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Doctora

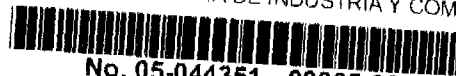
Alix Carmenza CÉSPEDES DE VERGEL

Jefe División de Nuevas Creaciones

Superintendencia de Industria y Comercio

E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-044351- -00005-0000

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Act. 444 RESPUESTAREQUE Folios: 149

REF: Expediente No.

05-044.351

Patente de Invención:

**"DERIVADOS DE CICLOHEXANO
ESPIROCICLICOS"**

Titular:

GRUNENTHAL GMBH

DESTINO: 444

HUMBERTO RUBIO CAMACHO, mayor de edad, domiciliado en Bogotá, D.C., identificado con la cédula de ciudadanía número 17'192.062 de Bogotá, abogado graduado portador de la Tarjeta Profesional No. 50.007 expedida por el Consejo Superior de la Judicatura, actuando en carácter de Apoderado de **GRUNENTHAL GMBH**, domiciliado en Zieglerstrasse 6, 52078 Aachen, Alemania; encontrándome dentro de la debida oportunidad procesal para dar respuesta al auto proferido por su Despacho, como resultado del examen de fondo **Artículo 45** y examen de patentabilidad **Artículo 46** mediante Oficios Nos. 4488 y 4489 y conceptos Técnicos Nos. 761 y 762, notificados por fijación en lista de 17 de abril de 2.009, me permito manifestar y anexar:

I.- Manifiesto y Anexo:

Artículo 46:

Para dar cumplimiento con el artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina, estamos anexando los artículos solicitados por el examinador:

- A. **MAYER J P E AL: Application Of The Pictet-Spengler Reaction In Combinatorial Chemistry" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, Bd. 37, Nr. 32, 5. August 1996 (1996-08-05), Seiten 5633-5636, XP004030498 ISSN: 0040-4039.**
- B. **NAGY T ET AL: "Synthesis and analgesic evaluation of some 1, 1-disubstituted 3-carboxy-4-phenyl-1,2,3,4-tetrahydro-beta-carboline derivatives "EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR, Bd. 30, Nr. 7, 1995, Seiten 575-586, XP004040182 ISSN: 0223-5234**

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Artículo 45

Para dar cumplimiento a las observaciones realizadas por el examinador una vez realizado el estudio de fondo de la presente solicitud, damos respuesta a cada una de las objeciones:

Del Capítulo Descriptivo y de las Reivindicaciones**1.1 Descripción**

1.1.1 El Examinador considera que las reivindicaciones 1 - 12 y 16 carecen de sustento en la sección descriptiva de la solicitud, dado que no hay datos comparativos que contrasten los compuestos de acuerdo al invento, con los compuestos de acuerdo al estado de la técnica más cercano (D1) lo que permitiría evaluar las ventajas técnicas.

El solicitante manifiesta que todos estos compuestos de los ejemplos fueron sintetizados y la actividad contra el receptor ORL1 fue investigada *in vitro*.

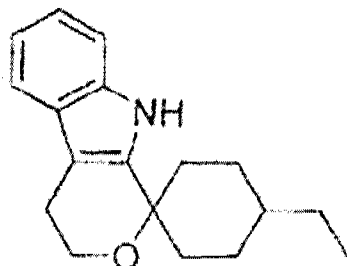
Hacemos notar al examinador que la actividad de los compuestos de ejemplo fue medida a una concentración de prueba comparativamente baja, 1 μM . Los compuestos que inhibieron el receptor de ORL1 en 1 μM por al menos un 15% o los compuestos que exhibieron un valor K_i de menos de 10 μM fueron calificados como activos ("+"). Con respecto a esto, notese que solo 8 de los prácticamente 1000 compuestos fueron clasificados como inactivos ("-") bajo esta definición; Si estos compuestos exhibían actividad suficiente a mayores concentraciones o no, no fue examinado.

1.1.2 El Examinador considera que D1 representa el estado de la técnica más cercano.

Como fue ya señalado correctamente por el examinador, los compuestos de acuerdo al presente invento difieren de los compuestos de acuerdo a D1 al menos en la presencia de un grupo amino en el anillo espirocíclico, es decir la mitad $-\text{NR}^1\text{R}^2$.

El grupo amino sustituido en el anillo espirocíclico mencionado es, sin embargo, esencial para la afinidad de los compuestos espirocíclicos de acuerdo al invento con el receptor ORL-1 (y con el receptor μ -opiáceo).

El siguiente compuesto, de acuerdo a D1, fue sintetizado:



Comparativo (ORL-1: -14%; μ : 4%)

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Respecto a esto, destacamos que el compuesto comparativo de arriba solo difiere del compuesto de ejemplo AA-1, de acuerdo al sumario de pruebas experimentales anexado, en que falta el grupo dimetilamino.

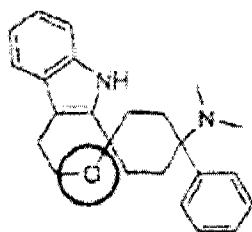
Se midió la afinidad del compuesto comparativo mencionado contra el receptor ORL-1 como también contra el receptor μ -opiáceo. Los resultados de las mediciones (-14% y 4% respectivamente) demuestran que compuestos de este tipo, es decir, compuestos sin un grupo amino en el anillo espirocíclico, no exhiben una afinidad significativa hacia el receptor ORL-1 ni el receptor μ -opiáceo.

De esta manera, puede ser considerada como la ventaja técnica de los compuestos, de acuerdo al presente invento, que llevan un grupo amino $-NR^1R^2$ en el anillo espirocíclico su afinidad al receptor ORL-1 y al receptor μ -opiáceo, en donde los compuestos de acuerdo a D1, que no tienen tal grupo amino, no se enlazan a estos receptores.

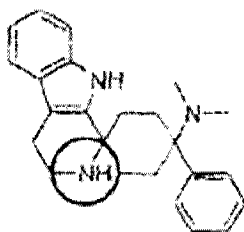
1.1.3 Además, los datos experimentales anexados demuestran que otros sustituyentes y residuos de la estructura espirocíclica de los compuestos de acuerdo al invento pueden ser variados dentro de amplios límites sin disminuir su excelente afinidad con el receptor ORL-1 y el receptor μ -opiáceo.

Esto se ve ilustrado más claramente en lo siguiente, donde las afinidades contra el receptor ORL-1 y contra el receptor μ -opiáceo están expresadas en porcentajes (%) a una concentración de prueba de 1 μ M;

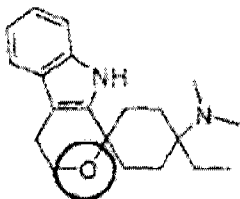
1.) X



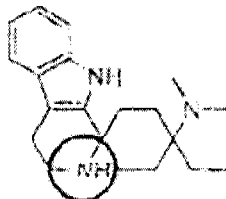
Ejemplo 1
(ORL1 99%; μ 99%)



BB-1
(ORL1 99%; μ 102%)



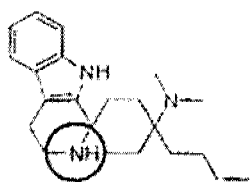
AA-1
(ORL1 91%; μ 98%)



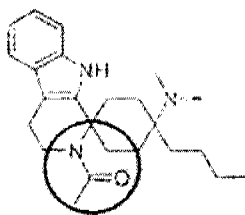
AA-3
(ORL1 97%; μ 99%)

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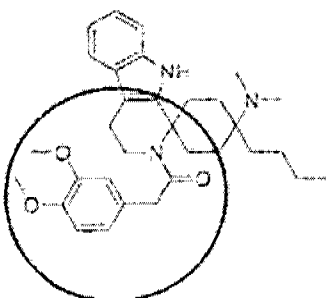
2.) R¹⁷



AA-9
(ORL1 99%; μ 101%)

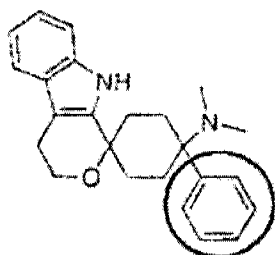


AA-10
(ORL1 99%; μ 97%)

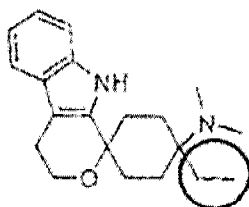


AA-13
(ORL1 99%; μ 98%)

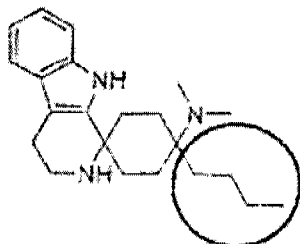
3.) R³



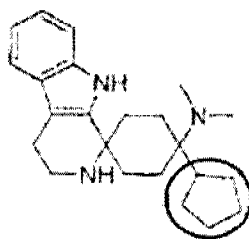
Ejemplo 1
(ORL1 99%; μ 99%)
101%)



AA-1
(ORL1 91%; μ 98%)



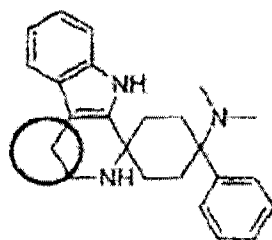
AA-9
(ORL1 99%; μ



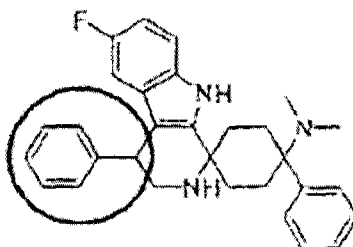
AA-29
(ORL1 99%; μ 100%)

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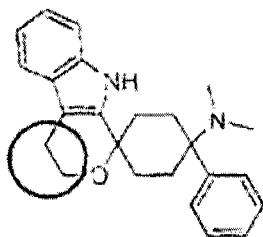
4.) R⁵/R⁶



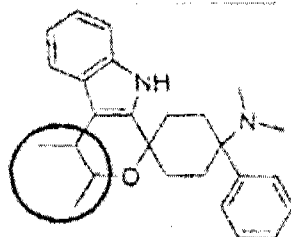
BB-1
(ORL1 99%; μ 102%)



BB-38
(ORL1 92%; μ 98%)

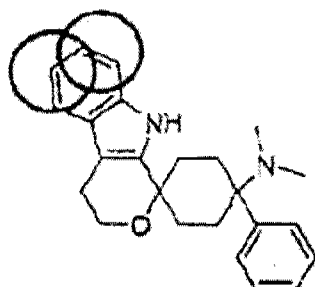


Ejemplo 1
(ORL1 99%; μ 99%)

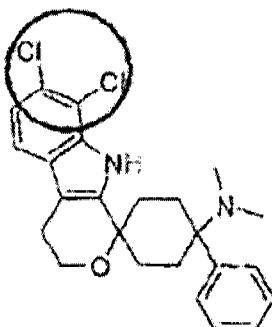


EE-35
(ORL1 98%; μ 100%)

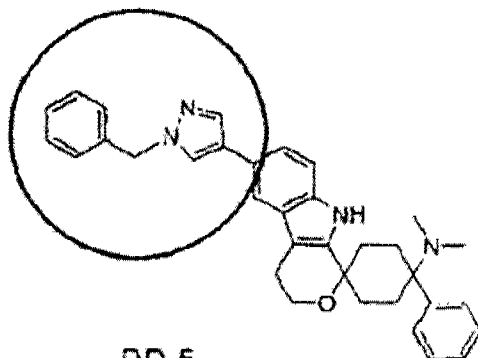
5.) R⁷ a R⁹



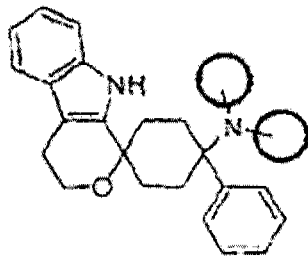
Ejemplo 1
(ORL1 99%; μ 99%)



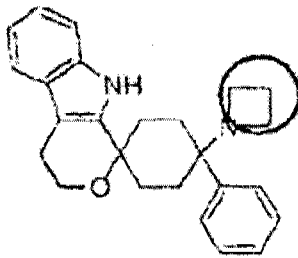
DD-8
(ORL1 96%; μ 101%)



DD-5
(ORL1 99%; μ 97%)

6.) R¹R²

Ejemplo 1
(ORL1 99%; μ 99%)



FF-20
(ORL1 91%; μ 101%)

Las comparaciones ejemplificadas arriba demuestran que la diversidad estructural de la definición de los compuestos de acuerdo a la reivindicación 1 esta totalmente justificada y que el grupo amino -NR¹R² es necesario para mantener la afinidad del compuesto hacia el receptor ORL-1 y al receptor μ -opiáceo.

1.2 Reivindicaciones

1.2.1 El Examinador objeta que la presente solicitud carece de concisión y objeta las reivindicaciones 1, 6, 8 y 9, en particular en contra de la definición de arilo, heteroarilo, cicloalquilo y los sustituyentes de los mismos como también los sustituyentes de alquilo.

Para mayor claridad de la materia reivindicada y teniendo en cuenta las observaciones del examinador, estamos presentando un nuevo Capitulo Reivindicatorio Modificado, que reemplaza el presentado con la solicitud inicial sin que implique ampliación de la invención.

Teniendo en cuenta lo anterior y el nuevo pliego de reivindicaciones presentado, el solicitante considera que se han superado las objeciones; adicionalmente el solicitante aclara que la definición general de "arilo" indicado en la reivindicacion puede comprender de 6 a 16 átomos de carbono. El sustento para esta afirmación se encuentra en la parte general de la descripción, donde los siguientes arilos son ejemplificados: fenil (C₆), indan (C₉), tetralin (C₁₀), naftil (C₁₀), fluoreno (C₁₃), fenantreno (C₁₄), y fluoranteno (C₁₆).

1.2.2 Se han modificado los aspectos objetados por el examinador en las reivindicaciones 13 a 15.

1.2.3 Siguiendo la sugerencia del examinador, se han eliminado los términos "solvatos" e "hidratos" de la reivindicación 16.

1.2.4 Confiamos en que la objeción levantada por el Examinador en contra de las múltiples posibilidades de medicinas obtenidas al combinar el compuesto de formula I con otras sustancias activas ha sido superada con lo expuesto en el punto 1.1.1.

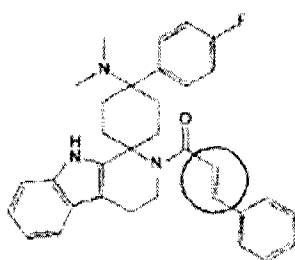
1.2.5 Respecto a la observación del examinador que indica que la reivindicación 23 está incompleta, consideramos que se trata de un error involuntario, teniendo en cuenta que el pliego de reivindicaciones presentado en esta solicitud contiene únicamente **18 reivindicaciones**.

1.2.6 Adicionalmente, nos permitimos realizar las siguientes aclaraciones en conexión con "C₁₋₅ alquilo" usualmente está explícitamente especificado en la reivindicación 1 que este residuo puede ser, entre otras cosas, "saturado o no saturado, ramificado o no ramificado".

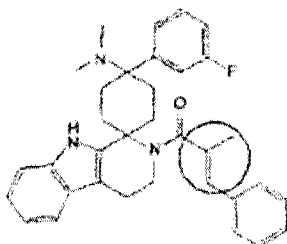
Sin embargo, en conexión con "C₁₋₃ alquilo" uniendo a arilo, C₃₋₈ cicloalquilo y heteroarilo, no se especifica explícitamente en la reivindicación 1 que "C₁₋₃ alquilo" también puede ser "saturado o no saturado, ramificado o no ramificado".

No obstante lo anterior en la descripción claramente se define que tanto "C₁₋₅ alquilo" como "C₁₋₃ alquilo" pueden ser "saturado o no saturado, ramificado o no ramificado" (descripción pagina 7).

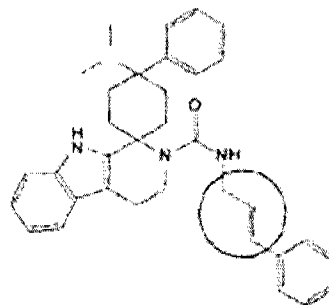
Algunos ejemplos representativos de compuestos realizando puentes de C₁₋₃ alquilo no saturados y enlaces de C₁₋₃ alquilo ramificados respectivamente, se demuestran:



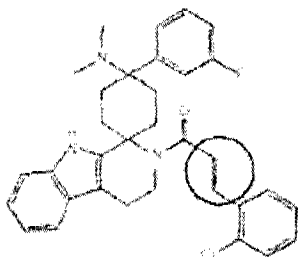
GG-199



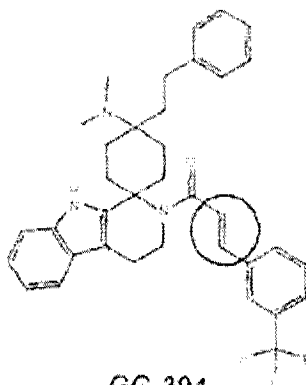
GG-124



BB-13



GG-129



GG-394

Así, basados en lo divulgado en la descripción, se han realizado las modificaciones pertinentes en la Reivindicaciones en lo que concierne a "C₁₋₅ alquilo" y "C₁₋₃ alquilo" en las definiciones de R³, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰ y R¹² b específicamente en la reivindicación 1 refiriéndose al significado a de "C₁₋₃ alquilo", "en cada caso saturado o no saturado, ramificado o no ramificado".

En cuanto a la definición R^{12} significa H; C_{1-5} alquilo, en cada caso saturado o no saturado, ramificado o no ramificado, mono- o poli-sustituido o no sustituido; C_{3-8} – cicloalquilo, en cada caso saturado o no saturado, ramificado o no ramificado, mono- o poli-sustituido o no sustituido; arilo, o heteroarilo, en cada caso saturado o no saturado, ramificado o no ramificado, mono- o poli-sustituido o no sustituido; o arilo, C_{3-8} – cicloalquilo, o heteroarilo, en cada caso saturado o no saturado, ramificado o no ramificado, mono- o poli-sustituido o no sustituido, anexado mediante C_{1-3} alquilo; **en cada caso saturado o no saturado, ramificado o no ramificado**; OR^{13} ; $NR^{15}R^{15}$.

Se realizan enmiendas correspondientes a R^3 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} en la reivindicación 1 adaptada las reivindicaciones dependientes a ésta de manera consecuente.

2. Unidad de Invención

El Examinador considera que las reivindicaciones 1 -16 carecen de unidad. Con respecto a eso, el Examinador considera los siguientes grupos separados de inventos:

- (i) compuestos de acuerdo a la formula I donde X es NR^{17} y W es NR^4 ;
- (ii) compuestos de acuerdo a la formula I donde X es NR^4 y W es O o S;
- (iii) medicinas que comprenden combinaciones de drogas.

En lo que respecta al grupo de inventos (iii), creemos que mediante la enmienda propuesta arriba para la reivindicación 16, la objeción por falta de unidad debería ser superada (ítem 1.1.1).

En lo que concierne al grupo (ii), debemos señalar que X no puede ser NR^4 (pero si NR^{17}).

Además, como ha sido demostrado por la extensiva recolección de datos experimentales adjuntos aquí, los compuestos de acuerdo al grupo de inventos (i) están relacionados a los compuestos de acuerdo al grupo de inventos (ii) para formar un concepto general de invención único, en otras palabras, la modulación del receptor ORL-1 (y el receptor μ -opioideo).

Este aspecto será discutido de manera más amplia en conexión con el análisis de nivel inventivo en el ítem 4.

Teniendo en cuenta lo anterior consideramos que las objeciones del examinador en cuanto a la falta de unidad, carecen de sustento en lo que respecta a los grupos de inventos (i) y (ii).

3. Definiendo el estado de la Técnica

El Examinador se refiere a AU 636 232 (D1), el equivalente australiano de EP-A 466 548, que fue también citado en procedimientos de examen internacional de la solicitud paralela PCT.

4. Análisis de Patentabilidad

Como ya fue señalado por el examinador y delineado bajo el ítem 1.1.3 señalado anteriormente, los compuestos de acuerdo al presente invento difieren de los compuestos de acuerdo a D1 en al menos la presencia del grupo amino en el anillo espirocíclico, es decir el grupo $-NR^1R^2$.

Como quedó demostrado por las pruebas comparativas discutidas ampliamente en el punto 1.1.3, los compuestos de acuerdo a D1 no exhiben afinidad ni al receptor ORL-1 ni al receptor μ -opiáceo. De esta manera, el efecto farmacológico de los compuestos de acuerdo a D1 tiene que diferir, basado en un principio de funcionamiento farmacológico, con el principio de funcionamiento farmacológico de los compuestos del presente invento.

Aun si las indicaciones médicas con respecto a D1 y las indicaciones médicas con respecto al presente invento se superponen parcialmente, existe un gran beneficio en proveer un medicamento alternativo para tratar la misma enfermedad o desorden basándose en un principio de acción farmacológica distinto y novedoso.

Un principio de acción farmacológica distinto resulta en diferentes riesgos para efectos secundarios, diferentes interacciones con otras drogas, etc. Un principio de acción farmacológica distinto puede requerir también una ruta de administración diferente para lograr un efecto terapéutico optimizado.

Adicionalmente, por ejemplo, debido a una disposición genética, algunos pacientes pueden ser más susceptibles a un tratamiento de alguna enfermedad en particular mediante la modulación del receptor ORL-1 y del receptor μ -opiáceo, que a la modulación del receptor que es modulado por los compuestos de acuerdo a D1. Así, los compuestos de acuerdo a la presente solicitud son ventajosos en comparación con los compuestos de acuerdo a D1, porque tienen un principio de funcionamiento farmacológico distinto.

No hay ningún indicio en D1 de que mediante la introducción de un grupo amino, es decir el residuo $-NR^1R^2$ al sistema de anillo espirocíclico, puedan ser logrados compuestos con afinidad al receptor ORL-1 (ni al receptor μ -opiáceo). Así, el tema de la reivindicación 1 no fue puesto en evidencia por D1. Lo mismo se aplica a todas las reivindicaciones restantes que dependen directa o indirectamente de la reivindicación 1.

Consideramos que con el nuevo pliego de reivindicaciones se levanten las observaciones de definición, claridad, concisión y sustento hechas por el examinador, teniendo en cuenta que los cambios se entienden comprendidos dentro

del ámbito de protección original de la solicitud y por lo tanto se considera que no hay materia nueva añadida..

De manera atenta solicito a su Despacho, tener en cuenta todos y cada una de las consideraciones expuestas anteriormente, al momento de estudiar el presente caso.

II. Anexo:

- 2.1 **MAYER J P E AL: Application Of The Pictet-Spengler Reaction In Combinatorial Chemistry" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL**
- 2.2 **NAGY T ET AL: "Synthesis and analgesic evaluation of some 1, 1-disubstituted 3-carboxy-4-phenyl-1,2,3,4-tetrahydro-beta-carboline derivatives "EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR**
- 2.3 Nuevo pliego de reivindicaciones.
- 2.4 Documento que contiene un sumario de ejemplos de compuestos
- 2.5 Documento que contiene compuestos ejemplares.

III. Petición:

Conforme a lo anterior, una vez atendidos los requerimientos y exigencias del examinador y al tener en cuenta el nuevo capítulo reivindicatorio, los documentos que contiene los compuestos que permiten evaluar las ventajas técnicas de la presente solicitud, así como los argumentos expuesto, solicito muy respetuosamente a su Despacho, continuar el trámite de rigor y de ser el caso se hagan las correspondientes observaciones con el ánimo de hacer lo pertinente dentro del presente trámite.

Atentamente,



HUMBERTO RUBIO CAMACHO
C.C. 17'192.062 de Bogotá
T.P. 50.007 Consejo Superior
de la Judicatura
COD. 4134

05/1249/P000287



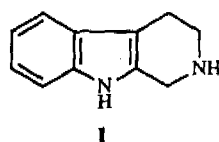
Application Of The Pictet-Spengler Reaction In Combinatorial Chemistry.

John P. Mayer*, Danute Bankaitis-Davis, Jingwen Zhang, Graham Beaton, Kirsten Bjergarde,
Catherine M. Andersen, Burton A. Goodman and Charles J. Herrera.

Amgen Boulder Inc., 3200 Walnut St., Boulder, CO, 80301

Abstract. Reaction of polymer bound tryptophan with a variety of aldehydes and ketones under Pictet-Spengler like conditions was found to produce 1,2,3,4-tetrahydro- β -carbolines in excellent yield. The straightforward, easily automated chemistry and the availability of numerous commercial aldehydes and ketones makes this approach ideal for combinatorial chemistry application. Copyright © 1996 Elsevier Science Ltd

Combinatorial technology, initially focused on peptides and peptide-like structures,^{1a-e} has recently begun to emphasize low molecular weight compounds for use in basic drug discovery. Renewed interest in polymer based synthetic methodology has dramatically expanded application of the original solid phase concept.² As a result, a number of pharmaceutically useful heterocyclic structures can now be prepared by solid phase methodology, including the benzodiazepines,^{3a,b} hydantoins,^{3b} lactones,^{3c} tetrahydrofurans,^{3d} thiazolidines^{3e} and pyrrolidines.^{3f} This repertoire continues to expand rapidly.

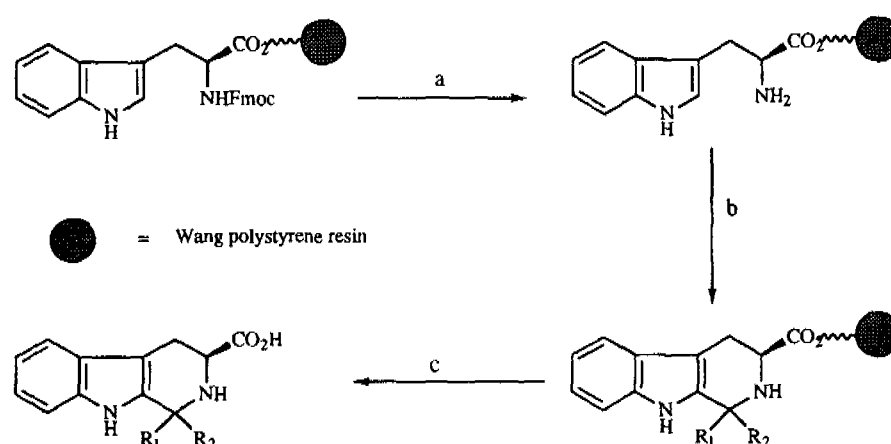


The β -carboline **1** is a key structural motif common to a large class of tryptophan derived natural product alkaloids. This class includes the simple tricyclic eleagnines and harmines as well as a number of structurally more complex examples such as yohimbine, ajmalicine, and the medicinally important reserpine.⁴ In addition to the diverse biological activity of the naturally occurring compounds, synthetically derived β -carbolines also exhibit significant bioactivity, particularly in the central nervous system, where several are known to interact at benzodiazepine,^{5a} serotonin,^{5b} and dopamine^{5c} receptor sites. The broad spectrum of biological activity and the rigid, heterocyclic skeleton of this unique pharmacophore presented an excellent opportunity for combinatorial application.

We and others⁶ have reasoned that access to this class of compounds could be realized through the Pictet-Spengler cyclization reaction⁷ in a solid phase protocol (Scheme 1). Due to the commercial

availability of a wide variety of aldehydes and ketones as well as a number of substituted tryptophan derivatives, a large number of β -carboline derivatives could be realistically proposed.

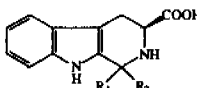
A key aspect of the methodology is the condensation of a polymer bound tryptophan and an aldehyde or ketone component at room temperature under acidic conditions. Use of 1% trifluoroacetic acid/methylene chloride reaction mixture was an ideal choice for several reasons: polystyrene based supports exhibit excellent swelling properties in both solvents; the Wang⁸ resin linker utilized in this procedure is stable to low (<5%) TFA concentrations; these conditions are also compatible with existing automated synthesis instruments.



Scheme 1. Generalized synthetic procedure. a) 2 x 20% piperidine/ DMF. b) 4 eq. aldehyde or ketone in 1% TFA/CH₂Cl₂, r.t. c) 95% TFA/H₂O 2hrs.

The following is a description of the general procedure: a 1g portion of Fmoc-L-Tryptophan-Wang resin (available from a number of commercial sources) with a typical loading range of 0.5 to 0.7 mmol/g was treated with two portions of 20% piperidine in DMF to remove the Fmoc protecting group. The resin was then washed several more times with DMF followed by CH₂Cl₂ before introduction of four equivalents of an aldehyde or ketone in a 1% solution of TFA in CH₂Cl₂. The reaction vessel was then agitated at room temperature for two to four hours in the case of the aldehydes and from 48 to 72 hours when utilizing ketone synthons. Reaction progress could be conveniently monitored by the Kaiser method.⁹ Cleavage from the support was accomplished by suspending and stirring the resin in neat trifluoroacetic acid for a period of two hours at room temperature and the product was recovered by filtering the suspension and concentrating the filtrate. Selected examples are summarized in Table 1. Analytical high performance liquid chromatography was used to analyze the crude samples and revealed the presence of both diastereomers in a majority of the aldehyde derived products, although no attempt was made to assign absolute stereochemistries. Purities of the crude compounds were typically in excess of 85% based on HPLC analysis; however, a number of methyl ketones (entries 5, 6 and 7 in Table 1) exhibited purities of only around 50%. In these cases the sole contaminant was identified as unreacted tryptophan. Preparative scale, liquid chromatography (0.1% HCl in

water/ acetonitrile, Vydac C-18 preparative column) was utilized for purification of representative samples. Characterization consisted of ¹H-NMR and electrospray mass spectroscopy.¹⁰



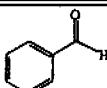
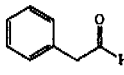
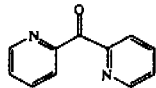
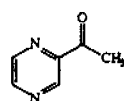
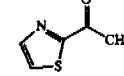
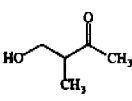
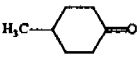
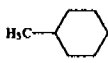
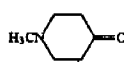
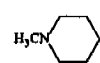
entry	aldehyde/ ketone	R ₁	R ₂	% HPLC ^{11a} purity	% mass ^{11b} recovery
2			H	90	85
3			H	92	89
4				87	98
5			CH ₃	56	97
6			CH ₃	46	91
7			CH ₃	53	99
8		spiro 		84	94
9		spiro 		97	95

Table 1. Structures of representative β -Carbolines.

Our results demonstrate the Pictet-Spengler reaction to be an efficient method for the solid phase synthesis of β -carbolines from tryptophan based substrates¹², a chemistry that is also compatible with our current methods of automation. We anticipate that this reaction will be an important tool for the construction of diverse arrays of small molecules based on β -carbolines and other related heterocycles.

Acknowledgement

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References and Notes

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- 10) Spectral data for compd **3**: ^1H NMR (CD_3OD , 300MHz) δ 7.0-7.6 (m, 9H), 4.9, 5.1 (m, 1H), 3.6-3.9 (m, 1H), 2.9-3.2 (m, 4H). ^{13}C NMR exhibited bridgehead (C-1) diastereomeric signals at 53.5ppm and 55.8ppm. Electrospray mass spectral characterization: 307 [MH^+], calc.: 306.
- 11) a) Analysis was carried out by HPLC (Vydac C18 column, 4.6 x 250mm, 0-50% acetonitrile/water containing 0.1% TFA) with integration of peak areas at 220nm. b) Mass recoveries were calculated from the weight of crude material and the initial loading level of Fmoc-Trp-Wang resin.
- 12) In preliminary experiments we have tried to increase diversity within the carboline scaffold through alkylation of the position 2 nitrogen. While activated alkylating reagents such as α -bromomethyl acetate efficiently alkylated some carbolines, this reaction was not reproducible over a wide series of substrates. This chemistry is under investigation.

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Synthesis and analgesic evaluation of some 1,1-disubstituted 3-carboxy-4-phenyl-1,2,3,4-tetrahydro- β -carboline derivatives

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Summary — New 4-phenyl-1,2,3,4-tetrahydro- β -carbolines were synthesized from β -phenyltryptophan ester. They were evaluated in induced pain on rodents. Amide **17b** proved to be the most powerful in the series. Several compounds display significant antiinflammatory properties.

β -substituted α -amino-acid / tryptophan / β -carboline / analgesia / inflammation

Introduction

In the course of previous studies on 1,1-disubstituted 3-carboxy-1,2,3,4-tetrahydro- β -carbolines we have synthesized structurally new compounds and studied their therapeutic potential [1]. Some of these compounds were found to possess significant analgesic activities associated with antiinflammatory properties. Based on these results, we planned a new programme of syntheses with the aim of reinforcing analgesic properties. The spiro derivative **1a,b** (scheme 1), which has interesting analgesic activity in several animal models at 50 mg/kg ip and inhibitory properties *in vitro* on 5-lipoxygenase, was chosen as a starting point. Unfortunately, **1a,b** proved to be inactive *via per os* administration in the same animal models and showed behavioural changes and other side effects with other conditions (eg, catalepsy ptosis, apathy, ataxia and respiratory depression) (G Adam, unpublished results). In order to determine structural requirements needed for high antinociceptive activity *via per os* administration and a high safety index, defined as the ratio of the ED₅₀ over the dose causing the first behavioural changes, we have explored the following pharmacomodulations:

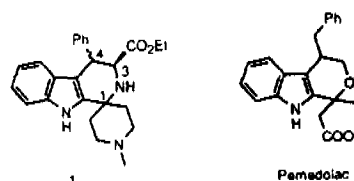
– replacement of the heterocyclic spiro system in **1** by carbocyclic or basic substituents,

- modification on the C-3 carboxylic function (amidification or esterification),
- incorporation of a second carboxylic group in position C-1 or C-3,
- change of configuration of the asymmetric carbons (C-1, C-3, C-4).

Some of these pharmacomodulations led to derivatives structurally related to the potent analgesic pemedolac [2, 3].

Chemistry

The 1,1-disubstituted 4-phenyltetrahydro- β -carbolines listed in tables I–III were prepared by the method shown in schemes 2–6. Chemically, a Pictet–Spengler cyclization [4] reaction was implied starting from the appropriately functionalized tryptophan derivatives. A β -phenyl substituent was incorporated by means of



Scheme 1.

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Table I. Physical data of 1,1-disubstituted tetrahydro- β -carboline derivatives.

