)-3-(4-METILPIPERAZINA-1-IL)-1-FENIL PROPANO-2-OL Y COMPUESTOS RELACIONADOS COMO MODULADORES DE LA ACTIVIDAD DE LA NOREPINEFRINA (NE) Y LA SEROTONINA (5-HT) Y LA RETOMA DE MONOAMINA PARA EL TRATAMIENTO DE SÍNTOMAS VASOMOTORES (VMS)

RESUMEN



La presente invención está dirigida a derivados de fenilaminopropanol de fórmula (I); o una sal farmacéuticamente aceptable de estos; en donde: la línea punteada entre Y y Z representa un doble enlace opcional; la línea punteada entre los dos grupos R_4 representan un anillo heterocíclico opcional de 4 a 6 átomos por anillo que se pueden formar entre los dos grupos R_4, junto con el nitrógeno a través del cual ellos estas unidos; Y es N, CR_6, o C=O; Z es N, CR_7, CR_5, o $C(R_5)_2$; R_2 es un arilo sustituido con 0-3 R_1 o heteroarilo sustituido con 0-3 R_1; R_3 es H o alquilo C_1-C_4; n es una forma entera 0 a 4; x es un entero de 1 a 2; y los otros sustituyentes se definen en las reivindicaciones; composiciones que contienen estos derivados, y métodos de su uso para la prevención o tratamientos de condiciones mejoradas por la retoma de monoamina que incluyen, *inter alia*, síntomas vasomotores (VMS), disfunción sexual, desórdenes gastrointestinal y genitourinario, síndrome de fatiga

crónica, síndrome de fibromialgia, desórdenes del sistema nerviosos, y combinaciones de estos, particularmente aquellas condiciones seleccionadas del grupo que consiste del desorden depresivo principal, síntomas vasomotores, tensión o incontinencia urinaria apremiante, fibromialgia, dolor, neuropatía diabética, y combinaciones de estos.

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FIGURA 1

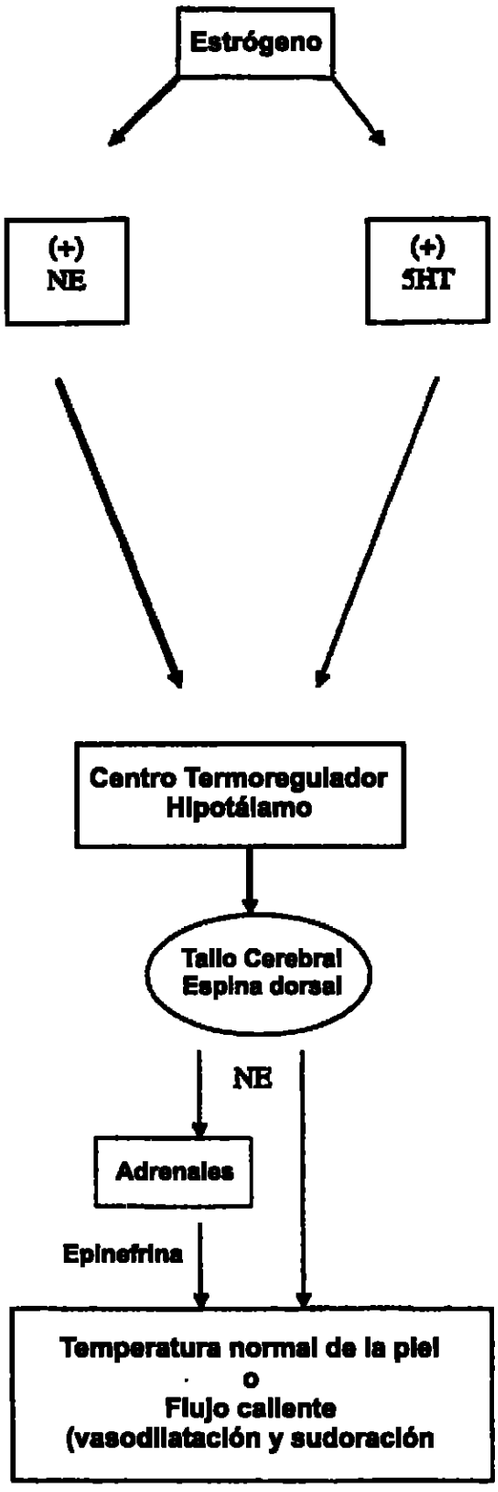
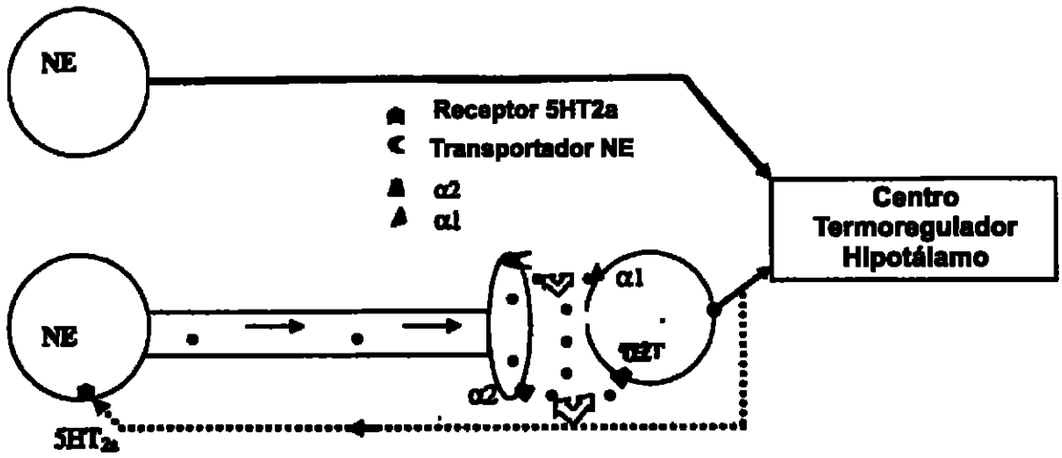


