



Industria y Comercio

SUPERINTENDENCIA

Q P

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

11-55206
SOLICITUD

PATENTE DE INVENCION

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 11-055206-00000-0000

Fecha: 2011-05-05 14:59:29 Dep. 2020 DIR.NUEVASCR
Tra 2 PATENTES Eve: 1 REGDEPOSITO
Act. 411 PRESENTACION Folios: 209

21. EXPEDIENTE No. _____

54. TÍTULO THE 1-BUTYL-2-HYDROXYALKYL PIPERAZINE DERIVATIVES
AND THE USES AS ANTI-DEPRESSION MEDICINE THEREOF.

51. CLASIFICACIÓN INTERNACIONAL _____

71. SOLICITANTE CBPC ZHONGQI PHARMACEUTICAL TECHNOLOGY (SHIJIAZHUANG).

DOMICILIO CHINA

74. APODERADO MAURICIO PINZÓN PINZÓN

22. BOGOTÁ, D.C., 5 DE MAYO DE 2011.

*Car, (i.k.), Absorbió una
03-05-2011 Solicitud PCT*

PETITORIO

**Industria y Comercio**
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

ión



No 11-055206-00000-0000

Fecha: 2011-05-05 14:59:29 Dep. 2020 DIR NUEVASCR
Tra. 2 PATENTES Eve: 1 REGDEPOSITO
Act. 411 PRESENTACION Folios: 209

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

SOLICITUD DE:

1

☒ Patente de Invención☐ Patente de Modelo de Utilidad

2

SOLICITANTE

Nombre: CSPC ZHONGQI PHARMACEUTICAL
TECHNOLOGY (SHIJIAZHUANG) CO., LTD.
Dirección: No. 278 ZHONGSHAN WEST ROAD,
SHIJIAZHUANG, HEBEI 050051, P.R. CHINA
Nacionalidad o Domicilio: CHINA
Lugar de Constitución:
Teléfono: Fax:
E-mail:

IDENTIFICACIÓN

☐ C.C. ☐ NIT
☐ C.E. ☐ OtroCúal
Número

3

REPRESENTANTE O
APODERADONombre: MAURICIO PINZÓN PINZÓN
Dirección: CALLE 99 NO. 12 - 39 PISO 4
Teléfono: 6 21 97 21 Fax: 6 21 96 71
E-mail: PINZONPINZON@PINZONPINZON.COM

IDENTIFICACIÓN

☒ C.C. ☐ NIT
☐ C.E. ☐ OtroCúal
Número 79.145.527 TP 37.230En caso de haber presentado poder general para asuntos que se adelanten ante la Delegatura de
Propiedad Industrial, sírvase indicar el número de radicación (del poder).

4

INVENTOR (ES)
(72)Nombre: LI, JIANQI; LV, NA; JIN, HUA; WENG, ZHIJIE; ZHENG YONGYONG
Dirección: NO. 1320 BEIJING WEST ROAD, SHANGHAI 200040, P.R. CHINA
Nacionalidad o Domicilio: CHINA

5

Título (54) THE 1-BUTY 1-2- HYDROXYARALKYL PIPERAZINE DERIVATIVES AND THE USES AS ANTI-DEPRESSION MEDICINE
THEREOF.

6

Número de reivindicaciones

7

Clasificación Internacional (51)

8

Prioridad

☒ SI ☐ NO

(33) País de Origen

CHINA

(32) Fecha

OCTUBRE 7 DE 2008

(31) Número de Solicitud

200810043821.8

9

Para publicar a partir de la fecha de la presente solicitud o de la prioridad invocada a los:

☒ Inmediato ☐ 6 meses ☐ 12 meses ☐ 18 meses

10

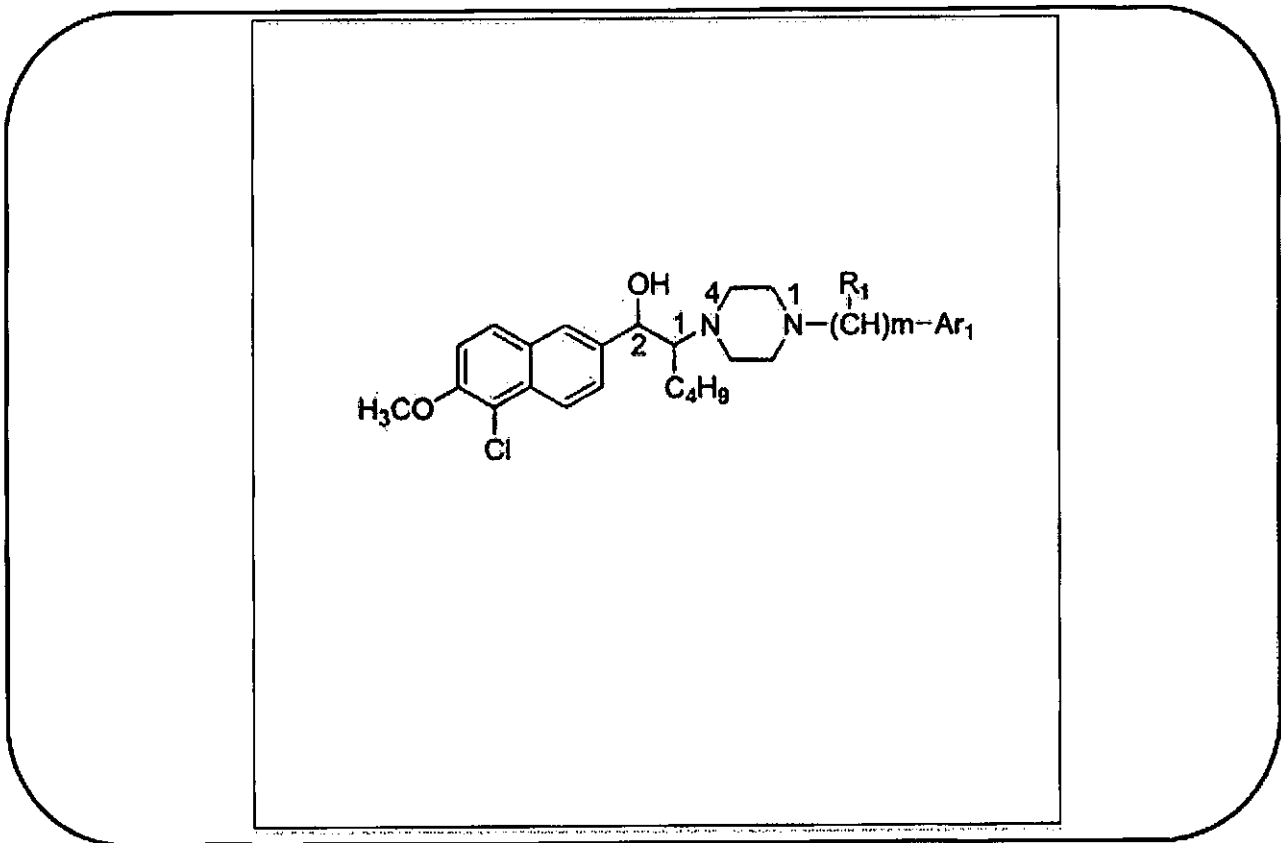
Comprobante de pago No. 09-70,858 / 11-41676 Fecha 22/09/2009 04/05/2011

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

11 Anexos

- ☒ Comprobante de pago de la tasa de presentación de la solicitud.
- ☐ Comprobante de pago de la tasa por concepto de excedente de palabras en la publicación.
- ☒ Comprobante de pago por reivindicación de prioridad.
- ☒ Documento que acredita la existencia y representación legal de la persona jurídica peticionaria, en cuanto no estén inscritas en alguna Cámara de Comercio Colombiana.
- ☒ Poder, si fuere el caso.
- ☒ Certificado de la fecha de presentación de la solicitud prioridad expedida por la autoridad correspondiente y una copia certificada de la primera solicitud, si se reivindica prioridad
- ☒ Traducción simple de la primera solicitud, si se reivindica prioridad.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☒ Resumen
- ☒ Descripción de la invención.
- ☒ Una o más reivindicaciones.
- ☒ Dibujos y/o planos necesarios.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico
- ☒ Arte final 12x12 cm.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.

12 FIGURA CARACTERÍSTICA:



13 Solicito la concesión de la patente,

NOMBRE: MAURICIO PINZÓN PINZÓN

FIRMA: C.C. 79.145.527 TP. 37.230

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

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

- / -

RECIBO DE CAJA

No. 11 - 0043107

Industria y Comercio

SUPERINTENDENCIA

Bogotá D.C., Mayo 05 de 2011 - 14:23:25

RECIBIDO DE : PINZON PINZON & ASOCIADOS ABOGADOS S.A.

NI 830.005.919

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	V.R. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	175179955	05/05/2011	391.000.00

*** Conceptos Pagados ***

CANT. RENTISTICO	CONCEPTO	Vr. UNIDITARIO	Vr. CONCEPTO
1 50005-01-09 PRORROGA DE TERMINOS	1609 S.DISTINTIVOS PRORROGA DE TERMINOS O PLAZO ADICIONAL	87.000.00	87.000.00
			\$87.000.00

=====

SON: **OCHENTA Y SIETE MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 11-055206- -00000-0000

Fecha: 2011-05-05 14:59:29 Dep. 2020 DIR.NULVASCH
 Tra. 2 PATENTES Eve: 1 REGDEPOSITO
 Act. 411 PRESENTACION Folios: 209

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

- / -

RECIBO DE CAJA

No. 11 - 0041676

Industria y Comercio

SUPERINTENDENCIA

Bogotá D.C., Mayo 04 de 2011 - 13:50:23

RECIBIDO DE : PINZON PINZON & ASOCIADOS ABOGADOS S.A.

NI 830.005.919

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	138584095	03/05/2011	298.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	VR. UNDITARIO	VR. CONCEPTO
1 50005-05	SERVICIOS ADMINISTRATIVOS	99 OTROS SERVICIOS ADMINISTRATIVOS	298.000.00	298.000.00
				\$298.000.00

=====

SON: **DOSCIENTOS NOVENTA Y OCHO MIL PESOS MONEDA CORRIENTE**

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 11-055206- -00000-0000

Fecha: 2011-05-05 14:59:29 Dep. 2020 DIR.NUEVASCR
 Tra. 2 PATENTES Eva: 1 REGDEPOSITO
 Act. 411 PRESENTACION Folios: 209

A. 20539.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 11-055206-00000-0000

Fecha: 2011-05-05 14:59:29 Dep. 2020 DIR NUEVASCR
 Tra. 2 PATENTES Eve: 1 REGDEPOSITO
 Act. 411 PRESENTACION Folios: 209

RECIBO OFICIAL DE CAJA : 09 - 70,858

FECHA : SEPTIEMBRE 22 DE 2009

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
PINZON PINZON	CONSIGNACION	BANCO DE BOGOTA	062754387	96110361	22/09/2009	2,827,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-06	REGISTRO DE CESION, CAMBIO NOM	
		13 NOMBRES Y ENSENAS COMERCIALES, MAR	273,000.00
		TOTAL :	\$ 273,000.00

SON: DOSCIENTOS SETENTA Y TRES MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

L.R.

Asig
20539

中国国际贸易促进委员会



China Council for the Promotion of International Trade
China Chamber of International Commerce

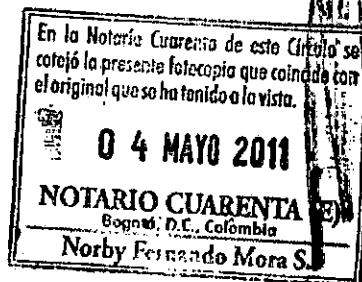
证明书

CERTIFICATE

号码 No. 111100B0/08851

兹证明： 所附注册号310106000120699号企业法人营业执照的影印件与原件相符，所附该执照的西文译本与中文本一致，原件上的上海市工商行政管理局静安分局的印章属实。

Por el presente se hace constar que la fotocopia de la Licencia de Operacion de la Persona Juridica de la Empresa de registro n.310106000120699 esta en conformidad con el original, y que la adjunta version espanola corresponde al documento en chino y que es autentico el sello alli estampado del Sucursal de Jing'an, Administracion de la Industria y Comercio de Shanghai.



Authorized Signature : CaoJing

日期：2011 年03月01日
(Date: MAR. 01, 2011)



企业法人营业执照

注册号 310106000120699

业 名 称 上海医药工业研究院
所 上海市北京西路1320号
定 代 表 人 周斌
册 资 金 人民币叁仟陆佰玖拾贰万元
济 性 质 国有企业(法人)
营 方 式 加工、制造、批发、零售、试制
营 范 围 对化学药品(原料、制剂)、中药(中药材、饮片、制剂)、生物制
品、抗生素、放射性药品、医药新技术、新材料、制药设备、药理、开发、
药理、实验动物、临床制剂、食品、保健品、化妆品的研究、开发、
试制及技术服务, 经营进出口, 培训。

有效期自 二〇〇一年七月十六日

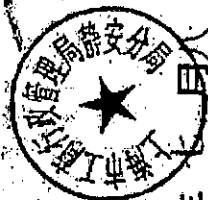
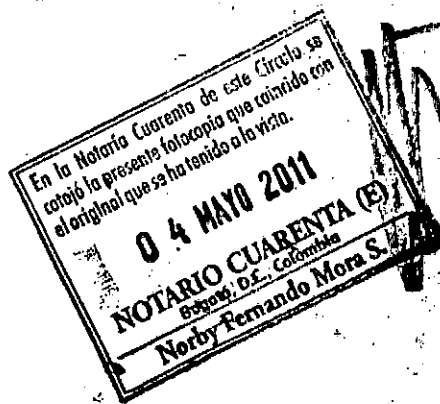
至 不约定期限

[有效期: 2008年07月08日 至 不约定期限]

证照编号 060000001200807080009
企业标识 000000001200107160001X

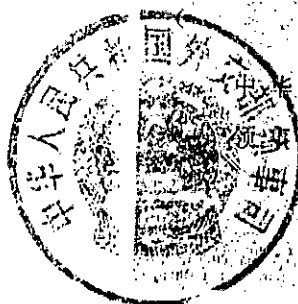
发 照 机 关

二〇〇八年七月八日



认字第11037870-002号

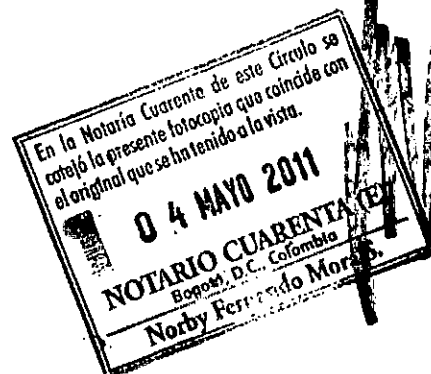
兹证明前面文书上中国国际贸易促进委员会商事证明专用章和授权签字人曹磊的签字属实。



中华人民共和国外交部
领事司 一等秘书

2011年03月07日

5234016



EL CONSULADO DE COLOMBIA EN BEIJING No. 0531
Prevía la confrontación correspondiente DA FE de que
la firma que aparece en este documento es similar a la
REGISTRADA aquí por la señora

WANG QINGLI

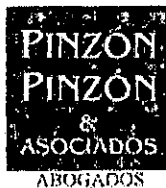
PRIMER SECRETARIO del Departamento Consular del
Ministerio de Relaciones Exteriores de China

BEIJING, 10 DE MARZO DE 2011

LUIS JORGE ROA CORREDOR
Primer Secretario

Encargado de Funciones Consulares (E)

CONSULADO DE COLOMBIA
BEIJING



POWER OF ATTORNEY

Be it known that

Cai. Dongchen

Legally representing and acting on behalf of

CSPC ZHONGQI PHARMACEUTICAL TECHNOLOGY (SHIJIAZHUANG) CO., LTD.

a corporation addressed in

No. 276 Zhongshan West Road, Shijiazhuang, Hebei 050051 P.R. China

does hereby grant **GENERAL POWER OF ATTORNEY** to:

**MAURICIO PINZON PINZON
SILVIA GARCIA CHACON**

Lawyers in practice, of legal age, residing in Bogota D.C., Republic of Colombia, so that they may act in his own name and representation in order to carry out all the necessary steps and processes before the judicial, administrative and other authorities of the Republic of Colombia in order to:

1) Obtain the registration and protection of the Intellectual Property Rights such as trademarks, designs, utility models, patents, commercial names and ensigns, copyrights, domain names, including all the steps, procedures and actions necessary for their defense, protection and conservancy, including the capability

PODER GENERAL

Compareció

Cai. Dongchen

Representante legal de

CSPC ZHONGQI PHARMACEUTICAL TECHNOLOGY (SHIJIAZHUANG) CO., LTD.

Sociedad domiciliada en

No. 276 Zhongshan West Road, Shijiazhuang, Hebei 050051, P. R. China

otorgo **PODER GENERAL** a:

**MAURICIO PINZON PINZON
SILVIA GARCIA CHACON**

Abogados en ejercicio, mayores de edad, vecinos de Bogotá D.C., República de Colombia, para que en su nombre y representación adelanten ante las autoridades judiciales, administrativas o de policía de la República de Colombia, así como ante terceras personas, todas las acciones o gestiones según sea el caso encaminadas a:

1) Obtener el registro y/o protección de los Derechos de propiedad intelectual tales como Signos Distintivos, Nuevas Creaciones, Derechos de Autor, nombres de dominio, comprendiendo todos los trámites, gestiones y acciones judiciales como administrativos que se hagan necesarios para su conservación y defensa, incluyendo la facultad de suscribir acuerdos y contratos en representación del



of granting licenses and to assign registrations.

2) Obtain the licenses or health registration or whatever necessary for the normal development of activities as well as the commercialization of its products.

In carrying out the present mandate the proxy will be able to receive, withdraw, compromise, conciliate, substitute, resume, and in general, carry out all kinds of actions which would lead to the obtention of the pursued matter.

The proxy also is expressly authorized to carry out for our bill the payments to third of rates, payments of services given for third parties in Colombia as in the exterior, bank commissions, freights, notarial expenses and in general all the rest expenses that are needed for the effects of the complete fulfillment of this mandate.

Note: This document must be signed before a Notary Public and then apostilled

poderdante, encaminados al cumplimiento de este mandato.

2) Obtener las Licencias o Registros Sanitarios o de cualquier otra índole, necesarios para el normal desarrollo de su actividad ordinaria, así como para la comercialización de sus productos.

En desarrollo del presente mandato los apoderados podrán recibir, desistir, transigir, conciliar, sustituir, reasumir y en general realizar todo tipo de actos que contribuyan a la obtención del objeto perseguido

Nuestros apoderados igualmente quedan expresamente facultados para efectuar por cuenta nuestra el pago a terceros de tasas, pagos de servicios prestados por terceros en Colombia como en el exterior, comisiones bancarias, portes, gastos notariales y en general todos los demás gastos que se requieran para los efectos del cabal cumplimiento de este mandato.

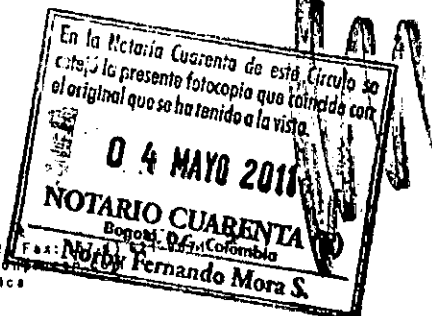
Nota: Este documento debe ser firmado ante Notario Público y luego apostillado

FIRMA :

[Handwritten signature]

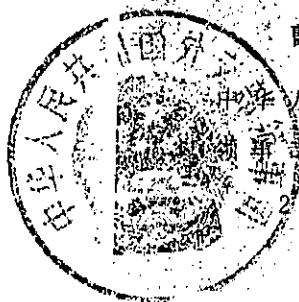


Chairman



认字第11037875-001号

兹证明前面文书上中国国际贸易促进委员会商事证明专用章和授权签字人曹晶的签字属实。

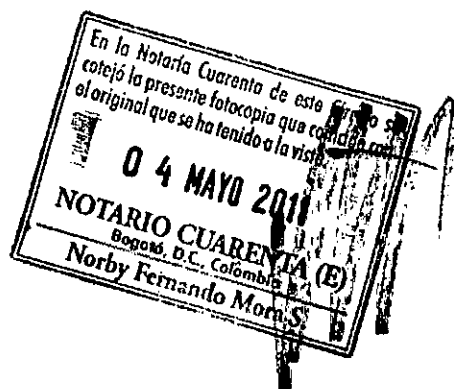


中华人民共和国外交部

一等秘书

2011年03月07日

5234013



EL CONSULADO DE COLOMBIA EN BEIJING No. 0529
 Previa la confrontación correspondiente DA FE de que
 la firma que aparece en este documento es similar a la
 REGISTRADA aquí por la señora

WANG QINGLI

PRIMER SECRETARIO del Departamento Consular del
Ministerio de Relaciones Exteriores de China

BEIJING, 10 DE MARZO DE 2011

[Signature]

LUIS JORGE ROA CORREDOR
 Primer Secretario

Encargado de Funciones Consulares (E)

CONSULADO DE COLOMBIA
 BEIJING

PAGADOS

IMPORTE DE TIMBRE NACIONAL US\$ 1.000

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2009/074314

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
CN1948297A	18.04.2007	WO2007041936A1	19.04.2007
		CN100415728C	03.09.2008
CN1384102A	11.12.2002	WO03101974A1	11.12.2003
		AU2003236135A1	19.12.2003
		US2005267121A1	01.12.2005
		CN1172919C	27.10.2004
CN1381448A	27.11.2002	WO03095437A1	20.11.2003
		AU2003236131A1	11.11.2003
		EP1553092A1	13.07.2005
		US2005153981A1	14.07.2005
		CN1181065C	22.12.2004
		US7326710B2	05.02.2008

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2009/074314

CLASSIFICATION OF SUBJECT MATTER

C07D295/084 (2006.01) i

A61K31/495 (2006.01) i

A61P25/24 (2006.01) i

国际检索报告

国际申请号
PCT/CN2009/074314

A. 主题的分类		
参见附加页		
按照国际专利分类(IPC)或者同时按照国家分类和 IPC 两种分类		
B. 检索领域		
检索的最低限度文献(标明分类系统和分类号)		
IPC: C07D, A61K, A61P		
包含在检索领域中的除最低限度文献以外的检索文献		
在国际检索时查阅的电子数据库(数据库的名称, 和使用的检索词(如使用))		
CPRS;CNKI;WPI;EPODOC;STN; 羟基, 芳烷基, 哌嗪, 抑郁, hydroxy, aralkyl, piperazine, depression, 结构式检索		
C. 相关文件		
类型*	引用文件, 必要时, 指明相关段落	相关的权利要求
A	CN1948297A (上海医药工业研究院), 18.4 月 2007 (18.04.2007), 本申请中所引用, 全文, 特别是实施例 1, 6	1-11
A	CN1384162A (上海医药工业研究院), 11.12 月 2002 (11.12.2002), 本申请中所引用, 全文, 特别是实施例 19	1-11
A	CN1381448A (上海医药工业研究院), 27.11 月 2002 (27.11.2002), 全文	1-11
☐ 其余文件在 C 栏的续页中列出。 ☒ 见同族专利附件。		
* 引用文件的具体类型: "A" 认为不特别相关的表示了现有技术一般状态的文件 "E" 在国际申请日的当天或之后公布在先申请或专利 "L" 可能对优先权要求构成存疑的文件, 或为确定另一篇引用文件的公布日而引用的或者因其他特殊理由而引用的文件(如具体说明的) "O" 涉及口头公开, 使用, 展览或其他方式公开的文件 "T" 公布日先于国际申请日但迟于所要求的优先权日的文件 "T" 在申请日或优先权日之后公布, 与申请不相抵触, 但为了理解发明之理论或原理的在后文件 "X" 特别相关的文件, 单独考虑该文件, 认定要求保护的发明不是新颖的或不具有创造性 "Y" 特别相关的文件, 当该文件与另一篇或者多篇该类型文件结合并且这种结合对于本领域技术人员为显而易见时, 要求保护的发明不具有创造性 "&" 同族专利的文件		
国际检索实际完成的日期 07.12 月 2009(07.12.2009)		国际检索报告邮寄日期 07.1 月 2010 (07.01.2010)
ISA/CN 的名称和邮寄地址: 中华人民共和国国家知识产权局 中国北京市海淀区门桥路 6 号 100088 传真号: (86-10)52019451		授权官员 何湘琼 电话号码: (86-10) 62085627

国际检索报告
关于同族专利的信息

国际申请号
PCT/CN2009/074314

检索报告中引用的 专利文件	公布日期	同族专利	公布日期
CN1948297A	18.04.2007	WO2007041936A1	19.04.2007
		CN100415728C	03.09.2008
CN1384102A	11.12.2002	WO03101974A1	11.12.2003
		AU2003236135A1	19.12.2003
		US2005267121A1	01.12.2005
		CN1172919C	27.10.2004
CN1381448A	27.11.2002	WO03095437A1	20.11.2003
		AU2003236131A1	11.11.2003
		EP1553092A1	13.07.2005
		US2005153981A1	14.07.2005
		CN1181065C	22.12.2004
		US7326710B2	05.02.2008