Compound	Yield (%)	Mp ($^{\circ}$ C)	Solvent	IR ν (cm^{-1})	MS m/z (%) M^{+}	Formula ^b
6	69	198–199	Ether/ <i>n</i> -hexane	3380 1725 1705	475 (61) 417 (50) 402 (49)	$\text{C}_{28}\text{H}_{33}\text{N}_3\text{O}_4$ (475.57)
7	56	160 (dec)	EtOH	3390 1740 1625	509 (3) 481 (24) 409 (24)	$\text{C}_{20}\text{H}_{27}\text{N}_3\text{O}_5 \cdot 2\text{H}_2\text{O}$ (545.58)
1a,b^a	82	105–107	Ether/ <i>n</i> -hexane	3400 2955 1725	403 (26) 344 (88) 330 (10)	$\text{C}_{25}\text{H}_{29}\text{N}_3\text{O}_5 \cdot 2\text{H}_2\text{O}$ (421.53)
9b	21	193–194 (HCl)	EtOH	3390 2960 1720	362 (1) 333 (100) 259 (38)	$\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_2 \cdot \text{HCl}$ (398.91)
10b	34	147–148	EtOH	3395 2960 1730	362 (2) 333 (100) 259 (36)	$\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_2$ (362.46)
11b	9	170–172	Ether	3380 2975 1725	434 (23) 405 (81) 347 (85)	$\text{C}_{26}\text{H}_{30}\text{N}_2\text{O}_4$ (434.52)
12b	25	167–168	Ether	3370 2970 1725	434 (5) 405 (100) 347 (44)	$\text{C}_{26}\text{H}_{30}\text{N}_2\text{O}_4$ (434.52)
13b	60	190–192	H_2O	3210 1710 1625	378 (1) 334 (18) 333 (71)	$\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$ (414.45)
15a	62	210–214 (HCl)	MeOH/ether	3280 1710 1660 1620	490 (2) 364 (18) 336 (100)	$\text{C}_{31}\text{H}_{30}\text{N}_4\text{O}_2 \cdot \text{HCl}$ (527.06)
17a	15	161–164	Ether	3280 2930 1650	441 (12) 398 (11) 315 (100)	$\text{C}_{29}\text{H}_{35}\text{N}_3\text{O} \cdot 0.5 \text{H}_2\text{O}$ (450.51)
17b	40.5	149–151	Ether	3410 2930 1645	441 (14) 316 (25) 315 (98)	$\text{C}_{29}\text{H}_{35}\text{N}_3\text{O} \cdot (\text{C}_2\text{H}_5)_2\text{O}$ (515.41)
22a	18	251 (dec)	Ether	3320 3260 1650	436 (8) 435 (26) 392 (2) 315 (36)	$\text{C}_{29}\text{H}_{29}\text{N}_3\text{O}$ (435.55)
22b	37	221–222	Ether	3305 3280 1660	436 (22) 435 (72) 392 (15) 337 (30)	$\text{C}_{29}\text{H}_{29}\text{N}_3\text{O}$ (435.55)

^aDiastereomeric mixture; ^belemental analyses (C, H, N) were within $\pm 0.4\%$ of the theoretical values.

Table II. ¹H-NMR spectral data of 1,1-disubstituted tetrahydro-β-carbolines.

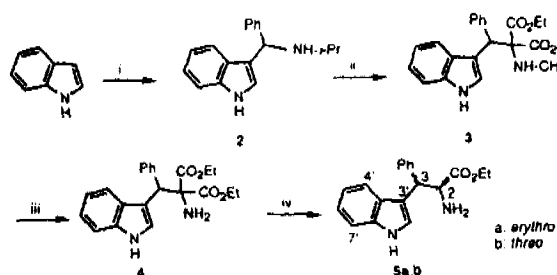
Compound	¹ H-NMR (CDCl ₃ , δ (relative to TMS as internal standard), J (Hz))
6	1.14 and 1.20 (t, <i>J</i> = 7.5, 2 × 3H, OCH ₂ CH ₃), 1.61–2.95 (m, 8H, piperidine-H), 2.05 (s, 1H, NH), 2.41 (s, 3H, N-CH ₃), 3.83, (dq, <i>J</i> ₁ = 10.5, <i>J</i> ₂ = 7.5, 1H, OCH ₂ CH ₃), 4.02 (dq, <i>J</i> ₁ = 10.5, <i>J</i> ₂ = 7.5, 2H, OCH ₂ CH ₃), 4.17 (dq, <i>J</i> ₁ = 10.5, <i>J</i> ₂ = 7.5, 1H, OCH ₂ CH ₃), 5.13 (s, 1H, H-4), 6.92–7.34 (m, 9H, aromatic), 8.91 (s, 1H, indole NH)
7	1.07 and 1.23 (t, <i>J</i> = 8, 2 × 3H, 2 × OCH ₂ CH ₃), 3.29 (s, 1H, NH), 3.79, 3.96, 4.08 and 4.32 (dq, <i>J</i> ₁ = 8, <i>J</i> ₂ = 5.5, 2 × 2H, OCH ₂ CH ₃), 5.40 (s, 1H, H-4), 6.58–7.61 (m, 13H, aromatic), 7.92 (s, 1H, isatin NH), 8.69 (s, 1H, indole NH)
1a,b ^a	1.01, (1.21) (t, <i>J</i> = 7.7, OCH ₂ CH ₃), 1.71–2.81 (m, 8H, piperidine-H), 2.42 (s, 3H, N-CH ₃), 3.66 (br d, <i>J</i> = 9, 1H, H-3), 4.04 (m, 2H, OCH ₂ CH ₃), (4.20) (dd, <i>J</i> ₁ = 12, <i>J</i> ₂ = 5, 1H, H-3), 4.23 (d, <i>J</i> = 9, 1H, H-4), (4.55) (d, <i>J</i> = 5, 1H, H-4), 5.25 (br s, 1H, NH), 6.53–7.38 (m, 9H, aromatic), (9.87), 9.81 (s, 1H, indole NH)
9b	1.03 (t, <i>J</i> = 7, 3H, CH ₂ CH ₃), 1.06 (t, <i>J</i> = 7, 3H, OCH ₂ CH ₃), 1.45 (s, 3H, CH ₃), 1.88 (qd, <i>J</i> ₁ = 27, <i>J</i> ₂ = 7, 2H, CH ₂ CH ₃), 1.93 (s, 1H, NH), 3.80 (d, <i>J</i> = 10, 1H, H-3), 4.05 (q, <i>J</i> = 7, 2H, OCH ₂ CH ₃), 4.25 (d, <i>J</i> = 10, 1H, H-4), 6.55 (d, <i>J</i> = 7, 1H, indole-H), 6.78 (t, <i>J</i> = 7, 1H, indole-H), 7.04 (t, <i>J</i> = 7, 1H, indole-H), 7.15–7.27 (m, 6H, phenyl, indole-H), 7.95 (s, 1H, indole NH)
10b	0.85 (t, <i>J</i> = 7, 3H, CH ₂ CH ₃), 1.02 (t, <i>J</i> = 7, 3H, OCH ₂ CH ₃), 1.55 (s, 3H, CH ₃), 1.88 (q, <i>J</i> = 7, 2H, CH ₂ CH ₃), 2.12 (br s, 1H, NH), 3.81 (d, <i>J</i> = 10, 1H, H-3), 4.02 (q, <i>J</i> = 7, 2H, OCH ₂ CH ₃), 4.23 (d, <i>J</i> = 10, 1H, H-4), 6.52 (d, <i>J</i> = 8, 1H, indole-H), 6.78 (t, <i>J</i> = 8, 1H, indole-H), 7.03 (t, <i>J</i> = 8, 1H, indole-H), 7.15–7.28 (m, 6H, phenyl, indole-H), 8.01 (s, 1H, indole NH)
11b	0.85 (t, <i>J</i> = 7.5, 3H, CH ₂ CH ₃), 1.01 (t, <i>J</i> = 7.5, 3H, OCH ₂ CH ₃), 1.26 (t, <i>J</i> = 7.5, 3H, OCH ₂ CH ₃), 1.90 (br s, 1H, NH), 2.05–2.31 (m, 2H, CH ₂ CH ₃), 2.92 (d, <i>J</i> = 16, 1H, CH ₂ CO ₂ Et), 3.08 (d, <i>J</i> = 16, 1H, CH ₂ CO ₂ Et), 3.73 (d, <i>J</i> = 9.5, 1H, H-3), 4.03 (q, <i>J</i> = 7.5, 2H, OCH ₂ CH ₃), 4.17 (q, <i>J</i> = 7.5, 2H, OCH ₂ CH ₃), 4.22 (d, <i>J</i> = 9.5, 1H, H-4), 6.50 (d, <i>J</i> = 8, 1H, indole-H), 6.78 (t, <i>J</i> = 8, 1H, indole-H), 7.02–7.28 (m, 7H, phenyl, indole-H), 8.89 (br s, 1H, indole NH)
12b	1.03 (t, <i>J</i> = 7, 3H, CH ₂ CH ₃), 1.05 (t, <i>J</i> = 7, 3H, OCH ₂ CH ₃), 1.20 (t, <i>J</i> = 7, 3H, OCH ₂ CH ₃), 2.05 (q, <i>J</i> = 7, 1H, CH ₂ CH ₃), 2.06 (q, <i>J</i> = 7, 1H, CH ₂ CH ₃), 2.28 (br s, 1H, NH), 2.75 (d, <i>J</i> = 16, 1H, CH ₂ CO ₂ Et), 2.91 (d, <i>J</i> = 16, 1H, CH ₂ CO ₂ Et), 3.78 (d, <i>J</i> = 10.5, 1H, H-3), 4.05 (q, <i>J</i> = 7, 2H, OCH ₂ CH ₃), 4.15 (q, <i>J</i> = 7, 2H, OCH ₂ CH ₃), 4.26 (d, <i>J</i> = 10.5, 1H, H-4), 6.52 (d, <i>J</i> = 7.5, 1H, indole-H), 6.78 (t, <i>J</i> = 7.5, 1H, indole-H), 7.06 (t, <i>J</i> = 7.5, 1H, indole-H), 7.16–7.32 (m, 6H, phenyl, indole-H), 9.28 (br s, 1H, indole NH)
15a ^b	0.55–1.75 (m, 10H, cyclohexane-H), 2.42 (br s, 1H, NH), 3.48 (m, 1H, CONH-cyclohexyl-H-1'), 4.84 (d, <i>J</i> = 5, 1H, H-3), 5.11 (d, <i>J</i> = 5, 1H, H-4), 6.21 (d, <i>J</i> = 9, 1H, CONH), 6.87 (d, <i>J</i> = 7.5, 1H, indole-H), 6.93 (t, <i>J</i> = 7.5, 1H, indole-H), 7.08–7.44 (m, 11H, phenyl, isatin, indole-H), 8.97 (br s, 1H, isatin NH), 9.48 (br s, 1H, indole NH)
17a	1.25–2.18 (m, 21 H, cyclohexane-H, NH), 3.67 (m, 1H, CONH-cyclohexyl-H-1'), 3.97 (dd, <i>J</i> ₁ = 4, <i>J</i> ₂ = 4, 1H, H-3), 4.93 (d, <i>J</i> = 4, 1H, H-4), 6.73 (d, <i>J</i> = 9, 1H, CONH-cyclohexyl), 6.95 (t, <i>J</i> = 7, indole-H), 7.10 (t, <i>J</i> = 7, 1H, indole-H), 7.17–7.27 (m, 6H, phenyl, indole-H), 7.32 (d, <i>J</i> = 7, 1H, indole-H), 8.15 (s, 1H, indole NH)
17b ^c	0.71–2.15 (m, 21 H, cyclohexane-H, NH), 3.42 (d, <i>J</i> = 9.2, 1H, H-3), 3.71 (m, 1H, CONH-cyclohexyl-H-1'), 4.29 (d, <i>J</i> = 9.2, H-4), 5.14 (d, <i>J</i> = 8.1, 1H, CONH-cyclohexyl), 6.57 (d, <i>J</i> = 7.5, 1H, indole-H), 6.78 (t, <i>J</i> = 7.5, 1H, indole-H), 7.02 (t, <i>J</i> = 7.5, 1H, indole-H), 7.18–7.31 (m, 6H, phenyl, indole-H), 8.07 (s, 1H, indole NH)
22a ^d	1.20–2.04 (m, 10H, cyclohexane-H), 2.38 (br d, <i>J</i> = 12, 1H, NH), 4.20 (dd, <i>J</i> ₁ = 12, <i>J</i> ₂ = 3.5, 1H, H-3), 4.68 (d, <i>J</i> = 3.5, 1H, H-4), 6.78–7.60 (m, 14H, phenyl, aniline, indole-H), 9.80 (s, 1H, CONH), 11.02 (s, 1H, indole NH)
22b ^d	1.25–2.28 (m, 11H, cyclohexane-H, NH), 3.78 (dd, <i>J</i> ₁ = 11, <i>J</i> ₂ = 9.4, 1H, H-3), 4.37 (d, <i>J</i> = 9.4, 1H, H-4), 6.38 (d, <i>J</i> = 7.5, 1H, indole-H), 6.67 (t, <i>J</i> = 7.5, 1H, indole-H), 6.95 (t, <i>J</i> = 7.5, 1H, indole-H), 7.04–7.55 (m, 11H, phenyl, aniline, indole-H), 9.73 (s, 1H, CONH), 10.93 (s, 1H, indole NH)

^aDiastereomeric mixture, signals in parentheses belong to the second diastereomer; ^bCDCl₃ + CD₃OD; ^cCDCl₃ + DMSO-*d*₆;^dDMSO-*d*₆.

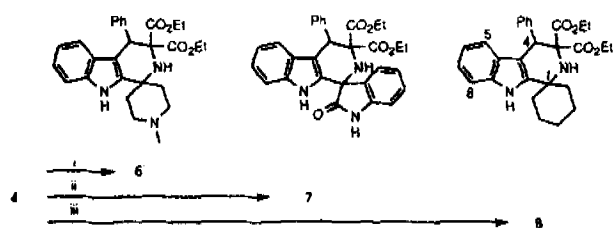
Table III. ^{13}C -NMR spectral data of 1,1-disubstituted tetrahydro- β -carbolines.

Compound	^{13}C -NMR (CDCl_3 , δ (relative to TMS as internal standard))
6	171.2 and 168.9 (CO), 140.0 (phenyl C-1'), 136.8* (C-9a), 136.4* (C-8a), 129.2** (phenyl C-2'), 127.9** (phenyl C-3'), 126.9 (phenyl C-4'), 126.4 (C-4b), 121.8 (C-7), 119.2 (C-6), 118.6 (C-5), 110.6 (C-8), 110.2 (C-4a), 69.1 (C-3), 61.6 and 61.5 (OCH_2CH_3), 50.8 (piperidine C-2'), 49.5 (C-1), 46.1 (N-CH_3), 42.3 (C-4), 39.9 (piperidine C-3'), 35.1 (piperidine C-3'), 13.7 and 13.6 (OCH_2CH_3)
7	178.5 (isatin CO), 170.2 and 168.8 (CO), 141.3* (C-9a), 140.1* (phenyl C-1'), 136.9 (C-9a), 130.5 (isatin C-7a'), 130.3 (isatin C-6'), 129.3 (phenyl C-2'), 128.6 (isatin C-3a'), 128.0 (phenyl C-3'), 127.1 (phenyl C-4'), 126.2 (C-4b), 125.2 (isatin C-5'), 123.2 (isatin C-4'), 122.7 (C-7), 119.6 (C-6), 119.2 (C-5), 113.2 (C-4a), 110.0 (C-8), 110.0 (isatin C-7'), 69.3 (C-3), 61.8 and 61.6 (OCH_2CH_3), 58.3 (C-1), 41.4 (C-4), 13.8 and 13.6 (CH_2CH_3)
1a,b ^a	171.6 (173.1) (CO), 140.1 (140.9) (phenyl C-1'), 140.0 (140.2) (C-9a), 136.3 (136.0) (C-8a), 128.6 (128.5) (phenyl C-2'), 128.1 (128.3) (phenyl C-3'), 126.9 (126.8) (phenyl C-4'), 126.2 (126.3) (C-4b), 121.7 (121.3) (C-7), 119.1 (119.8) (C-6), 118.3 (118.8) (C-5), 110.8 (110.7) (C-8), 110.2 (110.0) (C-4a), 57.4 (61.6) (C-3), 60.5 (60.4) (OCH_2CH_3), 50.8 (50.7), (piperidine C-2'), 50.4 (50.1) (piperidine C-2'), 50.0 (49.9) (C-1), 45.9 (NCH_3), 41.9 (46.4) (C-4), 38.1(37.6) (piperidine C-3'), 34.0 (34.8) (piperidine C-3'), 14.1 (13.7) (OCH_2CH_3)
9b	173.1 (CO), 141.1 (phenyl C-1'), 141.0 (C-9a), 135.7 (C-8a), 128.4* (phenyl C-2'), 128.3* (phenyl C-3'), 126.8 (phenyl C-4'), 126.4 (C-4b), 121.3 (C-7), 119.7 (C-6), 119.1 (C-5), 110.6 (C-8), 109.2 (C-4a), 61.9 (C-3), 60.6 (OCH_2CH_3), 53.0 (C-1), 46.0 (C-4), 33.7 (CH_2CH_3), 26.1 (CH_3), 13.8 (OCH_2CH_3), 8.7 (CH_2CH_3)
10b	173.1 (CO), 140.7 (phenyl C-1'), 139.5 (C-9a), 135.8 (C-8a), 128.7* (phenyl C-2'), 128.5* (phenyl C-3'), 126.8 (phenyl C-4'), 126.3 (C-4b), 121.2 (C-7), 119.8 (C-6), 119.0 (C-5), 110.6 (C-4a), 110.4 (C-8), 62.0 (C-3), 60.6 (OCH_2CH_3), 53.6 (C-1), 46.3 (C-4), 34.1 (CH_2CH_3), 28.0 (CH_3), 13.7 (OCH_2CH_3), 7.8 (CH_2CH_3)
11b	172.7 and 172.6 (CO), 140.7 (phenyl C-1'), 137.4 (C-9a), 135.9 (C-8a), 128.6* (phenyl C-2'), 128.3* (phenyl C-3'), 126.9 (phenyl C-4'), 125.9 (C-4b), 121.5 (C-7), 119.9 (C-6), 119.0 (C-5), 111.6 (C-4a), 110.7 (C-8), 61.7 (C-3), 60.8 and 60.6 (OCH_2CH_3), 54.7 (C-1), 46.3 (C-4), 44.7 ($\text{CH}_2\text{CO}_2\text{Et}$), 31.5 (CH_2CH_3), 14.1 and 13.9 (OCH_2CH_3), 7.8 (CH_2CH_3)
12b	172.8 and 172.1 (CO), 141.1 (phenyl C-1'), 139.0 (C-9a), 135.7 (C-8a), 128.5* (phenyl C-2'), 128.3* (phenyl C-3'), 126.8 (phenyl C-4'), 126.0 (C-4b), 121.4 (C-7), 119.9 (C-6), 118.9 (C-5), 110.8 (C-8), 109.9 (C-4a), 61.8 (C-3), 61.0 and 60.6 (OCH_2CH_3), 55.0 (C-1), 45.8 (C-4), 43.1 ($\text{CH}_2\text{CO}_2\text{Et}$), 31.4 (CH_2CH_3), 13.9 and 13.8 (OCH_2CH_3), 8.2 (CH_2CH_3)
15a ^b	178.5 (isatin CO), 170.6 (CO), 141.7* (phenyl C-1'), 139.5* (C-9a), 136.8 (C-8a), 130.7** (isatin C-7a'), 130.6** (isatin C-3a'), 130.2 (isatin C-6'), 129.3 (phenyl C-2'), 127.9 (phenyl C-3'), 126.8 (phenyl C-4'), 126.1 (C-4b), 124.5 (isatin C-5'), 122.9 (isatin C-4'), 122.3 (C-7), 119.3 (C-6), 118.7 (C-5), 114.3 (C-4a), 111.6*** (isatin C-7'), 111.0*** (C-8), 61.9 (C-1), 58.1 (C-3), 40.1 (C-4), 47.7, 32.5, 32.2, 25.2, 24.6, 24.5 (cyclohexane carbons)
17a	170.4 (CO), 141.7* (phenyl C-1'), 139.5* (C-9a), 136.1 (C-8a), 129.8** (phenyl C-2'), 127.9** (phenyl C-3'), 126.6 (phenyl C-4'), 126.5 (C-4b), 121.8 (C-7), 119.5 (C-6), 118.7 (C-5), 111.5 (C-4a), 110.7 (C-8), 58.6 (C-3), 54.3 (C-1), 39.8 (C-4), 47.2, 39.1, 34.4, 32.7, 32.6, 25.8, 25.5, 24.7, 24.4, 21.7, 21.4 (cyclohexane carbons)
17b	171.2 (CO), 142.6 (phenyl C-1'), 141.9 (C-9a), 135.7 (C-8a), 128.7* (phenyl C-2'), 128.4* (phenyl C-3'), 126.7 (C-4b), 126.6 (phenyl C-4'), 121.2 (C-7), 119.8 (C-6), 119.1 (C-5), 110.6 (C-8), 109.9 (C-4a), 62.8 (C-3), 52.0 (C-1), 45.2 (C-4), 47.8, 38.3, 36.2, 32.9, 32.8, 25.8, 25.4, 24.7, 24.6, 21.4, 21.0 (cyclohexane carbons)
22a ^c	169.5 (CO), 142.7* (phenyl C-1'), 140.9* (C-9a), 138.7 (aniline C-1'), 136.2 (C-8a), 129.1 (phenyl C-3'), 128.7** (phenyl C-2'), 127.8** (aniline C-3'), 126.4 (phenyl C-4'), 126.1 (C-4b), 123.4 (aniline C-4'), 120.8 (C-7), 119.8 (aniline C-2'), 118.5 (C-6), 117.7 (C-5), 111.2 (C-8), 109.1 (C-4a), 58.0 (C-3), 52.6 (C-1), 41.3 (C-4), 38.2, 34.1, 25.5, 21.4, 21.0 (cyclohexane carbons)
22b ^c	171.0 (CO), 143.0* (phenyl C-1'), 142.4* (C-9a), 139.0 (aniline C-1'), 135.9 (C-8a), 128.7** (phenyl C-3'), 128.6** (aniline C-3'), 128.2** (phenyl C-2'), 126.4 (phenyl C-4'), 126.3 (C-4b), 123.3 (aniline C-4'), 120.2 (C-7), 119.4 (aniline C-2'), 118.9 (C-6), 118.0 (C-5), 111.1 (C-8), 108.5 (C-4a), 62.5 (C-3), 52.4 (C-1), 44.5 (C-4), 37.1, 35.1, 25.6, 21.4, 20.8 (cyclohexane carbons)

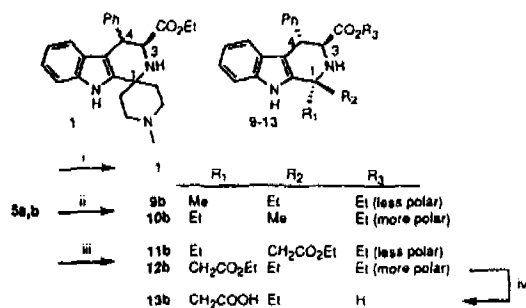
^aDiastereomeric mixture, signals in parentheses belong to the second diastereomer; ^b CDCl_3 + CD_3OD ; ^c $\text{DMSO}-d_6$; *, ** interchangeable carbons.



Scheme 2. Reagents: i: *N*-benzylidene-*L*-propylamine; ii: $\text{OCHNHCH}(\text{CO}_2\text{Et})$; iii: HCl/ether ; iv: NaOH , EtOH/water , H^+ then Δ .

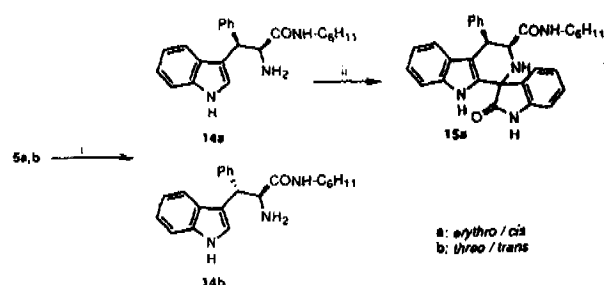


Scheme 3. Reagents: i: 1-methyl-4-piperidone, AcOH ; ii: isatin, AcOH ; iii: cyclohexanone, AcOH .

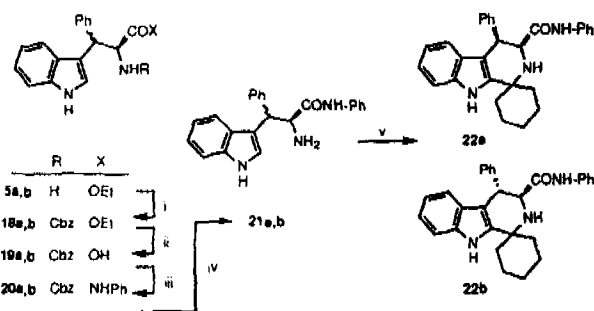


Scheme 4. Reagents: i: 1-methyl-4-piperidone, AcOH ; ii: methylethylketone, AcOH ; iii: ethyl-3-oxovalerate, AcOH ; iv: NaOH , EtOH/water .

'gramine chemistry' [5] known for this kind of reaction since the findings of Snyder *et al* [6, 7]. The transformation of 3 into β -phenyltryptophan was performed in two steps: partial hydrolysis followed by decarboxylation to give 5a,b as an equimolar diastereomeric mixture (scheme 2). It is worth noting that other approaches leading to diastereomerically [8] or enantiomerically [9] pure *threo* β -substituted tryptophan esters have also been published.



Scheme 5. Reagents: i: cyclohexylamine, sealed tube; ii: isatin, AcOH ; iii: LiCl , DMSO/water .



Scheme 6. Reagents: i: $\text{ClCO}_2\text{CH}_2\text{Ph}$, pyridine; ii: NaOH , MeOH/water ; iii: *N,N'*-carbonyl diimazole, aniline; iv: Pd/C , HCO_2NH_4 ; v: cyclohexanone, AcOH .

Condensation of 4 with 1-methyl-4-piperidone, isatin or cyclohexanone in acetic acid led smoothly to the corresponding cyclized compounds 6, 7 and 8, respectively (scheme 3). Similarly, on heating 5a,b in acetic acid in the presence of 1-methyl-4-piperidone, methylethyl ketone or ethyl-3-oxovalerate the expected Pictet-Spengler cyclization occurred giving the diastereomeric mixture of 1a/b, 9b/10b or 11b/12b, respectively (scheme 4). Separation of diastereomers by flash chromatography followed by NMR spectral analysis suggested a C-3/C-4 relative *trans* configu-

Table IV. Analgesic properties for the tested compounds.

Compound	Sigmund ^a PBQ (mice) (%)	<i>i</i> ^b	Koster ^c AA (rat) (%)	<i>i</i> ^b
1a,b	21	0.38	0	0
6	46*	0.83	0	0
7	47*	0.85	58*	0.75
9b	0	0	23	0.33
10b	45*	0.80	26	0.36
11b	17	0.30	17	0.23
12b	25	0.44	28	0.39
13b	2	0.03	0	0
15a	44*	0.80	62*	0.81
17a	11	0.20	30	0.39
17b	55**	1.00	20	0.26
22a	57**	1.19	49**	0.69
22b	30	0.62	56**	0.79

p* < 0.01, *p* < 0.001; ^aPBQ writhing, inhibition in % at 50 mg/kg *po*; ^bindex relative to aspirin; ^cacetic-acid-induced writhing, inhibition in % at 50 mg/kg *po*.

ration for diastereomers (9b, 10b, 11b and 12b), based upon a one-proton doublet (*J* = 9.5–10 Hz) at δ 4.22–4.26 ppm, attributed to H-4. Assignment of the stereochemistry of the C-1 carbon using ¹³C-NMR [10, 11] or mass fragmentation data [12] failed owing to the non-significant differences. However, 1,3-relative stereochemistry could be evidenced from the characteristic chemical shifts of the methyl protons of the ethyl group attached to C-1. Thus, in 10b and 11b an Et(C-1)/H(C-3) relative *cis* configuration was assigned on the basis of the chemical shift (δ 0.85 ppm) of the methyl protons of the ethyl group being in axial position, in the shielding zone of the indole ring system. For the same reason the three-proton triplet at δ 1.03 ppm in 9b and 12b corroborated with opposite (*trans*) 1,3-stereochemistry.

Saponification of the more polar (major) diastereomer 12b afforded acid 13b, which can be regarded as a structural analog of pemedolac (scheme 1) [2, 3].

With the aim of exploring the C-3 function, the preparation of sterically hindered carboxamides has also been envisaged (scheme 5). Direct aminolysis of the diastereomeric mixture 5a,b using cyclohexylamine in a sealed tube at 160°C led to the separable cyclohexylamides 14a (less polar) and 14b (more polar) in low yields (6 and 11%, respectively). Better overall yields (12.6 and 34% for 17a (less polar) and 17b (more polar)) could be achieved by using Pictet-Spengler cyclization of 4 with cyclohexanone followed by a Krapcho [13] decarboxylation–aminolysis sequence (4 → 8 → 16 → 17).

Determination of the relative stereochemistry of 17a (less polar) and 17b (more polar) has been

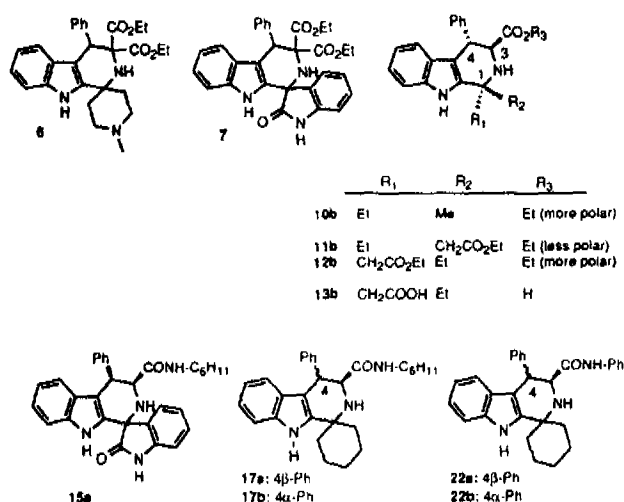
accomplished on the basis of their reactivity. Thus following the cyclization between a diastereomeric mixture 14a,b and cyclohexanone by TLC revealed a difference of reactivity in favour of the less polar 14b leading to the *trans* spiro derivative 17b.

The preparation of diastereomeric anilides 22a,b required a more laborious procedure involving an N₆-protection by benzyloxycarbonylation (Cbz) of 5a,b (scheme 6). Exposure of 19a,b to 1,1'-carbonyldiimidazole [14] and aniline led directly to 20a,b which was then deprotected [15] under hydrogen transfer conditions (Pd/C, HCOONH₄). Final cyclization between 21a,b and cyclohexanone completed the sequence. It is interesting to note that cyclizations starting from an equimolar mixture of 5a,b in acetic acid led exclusively (9–12) to the thermodynamically more stable C-3/C-4 relative *trans* diastereomers (*J*_{3,4} = 9.5–11 Hz).

Results and discussion

All the synthesized compounds were prescreened for analgesic activity at a standard dose of 50 mg/kg *per os* using the phenylquinone (PBQ) and acetic-acid writhing tests. The results were also expressed as an activity ratio *versus* aspirin to correct for slight variations in response between the same evaluation procedures, not performed simultaneously (table IV).

Prescreenings confirmed the lack of activity *via per os* administration of 1a,b: 21 and 0% of inhibition, in PBQ and acetic-acid, respectively, writhing tests *via per os* administration vs 100% in the PBQ writhing test *via ip* administration.



Scheme 7.

The analgesic activity of **1a,b** *via* ip administration was also confirmed in the hot-plate test in mice where this compound showed a significant increase in foot-licking latency (+112% $p < 0.01$, 64 mg/kg ip). In order to investigate possible mechanisms of action, binding studies were performed with **1a,b** and showed an absence of affinity for the opioid μ , δ and κ receptors.

Prescreening evaluation of some compounds also showed a marked difference in analgesic activity *via per os* administration between the tests performed in rats and in mice. Analgesic potency of **6**, **10b** and **17b** (scheme 7) was found to be higher in mice than in rats, with inhibitions of 46, 45 and 55% in mice *versus* 0, 26 and 20% in rats, respectively. Such a difference could be explained by a better absorption in mice or by a different metabolism between the two species.

As regards the structure-activity relationships, prescreening revealed the following. Firstly, the influence of the relative configuration of C-3/C-4 positions remained unclear. The difference in activity between the *cis* and *trans* isomers was sometimes contradictory depending on the nature of the substituent and the animal species. In mice **22a** was more active (57% inhibition) than its *trans* isomer **22b** (30% inhibition). In contrast, *cis* **17a** was less active (11% inhibition) than its isomer **17b** (55% inhibition).

Secondly, introduction of a second ester group in position C-3 in **6** resulted in a marked enhancement of analgesic activity in mice (46% inhibition) compared with the monoester analogue **1a,b**. Substitution at C-1 carbon with an additional ester group (**12b**, **11b**) or

Table V. Antiinflammatory properties.

Compound	Inhibition (%) of PGE ₂	Inhibition (%) of LTB ₄
1a,b	21 ± 8	71 ± 1
6	29 ± 8	78 ± 3
17b	-39 ± 8	18 ± 5
NDGA		97 ± 2
Ibuprofen	77 ± 3	

with a carboxylic function (**13b**) had no significant influence on activity compared with the parent monoester derivative **10b**.

Finally, replacement of the carbocyclic spiro system in **17a** by a heterocyclic appendage **15a**, without any other modification, resulted in an increased analgesic potency.

This prescreening procedure allowed the selection of four compounds **22a**, **22b**, **15a** and **7** as markedly more active than **1a,b** *via per os* administration. Unfortunately, none of these derivatives was found to be as potent as pemedolac.

Three of the synthesized compounds, **6**, **1a,b** and **17b** were also tested for antiinflammatory activity and their inhibition was evaluated *in vitro* on 5-lipoxygenase and cyclooxygenase (table V). Spiro-piperidine derivatives **1a,b** and **6** displayed significant activity on 5-lipoxygenase with inhibition values of 71 ± 1% and 78 ± 3% at 10⁻⁵ M, respectively.

Experimental protocols

Chemistry

Melting points were determined on a Reichert melting point apparatus and are uncorrected. IR spectra (ν , cm⁻¹) were recorded on a Bomem FTIR apparatus and a Cosmic interferometer; UV spectra were recorded on a Varian 634 spectrophotometer; ¹H- and ¹³C-NMR spectra were measured on a Bruker AC 300 apparatus at 300 MHz and 75 MHz, respectively. Mass spectra ($E = 70$ eV) were obtained on a Jeol JMS D-300 spectrometer; Kieselgel 60 PGF254 (Merck N° 7749) was used for thin-layer chromatography and Kieselgel 60 (Merck N° 9385) for flash chromatography.

Analyses indicated by the symbols of the elements were within ± 0.4% of theoretical values.