FIGURA 2


NE
Receptor 5HT2a
Transportador NE
α2
α1
Centro
Termoregulador
Hipotálamo
NE
α1
α2
5HT2a

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One Liberty Place
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Date of mailing *(day/month/year)* 09 December 2005 (09.12.2005)	
Applicant's or agent's file reference WYNC-1567 AM101666 (MILOWSKY)	IMPORTANT NOTIFICATION
International application No. PCT/US2005/010511	International filing date *(day/month/year)* 29 March 2005 (29.03.2005)
International publication date *(day/month/year)* 20 October 2005 (20.10.2005)	Priority date *(day/month/year)* 30 March 2004 (30.03.2004)
Applicant WYETH et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. *(If applicable)* The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

3. *(If applicable)* An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
30 March 2004 (30.03.2004)	60/557,651	US	29 April 2005 (29.04.2005)
11 May 2004 (11.05.2004)	60/569,863	US	05 December 2005 (05.12.2005)
28 March 2005 (28.03.2005)	11/091,885	US	06 June 2005 (06.06.2005)

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PCT

To:
WOODCOCK WASHBURN LLP
Attn. Lucci, Joseph
One Liberty Place - 46th Floor
Philadelphia, Pennsylvania 19103
UNITED STATES OF AMERICA

RECEIVED
AUG 17 2005
Woodcock Washburn

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference WYNC-1567 (PM 101666) Mulowsky	Date of mailing *(day/month/year)* 11/08/2005
International application No. PCT/US2005/010511	FOR FURTHER ACTION See paragraphs 1 and 4 below
Applicant WYETH	International filing date *(day/month/year)* 29/03/2005

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AUG 17 2005
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1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Federico Bonomelli

COPY SENT TO CLIENT
on 8/29/05

Form PCT/ISA/220 (January 2004) *(See notes on accompanying sheet)*

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 48.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

BNSDOCID: <XB____ISA220NOTES1_I_>

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

EN8DOCID: <XB_-___ISA220NCENP4_I_>

PATENT COOPERATION TREATY

PCT

00691 671

INTERNATI NAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
WYNC-1567		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2005/010511	29/03/2005	30/03/2004
Applicant		
WYETH		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      [ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. [ ] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. [ ] Certain claims were found unsearchable (See Box II).