国际检索报告

国际申请号
PCT/CN2009/074314

主题的分类

C07D295/084 (2006.01) i

A61K31/495 (2006.01) i

A61P25/24 (2006.01) i

PCT-SAFE

电子提交收据

兹确认, 一件PCT国际申请, 已通过国家知识产权局安全电子提交系统收到。收到时, 已自动给予申请号和收到日(PCT行政规程第7部分)。

提交号:	9875		
申请号:	PCT/CN2009/074314		
收到日:	2009年 9月 29日		
受理局:	中华人民共和国国家知识产权局		
申请人或代理人档案号:	IP0900920		
申请人:	石药集团中裕制药技术(石家庄)有限公司		
申请人地址:	7		
发明名称:	1-丁基-2-羟基苯磺酰磺酰衍生物及作为抗抑郁剂的应用		
所提交文件:	pc1101.0ML	7497	2009年 9月 29日 18:54:54
	IP0900920-mp01.xml	802	2009年 9月 29日 18:54:58
	IP0900920-req1.xml	8921	2009年 9月 29日 18:56:03
	IP0900920-focus.xml	2634	2009年 9月 29日 18:54:58
	IP0900920-post-000001.xml	478	2009年 9月 29日 18:54:58
	IP0900920-vlog.xml	2892	2009年 9月 29日 18:54:58
	IP0900920-othd-000001.pdf	1874138	2009年 9月 29日 18:43:20
	IP0900920-ebst.txt	2	2009年 9月 29日 18:54:10
	IP0900920-post-1000001.pdf	76597	2009年 9月 29日 18:51:32
签名人:	EMAILADDRESS=admin@cs-ip.com, CN=WANG Han, OU="www.vnrisign.com/repository/DPS Incorp. by Ref., LIAH, LTD(c)98", OU=WIPO Customer CA, O=World Intellectual Property Organization		
收到日期和时间:	2009年 9月 29日 17:26		
提交文件的正式信息摘要:	22:23:76:7A:2A:7D:8C:8D:DD:71:AC:24:06:4D:47:73:15:P8:72:35		

/北京, R0/CN/

IP090092C

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PCT请求书

打印件(原件为电子形式)

0	由受理局填写	
0-1	国际申请号	PCT/CN2009/074314
0-2	国际申请日	2009年 9月 29日 (29. 09. 2009)
0-3	受理局名称和 "PCT国际申请"	
0-4	PCT/RO/101表 PCT请求书	
0-4-1	软件版本	PCT-SAFE 版本 3. 51. 041. 217 NT/FOP 20090807/0. 20. 5. 17
0-5	请求 下列签字人请求按照专利合作条约的规定 处理本国际申请	
0-6	申请人指定的受理局	中华人民共和国国家知识产权局 (RO/CN)
0-7	申请人或代理人的档案号	IP090092C
I	发明名称	1-丁基-2-羟基芳烷哌嗪衍生物及作为抗抑郁剂的应用
II	申请人	申请人 (applicant only)
II-1	该人是	除美国以外的所有指定国 (all designated States except US)
II-2	是对下列国家的申请人	
II-4a	名称	石药集团中奇制药技术(石家庄)有限公司
II-4a	Name:	CSPC ZHONGQI PHARMACEUTICAL TECHNOLOGY (SHIJIAZHUANG) CO., LTD.
II-5a	地址	中国河北省石家庄市 中山西路276号 050051
II-5a	Address:	No. 276 Zhongshan West Road Shijiazhuang, Hebei 050051 China
II-6	国籍	中国 CN
II-7	居所	中国 CN

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PCT请求书

打印件(原件为电子形式)

III-1 III-1-1	申请人和/或发明人 该人是	申请人 (applicant only)
III-1-2	是对下列国家的申请人	除美国以外的所有指定国 (all designated States except US)
III-1-4 zh	名称	上海医药工业研究院
III-1-4 en	Name:	SHANGHAI INSTITUTE OF PHARMACEUTICAL INDUSTRY
III-1-5 zh	地址	中国上海市 北京西路1320号 200040
III-1-5 en	Address	No. 1320 Beijing West Road Shanghai 200040 China
III-1-6	国籍	中国 CN
III-1-7	居所	中国 CN
III-2 III-2-1	申请人和/或发明人 该人是	申请人和发明人 (applicant and inventor)
III-2-2	是对下列国家的申请人	美国 (US only)
III-2-4 zh	姓名:	李 建其
III-2-4 en	Name (LAST, First):	Li, Jianqi
III-2-5 zh	地址	中国上海市 北京西路1320号 200040
III-2-5 en	Address	No. 1320 Beijing West Road Shanghai 200040 China
III-2-6	国籍	中国 CN
III-2-7	居所	中国 CN
III-3 III-3-1	申请人和/或发明人 该人是	申请人和发明人 (applicant and inventor)
III-3-2	是对下列国家的申请人	美国 (US only)
III-3-4 zh	姓名:	吕 娜
III-3-4 en	Name (LAST, First):	LV, Na
III-3-5 zh	地址	中国上海市 北京西路1320号 200040
III-3-5 en	Address	No. 1320 Beijing West Road Shanghai 200040 China
III-3-6	国籍	中国 CN
III-3-7	居所	中国 CN

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PCT请求书

打印件(原件为电子形式)

III-4	申请人和/或发明人	申请人和发明人 (applicant and inventor) 美国 (US only) 金 华 JIN, Hua 中国上海市 北京西路1320号 200040 No.1320 Beijing West Road Shanghai 200040 China 中国 CN 中国 CN
III-4-1	该人是	
III-4-2	是对下列国家的申请人	
III-4-4	姓名:	
zh		
III-4-4	Name (LAST, First):	
en		
III-4-5	地址	
zh		
III-4-5	Address	
en		
III-4-6	国籍	
III-4-7	居所	
III-5	申请人和/或发明人	申请人和发明人 (applicant and inventor) 美国 (US only) 翁 志洁 WENG, Zhijie 中国上海市 北京西路1320号 200040 No.1320 Beijing West Road Shanghai 200040 China 中国 CN 中国 CN
III-5-1	该人是	
III-5-2	是对下列国家的申请人	
III-5-4	姓名:	
zh		
III-5-4	Name (LAST, First):	
en		
III-5-5	地址	
zh		
III-5-5	Address	
en		
III-5-6	国籍	
III-5-7	居所	
III-6	申请人和/或发明人	申请人和发明人 (applicant and inventor) 美国 (US only) 郑 永勇 ZHENG, Yongyong 中国上海市 北京西路1320号 200040 No.1320 Beijing West Road Shanghai 200040 China 中国 CN 中国 CN
III-6-1	该人是	
III-6-2	是对下列国家的申请人	
III-6-4	姓名:	
zh		
III-6-4	Name (LAST, First):	
en		
III-6-5	地址	
zh		
III-6-5	Address	
en		
III-6-6	国籍	
III-6-7	居所	

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PCT请求书

打印件(原样为电子形式)

IV-1	代理人, 共同代表或通信地址 下列人员被委托/已经被委托为代表申请人在主管国际单位办理事务的。	代理人 (agent)
IV-1-1a 名称		中科专利商标代理有限公司
IV-1-1b Name:		CHINA SCIENCE PATENT AND TRADEMARK AGENT LTD.
IV-1-2a 地址		中国北京市 海淀区王庄路1号清华同方科技大厦B座25层 100083
IV-1-2b Address:		25/F., Bldg. B, Tsinghua Tongfang Hi-Tech Plaza No. 1, Wangzhuang Rd., Haidian District Beijing 100083 China
IV-1-3 电话号码		86-10-82378686
IV-1-4 传真号码		86-10-82378400
IV-1-5 电子邮箱		csptal@csptal.com
IV-1-6 代理人登记号		11021
V	国家的指定	
V-1	根据细则4.9(a), 提交本请求书即为, 指定在国际申请日受PCT的规定的成员国, 以要求获得可以获得的专利保护类型, 适用情况下, 要求获得地区专利和国家专利。	
VI-1	要求在先国家申请的优先权	
VI-1-1 申请日		2008年 10月 07日 (07.10.2008)
VI-1-2 号码		200810043821.8
VI-1-3 国家		中国 CN
VI-2	优先权文件请求 请受理局准备并向国际局转交上述在先申请中标号加下的在先申请的证明副本:	VI-1
VI-3	援引加入: 如果条约11(1)(i)(ii)(d)或(e)规定的国际申请的某一项目, 或者细则20.5(a)规定的说明书, 权利要求书或附图的某一部分不包含在本国际申请中, 但是全部包含在一个在先申请中, 并且在受理局首次收到条约11(1)(iii)规定的一个或多个项目之日要求了该在先申请的优先权, 则该项目或该部分可以依据细则20.6确认, 为细则20.6的目的援引加入该国际申请中。	
VII-1	指定的国际检索单位	中华人民共和国国家知识产权局 (ISA/CN)
VIII	声明	声明范围
VIII-1	关于发明人身份的声明	
VIII-2	关于申请人在国际申请日有权申请和被授予专利的声明	
VIII-3	关于申请人在国际申请日有权要求在先申请的优先权的说明	
VIII-4	发明人资格声明(仅为附送美国目的)	
VIII-5	关于不影响新颖性的公开或缺乏新颖性的例外的声明	

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PCT请求书

打印件(原件为电子形式)

IX	清单	页数	附以电子文档
IX-1	请求书(包括声明页)	5	✓
IX-2	说明书	40	✓
IX-3	权利要求	3	✓
IX-4	摘要	1	✓
IX-5	附图	0	-
IX-7	共计	49	
附件		附以纸件	附以电子文档
IX-8	费用计算页	-	✓
IX-9	单独委托书原件	-	✓
IX-18	PCT-SAFE 物理载体	-	-
IX-20	应与摘要一起公布的附图图号		
IX-21	国际申请所用语言	中文	
X-1	申请人、代理人或共同代表的签字	(PKCS7数字签字)	
X-1-1	名称	中科专利商标代理有限公司	
X-1-2	签字人姓名	吴小明	
X-1-3	身份	代理人	

由受理局填写

10-1	据称的国际申请文件的实际收到日期	2009年 9月 29日 (29.09.2009)
10-2	附图:	
10-2-1	收到	
10-2-2	未收到	
10-3	由于国际局在期限内收到补充国际申请的文件或附图,更改的实际收到日期	
10-4	在期限内收到根据PCT第11(2)条所进行的改正的日期	
10-5	国际检索单位	ISA/CN
10-6	检索本的传送延迟到缴纳检索费后	

由国际局填写

11-1	国际局收到登记表的日期	
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专利合作条约

发信人：受理局

PCT

收信人

100083

中国北京市海淀区王庄路1号清华同方科技大厦B座25层

中科专利商标代理有限责任公司

吴小明

国际申请号和国际申请日通知书

(PCT 细则20.2(c))

发文日(日/月/年)

22.10月 2009 (22.10.2009)

申请人或代理人档案号

IP090092C

重要通知

国际申请号

PCT/CN2009/074314

国际申请日(日/月/年)

29.9月 2009 (29.09.2009)

优先权日(日/月/年)

07.10月 2008 (07.10.2008)

申请人

石药集团中奇制药技术(石家庄)有限公司 等

发明名称

1-丁基-2-羟基芳烷哌嗪衍生物及作为抗抑郁剂的应用

1. 通知申请人, 对国际申请给出上述国际申请号和国际申请日。

2. 通知申请人, 国际申请的登记本:

☒ 已于 22.10月 2009 (22.10.2009) 传送给国际局。

☐ 由于下列原因, 尚未传送给国际局; 本通知书副本已寄给国际局:

☐ 尚未获得国家安全检查的许可。

☐ 原因(具体的理由)

国际局监视受理局传递登记本, 并将收到该登记本情况通知申请人(用PCT/IB/301表)。如果自优先权日起14个月期满, 尚未收到国际申请登记本, 国际局将把该情况通知申请人(细则22.1(c))。

中华人民共和国国家知识产权局(RO/CN)

中国北京市海淀区衙门桥西北城路6号100088

传真号: (86—10) 62019451

授权官员

王书玮

电话号码: (86—10) 62088480

PCT/RO/105表 (2007年4月)

专利合作条约

PCT

发信人：国际检索单位

收信人

100083

中国北京市海淀区王庄路1号清华同方科技大厦B座25层
中科专利商标代理有限责任公司

吴小明

收到检索本的通知书

(PCT 细则 25.1)

发文日 (日/月/年):

22.10 月 2009 (22.10.2009)

申请人或代理人档案号:

IP090092C

重要通知

国际申请号:

PCT/CN2009/074314

国际申请日 (日/月/年):

29.9 月 2009 (29.09.2009)

优先权日 (日/月/年):

07.10 月 2008 (07.10.2008)

申请人

石药集团中奇制药技术(石家庄)有限公司 等

1. 国际检索单位和受理局不是同一个局:

通知申请人, 本国际检索单位在下面指出的日期已收到国际申请检索本。

国际检索单位和受理局是同一个局:

通知申请人, 在下面指出的日期已收到国际申请的检索本。

22.10 月 2009 (22.10.2009)

(收到日)。

2. ☐ 检索本附有包含核苷酸和/或氨基酸序列或与其相关的电子形式的表格。

3. ☐ 检索本包含核苷酸和/或氨基酸序列或与其相关的电子形式的表格。

4. 制定国际检索报告和国际检索单位书面意见的期限

告知申请人, 制定国际检索报告和国际检索单位书面意见的期限是自上述收到日起 3 个月或者自优先权日起 9 个月, 以后到期限为准 (细则 42.1 和 43 之二.1(a))。

5. 本通知副本已经传递国际局, 并且在第 1 段第 1 句适用时该副本已经传递受理局。

中华人民共和国国家知识产权局(ISA/CN)

中国北京市海淀区蓟门桥西土城路 6 号 100088

传真号: (86-10) 62019451

受权官员

王伟瑛

电话号码: 86-010 62088480

专利合作条约

发信人: 国际检索单位

收信人:

100083

中国北京市海淀区王庄路1号清华同方科技大厦B座25层

中科专利商标代理有限责任公司

吴小明

PCT

传送国际检索报告和国际检索单位书面意见或宣布的通知书

(PCT 细则 44.1)

发文日(日/月/年)

07.1 月 2010 (07.01.2010)

申请人或代理人的档案号

IP090092C

关于后续行为

见下面第1和第4段

国际申请号

PCT/CN2009/074314

国际申请日(日/月/年)

29.9 月 2009 (29.09.2009)

申请人

石药集团中奇制药技术(石家庄)有限公司 等

1. ☒ 兹通知申请人, 国际检索报告和国际检索单位书面意见已经做出并随本通知传送。

按条约第18条提出修改和声明:

如果申请人愿意, 可享受修改国际申请权利要求的权利(见细则46):

何时? 提出修改的期限通常是自国际检索报告送交日起二个月。

何地? 直接送往 WIPO 国际局 International Bureau of WIPO,

34 chemin des Colombettes

1211 Geneva 20, Switzerland.

Facsimile No.: +41 22 338 82 70

有关更详细的规程, 见附页上的说明。

2. ☐ 通知申请人, 将不做出任何国际检索报告, 根据条约 17(2)(a) 的关于不做出国际检索报告的宣布和国际检索单位书面意见随本通知书传送。

3. ☐ 就按细则 40.2 对附加费缴纳的任何异议, 通知申请人

☐ 异议及异议决定随申请人要求把异议及异议决定寄送指定局的请求已一起传送给国际局。

☐ 对异议至今尚未做出任何决定, 一旦做出决定, 将通知申请人。

4. 提请注意的事项:

国际申请自优先权日起满 18 个月后立即由国际局公布。如果申请人希望避免或延迟公布, 必须在国际公布的技术准备完成之前, 将分别按细则 90 之二.1 和 90 之二.3 规定的撤回国际申请或撤回优先权要求的通知送达国际局。

申请人可以就国际检索单位的书面意见向国际局提出非正式的意见, 国际局会将此意见副本寄往所有指定局, 除非国际初步审查报告已经或即将作出, 这些意见在自优先权日起三十个月届满之前不会公开。

对一些指定局而言, 如果申请人希望延迟到自优先权日起 30 个月进入国家阶段(在有些局甚至更晚些), 必须在自优先权日起 18 个月之内提出国际初步审查要求, 否则, 对于这些指定局, 申请人必须在自优先权日起 20 个月内完成进入国家阶段的规定行为。

对其他指定局而言, 即使未在 18 个月内提交要求书, 30 个月(或更晚)的期限仍然适用。

关于适用的时间期限的详细情况见 PCT/18/301 的附件, 关于各局适用的时间期限见《PCT 申请人指南》国家篇。

ISA/CN 的名称和邮寄地址:

中华人民共和国国家知识产权局

中国北京市海淀区蓟门桥西土城路 6 号 100088

传真号: (86-10)62019431

受权官员

何湘琼

电话号码 (86-10) 62085627

PCT/ISA/220 表 (2009 年 7 月)

(见附页上的说明)

PCT/ISA/220 表的说明

本说明目的在于给出关于按条约 19 条提交修改的基本规程。本说明以专利合作条约、该条约的细则和行政规程的要求为根据。当本说明和这些要求之间出现不一致的情况时，以后者为准。有关更详细的信息，也可查看《PCT 申请人指南》。

本说明中，“条 (Article)”、“条 (Rule)”和“条 (Section)”分别指 PCT 条约、PCT 细则和 PCT 行政规程的条款。

关于按条约第 19 条修改的规程

申请人在收到国际检索报告和国际检索单位书面意见后有一次修改国际申请权利要求的机会。可是应该强调，由于在国际初步审查程序中，国际申请的所有部分(权利要求书、说明书和附图)都可以修改，通常不需要按条约第 19 条提出对权利要求的修改，除非，例如申请人为临时保护的目需要公布修改后的权利要求或者有在国际公布之前修改权利要求的其它的理由，还应该强调，临时保护仅在某些国家可以获得(见《PCT 申请人指南》附录 B)。

申请人应注意如下事实：如国际检索单位按照条约第 17 (2) 作出不制定检索报告的宣布，则不允许按照条约第 19 条进行修改。(见《PCT 申请人指南》第 296 段)

国际申请的哪些部分可以修改？

按条约第 19 条的规定，只有权利要求可以被修改。

在国际阶段，也可以对国际初步审查单位提出按条约第 34 条修改(或进一步修改)的权利要求。只有在国际初步审查程序中，才可以按条约第 34 条对说明书和附图作修改。

在进入国家阶段时，按条约第 28 条，或在适用的情况下，按条约第 41 条，可以对国际申请的所有部分作出修改。

何时修改？自传送国际检索报告之日起两个月内或自优先权日起 16 个月内，以最后期限的期限为准。可是应该说明，如果国际局在适用的期限届满之后但在国际公布的技术准备完成之前收到修改，该修改将被认为按时收到(细则 46.1)。

不能向何处提交修改？

修改只能向国际局提出而不能向受理局或国际检索单位提出(细则 46.2)。

国际初步审查要求已被/被提交的，参见下面。

如何修改？删去一项或多项完整的权利要求，或者增加一项或多项新的权利要求或者修改一项或多项原提出的权利要求的内容。

包含一套完整权利要求替换原始权利要求的替换页或者页必须提交。

如果删去一个权利要求，不要求对其它权利要求重新编号。在权利要求重新编号的所有情况下，必须使用阿拉伯数字对权利要求连续编号(行政规程第 205 条(a))。

修改必须用国际申请公布时使用的语言做出。

什么文件必须/可以随修改附送？

信件(行政规程第 205 条(b))；

修改必须和一封信用一起提交。

信件不和国际申请以及修改后的权利要求一起公布。不应该把它和“按条约第 19 条(1)所作的声明”相混淆(参见下面，“按条约 19 第条(1)所作的声明”)。

信件必须使用英语或法语，可由申请人选择。可是，如果国际申请的语言是英语，信件必须用英语；如果国际申请的语言是法语，则信件必须用法语。

PCT/ISA/220 表的说明 (续页)

信件必须指明原始提交的权利要求与修改后的权利要求之间的区别,特别是必须结合国际申请中的每项权利要求(当然几项权利要求的相同说明可以组合在一起)予以说明,是否

- (i) 该权利要求未作改变;
- (ii) 该权利要求被删除;
- (iii) 该权利要求是新的;
- (iv) 该权利要求替换原始提交的一项或几项权利要求;
- (v) 该权利要求是分割一项原提出的权利要求的结果。

下面的例子说明必须以随附的信件来解释修改的做法:

1. [原权利要求 48 项,在修改几项权利要求后成为 51 项]:
“权利要求 1 至 29、31、32、34、35、37 至 48 被修改后的同样编号的权利要求替换;
权利要求 30、33 和 36 不变;权利要求 49 至 51 是新增加的。”
2. [原权利要求 15 项,在修改全部权利要求后成为 11 项]:
“权利要求 1 至 15 被修改后的权利要求 1 至 11 替换。”
3. [原权利要求 14 项,修改包括删去几项权利要求和增加新的权利要求]:
“权利要求 1 至 6 和 14 不变;权利要求 7 至 13 被删去;增加新的权利要求 15、16 和 17”。或者
“删去权利要求 7 至 13;增加新的权利要求 15、16 和 17;其余的权利要求全部不变。”
4. [作了各种不同的修改]:
“权利要求 1 至 10 不变;权利要求 11 至 13、18 和 19 被删去;权利要求 14、15、16 被修改后的权利要求 14 替换;权利要求 17 分成修改后的权利要求 15、16 和 17;增加新的的权利要求 20 和 21。”

“按照条约 19 条(1)所作的声明”(细则 46.4)

修改可以附有解释修改和说明该修改对说明书和附图可能产生的影响的声明(按条约第 19 条(1)说明书和附图不能修改)。

该声明和国际申请以及修改后的权利要求一起公布。

它必须使用国际申请公布时所用的语言。

它必须是简要的,如果使用英语或者翻译成英语,不得超过 500 字。

它不应当和说明原始提交的权利要求与修改后的权利要求之间区别的信件相混淆并且不应当代替该信件。它必须用单独的纸页提出并加上标题以便辨认,最好使用“按条约 19 第条(1)所作的声明”字样。

它不可以含有对国际检索报告或报告中所含引用文件之相关性的任何贬低性评论。只有在对特定的权利要求进行修改时,才可以涉及国际检索报告中与该权利要求有关的引用文件。

如果已经提出国际初步审查要求如何办?

如果在按条约第 19 条提出任何修改和任何伴随的声明之时,国际初步审查要求已经提出,申请人在向国际局提交修改(和任何声明)的同时也向国际初步审查单位提交上述修改(和任何声明)的副本以及,如果需要,提交这些修改的译文,以便进入该国际初步审查单位的程序(见细则 55.3(a)和 62.2,第 1 句)。进一步的信息见要求书表格(PCT/IPEA/401)的注释。

如果提出国际初步审查要求,国际检索单位的书面意见将被作为国际初步审查单位的一次书面意见,发出书面意见的单位与国际初步审查单位不是同一单位且已根据细则 66.1 之二(b)通知国际局的情况除外。如果提出初审要求,申请人自 PCT/ISA/220 发文之日起 3 个月或自优先权日起 22 个月内(以后届满者为准)向国际初步审查单位提交书面意见的答复以及修改(如适用)(细则 43 之二.1(c))。

为进入国家阶段而翻译国际申请如何办?