The 'A-type' extraction protocol involved evaporation of the acetic acid alkalization of the residue with 10% Na₂CO₃, extracted with CH₂Cl₂ (3 × 10–20 ml). The combined organic layers were washed with water (5 ml), dried over MgSO₄, filtered off and evaporated to dryness.

The 'B-type' extraction protocol involved evaporation of the solvent (t_{bath} 25–30°C). The residue was dissolved in water and extracted with ether (3 × 5 ml). The aqueous layer was partially evaporated to remove ether and acidified with AcOH to pH 4–5 with cooling.

N-Benzylidene-*i*-propylamine

To ice-cooled *i*-propylamine (15.4 g, 0.26 mol), freshly distilled benzaldehyde (27.6 g, 0.26 mol) was added dropwise over 2 h. After 30 min stirring at 0°C, water was eliminated by addition of KOH pellets, subsequent stirring and separation. The organic phase was allowed to stand at 0°C on KOH pellets overnight. It was then filtered and distilled from KOH under reduced pressure. Yield: 30.7 g (80%), colourless oil, bp 90–92°C/20 Torr. $n_D^{25} = 1.5268$. IR (film) ν 1648 cm⁻¹. ¹H-NMR (CDCl₃) δ 1.25 (d, $J = 6.8$ Hz, 6H, CH₃), 3.51 (m, 1H, CH(CH₃)₂), 7.31–7.75 (m, 5H, aromatic), 8.24 (s, 1H, PhCH=N).

N-[(3-indolyl)phenylmethyl]-*i*-propylamine 2

To a solution of *N*-benzylidene-*i*-propylamine (15.0 g, 0.102 mol) in benzene (20 ml) was added an acetic acid (60 ml) solution of indole (10.0 g, 0.085 mol) dropwise at 0°C, over 5 h period. The stirring was continued at 0°C for further 2 h. The main part of the solvent was evaporated *in vacuo* (t_{bath} 20°C) and the remaining reaction mixture was poured into 400 ml ice-water and 100 ml ether. After separation the aqueous layer was extracted with ether (2 x 100 ml), cooled to 0°C and made basic (pH 10–11) with 35% NaOH solution. The precipitate was extracted with CH₂Cl₂ (3 x 60 ml), and the combined extracts were dried (MgSO₄) and evaporated to dryness to afford 2 (10.8 g, 48%) as a light-yellow viscous oil. IR (film) ν 3405, 1610 cm⁻¹. ¹H-NMR (CDCl₃) δ 1.07 (d, $J = 7$ Hz, 3H, CH₃), 1.15 (d, $J = 7$ Hz, 3H, CH₃), 1.65 (br s, 1H, NH), 2.83 (m, 1H, CH(CH₃)₂), 5.26 (s, 1H, Ar₂CH-NH), 6.78 (d, $J = 2.8$ Hz, 1H, indole H-2), 7.01–7.23 (m, 3H), 7.18 (d, $J = 7$ Hz, 1H), 7.28 (dd, $J_1 = 7$, $J_2 = 8$ Hz, 2H), 7.45 (d, $J = 6$ Hz, 2H), 7.61 (d, $J = 8$ Hz, 2H, indole H-4), 8.08 (s, 1H, indole NH). ¹³C-NMR (CDCl₃) δ 144.3 (phenyl C-1'), 136.5 (C-7a), 128.2* (phenyl C-2'), 127.5* (phenyl C-3'), 126.7 (phenyl C-4'), 126.2 (C-3a), 122.2 (C-2), 121.9 (C-6), 119.9 (C-3), 119.3 (C-5), 119.2 (C-4), 111.2 (C-7), 57.0 (CH-Ph), 46.2 (CH(CH₃)₂), 22.7 and 23.7 (CH₃). MS m/z (%) 264 (M⁺, 2), 206 (100), 187 (9).

Diethyl (3-indolyl)phenylmethylformamidomalonate 3

A mixture of 2 (6.90 g, 26.1 mmol) and diethyl-*N*-formylamino-malonate (5.53 g, 27.2 mmol), dissolved in 100 ml of dry toluene, was heated at 90°C in the presence of potassium *tert*-butoxide (0.30 g, 2.68 mmol). A slow stream of nitrogen was bubbled through the reaction mixture to eliminate the cleaved *i*-propylamine. After the completion (24–30 h) the reaction mixture was diluted with toluene (100 ml), washed with water (10 ml), dried (MgSO₄) and evaporated to dryness. The residue was crystallized from ether to give 3 (6.4 g, 60%), as white crystals, mp 110–112°C (ether). IR (KBr) ν 3410, 1730, 1685 cm⁻¹. ¹H-NMR (CDCl₃) δ 0.88–1.28 (m, 6H OCH₂CH₃), 3.81–4.23 (m, 4H, OCH₂CH₃), 5.62 and 5.75 (s, 1H, CH-Ph), 6.85–7.65 (m, 11H, phenyl, indole, NH), 8.03 (d, $J = 8$ Hz, 1H, CHO), 8.43 (br s, 1H, indole NH). ¹³C-NMR (CDCl₃) δ 167.5 (167.1) (CO), 166.9 (166.8) (CO), 139.0 (138.0) (phenyl C-1'), 135.4 (135.2) (C-7a), 130.2* (129.9) (phenyl C-2'), 128.7* (128.5) (phenyl C-3'), 127.6 (126.8) (phenyl C-4'), 127.3 (C-3a), 123.6 (122.8) (C-2), 122.3 (121.9) (C-6), 119.5 (119.3) (C-5), 118.8 (C-4), 113.5 (112.3) (C-3), 70.9 (69.3) (CH(CO₂Et)₂), 63.3 (63.2) (OCH₂), 62.6 (62.3) (OCH₂), 46.9 (46.2) (CH-Ph), 13.7 (13.6) (CH₃), 13.3 (CH₃). Signals in parentheses are due to the other amide rotamer. MS m/z (%) 408 (M⁺, 1), 363 (2), 206 (100).

Diethyl (3-indolyl)phenylmethylaminomalonate 4

To a solution of 3 (5.0 g, 12.2 mmol) in ethanol (135 ml) was added 16 ml saturated HCl/ether solution. The reaction mixture

was kept at room temperature for 24 h. After evaporation the residue was alkalized with saturated NaHCO₃ and extracted with CH₂Cl₂ (3 x 50 ml). The organic layers were dried (MgSO₄), evaporated to dryness and crystallized from ether to give 4 (3.76 g, 81%), mp 99–101°C (ether). IR (KBr) ν 3380, 1720, 1705 cm⁻¹. ¹H-NMR (CDCl₃) δ 0.85 (t, $J = 7.5$ Hz, 3H, OCH₂CH₃), 1.21 (t, $J = 7.5$ Hz, 3H, OCH₂CH₃), 2.41 (br s, 2H, NH₂), 3.95 (q, $J = 7.5$ Hz, 2H, OCH₂), 4.15 (q, $J = 7.5$ Hz, 2H, OCH₂), 5.47 (s, 1H, CH-Ph), 6.97–7.75 (m, 10H, indole, phenyl), 8.21 (s, 1H, indole NH). ¹³C-NMR (CDCl₃) δ 170.9 and 170.1 (CO), 139.5 (phenyl C-1'), 135.4 (C-7a), 129.7* (phenyl C-2'), 128.0* (phenyl C-3'), 127.6 (C-3a), 126.9 (phenyl C-4'), 123.4 (C-2), 121.7 (C-6), 119.1 (C-5), 118.8 (C-4), 114.8 (C-3), 110.8 (C-7), 70.9 (CNH₂), 62.2 and 62.0 (OCH₂), 13.9 and 13.4 (CH₃). MS m/z (%) 380 (M⁺, 2), 234 (2), 206 (100). Anal calc for C₂₂H₂₄N₂O₄ (380.43): C, 69.45; H, 6.36; N, 7.36; found: C, 69.17; H, 6.46; N, 7.27.

(2S*,3R* and 2S*,3S*)-Ethyl 2-amino-3-(3'-indolyl)-3-phenylpropionate 5a,b

To a solution of 4 (3.0 g, 7.9 mmol) in EtOH (30 ml) water (7 ml), was added a solution of 35% NaOH (0.72 ml, 8.7 mmol) and the mixture was left to stand at room temperature for 24–48 h. The precipitate, resulting from the 'B-type' extraction protocol was filtered off, washed with water and dried in air. The solid was suspended in CH₂Cl₂ (20 ml) and EtOH (10 ml) and refluxed for 1–2 h, and then the solvent was removed under reduced pressure to afford 5a,b (1.51 g, 62%), as a viscous oil (diastereomeric mixture 1:1). IR (film) ν 3410, 1730 cm⁻¹. ¹³C-NMR (CDCl₃) δ 174.7 (174.3) (CO), 142.8 (142.0) (phenyl C-1'), 136.3 (136.1) (C-7a'), 129.0* (128.5) (phenyl C-3'), 128.8 (127.5) (C-3a'), 128.2* (128.1) (phenyl C-2'), 126.5 (126.4) (phenyl C-4'), 122.9 (122.7) (C-2'), 121.1 (121.0) (C-6'), 118.6 (118.5) (C-5'), 118.5 (118.4) (C-4'), 115.6 (114.3) (C-3'), 111.5 (111.4) (C-7'), 60.0 (59.9) (OCH₂), 59.3 (58.9) (CNH₂), 48.0 (46.9) (CHPh), 14.0 (13.9) (CH₃). MS m/z (%) 308 (M⁺, 2), 279 (2), 207 (58), 206 (100).

In order to determine the relative stereochemistry, the two diastereomers were separated by flash chromatography (eluent: CH₂Cl₂/MeOH 97:3). 5a (more polar) ¹H-NMR (CDCl₃) δ 0.98 (t, $J = 7.6$ Hz, 3H, OCH₂CH₃), 1.70 (s, 2H, NH₂), 3.95 (q, $J = 7.6$ Hz, 2H, OCH₂CH₃), 4.23 (d, $J = 8.5$ Hz, 1H, CHCO₂Et), 4.65 (d, $J = 8.5$ Hz, 1H, CHPh), 7.0–7.47 (m, 10H, aromatic), 8.35 (s, 1H, indole NH). 5b (less polar) ¹H-NMR (CDCl₃) δ 1.05 (t, $J = 7.6$ Hz, 3H, OCH₂CH₃), 1.60 (s, 2H, NH₂), 4.03 (q, $J = 7.6$ Hz, 2H, OCH₂CH₃), 4.22 (d, $J = 6.7$ Hz, 1H, CHCO₂Et), 4.68 (d, $J = 6.7$ Hz, 1H, CHPh), 6.95–7.41 (m, 10H, aromatic), 8.37 (s, 1H, indole NH).

3,3-Diethoxycarbonyl-1'-methyl-4-phenyl-1,2,3,4-tetrahydro-spiro[β -carboline-1,4'-piperidine] 6

A solution of amine 4 (0.45 g, 1.18 mmol) and 1-methyl-4-piperidone (0.14 g, 152 μ l, 1.24 mmol) in acetic acid (3 ml) was left to stand at room temperature under nitrogen for 36 h. After 'A-type' extraction the residue was crystallized from ether/*n*-hexane to give 6 (0.39 g, 69%). For physical data, see tables I–III.

3,3-Diethoxycarbonyl-2'-oxo-4-phenyl-1,2,2',3,3',4'-hexahydro-spiro[β -carboline-1,3'-1H-indole] 7

Amine 4 (0.40 g, 1.05 mmol) and isatin (0.17 g, 1.15 mmol) were heated in acetic acid (8 ml) at 80°C under nitrogen for 15 h. The residue resulting from an 'A-type' extraction was crystallized from ethanol to obtain 7 (0.30 g, 56%). For physical data, see tables I–III.

3,3-Diethoxycarbonyl-4-phenyl-1,2,3,4-tetrahydrospiro[β -carboline-1,1'-cyclohexane] 8

A solution of **4** (1.52 g, 4.0 mmol) and cyclohexanone (0.60 g, 0.63 ml, 6.1 mmol) in acetic acid (7 ml) was left to stand at room temperature under nitrogen for 72 h. After 'A-type' extraction the residue was crystallized from ether to afford **8** (1.59 g, 86%) as white crystals, mp 249–251°C. IR (KBr) ν 3410, 2920, 1725 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ 1.12 and 1.22 (t, J = 7 Hz, 2 $\times$ 3H, OCH_2CH_3), 1.31–2.12 (m, 10H, cyclohexane protons), 2.85 (br s, 1H, NH), 3.78–4.25 (m, 4H, OCH_2CH_3), 5.09 (s, 1H, H-4), 6.89–7.38 (m, 9H, aromatic), 7.81 (s, 1H, indole NH). $^{13}\text{C-NMR}$ (CDCl_3) δ 171.6 and 169.1 (CO), 140.2 (phenyl C-1'), 138.1 (C-2), 136.2 (C-8a), 129.3* (phenyl C-2'), 127.8* (phenyl C-3'), 126.9 (phenyl C-4'), 126.6 (C-4b), 121.6 (C-7), 119.3 (C-6), 118.6 (C-5), 110.5 (C-8), 109.7 (C-4a), 69.2 (C-3), 61.5 and 61.4 (OCH_2), 51.8 (C-1), 42.4 (C-4), 40.6, 35.6, 25.5, 21.5, 21.4 (cyclohexane carbons). MS m/z (%) 460 (M^+ , 20), 417 (23), 387 (31), 287 (35), 206 (100). Anal calc for $\text{C}_{28}\text{H}_{32}\text{N}_2\text{O}_4$ (460.56): C, 73.01; H, 7.00; N, 6.08; found: C, 72.69; H, 6.57; N, 5.97.

(3S*, 4R* and 3S*, 4S*)-3-Ethoxycarbonyl-1'-methyl-4-phenyl-1,2,3,4-tetrahydrospiro[β -carboline-1,4'-piperidine] 1a,b
Amine **5a,b** (0.37 g, 1.20 mmol) and 1-methyl-4-piperidone (0.15 g, 163 μl , 1.32 mmol) were reacted in acetic acid (3 ml) solution at room temperature for 48 h. After 'A-type' extraction, the residue was solidified with hexane to give **1a,b** (0.41 g, 82%) as a white solid. For physical data see tables I–III.

General method for the preparation of 1,1-disubstituted 4-phenyl-tetrahydro- β -carboline derivatives 9–12

A mixture of **5a,b** (0.60 g, 1.95 mmol) and the corresponding ketone (1.1 mmol) in acetic acid (5 ml) was heated at 60–90°C for 4–6 h. The residue, obtained after an 'A-type' extraction was purified by flash chromatography (eluent: cyclohexane/ethylacetate 5:1 to 2:1).

(1S*, 3S*, 4S* and 1R*, 3S*, 4S*)-3-Ethoxycarbonyl-1-ethyl-1-methyl-4-phenyl-1,2,3,4-tetrahydro- β -carboline 9b and 10b. **9b** (less polar): 0.15 g (21%). UV (MeOH) 215, 280, 290 nm. For other physical data, see tables I–III. **10b** (more polar): 0.24 g (34%). UV (MeOH) 215, 280, 290 nm. For the other physical data, see tables I–III.

(1S*, 3S*, 4S* and 1R*, 3S*, 4S*)-3-Ethoxycarbonyl-1-ethoxycarbonylmethyl-1-ethyl-4-phenyl-1,2,3,4-tetrahydro- β -carboline 11b and 12b. **11b** (less polar): 75 mg (9%), amorphous solid. UV (MeOH) 222, 280, 293 nm. For other physical data see tables I–III. **12b** (more polar): 0.21 g (25%). UV (MeOH) 220, 280, 295 nm. For the other physical data, see tables I–III.

(1R*, 3S*, 4S*)-(1-Carboxymethyl-1-ethyl-4-phenyl-1,2,3,4-tetrahydro- β -carbolin-3-yl)carboxylic acid 13b

To a solution of **12b** (0.25 g, 0.57 mmol) in EtOH (5 ml), a solution of NaOH (60 mg, 1.5 mmol) in water (1 ml) was added. The reaction mixture was allowed to stand at room temperature for 72 h. The precipitate, resulting from a 'B-type' extraction procedure was extracted with CH_2Cl_2 (3 $\times$ 10 ml), the organic layers were dried (MgSO_4), filtered off and evaporated to dryness to obtain **13b** (0.13 g, 60%) as a pale yellow solid. UV (MeOH) 220, 275, 294 nm. For other physical data, see table I.

(2S*, 3R* and 2S*, 3S*)-2-Amino-3-(3'-indolyl)-4-phenyl-N-cyclohexylpropionamide 14a and 14b

A diastereomeric mixture of **5a,b** (0.90 g, 2.92 mmol) in MeOH (6 ml) and cyclohexylamine (5.94 g, 60 mmol) was

heated in a sealed tube at 160°C for 72 h. After evaporation of the solvent the residue was purified by repeated column chromatography (eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 98:2) to obtain the two diastereomeric amides.

14a (less polar): white crystals (0.12 g, 11%). mp 128–131°C (ether). IR (KBr) ν 3390, 2945, 1645 cm^{-1} . $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ 0.95–1.86 (m, 10H, cyclohexane protons), 3.43 (br m, 3H, NH_2 , cyclohexane H-1'), 3.96 (d, J = 7 Hz, 1H, CHCONH), 4.56 (d, J = 7 Hz, 1H, CHPh), 6.98 (t, J = 8 Hz, 1H, indole-H), 7.02 (t, J = 8 Hz, 1H, indole-H), 7.12–7.71 (m, 7H, phenyl, indole-H), 10.89 (s, 1H, indole NH). $^{13}\text{C-NMR}$ ($\text{DMSO}-d_6$) δ 172.8 (CO), 142.4 (phenyl C-1'), 136.0 (C-7a), 129.0 (phenyl C-2'), 128.0 (phenyl C-3'), 127.0 (C-3a), 126.1 (phenyl C-4'), 122.7 (C-2), 120.9 (C-6), 118.7 (C-5), 118.2 (C-4), 115.9 (C-3), 111.2 (C-7), 58.8 (CHCONH-cyclohexyl), 46.7 (CHPh), 47.1, 32.4, 32.3, 25.3, 24.6, 24.5 (cyclohexane carbons). MS m/z (%) 362 (M^+ + 1, 2), 361 (M^+ , 1), 344 (8), 235 (18). Anal calc for $\text{C}_{23}\text{H}_{27}\text{N}_3\text{O}$ (361.48): C, 76.42; H, 7.53; N, 11.63; found: C, 76.79; H, 7.90; N, 11.32.

14b (more polar): white powder (60 mg, 6%). mp 150–153°C (ether). IR (KBr) ν 3405, 2935, 1640 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ 0.78–1.78 (m, 10H, cyclohexane protons), 1.91 (br s, 2H, NH_2), 3.58 (m, 1H, cyclohexane H-1'), 3.94 (d, J = 6.5 Hz, 1H, CHCONH), 4.84 (d, J = 6.5 Hz, 1H, CHPh), 6.49 (d, J = 8 Hz, 1H, CONH), 6.98 (t, J = 7 Hz, 1H, indole-H), 7.05–7.35 (m, 8H, phenyl, indole-H), 7.39 (d, J = 7 Hz, indole-H), 8.91 (s, 1H, indole NH). $^{13}\text{C-NMR}$ (CDCl_3) δ 172.3 (CO), 142.1 (phenyl C-1'), 136.4 (C-7a), 128.4 (phenyl C-2'), 128.2 (phenyl C-3'), 127.5 (C-3a), 126.5 (phenyl C-4'), 122.6 (C-2), 121.9 (C-6), 119.6 (C-5), 119.3 (C-4), 114.2 (C-3), 111.2 (C-7), 60.2 (CHCONH-cyclohexyl), 47.1 (CHPh), 47.6, 32.6, 32.5, 24.8, 24.6, 25.4 (cyclohexane carbons). MS m/z (%) 361 (M^+ , 1), 344 (4), 235 (21). Anal calc for $\text{C}_{23}\text{H}_{27}\text{N}_3\text{O} \cdot \text{H}_2\text{O}$ (379.49): C, 72.79; H, 7.70; N, 11.07; found: C, 72.89; H, 7.83; N, 11.01.

(3S*, 4R*)-3-Cyclohexylaminocarbonyl-2'-oxo-4-phenyl-1,2,2',3,3',4'-hexahydrospiro[β -carboline-1,3'-1H-indole] 15a

A mixture of **14a** (110 mg, 0.304 mmol) and isatin (50 mg, 0.34 mmol) in acetic acid (3 ml) was heated under argon at 80°C for 17 h. The residue after an 'A-type' extraction protocol was purified by preparative TLC (eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95:5) to give **15a** (93 mg, 62%), as a pale orange solid. UV (MeOH) 215, 225, 265, 285, 295 nm. For other physical data, see tables I–III.

(3S*, 4R* and 3S*, 4S*)-3-Cyclohexylaminocarbonyl-4-phenyl-1,2,3,4-tetrahydrospiro[β -carboline-1,1'-cyclohexane] 17a and 17b

A mixture of **8** (1.57 g, 3.41 mmol), lithium chloride (0.145 g, 3.41 mmol) and water (0.123 ml, 6.82 mmol) in DMSO (5 ml) was heated under nitrogen at 180°C for 7 h. It was then poured into ice-water (50 ml), stirred and the precipitate was filtered off. The solid was dissolved in CH_2Cl_2 (50 ml), washed with water (15 ml), dried (MgSO_4) and evaporated under reduced pressure to obtain a diastereomeric mixture **16a,b** (1.30 g, 98%) as a light-brown solid.

In order to characterize the diastereomers, a portion of the mixture was separated by TLC (eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 99:1) to obtain **16a** (less polar) and **16b** (more polar) in a 2:3 ratio.

16a (less polar): IR (KBr) ν 3400, 2935, 1725 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ 1.19 (t, J = 7.5 Hz, 3H, OCH_2CH_3), 1.45–2.10 (m, 11H, cyclohexane protons, NH), 4.04 (dd, J_1 = 7.5, J_2 = 8.2 Hz, 2H, OCH_2CH_3), 4.27 (dd, J_1 = 4.8, J_2 = 9 Hz, 1H, H-3), 4.54 (d, J = 4.8 Hz, 1H, H-4), 6.92 (t, J = 7.6 Hz, 1H, indole-H), 7.11 (t, J = 7.6 Hz, 1H, indole-H), 7.17 (m, 6H, phenyl and indole-H), 7.31 (d, J = 7.6 Hz, indole-H), 7.87 (br s, 1H, indole NH).

$^{13}\text{C-NMR}$ (CDCl_3) δ 171.9 (CO), 141.5 (phenyl C-1'), 140.2 (C-9a), 135.9 (C-8a), 128.8 (phenyl C-2'), 128.0 (phenyl C-3'), 126.8 (phenyl C-4'), 126.6 (C-4b), 121.7 (C-7), 119.9 (C-6), 118.4 (C-5), 110.7 (C-8), 110.1 (C-4a), 60.5 (OCH_2), 52.2 (C-1), 41.9 (C-4), 39.0, 34.7, 25.7, 21.4, 21.2 (cyclohexane carbons). MS m/z (%) 389 ($\text{M}^+ + 1$, 14), 388 (M^+ , 4), 346 (18), 267 (14).

16b (more polar): IR (film) ν 3395, 2935, 1730 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ 1.03 (t, $J = 7.5$ Hz, 3H, OCH_2CH_3), 1.22–2.15 (m, 11H, cyclohexane protons, NH), 3.71 (d, $J = 9.7$ Hz, 1H, H-3), 4.15 (dd, $J_1 = 7.5$, $J_2 = 9$ Hz, 2H, OCH_2CH_3), 4.23 (d, $J = 9.7$ Hz, 1H, H-4), 6.53 (d, $J = 8$ Hz, 1H, indole-H), 6.79 (t, $J = 8$ Hz, 1H, indole-H), 7.04 (t, $J = 8$ Hz, 1H, indole-H), 7.14–7.30 (m, 6H, phenyl and indole-H), 7.94 (br s, 1H, indole NH). $^{13}\text{C-NMR}$ (CDCl_3) δ 173.3 (CO), 141.8 (phenyl C-1'), 141.3 (C-9a), 135.6 (C-8a), 128.5 (phenyl C-2'), 128.3 (phenyl C-3'), 126.7 (phenyl C-4'), 126.5 (C-4b), 121.3 (C-7), 119.8 (C-6), 119.1 (C-5), 110.6 (C-8), 109.5 (C-4a), 61.6 (C-3), 60.5 (OCH_2), 52.3 (C-1), 38.4, 35.8, 25.8, 21.2, 20.9 (cyclohexane carbons), 13.9 (OCH_2CH_3). MS m/z (%) 389 ($\text{M}^+ + 1$, 71), 388 (M^+ , 7), 347 (21), 346 (74), 315 (25), 287 (49).

A crude diastereomeric mixture of **16a,b** (1.0 g, 2.57 mmol) and cyclohexylamine (8.32 g, 84 mmol), dissolved in MeOH (5 ml), was heated in a sealed tube at 160°C for 114 h. After evaporation, the residue was purified by repeated flash chromatography (eluent: CH_2Cl_2 /1% MeOH), to give **17a** (less polar, *cis*; 0.17 g, 15%) and **17b** (more polar, *trans*; 0.46 g, 40.5%) as white crystals, after crystallization from ether. **17a** HCl salt (less polar) mp 175 – 177°C . **17b** HCl salt (more polar) mp 200 – 203°C . For other physical data, see tables I–III.

(2S*,3R* and 2S*,3S*)-Ethyl 2-benzoyloxycarboxamido-3-(3'-indolyl)-3-phenylpropionate 18a,b

To an ice-cooled solution of **5a,b** (3.37 g, 10.9 mmol) in dry pyridine (16 ml), containing a catalytic amount of DMAP (65 mg, 0.53 mmol), benzyl chloroformate (3.35g, 19.6 mmol) was added dropwise over 15 min. After stirring at room temperature for 12 h the reaction mixture was poured on ice-water, acidified with 10% HCl and extracted with CHCl_3 (3 x 20 ml). The combined organic layers were washed with 5% HCl (10 ml), with water (10 ml), dried (MgSO_4), evaporated and the obtained oil was then purified by flash chromatography (eluent: CH_2Cl_2) to give a diastereomeric mixture **18a,b**, which was crystallized from ether, *n*-hexane. Yield: 3.30 g (68.4%). mp 124 – 125°C (ether, *n*-hexane). UV (MeOH) 220, 283, 293 nm. IR (KBr) ν 3340, 1725, 1713 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ 0.93 (1.08) (t, $J = 7$ Hz, 3H, OCH_2CH_3), 3.92 (4.07) (q, $J = 7$ Hz, 2H, OCH_2CH_3), 4.75–5.47 (m, 5H, CHPh, CHCO_2Et , $\text{NHCO}_2\text{CH}_2\text{Ph}$), 6.90–7.37 (m, 15H, aromatic), 8.26 (8.30) (br s, 1H, indole NH). $^{13}\text{C-NMR}$ (CDCl_3) δ 171.6 (171.8) (CO), 156.2 (156.0) (NCO), 140.2 (phenyl C-1'), 139.0 (138.9) (benzyl C-1'), 136.2 (136.1) (C-7a), 128.6, 128.5 (128.4), 128.3, 128.1 (128.0), 127.8, 127.2 (126.9) (phenyl, benzyl carbons), 126.7 (126.9) (C-3a), 122.1 (C-6), 122.0 (122.1) (C-2), 119.5 (119.3) (C-5), 118.9 (119.2) (C-4), 114.8 (114.0) (C-3), 111.2 (111.0) (C-7), 67.0 (66.9) (OCH_2Ph), 61.2 (61.4) (OCH_2CH_3), 58.2 (57.6) (CHCO_2Et), 44.8 (45.6) (CHPh), 13.6 (13.8) (CH_2CH_3). MS m/z (%) 442 (M^+ , 1), 369 (1), 334 (2), 206 (100). Anal calc for $\text{C}_{27}\text{H}_{26}\text{N}_2\text{O}_4 \cdot 0.5 \text{H}_2\text{O}$ (451.51): C, 71.82; H, 6.03; N, 6.20; found: C, 71.74; H, 5.93; N, 6.19. Signals in parentheses belong to the second diastereomer.

(2S*,3R* and 2S*,3S*)-2-Benzoyloxycarboxamido-3-(3'-indolyl)-3-phenyl propionic acid 19a,b

To a solution of **18a,b** (1.5 g, 3.39 mmol) in MeOH (20 ml) and CHCl_3 (3 ml) a solution of NaOH (0.30 g, 7.5 mmol) in

water (3 ml) was added and the reaction mixture was stirred at room temperature for 24 h. After a 'B-type' extraction protocol the precipitate was extracted with ether (4 x 15 ml), the organic layers were washed with brine, dried (MgSO_4) and evaporated to dryness. The obtained oil was solidified in *n*-hexane to give a diastereomeric mixture **19a,b** (1.28 g, 91%) as a white powder, mp 81 – 83°C (dec). UV (MeOH) 220, 285, 293 nm. IR (KBr) ν 3420, 3340, 1695 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ 4.83–5.48 (m, 5H, CHPh, CHCO_2H , $\text{NHCO}_2\text{CH}_2\text{Ph}$), 6.91–7.33 (m, 15H, aromatic), 8.12 (br s, 1H, indole NH), 8.21 (br s, 1H, COOH). $^{13}\text{C-NMR}$ (CDCl_3) δ 175.7 (175.8) (CO), 156.6 (156.5) (NCO), 138.8 (140.0) (phenyl C-1'), 136.3 (benzyl C-1'), 136.2 (135.9) (C-7a), 128.6 (128.7), 128.4, 128.2 (128.1), 127.9 (127.8), 127.4, 126.9 (phenyl, benzyl carbons), 126.7 (126.8) (C-3a), 122.8 (C-2), 122.1 (C-6), 119.3 (119.6) (C-5), 119.3 (119.2) (C-4), 114.6 (113.2) (C-3), 111.2 (111.3) (C-7), 67.3 (67.2) (OCH_2Ph), 57.5 (58.0) (CHCO_2H), 44.4 (44.6) (CHPh). MS m/z (%) 206 (100), 108 (70), 107 (35), 91 (58). Signals in parentheses belong to the second diastereomer.

(2S*,3R* and 2S*,3S*)-3-(3'-Indolyl)-2-benzoyloxycarboxamido-3,N-diphenylpropionamide 20a,b

A mixture of **19a,b** (1.73 g, 4.17 mmol) and *N,N'*-carbonyl diimidazole (0.68 g, 4.17 mmol) in dry THF was stirred at room temperature for 1.5 h. Then freshly distilled aniline (0.82 g, 0.8 ml, 8.8 mmol) was added and the reaction mixture was heated under reflux for 72 h. At the end of the reaction MeOH was added and the solvent was evaporated to dryness. The residue was portioned between 5% HCl (20 ml) and CH_2Cl_2 (30 ml), the organic layer was washed with 5% HCl (5 ml) and water (5 ml), dried (MgSO_4), filtered off and evaporated to dryness. The residue was crystallized from ether to give a diastereomeric mixture **20a,b** (1.56 g, 76.4%) as white powder, mp 174 – 176°C (ether). UV (MeOH) 210, 215, 246, 283, 295 nm. IR (KBr) ν 3420, 3320, 1675 cm^{-1} . $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ 4.65–5.25 (m, 5H, CHPh, CHCONHPh , $\text{NHCO}_2\text{CH}_2\text{Ph}$), 6.92–7.88 (m, 20H, aromatic), 9.93 (10.31) (s, 1H, CONHPh), 10.92 (br s, 1H, indole NH). $^{13}\text{C-NMR}$ ($\text{DMSO}-d_6$) δ 170.0 (169.8) (CONHPh), 155.9 (156.1) ($\text{NHCO}_2\text{CH}_2\text{Ph}$), 142.6 (141.7) (phenyl C-1'), 138.7 (138.9) (aniline C-1'), 137.2 (137.1) (benzyl C-1'), 135.9 (136.5) (C-7a), 128.8, 128.6, 128.4, 128.0, 127.8 (127.7), 127.3 (127.5), 126.2 (126.4), 123.5, 119.4 (119.7) (phenyl, aniline, benzyl carbons), 126.0 (127.1) (C-3a), 122.3 (C-2), 121.2 (121.1) (C-6), 118.6 (119.0) (C-5), 118.5 (118.4) (C-4), 114.9 (115.2) (C-3a), 111.4 (111.5) (C-8), 65.3 (65.5) (CH_2Ph), 59.4 (59.1) (CHCONHPh), 43.9 (45.4) (CHPh). MS m/z (%) 108 (93), 107 (53), 79 (100). Anal calc for $\text{C}_{31}\text{H}_{27}\text{N}_3\text{O}_3$ (489.56): C, 76.05; H, 5.56; N, 8.58; found: C, 75.69; H, 5.41; N, 8.58. Signals in parentheses belong to the second diastereomer.

(2S*,3R* and 2S*,3S*)-2-Amino-3-(3'-indolyl)-3-phenylpropionic acid 21a,b

To a solution of **20a,b** (1.55 g, 3.16 mmol) in a mixture of MeOH (60 ml), CH_2Cl_2 (15 ml) and DMF (8 ml) ammonium formate (0.60 g, 9.52 mmol) and palladium on activated carbon (10%) (0.4 g) were added in portion at room temperature under argon. After 1 h stirring the catalyst was filtered off on celite and the solvent was partially evaporated. The DMF solution was poured on ice-water, alkalized to pH 10 (10% Na_2CO_3) and stirred for 1 h. The precipitate was filtered off, washed with water and dried on air to give the diastereomeric mixture **21a,b** (1.05 g, 93%) as a white powder, mp 176 – 178°C (water). UV (MeOH) 210, 223, 244, 283, 293 nm. IR (KBr) ν 3430–3260 (br), 1680, 1655 cm^{-1} . $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ 2.01 (br s, 2H, NH_2), 4.22 (d, $J = 8.2$ Hz, 1H, CHCONHPh), 4.64 (d, $J =$

8.2 Hz, 1H, CHPh), 6.85–7.65 (m, 14H, aromatic), 9.87 (br s, 1H, CONHPh), 10.98 (s, 1H, indole NH). ¹³C-NMR (DMSO-*d*₆) δ 173.3 (172.8) (CO), 143.4 (142.6) (phenyl C-1'), 139.2 (138.9) (aniline C-1'), 136.1 (136.5) (C-7a), 129.1 (128.7) (phenyl C-3'), 128.8 (128.5) (phenyl C-2'), 128.2 (128.0) (aniline C-3'), 127.0 (127.3) (C-3a), 126.2 (126.0) (phenyl C-4'), 123.3 (123.4) (aniline C-4'), 122.3 (122.4) (C-2), 121.1 (121.1) (C-6), 119.4 (119.6) (aniline C-2'), 118.8 (119.0) (C-5), 118.4 (118.5) (C-4), 116.2 (114.5) (C-3), 111.4 (111.6) (C-7), 59.8 (60.1) (CH-CONH), 46.6 (47.8) (CH-Ph). MS *m/z* (%) 355 (M⁺, 4), 354 (6), 267 (10), 218 (21), 206 (100). Anal calc for C₂₃H₂₁N₃O (355.43): C, 77.72; H, 5.96; N, 11.82; found: C, 77.33; H, 5.63; N, 11.98. Signals in parentheses belong to the same diastereomer. Treatment of the diastereomeric mixture with ether allowed the separation of the less polar diastereomer.