3. [ ] Unity of invention is lacking (see Box III).

4. With regard to the title,
   [ ] the text is approved as submitted by the applicant.
   [X] the text has been established by this Authority to read as follows:

HETEROCYCLIC

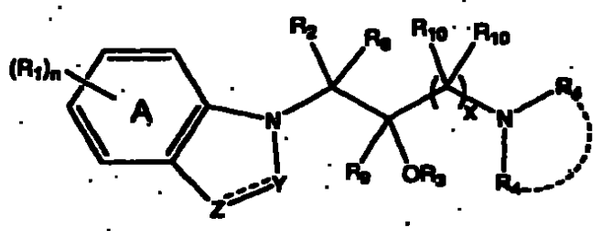
~~1-(1H-INDOL-1-YL)-3-(4-METHYLDIBENZO[B,F][1,4]OXEPIN-11-YL)~~-1-PHENYL PROPAN-2-OL DERIVATIVES AND RELATED COMPOUNDS AS MODULATORS OF THE NOREPINEPHRINE (NE) AND THE SEROTONINE (5-HT) ACTIVITY AND THE MONOAMINE REUPTAKE FOR THE TREATMENT OF VASOMOTOR SYMPTOMS (VMS)

5. With regard to the abstract,
   [ ] the text is approved as submitted by the applicant.
   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,
   a. the figure of the drawings to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant.
      [ ] as selected by this Authority, because the applicant failed to suggest a figure.
      [ ] as selected by this Authority, because this figure better characterizes the invention.
   b. [X] none of the figures is to be published with the abstract.

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The present invention is directed to phenylaminopropanol derivatives of formula I:



I

or a pharmaceutically acceptable salt thereof;

wherein:

the dotted line between Y and Z represents an optional double bond;

the dotted line between the two R_4 groups represents an optional heterocyclic ring of 4 to 6 ring atoms that may be formed between the two R_4 groups, together with the nitrogen through which they are attached;

Y is N, CR_6, or C=O;

Z is N, NR_7, CR_6, or $C(R_6)_2$;

R_2 is aryl substituted with 0-3 R_1 or heteroaryl substituted with 0-3 R_1;

R_3 is H or C_1-C_4 alkyl;

n is an integer from 0 to 4;

x is an integer from 1 to 2; and

the other substituents are defined in the claims;

compositions containing these derivatives, and methods of their use for the prevention and treatment of conditions ameliorated by monoamine reuptake including, *inter alia*, vasomotor symptoms (VMS), sexual dysfunction, gastrointestinal and genitourinary disorders, chronic fatigue syndrome, fibromyalgia syndrome, nervous system disorders, and combinations thereof, particularly those conditions selected from the group consisting of major depressive disorder, vasomotor symptoms, stress and urge urinary incontinence, fibromyalgia, pain, diabetic neuropathy, and combinations thereof.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US2005/010511

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/08 C07D209/30 C07D209/42 C07D265/36 C07D241/42
C07D235/06 C07D471/04 A61K31/4045 A61P15/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99/55694 A (AMERICAN HOME PRODUCTS) 4 November 1999 (1999-11-04) the whole document	1-54
A	WO 03/010169 A (WYETH) 6 February 2003 (2003-02-06) the whole document	1-54
A	EP 0 135 905 A (DEGUSSA) 3 April 1985 (1985-04-03) the whole document	1-54

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 July 2005	11/08/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Cortés, J

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/010511

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 29-54 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATI NAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2005/010511 00695