请申请人注意这一事实,在进入国家阶段时,必须向指定/选定局提供按照条约第 19 条修改的权利要求的译本,以代替原始提交的权利要求的译本,或者同时提供原始提交的权利要求的译本。

关于各个指定/选定局的要求的进一步的细节,参见《PCT 申请人指南》国家篇。

专利合作条约

PCT

国际检索报告

(PCT 第 18 条和细则 43 和 44)

申请人或代理人的档案号 IP090092C	关于后续 行为	见 PCT/ISA/220 表和 适用时, 见下面第 5 项
国际申请号 PCT/CN2009/074314	国际申请日 (日/月/年) 29.9 月 2009(29.09.2009)	(最早的)优先权日 (日/月/年) 07.10 月 2008(07.10.2008)
申请人 石药集团中奇制药技术(石家庄)有限公司 等		

按照条约第 18 条, 本国际检索报告由本国际检索单位做出并送交申请人。报告副本送交国际局。

本国际检索报告总计 4 页。

☐ 它还附有本报告所引用的各现有技术文件的副本。

1. 报告的基础

a. 关于语言, 进行国际检索基于:

☒ 国际申请提交时使用的语言。

☐ 该国际申请的____语言译文, 为了国际检索的目的提供该种语言的译文(细则 12.3(a)和 23.1(b))。

b. ☐ 本国际检索报告考虑了本单位许可或被通知的根据细则 91 所做出的明显错误更正。(细则 43.6 之二 (a))。

c. ☐ 关于国际申请中公开的任何核苷酸和/或氨基酸序列, 见第 I 栏。

2. ☐ 某些权利要求被认为是不能检索的(见第 II 栏)。

3. ☐ 缺乏发明的单一性(见第 III 栏)。

4. 关于发明名称。

☒ 同意申请人提出的发明名称。

☐ 发明名称由本单位确定如下:

5. 关于摘要。

☒ 同意申请人提出的摘要。

☐ 根据细则 38.2(b), 摘要由本单位制定, 如第 IV 栏中所示。自本国际检索报告发文日起一个月内, 申请人可以向本单位提出意见。

6. 关于附图。

a. 随摘要一起公布的附图是: _____

☐ 按照申请人建议的。

☐ 由本单位选择的, 因为申请人没有建议一幅图。

☐ 由本单位选择的, 因为该图能更好地表示发明的特征。

b. ☐ 没有与摘要一起公布的附图

国际检索报告

国际申请号

PCT/CN2009/074314

A. 主题的分类

参见附加页

按照国际专利分类(IPC)或者同时按照国家分类和 IPC 两种分类

B. 检索领域

检索的最低限度文献(标明分类系统和分类号)

IPC: C07D, A61K, A61P

包含在检索领域中的除最低限度文献以外的检索文献

在国际检索时查阅的电子数据库(数据库的名称, 和使用的检索词(如使用))

CPRS;CNKI;WPI;EPODOC;STN: 羟基, 芳烷基, 咪唑, 抑郁, hydroxy, aralkyl, piperazine, depression, 结构式检索

C. 相关文件

类型*	引用文件, 必要时, 指明相关段落	相关的权利要求
A	CN1948297A (上海医药工业研究院), 18.4 月 2007 (18.04.2007), 本申请中所引用, 全文, 特别是实施例 1, 6	1-11
A	CN1384102A (上海医药工业研究院), 11.12 月 2002 (11.12.2002), 本申请中所引用, 全文, 特别是实施例 19	1-11
A	CN1381448A (上海医药工业研究院), 27.11 月 2002 (27.11.2002), 全文	1-11

☐ 其余文件在 C 栏的续页中列出。☒ 见同族专利附件。

* 引用文件的具体类型:

“A” 认为不特别相关的表示了现有技术一般状态的文件

“E” 在国际申请日的当天或之后公布的在先申请或专利

“L” 可能对优先权要求构成怀疑的文件, 或为确定另一篇引用文件的公布日期引用的或者因其他特殊理由引用的文件(如具体说明的)

“O” 涉及口头公开、使用、展览或其他方式公开的文件

“P” 公布日先于国际申请日但迟于所要求的优先权日的文件

“T” 在申请日或优先权日之后公布, 与申请不相抵触, 但为了理解发明之理论或原理的在后文件

“X” 特别相关的文件, 单独考虑该文件, 认定要求保护的发明不是新颖的或不具有创造性

“Y” 特别相关的文件, 当该文件与另一篇或者多篇该类型文件结合并且这种结合对于本领域技术人员为显而易见时, 要求保护的发明不具有创造性

“Z” 同族专利的文件

国际检索实际完成的日期

07.12 月 2009(07.12.2009)

国际检索报告邮寄日期

07.1 月 2010 (07.01.2010)

ISA/CN 的名称和邮寄地址:

中华人民共和国国家知识产权局

中国北京市海淀区门桥西土城路 6 号 100088

传真号: (86-10)62019451

受权官员

何湘琼

电话号码: (86-10) 62085627

国际检索报告
关于同族专利的信息

国际申请号
PCT/CN2009/074314

检索报告中引用的 专利文件	公布日期	同族专利	公布日期
CN1948297A	18.04.2007	WO2007041936A1	19.04.2007
		CN100415728C	03.09.2008
CN1384102A	11.12.2002	WO03101974A1	11.12.2003
		AU2003236135A1	19.12.2003
		US2005267121A1	01.12.2005
		CN1172919C	27.10.2004
CN1381448A	27.11.2002	WO03095437A1	20.11.2003
		AU2003236131A1	11.11.2003
		EP1553092A1	13.07.2005
		US2005153981A1	14.07.2005
		CN1181065C	22.12.2004
		US7326710B2	05.02.2008

国际检索报告

国际申请号

PCT/CN2009/074314

主题的分类

C07D295/084 (2006.01) i

A61K31/495 (2006.01) i

A61P25/24 (2006.01) i

发信人: 国际检索单位

收信人:

100083

中国北京市海淀区王庄路1号清华同方科技大厦
B座25层
中科专利商标代理有限责任公司
吴小明

PCT

国际检索单位书面意见
(PCT 细则 43 之二 .1)

发文日(日/月/年)

07.1 月 2010 (07.01.2010)

申请人或代理人的档案号

IP090092C

后续行为

见下面第 2 段

国际申请号

PCT/CN2009/074314

国际申请日(日/月/年)

29.9 月 2009(29.09.2009)

优先权日(日/月/年)

07.10 月 2008(07.10.2008)

国际专利分类(IPC)或国家分类和 IPC 两种分类

参见补充栏

申请人

石药集团中奇制药技术(石家庄)有限公司 等

1. 本意见包括关于下列各项标明的内容:

- ☒ 第I栏 意见的基础
- ☐ 第II栏 优先权
- ☐ 第III栏 不做出关于新颖性、创造性和工业实用性的意见
- ☐ 第IV栏 缺乏发明的单一性
- ☒ 第V栏 按照细则 43 之二.1(a)(i)关于新颖性、创造性或工业实用性的推断性声明; 支持这种声明的引证和解释
- ☐ 第VI栏 某些引用的文件
- ☐ 第VII栏 国际申请中的某些缺陷
- ☒ 第VIII栏 对国际申请的某些意见

2. 后续行为

如果提出初步审查要求书, 本次意见将被视为国际初步审查单位(IPEA)的一次书面意见, 除非申请人选择的国际初步审查单位非本机构, 而且所选国际初步审查单位已按照细则 66.1 之二(b)通知国际局将不考虑国际检索单位的书面意见时例外。

如本书面意见被视为国际初步审查单位的书面意见, 则请申请人在自 PCT/ISA/220 表发文日起 3 个月或自优先权日起 22 个月内(以后届满者为准)向国际初步审查单位提交书面答复并提交修改(如适用)。

进一步的选择参见 PCT/ISA/220 表。

3. 详细信息见 PCT/ISA/220 表格的说明

ISA/CN 的名称和邮寄地址:

中华人民共和国国家知识产权局
中国北京市海淀区蓟门桥西土城路 6 号 100088

传真号: (86-10)62019451

完成本意见的日期

28.12 月 2009
(28.12.2009)

受权官员

何湘琼
电话号码: (86-10)
62085627

第1栏 意见的基础

1. 关于语言, 本意见的制定基于:

☒ 国际申请提交时使用的语言。☐ 该国际申请的____语言译文, 为了国际检索的目的提供该种语言的译文(细则 12.3(a)和 23.1(b))。2. ☐ 本意见的制定考虑了本单位许可或被通知的根据细则 91 所做出的明显错误更正(细则 43 之二 1(a))。3. ☐ 关于国际申请中所公开的任何对要求保护的发明必要的核苷酸和/或氨基酸序列, 本意见是在下列基础上制定的:

a. 序列表的提交或提供

☐ 纸件形式☐ 电子形式

b. 提交或提供时间

☐ 包括于已提交的国际申请;☐ 以电子形式与国际申请一起提交。☐ 为检索目的随后提交给本单位。4. ☐ 另外, 在提交/提供了多个版本或副本的序列表的情况下, 提供了随后或附加副本中的信息与申请时提交的申请中的信息相同或未超出申请时提交的申请中的信息范围(如适用)的所需声明。

5. 补充意见

第V栏 按细则 43 之二.1 (a) (i) 关于新颖性、创造性或工业实用性的推测性声明：支持这种声明的引证和解释

1. 声明

新颖性(N)	权利要求 1-11	是
	权利要求	否
创造性(IS)	权利要求 1-11	是
	权利要求	否
工业实用性(IA)	权利要求 1-11	是
	权利要求	否

2. 引证和解释

关于权利要求 1 的新颖性、创造性、工业实用性的意见是基于合理预期的主题作出的，详情参见第 VIII 栏。

1. 本书面意见引用如下对比文件

D1: CN1948297A (上海医药工业研究院), 18.4 月 2007 (18.04.2007)

2. 新颖性

现有技术没有公开本申请的式 I 化合物，因此权利要求 1-11 的技术方案是新的，满足 PCT Art.33(2)的要求。

3. 创造性

D1 是本申请最接近的现有技术。本申请要解决的技术问题是提供一种 1-丁基-2-羟基羟基芳烷脲衍生物，它具有抗抑郁活性并且具有较长的半衰期。D1 中具体公开了具有抗抑郁活性的化合物 SIP15286 (参见说明书实施例 1, 6)。与 D1 相比，本申请权利要求 1 式 (I) 化合物的区别主要在于式 (I) 化合物 C1 位置为丁基取代基，而 D1 中为甲基取代基。当 C1 位置为丁基时，化合物获得了更长的半衰期，具有很好的成药性。本领域普通技术人员在 D1 的教导下，不能显而易见地获得本申请权利要求 1 的技术方案。因此权利要求 1 符合 PCT Art.33(3)的要求。

权利要求 2-11 都涉及了权利要求 1 的化合物，因此权利要求 2-11 也符合 PCT Art.33(3)的要求。

4. 实用性

权利要求 1-11 的技术方案在工业上是可实施的，因此它们符合 PCT Art.33(4)的要求。

第VIII栏 对国际申请的某些意见

就权利要求、说明书和附图的清楚性或者就权利要求是否得到说明书的充分支持提出以下意见:

当 Ar1 或 R1 为取代苯基时, 权利要求 1 涉及了大量化合物。但是, 在说明书中仅仅给出了少数几种结构的化合物符合 PCT 条约第 6 条关于支持的规定和/或 PCT 条约第 5 条关于充分公开的规定。因此在本申请中, 权利要求 1 中所述化合物范围太大, 其没有得到说明书的支持, 且相应的技术方案在说明书中也没有充分公开, 不符合 PCT 条约第 5 条和第 6 条的规定。本书面意见仅针对其中涉及得到支持的化合物的技术方案。也就是, Ar1 为如权利要求 2 中所定义, R1 为如权利要求 3 中所定义。

国际检索单位书面意见

国际申请号

PCT/CN2009/074314

补充栏

(当前面的任何一栏篇幅不够时使用本栏)

续：国际专利分类 (IPC) 或者国家分类和 IPC 两种分类

C07D295/084 (2006.01) I.

A61K31/495 (2006.01) I

A61P25/24 (2006.01) I

PATENT COOPERATION TREATY

PCT/CN2009/074314

From the INTERNATIONAL BUREAU

PCTNOTIFICATION OF RECEIPT OF
RECORD COPY

(PCT Rule 24.2(a))

To:

CHINA SCIENCE PATENT AND TRADEMARK
AGENT LTD.
25/F., Bldg.B, Tsinghua Tongfang Hi-Tech Plaza
No.1, Wangzhuang Rd., Haidian District
Beijing 100083
CHINE

Date of mailing (day/month/year) 06 November 2009 (06.11.2009)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference IP090092C	International application No. PCT/CN2009/074314

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

CSPC ZHONGQI PHARMACEUTICAL TECHNOLOGY (SHIJIAZHUANG) CO., LTD. et al (for all designated States except US)
Li, Jianqi et al (for US)

International filing date: 29 September 2009 (29.09.2009)

Priority date(s) claimed: 07 October 2008 (07.10.2008)

Date of receipt of the record copy by the International Bureau: 26 October 2009 (26.10.2009)

List of designated Offices:

AP: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW

EA: AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

EP: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR

OA: BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

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

ATTENTION: The applicant should carefully check the data appearing in this notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau. In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- time limits for entry into the national phase - see updated important information (as of April 2002)
- requirements regarding priority documents (if applicable)

A copy of this notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Higuera Luis

e-mail pt02.pct@wipo.int

Telephone No. +41 22 338 74 02

Facsimile No. +41 22 338 89 65

INFORMATION ON ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated on the cover sheet of this notification by paying national fees and furnishing translations, as prescribed by Articles 22 and 39 and the applicable national laws. In addition, the applicant may also have to comply with other special requirements applicable in certain Offices. It is the applicant's responsibility to ensure that the necessary steps to enter the national phase are taken in a timely fashion. Most Offices do not issue reminders to applicants in connection with the entry into the national phase.

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date (see Article 39(1)), but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette* ("Section IV" part published on a weekly basis), to the *PCT Newsletter* (on a monthly basis) and to the relevant National Chapters in Volume II of the *PCT Applicant's Guide* (the paper version of which is updated usually twice a year and the Internet version of which is updated usually on a weekly basis). Finally, a cumulative table of all applicable time limits for entering the national phase is available from WIPO's Internet site, via links from various pages of the site, including those of the *Gazette*, *Newsletter* and *Guide*, at <http://www.wipo.int/pct/en/index.html>.

Information about the requirements for filing a demand for international preliminary examination is set out in the *PCT Applicant's Guide*, Volume I/A, Chapter IX. Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before the date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 16-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau and if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances (Rule 17.1(c)).

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit (and all other PCT time limits) is the filing date of the earliest application whose priority is claimed (Article 2(xi)(b)).

PATENT COOPERATION TREATY

PCT/CN2009/074314

From the INTERNATIONAL BUREAU

PCTNOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

CHINA SCIENCE PATENT AND TRADEMARK
AGENT LTD.
25/F., Bldg.B, Tsinghua Tongfang Hi-Tech Plaza
No.1, Wangzhuang Rd., Haidian District
Beijing 100083
CHINE

Date of mailing (day/month/year) 09 November 2009 (09.11.2009)	
Applicant's or agent's file reference IP090092C	IMPORTANT NOTIFICATION
International application No. PCT/CN2009/074314	International filing date (day/month/year) 29 September 2009 (29.09.2009)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 07 October 2008 (07.10.2008)
Applicant CSPC ZHONGQI PHARMACEUTICAL TECHNOLOGY (SHIJIAZHUANG) CO., LTD. et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. (If applicable) The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
3. (If applicable) An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
07 October 2008 (07.10.2008)	200810043821.8	CN	05 November 2009 (05.11.2009)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Genève 20, Switzerland

Authorized officer

Ellen Moyse

e-mail PT02.PCT@WIPO.INT

Telephone No. +41 22 338 74 02

Facsimile No. +41 22 338 82 70

PATENT COOPERATION TREATY

WO 2010/040315
PCT/CN2009/074314

From the INTERNATIONAL BUREAU

PCT

FIRST NOTICE INFORMING THE APPLICANT OF
THE COMMUNICATION OF THE INTERNATIONAL
APPLICATION (TO DESIGNATED OFFICES WHICH
DO NOT APPLY THE 30 MONTH TIME LIMIT
UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To:

CHINA SCIENCE PATENT AND TRADEMARK AGENT
LTD.
25/F., Bldg.B, Tsinghua Tongfang Hi-Tech Plaza
No.1, Wangzhuang Rd., Haidian District
Beijing 100083
CHINE

Date of mailing (day/month/year) 14 May 2010 (14.05.2010)		
Applicant's or agent's file reference IP090092C		IMPORTANT NOTICE
International application No. PCT/CN2009/074314	International filing date (day/month/year) 29 September 2009 (29.09.2009)	Priority date (day/month/year) 07 October 2008 (07.10.2008)
Applicant CSPC ZHONGQI PHARMACEUTICAL TECHNOLOGY (SHUJIAZHUANG) CO., LTD. et al		

1. **ATTENTION:** For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), does apply, please see Form PCT/IB/308(Second and Supplementary Notice) (to be issued promptly after the expiration of 28 months from the priority date).
2. Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, does not apply, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93bis.1. The International Bureau has effected that communication on the date indicated below:
15 April 2010 (15.04.2010)

None

In accordance with Rule 47.1(c-bis)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

3. The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, does not apply, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93bis.1:

LU, TZ, UG

In accordance with Rule 47.1(c-bis)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

4. **TIME LIMITS** for entry into the national phase

For the designated Office(s) listed above, and unless a demand for international preliminary examination has been filed before the expiration of 19 months from the priority date (see Article 39(1)), the applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 20 MONTHS from the priority date.

In practice, time limits other than the 20-month time limit will continue to apply, for various periods of time, in respect of certain of the designated Offices listed above. For regular updates on the applicable time limits (20 or 21 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

It is the applicant's sole responsibility to monitor all these time limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Ellen Moyse

PATENT COOPERATION TREATY

WO 2010/040315
PCT/CN2009/074314

From the INTERNATIONAL BUREAU

PCT

SECOND AND SUPPLEMENTARY NOTICE
INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION (TO DESIGNATED OFFICES
WHICH APPLY THE 30 MONTH TIME
LIMIT UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To:

CHINA SCIENCE PATENT AND TRADEMARK AGENT
LTD.
25/F., Bldg. B, Tsinghua Tongfang Hi-Tech Plaza
No. 1, Wangzhuang Rd., Haidian District
Beijing 100083
CHINE

Date of mailing (day/month/year) 10 February 2011 (10.02.2011)		IMPORTANT NOTICE	
Applicant's or agent's file reference IP090092C			
International application No. PCT/CN2009/074314	International filing date (day/month/year) 29 September 2009 (29.09.2009)	Priority date (day/month/year) 07 October 2008 (07.10.2008)	
Applicant CSPC ZHONGQI PHARMACEUTICAL TECHNOLOGY (SHIJIAZHUANG) CO., LTD. et al			

- ATTENTION:** For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), does not apply, please see Form PCT/IB/308 (First Notice) issued previously.
- Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, does apply, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93bis.1. The International Bureau has effected that communication on the date indicated below:
15 April 2010 (15.04.2010)

AU, AZ, BY, CN, CO, DZ, EP, HU, KG, KP, KR, MD, MK, MY, MZ, NA, NG, PG, RU, SY, TM, US

In accordance with Rule 47.1(c-bis)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

- The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, does apply, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93bis.1:

AE, AG, AL, AM, AO, AP, AT, BA, BB, BG, BH, BR, BW, BZ, CA, CH, CL, CR, CU, CZ, DE, DK, DM, DO, EA, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, ID, IL, IN, IS, JP, KE, KM, KN, KZ, LA, LC, LK, LR, LS, LT, LY, MA, ME, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PE, PH, PL, PT, RO, RS, SC, SD, SE, SG, SK, SL, SM, ST, SV, TJ, TN, TR, TT, UA, UZ, VC, VN, ZA, ZM, ZW

In accordance with Rule 47.1(c-bis)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

- TIME LIMITS** for entry into the national phase

For the designated or elected Office(s) listed above, the applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain of the designated or elected Office(s) listed above. For regular updates on the applicable time limits (30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

It is the applicant's sole responsibility to monitor all these time limits.

PATENT COOPERATION TREATY

WO 2010/040315
PCT/CN2009/074314

From the INTERNATIONAL BUREAU

PCTNOTIFICATION CONCERNING
AVAILABILITY OF THE PUBLICATION
OF THE INTERNATIONAL APPLICATION

To:

CHINA SCIENCE PATENT AND TRADEMARK AGENT
LTD.
25/F., Bldg. B, Tsinghua Tongfang Hi-Tech Plaza
No. 1, Wangzhuang Rd., Haidian District
Beijing 100083
CHINADate of mailing (day/month/year)
15 April 2010 (15.04.2010)Applicant's or agent's file reference
IP090092C

IMPORTANT NOTICE

International application No.
PCT/CN2009/074314International filing date (day/month/year)
29 September 2009 (29.09.2009)Priority date (day/month/year)
07 October 2008 (07.10.2008)

Applicant

CSPC ZHONGQI PHARMACEUTICAL TECHNOLOGY (SHIJIAZHUANG) CO., LTD. et al

The applicant is hereby notified that the International Bureau:

☒ has published the above-indicated international application on 15 April 2010 (15.04.2010) under
No. WO 2010/040315☐ has republished the above-indicated international application on under
No. WOFor an explanation as to the reason for this republication of the international application, reference is made to INTD codes (15), (48)
or (88) (as the case may be) on the front page of the published international application.A copy of the international application is available for viewing and downloading on WIPO's website at the following address:
www.wipo.int/pctdb (in the appropriate field of the structured search, enter the PCT or WO number).The applicant may also obtain a paper copy of the published international application from the International Bureau by sending an e-mail to
patentscope@wipo.int or by submitting a written request to the contact details provided below.The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Ellen Moyse

From the INTERNATIONAL BUREAU

PCT

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Article 31(7) and Rule 61.3)

To:

CHINA SCIENCE PATENT AND TRADEMARK AGENT LTD.
25/F., Bldg B, Tsinghua Tongfang Hi-Tech Plaza
No.1, Wangzhuang Rd., Haidian District
Beijing 100083
CHINE

Date of mailing (day/month/year) 15 April 2010 (15.04.2010)		IMPORTANT INFORMATION	
Applicant's or agent's file reference IP090092C			
International application No PCT/CN2009/074314	International filing date (day/month/year) 29 September 2009 (29.09.2009)	Priority date (day/month/year) 07 October 2008 (07.10.2008)	
Applicant CSPC ZHONGQI PHARMACEUTICAL TECHNOLOGY (SHIJIAZHUANG) CO., LTD. et al			

- The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:
EP: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR
National: BG, CA, CL, CN, CZ, DE, JP, KP, KR, MN, MY, NO, PE, PL, RO, SK
 - The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:
AP: BW, CH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW
EA: AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
OA: BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
National: AF, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BH, BR, BW, BY, BZ, CH, CO, CR, CU, DK, DM, DO, DZ, EC, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, KE, KG, KM, KN, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MW, MX, MZ, NA, NG, NI, NZ, OM, PG, PH, PT, RS, RU, SC, SD, SE, SG, SI, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
 - Since the election(s) was (were) made before the expiration of 19 months from the priority date, the applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any abstract of the international preliminary report on patentability (Chapter II of the Patent Cooperation Treaty) (Article 36(3)(b) and Rule 74.1).
- Some Offices have fixed time limits expiring later than the above-mentioned time limit. See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters, the *PCT Newsletter* and the WIPO Internet site, updated regularly.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Ellen Moyse
Facsimile No +41 22 338 92 70	e-mail: p02.pct@wipo.int

专利合作条约

发信人: 国际初步审查单位

收信人: 100083

中国北京市海淀区王庄路1号清华同方科技大厦B座25层
中科专利商标代理有限公司

吴小明

PCT

传送专利性国际初步报告的通知书

(PCT第II章)

(PCT 细则 71.1)

发文日(日/月/年)

20.1 月 2011 (20.01.2011)

申请人或代理人的档案号

IP090092C

重要通知

国际申请号

PCT/CN2009/074314

国际申请日(日/月/年)

29.9 月 2009(29.09.2009)

优先权日(日/月/年)

07.10 月 2008(07.10.2008)

申请人

石药集团中奇制药技术(石家庄)有限公司 等

1. 通知申请人,本国际初步审查单位随本通知书传递对国际申请制定的专利性国际初步报告及其附件(如果有附件的话)。

2. 报告及其附件(如果有附件的话)的副本同时送交国际局,以便送达所有选定局。

3. 任何选定局提出要求时,国际局将作出报告的英文译文(但不是任何附件的译文),并将该译文传送给这些选定局。

4. 提示

在自优先权日起 30 个月内(或者在有些局更迟)申请人必须完成一定的行为(提交译本和缴纳国家费)进入各选定局的国家阶段(条约 39 (1)) (参见国际局寄送的 PCT/IB/301 表所附的提示)。

国际申请的译本必须向选定局提供时,该译本还必须包括专利性国际初步报告附件的译文。作出并直接向各有关选定局提供该译文是申请人的责任。

有关各选定局适用的期限和要求的详情,参见《PCT 申请人指南》第 II 卷。

申请人注意:条约 33 (5) 规定,条约 33 (2) 至 (4) 描述的关于新颖性、创造性、工业实用性的标准只供国际初步审查之用。“任何缔约国为了决定请求保护的发明在该国是否可以获得专利,可以采用附加的或不同的标准”。(参见条约 27 (5)) 例如,这种附加标准可涉及例如不授予专利权的主题,说明书和权利要求书是否清楚,以及权利要求书是否得到说明书的支持。

中华人民共和国国家知识产权局 (IPEA/CN)

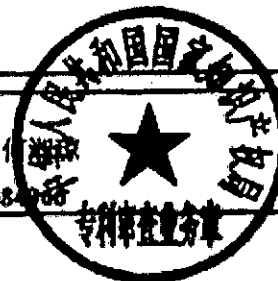
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PCT/IPEA/416 (2004 年 1 月)



专利合作条约

PCT

专利性国际初步报告

(PCT 第II章)

(PCT 第 36 条和细则 70)

申请人或代理人的档案号 IP090092C	关于后续行为 参见PCT/IPEA/416表	
国际申请号 PCT/CN2009/074914	国际申请日(日/月/年) 29.9月 2009(29.09.2009)	优先权日(日/月/年) 07.10月 2008(07.10.2008)
国际专利分类(IPC)或者国家分类和 IPC 参见补充栏		
申请人 石药集团中奇制药技术(石家庄)有限公司 等		

1. 本报告是国际初步审查单位根据条约第 35 条制定的国际初步审查报告, 并依照条约第 36 条传送给申请人。
2. 本报告共计 2 页, 包括本扉页。
3. 本报告还有附件, 包括:
 - a. ☐ (传送给申请人和国际局) 共计 页, 如下:
 - ☐ 修改后的并且作为本报告基础的说明书修改页、权利要求修改页和/或附图修改页, 和/或由本单位许可的更正页(见细则 70.16 和行政规程第 607 条)。
 - ☐ 取代在先页的修改页, 本单位认为这些修改页含有的修改超出了国际申请提交时的公开范围, 如第 I 栏第 4 项和补充栏所示。
 - b. ☐ (仅传送给国际局) 共计 (指明电子载体的类型和数量) , 包含有在与序列表有关的补充栏中指明的仅为电子形式的序列表和/或与其相关的表格。(见行政规程第 802 条)

4. 本报告包括关于下列各项标明的内容:

- ☒ 第I栏 报告的基础
- ☐ 第II栏 优先权
- ☐ 第III栏 不做出关于新颖性、创造性和工业实用性的意见
- ☐ 第IV栏 缺乏发明的单一性
- ☒ 第V栏 按条约第 35 条(2)关于新颖性、创造性或工业实用性的推断性声明, 支持这种声明的引证和解释
- ☐ 第VI栏 某些引用的文件
- ☐ 第VII栏 国际申请中的某些缺陷
- ☒ 第VIII栏 对国际申请的某些意见

提交要求书的日期 21.1月 2010(21.01.2010)	完成本报告的日期 05.1月 2010
IPEA/CH 的名称和邮寄地址: 中华人民共和国国家知识产权局 中国北京市海淀区门桥西土城路 8 号 100088 传真号: (86-10) 62010451	受权官员 何翔球 电话号码 (86-10) 62084366



PCT/IPEA/409 表(扉页) (2009 年 7 月)

专利性国际初步报告

国际申请号

PCT/CN2009/074314

第I栏 报告的基础

1. 关于语言, 本报告的制定基于:

- ☒ 国际申请提交时使用的语言。
☐ 该国际申请的____语言译文, 提供该种语言的译文是为了:
☐ 国际检索(细则12.3(a)和23.1(b))。
☐ 国际申请的公布(细则12.4(a))。
☐ 国际初步审查(细则55.2(a)和/或55.3(a))。

2. 关于国际申请中各个部分, 本报告基于(申请人为答复受理局根据条约14所发通知而提供的替换页, 在本报告中视为“原始提交”的文件, 不作为本报告的附件)

☒ 原始提交/提供的国际申请。

- ☐ 说明书: 第_____页 原始提交/提供的。
 第_____页*, _____ 本单位收到的。
 第_____页*, _____ 本单位收到的。
☐ 权利要求: 第_____页, 原始提交/提供的。
 第_____页*, 按条约19条修改的(附有任何声明),
 第_____页*, _____ 本单位收到的。
 第_____页*, _____ 本单位收到的。

- ☐ 附图: 第_____页, 原始提交/提供的。
 第_____页*, _____ 本单位收到的。
 第_____页*, _____ 本单位收到的。

- ☐ 序列表和/或任何相关表格——见与序列表有关的补充栏。

3. 修改导致以下内容的删除:

- ☐ 说明书: 第_____页
☐ 权利要求: 第_____项
☐ 附图: 第_____页/图_____
☐ 序列表(具体说明): _____

4. ☐ 由于本报告附件的(某些)修改, 如下所列, 被认为超出了原始公开的范围, 如补充栏所示, 因此本报告是按照没有修改的情况做出的(细则70.2(c))。

- ☐ 说明书: 第_____页
☐ 权利要求: 第_____项
☐ 附图: 第_____页/图_____
☐ 序列表(具体说明): _____

5. ☐ 本报告考虑了本单位许可的或被通知的检索细则91所做出的明显错误更正。(细则70.2(e))6. ☐ 本报告考虑了申请人关于国际检索单位的书面意见的答复和/或意见, 该答复和/或意见由本单位于_____收到。7. ☐ 由_____作出的补充国际检索报告已经收到并且在制定本意见时已经考虑了该报告。

*如果第4项适用, 一些或全部的文件页可能做出“被取代”标记。

专利性国际初步报告

国际申请号

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第V栏 按照条约第35条(2)关于新颖性、创造性或工业实用性的推断性声明, 支持这种声明的引证和解释

1. 声明

新颖性(N)	权利要求 1-11	是
	权利要求	否
创造性(IS)	权利要求 1-11	是
	权利要求	否
工业实用性(LA)	权利要求 1-11	是
	权利要求	否

2. 引证和解释 (细则 70.7)

关于权利要求 1 的新颖性、创造性、工业实用性的意见是基于合理预期的主题作出的, 详情参见第 VIII 栏。

1: 本意见引用如下对比文件

D1: CN1948297A (上海医药工业研究院), 18.4 月 2007 (18.04.2007)

2: 新颖性

现有技术没有公开本申请的式 I 化合物, 因此权利要求 1-11 的技术方案是新的, 满足 PCT Art.33(2)的要求。

3. 创造性

D1 是本申请最接近的现有技术, 本申请要解决的技术问题是提供一种 1-丁基-2-羟基羟基芳烷哌嗪衍生物, 它具有抗抑郁活性并且具有较长的半衰期。D1 中具体公开了具有抗抑郁活性的化合物 SIPL5286 (参见说明书实施例 1, 6)。与 D1 相比, 本申请权利要求 1 式 (1) 化合物的区别在于式 (1) 化合物 C1 位置为丁基取代基, 而 D1 中为甲基取代基。当 C1 位置为丁基时, 化合物获得了更长的半衰期, 具有很好的成药性。本领域普通技术人员在 D1 的教导下, 不能显而易见地获得本申请权利要求 1 的技术方案。因此权利要求 1 符合 PCT Art.33(3)的要求。

权利要求 2-11 都涉及了权利要求 1 的化合物, 因此权利要求 2-11 也符合 PCT Art.33(3)的要求。

4. 实用性

权利要求 1-11 的技术方案在工业上是可实施的, 因此它们符合 PCT Art.33(4)的要求。

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第VIII栏 对国际申请的某些意见

就权利要求、说明书和附图的清楚性，或者权利要求是否得到说明书的充分支持提出以下意见：

当 Ar1 或 R1 为取代苯基时，权利要求 1 涉及了大量化合物。但是，在说明书中仅仅给出了少数几种结构的化合物符合 PCT 条约第 6 条关于支持的规定和/或 PCT 条约第 5 条关于充分公开的规定。因此在本申请中，权利要求 1 中所述化合物范围太大，其没有得到说明书的支持，且相应的技术方案在说明书中也没有充分公开，不符合 PCT 条约第 5 条和第 6 条的规定。

本书面意见仅针对其中涉及得到支持的化合物的技术方案。也就是，Ar1 为如权利要求 2 中所定义，R1 为如权利要求 3 中所定义。

专利性国际初步报告

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补充栏

当前面的任何一栏地方不够时使用

续：国际专利分类（IPC）或者国家分类和IPC两种分类

C07D295/084 (2006.01) f

A61K31/495 (2006.01) f

A61P25/24 (2006.01) f

**Los derivados de 1-butilo-2-hidroxiaralquilo piperazina y sus
usos como medicina anti-depresiva**

CAMPO DE INVENCIÓN

[01] La presente invención se relaciona con los derivados de 1-butil-2-hidroxiaralquilo piperazina y sus usos como antidepresivos de amplio espectro.

ANTECEDENTES DE LA INVENCIÓN

[02] La depresión es un síndrome caracterizado por un bajo estado de ánimo significativo y de larga duración, el cual se manifiesta principalmente como un desorden afectivo. Los síntomas incluyen un estado de ánimo bajo, poca habla, pensamientos y locomoción lentos e incluso, intento de suicidio. La depresión como una enfermedad mental crónica, se ha convertido en un serio problema que afecta al servicio de salud en China, dado su largo tratamientos, lenta mejoría y alta probabilidad de recaída, discapacidad y suicidio. De acuerdo al documento "World Health Reports" publicado por la Organización Mundial de la Salud (OMS), la depresión se ha convertido en la cuarta enfermedad a nivel mundial, y se espera que la misma pueda llegar a convertirse en la segunda enfermedad más recurrente después de la enfermedad cardíaca para el año 2020, y por tanto, convertirse en un serio problema para la salud de toda la humanidad.

[03] Actualmente, el mecanismo de acción de los antidepresivos no ha podido ser demostrado con claridad. Los medicamentos que tienen un efecto real, actúan de manera sustancial sobre las sinapsis de las terminaciones nerviosas y ejercen sus efectos curativos mediante el ajuste del nivel de los neurotransmisores en el espacio sináptico. El estudio bioquímico sobre la etiología indicó que la depresión se relaciona principalmente con cinco tipo de neurotransmisores, a saber; central 5- hidroxitriptamina (5- HT), noradrenalina (NA)), dopamina (DA), acetilcolina (Ach), y γ -ácido amino-butírico (GABA).

Los antidepresivos pueden ser clasificados en dos categorías: antidepresivos de primera generación no selectivos, e inhibidores selectivos de recaptación novedosos. Los antidepresivos no selectivos incluyen los inhibidores monoamínicos de oxidasa (MAOIs) y antidepresivos tricíclicos (TCAs); los inhibidores selectivos de recaptación comprenden principalmente 5-hidroxitriptamina (5-HT) inhibidores de recaptación (SSRIs), noradrenalina (NA) inhibidores de recaptación (NRIs), noradrenérgicos e inhibidores de recaptación 5-HT específicos (NDRIs), 5-HT e inhibidores de recaptación dual NA (SNRIs), 5-HT potenciadores de re-absorción y similares.

[04] Los inhibidores monoamínicos oxidasa y los tricíclicos antidepresivos tienen reacciones adversas severas; en lo relacionado con los inhibidores de recaptación NA selectivos y los inhibidores de recaptación selectivos 5-HT, a pesar que éstos tienen reacciones adversas menos severas, todavía se sostienen desventajas tales como baja eficacia, lento progreso y similares. Por tanto, los efectos de todos los tipos de medicamentos antes mencionados para el tratamiento de la depresión no son satisfactorios. Hasta ahora, los antidepresivos que se encuentran en el mercado no han alcanzado los requerimientos que demanda el tratamiento clínico.

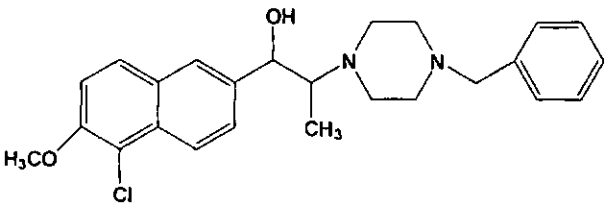
[05] Venlafaxina el primer inhibidor de recaptación dual de 5-HT y NA comercializado en América en 1997, y dutoxetina comercializada en 2004, presentan ventajas por su rápida acción en comparación a los inhibidores de recaptación de 5-hidroxitriptamina tales como la fluoxetina, e inhibidores de recaptación de noradrenalina tales como reboxetina, tienen efectos significativos tanto en la depresión seria y en la refractiva. Desde la venlafaxina, el desarrollo de novedosos antidepresivos que tiene rutas de acción dual de 5-HT y NA, acción más rápida, menores efectos secundarios y efectos más fuertes, sobreviene el énfasis de investigación y una dirección de desarrollo importante.

[06] Actualmente, muchos estudios indican que la adición de

inhibidores de recaptación de DA en inhibidores de recaptación dual puede resultar en un mejor efecto antidepresivo. Los inhibidores de recaptación triple de 5-HT, NA y DA (también conocidos como antidepresivos de "amplio espectro"), desarrollados con base de inhibidores de recaptación dual, todavía se encuentran en la fase de investigación clínica. Por ejemplo, el inhibidor de recaptación selectivo triple DOV-216303 desarrollado por DOV Pharmaceutical Inc. se encuentra en la fase III de las pruebas clínicas; NS-2359 desarrollado en conjunto por GlaxoSmithKline y NeuroSearch Inc. Se encuentra ahora en la fase II de las pruebas clínicas antidepresivas. Estos transmisores monoamínicos inhibidores de recaptación selectivos triples poseen como ventajas su alta efectividad y rápida acción y se encuentran consolidándose como claves en el desarrollo de antidepresivos.

[07] El solicitante ha revelado los derivados de arilo alkanol piperazina y su uso en la preparación de antidepresivos en la patente china No. ZL02111934.1. Un compuesto preferido entre éstos, es N¹-bencilo-N⁴-[1-metilo-2-(5'-cloro-6'-metoxilo-2'-naftil)

hidroxietilo]piperazina (IV-19, SIPlly24 , ver formula A abajo), tiene un efecto inhibitorio de recaptación dual de 5-HT y NA, al igual que tiene una fuerte actividad biológica antidepresiva en animales. No obstante, una investigación posterior develo que el efecto antidepresivo todavía no es satisfactorio y por ende, la reacción adversa es obvia.



Formula A

[08] Subsecuentemente, el solicitante reveló los isómeros ópticos del compuesto SIPlly24 y su uso en la patente china No. ZL 200510030354.1. El estudio muestra que el isomer óptico (1S,2R) de SIPlly24 (código SIPI5286) tienen un efecto inhibitorio de recaptación

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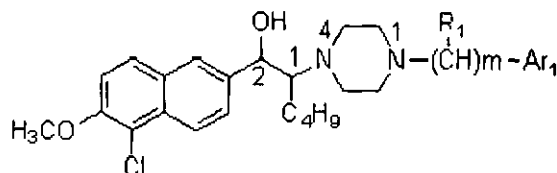
de tres tipo de transmisores monoamínicos, a saber; 5-HT, NA y DA. Es un novedoso inhibidor de recaptación triple, con mayor actividad antidepresiva y seguridad que aquel mostrado por su competidor, y es por tal, digno de ser un antidepresivo novedoso. Sin embargo, se ha encontrado en estudios posteriores, que la vida media del SIPI5286 es muy corta, y por tanto no es susceptible de ser formulado en un medicamento.

DESCRIPCIÓN DE LA INVENCION

[09] Uno de los problemas técnicos a ser resuelto en la presente invención es el de revelar como un derivado de 1-butilo-2-hidroxil aralquilo piperazina puede superar los defectos antes del arte, a saber; baja efectividad, efectos secundarios prominentes y acción lenta, y por ende, resolver los problemas químicos y reunir los requerimientos para su aplicabilidad clínica.

[10] Otro problema técnico a ser resuelto en la presente invención recae en develar el uso del derivado antes mencionado en la preparación de antidepresivos.

[11] El derivado de 1-butilo-2-hidroxil aralquilo piperazina mencionado en la presente invención es el alkali libre o la sal del compuesto de la formula (1), o el alkali libre o la sal de los isómeros ópticos de compuesto de la formula (1):



(1)

donde:

Ar₁ representa benceno; substituido por fenilo; un heretociclo aromático de 5-miembros o 6-miembros conteniendo N, O o S, o

cinnamenilo, donde el fenilo sustituido es un fenilo que contiene de uno a cuatro sustitutos (1, 2, 3 or 4) en el aro de benceno, donde los sustitutos son halogeno, hidroxilo, alquilo, nitro, alkoxi o amino;

m es un integral de 0~5, preferiblemente 0 o 1;

R₁ representa hidrogeno, C₁-C₅ alquilo (preferiblemente C₁-C₃ alquilo y preferiblemente metilo), C₅ or C₆ aro alicíclico, benceno, sustituido por fenilo, hidroxilo, amino, amino, C₁-C₄ alkoxi sustituto, C₁-C₄ acilo, halogeno, ácido carboxílico o eter carboxílico, donde el amino sustituto es un animo sustituido con C₁-C₄ alquilo, C₅ o C₆ aro alicíclico, benceno o sustituido con fenilo; el fenilo sustituto es un fenilo con uno a cuatro sustitutos en el aro de benceno, el sustituto siendo halogeno (preferiblemente cloro), hidroxilo, alquilo (preferiblemente C₁-C₃ alquilo y mejor C₁-C₃ cadena linear de alquilo), nitro, alkoxi o amino; el alquilo C₁-C₅ (preferiblemente alquilo C₁-C₃) y el alquilo moiety en C₁-C₄ alkoxe, C₁-C₄ acilo y C₅ o C₆ aro alicíclico ring es preferible la cadena linear de alquilo la cual puede sustituirse opcionalmente con átomos de flúor 1~3;

[12] Los átomos de carbón asimétricos en la estructura aquiral o quiral de átomos de carbono; para los átomos de carbono quirales, la configuración de C₁ y C₂ es respectivamente (1S,2R), (1S,2S), (1R,2S) o (1R,2R); donde el isómero (1SR,2RS) es un eritro isómero y el isómero (1SR,2SR) es un tereo isómero.

[13] Donde el compuesto de la formula (1) es un alkali libre, y puede formar varias sales con varios ácidos inorgánicos y ácidos orgánicos.

[14] En una representación, la sale es una sal que contiene anionens farmacológicamente aceptados, por ejemplo, hidrocioruro, hidrobromuro, hidriodide, nitrato, sulfato r hidrosulfato, fosfato o ácido fosfórico, acetato, lactato, citrato, tartrato, maleato, fumarato, gluconato, sacarato, benzoato, metanosulfonato, metanosulfonato, etanosulfonato, benceno sulfonato o p-toluenesulfonato, y preferiblemente hidrocioruro, hidrobromuro, sulfato, trifluoroacetato y metanosulfonato.

[15] En otra representación, la sal contiene 0.5~4 moléculas de agua cristalina.

[16] Preferiblemente, los derivados de 1-butilo-2-hidroxil aralquilo piperazina se seleccionan de un grupo consistente de:

VIII-1

(1SR,2RS)-N¹-p-metoxilofenilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil) hidroxietilo]piperazina,

VIII-2

(1SR,2SR)-N¹-p-metoxilofenilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil) hidroxietilo]piperazina,

VIII-3

(1SR,2RS)-N¹-o-metoxilofenilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina,

VIII-4

(1SR,2SR)-N¹-o-metoxilofenilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo] piperazina,

VIII-5

(1SR,2RS)-N¹-m-clorofenilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina,

VIII-6

(1SR,2SR)-N¹-m-clorofenilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina,

VIII-7

(1SR,2RS)-N¹-(2,3-dimetilofenilo)-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina,

VIII-8

(1SR,2SR)-N¹-(2,3-dimetilofenilo)-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina,

VIII-9

(1SR,2RS)-N¹-bencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil) hidroxietilo]piperazina,

VIII-10

(1SR,2SR)-N¹-bencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)

hidroxietilo]piperazina,

VIII-11

(1SR,2RS)-N¹-p-nitrobencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-
 naftil)hidroxietilo]piperazina,

VIII-12

(1SR,2SR)-N¹-p-nitrobencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-
 naftil)hidroxietilo]piperazina,

VIII-13

(1SR,2RS)-N¹-p-aminobencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-
 naftil)hidroxietilo]piperazina,

VIII-14

(1SR,2SR)-N¹-p-aminobencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-
 naftil)hidroxietilo]piperazina,

VIII-15

(1SR,2RS)-N¹-(3',4',5'-trimethoxybencilo)-N⁴-[1-butilo-2-(5'-cloro-6'-
 metoxilo-2'-naftil)hidroxietilo] piperazina,

VIII-16 (1SR,2SR)-N¹-(3',4',5'-

trimethoxybencilo)-N⁴-[1-butilo-2-(5'-cloro-6'-
 metoxilo-2'-naftil)hidroxietilo]piperazina,

VIII-17

(1SR,2RS)-N¹-α-phenemyl-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-
 naftil)hidroxietilo]piperazina,

VIII-18

(1SR,2SR)-N¹-α-phenemyl-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-
 naftil)hidroxietilo]piperazina,

VIII-19

(1SR,2RS)-N¹-benzhydryl-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-
 Naftil)hidroxietilo]piperazina,

VIII-20

(1SR,2SR)-N¹-benzhydryl-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-
 Naftil)hidroxietilo]piperazina,

VIII-21 (1SR,2RS)-N¹-cinnamyl-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-
 Naftil)hidroxietilo]piperazina,

VIII-22 (1SR,2SR)-N¹-cinnamyl-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-

- naftil)hidroxietilo]piperazina,
IX-23 (1S,2R)-N¹-bencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)
hidroxietilo] piperazina,
IX-24 (1S,2S)-N¹-bencilo-N⁴-[1-butilo -2-(5'-cloro-6'-metoxilo-2'-naftil)
hidroxietilo]piperazina,
IX-25 (1R,2S)-N¹-bencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)
hidroxietilo]piperazina, y
IX-26 (1R,2R)-N¹-bencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)
hidroxietilo]piperazina.

[17] Most preferred are:

VIII-9

(1SR,2RS)-N¹-bencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)
hidroxietilo]piperazina,

VIII-10 (1SR,2SR)-N¹-bencilo

-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)

hidroxietilo]piperazina,

IX-23 (1S,2R)-N¹-bencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)
hidroxietilo]piperazina,

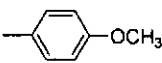
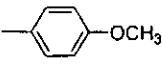
IX-24 (1S,2S)-N¹-bencilo-N⁴-[1-butilo -2-(5'-cloro-6'-metoxilo-2'-naftil)
hidroxietilo]piperazina,

IX-25 (1R,2S)-N¹-bencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)
hidroxietilo]piperazina, y

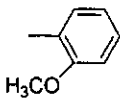
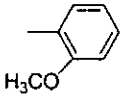
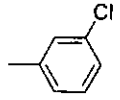
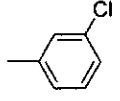
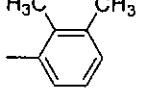
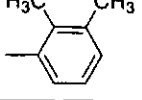
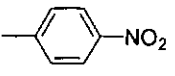
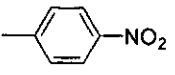
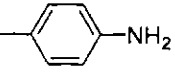
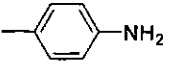
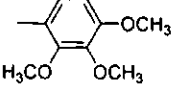
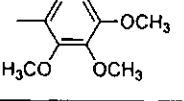
IX-26 (1S,2R)-N¹-bencilo-N⁴-[1-butilo -2-(5'-cloro-6'-metoxilo-2'-naftil)
hidroxietilo]piperazina.

[18] Las estructuras de los compuestos se muestran en la Tabla 1.

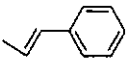
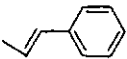
Tabla 1, estructuras de los compuestos

Código	Configuración	Ar ₁	R ₁	m
VIII-1	(1SR,2RS)		H	0
VIII-2	(1SR,2SR)		H	0

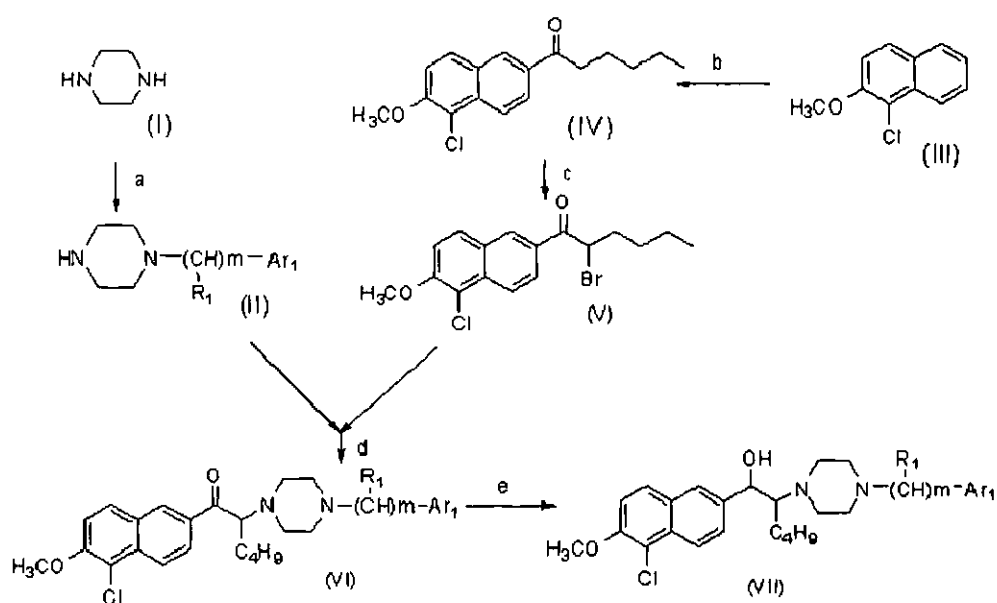
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VIII-3	(1SR,2RS)		H	0
VIII-4	(1SR,2SR)		H	0
VIII-5	(1SR,2RS)		H	0
VIII-6	(1SR,2SR)		H	0
VIII-7	(1SR,2RS)		H	0
VIII-8	(1SR,2SR)		H	0
VIII-9	(1SR,2RS)	Ph	H	1
VIII-10	(1SR,2SR)	Ph	H	1
VIII-11	(1SR,2RS)		H	1
VIII-12	(1SR,2SR)		H	1
VIII-13	(1SR,2RS)		H	1
VIII-14	(1SR,2SR)		H	1
VIII-15	(1SR,2RS)		H	1
VIII-16	(1SR,2SR)		H	1

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VIII-17	(1SR,2RS)	Ph	CH ₃	1
VIII-18	(1SR,2SR)	Ph	CH ₃	1
VIII-19	(1SR,2RS)	Ph	Ph	1
VIII-20	(1SR,2SR)	Ph	Ph	1
VIII-21	(1SR,2RS)		H	1
VIII-22	(1SR,2SR)		H	1
IX-23	(1S,2R)	Ph	H	1
IX-24	(1S,2S)	Ph	H	1
IX-25	(1R,2S)	Ph	H	1
IX-26	(1R,2R)	Ph	H	1

[19] En una representación, los compuestos de VIII-1~VIII-22, que son eretro o treo isómeros, pueden sintetizarse de acuerdo al siguiente método:



a: $\text{Ar}_1(\text{CH}_2)_m\text{X}$, KOH, CTBA, Ph/H₂O

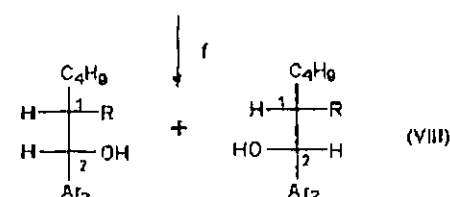
b: $\text{X}-\text{C}(=\text{O})-\text{C}_6\text{H}_{11}$, AlCl_3 , CH_2Cl_2

c: CuBr_2 , CHCl_3 , EtOAc

d: K_2CO_3 , KI, CH_3COCH_3

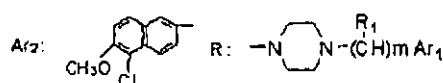
e: NaBH_4 , $\text{CH}_3\text{OH}/\text{Al}(\text{O}i\text{Pr})_3$, $i\text{-PrOH}$

f: separation



erythro isomer

threo isomer



[20] La piperazina se utiliza como el material de comienzo. Primero, se configura una reacción de sustitución nucleofílica con el arialalkano halogenado correspondiente con el fin de obtener el compuesto N-monoalquilado (II). Esta reacción se realiza bajo la fase de transferencia catalítica. La N-monoalquilación de la piperazina

puede realizarse mediante una reacción con KOH en un medio de reacción de benceno/agua utilizando cetil trimetiloamonio bromuro (CTAB) como el catalizador de la fase de transferencia, y con un rendimiento de hasta el 86%. El catalizador de la fase de transferencia es aquel reportado en la patente china No. ZL02111934.1.