21a: ¹H-NMR (DMSO-*d*₆) δ 1.78 (br s, 2H, NH₂), 4.18 (d, *J* = 8.1 Hz, 1H, CHCONHPh), 4.64 (d, *J* = 8.1 Hz, 1H, CH-Ph), 6.90 (t, *J* = 8 Hz, 1H, indole-H), 7.02 (t, *J* = 8 Hz, 2H, indole-H), 7.18 (t, *J* = 8 Hz, 1H, indole-H), 7.24–7.62 (m, 11H, aromatic), 10.05 (br s, 1H, CONHPh), 10.90 (s, 1H, indole NH). ¹³C-NMR (DMSO-*d*₆) δ 173.4 (CO), 142.7 (phenyl C-1'), 139.2 (aniline C-1'), 136.1 (C-7a), 129.1 (phenyl C-3'), 128.8 (phenyl C-2'), 128.2 (aniline C-3'), 127.1 (C-3a), 126.3 (phenyl C-4'), 123.4 (aniline C-4'), 122.4 (C-2), 121.2 (C-6), 119.4 (aniline C-2'), 118.8 (C-5), 118.5 (C-4), 116.3 (C-3), 111.5 (C-7), 59.9 (CHCONH), 46.6 (CHPh).

(3S*,4R* and 3S*,4S*)-4-Phenyl-3-phenylaminocarbonyl-1,2,3,4-tetrahydrospiro[β-carboline-1,1'-cyclohexane] **22a** and **22b**
A mixture of **21a,b** (0.60 g, 1.69 mmol) and cyclohexanone (0.25 g, 265 μl, 2.55 mmol), dissolved in acetic acid (10 ml) was heated under argon at 100–110°C for 5 h. After an 'A-type' extraction, the remaining oil was separated by flash chromatography (eluent: CH₂Cl₂) to give the two diastereomers **22a** (0.16 g, less polar) and **22b** (0.33 g, more polar) in oil form. Crystallization from ether gave **22a** (0.13 g, 18%) and **22b** (0.27 g, 37%) as white crystals.

22a (less polar) UV (MeOH) 210, 227, 250, 285, 293 nm. For other physical data, see table I–III.

22b (more polar) UV (MeOH) 210, 226, 250, 285, 294 nm. For other physical data, see table I–III.

Pharmacology

PBQ writhing in mice

Male CD-1 mice in the weight range of 20 to 25 g were used for studies. The mice were fasted overnight prior to the test day. Test compounds were suspended in 0.5% carboxymethylcellulose at the doses required immediately prior to dosing [16, 17]. Mice were dosed orally with either test compound or vehicle using a constant dose volume of 10 ml/kg. There were seven animals in the vehicle-treated groups and five in each of the treatment groups. Thirty minutes after oral treatment each mouse received an intraperitoneal injection of 0.25 ml of a solution containing 0.01% phenylquinone in 5% ethanol. The number of writhes elicited in each mouse during the period between the 5th and 25th minute after phenylquinone administration was recorded (table IV).

Acetic-acid-induced writhing in rat

Male Wistar rats in the weight range of 140 to 160 g were used for studies. The rats were fasted overnight prior to the test day. The test compounds were suspended in 0.5% carboxymethylcellulose at each of the required doses immediately prior to dosing [18]. Acetic acid was diluted in distilled water to give 1% concentration. Rats were dosed orally with either the test

compound or the vehicle using a constant dose volume of 10 ml/kg. There were seven animals in the vehicle-treated group and five in each of the treatment groups. Thirty minutes after the oral treatment each rat received an intraperitoneal injection of 1.0 ml of a solution containing 1% acetic acid in distilled water. The number of writhes elicited in the following 25 min period was recorded (table IV).

Hot plate in mice

According to the method described by Eddy [19], mice were placed on a heated plate (55°C) inside a Plexiglass cylinder. The latency before the animals start to lick their feet was measured. If no reaction was observed the test was terminated after 120 s. Ten animals were studied per dose (dispersed in a 5% acacia gum suspension at a volume of 0.25 mg/20 g). The compound administration was performed 1 h (PO) or 30 min (IP) before the test.

Evaluation of toxic, physiological and behavioural effects in mice

Three animals per dose were treated with the test compound (dispersed in a 5% acacia gum suspension at a volume of 0.25 mg/20 g) and were observed according to a standardized observation grid at regular intervals for up to 24 h. The presence or absence and the intensity of various symptoms were noted [20, 21].

Receptor binding assay

Receptor binding assays [22–24] were performed by incubating membranes prepared from the rat central nervous system with [³H]-DAMGO, [³H]-PCL-PHE-DPDPE, respectively for receptors μ and δ. For receptor κ membrane was prepared from guinea-pig cerebellum, incubated with [³H] U-69593. After the incubation period, bound and unbound radioligands were separated by filtration. Radioactivity bound to membranes, in the absence and presence of compounds, was measured by liquid-scintillation counter. Compounds were studied at two concentrations (10^{−7} and 10^{−5} M).

Antiinflammatory properties

Isolated rabbit granulocytes were stimulated by calcic ionophore (A 23187) and incubated for 15 min with the compounds at 10 μM [25]. The cyclooxygenase and lipoxygenase activities were determined by radioimmunoassay dosage of PGE₂ and LTB₄, respectively. Results were expressed as a percentage of control activity (table V).

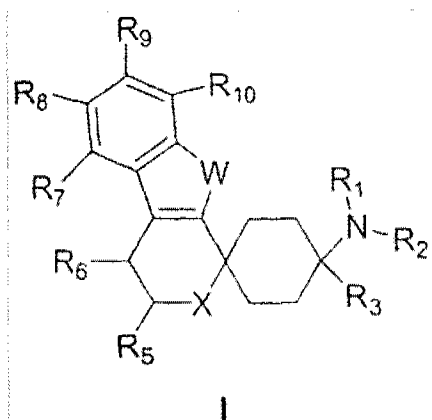
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Reivindicaciones de patente

1. Derivados de ciclohexano espirrocíclicos de la siguiente fórmula general I,



en la que

5 R^1 y R^2 son en forma independiente entre sí para H; CHO; alquilo C_{1-5} respectivamente saturado o no saturado, ramificado o no ramificado, sustituido en forma individual o múltiple o no sustituido; cicloalquilo C_{3-8} , respectivamente saturado o no saturado, sustituido en forma individual o múltiple o no sustituido; o arilo cicloalquilo C_{3-8} o heteroarilo unido por alquilo C_{1-3} , respectivamente sustituido en forma individual o múltiple o no sustituido;

o los restos R^1 y R^2 son juntos para $CH_2CH_2OCH_2CH_2$, $CH_2CH_2NR^{11}CH_2CH_2$ o $(CH_2)_{3-6}$,

15 donde R^{11} significa H; alquilo C_{1-5} , respectivamente saturado o no saturado, ramificado o no ramificado, sustituido en forma individual o múltiple o no sustituido; cicloalquilo C_{3-8} , respectivamente saturado o no saturado, sustituido en forma individual o múltiple o no sustituido; arilo-, o heteroarilo, respectivamente sustituido en forma individual o múltiple o no sustituido; o arilo, cicloalquilo C_{3-8} o heteroarilo unido por alquilo C_{1-3} , respectivamente sustituido en forma individual o múltiple o no sustituido;

20 R^3 es para alquilo C_{1-5} , respectivamente saturado o no saturado, ramificado o no ramificado, sustituido en forma individual o múltiple o no sustituido; cicloalquilo C_{3-8} , respectivamente saturado o no saturado, sustituido en

forma individual o múltiple o no sustituido; arilo, respectivamente no sustituido o sustituido en forma individual o múltiple; arilo, o cicloalquilo C_{3-8} unido por el grupo alquilo C_{1-3} , respectivamente no sustituido o sustituido en forma individual o múltiple;

5 W es para NR^4 , O o S

y

R^4 es para H; alquilo C_{1-5} , saturado o no saturado, ramificado o no ramificado, no sustituido o sustituido en forma individual o múltiple; arilo, o heteroarilo, respectivamente sustituido o no sustituido; arilo, heteroarilo o cicloalquilo unido por el grupo alquilo C_{1-3} , respectivamente sustituido en forma individual o múltiple o no sustituido; COR^{12} ; SO_2R^{12} ,

10 donde R^{12} significa H; alquilo C_{1-5} , en cada caso saturado o no saturado, ramificado o no ramificado, mono- o poli-sustituido o no sustituido; C_{3-8} – cicloalquilo, en cada caso saturado o no saturado, ramificado o no ramificado, mono- o poli-sustituido o no sustituido; arilo, o heteroarilo, en cada caso saturado o no saturado, ramificado o no ramificado, mono- o poli-sustituido o no sustituido; o arilo; C_{3-8} – cicloalquilo, o heteroarilo, en cada caso saturado o no saturado, ramificado o no ramificado, mono- o poli-sustituido o no sustituido, anexando mediante

20 C_{1-3} alquilo; en cada caso saturado o no saturado, ramificado o no ramificado; OR^{13} ; $NR^{14}R^{15}$;

R^5 es para $=O$; H; $COOR^{13}$, $CONR^{13}$, OR^{13} ; alquilo C_{1-5} , saturado o no saturado, ramificado o no ramificado, no sustituido o sustituido en forma individual o múltiple; cicloalquilo C_{3-8} , saturado o no saturado, no sustituido o sustituido en forma individual o múltiple; arilo-, o heteroarilo, no sustituido o sustituido en forma individual o múltiple; o arilo, cicloalquilo C_{3-8} o heteroarilo unido por alquilo C_{1-3} , no sustituido o sustituido en forma individual o múltiple;

R^6 es para H; F, Cl, NO_2 , CF_3 , OR^{13} , SR^{13} , SO_2R^{13} , $\text{SO}_2\text{OR}^{13}$, CN, COOR^{13} , $\text{NR}^{14}\text{R}^{15}$; alquilo C_{1-5} , saturado o no saturado, ramificado o no ramificado, no sustituido o sustituido en forma individual o múltiple; cicloalquilo C_{3-8} , saturado o no saturado, no sustituido o sustituido en forma individual o múltiple; arilo-, o heteroarilo, no sustituido o sustituido en forma individual o múltiple; o arilo, cicloalquilo C_{3-8} o heteroarilo unido por alquilo C_{1-3} , no sustituido o sustituido en forma individual o múltiple;

o R^5 y R^6 significan juntos $(\text{CH}_2)_n$ con $n = 2, 3, 4, 5$ ó 6 , donde átomos de hidrógeno individuales pueden estar reemplazados también por F, Cl, Br, I, NO_2 , CF_3 , OR^{13} , CN o alquilo C_{1-5} ;

R^7 , R^8 , R^9 y R^{10} son en forma independiente entre sí para H, F, Cl, Br, I, NO_2 , CF_3 , OR^{13} , SR^{13} , SO_2R^{13} , $\text{SO}_2\text{OR}^{13}$, SO_2NH_2 , CN, COOR^{13} , $\text{NR}^{14}\text{R}^{15}$; alquilo C_{1-5} , cicloalquilo C_{3-8} , no sustituido o sustituido en forma individual o múltiple; arilo-, o heteroarilo, no sustituido o sustituido en forma individual o múltiple; o arilo, cicloalquilo C_{3-8} o heteroarilo unido por alquilo C_{1-3} , no sustituido o sustituido en forma individual o múltiple;

donde R^{13} significa H; alquilo C_{1-5} respectivamente saturado o no saturado, ramificado o no ramificado, no sustituido o sustituido en forma individual o múltiple; cicloalquilo C_{3-8} , respectivamente saturado o no saturado, no sustituido o sustituido en forma individual o múltiple; arilo-, o heteroarilo, no sustituido o sustituido en forma individual o múltiple; o arilo, cicloalquilo C_{3-8} o heteroarilo unido por alquilo C_{1-3} , no sustituido o sustituido en forma individual o múltiple;

R^{14} y R^{15} significan en forma independiente entre sí H; alquilo C_{1-5} , respectivamente saturado o no saturado, ramificado o no ramificado, no sustituido o sustituido en forma individual o múltiple; o cicloalquilo C_{3-8} , respectivamente saturado o no saturado, no sustituido o sustituido en forma individual o múltiple; arilo-, o heteroarilo, no sustituido o sustituido en forma

individual o múltiple; o arilo, cicloalquilo C_{3-8} o heteroarilo unido por alquilo C_{1-3} , no sustituido o sustituido en forma individual o múltiple;

o R^{14} y R^{15} forman juntos $CH_2CH_2OCH_2CH_2$, $CH_2CH_2NR^{16}CH_2CH_2$ o $(CH_2)_{3-6}$,

5 donde R^{16} significa H; alquilo C_{1-5} saturado o no saturado, ramificado o no ramificado, no sustituido o sustituido en forma individual o múltiple;

X es para O, S, SO, SO_2 o NR^{17} ;

R^{17} representa H; C_{1-5} -alquilo, saturado o no saturado, ramificado o no ramificado; COR^{12} o SO_2R^{12} , CARACTERIZADO porque en conexión con
 10 "alquilo", "sustituido" se entiende como una sustitución de uno o más radicales de hidrogeno por F, Cl, Br, I, -CN, NH_2 , NH-alquilo, NH-arilo, NH-heteroarilo, NH-cicloalquilo, NH-alquil-aril, NH-alquil-heteroarilo, NH-alquil-OH, N(alquilo)₂, N(alquilo-arilo)₂, N(alquilo-heteroarilo)₂, N(cicloalquilo)₂, N(alquilo-OH)₂, NO_2 , SH, S-alquilo, S-arilo, S-heteroarilo, S-alquil-aril, S-alquil-heteroaril, S-cicloalquilo, S-alquilo-OH, S-alquilo-SH, OH, O-alquilo, O-arilo, O-heteroarilo, O-alquil-aril, O-alquil-heteroaril, O-cicloalquilo, O-alquilo-OH, CHO, $C(=O)Cl$ -6-alquilo, $C(=S)Cl$ -6-alquilo, $C(=O)$ arilo, $C(=S)$ arilo, $C(=O)Cl$ -6-alquilo-arilo, $C(=S)Cl$ -6-alquilo-arilo, $C(=O)$ -heteroarilo, $C(=S)$ -heteroarilo, $C(=O)$ -cicloalquilo, $C(=S)$ -cicloalquilo, CO_2H , CO_2 -alquilo, CO_2 -alquilo-arilo, $C(=O)NH_2$, $C(=O)NH$ -alquilo, $C(=O)NH$ -arilo, $C(=O)NH$ -cicloalquilo, $C(=O)N$ (alquilo)₂, $C(=O)N$ (alquilo-arilo)₂, $C(=O)N$ (alquilo-heteroarilo)₂, $C(=O)N$ (cicloalquilo)₂, SO -alquilo, SO_2 -alquilo, SO_2NH_2 , SO_3H , $PO(OCi-6-alquilo)_2$, $Si(Cl-6-alquilo)_3$, $Si(C_{3-8}$ -cicloalquilo)₃, $Si(CH_2-C_{3-8}$ -cicloalquilo)₃, Si(fenil)₃, cicloalquilo, arilo o heteroarilo;

25

donde en conexión con "arilo", "heteroarilo" y "cicloalquilo", "mono o poli-sustituido" se entiende como una mono o poli-sustitución de uno o más átomos de hidrogeno del anillo del sistema por F, Cl, Br, I, -CN, NH_2 , NH-alquilo, NH-arilo, NH-heteroarilo, NH-cicloalquilo, NH-alquil-aril, NH-alquil-

heteroaril, NH-alquilo-OH, N(alquilo)₂, N(alquilo-arilo)₂, N(alquilo-heteroarilo)₂, N(cicloalquilo)₂, N(alquilo-OH)₂, NO₂, SH, S-alquilo, S-arilo, S-heteroarilo, S-alquil-aril, S-alquil-heteroaril, S-cicloalquilo, S-alquilo-OH, S-alquilo-SH, OH, O-alquilo, O-arilo, O-heteroarilo, O-alquilo-arilo, O-alquil-heteroaril, O-cicloalquilo, O-alquilo-OH, CHO, C(=O)Cl-6-alquilo, C(=S)Cl-6-alquilo, C(=O)arilo, C(=S)arilo, C(=O)Cl-6-alquilo-arilo, C(=S)Cl-6-alquilo-arilo, C(=O)-heteroarilo, C(=S)-heteroarilo, C(=O)-cicloalquilo, C(=S)-cicloalquilo, CO₂H, CO₂-alquilo, CO₂-alquilo-arilo, C(=O)NH₂, C(=O)NH-alquilo, C(=O)NH-arilo, C(=O)NH-cicloalquilo, C(=O)N(alquilo)₂, C(=O)N(alquilo-arilo)₂, C(=O)N(alquilo-heteroarilo)₂, C(=O)N(cicloalquilo)₂, S(O)-alquilo, S(O)-arilo, SO₂-alquilo, SO₂-arilo, SO₂NH₂, SO₃H, CF₃, =O, =S; alquilo, cicloalquilo, arilo y/o heteroarilo;

donde el término "arilo" significa un sistema de anillo carbo-cíclico con al menos un anillo aromático, pero con no heteroátomos en solo un de los anillos, en donde los residuos de arilo pueden estar opcionalmente fusionados con más sistemas de anillos aromáticos, saturados, o (parcialmente) no saturados;

donde el término "heteroarilo" denota un residuo aromático cíclico de 5-, 6- o 7- miembros que contiene al menos 1, opcionalmente 2, 3, 4 o 5 heteroátomos, en donde los heteroátomos idénticos o diferentes, son nitrógeno, oxígeno o sulfuro y en donde el heterociclo puede también ser parte de un sistema bi- o poli-cíclico;

donde el término "cicloalquilo" denota un hidrocarburo cíclico con 3, 4, 5, 7, 7 o 8 átomos de carbono, en donde el hidrocarburo puede ser saturado o no saturado, pero no aromático, y donde opcionalmente uno o dos átomos de carbono pueden ser reemplazados por un heteroátomo S, N o O;

en la forma del racemato; de los enantiómeros, diastereómeros, mezclas de los enantiómeros o diastereómeros o de un enantiómero o diastereómero individual; de las bases y/o sales de ácidos o cationes fisiológicamente compatibles.

2. Derivados de ciclohexano espirocíclicos conforme a la reivindicación 1, caracterizados porque

R^1 y R^2 son en forma independiente entre sí para H, alquilo C_{1-5} , ramificado o no ramificado, saturado o no saturado, no sustituido o sustituido en forma individual o múltiple, o CHO, y/o

R^3 es para fenilo, bencilo o fenetilo, respectivamente no sustituido o sustituido en el anillo en forma individual o múltiple.

3. ✓ Derivados de ciclohexano espirocíclicos conforme a una de las reivindicaciones 1 ó 2, caracterizados porque R^5 es para H, alquilo C_{1-5} , ramificado o no ramificado, no sustituido o sustituido en forma individual o múltiple o $COOR^{13}$ y R^6 significa H o alquilo C_{1-5} .

4. ✓ Derivados de ciclohexano espirocíclicos conforme a una de las reivindicaciones 1 - 3, caracterizados porque R^7 , R^8 , R^9 y R^{10} son en forma independiente entre sí para H; alquilo C_{1-5} , ramificado o no ramificado, no sustituido o sustituido en forma individual o múltiple; F, Cl, Br, I, CF_3 , OH, OCH_3 , NH_2 , $COOH$, $COOCH_3$, $NHCH_3$, $N(CH_3)_2$, NO_2 , SO_3H , SO_2NH_2 , piridilo o fenilo.

5. ✓ Derivados de ciclohexano espirocíclicos conforme a la reivindicación 1, caracterizados porque

W es para NR^4 , O o S y X significa O, S, SO, SO_2 o NR^{17} .

R^1 y R^2 son en forma independiente entre sí para H; alquilo C_{1-4} , ramificado o no ramificado, sustituido en forma individual o múltiple o no sustituido; o CHO;

R^3 es para $(CH_2)_n$ -arilo, respectivamente no sustituido o sustituido en arilo en forma individual o múltiple, con $n = 0 - 2$;

R^4 es para H; alquilo C_{1-3} , sustituido en forma individual o múltiple o no sustituido;

$CO(CH_2)_mH$ es con $m = 0$ a 2, y/o

R^5 y R^6 son respectivamente para H y/o

R^7 , R^8 , R^9 y R^{10} son en forma independiente entre sí para H, alquilo C_{1-5} , Oalquilo C_{1-3} , respectivamente ramificado o no ramificado, saturado o no saturado, no sustituido o sustituido en forma individual o múltiple; F, Cl, Br, I, CF_3 , OH, SH, SCH_3 , OCH_3 , NH_2 , $COOH$, $COOCH_3$, $NHCH_3$, $N(CH_3)_2$, NO_2 , SO_3H , SO_2NH_2 , piridilo o fenilo.

6. ✓ Derivados de ciclohexano espirocíclicos conforme a una de las reivindicaciones 1 – 5, caracterizados porque R^1 y R^2 significan en forma independiente entre sí H o CH_3 , donde R^1 y R^2 no significan al mismo tiempo H.

7. ✓ Derivados de ciclohexano espirocíclicos conforme a una de las reivindicaciones 1 – 6, caracterizados porque R^3 significa fenilo, bencilo o fenetilo, respectivamente no sustituido o sustituido en el anillo en forma individual o múltiple,

en especial

fenilo, bencilo, fenetilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 2-clorofenilo, 4-clorofenilo, 3-clorofenilo, 2-bromofenilo, 3-bromofenilo, 4-bromofenilo, 2-cianofenilo, 3-cianofenilo, 4-cianofenilo, 2-metilfenilo, 3-metilfenilo, 4-metilfenilo, 2-metoxifenilo, 3-metoxifenilo, 4-metoxifenilo, 2-trifluoro metilfenilo, 3-trifluoro metilfenilo, 3-trifluoro metilfenilo, 2-etilfenilo, 3-etilfenilo, 4-etilfenilo, 2-etoxifenilo, 3-etoxifenilo, 4-etoxifenilo, 2-hidroxifenilo, 3-hidroxifenilo, 4-hidroxifenilo, 2,3-diclorofenilo, 3,4-diclorofenilo, 3,5-diclorofenilo, 2,4-diclorofenilo, 2,3-difluorofenilo, 3,4-difluorofenilo, 3,5-difluorofenilo, 2,4-difluorofenilo, 2-fluoro- 3-clorofenilo, 2-cloro- 3-fluorofenilo, 2-cloro- 4-fluorofenilo, 2-fluoro- 4-clorofenilo, 4-fluoro- 3-clorofenilo, 4-fluoro- 3-metilfenilo, 4-butilo terc.- fenilo, 4-fluoro- 3-clorofenilo, 4-bromo- 3-fluorofenilo, 3,5-bis(trifluorometil) fenilo, 4-cloro- 2-trifluorometilfenilo, 2-metoxi- 5-

metilfenilo, 5-cloro- 2-metoxifenilo, 4-fenoxifenilo, 2-metiltiofenilo, 3-metiltiofenilo, 4-metiltiofenilo, 5-fluoro-2- metoxifenilo, 4-cloro-3-trifluorometilo o 4-bromo-2- metilfenilo

con especial preferencia, fenilo, bencilo, fenetilo, 4-fluorofenilo y 3-fluorofenilo.

8. Derivados de ciclohexano espirocíclicos conforme a una de las reivindicaciones 1 – 5, caracterizados porque

W es para NR^4 y X significa O, NH o NCOR^{12} ,

R^1 y R^2 son en forma independiente entre sí para H; alquilo C_{1-4} , ramificado o no ramificado, sustituido en forma individual o múltiple o no sustituido; o CHO,

R^3 es para $(\text{CH}_2)_n$ -arilo, respectivamente no sustituido o sustituido en arilo en forma individual o múltiple, con $n = 0 - 2$,

R^4 es para H; alquilo C_{1-3} , sustituido en forma individual o múltiple o no sustituido; $\text{CO}(\text{CH}_2)_m\text{H}$ con $m = 0$ a 2,

R^5 y R^6 son respectivamente para H y/o

R^7 , R^8 , R^9 y R^{10} son en forma independiente entre sí para H; alquilo C_{1-5} , Oalquilo C_{1-3} , respectivamente ramificado o no ramificado, saturado o no saturado, no sustituido o sustituido en forma individual o múltiple; F, Cl, Br, I, CF_3 , OH, SH, SCH_3 , OCH_3 , NH_2 , COOH , COOCH_3 , NHCH_3 o $\text{N}(\text{CH}_3)_2$, NO_2 , SO_3H , SO_2NH_2 , piridilo o fenilo.

9. ✓ Derivados de ciclohexano espirocíclicos conforme a una de las reivindicaciones 1 – 8, caracterizados porque

el resto R^5 es para H, CH_3 , COOH , COOCH_3 o CH_2OH ,

el resto R^6 es para H,

los restos R^7 , R^8 , R^9 y R^{10} son para H

o

uno de los restos R^7 , R^8 , R^9 y R^{10} son para H; alquilo C_{1-5} , ramificado o no ramificado, no sustituido o sustituido en forma individual o múltiple; F, Cl, Br, I, OH, OCH_3 , $COOH$, $COOCH_3$, NH_2 , $NHCH_3$, $N(CH_3)_2$, NO_2 , SO_3H , SO_2NH_2 , piridilo o fenilo, en tanto que los restos restantes significan H,

5 o

dos de los restos R^7 , R^8 , R^9 y R^{10} son en forma independiente entre sí para H; alquilo C_{1-5} , ramificado o no ramificado, no sustituido o sustituido en forma individual o múltiple; F, Cl, Br, I, OH, OCH_3 , $COOH$, $COOCH_3$, NH_2 , $NHCH_3$, $N(CH_3)_2$, NO_2 , SO_3H , SO_2NH_2 , piridilo o fenilo, en tanto que los restos restantes significan H.

10

10. ✓ Derivados de ciclohexano espirocíclicos conforme a una de las reivindicaciones 1 – 9, caracterizados porque R^1 y R^2 significan CH_3 y R^3 significa fenilo.

11. ~~Derivados de ciclohexano espirocíclicos conforme a una de las~~
reivindicaciones 1 – 10, caracterizados porque W significa NR^4 , donde R^4 es para H, CH_3 , C_2H_5 , acetilo, fenilo, bencilo o COR^{12} , y X significa O, NH, y

15

$NCOR^{12}$

12. Derivados de ciclohexano espirocíclicos conforme a una de las reivindicaciones 1 – 11 del grupo compuesto por

20

1,1-(3-dimetil amino- 3-fenil pentametilen)- 1,3,4,9- tetrahidropirano [3,4-b] indol clorhidrato

1,1-(3-dimetil amino-3-fenil pentametilen)-1,3,4,9- tetrahidropirano [3,4-b] indol hemicitrato

25

1,1-(3-dimetil amino-3-fenil pentametilen)-1,3,4,9- tetrahidro- 2-tia-9-azafluoreno hemicitrato

1,1-(3-dimetil amino-3-fenil pentametilen)-1,3,4,9- tetrahidro-2-tia- 9-azafluoreno citrato

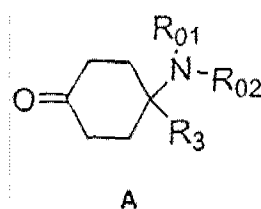
- 1,1-(3-dimetil amino-3-fenil pentametilen)- 3,4-dihidro-1H- 2-oxa-9-tiafluoreno L-tartrato ✓
- 1,1-(3-dimetil amino-3-(4-fluorofenil) pentametilen)-3,4-dihidro- 1H-2-oxa-9-tiafluoreno triflato ✓
- 5 1,1-(3-dimetil amino-3-fenil pentametilen), 3,4-dihidro- 1H-2,9-dioxafluoreno hemicitrato ✓
- 1,1-(3-dimetil amino-3-fenil pentametilen)- 3,4-dihidro- 1H-2,9-diazafluoreno diclorhidrato ✓
- 10 2-acetil-1,1- (3-dimetil amino-3-fenil pentametilen)- 3,4-dihidro- 1H-2,9-diazafluoreno clorhidrato
- 1,1-(3-dimetil amino-3-fenil pentametilen)- 6-metoxi- 1,3,4,9-tetrahidropirano [3,4-b] indol clorhidrato ✓
- 1,1-(3-dimetil amino-3-fenil pentametilen)- 3-metil- 1,3,4,9- tetrahidropirano [3,4-b] indol citrato ✓
- 15 6-bromo-1,1- (3-dimetil amino-3-fenil pentametilen)- 3-metil-1,3,4,9-tetrahidropirano [3,4-b] indol hemicitrato ✓
- 1,1-(3-dimetil amino-3-fenil pentametilen)- 3-metil-6- nitro-1,3,4,9-tetrahidropirano [3,4-b] indol citrato ✓
- 20 6-cloro-1,1- (3-dimetil amino-3-fenil pentametilen)- 3-metil-1,3,4,9-tetrahidropirano [3,4-b] indol citrato ✓
- 3,9-dimetil- 1,1-(3-dimetil amino-3-fenil pentametilen)- 1,3,4,9-tetrahidropirano [3,4-b] indol citrato ✓
- 1,1-(3-dimetilamino- 3-(4-fluorofenil) pentametilen)- 1,3,4,9- tetrahidropirano [3,4-b] indol hemicitrato ✓
- 25 1,1-(3-dimetilamino- 3-(3-fluorofenil) pentametilen)- 1,3,4,9- tetrahidropirano [3,4-b] indol hemicitrato ✓
- 1,1-(3-dimetil amino-3-fenil pentametilen)- 6-fluoro- 1,3,4,9- tetrahidropirano [3,4-b] indol hemicitrato ✓

- ✓ 1,1-(3-dimetil- amino-3-fenil pentametilen)- 6-metil- 1,3,4,9- tetrahidropirano
[3,4-b] indol hemicitrato
- ✓ 1,1-(3-dimetil amino-3-fenil pentametilen)- 9-fenil-1,3,4,9- tetrahidropirano
[3,4-b] indol citrato
- 5 ✓ 1,1-(3-metil amino-3-fenil pentametilen)- 1,3,4,9- tetra-hidro-pirano [3,4-b]
indol hemicitrato
- ✓ 1,1-(3-dimetil amino-3-fenil pentametilen)- 6-metil-3,4-dihidro- 1H-2,9-
diazafluoreno citrato
- ✓ 2-acetil-1,1 – (3-dimetil amino-3-fenil pentametilen)- 6-metil-3,4- dihidro-1H-
10 2,9- diazafluoreno citrato
- ✓ 1,1-(3-dimetil amino-3-fenil pentametilen)- 7-fluoro-3,4- dihidro-1H-2,9-
diazafluoreno citrato
- ✓ 2-acetil- 1,1-(3-dimetil amino-3-fenil pentametilen)-7-fluoro-3,4- dihidro-1H-
2,9- diazafluoreno citrato
- 15 ✓ 1,1-(3-dimetil amino-3-fenil pentametilen)- 3-metil-3,4- dihidro-1H-2,9-
diazafluoreno citrato
- ✓ 1,1-(3-dimetil amino-3-fenilpentametilen)- 6-fluoro-3,4- dihidro-1H-2,9-
diazafluoreno diclorhidrato
- ✓ 1,1-(3-dimetil amino-3-fenil pentametilen)- 6-fluoro-3- metil-1,3,4,9- tetra-
20 hidro-pirano [3,4-b] indol hemicitrato
- ✓ 3,6-dimetil- 1,1-(3-dimetil amino-3-fenil pentametilen)- 1,3,4,9- tetra-hidro-
pirano [3,4-b] indol hemicitrato
- ✓ 3,6-dimetil- 1,1-(3-dimetil amino-3-fenil pentametilen), 1,3,4,9- tetra-hidro-
pirano- [3,4-b] indol citrato
- 25 ✓ 1,1-(3-dimetil amino-3-fenil pentametilen)-3-metil-9- fenil-1,3,4,9-
tetrahidropirano [3,4-b] indol citrato
- ✓ 1,1-(3-dimetil amino-3-(4-fluorofenil) pentametilen)- 1,3,4,9- tetra-hidro-2-
tia-9-azafluoreno metanosulfonato

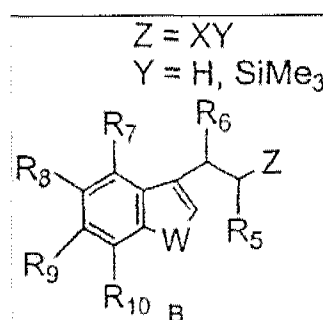
- ✓ 1,1-(3-dimetil amino-3-(3- fluorofenil) pentametilen)- 1,3,4,9-tetra – hidro-2-tia- 9-azafluoreno metanosulfonato
- ✓ 1,1-(3-dimetil amino-3-fenil pentametilen)- 3,4-dihidro- 1H-9-oxa-2-tiafluoreno citrato
- 5 1,1-(3-dimetil amino-3-fenil pentametilen)- 1,2,3,4- tetrahidro-benzo [4,5] furo [2,3-c] piridina citrato
- ✓ 6,6-(3-dimetil amino-3-fenil pentametilen)- 1,2,3,4,4a,6,7,11c- octahidro-5-oxa- 7-azabenzó [c] fluoreno citrato
- ✓ 1,1-(3-dimetil amino-3-fenil pentametilen)-6-bromo- 1,3,4,9- tetrahidropirano
- 10 [3,4-b] indol hemicitrato
- ✓ 1,1-(3-dimetil amino-3-fenil pentametilen)- 1,3,4,9-tetra-hidro-pirano [3,4-b] indol-6-ol citrato
- ✓ (3S)-1,1-(3-dimetil amino-3-fenil pentametilen)- 3,4-dihidro-3-metoxicarbonil- 1H-2,9-diazafluoreno citrato
- 15 ✓ (3S)- 1,1-(3-dimetil amino-3-fenil pentametilen)- 3,4-dihidro- 1H-2,9-diazafluoren- 3-metanol citrato
- ✓ 1,1-(3-dimetil amino-3-feniletil- pentametilen)- 3,4-dihidro- 1H-2,9-diazafluoreno
- ✓ 1,1-(3-metil amino-3-fenil pentametilen)- 6-fluoro-1,3,4,9- tetrahidropirano
- 20 [3,4-b] indol hemicitrato
- ✓ 1,1-(3-dimetil amino-3-(4- fluorofenil) pentametilen)- 3,4-dihidro-1H- 2,9-ditiafluoreno metanosulfonato
- ✓ 1,1-(3-dimetil amino-3-fenil pentametilen), 3,4-dihidro- 1H-2,9- ditiafluoreno citrato
- 25 ✓ 1,1-(3-dimetil amino-3-fenil pentametilen)- 1,3,4,9- tetra-hidro- 2-tia-9-aza-fluoreno 2-óxido citrato
- 1,1-(3-dimetil amino-3-bencil pentametilen)- 3,4-dihidro- 1H-2,9-ditiafluoreno

en la forma del racemato; de los enantiómeros, diastereómeros, mezclas de los enantiómeros o diastereómeros o de un enantiómero o diastereómero individual; de las bases y/o sales de ácidos o cationes fisiológicamente compatibles.