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9955694	A	04-11-1999	AT	282606 T	15-12-2004
			AU	3667699 A	16-11-1999
			CA	2330436 A1	04-11-1999
			CN	1307574 A ,C	08-08-2001
			DE	69921983 D1	23-12-2004
			DE	69921983 T2	07-04-2005
			EP	1075471 A1	14-02-2001
			ES	2232132 T3	16-05-2005
			JP	2002513015 T	08-05-2002
			TW	528754 B	21-04-2003
			WO	9955694 A1	04-11-1999
WO 03010169	A	06-02-2003	WO	03010169 A1	06-02-2003
			US	2003078268 A1	24-04-2003
			US	2004235851 A1	25-11-2004
EP 0135905	A	03-04-1985	AU	564272 B2	06-08-1987
			AU	3352784 A	04-04-1985
			CA	1229622 A1	24-11-1987
			DD	220304 A5	27-03-1985
			DE	3434199 A1	18-04-1985
			DK	466084 A	30-03-1985
			EP	0135905 A2	03-04-1985
			ES	8506260 A1	01-11-1985
			ES	8505640 A1	01-10-1985
			FI	843827 A	30-03-1985
			HU	35631 A2	29-07-1985
			HU	194804 B	28-03-1988
			JP	60105648 A	11-06-1985
			NO	843906 A	01-04-1985
			PT	79272 A ,B	01-10-1984
			SU	1319783 A3	23-06-1987
			ZA	8407681 A	27-11-1985

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/010511	29.03.2005	30.03.2004

International Patent Classification (IPC) or both national classification and IPC
C07D209/08, C07D209/30, C07D209/42, C07D265/36, C07D241/42, C07D235/06, C07D471/04, A61K31/4045,

Applicant
WYETH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Cortés, J Telephone No. +49 89 2399-8206

Form (PCT/ISA/237) (Cover Sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/010511

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/010511

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 29-54

because:

☒ the said international application, or the said claims Nos. 29-54 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/010511

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-54
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-54
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-28
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

N n-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 29 to 54 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion with regard to the industrial applicability will be formulated for these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step r industrial applicability; citations and explanations supporting such statement

The following documents have been cited in the International Search Report:

D1: WO 99/55694 A (AMERICAN HOME PRODUCTS) 4 November 1999 (1999-11-04)
D2: WO 03/010169 A (WYETH) 6 February 2003 (2003-02-06)
D3: EP-A-0 135 905 (DEGUSSA) 3 April 1985 (1985-04-03)

Novelty (Article 33(2) PCT)

The present compounds differ from the prior art compounds in D1 and D2 in R2 and from the compounds in D3 in the heterocycle A. The present compounds are therefore new.

Inventive Step (Article 33(3) PCT)

D1 to D3 diclose compounds with a related pharmacology and/or related medical uses. D1 could be regarded as the closest prior art.

The problem of the invention was the provision of new modulators of the monoamine reuptake for the treatment of vasomotor symptoms.

The present compounds are not anticipated or suggested by any of D1 to D3 alone or in any combination. The present invention is therefore based on an inventive step.

WOODCOCK WASHBURN
INTELLECTUAL PROPERTY LAW

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FACSIMILE

DATE: **Friday, September 09, 2005** JOB CODE:

Please deliver this and the following pages to:

Name:

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Your Ref.:

SENDER'S NAME: **Wendy A. Choi**

PAGES TO FOLLOW: **1**

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CLIENT MATTER NO.: AM101666 (WYNC-1567)

BEFORE THE EUROPEAN PATENT OFFICE (PCT/ISA)
FOR THE PATENT COOPERATION TREATY

Via Facsimile to 9-001-31-70-340-3016

In re application of : Wyeth, *et al.*
International Application No. : PCT/US2005/010511
International Filing Date : 29 March 2005
Amended Title:
1-(1H-INDOL-1-YL)-3-(4-METHYLPIPERAZIN-1-YL)-1-PHENYL PROPAN-2-OL DERIVATIVES AND RELATED COMPOUNDS AS MODULATORS OF THE NOREPINEPHRINE (NE) AND THE SEROTONINE (5-HT) ACTIVITY AND THE MONOAMINE REUPTAKE FOR THE TREATMENT OF VASOMOTOR SYMPTOMS (VMS)

European Patent Office
Authorized Officer Federico Bonomelli
P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
NETHERLANDS

COMMUNICATION REGARDING THE TITLE AS AMENDED BY THE ISA/EP

Dear Sir:

In response to the International Search Report and Written Opinion issued on August 11, 2005, we would like to comment on the title as amended by the ISA/EPO.