[21] El Compuesto (III) se reacciona con el correspondiente acilo cloruro para realizar la reacción Friedel-Crafts con el fin de obtener arilo alkanone (IV). Esta reacción se realiza a temperatura ambiente, utilizando diclorometano como solvente y cloruro de aluminio anhidroso como catalizador. El rendimiento es de alrededor del 80%.

[22] El Compuesto (IV) es brominado para producir arilo alkanone halogenado (V). Esta reacción se realiza mediante el calentamiento bajo reflujo, utilizando CuBr_2 como agente brominador y una mezcla de la solución de cloroformo y etilo acetato como solvente. El rendimiento es al rededor de un 85%.

[23] El Compuesto (II) puede reaccionarse con el compuesto (V) para producir la reacción de alquilación N^4 , produciendo así un compuesto de arilo alkanone piperazina (VI). La reacción se realiza mediante el reflujo por un periodo de 8-24 horas utilizando K_2CO_3 /acetona como sistema de reacción. El rendimiento es de 80%.

[24] El Compuesto (VI) se reacciona con NaBH_4 en metanol a temperatura ambiente por 0.5-1 horas, o con aluminio isopropoxido en isopropanol a 60-65°C por 24-48 horas, para reducir el grupo carbonilo, y así obtener el correspondiente compuesto de arilo alkanol piperazina compuesto (VII).

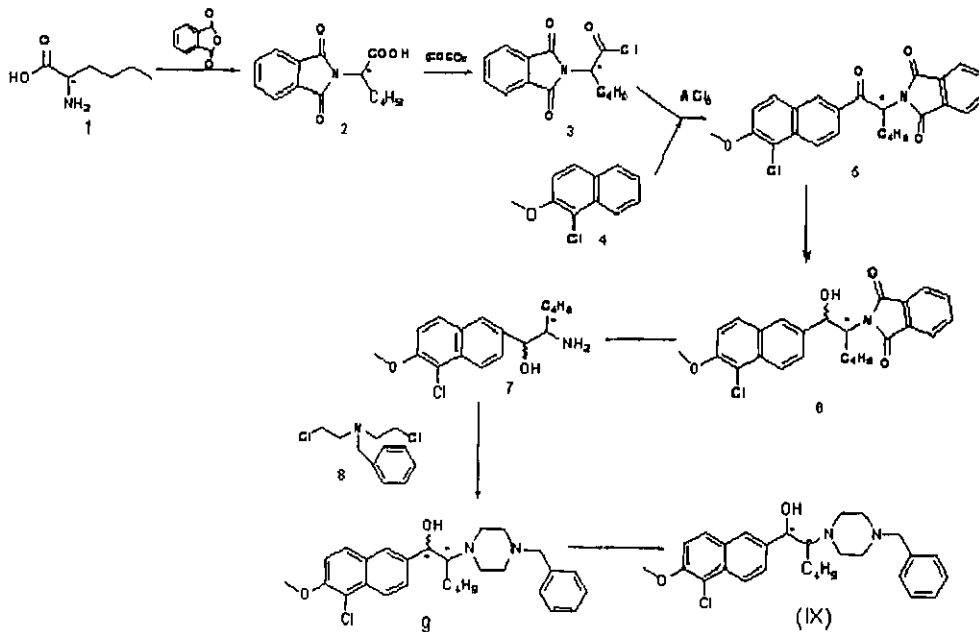
[25] El compuesto (VII) es separado mediante una cromatografía de columna y así se obtienen los derivados eritro y treo isómeros (VIII) de 1-butilo-2-hidroxil aralquilo piperazina. Los compuestos 1-22 de interés pueden obtenerse utilizando el método anterior.

[26] Los compuesto haloariloalkane en el paso a, y el compuesto de ácido cloruro y el III en el paso b se encuentran en el mercado o

pueden prepararse mediante métodos convencionales reportados en la literatura.

[27] Para los isómeros ópticos de los compuestos IX-23~IX-26, puede utilizarse el siguiente método de sintetización:

[28] El Compuesto 3 se obtiene comenzando en quiral norleucina 1, protegiendo el grupo de amino con phthaloyl y acilating grupo carboxyl con oxalyl cloruro; después el Compuesto 3 se reacciona con el Compuesto 4 para realizar la reacción Fiedel-Crafts, y así obteniendo el compuesto 5. El Compuesto 5 se reduce con aluminio isopropoxida, y después es hidrolizado para obtener el Compuesto 7. El Compuesto 7 se condensa con el Compuesto 8 para obtener el Compuesto 9, y después se obtiene el producto óptico puro de interés (IX) mediante la separación por cromatografía de columna. El esquema de síntesis detallado se muestra abajo:



[29] La presente invención utiliza el método proquiral para sintetizar cuanto isómeros del compuesto N¹-bencilo-N⁴-(1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina:

[30] Se sintetizó una mezcla del isómero (1S,2R) y el isómero (1S,2S) utilizando sing L-norleucina como material de comienzo, luego se separó mediante una cromatografía de columna utilizando gel de silica gel o alumina como medio y la solución de metileno cloruro y metanol con un índice de volumen de 200:1 como eluant, para así obtener (1S,2S)-N¹-bencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina (IX-24) y (1S,2R)-N¹-bencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo] piperazina (IX-23). Si se utiliza la D-norleucina como material de comienzo, de acuerdo con el mismo método se obtienen (1S,2S)-N¹-bencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naphthy)hidroxietilo]piperazina (IX-25) y (1S,2R)-N¹-bencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina (IX-26).

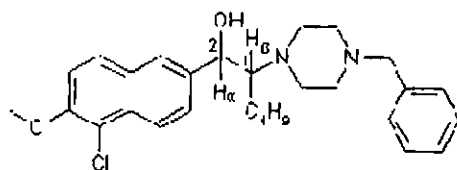
[31] Para la síntesis del anterior método, los materiales se encuentran disponibles, los productos no requieren resolución y se obtienen con una alta pureza óptica y un rendimiento alto en promedio. La pureza de los cuatro isómeros ópticos se determina mediante un líquido de alto rendimiento en una cromatografía con una columna quiral y consiguiendo un exceso (ee) enantiomérico de más de un 99%. [Condición de detección OJ-H columna quiral (de Daicel industries.Co. Ltd., JP) 4.6×250mm; fase móvil: n-hexane:etanol: dietiloamina = 40:60:0.1(v/v/v); largo de honda ultravioleta:UV220nm; temperatura de columna:35°C]

[32] Las configuraciones de los cuatro isómeros ópticos puede presumirse a partir de la configuración del material de comienzo y el acoplamiento constante del producto. En el curso de la reacción, las juntas que conectan el centro quiral no se rompen y el tamaño relativos de los grupos conectados no cambia, la configuración de C1 conectando en N en el producto final es la misma que aquella del material de comienzo de la norleucina. Adicional, la configuración de C2 puede presumirse a partir del acoplamiento entre H α y H β conectando el centro quiral. Específicamente, el acoplamiento bajo

constante de $J_{\alpha\beta}$ representa la eritro forma, y corresponde a la configuración de (1S,2R) o (1R,2S); el acoplamiento alto constante de $J_{\alpha\beta}$ representa la treo forma, y corresponde a la configuración de (1S,2S) o (1R,2R).El detalle se muestra en la tabla 2.

[33] Los isómeros (1S,2R) y (1S,2S) se preparan utilizando L-norleucina como el material de comienzo; y los isómeros (1R,2S) y (1R,2R) se preparan utilizando D-norleucina como material de comienzo.

Tabla 2 Configuración presumida de los cuatro isómeros ópticos



compue sto	configuraci ón de norleucina	configuraci ón de C ₁	Acopla miento constan te $J_{\alpha\beta}$ /Hz	Eritro/ Treo	configuraci ón de C ₂	configuraci ón del producto
IX-23	L	S	2.0	Eritro	R	1S , 2R
IX-24	L	S	9.6	Treo	S	1S , 2S
IX-25	D	R	2.0	Eritro	S	1R , 2S
IX-26	D	R	9.6	Treo	R	1R , 2R

[34] El experimento de inhibición de recaptación in vitro en los transmisores monoamininos mostró que los derivados de 1-butilo-2-hidroxil aralquilo piperazina y los isómeros ópticos

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correspondientes de la presente invención, son inhibidores de recaptación triple, lo cual tiene un efecto inhibitorio in vitro más fuerte en la recaptación de los transmisores monoamínicos DA, NE y 5-HT. El compuesto preferido VIII-10 tienen un efecto de inhibición in vitro equivalente en la recaptación de 5-HT y NA en comparación con la venlafaxina y SIPIyy24, y tiene un actividad de inhibición de recaptación más potente para DA en comparación con la venlafaxina, SIPIyy24 y SIPI5286; el compuesto VIII-9 tiene una actividad de inhibición en la recaptación de los tres transmisores monoamínicos en comparación a la venlafaxina, SIPIyy24 y SIPI5286.

[35] Estudios de la actividad antidepresiva in vivo en animales mostró que: el compuesto VIII-9 tienen una actividad antidepresiva in vivo equivalente a aquella de la venlafaxina y SIPI5286, y tiene una diferencia comparativa con el grupo de control; y la actividad antidepresiva in vivo del Compuesto VIII-10 es más fuerte que aquella de la venlafaxina y SIPI5286.

[36] El estudio de toxicidad aguda mostró que LD₅₀ (95% límite de confianza) del compuesto preferido VIII-10 es 1048.5 (751.33~1433.7) mg/kg, MLD(dosis letal mínima) de VIII-9 es mas de 2844.7 mg/kg. Su toxicidad aguda es menor que aquella de SIPIyy24 (un compuesto preferido en la patente china No. ZL02111934.1) y SIPI5286 (un compuesto preferido en la patente china No ZL200510030354.1)

[37] El estudio de farmacogenesis mostró que la vida media del compuesto VIII-10 administrado oralmente es de 16.41 horas, lo cual es mayor que aquella de VIII-9 (5.89 horas) y SIPI5286 (5.71 horas). La biodisponibilidad del compuesto VIII-10 administrado oralmente es de 63.78%, lo cual es mayor que aquella de VIII-9 (16.32%) y SIPI5286 (51.63%). Por tanto, el compuesto VIII-10 posee un buen manejo farmacológico.

[38] Los derivados de 1-butilo-2-hidroxil aralquilo piperazina de la presente invención tienen un efecto inhibitorio de recaptación triple de 5-HT, NA y DA, y pueden ser utilizados en la preparación de

antidepresivos.

[39] Los derivados de la presente invención pueden ser administrados en pacientes que los necesiten en la forma de composición, vía oral o inyectado, o similares.

[40] La actual invención también se relaciona con un método para tratar a un paciente con depresión, abarcando la administración de una cantidad terapéuticamente eficaz de los derivados de la invención o de la composición que contenga los mismo, al paciente. La ruta de la administración puede ser administración oral o inyección.

[41] La composición contiene la cantidad terapéuticamente eficaz de derivados de la actual invención como ingrediente activo, junto con unos o más portadores farmacéutico aceptables.

[42] El portador significa los portadores convencionales en campo farmacéutico, por ejemplo, los diluyentes, excipientes tales como agua; pegamento tal como derivados de la celulosa, gelatina, polyvinylpyrrolidone y similares; llenadores tales como almidón y similares; agentes de desintegración tales como carbonato de calcio, bicarbonato de sodio y similares; además, otros coadyuvantes tales como dulcificantes de las sustancias aromáticas y se pueden agregar en la composición.

[43] Para la administración oral, podrá formularse en preparaciones sólidas convencionales tales como tabletas, polvo o cápsulas; para la administración inyectada, podrá formularse como una solución inyectable.

[44] Varias preparaciones de la composición según la actual invención se pueden preparar usando métodos convencionales en campo farmacéutico, en donde el contenido del ingrediente activo es 0.1% a 99.5% (por peso).

[45] La cantidad administrada en la actual invención puede variar según la ruta de la administración, peso del paciente, tipo severidad de y de la enfermedad siendo tratada, y similares de la edad y, la dosis

diaria es 5-30 mg/kg del peso corporal (oral) o 1-10 mg/kg del peso corporal (inyección). Los derivados de la actual invención demostraron el antagonismo contra la depresión en ensayos de los animales.

[46] Para superar el defecto de SIPI5286, la modificación de la estructura se realiza usando SIPI5286 como el compuesto líder. El actual inventor encontró que, cuando el grupo del sustituto de C1 es hidrocarbano graso, con el incremento de la cadena del carbón a partir de la 1 a 4, los isómeros del treó del eritro y de la demostración de los compuestos mejora la inhibición en el recaptación de 5-HT, NA y DA, comparable con SIPIlyy24 y la venlafaxine como control positivo. Cuando el sustituto es butilo, que es derivados de 1 de butilo-2-hidroxil piperazina del aralquilo de la actual invención, la actividad de la inhibición en el recaptación de 5-HT, NA y DA del alcance de los isómeros del treó del eritro alcanzan el máximo, más alto que el de SIPIlyy24, SIPI5286 y la venlafaxina como control positivo. Sin embargo, cuando el sustituto de C1 es pentyl, la actividad de la inhibición disminuye agudamente. Cuando la calificación de la estructura fue realizada en otros compuestos en ZL02111934.1, el actual inventor encontró que cuando el sustituto de C1 es butilo, la actividad de la inhibición en el recaptación de 5-HT, NA y DA alcanzó el valor máximo para todos. Por lo tanto, el actual inventor consideró que los derivados de 1 de butilo-2-hidroxil piperazina del aralquilo tienen la actividad más fuerte que aquella mostrada por los derivados del piperazina del alkanol del arilo.

[47] El estudio in vivo en animales subsecuente también muestra que en comparación con los derivados de arilo alkanol piperazina develados en la patente china No. ZL02111934.1 y el isómero óptico develado en la patente china No. ZL200510030354.1, los derivados de 1-butilo-2-hidroxil aralquilo piperazina de la presente invención poseen ventajas mas fuertes en la actividad antidepresiva, menor toxicidad, mayor vida media y mayor manejabilidad farmacológica.

[48] En conclusión, los derivados de 1-butilo-2-hidroxil aralquilo piperazina en la presente invención, en comparación con los depresores clínicos de doble acción (por ejemplo, venlafaxina) pueden ser más potentes, mayores indicaciones de uso, menor toxicidad y menor cantidad de efectos neurotóxicos secundarios. Los derivados tienen como ventajas su mayor actividad antidepresiva, menor toxicidad, mayor biodisponibilidad, mayor vida media y mejor manejabilidad farmacológica en comparación con los derivados de arilo alkanol piperazina develados en la patente china No.ZL02111934.1 y los isómeros ópticos develados en la patente china No.ZL200510030354.1.

Modos específicos para desarrollar la Invención

Método general 1:síntesis de N-aralquilo piperazina hidrocloreuro(II)

[49] El hexahydrate de Piperazina (350mmol, de la estación química el reactivo de Shanghai), KOH del sólido (100mmol) y CTAB (bromuro de Hexadecyl Trimetiloammonium, 1mmol) fue agregado a 18 ml de agua y calentado para disolver. Se adicionaron 40 ml de cloruro de aralquilo (100mmol, comercialmente disponible) en benceno, gota a gota a una temperatura de 70°. Después del goteo, el reactivo fue reflujo por 1.5 horas, y se le permitió reposar, seguido, la fase orgánico fue lavada con 50ml de agua y 50ml de solución saturada de NaCl respectivamente y secada con filtrado de MgSO₄. El solvente fue evaporado bajo presión reducida, y el concentrado entonces fue disuelto en 50ml el alcohol absoluto y el pH ajustado a 3 mediante el goteo de la solución de HCl/C₂H₅OH. A continuación, el precipitado sólido fue filtrado y secado. El hidrocloreuro del piperazina de N-aralquilo fue obtenido por la recristalización en etanol. El rendimiento fue de 80%-86%.

Método general 2: síntesis of 2-hexanone-5-cloro-6-metoxilonaphthaline(IV)

[50] El compuesto (III) (28.4mmol) fue disuelto en diclorometano (30ml). Se adicionó AlCl₃ (30.8mmol), el reactor fue mezclado por 1

hora a temperatura ambiente. Con el AlCl_3 disolviéndose gradualmente, el color de la solución se torno de oscuro a marrón claro. Se adicionó Hexanoyl cloruro(23.7mmol) a cuenta gotas lentamente a la mezcla, con una temperatura controlada por debajo de 10° . Después del goteo, el reactor fue calentado naturalmente a temperatura ambiente y mezclado por 1h. El color de la solución de reacción se torno de oscuro a marrón. La solución de reacción fue vertida en una mezcla de ácido hidrociorídico (20ml)/hielo picado (50g) bajo mezcla y el color de la fase orgánica se tornó de amarillo claro a amarillo. La fase orgánica fue separada, lavada con agua (20ml $\times$ 3) hasta que la fase acuosa se tornara neutral y luego secada con Na_2SO_4 anhidrido durante la noche. El disecante fue filtrado, y el residuo fue lavado con una pequeña cantidad de diclorometano. Seguido, el solvente del filtrado fue evaporado y se obtuvo una sustancia oleosa amarillo claro. El producto IV fue separado como un producto oleoso amarillo claro mediante una cromatografía de columna (acetato de etilo: éter de petróleo=1:400~1:60), permitiéndole el reposo y solidificación. El rendimiento fue de alrededor 80%.

Método general 3: síntesis de 2-(α -bromo-hexanone)- 5-cloro - 6-metoxilonaphthaline (V)

[51] El compuesto (IV) (21mmol) fue disuelto en una meza de acetato de etilo (50ml) y cloroformo (50ml), luego se adicionó CuBr_2 (40.2mmol), la reacción se realizó bajo reflujo durante 3 horas. El CuBr producido fue filtrado. El filtrado fue lavado con agua (20ml $\times$ 3), y secado con Na_2SO_4 anhidrido durante la noche. El disecante fue filtrado, con el residuo lavado con una pequeña cantidad de acetato de etilo. El solvente del filtrado fue evaporado. Se obtuvo un sólido cristalino amarillo claro mediante la recrystalización con etanol. El rendimiento fue de alrededor 85%.

Método general 4:

síntesis de

**N^1 -aralquilo- N^4 -[1-(5'-cloro-6'-metoxilo-2'-naphthoyl)pentyl]
 piperazina hidrocioruro(VI)**

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[52] Se colocó en en acetona (50ml), N-aralquilo piperazina hidrocloreuro (II) (10mmol), 2-(α -bromo-hexanone)-5-cloro-6-metoxilonaftalene (V) (12mmol), potasio yodado (1mmol) y anhídrido K_2CO_3 (35mmol). La reacción fue realizada mediante la mezcla bajo reflujo por un periodo de 8 a 12 horas. Después fue filtrado, y el solvente fue evaporado hasta secarse bajo presión reducida. Se adicionaron 50ml de agua, el reactor fue extraído con EtOAc (100ml $\times$ 3). Las capas de ester fueron sacadas y lavadas con 20ml agua y 30ml de solución excesivamente saturada de NaCl, luego secadas con $MgSO_4$. Después de la filtración, el solvente fue evaporado. El concentrado fue disuelto mediante la adición de 30ml de etanol, y pH ajustado a 2 con HCl/ C_2H_5OH (5N). El precipitado sólido fue filtrado y recristalizado en etanol/agua o metanol para obtener el compuesto (VI) con un rendimiento de 60%~85%.

Método general 5:

síntesis de

N¹-aralquilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil) hidroxietilo] piperazina hidrocloreuro(VII)

[53] Se disolvió aluminio isopropoxide (35mmol) en 80ml de isopropanol, y se adicionó $AlCl_3$ abhídrico (3.5mmol). Seguido se calentó a 45-50 $^{\circ}C$, la mezcla fue revuelta por 30min hasta tornarse transparente, se adicionó N¹-aralquilo-N⁴-aralquiloacilo alquilopiperazina(10mmol) en isopropanol. La temperatura se incrementó a 60-65 $^{\circ}C$, la reacción se realizó hasta que el material objetivo se desapareciera (detección TLC, 6-48 horas). A continuación, se adicionó 15% de solución de NaOH (por peso) para ajusta el pH a alrededor de 7. Se realizó la extracción con diclorometano o acetato de etilo y el extracto fue lavado con solución saturada de NaCl (20ml) y secado con $MgSO_4$. Después de la filtración, el solvente del filtrado fue evaporado bajo condiciones de presión reducida. El residuo fue disuelto en 20ml de etanol, y el pH ajustado a 2 con HCl/ C_2H_5OH . El precipitado sólido fue filtrado con un rendimiento de 85%~95%.

Ejemplo 1**VIII-1**

(1SR,2RS)-N¹-p-metoxilofenilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina (eritro forma)

[54] Se sintetizaron 4.2g of N¹-p-metoxilofenilo-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxy naphthalene-2-yl)] etilopiperazina hidrocloreto utilizando N¹-p-metoxilofenilopiperazina (10mmol) y 2-(α-bromo-hexanone)-5-cloro-6-metoxilonaftalina (10mmol), de acuerdo con el método general 2 al método general 4, con un rendimiento de 79%, m.p=231.5-233.6°(dec). Después se realizó la reducción de carbonilo en N¹-p-metoxilofenilo-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxy naphthalene-2-yl)]etilopiperazina de acuerdo con el método general 5, obteniéndose 3.78g de N¹-p-metoxilofenilo-N⁴-[1-butilo-2-hidroxi-2-(5-cloro-6-methoxynaphthalene-2-yl)]etilopiperazina hidrocloreto, con un rendimiento del 90%. El compuesto fue después transformado en un alkali libre, y separado mediante cromatografía de columna para obtener una eritro forma, seguido se disolvió en etanol, y se ajustó a un pH de 2 con HCl/C₂H₅OH(5N). El precipitado sólido fue filtrado y el compuesto (VIII-1) se obtuvo mediante la recristalización en etanol/agua o metanol. El análisis de los elementos del compuesto mostró que el compuesto contenía 0.5 moléculas de agua cristalina.

m.p=221.6-223.2°(dec). MS : m/z 483 (M⁺).

¹HNMR(DMSO-d₆): δ 0.73-1.66(m, 9H, CH₂CH₂CH₂CH₃), 2.65-2.91(m, 9H, CH+piperazina-H), 3.76(s, 3H, OCH₃), 3.87(s, 3H, OCH₃), 5.0 (d, 1H, CH, J=4.0), 5.17(d, 1H, OH), 6.84-8.04(m,9H, Ar-H)

Ejemplo 2**VIII-2**

(1SR,2SR)-N¹-p-metoxilofenilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina (treo forma)

[55] Se sintetizaron 4.2g de N¹-p-metoxilofenilo-N⁴-[1-butilo-2-

-carbonilo-2-(5-cloro-6-methoxy naphthalene-2-yl)]etilopiperazina hidrocioruro utilizando N¹-p- metoxilo fenilopiperazina (10mmol) y 2-(α -bromo-hexanone)-5-cloro-6- metoxilonaftalina (10mmol), de acuerdo con el método general 2 al método general 4, con un rendimiento de 79%, m.p.=231.5-233.6 $\square$ (dec). Después se realizó la reducción de carbonilo en N¹-p-metoxilofenilo-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-metoxi naphthalene-2-yl)]etilopiperazina de acuerdo con el método general 5, y 3.78g de N¹-p-metoxilofenilo-N⁴-[1-butilo-2-hidroxi-2-(5-cloro-6-methoxynaphthalene-2-yl)]etilopiperazina hidrocioruro fue obtenido con un rendimiento de 90%. El compuesto fue después transformado en un alkali libre, y separado mediante cromatografía de columna. La treo forma obtenida se disolvió en etanol, y se ajustó a un pH de 2 con HCl/C₂H₅OH(5N). El precipitado sólido fue filtrado y el compuesto (VIII-2) se obtuvo mediante la recristalización en etanol/agua o metanol. El análisis de los elementos del compuesto mostró que el compuesto contenía 2 moléculas de agua cristalina.

m.p.=220.4-222.8 $\square$ (dec). MS: m/z 483 (M⁺)

¹HNMR(DMSO-d₆): δ 0.65-1.51(m, 9H, CH₂CH₂CH₂CH₃), 2.49-2.97(m, 9H, CH+piperazina-H), 3.78(s, 3H, OCH₃), 3.87(s, 3H, OCH₃), 4.6 (d, 1H, CH, J=8.0), 5.14(d, 1H, OH), 6.86-8.06(m, 9H, Ar-H).

Ejemplo 3

VIII-3

(1SR,2RS)-N¹-o-metoxilofenilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina (eritro forma)

[56] Se sintetizaron 4.03g de N¹-o-metoxilofenilo-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxy naphthalene-2-yl)]etilopiperazina hidrocioruro utilizando N¹-o-metoxilofenilopiperazina (10mmol) y 2-(α -bromo-hexanone)-5-cloro-6- metoxilonaftalina (10mmol), de acuerdo con el método general 2 al método general 4, con un

rendimiento de 78%, m.p=232.4-234.1°C(dec).

[57] Después se realizó la reducción de carbonilo en N¹-o-metoxilofenilo-N⁴-[1-butilo-2-carbonilo -2 -(5- cloro- 6- metoxi naftaleno-2-yl)] etilopiperazina de acuerdo con el método general 5, y 3.58g de N¹-o-metoxilofenilo-N⁴-[1-butilo-2-hidroxi-2-(5-cloro-6-methoxynaphth alene-2-yl)]etilopiperazina hidrocloreto fue obtenido con un rendimiento del 89%. El compuesto fue después transformado en un alkali libre, y separado mediante cromatografía de columna. La trea forma obtenida se disolvió en etanol, y se ajustó a un pH de 2 con HCl/C₂H₅OH(5N). El precipitado sólido fue filtrado y el compuesto (VIII-3) se obtuvo mediante la recristalización en etanol/agua o metanol. El análisis de los elementos del compuesto mostró que el compuesto contenía 2 moléculas de agua cristalina.

m.p=227.3-229.1°C(dec). MS: m/z 483 (M⁺).