- 5 13. Procedimiento para elaborar los derivados de ciclohexano espirocíclicos conforme a una de las reivindicaciones 1 – 12, caracterizado porque se transforma un educto de la siguiente fórmula general A



donde los restos R^{01} y R^{02} tienen el significado indicado para R^2 y pueden ser en forma adicional para un grupo de protección, mediante la adición de ácido, o su éster trimetilsilílico, por ejemplo, éster trimetilsilílico del ácido trifluorometansulfónico, ácido trifluorometansulfónico, ácido acético, ácido fosfórico, ácido metansulfónico o ácido trifluoroacético, en un disolvente apropiado, dicloroetano, diclorometano, cloroformo, acetonitrilo, éter dietílico o nitrometano, con un educto de la siguiente fórmula general B



donde los restos R^1 - R^9 tienen los significados indicados en la reivindicación

- 1.
14. Procedimiento para elaborar derivados de ciclohexano espirocíclicos conforme a la reivindicación 1, en los cuales X significa NR^{17} y R^{17} significa COR^{12} o SO_2R^{12} , caracterizado porque se transforma un derivado de

ciclohexano espirocíclico, en el cual X significa NH, bajo la adición de base, como, trietilamina, con un anhídrido o un cloruro de ácido, de preferencia, bajo irradiación de microondas.

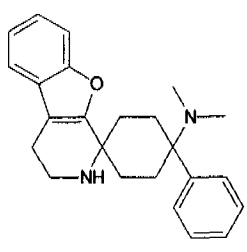
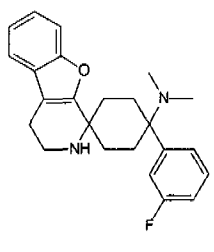
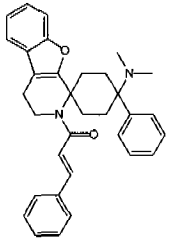
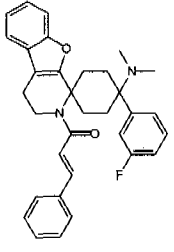
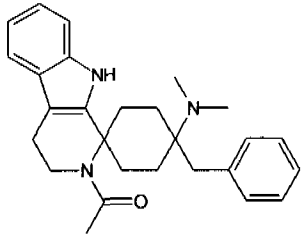
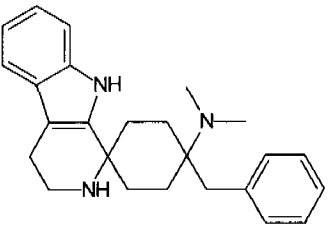
15. Procedimiento para elaborar derivados de ciclohexano espirocíclicos conforme a la reivindicación 1, en los cuales X significa SO o SO₂, caracterizado porque se oxida un derivado de ciclohexano espirocíclico en el cual X significa S, con la ayuda de un agente de oxidación - H₂O₂.

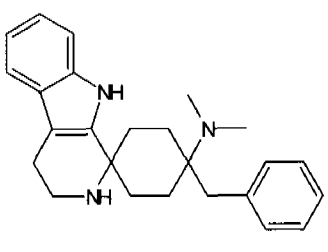
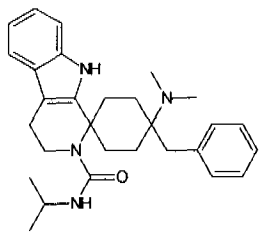
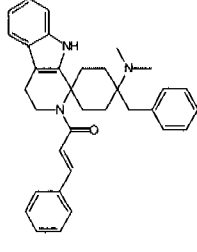
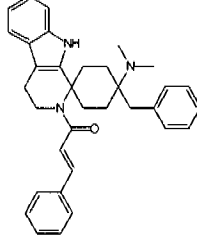
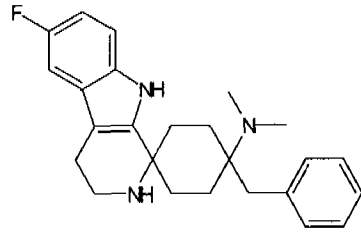
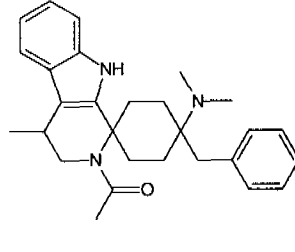
16. Medicamento que contiene por lo menos un derivado de ciclohexano espirocíclico conforme a una de las reivindicaciones 1 a 12, en forma opcional en la forma de su racemato, de los esteroisómeros puros, en especial enantiómeros y diastereómeros, en cualquier proporción de mezcla; en la forma de sus ácidos o sus bases o en la forma de sus sales, en especial de las sales fisiológicamente compatibles o sales de ácidos o cationes fisiológicamente compatibles; como también en forma opcional, que contiene sustancias accesorias y/o sustancias auxiliares y/o, en forma opcional, otras sustancias activas.

17. Derivado de ciclohexano espirocíclico conforme a una de las reivindicaciones 1 a 12, en forma opcional, en la forma de su racemato, de los esteroisómeros puros, en especial enantiómeros y diastereómeros, en cualquier proporción de mezcla; en la forma de sus ácidos o sus bases o en la forma de sus sales, en especial de las sales fisiológicamente compatibles o sales de ácidos o cationes fisiológicamente compatibles; o en la forma de sus solvatos, en especial de los hidratos; para elaborar un medicamento para el tratamiento del dolor, en especial del dolor agudo, neuropático o crónico.

18. Derivado de ciclohexano espirocíclico conforme a una de las reivindicaciones 1 a 12 para elaborar un medicamento para el tratamiento de los estados de ansiedad, del estrés y de síndromes asociados al estrés,

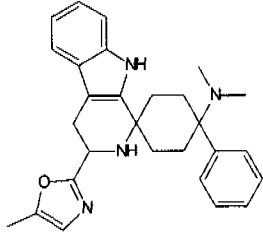
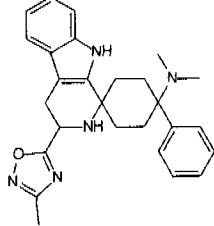
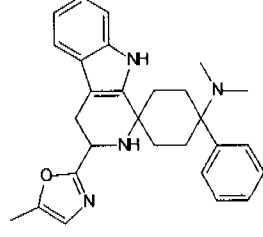
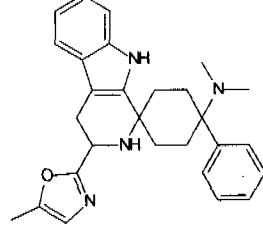
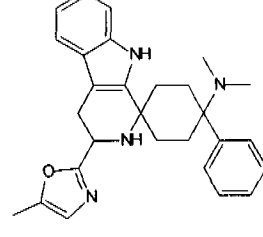
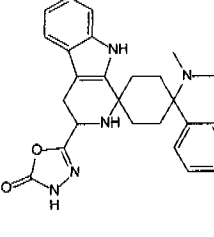
depresiones, epilepsia, enfermedad de Alzheimer, demencia senil, disfunciones cognitivas generales, trastornos del aprendizaje y de la memoria (como nootrópico), síntomas de abstinencia, abuso y/o dependencia del alcohol y/o drogas y/o medicamentos, disfunciones sexuales, enfermedades cardiovasculares, hipotensión, hipertensión, tinnitus, prurito, migraña, sordera, motilidad intestinal deficiente, problemas de absorción de sustancias nutritivas, anorexia, obesidad, trastornos locomotores, diarrea, caquexia, incontinencia urinaria o bien como relajante muscular, anticonvulsivo o anestésico o bien para la co-administración en el tratamiento con un analgésico opioide o con un anestésico, para la diuresis o antinatriuresis, ansiolisis, para la modulación de la actividad motora, para la modulación de la liberación de neurotransmisores y el tratamiento de enfermedades neurodegenerativas asociadas a ello, para el tratamiento de síntomas de abstinencia y/o para la reducción del potencial de adicción de los opioides.

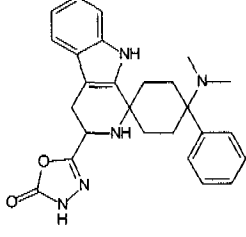
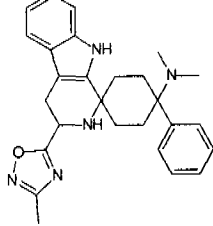
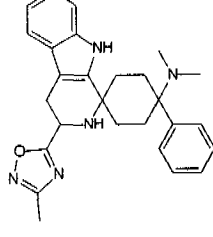
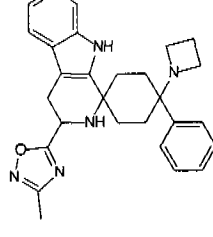
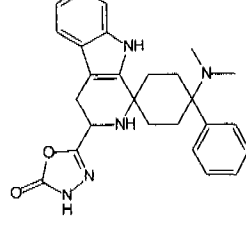
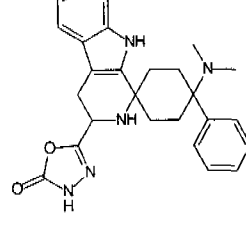
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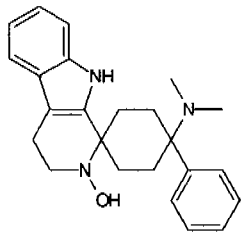
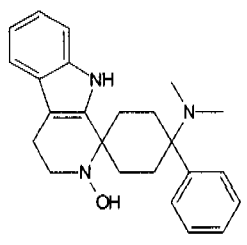
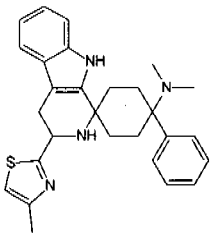
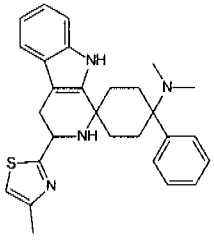
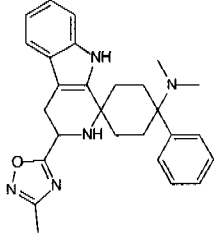
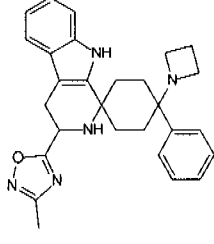
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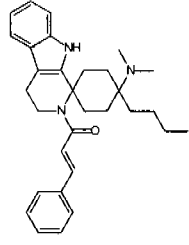
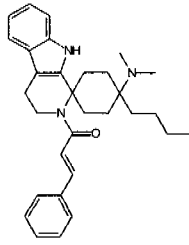
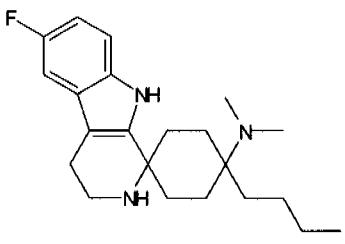
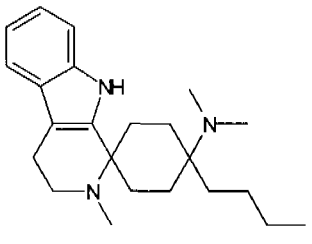
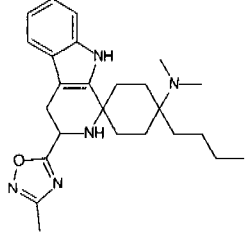
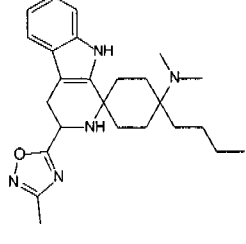
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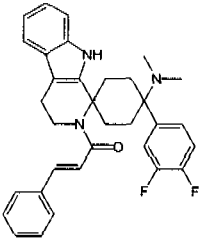
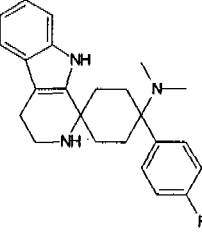
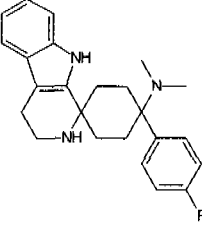
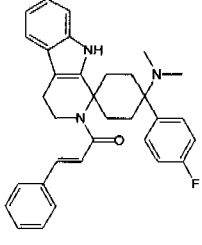
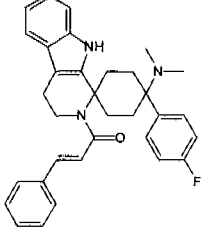
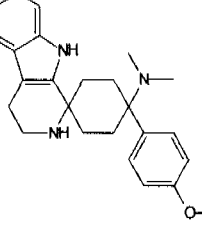
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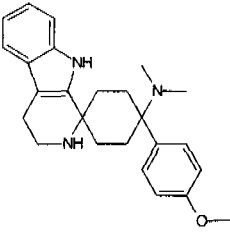
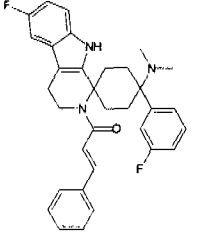
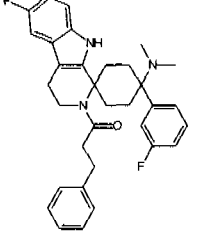
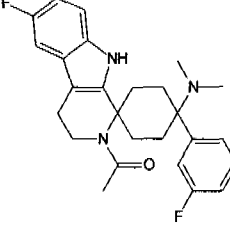
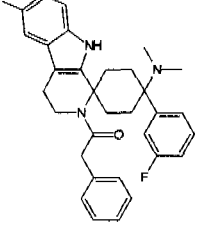
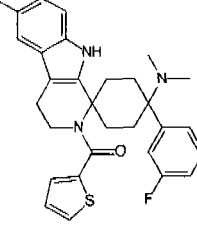
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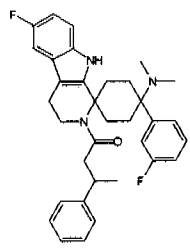
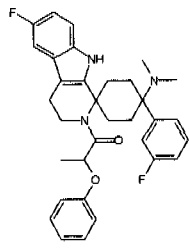
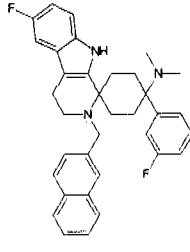
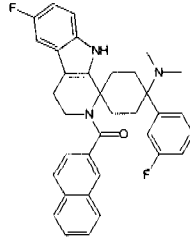
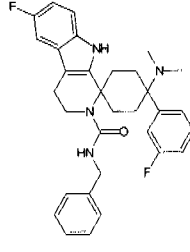
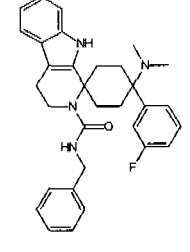
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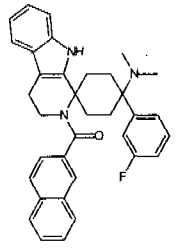
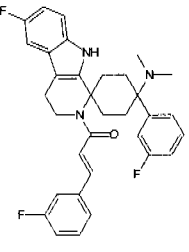
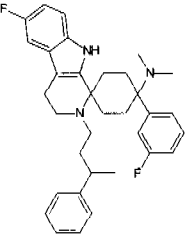
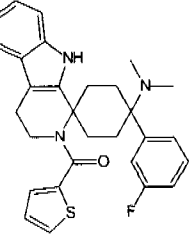
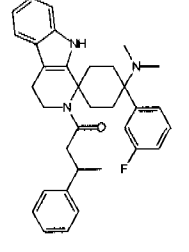
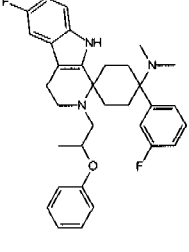
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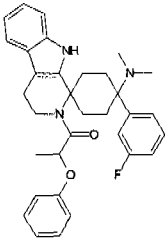
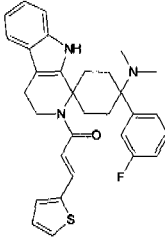
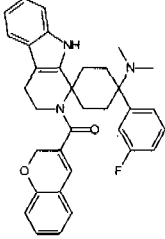
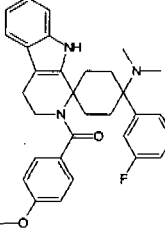
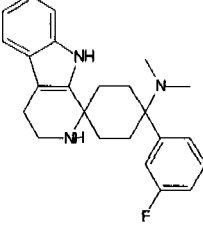
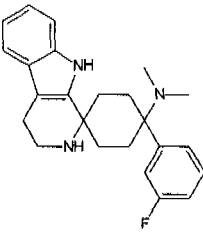
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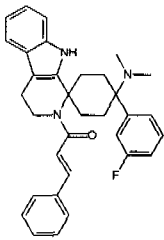
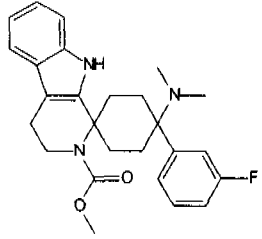
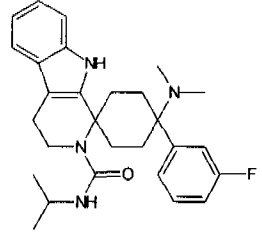
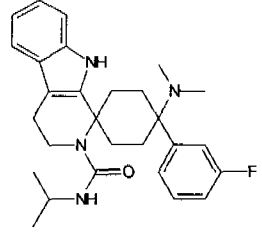
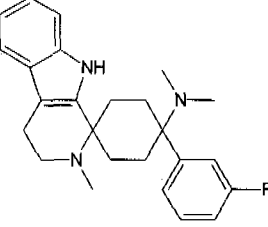
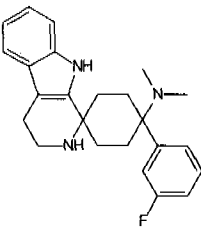
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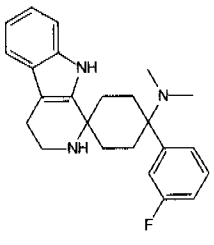
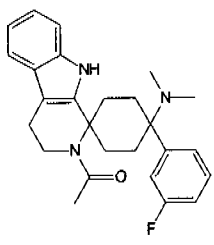
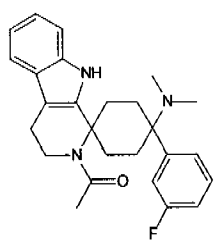
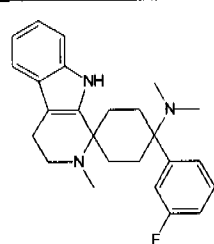
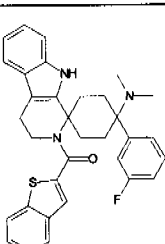
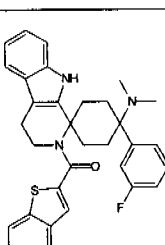
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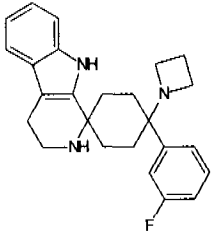
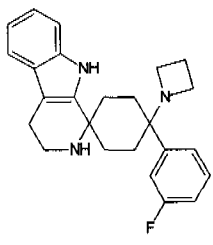
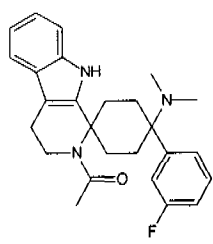
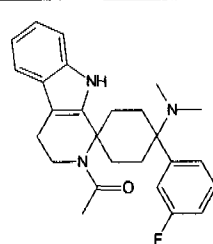
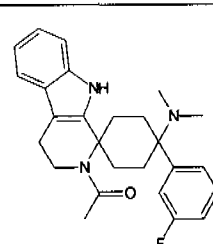
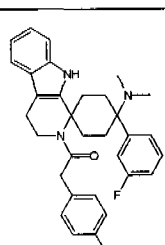
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QQ -76		+
QQ -77		+
QQ -78		+

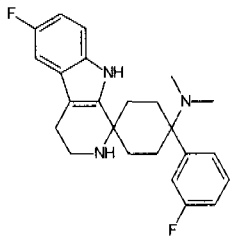
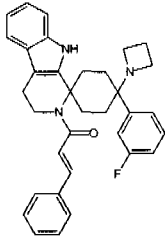
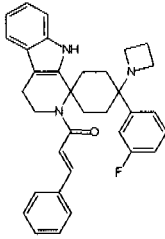
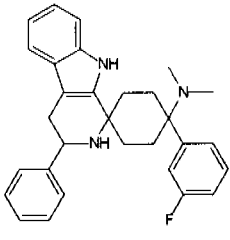
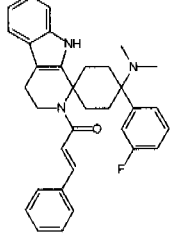
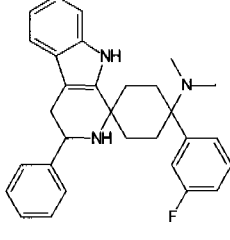
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QQ -81		+
QQ -82		+
QQ -83		+
QQ -84		+

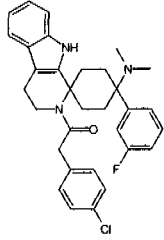
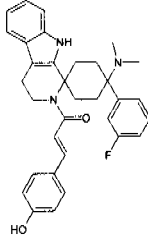
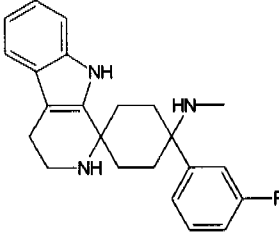
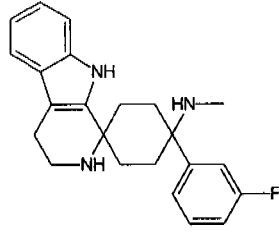
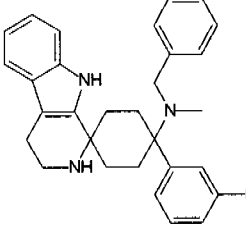
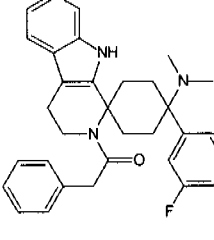
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QQ -87		+
QQ -88		+
QQ -89		+
QQ -90		+

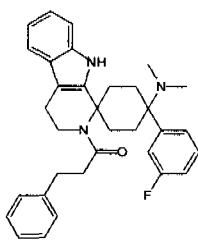
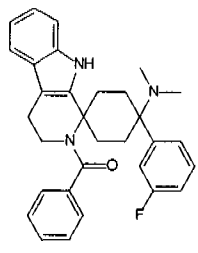
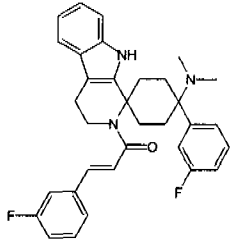
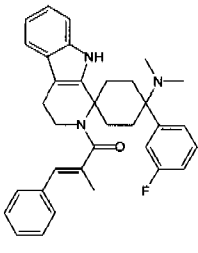
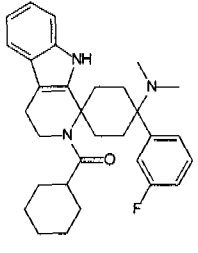
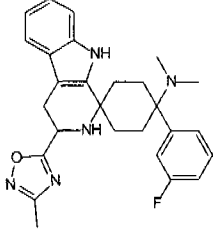
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QQ -93		+
QQ -94		+
QQ -95		+
QQ -96		+

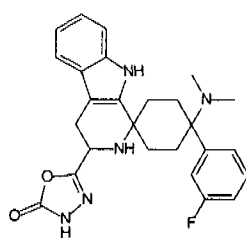
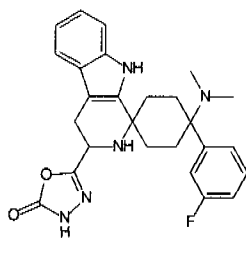
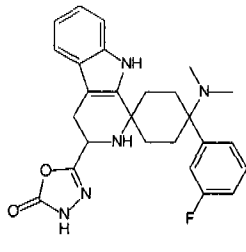
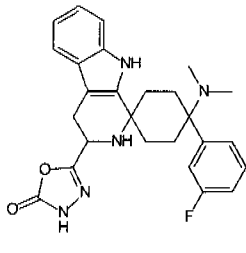
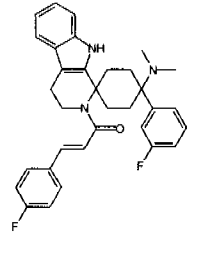
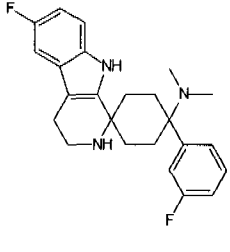
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QQ -98		+
QQ -99		+
QQ -100		+
QQ -101		+
QQ -102		+

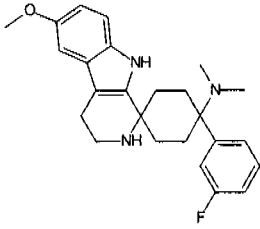
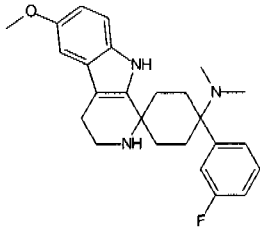
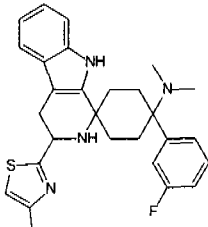
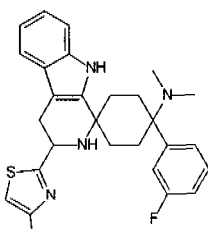
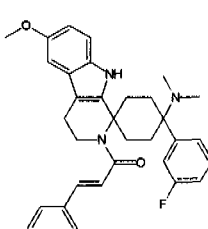
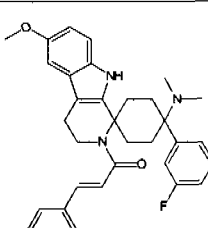
QQ -103		+
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QQ -105		+
QQ -106		+
QQ -107		+
QQ -108		+

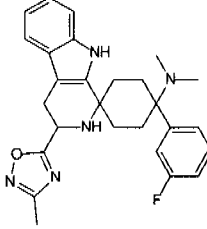
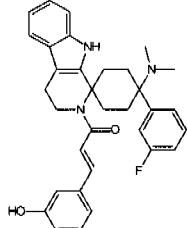
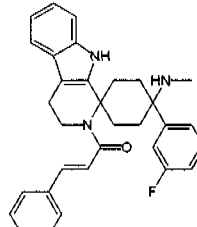
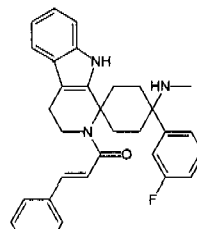
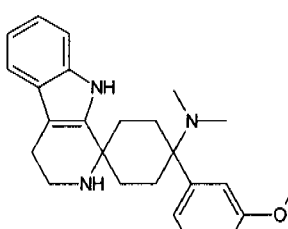
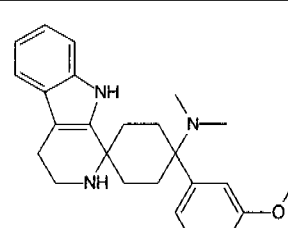
QQ - 109		+
QQ - 110		+
QQ - 111		+
QQ - 112		+
QQ - 113		+
QQ - 114		+

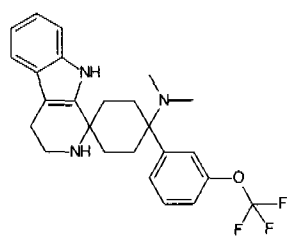
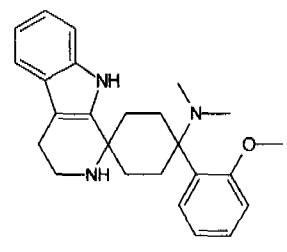
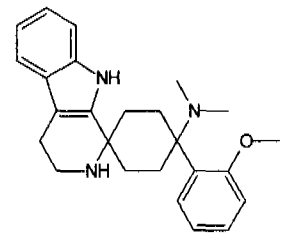
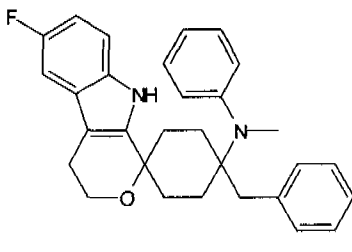
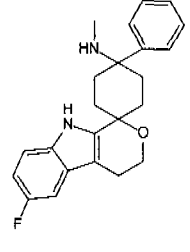
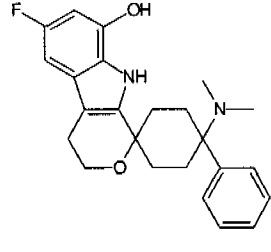
QQ - 115		+
QQ - 116		+
QQ - 117		+
QQ - 118		+
QQ - 119		+
QQ - 120		+

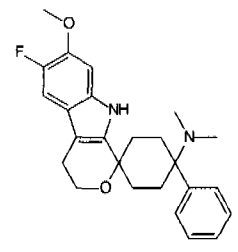
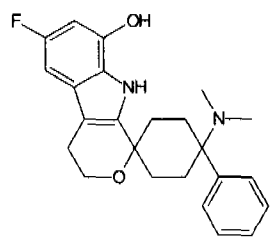
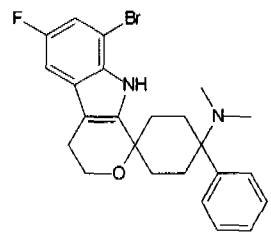
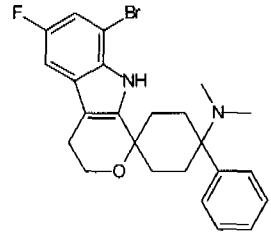
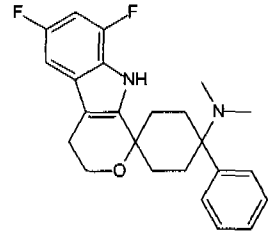
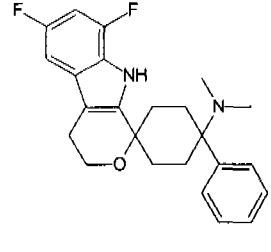
QQ - 121		+
QQ - 122		+
QQ - 123		+
QQ - 124		+
QQ - 125		+
QQ - 126		+

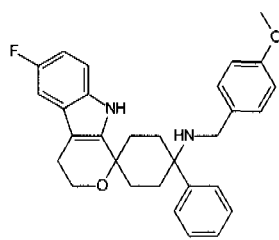
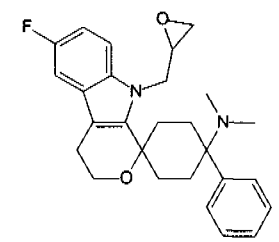
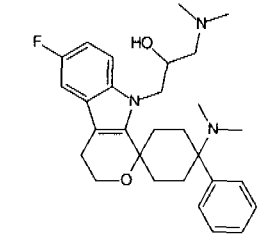
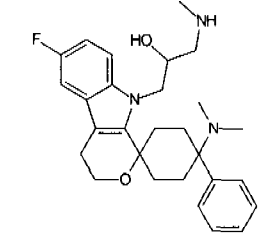
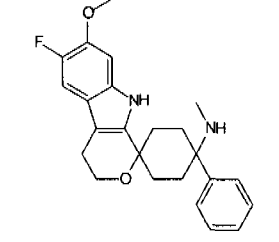
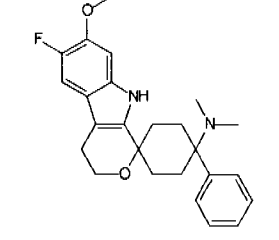
QQ - 127		+
QQ - 128		+
QQ - 129		+
QQ - 130		+
QQ - 131		+
QQ - 132		+

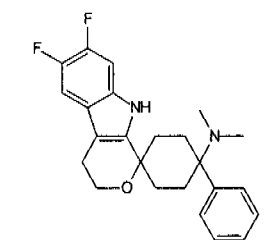
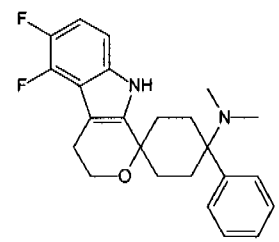
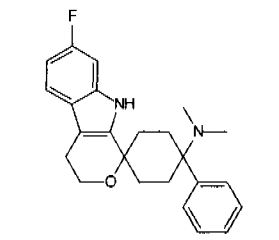
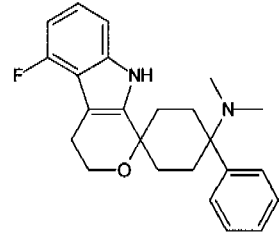
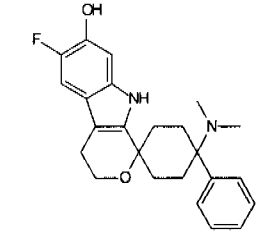
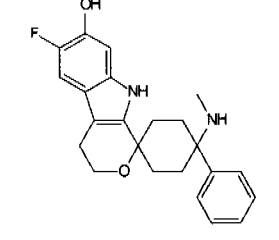
QQ - 133		+
QQ - 134		+
QQ - 135		+
QQ - 136		+
QQ - 137		+
QQ - 138		+

QQ - 139		+
QQ - 140		+
QQ - 141		+
QQ - 142		+
QQ - 143		+
QQ - 144		+

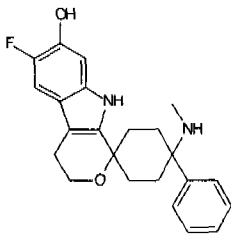
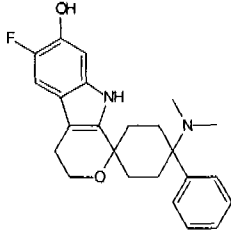
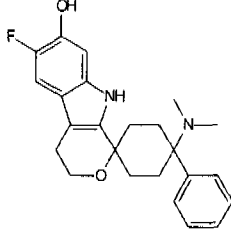
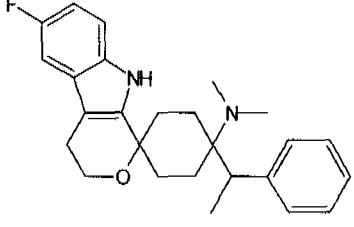
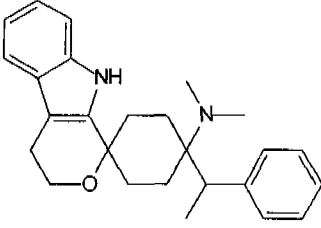
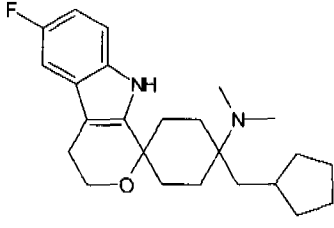
QQ - 145		+
QQ - 146		+
QQ - 147		+
QQ - 148		+
QQ - 149		+
QQ - 150		+