Applicant respectfully requests that the following title be considered in place of the title as amended by the ISA because it is a more accurate description of the compounds disclosed and claimed in the application:

HETEROCYCLIC PHENYL PROPAN-2-OL DERIVATIVES AND RELATED COMPOUNDS AS MODULATORS OF THE NOREPINEPHRINE (NE) AND THE SEROTONIN (5-HT) ACTIVITY AND THE MONOAMINE REUPTAKE FOR THE TREATMENT OF VASOMOTOR SYMPTOMS (VMS)

Respectfully submitted,

Wendy A. Choi
Registration No. 36,697

Date: September 9, 2005

WOODCOCK WASHBURN LLP
One Liberty Place – 46th Floor
Philadelphia, PA 19103
(215) 568-3100

Confirmation Report

Page : 001
Date & Time: 09-Sep-2005 05:53pm
Line 1 : 404 459 4217
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Nbr.	Job	Date	Time	Duration	pgs	To	Dept.nbr	Account	Comm. code	Status
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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

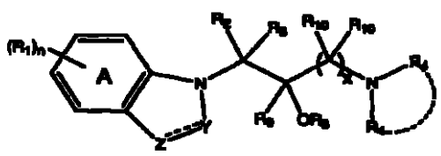
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(21) N° de solicitud: 06 - 98495	(51) Int Cl: C07D 209/08, 209/30, 209/42, 265/38, 241/42, 235/06, 471/04; A61K 31/4045; A61P 15/10
22) Fecha de solicitud: 29/09/06	(71)Solicitante(s) WYETH
(30) Prioridad (31) No. 32) Fecha (33) País 60/557,651 30/03/2004 US 60/569,863 11/05/2004 US 11/091,885 28/03/2005 US	(72) Inventor(es) KIM, Caliain, Younghee Otros
	(74) Apoderado: ALVARO CORREA ORDOÑEZ
(85) Fecha límite inicio fase nacional: 30/10/2006 (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud: 29/03/2005 No. de solicitud PCT/US2005/010511	(87) Publicación internacional Fecha: 20/10/2005 N° publicación: WO 2005/097744

(54) Título: **DERIVADOS HETEROCICLICOS DE FENIL PROPANO-2-OL Y COMPUESTOS RELACIONADOS COMO MODULADORES DE LA ACTIVIDAD DE LA NOREPINEFRINA (NE) Y LA SEROTONINA (5-HT) Y LA RETOMA DE MONOAMINA PARA EL TRATAMIENTO DE SÍNTOMAS VASOMOTORES (VMS)**

Reivindicación(es):

1. Un compuesto de fórmula I:



I

O una sal farmacéuticamente aceptable de estos;
En donde:

La líneas punteadas entre Y y Z representa un enlace doble opcional;

La línea punteada entre los dos grupos R_4 representa un anillo heterocíclico opcional de 4 a 6 átomos de anillo y se puede formar entre los dos grupos R_4, junto con el nitrógeno al cual ellos están unidos;

Y es N, CR_8 O C=O;
Z es N, NR_7, CR_8, o $C(R_8)_2$;

R1 es, independientemente a cada ocurrencia, alquilo, alcoxi, halo, CF_3, OCF_3, arilalquiloxi sustituido con 0-3 R_{11}, ariloxi sustituido con 0-3 R_{11}, arilo sustituido con 0-3 R_{11}, heteroarilo sustituido con 0-3 R_{11}, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo alquinilo, alquilsulfóxido, fenilsulfóxido sustituido con 0-3 R_{11}, alquilsulfona, fenilsulfona sustituido con 0-3 R_{11}, alquilsulfonamida, fenilsulfonamida sustituido con 0-3 R_{11}, heteroariloxi sustituido con 0-3 R_{11}, heteroarilmetoxi sustituido con 0-3 R_{11}, alquilamida, o arilamida sustituido con 0-3 R_{11}; o dos R_1 adyacentes también representan metilenodioxi;