¹HNMR(DMSO-d₆): δ 0.73-1.66(m, 9H, CH₂CH₂CH₂CH₃), 2.65-2.91(m, 9H, CH+ piperazina-H), 3.76(s, 3H, OCH₃), 3.98(s, 3H, OCH₃), 5.0 (d, 1H, CH, J=4.0), 5.17(d, 1H, OH), 6.84-8.04(m, 9H, Ar-H)

Ejemplo 4

VIII-4

(1SR,2SR)-N¹-o-metoxilofenilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'- naftil) hidroxietilo]piperazina (treo forma)

[58] Se sintetizaron 4.03g de N¹-o-metoxilofenilo-N⁴-[1-butilo-2 -carbonilo-2-(5-cloro-6-methoxy naphthalene-2-yl)]etilopiperazina hidrocloreto utilizando N¹-o-metoxilofenilopiperazina (10mmol) y 2-(α-bromo-hexanone)-5-cloro-6- metoxilonaftalina (10mmol), de acuerdo con el método general 2 al método general 4, con un rendimiento de 78%, m.p=232.4-234.1°C(dec).

[59] Después se realizó la reducción de carbonilo en N¹-o-metoxilofenilo-N⁴-[1-butilo-2-carbonilo -2 -(5- cloro- 6- metoxi

naftaleno-2-yl)] etilopiperazina de acuerdo con el método general 5, y 3.58g de N¹-o-metoxilofenilo-N⁴-[1-butilo-2-hidroxi-2-(5-cloro-6-methoxynaphthalene-2-yl)]etilopiperazina hidrocioruro fue obtenido con un rendimiento del 89%. El compuesto fue después transformado en un alkali libre, y separado mediante cromatografía de columna. La treo forma obtenida se disolvió en etanol, y se ajustó a un pH de 2 con HCl/C₂H₅OH(5N). El precipitado sólido fue filtrado y el compuesto (VIII-4) se obtuvo mediante la recristalización en etanol/agua o metanol. El análisis de los elementos del compuesto mostró que el compuesto contenía 2 moléculas de agua cristalina.

m.p.=223.5-225.0°C(dec). MS: m/z 483 (M⁺).

¹HNMR(DMSO-d₆): δ 0.65-1.51(m, 9H, CH₂CH₂CH₂CH₃), 2.49-2.97(m, 9H, CH+ piperazina-H), 3.78(s, 3H, OCH₃), 3.98(s, 3H, OCH₃), 4.6 (d, 1H, CH, J=8.0), 5.14(d, 1H, OH), 6.86-8.06(m, 9H, Ar-H).

Ejemplo 5

VIII-5

(1SR,2RS)-N¹-m-clorofenilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil) hidroxietilo]piperazina(eritro forma)

[60] Se sintetizaron 4.20g de N¹-o-metoxilofenilo-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxy naphthalene-2-yl)]etilopiperazina hidrocioruro utilizando N¹-o-metoxilofenilopiperazina (10mmol) y 2-(α-bromo-hexanone)-5-cloro-6- metoxilonaftalina (10mmol), de acuerdo con el método general 2 al método general 4, con un rendimiento del 79%, m.p.=231.5-233.6°C(dec).

[61] Después se realizó la reducción de carbonilo en N¹-o-metoxilofenilo-N⁴-[1-butilo-2-carbonilo -2 -(5- cloro- 6- metoxi naftaleno-2-yl)] etilopiperazina de acuerdo con el método general 5, y 3.78g de N¹-o-metoxilofenilo-N⁴-[1-butilo-2-hidroxi-2-(5-cloro-6-methoxynaphthalene-2-yl)]etilopiperazina hidrocioruro fue obtenido con un

rendimiento del 90%. El compuesto fue después transformado en un alkali libre, y separado mediante cromatografía de columna. La eritro forma obtenida se disolvió en etanol, y se ajustó a un pH de 2 con HCl/C₂H₅OH(5N). El precipitado sólido fue filtrado y el compuesto (VIII-5) se obtuvo mediante la recristalización en etanol/agua o metanol.

m.p=224.2-226.8°C(dec). MS: m/z 487 (M⁺).

¹HNMR(DMSO-d₆): δ 0.73-1.66(m, 9H, CH₂CH₂CH₂CH₃), 2.65-2.91(m, 9H, CH+ piperazina-H), 3.76(s, 3H, OCH₃), 5.0 (d, 1H, CH, J=4.0), 5.17(d, 1H, OH), 6.84-8.04(m, 9H, Ar-H)

Ejemplo 6

VIII-6

(1SR,2SR)-N¹-m-clorofenilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina (treo forma)

[62] Se sintetizaron 4.20g de N¹-o-metoxilofenilo-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxy naphthalene-2-yl)]etilopiperazina hidrocloreto utilizando N¹-o-metoxilofenilopiperazina (10mmol) y 2-(α-bromo-hexanone)-5-cloro-6- metoxilonaftalina (10mmol), de acuerdo con el método general 2 al método general 4, con un rendimiento del 79%, m.p=231.5-233.6°C(dec).

[63] Después se realizó la reducción de carbonilo en N¹-o-metoxilofenilo-N⁴-[1-butilo-2-carbonilo -2 -(5- cloro- 6- metoxi naftaleno-2-yl)] etilopiperazina de acuerdo con el método general 5, y 3.78g de N¹-o-metoxilofenilo-N⁴-[1-butilo-2-hidroxi-2-(5-cloro-6-methoxynaphthalene-2-yl)]etilopiperazina hidrocloreto fue obtenido con un rendimiento del 90%. El compuesto fue después transformado en un alkali libre, y separado mediante cromatografía de columna. La treo forma obtenida se disolvió en etanol, y se ajustó a un pH de 2 con HCl/C₂H₅OH(5N). El precipitado sólido fue filtrado y el compuesto (VIII-6) se obtuvo mediante la recristalización en etanol/agua o metanol.

[64] m.p=220.4-222.8°C(dec). MS: m/z 487 (M⁺).

¹HNMR(DMSO-d₆): δ 0.65-1.51(m, 9H, CH₂CH₂CH₂CH₃), 2.49-2.97(m, 9H, CH+ piperazina-H), 3.78(s, 3H, OCH₃), 4.6 (d, 1H, CH, J=8.0), 5.14(d, 1H, OH), 6.86-8.06(m, 9H, Ar-H).

Ejemplo 7

VIII-7

(1SR,2RS)-N¹-(2,3-dimetilofenilo)-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina (eritro forma)

[65] Se sintetizaron 3.80g de N¹-(2,3-dimetilofenilo)-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxynaphthalene-2-yl)]etilopiperazina hidrocioruro utilizando N¹-(2,3-dimetilofenilo)piperazina (10mmol) y 2-(α-bromo-hexanone)-5-cloro-6- metoxilonaftalina (10mmol), de acuerdo con el método general 2 al método general 4, in a rendimiento of 80%, m.p=232.5-235.6°C(dec).

[66] Después se realizó la reducción de carbonilo en N¹-(2,3-dimetilofenilo)-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxyna phthalene-2-yl)]etilopiperazina de acuerdo con el método general 5, y 3.34g de N¹-(2,3-dimetilofenilo)-N⁴-[1-butilo-2-hidroxi-2-(5-cloro-6-methoxynaphthalene-2-yl)]etilopiperazina hidrocioruro fue obtenido con un rendimiento del 88%. El compuesto fue después transformado en un alkali libre, y separado mediante cromatografía de columna. La treo forma obtenida se disolvió en etanol, y se ajustó a un pH de 2 con HCl/C₂H₅OH(5N). El precipitado sólido fue filtrado y el compuesto (VIII-7) se obtuvo mediante la recristalización en etanol/agua o metanol.

[67] m.p=218.5-220.8°C(dec). MS: m/z 481 (M⁺).

¹HNMR(DMSO-d₆):δ 0.74-0.77(m, 3H, CH₂CH₂CH₃), 1.13-2.11(m, 6H, CH₂CH₂CH₂CH₃), 2.15 (s, 3H, CH₃), 2.20(s, 3H, CH₃), 2.50-2.87(m, 9H, piperazina -CH), 3.99(s, 3H, OCH₃), 5.06-5.07(m, 1H,

CH, J=4.0), 5.18-5.19(d, 1H, OH), 6.83-8.05(m, 8H, Ar-H).

Ejemplo 8

VIII-8

(1SR,2SR)-N¹-(2,3-dimetilofenilo)-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina (treo forma)

[68] Se sintetizaron 3.80g de N¹-(2,3-dimetilofenilo)-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxynaphthalene-2-yl)]etilopiperazina hidrocioruro utilizando N¹-(2,3-dimetilofenilo)piperazina (10mmol) y 2-(α -bromo-hexanone)-5-cloro-6- metoxilonaftalina (10mmol), de acuerdo con el método general 2 al método general 4, in a rendimiento of 80%, m.p=232.5-235.6°C(dec).

[69] Después se realizó la reducción de carbonilo en N¹-(2,3-dimetilofenilo)-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxyna phthalene-2-yl)]etilopiperazina de acuerdo con el método general 5, y 3.34g de N¹-(2,3-dimetilofenilo)-N⁴-[1-butilo-2-hidroxi-2-(5-cloro-6-methoxynaphthalene-2-yl)]etilopiperazina hidrocioruro fue obtenido con un rendimiento del 88%. El compuesto fue después transformado en un alkali libre, y separado mediante cromatografía de columna. La treo forma obtenida se disolvió en etanol, y se ajustó a un pH de 2 con HCl/C₂H₅OH(5N). El precipitado sólido fue filtrado y el compuesto (VIII-8) se obtuvo mediante la recrystalización en etanol/agua o metanol.

m.p=220.4-222.8°C(dec). MS: m/z 481 (M⁺).

¹HNMR(DMSO-d₆): δ 0.66-0.69(m, 3H, CH₂CH₂CH₃), 0.96-1.53(m, 6H, CH₂CH₂CH₂CH₃), 2.17(s, 3H, CH₃), 2.21(s, 3H, CH₃), 2.80-2.96(m, 9H, piperazina -CH), 3.99(s, 3H, OCH₃), 4.59-4.61(m, 1H, CH, J=8.4), 5.14 (d, 1H, OH), 6.83-8.05(m, 8H, Ar-H).

Ejemplo 9

VIII-9

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(1SR,2RS)-N¹-bencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina (eritro forma)

[70] Se sintetizaron 4.20g de N¹-bencilo-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxynaphthalene-2-yl)] etilopiperazina hidrocioruro utilizando N¹-bencilopiperazina (10mmol) y 2-(α-bromo-hexanone)-5-cloro-6-metoxilonaftalina (10mmol), de acuerdo con el método general 2 al método general 4, con un rendimiento del 78%, m.p=241.7-243.3°C (dec).

[71] Después se realizó la reducción de carbonilo en N¹-bencilo-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxynaphthalene-2-yl)] etilopiperazina de acuerdo con el método general 5, y 3.73g de N¹-bencilo-N⁴-[1-butilo-2-hidroxi-2-(5-cloro-6-methoxynaphthalene-2-yl)]etilopiperazina hidrocioruro fue obtenido con un rendimiento del 89%. El compuesto fue después transformado en un alkali libre, y separado mediante cromatografía de columna. La eritro forma obtenida se disolvió en etanol, y se ajustó a un pH de 2 con HCl/C₂H₅OH(5N). El precipitado sólido fue filtrado y el compuesto (VIII-9) se obtuvo mediante la recristalización en etanol/agua o metanol. El análisis de los elementos del compuesto mostró que el compuesto contenía 2 moléculas de agua cristalina.

m.p=225.0-225.8°C(dec). MS: m/z 467 (M⁺).

¹HNMR(DMSO-d₆): δ 0.72-1.60(m, 9H, CH₂CH₂CH₂CH₃), 2.27-2.70(m, 9H, CH+ piperazina -H), 3.40(s, 2H, CH₂ Ph), 3.98(s, 3H, OCH₃), 5.0 (d, 1H, CH, J=4.4), 5.10(s, 1H, OH), 7.20-8.02(m, 10H, Ar-H).

Ejemplo 10

VIII-10

(1SR,2SR)-N¹-bencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina(treo forma)

[72] Se sintetizaron 4.20g de N¹-bencilo-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxynaphthalene-

2-yl)] etilopiperazina hidrocloreto utilizando N¹-bencilopiperazina (10mmol) y 2-(α -bromo-hexanone)-5-cloro-6-metoxilonaftalina (10mmol), de acuerdo con el método general 2 al método general 4, con un rendimiento del 78%, m.p.=241.7-243.3°C (dec).

[73] Después se realizó la reducción de carbonilo en N¹-bencilo-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxynaphthalene-2-yl)] etilopiperazina de acuerdo con el método general 5, y 3.73g de N¹-bencilo-N⁴-[1-butilo-2-hidroxi-2-(5-cloro-6-methoxynaphthalene-2-yl)]etilopiperazina hidrocloreto fue obtenido con un rendimiento del 89%. El compuesto fue después transformado en un alkali libre, y separado mediante cromatografía de columna. La trea forma obtenida se disolvió en etanol, y se ajustó a un pH de 2 con HCl/C₂H₅OH(5N). El precipitado sólido fue filtrado y el compuesto (VIII-10) se obtuvo mediante la recristalización en etanol/agua o metanol. El análisis de los elementos del compuesto mostró que el compuesto contenía 2 moléculas de agua cristalina.

m.p.=223.1-224.3°C(dec).MS: m/z 467 (M⁺).

¹HNMR(DMSO-d₆): δ 0.66-1.50(m, 9H, CH₂CH₂CH₂CH₃), 2.42-2.84(m, 9H, CH+ piperazina -H), 3.49(s, 2H, CH₂ Ph), 4.02(s, 3H, OCH₃), 4.5(d, 1H, CH, J=8.8), 5.10(s, 1H, OH), 7.26-8.08(m, 10H, Ar-H).

Ejemplo 11

VIII-11

(1SR,2RS)-N¹-p-nitrobencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxiletilo]piperazina (eritro forma)

[74] Se sintetizaron 3.94g of N¹-p-nitrobencilo-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxy naphthalene -2-yl)]etilopiperazina hidrocloreto utilizando N¹-p-nitrobencilopiperazina (10mmol) y 2-(α -bromo-hexanone)-5-cloro-6- metoxilonaftalina (10mmol), de acuerdo con el método general 2 al método general 4, con un

rendimiento del 77%, m.p=233.5-235.7°C(dec).

[75] Después se realizó la reducción de carbonilo en N¹-p-nitrobencilo-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxynaphth alene-2-yl)] etilopiperazina de acuerdo con el método general 5, y 3.47g

de N¹-p-nitrobencilo-N⁴-[1-butilo-2-hidroxi-2-(5-cloro-6-methoxynaphth alene-2-yl)] etilopiperazina hidrocloreto fue obtenida con un rendimiento del 88%. El compuesto fue después transformado en un alkali libre, y separado mediante cromatografía de columna. La eritro forma obtenida se disolvió en etanol, y se ajustó a un pH de 2 con HCl/C₂H₅OH(5N). El precipitado sólido fue filtrado y el compuesto (VIII-2) se obtuvo mediante la recristalización en etanol/agua o metanol.

m.p=228.7-221.0°C(dec). MS: m/z 512 (M⁺).

¹HNMR(DMSO-d₆): δ 0.72-1.60(m, 9H, CH₂CH₂CH₂CH₃), 2.27-2.70(m, 9H, CH+ piperazina -H), 3.40(s, 2H, CH₂ Ph), 3.98(s, 3H, OCH₃), 5.0 (d, 1H, CH, J=4.4), 5.10(s, 1H, OH), 7.20-8.02(m, 9H, Ar-H).

Ejemplo 12

VIII-12

(1SR,2SR)-N¹-p-nitrobencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina (treo forma)

[76] Se sintetizaron 3.94g of N¹-p-nitrobencilo-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxy naphthalene -2-yl)]etilopiperazina hidrocloreto utilizando N¹-p-nitrobencilopiperazina (10mmol) y 2-(α-bromo-hexanone)-5-cloro-6- metoxilonaftalina (10mmol), de acuerdo con el método general 2 al método general 4, con un rendimiento del 77%, m.p=233.5-235.7°C(dec).

[77] Después se realizó la reducción de carbonilo en N¹-p-nitrobencilo-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxynaphth alene-2-yl)] etilopiperazina de acuerdo con el método general 5, y

3.47g

de N¹-p-nitrobencilo-N⁴-[1-butilo-2-hidroxi-2-(5-cloro-6-methoxynaphthalene-2-yl)] etilopiperazina hidrocloreto fue obtenida con un rendimiento del 88%. El compuesto fue después transformado en un alkali libre, y separado mediante cromatografía de columna. La trea forma obtenida se disolvió en etanol, y se ajustó a un pH de 2 con HCl/C₂H₅OH(5N). El precipitado sólido fue filtrado y el compuesto (VIII-12) se obtuvo mediante la recristalización en etanol/agua o metanol.

m.p.=226.8-229.0°C(dec). MS: m/z 512 (M⁺).

¹HNMR(DMSO-d₆): δ 0.65-1.51(m, 9H, CH₂CH₂CH₂CH₃), 2.49-2.97(m, 9H, CH+ piperazina -H), 3.78(s, 3H, OCH₃), 4.6 (d, 1H, CH, J=8.0), 5.14(d, 1H, OH), 6.96-8.16(m, 9H, Ar-H).

Ejemplo 13

VIII-13

(1SR,2RS)-N¹-p-aminobencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina (eritro forma)

[78] Se sintetizaron 3.76g de N¹-p-aminobencilo-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxy naphthalene-2-yl)]etilopiperazina hidrocloreto utilizando N¹-p-aminobencilopiperazina (10mmol) y 2-(α-bromo-hexanone)-5-cloro-6- metoxilonaftalina (10mmol), de acuerdo con el método general 2 al método general 4, con un rendimiento del 78%, m.p.=233.6-235.9°C(dec).

[79] Después se realizó la reducción de carbonilo en N¹-p-aminobencilo-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxy naphthalene-2-yl)] etilopiperazina de acuerdo con el método general 5, y 3.27g de N¹-p-aminobencilo-N⁴-[1-butilo-2-hidroxi-2-(5-cloro-6-methoxynaphthalene-2-yl)] etilopiperazina hidrocloreto fue obtenido con un rendimiento del 87%. El compuesto fue después transformado en un alkali libre, y separado mediante cromatografía de columna. La eritro

forma obtenida se disolvió en etanol, y se ajustó a un pH de 2 con HCl/C₂H₅OH(5N). El precipitado sólido fue filtrado y el compuesto (VIII-13) se obtuvo mediante la recristalización en etanol/agua o metanol.

m.p.=219.4-221.0°C(dec). MS: m/z 482 (M⁺).

¹HNMR(DMSO-d₆): δ 0.72-1.60(m, 9H, CH₂CH₂CH₂CH₃), 2.27-2.70(m, 9H, CH+ piperazina -H), 3.40(s, 2H, CH₂ Ph), 3.98(s, 3H, OCH₃), 4.0(m, 2H, NH₂), 5.0 (d, 1H, CH, J=4.4), 5.10(s, 1H, OH), 7.20-8.02(m, 9H, Ar-H).

Ejemplo 14

VIII-14

(1SR,2SR)-N¹-p-aminobencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina (treo forma)

[80] Se sintetizaron 3.76g de N¹-p-aminobencilo-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxy naphthalene-2-yl)]etilopiperazina hidrocioruro utilizando N¹-p-aminobencilopiperazina (10mmol) y 2-(α-bromo-hexanone)-5-cloro-6- metoxilonaftalina (10mmol), de acuerdo con el método general 2 almétodo general 4, con un rendimiento del 78%, m.p.=233.6-235.9°C(dec).

[81] Después se realizó la reducción de carbonilo en N¹-p-aminobencilo-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxy naphthalene-2-yl)] etilopiperazina de acuerdo con el método general 5, y 3.27g de N¹-p-aminobencilo-N⁴-[1-butilo-2-hidroxi-2-(5-cloro-6-methoxynaphthalene-2-yl)] etilopiperazina hidrocioruro fue obtenido con un rendimiento del 87%. El compuesto fue después transformado en un alkali libre, y separado mediante cromatografía de columna. La treo forma obtenida se disolvió en etanol, y se ajustó a un pH de 2 con HCl/C₂H₅OH(5N). El precipitado sólido fue filtrado y el compuesto (VIII-14) se obtuvo mediante la recristalización en etanol/agua o metanol.

m.p=215.2-218.0°C(dec). MS: m/z 482 (M^+).

$^1\text{HNMR}$ (DMSO- d_6): δ 0.65-1.51(m, 9H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2.49-2.97(m, 9H, CH+ piperazina -H), 3.78(s, 3H, OCH_3), 3.87(s, 3H, OCH_3), 4.0(m, 2H, NH_2), 4.6 (d, 1H, CH, $J=8.0$), 5.14(d, 1H, OH), 6.86-8.06(m, 9H, Ar-H).

Ejemplo 15

VIII-15

(1SR,2RS)- N^1 -(3',4',5'-trimethoxybencilo)- N^4 -[1-butilo-2-(5'-cloro-6'-metoxilo-2'- naftil)hidroxietilo]piperazina (eritro forma)

[82] Se sintetizaron 4.18g de N^1 -(3',4',5'-trimethoxybencilo)- N^4 -[1-butilo-2-carbonilo-2-(5-cloro-6-methoxynaphthalene-2-yl)]etilopiperazina hidrocioruro utilizando N^1 -(3',4',5'-trimethoxybencilo)piperazina (10mmol) y 2-(α -bromo-hexanone)-5- cloro-6-metoxilonaftalina (10mmol), de acuerdo con el método general 2 al método general 4, con un rendimiento del 75%, m.p=235.5-238.6°C(dec).

[83] Después se realizó la reducción de carbonilo en N^1 -(3',4',5'-trimethoxybencilo)- N^4 -[1-butilo-2-carbonilo-2-(5-cloro-6-methoxynaphthalene-2-yl)]etilopiperazina de acuerdo con el método general 5, y 3.63g de N^1 -(3',4',5'-trimethoxybencilo)- N^4 -[1-butilo-2-hidroxi-2-(5-cloro-6-methoxynaphthalene-2-yl)] etilopiperazina hidrocioruro fue obtenido con un rendimiento del 87%. El compuesto fue después transformado en un alkali libre, y separado mediante cromatografía de columna. La eritro forma obtenida se disolvió en etanol, y se ajustó a un pH de 2 con $\text{HCl}/\text{C}_2\text{H}_5\text{OH}(5\text{N})$. El precipitado sólido fue filtrado y el compuesto (VIII-15) se obtuvo mediante la recristalización en etanol/agua o metanol.

m.p=221.3-223.6°C(dec). MS: m/z 557 (M^+).

$^1\text{HNMR}$ (DMSO- d_6): δ 0.72-1.60(m, 9H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2.27-2.70(m, 9H, CH+ piperazina -H), 3.40(s, 2H, CH_2 Ph), 3.70(m, 9H, OCH_3), 3.98(s, 3H, OCH_3), 4.0(m, 2H, NH_2), 5.0 (d, 1H, CH, $J=4.4$),

5.10(s, 1H, OH), 7.20-8.02(m, 7H, Ar-H).

Ejemplo 16

VIII-16

(1SR,2SR)-N¹-(3',4',5'-trimethoxybencilo)-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina (treo forma)

[84] Se sintetizaron 4.18g de N¹-(3',4',5'-trimethoxybencilo)-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxynaphthalene-2-yl)]etilopiperazina hidrocioruro utilizando N¹-(3',4',5'-trimethoxybencilo)piperazina (10mmol) y 2-(α-bromo-hexanone)-5- cloro-6-metoxilonaftalina (10mmol), de acuerdo con el método general 2 al método general 4, con un rendimiento del 75%, m.p.=235.5-238.6°C(dec).

[85] Después se realizó la reducción de carbonilo en N¹-(3',4',5'-trimethoxybencilo)-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxynaphthalene-2-yl)]etilopiperazina de acuerdo con el método general 5, y 3.63g de N¹-(3',4',5'-trimethoxybencilo)-N⁴-[1-butilo-2-hidroxi-2-(5-cloro-6-methoxynaphthalene-2-yl)] etilopiperazina hidrocioruro fue obtenido con un rendimiento del 87%. El compuesto fue después transformado en un alkali libre, y separado mediante cromatografía de columna. La treo forma obtenida se disolvió en etanol, y se ajustó a un pH de 2 con HCl/C₂H₅OH(5N). El precipitado sólido fue filtrado y el compuesto (VIII-16) se obtuvo mediante la recristalización en etanol/agua o metanol.

m.p.=226.5-228.8°C(dec). MS: m/z 557 (M⁺).

¹HNMR(DMSO-d₆): δ 0.65-1.51(m, 9H, CH₂CH₂CH₂CH₃), 2.49-2.97(m, 9H, CH+ piperazina -H), 3.70(m, 9H, OCH₃), 3.78(s, 3H, OCH₃), 3.87(s, 3H, OCH₃), 4.6 (d, 1H, CH, J=8.0), 5.14(d, 1H, OH), 6.86-8.06(m, 7H, Ar-H).

Ejemplo 17

VIII-17

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(1SR,2RS)-N¹-α-phenemyl-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina (eritro forma)

[86] Se sintetizaron 4.22g de N¹-α-phenemyl-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxynaphthalene-2-yl)]etilopiperazina hidrocioruro utilizando N¹-α-phenemyl piperazina (10mmol) y 2-(α-bromo-hexanone)-5-cloro-6- metoxilonaftalina (10mmol), de acuerdo con el método general 2 al método general 4, con un rendimiento del 78%, m.p=241.7-243.3°C(dec).