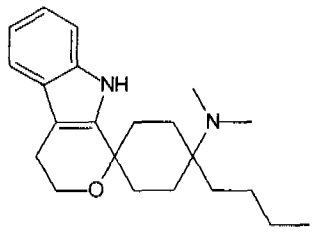
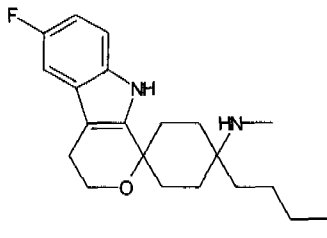
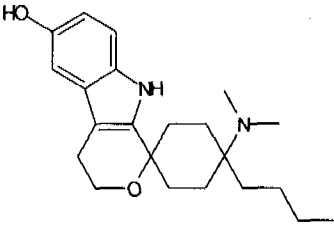
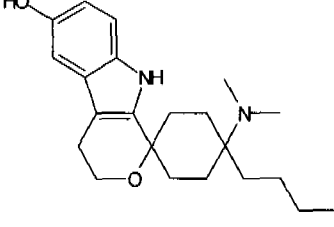
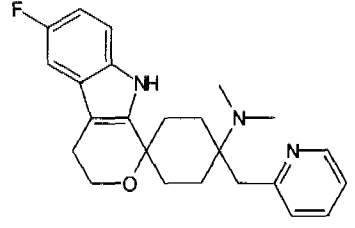
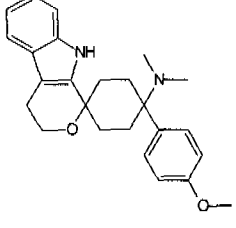
QQ - 151		+
QQ - 152		+
QQ - 153		+
QQ - 154		+
QQ - 155		+
QQ - 156		+

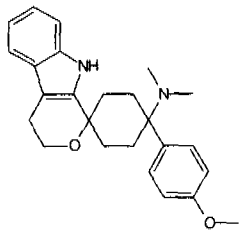
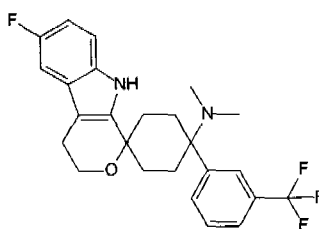
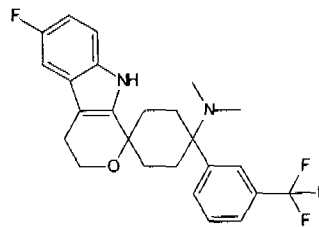
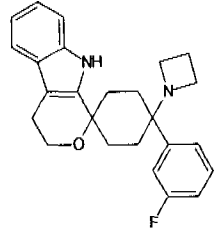
QQ - 157		+
QQ - 158		+
QQ - 159		+
QQ - 160		+
QQ - 161		+
QQ - 162		+

QQ - 163		+
QQ - 164		+
QQ - 165		+
QQ - 166		+
QQ - 167		+
QQ - 168		+

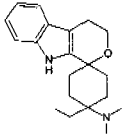
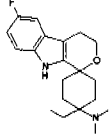
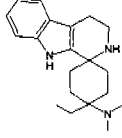
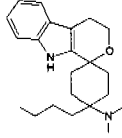
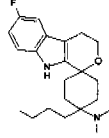
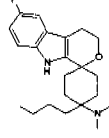
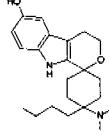
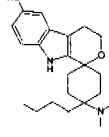
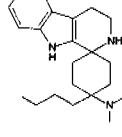
284

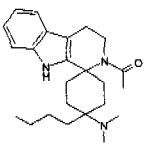
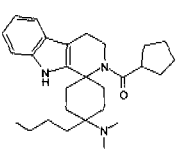
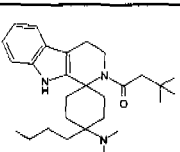
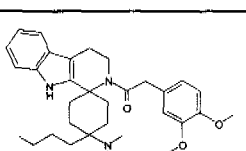
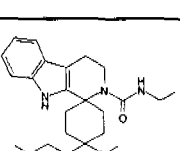
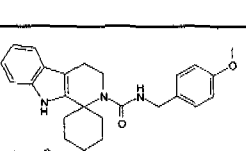
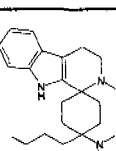
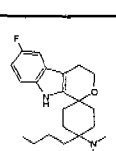
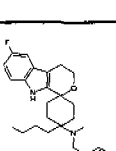
QQ - 169		+
QQ - 170		+
QQ - 171		+
QQ - 172		+
QQ - 173		+
QQ - 174		+

QQ - 175		+
QQ - 176		+
QQ - 177		+
QQ - 178		+
QQ - 179		+
QQ - 180		+

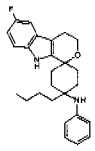
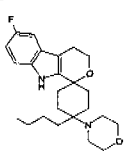
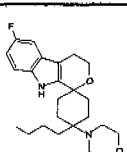
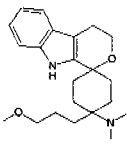
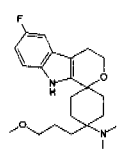
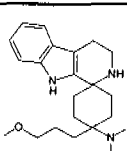
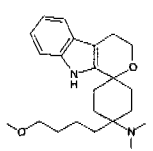
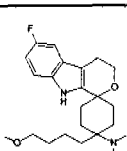
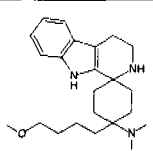
QQ - 181		+
QQ - 182		+
QQ - 183		+
QQ - 184		+

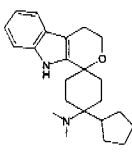
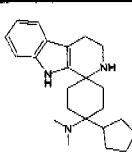
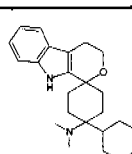
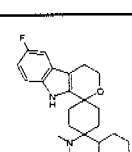
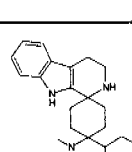
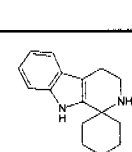
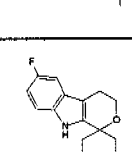
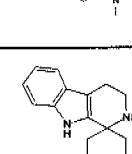
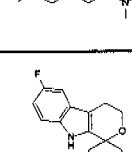
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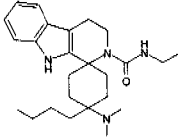
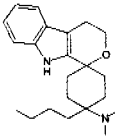
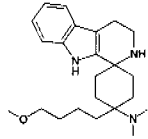
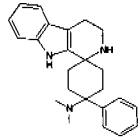
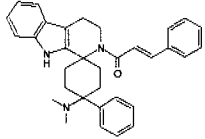
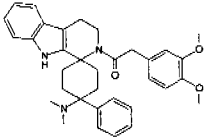
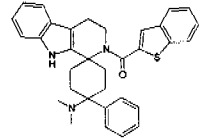
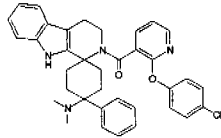
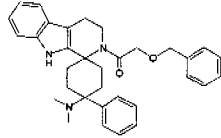
declaration example no./example no. from application	base	salt with	diastereomeric form	active
AA-1		citric acid	1 of 2 possible diastereomers	+
AA-2		citric acid	more apolar diastereomer	+
AA-3		citric acid	1 of 2 possible diastereomers	+
AA-4		citric acid	1 of 2 possible diastereomers	+
AA-5		citric acid	1 of 2 possible diastereomers	+
AA-6		citric acid	1 of 2 possible diastereomers	+
AA-7		citric acid	1 of 2 possible diastereomers	+
AA-8		citric acid	1 of 2 possible diastereomers	+
AA-9		citric acid	more apolar diastereomer	+

declaration example no./example no. from application	base	salt with	diastereomeric form	active
AA-10		citric acid	more apolar diastereomer	+
AA-11		citric acid	more apolar diastereomer	+
AA-12		citric acid	more apolar diastereomer	+
AA-13		citric acid	more apolar diastereomer	+
AA-14		citric acid	more apolar diastereomer	+
AA-15			more polar diastereomer	+
AA-16		citric acid	more apolar diastereomer	+
AA-17		citric acid	1 of 2 possible diastereomers	+
AA-18			1 of 2 possible diastereomers	+

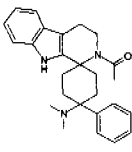
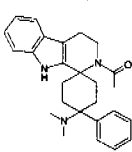
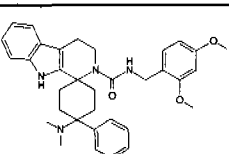
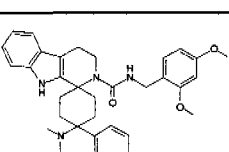
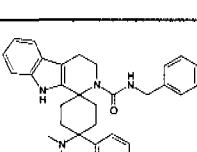
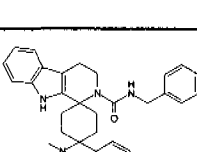
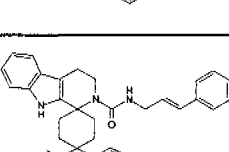
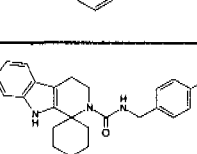
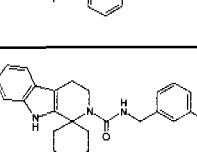
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declaration example no./example no. from application	base	salt with	diastereomeric form	active
AA-19			1 of 2 possible diastereomers	+
AA-20			more apolar diastereomer	+
AA-21			more polar diastereomer	+
AA-22		citric acid	1 of 2 possible diastereomers	+
AA-23		citric acid	more apolar diastereomer	+
AA-24		citric acid	more apolar diastereomer	+
AA-25		citric acid	1 of 2 possible diastereomers	+
AA-26		citric acid	more polar diastereomer	+
AA-27		citric acid	more apolar diastereomer	+

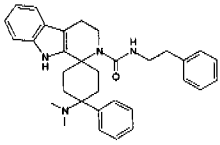
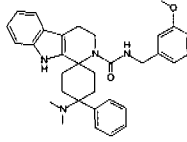
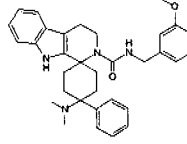
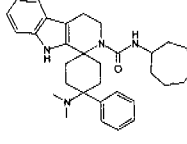
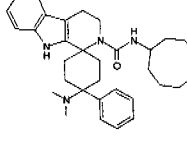
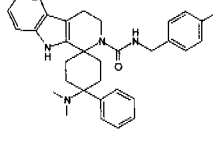
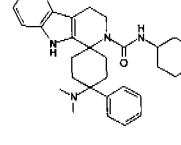
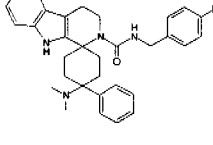
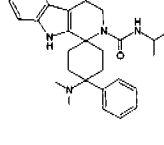
declaration example no./example no. from application	base	salt with	diastereomeric form	active
AA-28		citric acid	1 of 2 possible diastereomers	+
AA-29		citric acid	1 of 2 possible diastereomers	+
AA-30		citric acid	1 of 2 possible diastereomers	+
AA-31		citric acid	1 of 2 possible diastereomers	+
AA-32		citric acid	1 of 2 possible diastereomers	+
AA-33		citric acid	more polar diastereomer	+
AA-34		citric acid	more polar diastereomer	+
AA-35		citric acid	more polar diastereomer	+
AA-36		citric acid	more polar diastereomer	+

declaration example no./example no. from application	base	salt with	diastereomeric form	active
AA-37			more polar diastereomer	+
AA-38		citric acid	more polar diastereomer	+
AA-39		citric acid	more polar diastereomer	+
BB-1			more apolar diastereomer	+
BB-2		methanesulfonic acid	1 of 2 possible diastereomers	+
BB-3		methanesulfonic acid	1 of 2 possible diastereomers	+
BB-4		methanesulfonic acid	1 of 2 possible diastereomers	+
BB-5		methanesulfonic acid	1 of 2 possible diastereomers	+
BB-6		methanesulfonic acid	1 of 2 possible diastereomers	+

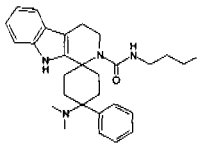
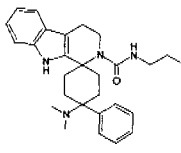
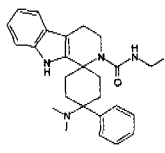
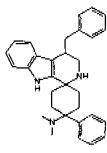
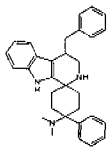
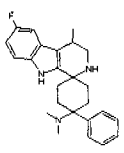
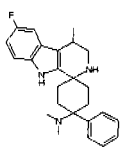
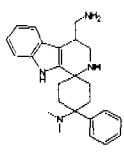
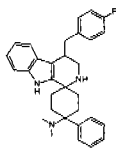
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declaration example no./example no. from application	base	salt with	diastereomeric form	active
BB-7		hydrochloric acid	more apolar diastereomer	+
BB-8				+
BB-9			more apolar diastereomer	+
BB-10			more polar diastereomer	+
BB-11			more polar diastereomer	+
BB-12			more apolar diastereomer	+
BB-13			more polar diastereomer	+
BB-14			more apolar diastereomer	+
BB-15			more polar diastereomer	+

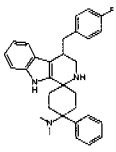
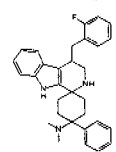
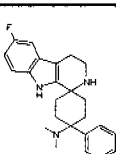
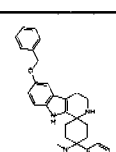
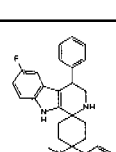
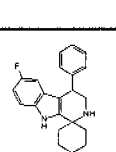
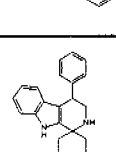
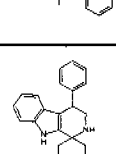
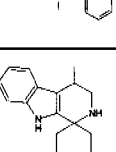
792

declaration example no./example no. from application	base	salt with	diastereomeric form	active
BB-16			more polar diastereomer	+
BB-17			more apolar diastereomer	+
BB-18			more polar diastereomer	+
BB-19			more polar diastereomer	+
BB-20			more polar diastereomer	+
BB-21			more polar diastereomer	+
BB-22			more polar diastereomer	+
BB-23			more polar diastereomer	+
BB-24			more polar diastereomer	+

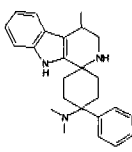
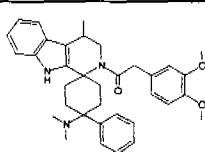
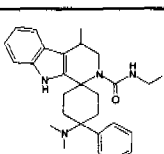
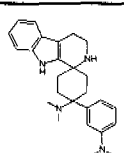
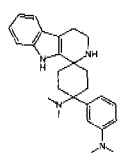
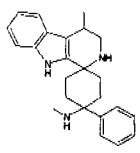
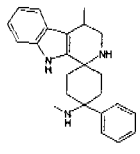
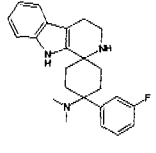
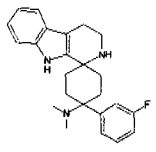
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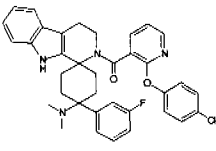
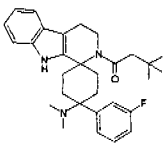
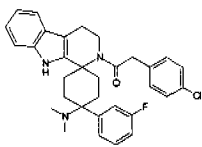
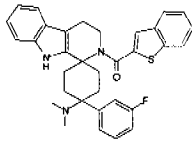
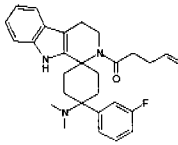
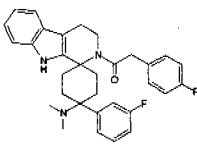
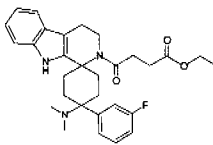
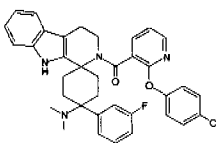
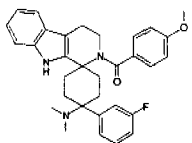
declaration example no./example no. from application	base	salt with	diastereomeric form	active
BB-25			more polar diastereomer	+
BB-26			more polar diastereomer	+
BB-27			more polar diastereomer	+
BB-28		citric acid	more polar diastereomer	+
BB-29		citric acid	more apolar diastereomer	+
BB-30		citric acid	more apolar diastereomer	+
BB-31		citric acid	more polar diastereomer	+
BB-32		citric acid	1 of 2 possible diastereomers	+
BB-33		citric acid	more apolar diastereomer	+

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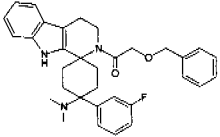
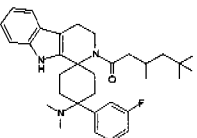
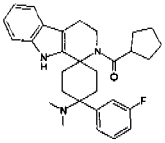
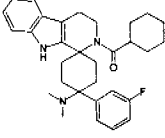
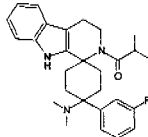
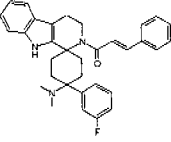
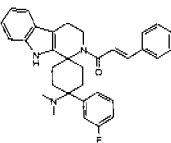
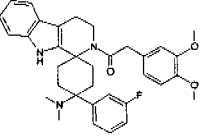
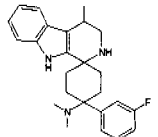
declaration example no./example no. from application	base	salt with	diastereomeric form	active
BB-34		citric acid	more polar diastereomer	+
BB-35		citric acid	diastereomeric mixture (80:20 polar:apolar)	+
BB-36 / I-6			1 of 2 possible diastereomers	+
BB-37		citric acid	diastereomeric mixture	+
BB-38		citric acid	more apolar diastereomer	+
BB-39		citric acid	more polar diastereomer	+
BB-40		citric acid	more apolar diastereomer	+
BB-41		citric acid	more polar diastereomer	+
BB-42		citric acid	more polar diastereomer	+

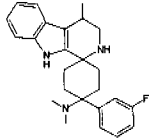
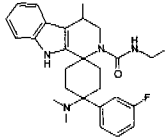
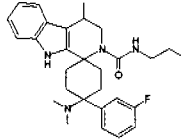
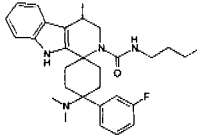
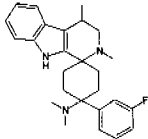
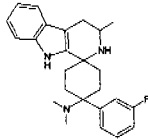
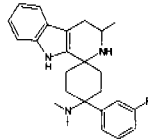
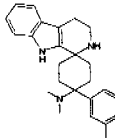
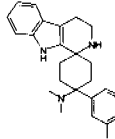
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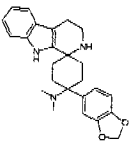
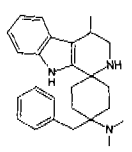
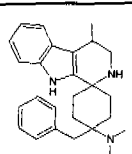
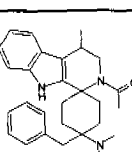
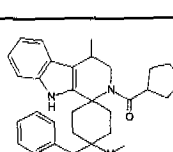
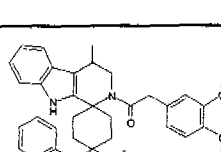
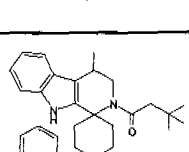
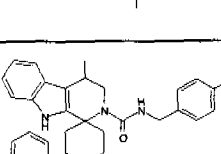
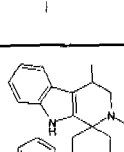
declaration example no./example no. from application	base	salt with	diastereomeric form	active
BB-43		citric acid	more apolar diastereomer	+
BB-44			more polar diastereomer	+
BB-45			more polar diastereomer	+
BB-46		citric acid	more apolar diastereomer	+
BB-47		citric acid	more polar diastereomer	+
BB-48		citric acid	more polar diastereomer	+
BB-49		citric acid	more apolar diastereomer	+
BB-50			1 of 2 possible diastereomers	+
BB-51		citric acid	1 of 2 possible diastereomers	+

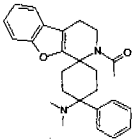
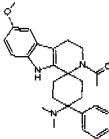
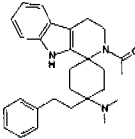
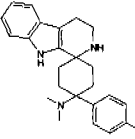
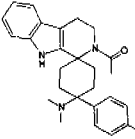
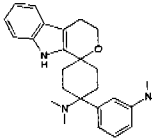
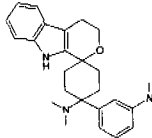
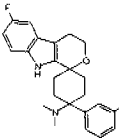
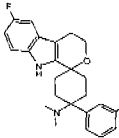
declaration example no./example no. from application	base	salt with	diastereomeric form	active
BB-52			1 of 2 possible diastereomers	+
BB-53		citric acid		+
BB-54				+
BB-55			1 of 2 possible diastereomers	+
BB-56		methanesulfonic acid	1 of 2 possible diastereomers	+
BB-57		methanesulfonic acid	1 of 2 possible diastereomers	+
BB-58		citric acid		+
BB-59		citric acid		+
BB-60		methanesulfonic acid	1 of 2 possible diastereomers	+

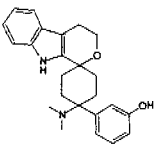
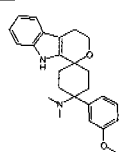
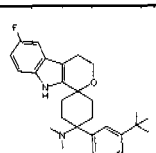
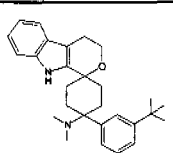
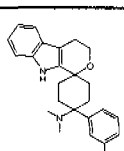
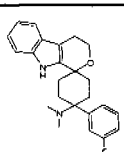
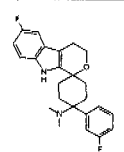
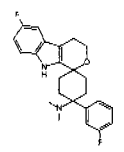
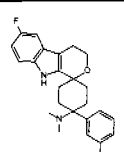
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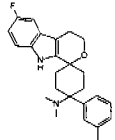
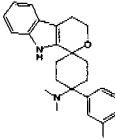
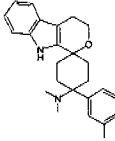
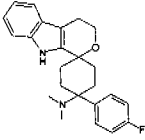
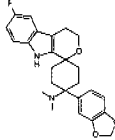
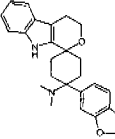
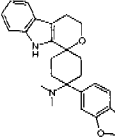
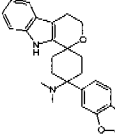
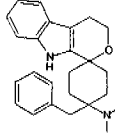
declaration example no./example no. from application	base	salt with	diastereomeric form	active
BB-61		methanesulfonic acid	1 of 2 possible diastereomers	+
BB-62		methanesulfonic acid	1 of 2 possible diastereomers	+
BB-63				+
BB-64				+
BB-65				+
BB-66				+
BB-67		citric acid		+
BB-68			1 of 2 possible diastereomers	+
BB-69		citric acid	more polar diastereomer	+

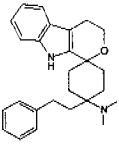
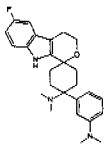
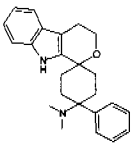
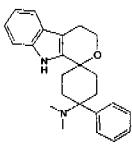
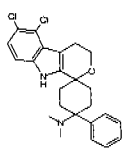
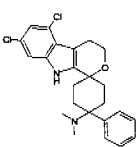
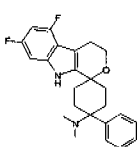
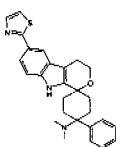
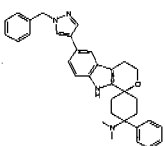
declaration example no./example no. from application	base	salt with	diastereomeric form	active
BB-70		citric acid	more apolar diastereomer	+
BB-71			more polar diastereomer	+
BB-72			more polar diastereomer	+
BB-73			more polar diastereomer	+
BB-74		citric acid	more polar diastereomer	+
BB-75		citric acid	more apolar diastereomer	+
BB-76		citric acid	more polar diastereomer	+
BB-77		citric acid	more polar diastereomer	+
BB-78		citric acid	more apolar diastereomer	+

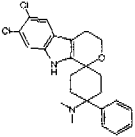
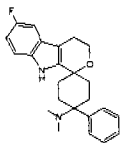
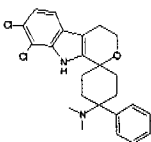
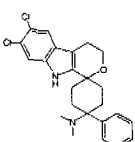
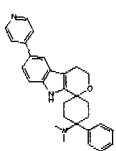
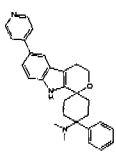
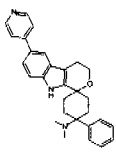
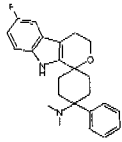
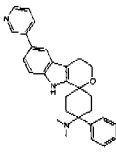
declaration example no./example no. from application	base	salt with	diastereomeric form	active
BB-79		citric acid	1 of 2 possible diastereomers	+
BB-80		citric acid	more apolar diastereomer	+
BB-81		citric acid	more polar diastereomer	+
BB-82		citric acid	more apolar diastereomer	+
BB-83		citric acid	more apolar diastereomer	+
BB-84		citric acid	more apolar diastereomer	+
BB-85		citric acid	more apolar diastereomer	+
BB-86			more apolar diastereomer	+
BB-87		citric acid	more apolar diastereomer	+

declaration example no./example no. from application	base	salt with	diastereomeric form	active
BB-88		citric acid	1 of 2 possible diastereomers	+
BB-89		citric acid	diastereomeric mixture	+
BB-90		hydrochloric acid	1 of 2 possible diastereomers	+
BB-91			diastereomeric mixture (ca. 20 % apolar, 80 % polar)	+
BB-92		citric acid	mixture (ca. 20 % apolar, 80 % polar)	+
CC-1		citric acid	more apolar diastereomer	+
CC-2		citric acid	more polar diastereomer	+
CC-3		citric acid	more apolar diastereomer	+
CC-4		citric acid	more polar diastereomer	+

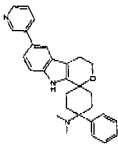
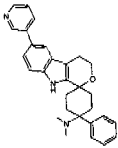
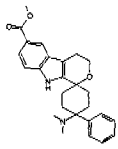
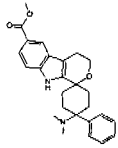
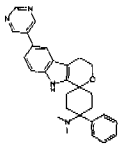
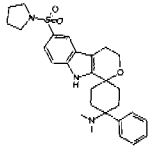
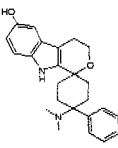
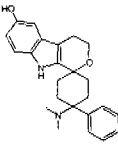
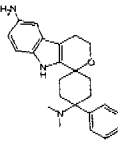
declaration example no./example no. from application	base	salt with	diastereomeric form	active
CC-5		methanesulfonic acid		+
CC-6		citric acid		+
CC-7		citric acid	more apolar diastereomer	+
CC-8		citric acid	more apolar diastereomer	+
CC-9		citric acid	more apolar diastereomer	+
CC-10		citric acid	more polar diastereomer	+
CC-11		citric acid	more polar diastereomer	+
CC-12		citric acid	more apolar diastereomer	+
CC-13		citric acid	more polar diastereomer	+

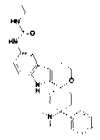
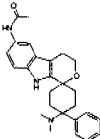
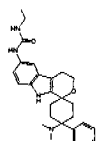
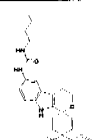
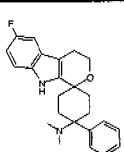
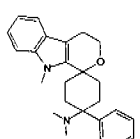
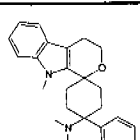
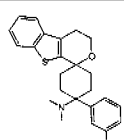
declaration example no./example no. from application	base	salt with	diastereomeric form	active
CC-14		citric acid	more apolar diastereomer	+
CC-15		citric acid	more polar diastereomer	+
CC-16		citric acid	more apolar diastereomer	+
CC-17		citric acid		+
CC-18		citric acid	1 of 2 possible diastereomers	+
CC-19		citric acid	more polar diastereomer	+
CC-20		methanesulfonic acid	more apolar diastereomer	+
CC-21		citric acid	more apolar diastereomer	+
CC-22		methanesulfonic acid		+

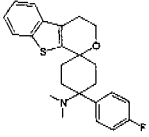
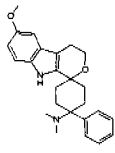
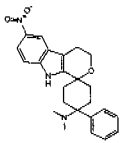
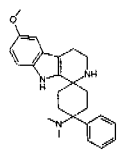
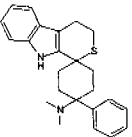
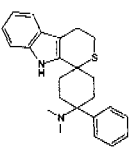
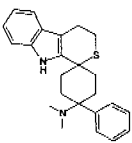
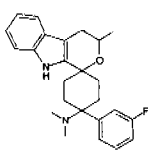
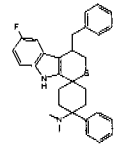
declaration example no./example no. from application	base	salt with	diastereomeric form	active
CC-23		citric acid		+
CC-24		citric acid	1 of 2 possible diastereomers	+
CC-25			more apolar diastereomer	+
CC-26			more polar diastereomer	+
DD-1		citric acid		+
DD-2		citric acid		+
DD-3		methanesulfonic acid		+
DD-4		citric acid		+
DD-5		hydrochloric acid		+

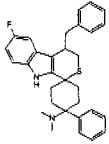
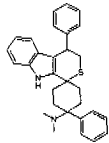
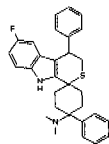
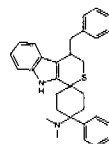
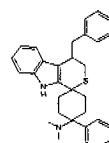
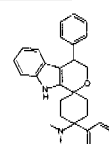
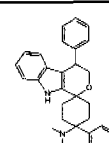
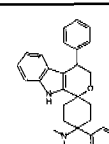
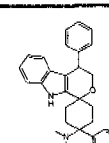
declaration example no./example no. from application	base	salt with	diastereomeric form	active
DD-6		citric acid		+
DD-7		citric acid		+
DD-8		methanesulfonic acid		+
DD-9		citric acid		+
DD-10		methanesulfonic acid		+
DD-11		citric acid		+
DD-12		citric acid		+
DD-13		methanesulfonic acid	more apolar diastereomer	+
DD-14		methanesulfonic acid		+

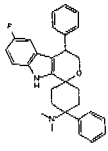
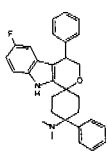
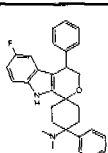
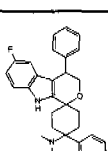
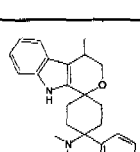
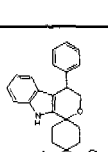
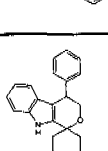
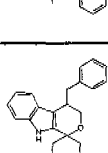
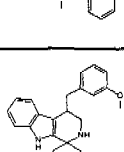
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declaration example no./example no. from application	base	salt with	diastereomeric form	active
DD-15		citric acid		+
DD-16		citric acid		+
DD-17		citric acid		+
DD-18		citric acid		+
DD-19		hydrochloric acid		+
DD-20		citric acid		+
DD-21		citric acid		+
DD-22		citric acid	more polar diastereomer	+
DD-23		citric acid	1 of 2 possible diastereomers	+

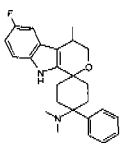
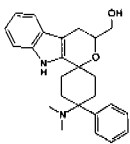
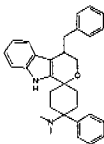
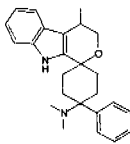
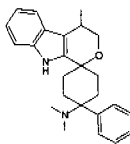
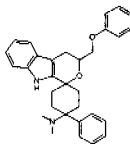
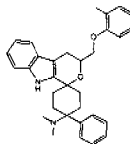
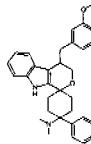
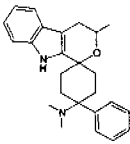
declaration example no./example no. from application	base	salt with	diastereomeric form	active
DD-24		citric acid	1 of 2 possible diastereomers	+
DD-25		hydrochloric acid	1 of 2 possible diastereomers	+
DD-26		citric acid	1 of 2 possible diastereomers	+
DD-27		citric acid	1 of 2 possible diastereomers	+
DD-28		citric acid	1 of 2 possible diastereomers	+
DD-29				+
DD-30		hydrochloric acid		+
DD-31		hydrochloric acid		+
DD-32		L-tartaric acid		+

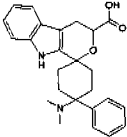
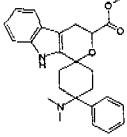
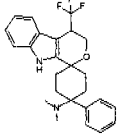
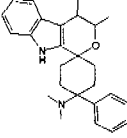
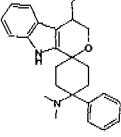
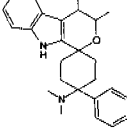
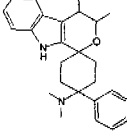
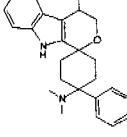
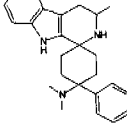
declaration example no./example no. from application	base	salt with	diastereomeric form	active
DD-33		L-tartaric acid	1 of 2 possible diastereomers	+
DD-34		citric acid	more apolar diastereomer	+
DD-35		citric acid	1 of 2 possible diastereomers	+
DD-36		citric acid	mixture (1:1)	+
DD-37		trifluoromethane sulfonic acid	1 of 2 possible diastereomers	+
DD-38		L-tartaric acid	1 of 2 possible diastereomers	+
DD-39		citric acid		+
EE-1		citric acid	more apolar diastereomer	+
EE-2		citric acid	mixture of both diastereomers	+