R_2 es un arilo sustituido con 0-3 R_1 o heteroarilo sustituido con 0-3 R_1;

R_3 es H o alquilo C_1-C_4;

R_4 es, independientemente a cada ocurrencia, H, alquilo C_1-C_4, arilalquilo, heteroarilmetilo, cicloheptilmetilo, ciclohexilmetilo, ciclopentilmetilo, o ciclobutilmetilo; o

Ambos grupos R_4, junto con el nitrógeno al cual ellos están unidos, forman una anillo heterocíclico de 4 a 6 átomos por anillo, en donde un carbono puede ser opcionalmente reemplazado con N, O, S, o SO_2, y en donde cualquier átomo del anillo de carbono o el átomo de N adicional puede ser opcionalmente sustituido con alquilo C_1-C_4 o CF_3;

R_5 es, independientemente a cada ocurrencia, H, alquilo C_1-C_4, arilo sustituido con 0-3 R_1 o ciano; o cuando dos R_5 están presentes, ellos forman un anillo carbocíclico de 3-7 carbonos;

R_6 es H, alquilo C_1-C_4, o ciano;

R_7 es H, alquilo C_1-C_4, cicloalquilo C_3-C_8, o arilo sustituido con 0-3 R_1;

R_8 es H, o alquilo C_1-C_4;
R_9 es H, o alquilo C_1-C_4;

R_{10} es, independientemente de cada ocurrencia, H, o alquilo C_1-C_4; o R_{10} y R_4 juntos con el nitrógeno al cual R_4 esta unido forma un anillo que contiene nitrógeno que contiene 3-6 átomos de carbono;

n es un entero de 0 a 4;
x es un entero de 1 a 2; y

R_{11} es alquilo, alcoxi, halo, CF_3, OCF_3, hidroxi, alcanoiloxi, nitro, nitrilo, alquenilo, alquinilo, alquilsulfóxido, alquilsulfona, alquilsulfonamida, o alquilamida;

o dos R_{11} adyacentes también representan metilenodioxi;

En donde 1-3 átomos de carbono en el anillo A pueden opcionalmente ser reemplazados con N.

f.l:os 706 y 707
Tarjetas temáticas

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 08-098495- -00000-0000
Fec: 2008-09-29 15:58:49 Dep. 2020 NUECREACIONES
Tra. 11 PATENTEIYII
Eve: 378 FASENACIONALI
Act 411 PRESENTACION Folios: 707

Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN (✓) MODELO DE UTILIDAD ( )	( )	(✓)
-Indicación de que se solicita la concesión de una patente.	( )	(✓)
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	(✓)
-Descripción de la Invención.	( )	(✓)
-Dibujos de ser estos pertinentes.	( )	( )
-Comprobante de Pago de las tasas establecidas.	( )	(✓)
COMPLETA (✓) INCOMPLETA ( )	( )	( )
DISEÑO INDUSTRIAL ( )		
-Indicación de que se solicita el registro de Diseño Industrial.	( )	( )
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
-Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
-Comprobante de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )
ESQUEMA DE TRAZADO ( )		
-Indicación de que se solicita el registro de Diseño Industrial.	( )	( )
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
-Representación gráfica del Esquema Trazado.	( )	( )
-Comprobante de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )

Firma Responsable: _____

Fecha: _____

709
687

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCI

Bogotá,
2020

Doctor(a)
CORREA ORDOÑEZ ALVARO

REFERENCIA	Radicación No.	06 98495
	Solicitud internacional	PCT/US2005/010511
	Fecha inicio fase nacional	30/10/2006
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	00013583

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

2. La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 24 NOV. 2006
aalvarado