[87] Después se realizó la reducción de carbonilo en N¹-α-phenemyl-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxynaphthalene-2-yl)] etilopiperazina de acuerdo con el método general 5, y 3.75g de N¹-α-phenemyl-N⁴-[1-butilo-2-hidroxi-2-(5-cloro-6-methoxynaphthalene-2-yl)]etilopiperazina hidrocioruro fue obtenido con un rendimiento del 89%. El compuesto fue después transformado en un alkali libre, y separado mediante cromatografía de columna. La eritro forma obtenida se disolvió en etanol, y se ajustó a un pH de 2 con HCl/C₂H₅OH(5N). El precipitado sólido fue filtrado y el compuesto (VIII-17) se obtuvo mediante la recristalización en etanol/agua o metanol.

m.p=235.0-237.6°C (dec). MS: m/z 481.1 (M⁺).

¹HNMR(DMSO-d₆):δ 0.54-0.63(m, 3H, CH₂CH₂CH₃), 0.78-1.24(m, 6H, CH₂CH₂CH₂CH₃), 1.57-1.75(m, 3H, CHCH₃), 1.83-1.86(m, 2H, CH₂CH₂CH₂CH₃), 3.44-3.59(m, 8H, piperazina -H), 3.99(s, 3H, OCH₃), 4.57(m,1H, CH₃-CH-Ph), 4.57(m, 1H, CH), 5.66-5.67(d, 1H, CH, J=4.8), 7.48-8.11(m, 10H, Ar-H).

Ejemplo 18

VIII-18

(1SR,2SR)-N¹-α-phenemyl-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina (treo forma)

[88] Se sintetizaron 4.22g de N¹-α-phenemyl-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-

methoxynaphthalene-2-yl)]etilopiperazina hidrocloreuro utilizando
 N¹-α-phenemyl piperazina (10mmol) y
 2-(α-bromo-hexanone)-5-cloro-6- metoxilonaftalina (10mmol), de
 acuerdo con el método general 2 al método general 4, con un
 rendimiento del 78%, m.p=241.7-243.3°C(dec).

[89] Después se realizó la reducción de carbonilo en
 N¹-α-phenemyl-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxynaphthal
 ene-2-yl)] etilopiperazina de acuerdo con el método general 5, y 3.75g
 de N¹-α-phenemyl
 -N⁴-[1-butilo-2-hidroxi-2-(5-cloro-6-methoxynaphthalene-2-yl)]etilope
 razina hidrocloreuro fue obtenido con un rendimiento del 89%. El
 compuesto fue después transformado en un alkali libre, y separado
 mediante cromatografía de columna. La trea forma obtenida se
 disolvió en etanol, y se ajustó a un pH de 2 con HCl/C₂H₅OH(5N). El
 precipitado sólido fue filtrado y el compuesto (VIII-18) se obtuvo
 mediante la recristalización en etanol/agua o metanol.
 m.p=224.0-226.1°C. MS: m/z 481 (M⁺).

¹HNMR(DMSO-d₆):δ 0.61-0.65(m, 3H, CH₂CH₂CH₃), 0.88-1.06(m,
 6H, CH₂CH₂CH₂CH₃), 1.28-1.29(m, 3H, CHCH₃), 2.33-2.76(m, 8H,
 piperazina), 2.50-2.510(m, 1H, CH-N), 3.25-3.39(m, 1H,
 CH₃-CH-Ph), 3.99(s, 3H, OCH₃), 4.47-4.51(m, 1H, CH, J=8.4), 5.05(d,
 1H, OH), 7.23-8.03(m, 10H, Ar-H).

Ejemplo 19

VIII-19

(1SR,2RS)-N¹-benzhydryl-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-
 naftil)hidroxietilo]piperazina (eritro forma)

[90] Se sintetizaron 4.68g
 de N¹-benzhydryl-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxy
 naphthalene-2-yl)]etilopiperazina hidrocloreuro utilizando N¹-benzhydryl
 piperazina (10mmol) y 2-(α-bromo-hexanone)-5-cloro-6-metoxilo
 naftalina (10mmol), de acuerdo con el método general 2 al método
 general 4, con un rendimiento of 76%, m.p=212.9-215.2°C(dec).

[91] Después se realizó la reducción de carbonilo en N¹-benzhydryl-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxynaphthalene-2-yl)]etilopiperazina according to método general 5, y 4.83g of N¹-benzhydryl -N⁴-[1-butilo-2-hidroxi-2-(5-cloro-6-methoxynaphthalene-2-yl)]etilopiperazina hidrocloreto fue obtenido con un rendimiento del 85%. El compuesto fue después transformado en un alkali libre, y separado mediante cromatografía de columna. La eritro forma obtenida se disolvió en etanol, y se ajustó a un pH de 2 con HCl/C₂H₅OH(5N). El precipitado sólido fue filtrado y el compuesto (VIII-19) se obtuvo mediante la recristalización en etanol/agua o metanol. m.p=183.0-184.6°C(dec). MS : m/z 543 (M⁺).

¹HNMR(DMSO-d₆): δ 0.71-1.60(m, 9H, CH₂CH₂CH₂CH₃), 2.24-2.74(m, 9H, CH+ piperazina -H), 4.22(s, 1H, CH Ph₂), 3.98(s, 3H, OCH₃), 5.0 (d, 1H, CH, J=3.6), 5.11(d, 1H, OH), 7.14-8.01(m, 15H, Ar-H).

Ejemplo 20

VIII-20

(1SR,2SR)-N¹-benzhydryl-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina (treo forma)

[92] Se sintetizaron 4.68g de N¹-benzhydryl-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxy naphthalene-2-yl)]etilopiperazina hidrocloreto utilizando N¹-benzhydryl piperazina (10mmol) y 2-(α-bromo-hexanone)-5-cloro-6-metoxilo naftalina (10mmol), de acuerdo con el método general 2 al método general 4, con un rendimiento of 76%, m.p=212.9-215.2°C(dec).

[93] Después se realizó la reducción de carbonilo en N¹-benzhydryl-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxynaphthalene-2-yl)]etilopiperazina de acuerdo con el método general 5, y 4.83g de N¹-benzhydryl -N⁴-[1-butilo-2-hidroxi-2-(5-cloro-6-methoxynaphthalene-2-yl)]etilopiperazina

hidrocloruro fue obtenido con un rendimiento del 85%. El compuesto fue después transformado en un alkali libre, y separado mediante cromatografía de columna. La treo forma obtenida se disolvió en etanol, y se ajustó a un pH de 2 con HCl/C₂H₅OH(5N). El precipitado sólido fue filtrado y el compuesto (VIII-20) se obtuvo mediante la recrystalización en etanol/agua o metanol. m.p=179.3-181.1°C(dec). MS: m/z 543 (M⁺).

¹HNMR(DMSO-d₆): δ 0.63-1.46(m, 9H, CH₂CH₂CH₂CH₃), 2.33-2.82(m, 9H, CH+ piperazina -H), 4.28(s, 1H, CH Ph₂), 3.98(s, 3H, OCH₃), 4.5 (d, 1H, CH, J=8.4), 5.06(s, 1H, OH), 7.16-8.03(m, 15H, Ar-H).

Ejemplo 21

VIII-21

(1SR,2RS)-N¹-cinnamyl-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina (eritro forma)

[94] Se sintetizaron 4.61g de N¹-cinnamyl-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxy naphthalene-2-yl)]etilopiperazina hidrocloruro utilizando N¹-cinnamylpiperazina (10mmol) y 2-(α-bromo-hexanone)-5-cloro-6-metoxilonaftalina (10mmol), de acuerdo con el método general 2 al método general 4, con un rendimiento of 82%, m.p=232.2-234.0°C(dec).

[95] Después se realizó la reducción de carbonilo en N¹-cinnamyl-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxynaphthalene-2-yl)] etilopiperazina de acuerdo con el método general 5, y 4.19g of N¹-cinnamyl-N⁴-[1-butilo-2-hidroxi-2-(5-cloro-6-methoxynaphthalene-2-yl)]etilopiperazina hidrocloruro fue obtenido con un rendimiento del 91%. El compuesto fue después transformado en un alkali libre, y separado mediante cromatografía de columna. La eritro forma obtenida se disolvió en etanol, y se ajustó a un pH de 2 con HCl/C₂H₅OH(5N). El precipitado sólido fue filtrado y el compuesto (VIII-21) se obtuvo

mediante la recristalización en etanol/agua o metanol.
m.p=228.8-230.1°C(dec). MS : m/z 493 (M⁺).

¹HNMR(DMSO-d₆): δ 0.73-1.60(m, 9H, CH₂CH₂CH₂CH₃), 2.31-3.04(m, 11H, CH+ CH₂+ piperazina -H), 3.98(s, 3H, OCH₃), 4.9 (d, 1H, CH, J=4.0), 5.11(d, 1H, OH), 6.23-6.52(m, 2H, CH=CH), 7.22-8.02(m, 10H, Ar-H).

Ejemplo 22

VIII-22

(1SR,2SR)-N¹-cinnamyl-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina (treo forma)

[96] Se sintetizaron 4.61g de N¹-cinnamyl-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxynaphthalene-2-yl)]etilopiperazina hidrocioruro utilizando N¹-cinnamylpiperazina (10mmol) y 2-(α -bromo-hexanone)-5-cloro-6-metoxilonaftalina (10mmol), de acuerdo con el método general 2 al método general 4, con un rendimiento of 82%, m.p=232.2-234.0°C(dec).

[97] Después se realizó la reducción de carbonilo en N¹-cinnamyl-N⁴-[1-butilo-2-carbonilo-2-(5-cloro-6-methoxynaphthalene-2-yl)]etilopiperazina de acuerdo con el método general 5, y 4.19g of N¹-cinnamyl-N⁴-[1-butilo-2-hidroxi-2-(5-cloro-6-methoxynaphthalene-2-yl)]etilopiperazina hidrocioruro fue obtenido con un rendimiento del 91%. El compuesto fue después transformado en un alkali libre, y separado mediante cromatografía de columna. La treo forma obtenida se disolvió en etanol, y se ajustó a un pH de 2 con HCl/C₂H₅OH(5N). El precipitado sólido fue filtrado y el compuesto (VIII-22) se obtuvo mediante la recristalización en etanol/agua o metanol. m.p=194.1-195.6°C(dec). MS : m/z 493 (M⁺).

¹HNMR(DMSO-d₆): δ 0.36-1.49(m, 9H, CH₂CH₂CH₂CH₃), 2.43-3.27(m, 11H, CH+ CH₂+ piperazina -H), 3.98(s, 3H, OCH₃), 4.5 (d, 1H, CH, J=8.0), 5.18(s, 1H, OH), 6.24-6.55(m, 2H, CH=CH),

7.21-8.05(m, 10H, Ar-H).

Ejemplo 23

Síntesis of (S)-2-(1,3-dicarboniloisoindole)hexanoic acid (2)

[98] Se adicionaron 6.55g of L-norleucina(0.05mol), 7.40g de phthalic anhydride (0.05mol), 0.8ml de trietiloamina a 150ml de toleno abjo mezcla a 110°C. Después de la reacción por reflujo por 24 horas, la reacción se completo. El solvente fue evaporado después de seu enfriamiento y se adicionaron 50ml de agua. La extracaión se realice con acetate de etilo(50ml×3) , y la capa de acetate de etilo fue lavada con solución saturada de NaCl, y secada con MgSO₄ anhidrico. El solvent de filtrado fue evaporado tras la filtración de la mezcla, obteniendose así 12.28g de sólido blanco con un rendimiento de 90.3%. MS : m/z 262(M+). ¹HNMR(DMSO-d₆): δ 0.86-1.37(m, 9H, CH₂CH₂CH₂CH₃), 4.46 (m, 1H, CH), 7.25-7.86 (m, 4H, Ar-H).

Ejemplo 24

[99] La preparación de (R)-2-(1,3-dicarboniloisoindole) ácido hexanoico fue la misma que aquella de (S)-2-(1,3-dicarboniloisoindole) ácido hexanoico (2). El rendimiento fue de 87.6%.

MS : m/z 262(M+). ¹HNMR(DMSO-d₆): δ 0.90-1.25(m, 9H, CH₂CH₂CH₂CH₃), 4.68 (m, 1H, CH), 7.42-7.91 (m, 4H, Ar-H)。

Ejemplo 25

Síntesis de
 (S)-2-[2-(1,3-dicarboniloisoindole)hexanoyl]-5-chloo-6-metoxilo
 naftalina (5)

[100] Se disolvieron 10.45g del compuesto 2 (0.04mol) en 100ml de diclorometano a 0°C , y 8.15ml (0.1mol) de oxalyl cloruro fueron adicionado a cuenta gotas en un baño de hielo. Después del goteo, 8

gotas de piridina fueron adicionadas. La temperatura se aumentó lentamente a temperatura ambiente y la mezcla fue provocada por 20 horas. Se evaporaron el disolvente de cloruro de acilo superfluo mediante evaporación rotatoria en 35°, el concentrado fue diluido en 100 ml de diclorometano. g 9,25 de 4 Compuesto (0.048mol) y 6,41 g de AlCl₃ anhidrico (0.048mol) se agregaron a reaccionar para 30 días a temperatura ambiente. El reactivo se combinó lentamente en y mezcla de 1N HCl(100ml) hielo/dicloromethane (100 ml), se dejó reposar para permitir las separación de las capas. La capa acuosa se extrajo con dicloromethane(100ml×2). Las capas de dicloromethane se combinaron y, a continuación, fueron lavadas con solución saturada de NaCl, secadas mediante MgSO₄ anhidrico. El solvente del filtrado se evaporó tras la filtración. Se obtuvo una sustancia aceitosa marrón oscuro, y se separó por cromatografía de columna (alúmina neutral, acetato de etilo: éter de petróleo = 3: 1). Se obtuvieron g 4.68 de sustancia amarilla aceitosa con un rendimiento de 26,8%. MS : m/z 438(M⁺). ¹HNMR(DMSO-d₆): δ 0.96-1.77(m, 9H, CH₂CH₂CH₂CH₃), 3.73(s,3H,OCH₃),5.09 (m, 1H, CH), 7.64-8.34 (m, 9H, Ar-H).

Ejemplo 26

[101] Preparación de
 (R)-2-[2-(1,3-dicarboniloisoindole)hexanoyl]-5-cloro-6-metoxilo
 naftalina fue igual que aquella de
 (S)-2-[2-(1,3-dicarboniloisoindole)hexanoyl]-

5-cloro-6-metoxilonaftalina(5) in a rendimiento of 28.4%. MS : m/z 438(M⁺). ¹HNMR(DMSO-d₆): δ 1.03-1.62(m, 9H, CH₂CH₂CH₂CH₃), 3.10(s,3H,OCH₃),5.14 (m, 1H, CH), 7.35-8.11 (m, 9H, Ar-H).

Ejemplo 27

Síntesis de
 (2S)-2-[1-hidroxi-2-(1,3-dicarboniloisoindole)hexyl]-5-cloro-6- metoxilo
 naftalina (6)

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[102] Se disolvieron 4.36 g de 5(0.01mol) del compuesto en la mezcla de 19,2 ml de tolueno y 12,6 ml de isopropanol y, a continuación, 10.2 g (0.05mol) de isopropoxide de aluminio se añadieron para reaccionar en 100° durante 4 horas. Después de completada la reacción, la mezcla fue enfriada, el disolvente se evaporó y se agregó 1N y de HCl (50 ml). La extracción se realizó con acetato de etilo (50 ml x 3). La capa de acetato de etilo se lavó con una pequeña cantidad de agua y solución saturada de NaCl, secada con MgSO₄ anhidrico. El disolvente se evaporó tras la filtración, y g 4,32 de luz sólido amarillo fueron obtenidos con un rendimiento del 98,6%. MS: m/z 439(M⁺). ¹HNMR(DMSO-d₆): δ 0.96-1.58(m, 9H, CH₂CH₂CH₂CH₃), 3.73(s, 3H, OCH₃), 4.05(m, 1H, CHN), 5.12 (m, 1H, CHOH), 7.34-8.08 (m, 9H, Ar-H).

Ejemplo 28

[103] Preparación de (metoxilonaftalina 2R)-2-[1-hidroxi-2-(1,3-dicarboniloisoindole)hexyl]-5-cloro-6-fue la misma que la de (2S)-2-[1-hidroxi-2-(1,3-dicarbonilo isoindole) hexil]-5-cloro-6-metoxilonaftalina (6) con un rendimiento de 97,4%. MS: m/z 439(M⁺). ¹HNMR(DMSO-d₆): δ 0.89-1.44 (m, 9H, CH₂CH₂CH₂CH₃), 3.70(s, 3H, OCH₃), 4.19(m, 1H, CHN), 5.07 (m, 1H, CHOH), 7.12-8.00 (m, 9H, Ar-H).

Ejemplo 29

Síntesis de (1S)-2-(5-cloro-6-metoxilonaftalina)-2-hidroxi-1-butilo etiloamina (7)

[104] Se disolvieron 2.15 g de 6(0.005mol) del compuesto en 15 ml de metanol, se adicionaron 5 ml de hidrato de hidrazina (0.01mol). La mezcla se agitó por 3 horas a temperatura ambiente y so obtuvo un sólido blanco. Tras la filtración, el disolvente de filtrado se evaporó y se realizó una extracción con agua(20ml)/diclorometano(20ml×3). La capa de diclorometano combinada fue lavada con solución saturada de NaCl, secada con MgSO₄ anidrico. Tras la filtración, el disolvente de filtrado fue evaporado, y 1,13 g de sólido blanco fueron obtenidos

con un rendimiento de 73,4%. MS: m/z 309 (M⁺). ¹HNMR(DMSO-d₆): (0,93-1.54(m, 9H, CH₂CH₂CH₂CH₃), 3,08 (1 H, m, CHN), 3.77(s,3H,OCH₃), 4,75 (1 H, m, CHOH), 7.50-8.17 (m, 5 H, Ar-H).

Ejemplo 30

[105] Preparación de (1R) -2-(5-cloro-6-metoxilonaftalina)-2-hidroxi-1-butiloetilo amino fue igual que aquella de (1S)-2-(5-cloro-6-metoxilonaftalina)-2-hidroxi- 1-butiloetiloamine (7) con un rendimiento de 70.1%. MS: m/z 309 (M⁺). ¹HNMR(DMSO-d₆): δ 1.11-1.77(m, 9H, CH₂CH₂CH₂CH₃), 3.14(m, 1H, CHN), 3.58(s,3H,OCH₃), 4.69 (m, 1H, CHOH), 7.75-8.29 (m, 5H, Ar-H).

Ejemplo 31

Preparación de
 (1S,2R)-N¹-bencilo-N⁴-[1-butilo-2-hidroxi-2-(5'-cloro-6'-metoxilo-2')-naftiletilo]piperazina hidrocloreuro (IX-23) y
 (1S,2S)-N¹-bencilo-N⁴-[1-butilo-2-hidroxi-2-(5'-cloro-6'-metoxilo-2')-naftiletilo]piperazina hidrocloreuro (IX-24).

[106] A 0.924g del compuesto 7(0.003mol) se adicionaron 10ml de acetonitrilo, 2ml de trietiloamina y 1.624g del compuesto 8(0.007mol, preparado c.f. patente US4748726). La mezcla fue calentada y refluada por 20 horas hasta que la reacción se completo, detectada por TLC. Se evaporo acetonitrilo, la extracción se realizó con cloroformo(50ml×3) y agua. Las capas de cloroformo fueron agrupadas y secadas mediante MgSO₄. Se evaporó el cloroformo, obteniendo una sustancia aceitosa y amarilla, que fue la mezcla de dos isómeros (9). MS: m/z 465(M⁺).

[107] La mezcla (9) fue separada por cromatografía de columna de gel de sílice con diclorometano: metanol = 200 como el elusor. g 0,47 de amarillo aceitoso (1S, 2S) isómero (rendimiento:34%) en primer lugar fue elucionado y disuelto en 20 ml de metanol. Se utilizó ácido hidroclorehídrico/etanol para ajustar el pH a 2. Se obtuvo un precipitado

blanco sólido y 0,25 g de producto blanco mediante filtración.

[108] Se elucionaron en agua, 0,12 g de grasa de amarilla (1S, 2R) isómero (rendimiento:8.5%) y posteriormente disuelta en 10 ml de metanol. Se utilizó ácido hidroclicorico/etanol para ajustar el pH a 2. Se obtuvo un precipitado sólido amarillo, y 0,05 g de producto amarillo mediante filtración y calefacción a sequedad.

IX-23: mp: 225.0 ~ 225.8°C(dec); MS: m/z 467 (M+);
¹HNMR(DMSO-d6): δ 0.36-1.86(m, 9H, CH₂CH₂CH₂CH₃), 3.54-3.80(m, 9H, CH+piperazina-H), 3.96(s, 2H, CH₂-Ph), 4.42(s, 3H, OCH₃), 5.519-5.524 (d, 1H, CH, J=2.0), 7.43-8.14(m, 10H, Ar-H).

IX-24: mp: 223.1 ~ 224.3°C(dec) ; MS: m/z 467 (M+);
¹HNMR(DMSO-d6): δ 0.33-1.58(m, 9H, CH₂CH₂CH₂CH₃), 3.62-3.79(m, 9H, CH+ piperazina-H), 3.95(s, 2H, CH₂-Ph), 4.42(s, 3H, OCH₃), 4.913-4.937(d, 1H, CH, J=9.6), 7.43-8.17(m, 10H, Ar-H).

Ejemplo 32

[109] Preparación de
(1S,2S)-N¹-bencilo-N⁴-[1-butilo-2-hidroxi-2-(5'-cloro-6'-metoxilo-2')-naftiletilo]piperazina hidroclicoruro (IX-25) y
(1S,2R)-N¹-bencilo-N⁴-[1-butilo-2-hidroxi-2-(5'-cloro-6'-metoxilo-2')-naftiletilo]piperazina hidroclicoruro(IX-26) fue igual que el Ejemplo31.

IX-25: mp: 225.0 ~ 225.8°C(dec); MS: m/z 467 (M+) ;
¹HNMR(DMSO-d6): δ 0.36-1.86(m, 9H, CH₂CH₂CH₂CH₃), 3.54-3.80(m, 9H, CH+ piperazina-H), 3.96(s, 2H, CH₂-Ph), 4.42(s, 3H, OCH₃), 5.519-5.524 (d, 1H, CH, J=2.0), 7.43-8.14(m, 10H, Ar-H).

IX-26: mp: 223.1 ~ 224.3°C(dec); MS: m/z 467 (M+);
¹HNMR(DMSO-d6): δ 0.33-1.58(m, 9H, CH₂CH₂CH₂CH₃), 3.62-3.79(m, 9H, CH+ piperazina-H), 3.95(s, 2H, CH₂-Ph), 4.42(s, 3H, OCH₃), 4.913-4.937(d, 1H, CH, J=9.6), 7.43-8.17(m, 10H, Ar-H).

Ejemplo 33

Tableta:

Derivado de la presente invención 10mg

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sucrosa	150mg
almidón de maíz	38mg
esterato de calico	2mg

[110] Preparación: el ingrediente activo fue mezclado con almidón de maíz y de sacarosa y, a continuación, la mezcla fue humedecida mediante la adición de agua, mezclada uniformemente, secada, triturado y examinada, seguido se agregó estearato de calcio. La mezcla obtenida fue provocada uniformemente y, a continuación, presionada en tabletas. El peso de la tableta fue 200 mg por comprimido, que contiene 10 mg de ingrediente activo.

Ejemplo 34

Inyección:

Derivado de la presente invención	20mg
agua para la inyección	80mg

[111] Preparación: el ingrediente activo se disolvió y mezcló uniformemente con agua para su inyección, y después se filtró. La mezcla obtenida se dividió en ampollas bajo condiciones estériles. El peso fue de 10mg por ampolla, conteniendo 2mg del ingrediente activo.

Ejemplo 35

Efecto inhibitorio de los compuestos en la recaptación de 5-HT, NA y DA mediante sinaptosomas de cerebro

[112] Se realizaron estudios sobre la inhibición de recaptación de los neurotransmisores monoamínicos mediante sinaptosomas cerebrales, que es un medio importante actualmente adoptado en todo el mundo en estudios farmacológicos del sistema central nervioso. Este método puede utilizarse no sólo para estudiar el mecanismo de acción de un medicamento, sino también puede utilizarse para la detección de nuevos fármacos por este mecanismo. En la presente invención, los estudios sobre el efecto de la inhibición de los compuestos en la recaptación de 5-HT, NA y DA por sinaptosomas del cerebro se realizó, con venlafaxina (un eficaz doble

inhibidor de la recaptación de 5-HT y NA) y 6-hidroxi DA como los controles positivos.