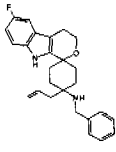
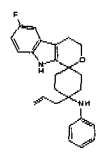
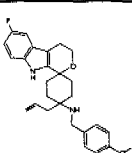
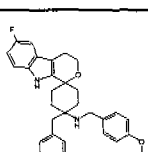
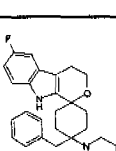
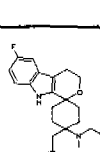
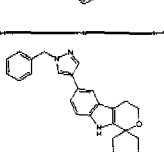
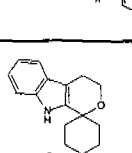
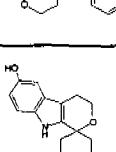
declaration example no./example no. from application	base	salt with	diastereomeric form	active
EE-3		citric acid	more polar diastereomer	+
EE-4		citric acid	more apolar diastereomer from (S)-styreneoxide	+
EE-5		citric acid	one of 2 possible diastereomers from (R)- styreneoxid	+
EE-6		citric acid	more polar diastereomer	+
EE-7		citric acid	more apolar diastereomer	+
EE-8			more apolar diastereomer from (S)-styreneoxide	+
EE-9			more polar diastereomer from (S)-styreneoxide	+
EE-10		citric acid	more apolar diastereomer from (S)-styreneoxide	+
EE-11		citric acid	more polar diastereomer from (S)-styreneoxide	+

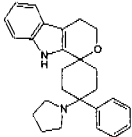
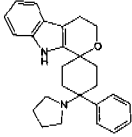
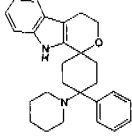
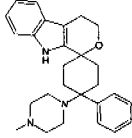
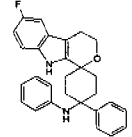
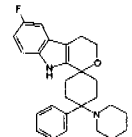
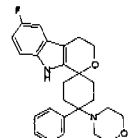
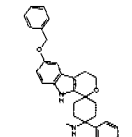
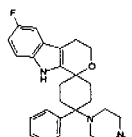
declaration example no./example no. from application	base	salt with	diastereomeric form	active
EE-12		citric acid	more apolar diastereomer from (S)-styreneoxide	+
EE-13		citric acid	more polar diastereomer from (S)-styreneoxide	+
EE-14		citric acid	more apolar diastereomer from (R)-styreneoxide	+
EE-15		citric acid	more polar diastereomer from (R)-styreneoxide	+
EE-16		citric acid	more apolar diastereomer	+
EE-17			more apolar diastereomer from (R)-styreneoxide	+
EE-18		citric acid	more polar diastereomer from (R)-styreneoxide	+
EE-19		citric acid	more polar diastereomer	+
EE-20		citric acid	more polar diastereomer	+

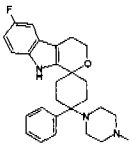
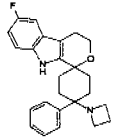
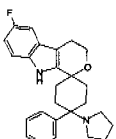
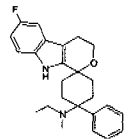
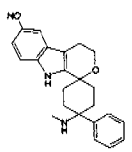
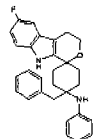
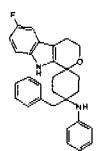
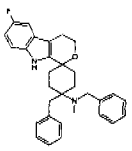
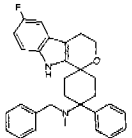
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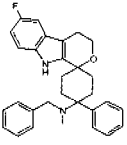
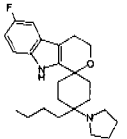
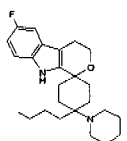
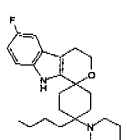
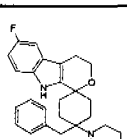
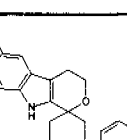
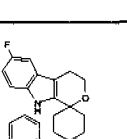
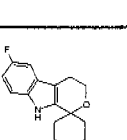
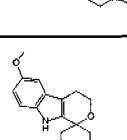
declaration example no./example no. from application	base	salt with	diastereomeric form	active
EE-21		citric acid	more apolar diastereomer	+
EE-22		citric acid	1 of 2 possible diastereomers	+
EE-23		citric acid	more apolar diastereomer	+
EE-24		citric acid	ca. 85% more apolar diastereomer	+
EE-25		citric acid	ca. 85% more apolar diastereomer	+
EE-26		citric acid	1 of 2 possible diastereomers	+
EE-27		citric acid	1 of 2 possible diastereomers	+
EE-28		citric acid	more apolar diastereomer	+
EE-29				+

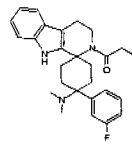
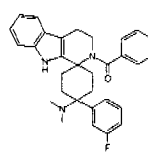
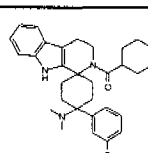
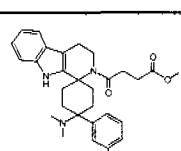
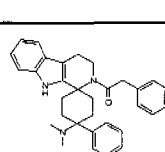
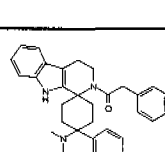
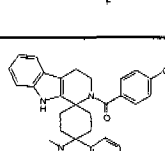
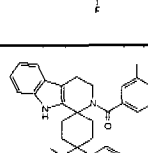
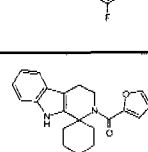
declaration example no./example no. from application	base	salt with	diastereomeric form	active
EE-30				+
EE-31		hydrochloric acid		+
EE-32		citric acid	mixture from 75% apolar and 25% polar diastereomer	+
EE-33		citric acid	1 of 2 possible diastereomers	+
EE-34		citric acid	more apolar diastereomer	+
EE-35		citric acid	more apolar diastereomer	+
EE-36		citric acid	more polar diastereomer (Racemat)	+
EE-37		citric acid	more apolar diastereomer	+
EE-38		hydrochloric acid	mixture of 2 diastereomers	+

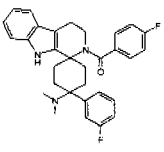
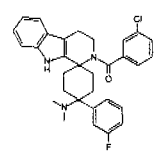
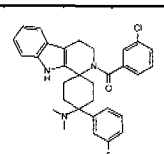
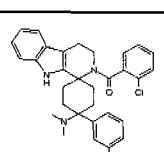
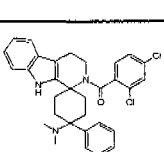
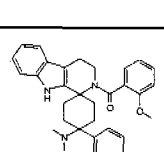
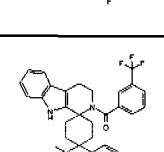
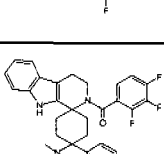
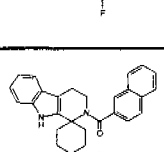
declaration example no./example no. from application	base	salt with	diastereomeric form	active
FF-1		citric acid	1 of 2 possible diastereomers	+
FF-2				+
FF-3			1 of 2 possible diastereomers	+
FF-4		citric acid	1 of 2 possible diastereomers	+
FF-5			1 of 2 possible diastereomers	-
FF-6		citric acid	1 of 2 possible diastereomers	+
FF-7			more polar diastereomer	-
FF-8		methanesulfonic acid		-
FF-9		citric acid		+

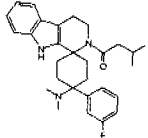
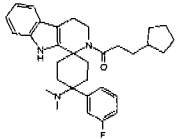
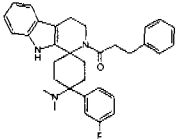
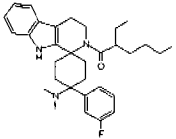
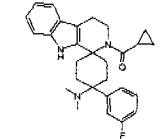
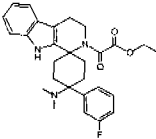
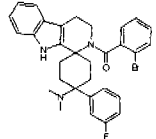
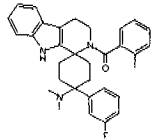
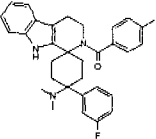
declaration example no./example no. from application	base	salt with	diastereomeric form	active
FF-10		citric acid	more apolar diastereomer	+
FF-11		citric acid	more polar diastereomer	+
FF-12		methanesulfonic acid	1 of 2 possible diastereomers	+
FF-13		methanesulfonic acid	1 of 2 possible diastereomers	-
FF-14			1 of 2 possible diastereomers	+
FF-15		citric acid	1 of 2 possible diastereomers	+
FF-16			1 of 2 possible diastereomers	-
FF-17		citric acid	mainly 1 of 2 possible diastereomers	+
FF-18		citric acid	diastereomeric mixture	+

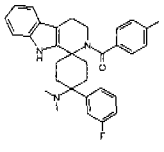
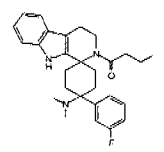
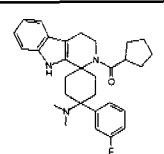
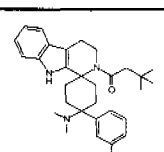
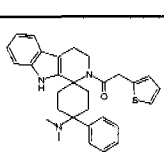
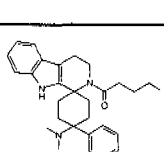
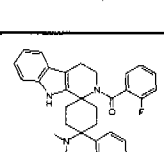
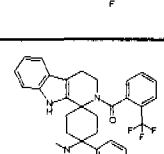
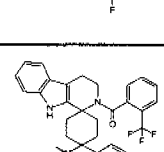
declaration example no./example no. from application	base	salt with	diastereomeric form	active
FF-19			diastereomeric mixture	+
FF-20		citric acid	1 of 2 possible diastereomers	+
FF-21		citric acid	1 of 2 possible diastereomers	+
FF-22		citric acid	1 of 2 possible diastereomers	+
FF-23		citric acid	more apolar diastereomer	+
FF-24			more polar diastereomer	not yet determined
FF-25			diastereomeric mixture	-
FF-26			1 of 2 possible diastereomers	+
FF-27			more apolar diastereomer	+

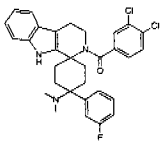
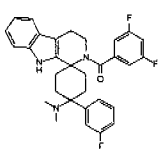
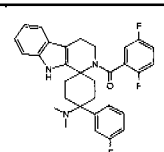
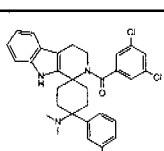
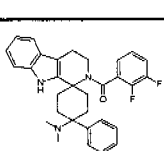
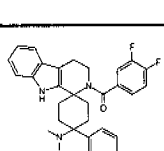
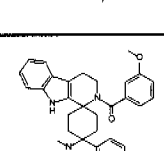
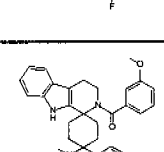
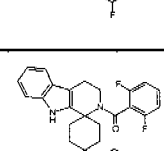
declaration example no./example no. from application	base	salt with	diastereomeric form	active
FF-28			more polar diastereomer	+
FF-29		citric acid	1 of 2 possible diastereomers	+
FF-30			more apolar diastereomer	+
FF-31		citric acid	more polar diastereomer	+
FF-32		citric acid	1 of 2 possible diastereomers	+
FF-33				+
FF-34		citric acid	1 of 2 possible diastereomers	+
FF-35		citric acid	1 of 2 possible diastereomers	+
FF-36		citric acid	1 of 2 possible diastereomers	+

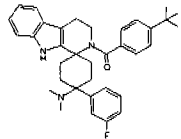
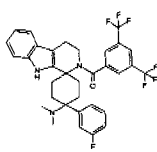
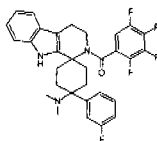
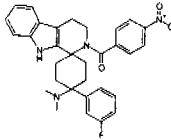
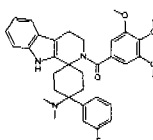
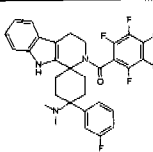
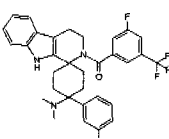
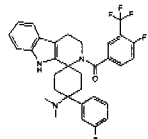
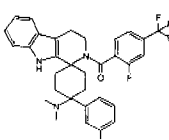
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-1				+
GG-2				+
GG-3				+
GG-4				+
GG-5				+
GG-6				+
GG-7				+
GG-8				+
GG-9				+

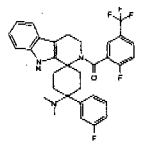
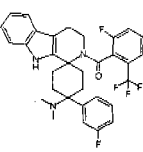
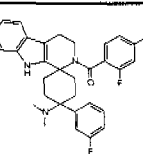
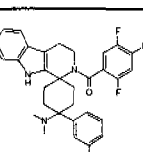
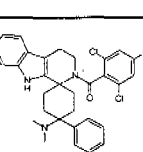
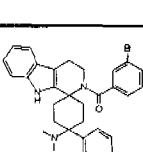
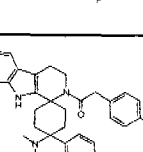
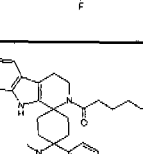
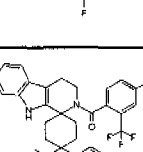
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-10				+
GG-11				+
GG-12				+
GG-13				+
GG-14				+
GG-15				+
GG-16				+
GG-17				+
GG-18				+

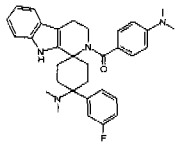
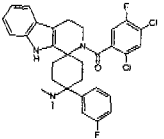
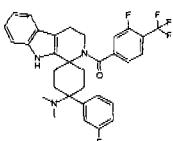
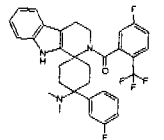
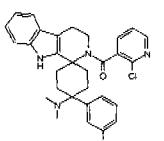
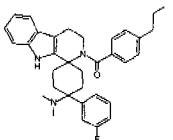
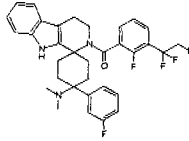
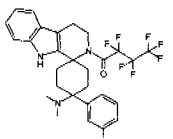
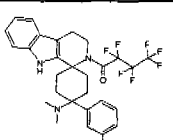
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-19				+
GG-20				+
GG-21				+
GG-22				+
GG-23				+
GG-24				+
GG-25				+
GG-26				+
GG-27				+

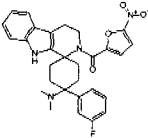
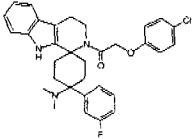
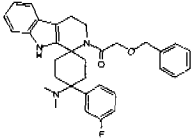
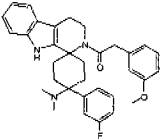
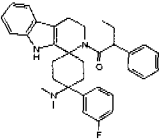
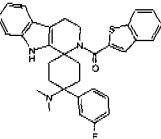
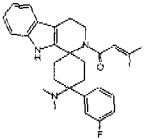
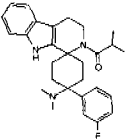
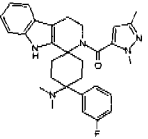
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-28				+
GG-29				+
GG-30				+
GG-31				+
GG-32				+
GG-33				+
GG-34				+
GG-35				+
GG-36				+

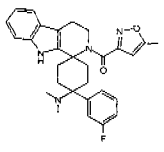
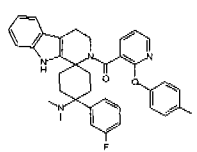
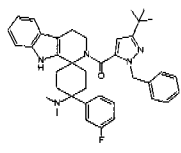
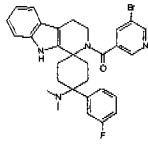
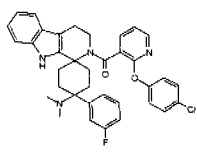
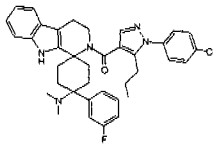
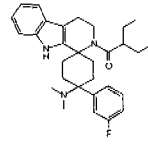
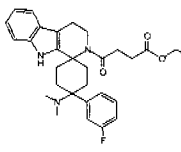
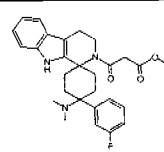
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-37				+
GG-38				+
GG-39				+
GG-40				+
GG-41				+
GG-42				+
GG-43				+
GG-44				+
GG-45				+

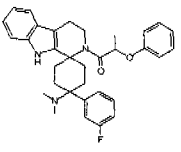
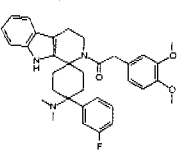
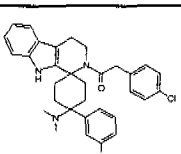
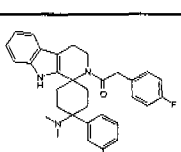
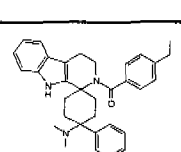
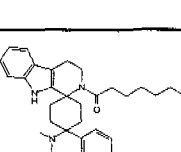
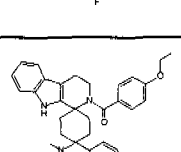
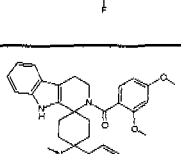
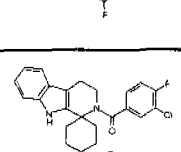
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-46				+
GG-47				+
GG-48				+
GG-49				+
GG-50				+
GG-51				+
GG-52				+
GG-53				+
GG-54				+

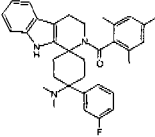
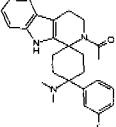
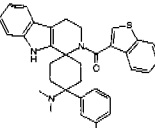
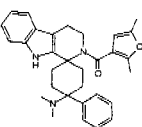
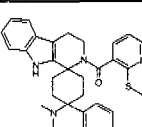
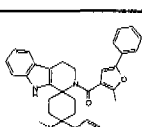
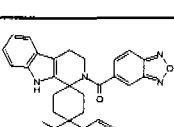
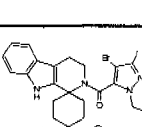
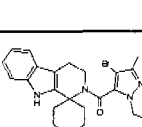
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-55				+
GG-56				+
GG-57				+
GG-58				+
GG-59				+
GG-60				+
GG-61				+
GG-62				+
GG-63				+

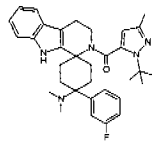
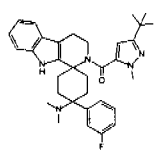
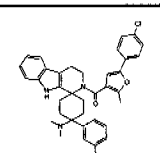
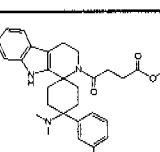
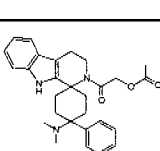
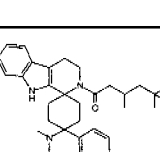
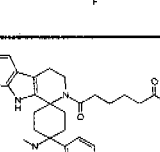
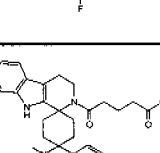
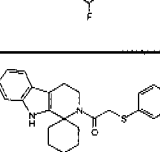
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-64				+
GG-65				+
GG-66				+
GG-67				+
GG-68				+
GG-69				+
GG-70				+
GG-71				+
GG-72				+

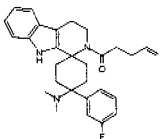
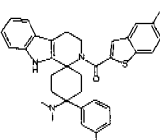
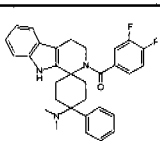
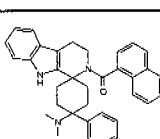
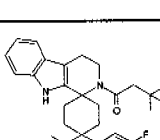
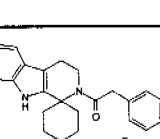
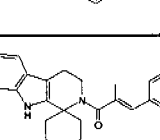
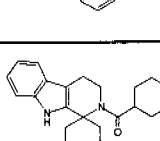
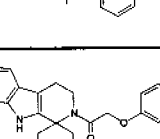
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-73				+
GG-74				+
GG-75				+
GG-76				+
GG-77				+
GG-78				+
GG-79				+
GG-80				+
GG-81				+

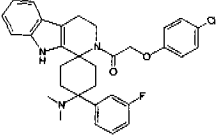
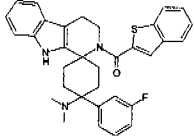
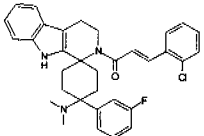
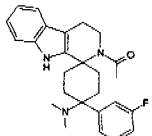
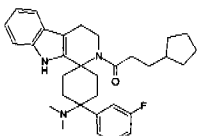
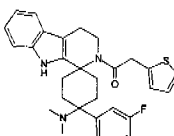
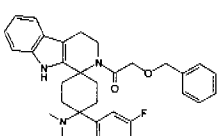
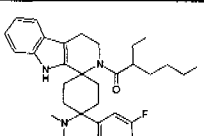
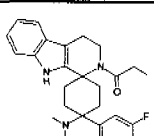
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-82				+
GG-83				+
GG-84				+
GG-85				+
GG-86				+
GG-87				+
GG-88				+
GG-89				+
GG-90				+

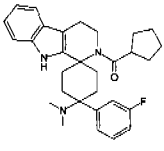
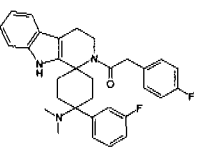
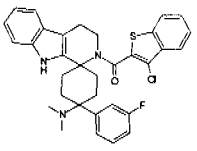
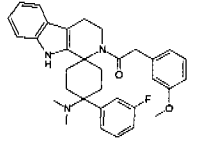
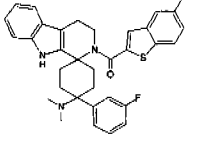
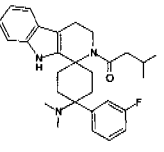
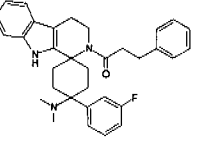
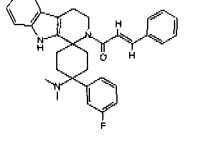
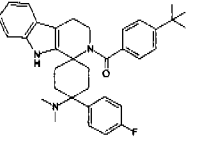
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-91				+
GG-92				+
GG-93				+
GG-94				+
GG-95				+
GG-96				+
GG-97				+
GG-98				+
GG-99				+

declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-100				+
GG-101				+
GG-102				+
GG-103				+
GG-104				+
GG-105				+
GG-106				+
GG-107				+
GG-108				+

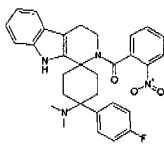
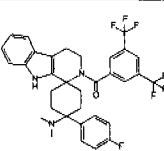
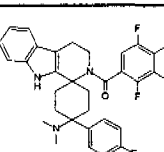
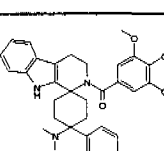
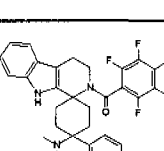
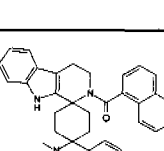
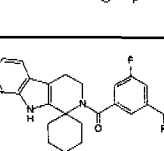
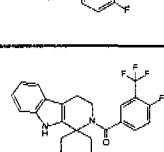
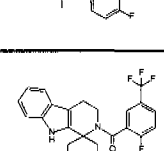
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-109				+
GG-110				+
GG-111				+
GG-112				+
GG-113				+
GG-114				+
GG-115				+
GG-116				+
GG-117				+

declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-118				+
GG-119				+
GG-120				+
GG-121				+
GG-122				+
GG-123				+
GG-124				+
GG-125				+
GG-126				+

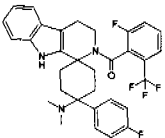
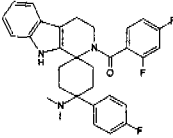
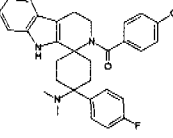
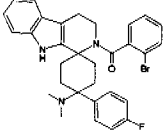
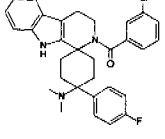
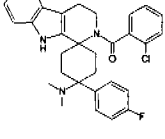
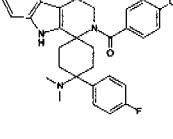
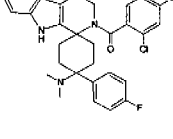
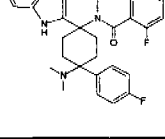
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-127				+
GG-128				+
GG-129				+
GG-130				+
GG-131				+
GG-132				+
GG-133				+
GG-134				+
GG-135				+

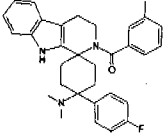
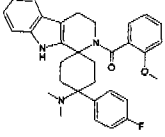
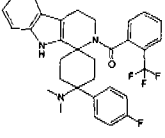
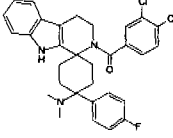
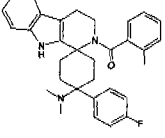
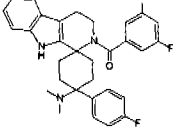
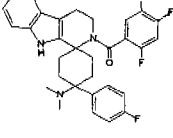
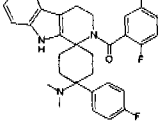
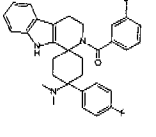
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-136				+
GG-137				+
GG-138				+
GG-139				+
GG-140				+
GG-141				+
GG-142				+
GG-143				+
GG-144				+

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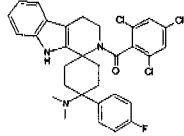
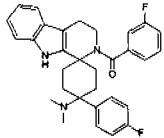
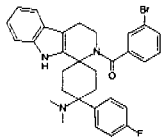
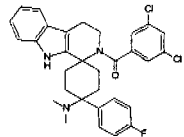
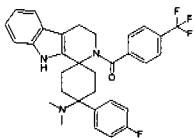
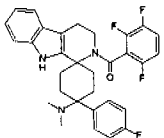
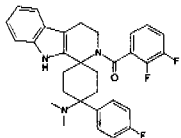
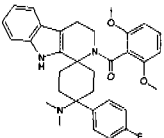
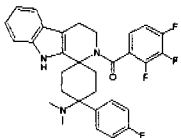
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-145				+
GG-146				+
GG-147				+
GG-148				+
GG-149				+
GG-150				+
GG-151				+
GG-152				+
GG-153				+

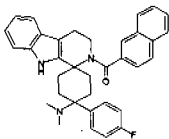
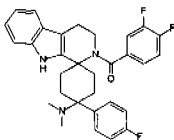
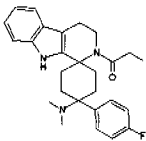
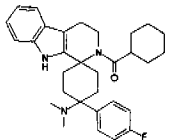
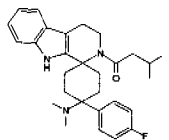
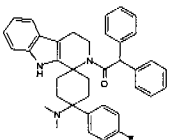
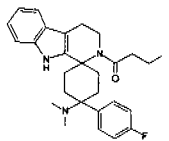
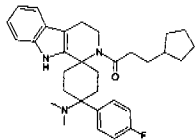
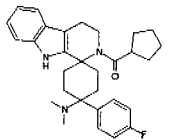
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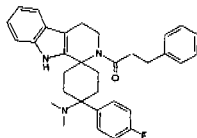
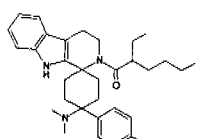
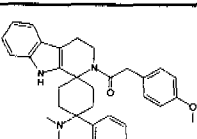
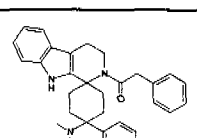
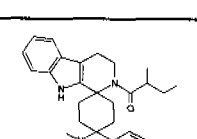
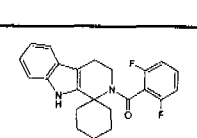
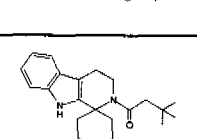
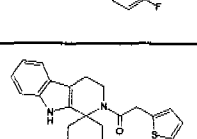
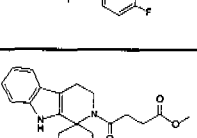
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-154				+
GG-155				+
GG-156				+
GG-157				+
GG-158				+
GG-159				+
GG-160				+
GG-161				+
GG-162				+

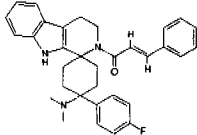
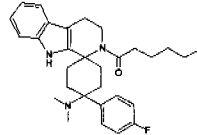
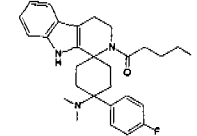
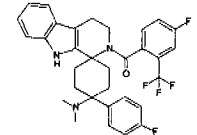
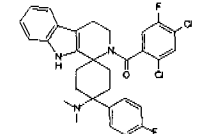
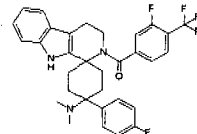
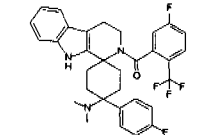
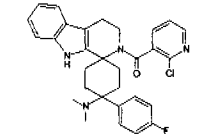
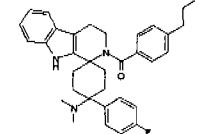
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-163				+
GG-164				+
GG-165				+
GG-166				+
GG-167				+
GG-168				+
GG-169				+
GG-170				+
GG-171				+

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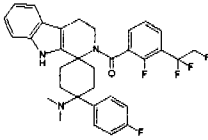
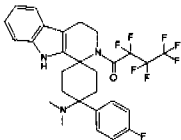
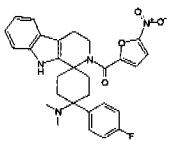
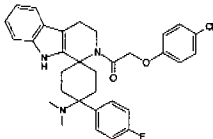
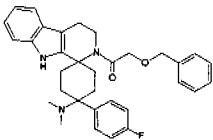
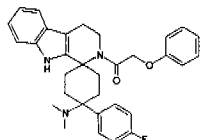
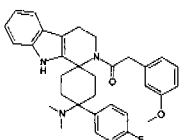
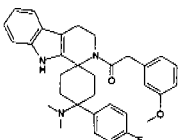
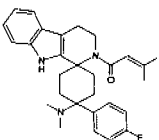
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-172				+
GG-173				+
GG-174				+
GG-175				+
GG-176				+
GG-177				+
GG-178				+
GG-179				+
GG-180				+

declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-181				+
GG-182				+
GG-183				+
GG-184				+
GG-185				+
GG-186				+
GG-187				+
GG-188				+
GG-189				+

declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-190				+
GG-191				+
GG-192				+
GG-193				+
GG-194				+
GG-195				+
GG-196				+
GG-197				+
GG-198				+

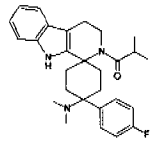
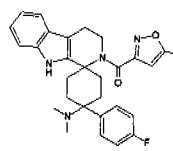
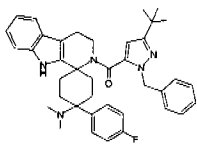
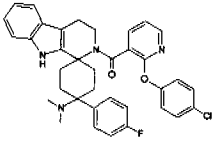
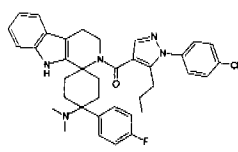
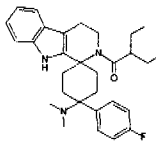
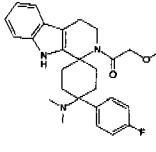
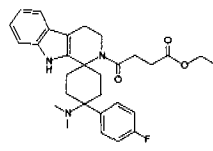
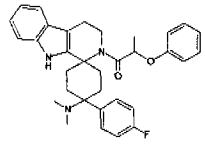
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-199				+
GG-200				+
GG-201				+
GG-202				+
GG-203				+
GG-204				+
GG-205				+
GG-206				+
GG-207				+

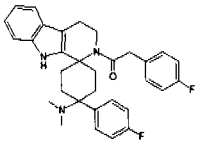
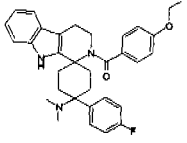
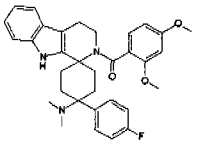
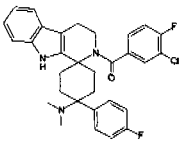
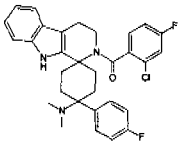
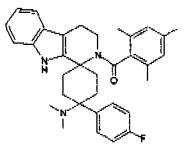
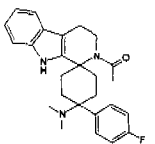
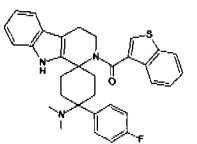
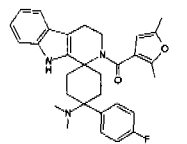
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declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-208				+
GG-209				+
GG-210				+
GG-211				+
GG-212				+
GG-213				+
GG-214				+
GG-215				+
GG-216				+

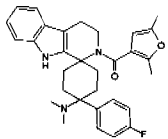
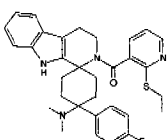
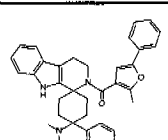
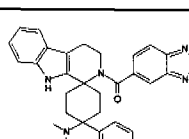
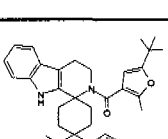
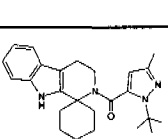
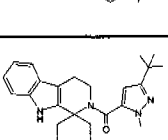
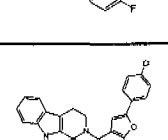
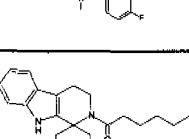
111

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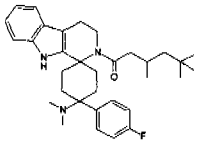
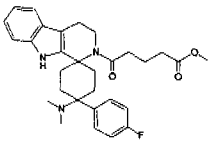
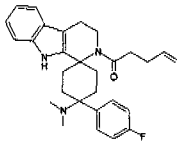
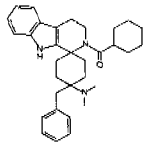
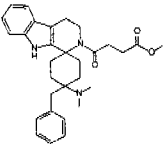
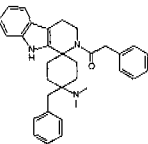
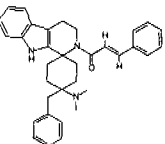
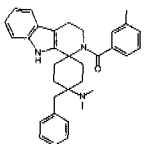
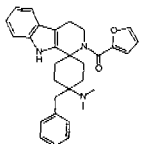
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-217				+
GG-218				+
GG-219				+
GG-220				+
GG-221				+
GG-222				+
GG-223				+
GG-224				+
GG-225				+

declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-226				+
GG-227				+
GG-228				+
GG-229				+
GG-230				+
GG-231				+
GG-232				+
GG-233				+
GG-234				+

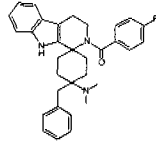
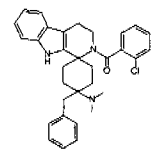
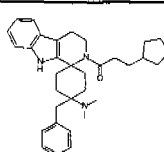
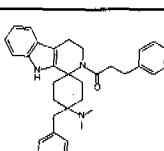
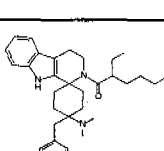
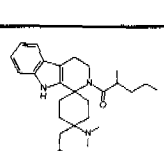
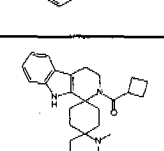
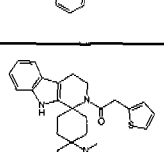
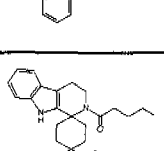
343

declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-235				+
GG-236				+
GG-237				+
GG-238				+
GG-239				+
GG-240				+
GG-241				+
GG-242				+
GG-243				+

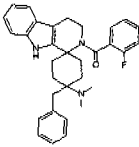
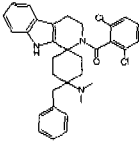
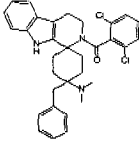
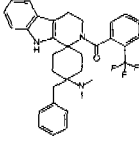
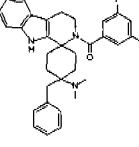
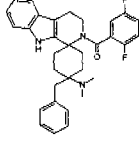
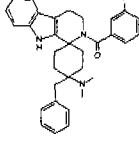
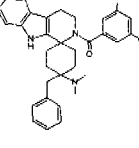
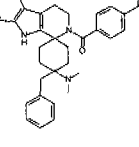
304

declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-244				+
GG-245				+
GG-246				+
GG-247				+
GG-248				+
GG-249				+
GG-250				+
GG-251				+
GG-252				+

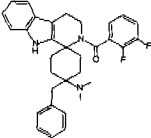
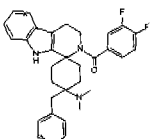
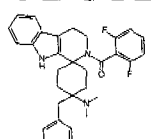
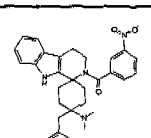
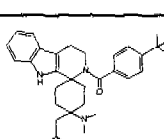
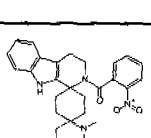
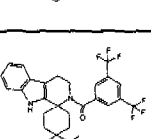
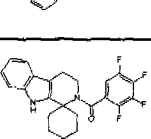
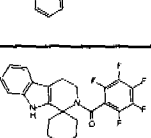
345

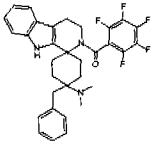
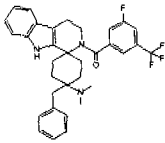
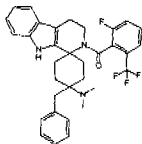
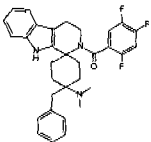
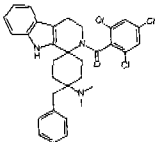
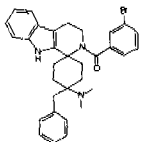
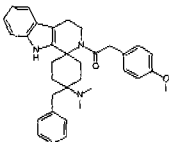
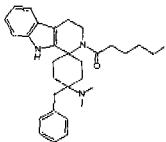
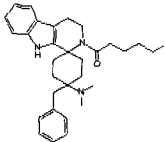
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-253				+
GG-254				+
GG-255				+
GG-256				+
GG-257				+
GG-258				+
GG-259				+
GG-260				+
GG-261				+

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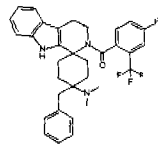
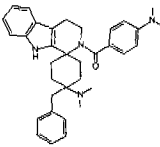
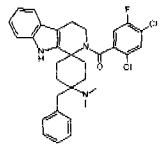
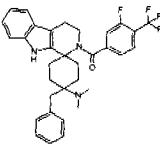
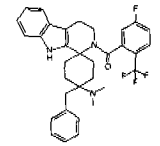
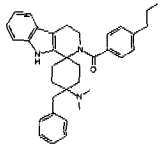
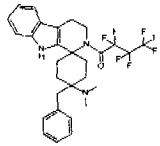
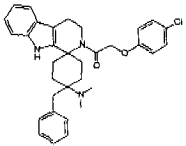
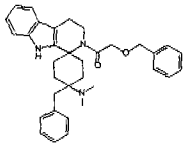
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-262				+
GG-263				+
GG-264				+
GG-265				+
GG-266				+
GG-267				+
GG-268				+
GG-269				+
GG-270				+

347

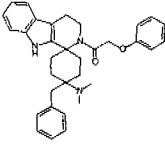
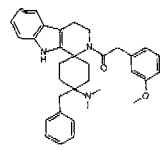
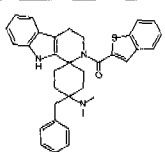
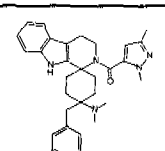
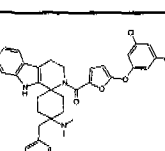
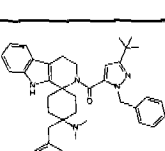
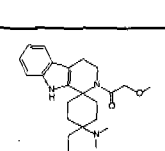
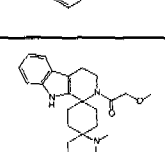
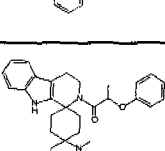
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-271				+
GG-272				+
GG-273				+
GG-274				+
GG-275				+
GG-276				+
GG-277				+
GG-278				+
GG-279				+

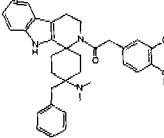
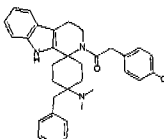
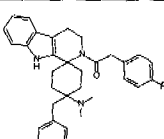
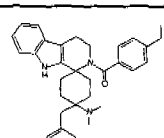
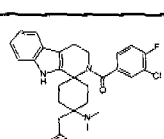
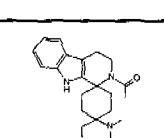
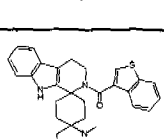
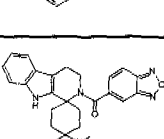
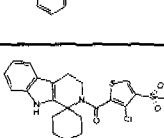
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-280				+
GG-281				+
GG-282				+
GG-283				+
GG-284				+
GG-285				+
GG-286				+
GG-287				+
GG-288				+

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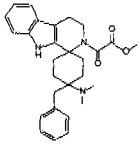
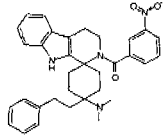
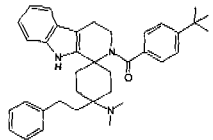
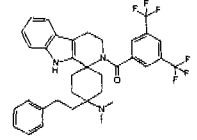
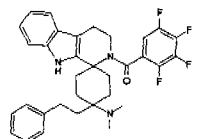
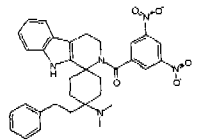
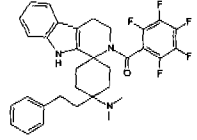
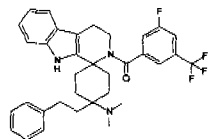
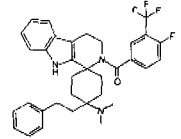
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-289				+
GG-290				+
GG-291				+
GG-292				+
GG-293				+
GG-294				+
GG-295				+
GG-296				+
GG-297				+

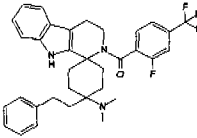
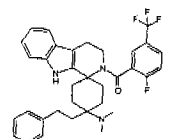
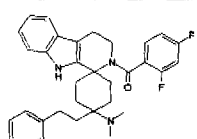
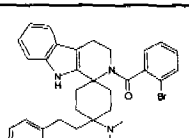
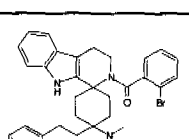
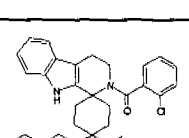
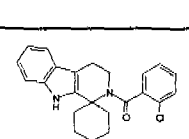
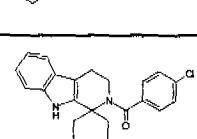
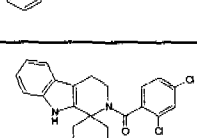
350

declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-298				+
GG-299				+
GG-300				+
GG-301				+
GG-302				+
GG-303				+
GG-304				+
GG-305				+
GG-306				+

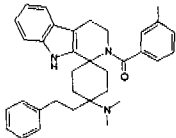
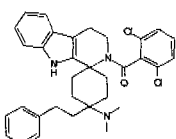
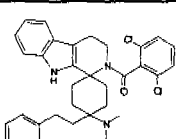
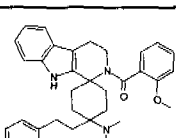
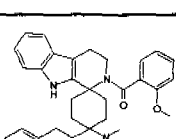
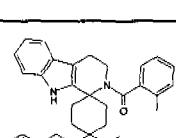
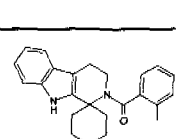
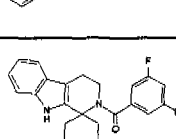
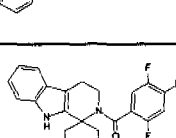
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-307				+
GG-308				+
GG-309				+
GG-310				+
GG-311				+
GG-312				+
GG-313				+
GG-314				+
GG-315				+

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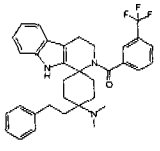
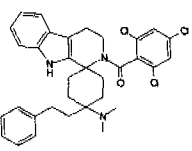
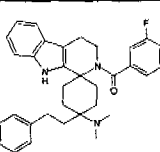
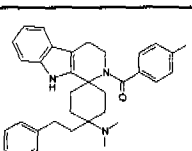
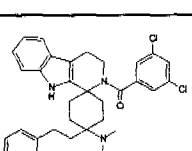
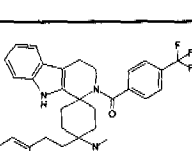
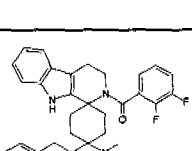
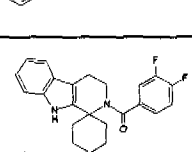
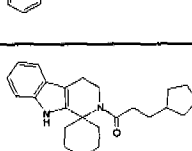
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-316				+
GG-317				+
GG-318				+
GG-319				+
GG-320				+
GG-321				+
GG-322				+
GG-323				+
GG-324				+

declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-325				+
GG-326				+
GG-327				+
GG-328				+
GG-329				+
GG-330				+
GG-331				+
GG-332				+
GG-333				+

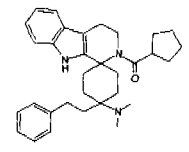
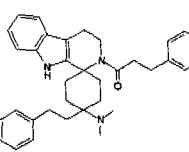
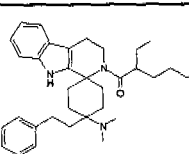
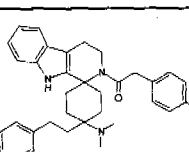
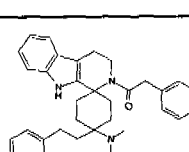
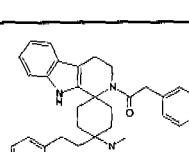
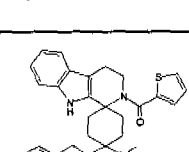
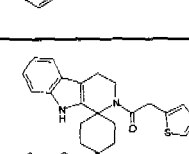
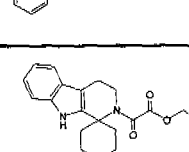
254

declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-334				+
GG-335				+
GG-336				+
GG-337				+
GG-338				+
GG-339				+
GG-340				+
GG-341				+
GG-342				+

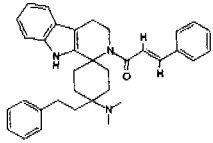
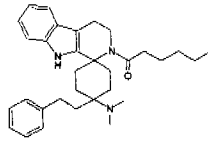
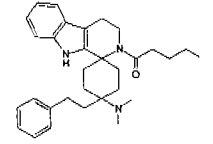
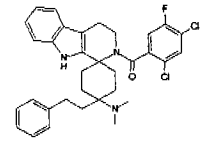
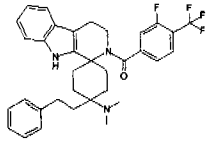
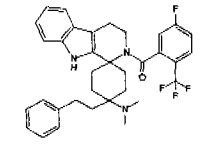
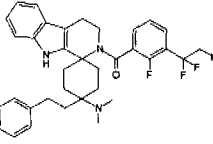
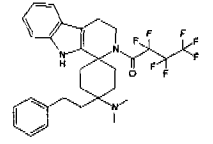
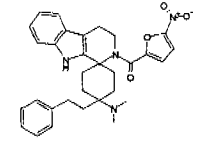
355

declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-343				+
GG-344				+
GG-345				+
GG-346				+
GG-347				+
GG-348				+
GG-349				+
GG-350				+
GG-351				+

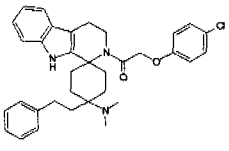
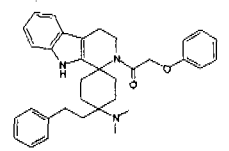
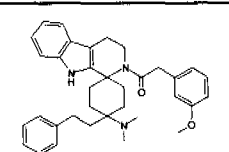
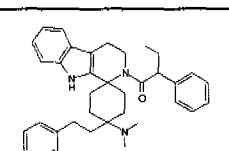
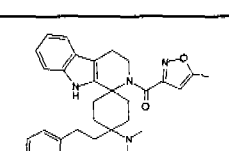
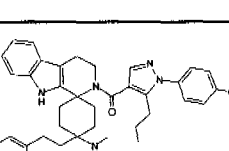
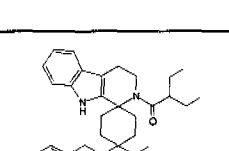
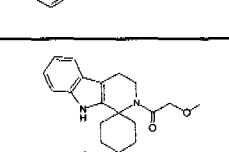
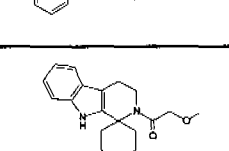
351

declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-352				+
GG-353				+
GG-354				+
GG-355				+
GG-356				+
GG-357				+
GG-358				+
GG-359				+
GG-360				+

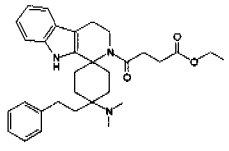
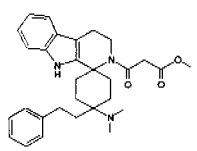
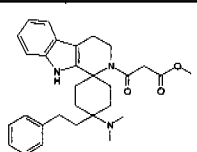
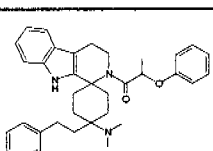
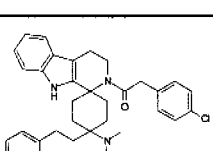
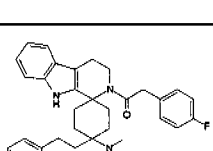
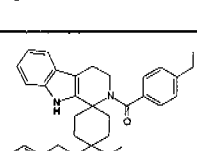
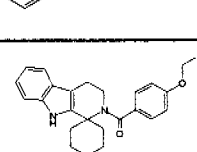
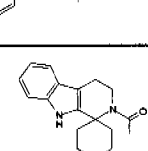
352

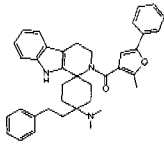
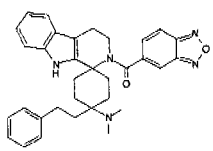
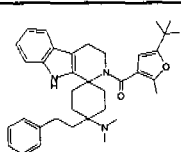
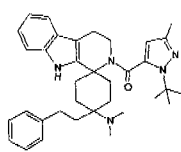
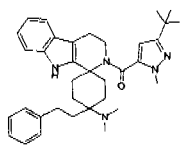
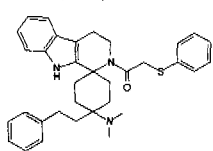
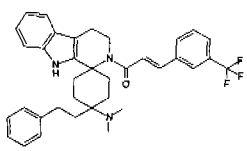
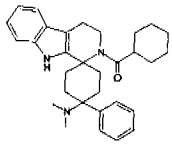
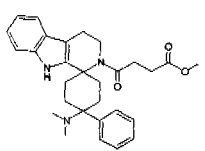
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-361				+
GG-362				+
GG-363				+
GG-364				+
GG-365				+
GG-366				+
GG-367				+
GG-368				+
GG-369				+

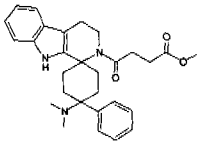
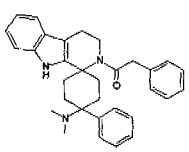
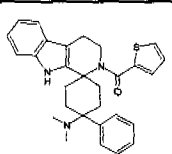
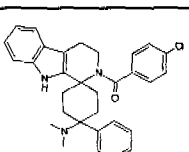
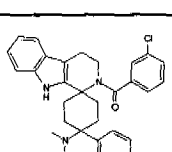
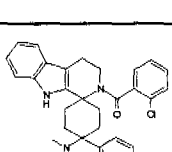
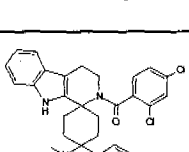
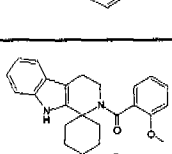
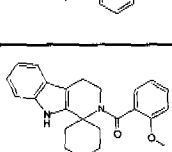
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declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-370				+
GG-371				+
GG-372				+
GG-373				+
GG-374				+
GG-375				+
GG-376				+
GG-377				+
GG-378				+

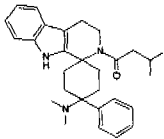
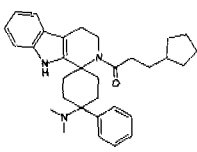
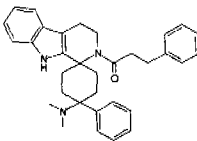
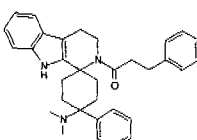
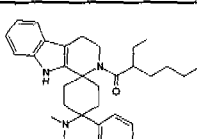
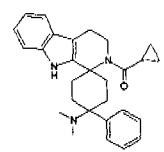
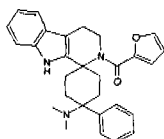
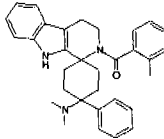
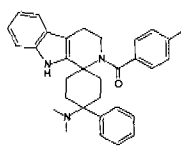
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declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-379				+
GG-380				+
GG-381				+
GG-382				-
GG-383				+
GG-384				+
GG-385				+
GG-386				+
GG-387				+

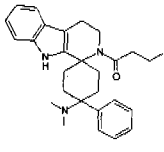
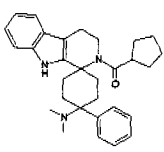
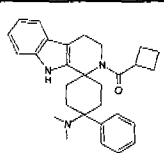
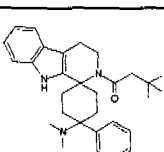
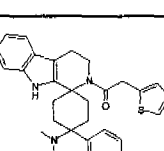
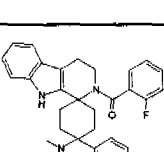
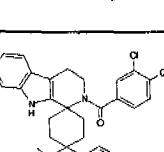
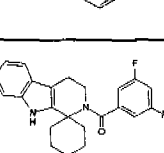
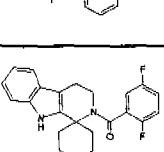
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-388				+
GG-389				+
GG-390				+
GG-391				+
GG-392				+
GG-393				+
GG-394				+
GG-395				+
GG-396				+

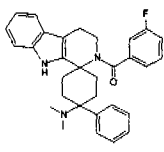
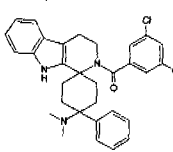
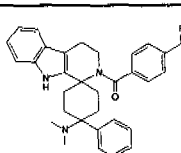
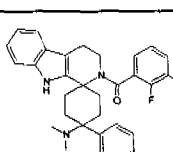
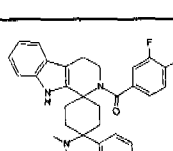
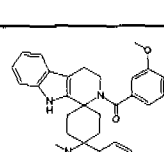
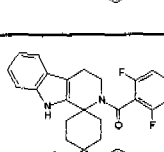
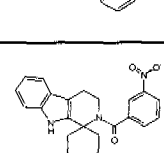
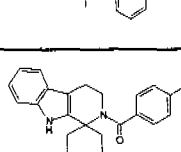
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-397				+
GG-398				+
GG-399				+
GG-400				+
GG-401				+
GG-402				+
GG-403				+
GG-404				+
GG-405				+

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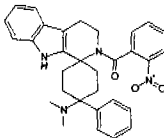
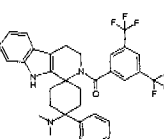
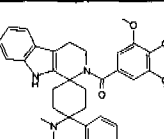
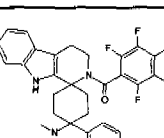
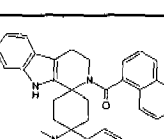
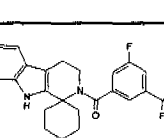
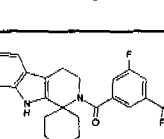
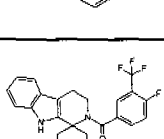
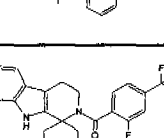
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-406				+
GG-407				+
GG-408				+
GG-409				+
GG-410				+
GG-411				+
GG-412				+
GG-413				+
GG-414				+

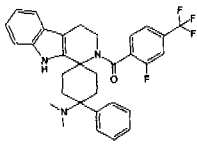
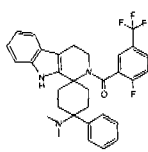
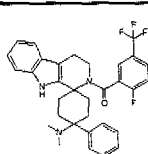
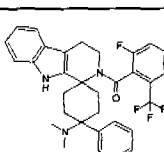
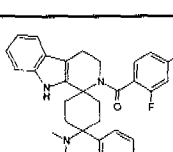
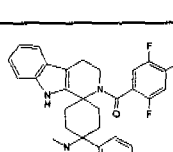
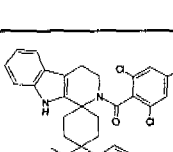
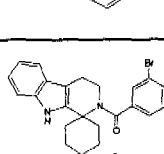
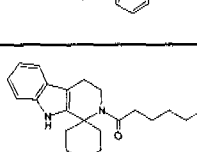
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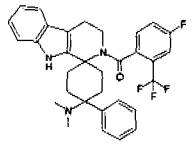
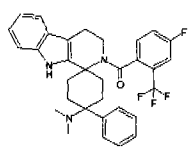
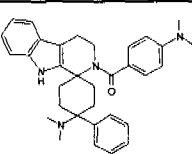
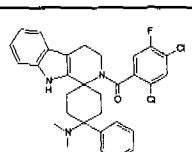
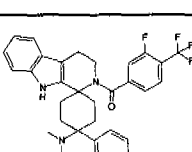
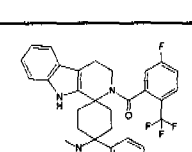
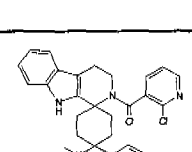
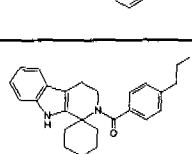
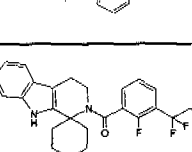
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-415				+
GG-416				+
GG-417				+
GG-418				+
GG-419				+
GG-420				+
GG-421				+
GG-422				+
GG-423				+

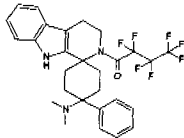
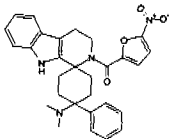
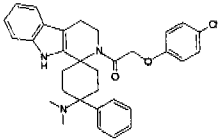
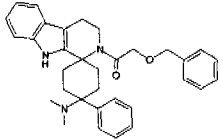
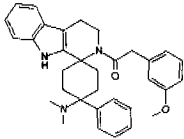
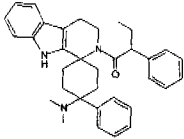
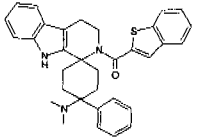
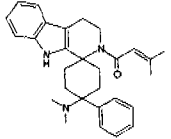
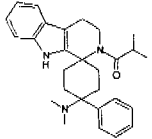
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-424				+
GG-425				+
GG-426				+
GG-427				+
GG-428				+
GG-429				+
GG-430				+
GG-431				+
GG-432				+

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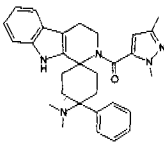
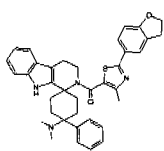
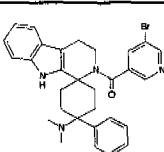
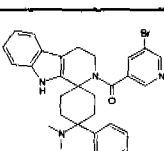
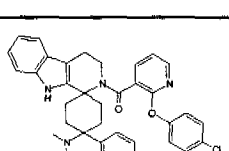
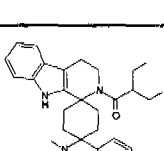
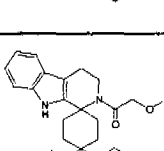
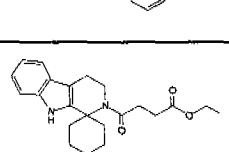
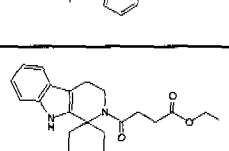
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-433				+
GG-434				+
GG-435				+
GG-436				+
GG-437				+
GG-438				+
GG-439				+
GG-440				+
GG-441				+

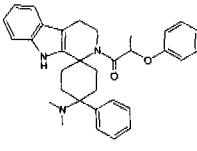
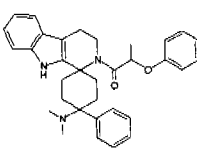
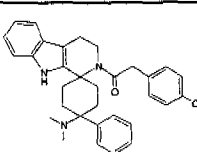
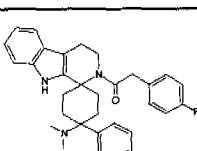
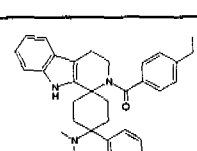
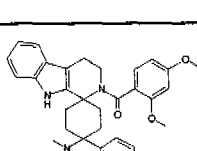
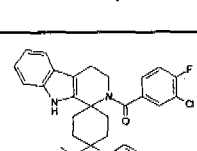
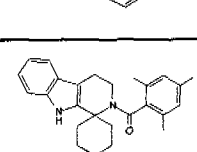
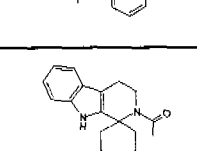
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-442				+
GG-443				+
GG-444				+
GG-445				+
GG-446				+
GG-447				+
GG-448				+
GG-449				+
GG-450				+

declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-451				+
GG-452				+
GG-453				+
GG-454				+
GG-455				+
GG-456				+
GG-457				+
GG-458				+
GG-459				+

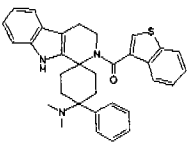
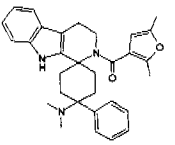
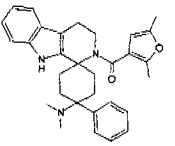
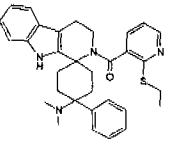
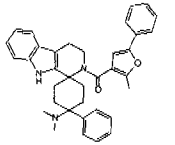
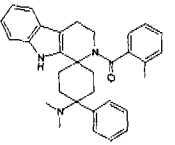
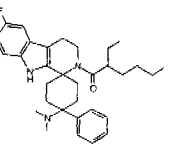
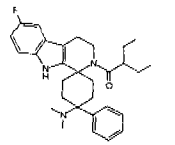
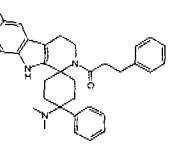
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-460				+
GG-461				+
GG-462				+
GG-463				+
GG-464				+
GG-465				+
GG-466				+
GG-467				+
GG-468				+

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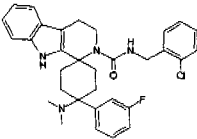
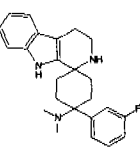
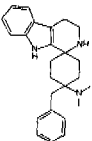
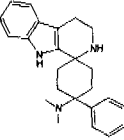
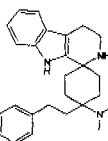
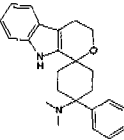
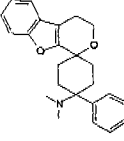
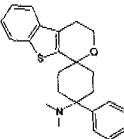
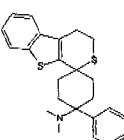
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-469				+
GG-470				+
GG-471				+
GG-472				+
GG-473				+
GG-474				+
GG-475				+
GG-476				+
GG-477				+

declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-478				+
GG-479				+
GG-480				+
GG-481				+
GG-482				+
GG-483				+
GG-484				+
GG-485				+
GG-486				+

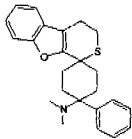
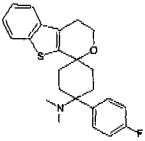
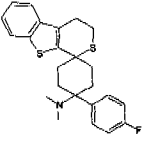
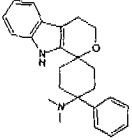
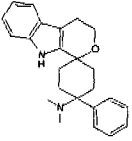
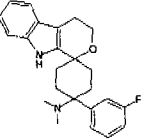
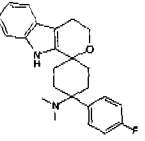
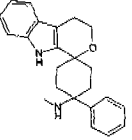
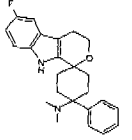
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declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-487				+
GG-488				+
GG-489				+
GG-490				+
GG-491				+
GG-492				+
GG-493				+
GG-494				+
GG-495				+

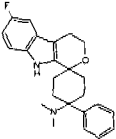
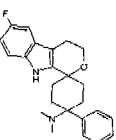
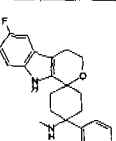
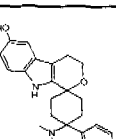
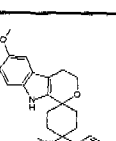
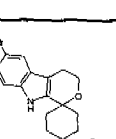
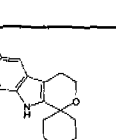
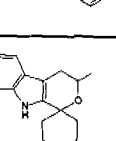
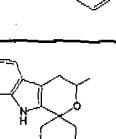
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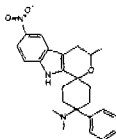
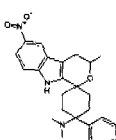
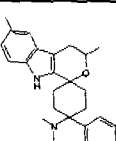
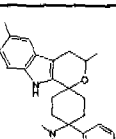
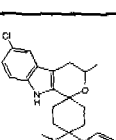
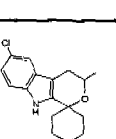
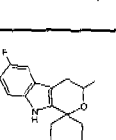
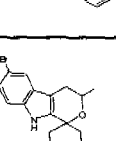
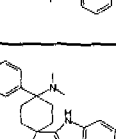
declaration example no./example no. from application	base	salt with	diastereomeric form	active
GG-496				+
I-1			1 of 2 possible diastereomers	+
I-2			mixture ca. 15:85 (apolar:polar)	+
I-3			more polar diastereomer	+
I-4				+
example 3		hydrochloric acid		+
example 8		citric acid		+
example 6		L-tartaric acid		+
example 51		citric acid		+

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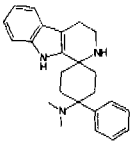
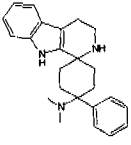
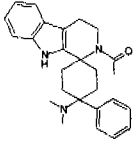
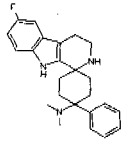
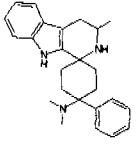
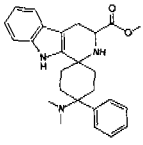
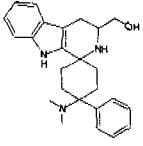
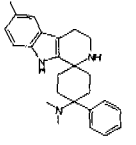
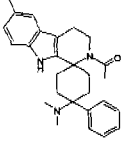
declaration example no./example no. from application	base	salt with	diastereomeric form	active
example 41		citric acid		+
example 7		trifluoromethane sulfonic acid		+
example 50		methanesulfonic acid		-
example 1		hydrochloric acid		+
example 2		hydrochloric acid		+
example 23		citric acid		+
example 22		citric acid		+
example 28		citric acid		+
example 24		citric acid		+

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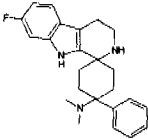
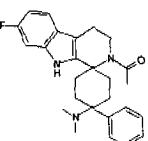
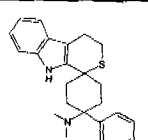
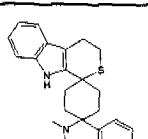
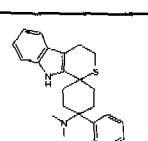
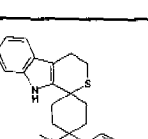
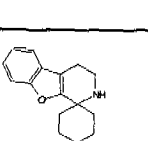
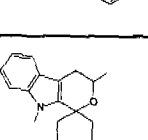
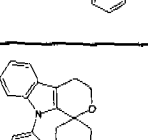
declaration example no./example no. from application	base	salt with	diastereomeric form	active
example 24		citric acid		+
example 25		citric acid		+
example 49		citric acid		+
example 45		citric acid		+
example 13		hydrochloric acid		+
example 44		citric acid		+
example 26		citric acid		+
example 14		citric acid		+
example 15		citric acid		+

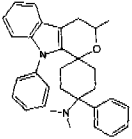
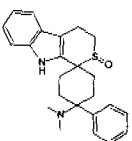
declaration example no./example no. from application	base	salt with	diastereomeric form	active
example 17		citric acid		+
example 18		citric acid		+
example 37		citric acid		+
example 36		citric acid		+
example 19		citric acid		+
example 20		citric acid		+
example 35		citric acid		+
example 16		citric acid		+
example 43		citric acid		+

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declaration example no./example no. from application	base	salt with	diastereomeric form	active
example 10		hydrochloric acid		+
example 9		hydrochloric acid		+
example 12		hydrochloric acid		+
example 34		hydrochloric acid		+
example 33		citric acid		+
example 46		citric acid		+
example 47		citric acid		+
example 29		citric acid		+
example 30		citric acid		+

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declaration example no./example no. from application	base	salt with	diastereomeric form	active
example 31		citric acid		+
example 32		citric acid		+
example 4		citric acid		+
example 5		citric acid		+
example 40		methanesulfonic acid		+
example 39		methanesulfonic acid		+
example 42		citric acid		+
example 21		citric acid		+
example 27		citric acid		+

declaration example no./example no. from application	base	salt with	diastereomeric form	active
example 38		citric acid		+
example 52		citric acid		+