1. Preparación de sinaptosomas de cerebro de rata

[113] Ratas machos SD fueron sacrificados por dislocación cervical y luego los cerebros de los mismos fueron tomados rápidamente y colocados sobre hielo. Se tomaron tejidos de lluvia relacionados (para el experimento de recaptación de NA de 5-HT y [3 H] de [3 H], fue tomada la corteza prefrontal; para el experimento de recaptación [3 H] DA, se tomó cuerpo estriado) fueron separados y pesados. Se adicionó 10 veces (V/W) de 0.32mol / solución de sacarosa helada l y se homogeneizó eléctricamente con Teflón de vidrio. El homogenado fue centrifugado a $4 \times 1000 \text{ g} \times 10 \text{ min}$. Seguido, el sobrenadante fue tomado y centrifugado a $4 \times$ en $17000\text{g} \times 20 \text{ min}$. La precipitación fue suspendida en 30 volúmenes de búfer de KRH (125 mM (NaCl), 4,8 mM KCl, 1,2 mM CaCl_2 , 1,2 mM MgSO_4 , 1,0 mM KH_2P_4 , 22 mM NaHCO_3 , 25 mM HEPES, 10 mM glucosa, μM 10 Pargyline, ácido ascórbico de 0,2 mg/ml) y luego fue conservado en un baño de hielo para utilizar. (para el experimento de recaptación de NA, la corteza necesaria se suspendió en 20 volúmenes de búfer de KRH) 2. [3 H]

2. Experimentos de recaptación de 5-HT/NA/DA.

[114] Solución madre de la sustancia de ensayo fue descongelada inmediatamente antes del uso y diluida con búfer KBH a $100\mu\text{mol/L}$, se adicionaron $50\mu\text{l}$ en $500\mu\text{l}$ de sistema de reacción total, y la concentración final fue $10\mu\text{mol/l}$. Luego se adicionaron $50\mu\text{l}$ suspendidos sináptica preparados anteriormente y mezclados uniformemente, incubados en baño de agua durante 30 minutos en 37° . Luego se adicionaron 10nmol/L [3 H] 5-HT (50nmol/L [3 H] DA o [3 H] NA 60nmol/L). Después de la incubación a 37° durante 10 minutos, el sistema de reacción inmediatamente fue parado y la reacción fue detenida añadiendo 2 ml de solución helada 150mmol/L Tris-HCl. Las muestras fueron recogidas en la membrana circular de fibra de vidrio por filtración al vacío, y la membrana fue lavada 3 veces

con 3 ml de solución helada de Tris-HCl. Se eliminó la membrana de filtración, durante 15 minutos se colocó en un horno infrarrojo lejano en un tubo de EP. Se adicionaron 1,5ml de líquido de centelleo durante la noche y fue probado mediante un contador de centelleo líquido. Para el tubo de enlace total y el tubo de enlace no específico, no se agregó ninguna sustancia; para el tubo de enlace total, agregó 50µl solvente.

3. Resultados:

[115] Teniendo la tasa inhibitoria de 0,1 mM de venlafaxina y 6-hidroxi DA en la recaptación de monoaminas como 100%, la intensidad inhibitoria de los compuestos, en comparación con venlafaxina y DA 6-hidroxi es mostrada en la tabla 3.

Tabla 3 porcentaje inhibitorio (%) sobre la recaptación de 5-HT, NA y DA mediante sinaptosomas cerebrales.

Compuest os	Inhibición sobre la recaptación de 5-HT(%)	Inhibición sobre la recaptación de NA(%)	Inhibición sobre la recaptación de DA(%)
Venlafaxin a	100	100	/
6-hidroxi DA	/	/	100
VIII-3	65.1	144	96
VIII-4	23	146.5	68
VIII-9	125	155.2	117
VIII-10	136	145	133
VIII-19	73.4	103.6	95
VIII-20	0	78	57
VIII-21	81	87.5	90

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VIII-22	82.3	78.9	94
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4. Conclusión

[116] Los derivados de 1-butilo-2-hidroxi aralquilo piperazina en la presente invención, fueron inhibidores de recaptación triples, los cuales tienen una fuerte inhibición in vitro en la recaptación de transmisores monoamínicos DA, NE y 5-HT. La actividad de inhibición de recaptación triple de los compuestos preferidos VIII-9 y VIII-10 fue mayor que aquella mostrada por el control positivo, venlafaxina.

Ejemplo 36

Determinación de IC₅₀ de los compuestos preferidos VIII-9 y VIII-10 para inhibir la recaptación de 5-HT, NA y DA mediante sinaptosomas de cerebro de ratas

- 1. Preparación de sinaptosomas de cerebro de rata (el mismo que el Ejemplo 35)
- 2. Investigación sobre la inhibición en la recaptación de (IC₅₀) en [³H]5-HT/NA/DA

[117] Se utilizaron los compuestos para el estudio sobre el efecto inhibitorio (IC₅₀) en la recaptación de [³H]5-HT/NA/DA. Al menos cinco concentraciones en cada oportunidad fueron dispuestas para cada prueba compuesto. Cada concentración fue determinada por la media de dos tubos dobles y a prueba fue repetida en más de 3 oportunidades. Una serie de concentraciones de los compuestos fueron preparados por dilución degradada antes de su uso. Se adicionaron 50µl en el sistema de reacción total. Luego membrana se adicionaron 50µl de membrana sináptica suspendida y se mezcló uniformemente, incubados en baño de agua a 37° durante 30 minutos. Seguido, se adicionaron 10nmol/L [3 H] 5-HT (o 50nmol/L [3 H] DA o 40nmol/L [3 H] NA) y se incubó en baño de agua a 37° durante 10 minutos ([3 H] NA, incubado durante 5 minutos). Para el experimento de recaptación de 5-HT [3 H], se adicionaron 50µL de fluoxetina (100µmol/L) al tubo de enlace no específico; para el experimento de recaptación [3 H] DA, se adicionaron 50µL de cocaína


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(600µmol/L) al tubo de enlace no específico; para el experimento de recaptación [³H]NA se adicionaron 50µL de desipramina (100µmol/L) al tubo de enlace no específico; para el control de disolvente, se adicionó solvente al tubo de enlace total, pero ningún compuesto de prueba fue agregado.

3. Procesamiento de fechas

[118] El valor CPM de enlace específico para cada tubo de muestra de ensayo = valor CPM de enlace total para cada tubo de muestra de ensayo - valor CPM de enlace no específicos para cada tubo de muestra de ensayo; tasa de inhibición de la compuesto (%) de la recaptación de [3 H] 5-HT/NA/DA por la corteza prefrontal y estriado = enlace 100% específicos para cada tubo de muestra de ensayo (valor CPM) / disolvente específico vinculante (valor CPM) × 100%. Se realiza un ajuste de curvas sigmoideas para los datos obtenidos de todos los medicamentos de prueba por origen 6.1, y se calculó el valor de la ICL₅₀.

4. IC₅₀ resultados determinantes

[119] La inhibición de los compuestos (IC₅₀) sobre la recaptación de 5-HT, NA y DA mediante la corteza prefrontal y el cuerpo estriado se muestra en la Tabla 4.

Tabla 4 efecto inhibitorio de los compuestos en la recaptación de [³H]5-HT/NA/DA IC₅₀(medio±SE, n=3~4)

Compuestos	IC ₅₀ (nmol/L)		
	[³ H]5-HT	[³ H]NA	[³ H]DA
venlafaxina	145	1420	3070
SIPlly24	200	1000	No se detectó actividad
SIPi5286	12	185	1150
VIII-9	73.28	2.8	2.1

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VIII-10	271.51	4726.1	165.4
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nota: El Compuesto SIPIyy24 fue el compuesto preferido en la patente ZL02111934.1; El Compuesto SIPI5286 fue el compuesto preferido en la patente ZL200510030354.1.

5. Conclusion

[120] El Compuesto VIII-10 tuvo un actividad de inhibición in vitro sobre la recaptación de 5-HT y NA, comparable con la venlafaxina y SIPIyy24, y tuvo una mayor actividad de inhibición en la recaptación de DA, comparado con la venlafaxina, SIPIyy24 y SIPI5286; El Compuesto VIII-9 tuvo una mayor actividad de inhibición sobre la recaptación de tres tipos de transmisores monoamínicos, comparado con la venlafaxina, Slyy24 y SIPI5286.

Ejemplo 37

Efecto de inhibición in vitro en cuatro isómeros ópticos IX-23~IX-26 sobre la recaptación de tres transmisores monoamínicos

1. Experimentos, materiales y métodos

Experimentos	Materiales	Control	Métodos (referencias)
Recaptación de NE	Sinaptosomo del hipotalamo de rata	protriptyline	Perovic y Muller W.E.G. Perfil farmacologico del extracto de hipérico en la recaptación de serotonina mediante los receptores postsinápticos. Arzneim-Forsch. Drug Res., 1995, 45:1145-1148.
recaptación	Sinaptosomas	GBR	Janowsky; Berger, P.;

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de DA	de cuerpo estriado de rata	12909	Vocci, F.; Labarca, R., Skolnick, P.; Paul, S.M. Caracterización del acoplamiento sodio dependiente de[3H]GBR -12935 en el cerebro: un etiquetamiento selective de radiología para el complejo de transporte de dopamina. J. Neurochem., 1986, 46:1272-1276.
recaptación de 5-HT	Sinaptosomas en cerebro de rata	imipramina	Perovic y Muller W.E.G. Perfil farmacológico del extracto de hypericum en la recaptación de serotonina mediante los receptores pos sinápticos. Arzneim-Forsch. Drug Res., 1995, 45:1145-1148.

2. Condiciones de Experimento

Experimentos	Etiqueta	Incubación	Producto de la reacción	Método de detección
NE recaptación	[3H]NE(μ0.2Ci/ml)	20min./37°C	[3H]NE sinaptosoma de	scint counting

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			acoplamiento	
DA recaptación	[3H] DA (μ0.2Ci/ml)	15min./37°C	[3H] DA sinaptosoma de acoplamiento	scintiscouting
5-HT recaptación	[3H] 5-HT (μ0.2Ci/ml)	15min./37°C	[3H] 5-HT sinaptosoma de acoplamiento	scintiscouting

3. Los resultados del experimento (valor IC₅₀ se obtuvo mediante el análisis de regresión no lineal de la curva de respuesta rata/concentración de inhibición)

Compuestos	configuración	IC ₅₀ (nM)		
		5-HT	NE	DA
IX-23	(1S,2R)	1900	2100	1000
IX-24	(1S,2S)	3100	1400	1100
IX-25	(1R,2S)	830	140	670
IX-26	(1R,2R)	1200	1200	1100

4. Conclusion

[121] Los cuatro isómeros ópticos IX-23~IX-26 tuvo una fuerte actividad de inhibición in vitro en la recaptación de tres transmisores monoamínicos DA, NE y 5-HT, y pertenece a los inhibidores de recaptación triple.

Ejemplo 38

Estudios sobre la actividad antidepresiva *in vivo* en animales con los compuestos preferidos VIII-9 y VIII-10.

[122] Los estudios realizados sobre el efecto antidepresivo *in vivo*

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de los compuestos VIII-9 y VII-10 utilizando la prueba de nado forzado en ratones ratones en el "Learned Helplessness Experiment" (Zhang Juntian, Modern Pharmacological Experiments Mothods (first volume). Beijing Medical University y Peking Union Medical University Joint Publishing House, 1998:1064-1066), con venlafaxina como el control positivo.

Tabla 5 efecto de la administración oral única sobre la prueba de nado en ratones ICR (n=12, $\Delta \pm SE$)

Grupos	Dosis	Prueba de nadado: tiempo(s) de inmovilidad
Control	N.S	109.4±66.19
venlafaxina	50mg/kg	46.5±25.14**
VIII-9	48mg/kg	104.3±75.81
	28.8mg/kg	77.4±53.81
	17.3mg/kg	119.4±28.02
	10.4mg/kg	74.3±46.63
VIII-10	48mg/kg	64.4±43.01
	28.8mg/kg	40.8±40.24**
	17.3mg/kg	43.4±35.41**
	10.4mg/kg	81.8±39.34
SIPI5286	48mg/kg	90.1±26.02**
	28.8mg/kg	92.1±23.11**
	17.3mg/kg	105.4±33.11
	10.4mg/kg	107.9±37.19

* p<0.05, **p<0.01 comparado con el grupo de control

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Los resultados de la prueba de nado en ratones ICR con administración oral, demostró que los compuestos VIII-9 y VIII-10 tienen un actividad antidepresiva *in vivo* similar en comparación con la venlafaxina y SIPI5286, y tuvieron una diferencia significativa en comparación con el grupo de control. El ED₅₀ of VIII-9 fue de 34.3mg/kg, ED₅₀ de VIII-10 fue de 11.8mg/kg y ED₅₀ de SIPI5286 fue de 28.9mg/kg. VIII-10 tuvo la mayor actividad antidepresiva *in vivo*.

Tabla 6 efectos una semana después de la administración oral sobre la prueba de nado en ratones ICR (n=12, $\bar{x} \pm SD$)

grupos	dosis	prueba de nado: tiempo(s) de inmovilidad
control	N.S	133.2±35.88
venlafaxina	50mg/kg	83.5±29.0**
VIII-9	48mg/kg	91.5±58.14**
	28.8mg/kg	87.2±40.07**
	17.3mg/kg	82.1±44.06**
	10.4mg/kg	93.4±26.71**
VIII-10	48mg/kg	68.3±34.01**
	28.8mg/kg	51.9±51.23**
	17.3mg/kg	78.2±25.63**
	10.4mg/kg	77.6±24.69**
SIPI5286	48mg/kg	95.5±27.0**
	28.8mg/kg	97.2±28.33**
	17.3mg/kg	102.9±37.94
	10.4mg/kg	123.8±21.68

* p<0.05, **p<0.01 comparado con el grupo de control

[123] Los resultados de la prueba de nado con administración oral continua durante una semana en ratones ICR, mostraron que el compuesto VIII-9 tuvo una actividad antidepresiva *in vivo* equivalente a la de la venlafaxina y SIPI5286, y mostró una diferencia significativa en comparación al grupo de control. La actividad antidepresiva *in vivo* del Compuesto VIII-10 fue mayor que aquella de la venlafaxine y SIPI5286.

Ejemplo 39

Estudios sobre la toxicidad aguda del Compuesto VIII-9 y VIII-10

Estudios sobre la toxicidad aguda en la administración oral del Compuesto VIII-9 y VIII-10 se realizaron (Zhang Juntian, Modern Pharmacological Experiments Mothods (last volume), en Beijing Medical University y Peking Union Medical University Joint Publishing House, 1998:1818-1821). Los resultados obtneidos fueron los siguientes:

gen erp	dosis mg/kg	Dosis logarit mica	Núme ro de anima l	Distribucipin de muertes de animales (día)								Núme re de anima les muert os	mortal idad (%)	Rata de regresi ón	LD ₅₀ (95 % límite confiden cial) mg/kg
				1h	2h	4h	1	4	7	10	14				
Hem bra & mac ho	2844. 7	3.454	6	0	0	0	0	0	0	0	0	0	0		MLD> 2844.7 mg/kg
VIII-9	1849. 1	3.267	5	0	0	0	0	0	0	0	0	0	0		
	1201. 9	3.0799	6	0	0	0	0	0	0	0	0	0	0		

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	781.2	2.8928	6	0	0	0	0	0	0	0	0	0	0			
	507.8	2.7057	6	0	0	0	0	0	0	0	0	0	0			
mal e & 7 fem ale	2844.	3.454	6	0	0	0	6	0	0	0	0	6	100	7.2765	1048.5 (751.33	
VIII-10	1849. 1	3.267	6	0	0	0	5	0	0	0	0	5	83.3	6.2940	~	
	1201. 9	3.0799	6	0	0	0	4	0	0	0	0	4	66.7	5.3113	1433.7)	
	781.2	2.8928	6	0	0	0	2	0	0	0	0	2	33.3	4.3286		
	507.8	2.7057	6	0	0	0	0	0	0	0	0	0	0.00	3.3461		

[124] Resultado: Después de ser estadísticamente tratados con el método Bliss, LD₅₀ de VIII-10 (95% límite confidencial) fue 048.5(751.33~1433.7) mg/kg, dosis letal mínima (MLD) de VIII-9 fue de mas de 2844.7mg/kg. La toxicidad aguda por ende fue menor que aquella mostrada por el compuesto preferido SIPIyy24 en la patente ZL02111934.1 y de aquella mostrada por el compuesto SIPI5286 en la patente ZL200510030354.1)

Ejemplo 40

Estudios sobre la farmacogenética de los Compuestos VIII-9 y VIII-10

1. Propósito de la prueba

[125] El estudio sobre los parámetros farmacogenéticos y de biodisponibilidad de VIII-9, VIII-10 y SIPI5286 via inyección y administración oral en ratas SD

2. Método de prueba:

Se rionizaron dieciocho ratas macho en 6 grupos y se les administraron tres compuestos via inyección y oral, respectivamente. La dosis fue de 10mg/kg (IV) y 50mg/kg (PO). La sustancia de prueba

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se disolvió en la solución de 5%DMSO/95%HP-β-CD, solución acuosa (30%), y ésta les fue administrada a los animales vía inyección y oral. Se recolectó el plasma de la sangre en una serie de tiempos después de la administración vía oral o inyección, y se determinaron las concentraciones del medicamento en la sangre mediante LC/MS/MS. Seguido, se calcularon los parámetros farmacocinéticos y de biodisponibilidad con base en las concentraciones de medicamento en la sangre.

2. Resultados de la prueba:

Compuestos	Modo de administración	dosis mg/kg	C _{max} (µg/L)	T _{max}	AUC(0-t) (hr*µg/L)	Vida media (T1/2) (hr)	biodisponibilidad
VIII-9	inyección	10	2640.94 (5min)		4060.59	7.83	
	oral	50	352.27	1.50 hr	3345.73	5.89 hr	16.32%
VIII-10	inyección	10	2998.49 (5min)		2932.05	9.06 hr	
	oral	50	727.20	1.67 hr	5552.24	16.41 hr	63.78%
SIP15286	inyección	10	13876.57 (5min)		12564.22	3.41 hr	

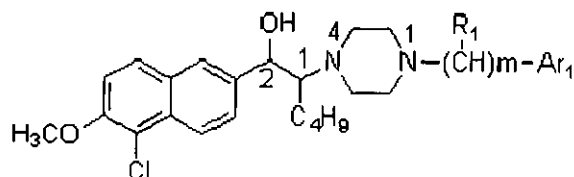
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	oral	50	6856 .69	0.50 hr	30255. 45	5.71 hr	51.63%
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4. Conclusión

[126] La vida media de la administración oral del Compuesto VIII-10 fue de 16.41 horas, lo cual fue mayor que aquella del Compuesto VIII-9(5.89 horas) y SIPI5286(5.71horas). La biodisponibilidad para la administración oral del compuesto VIII-10 fue de 63.78%, mayor que aquella del Compuesto VIII-9(16.32%) y SIPI5286 (51.63%). El Compuesto VIII-10 tiene una buena disponibilidad para medicamentos. Lo que se reclama es:

1. El derivado de 1-butilo-2-hidroxil aralquilo piperazina, caracterizado por cuanto el éste es un alkali libre o su sal esta compuesta por la formula (1), o su alkali libre o la sal de los isómeros ópticos es un compuesto de la formula (1):



(1)

donde,

Ar₁ representa benceno, sustituido por fenilo, un heretociclo aromatico de 5-miembros o 6-miembros conteniendo N, O o S, o cinnamenilo;

m es un integral de 0~5;

R₁ reprenta hidrogeno, C₁-C₅ alquilo, C₅ o C₆ aro aliciclico, benceno, sustituido de fenilo, hidroxil, amino, sustituido de amino, C₁-C₄ alkoxy, C₁-C₄ acilo, halogeno, ácido carboxilico o eter carboxilico. .

2. El derivado de 1-butilo-2-hidroxil aralquilo piperazina de acuerdo con la reclamación 1, caracterizado por cuanto Ar₁ representa

un sustituto de fenilo donde el aro de benceno contiene de uno a cuaros sustitutos y éstos sustitutos son halogeno, hidroxil, alquilo, nitro, alkoxy o amino.

3. El derivado de 1-butilo-2-hidroxil aralquilo piperazina de acuerdo con la reclamación 1, caracterizado por cuanto R_1 representa un sustituto de amino donde el amino contiene C_1 - C_4 alquilo, C_5 o C_6 aro alicíclico, benceno o sustituto de fenilo como sustitutos; donde el fenilo sustituto es un fenilo que contiene de uno a cuatro sustituentes en el aro de benceno, donde esto seon halogeno, hidroxil, alkoxy o el grupo amino.

4. El derivado de 1-butilo-2-hidroxil aralquilo piperazina de acuerdo con la reclamación 3, caracterizado por cuanto el alquilo moiety en C_1 - C_5 alquilo, C_1 - C_4 alkoxy, C_1 - C_4 acilo y C_5 o C_6 aro alicíclico puede ser sustituido opcionalmente con 1~3 átomos de fluor.

5. El derivado de 1-butilo-2-hidroxil aralquilo piperazina de acuerdo con la reclamación 1, caracterizado por cuanto los átomos de carbono en la estructura son átomos quirales o aquirales; para los átomos de carbono quirales la configuración es C_1 y C_2 , respectivamente (1S,2R), (1S,2S), (1R,2S) o (1R,2R); donde, (1SR,2RS) es un eritro isómero y (1SR,2SR) es un treo isómero.

6. El derivado de 1-butilo-2-hidroxil aralquilo piperazina de acuerdo con la reclamación 1, caracterizado por cuanto que la sal, es una sal que contiene aniones farmacéuticamente aceptables.

7. El derivado de 1-butilo-2-hidroxil aralquilo piperazina de acuerdo con la reclamación 6, caracterizado por cuanto la sal es hidrocloruro, hidrobromuro, sulfato, trifluoroacetato o metanosulfonato.

8. El derivado de 1-butilo-2-hidroxil aralquilo piperazina de acuerdo con la reclamación 1, caracterizado por cuanto la sal contiene de 0.5~4 moléculas de agua cristalina are contained in the salt.

9. El derivado de 1-butilo-2-hidroxil aralquilo piperazina de

acuerdo con cualquiera de las reclamaciones 1~8, el cual se selecciona de un grupo consistente de:

VIII-1

(1SR,2RS)-N¹-p-metoxilofenilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil) hidroxietilo]piperazina,

VIII-2

(1SR,2SR)-N¹-p-metoxilofenilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil) hidroxietilo]piperazina,

VIII-3

(1SR,2RS)-N¹-o-metoxilofenilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina,

VIII-4

(1SR,2SR)-N¹-o-metoxilofenilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina,

VIII-5

(1SR,2RS)-N¹-m-clorofenilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina,

VIII-6

(1SR,2SR)-N¹-m-clorofenilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina,

VIII-7

(1SR,2RS)-N¹-(2,3-dimetilofenilo)-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina,

VIII-8

(1SR,2SR)-N¹-(2,3-dimetilofenilo)-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina,

VIII-9

(1SR,2RS)-N¹-bencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil) hidroxietilo]piperazina,

VIII-10

(1SR,2SR)-N¹-bencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil) hidroxietilo]piperazina,

VIII-11

(1SR,2RS)-N¹-p-nitrobencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina,

VIII-12

(1SR,2SR)-N¹-p-nitrobencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina,

VIII-13

(1SR,2RS)-N¹-p-aminobencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina,

VIII-14

(1SR,2SR)-N¹-p-aminobencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina,

VIII-15

(1SR,2RS)-N¹-(3',4',5'-trimethoxybencilo)-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina,

VIII-16

(1SR,2SR)-N¹-(3',4',5'-trimethoxybencilo)-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina,

VIII-17

(1SR,2RS)-N¹-α-phenemyl-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina,

VIII-18

(1SR,2SR)-N¹-α-phenemyl-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina,

VIII-19

(1SR,2RS)-N¹-benzhydryl-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-Naftil)hidroxietilo]piperazina,

VIII-20

(1SR,2SR)-N¹-benzhydryl-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-Naftil)hidroxietilo]piperazina,

VIII-21 (1SR,2RS)-N¹-cinnamyl-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-Naftil)hidroxietilo]piperazina,

VIII-22 (1SR,2SR)-N¹-cinnamyl-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)hidroxietilo]piperazina,

IX-23 (1S,2R)-N¹-bencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)

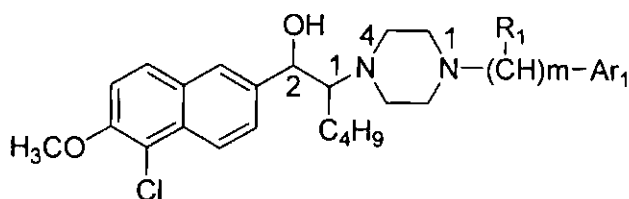
- hidroxietilo]piperazina,
 IX-24 (1S,2S)-N¹-bencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)
 hidroxietilo]piperazina,
 IX-25 (1R,2S)-N¹-bencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)
 hidroxietilo]piperazina,
 IX-26 (1R,2R)-N¹-bencilo-N⁴-[1-butilo-2-(5'-cloro-6'-metoxilo-2'-naftil)
 hidroxietilo]piperazina.

10. Una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de derivados de 1-butilo-2-hidroxil aralquilo piperazina de acuerdo con cualquiera de las reclamaciones 1-9, junto con medios farmacéuticamente aceptables.

11. El uso de los derivados de 1-butilo-2-hidroxil aralquilo piperazina en la fabricación de antidepresivos es una de las reclamaciones 1-9.

RESUMEN

La invención revela los derivados de 1-butilo-2-hidroxil aralquilo piperazina y sus usos como antidepresivos. Los derivados en la presente invención tienen un efecto inhibitorio de recaptación triple de 5-HT, NA y DA, y pueden ser administrados a pacientes que los requirieran ya sea por vía oral, inyección o similares. En comparación con los antidepresivos de doble acción actualmente utilizados (tales como la venlafaxina), dichos derivados pueden tener un mayor efecto antidepresivo, mayores indicaciones, mayor rapidez de acción, menor neurotoxicidad y efectos secundarios; y dichos derivados tienen mayor actividad antidepresiva, menor toxicidad, mayor biodisponibilidad, mayor vida media y mejor manejo farmacéutico en comparación con los derivados de arilo alkanol piperazina y los correspondiente isómeros ópticos revelados en el anterior documento. El derivado de 1-butilo-2-hidroxil aralquilo piperazina es un alkali libre o la sal de un compuesto de la siguiente formula:



The 1-butyl-2-hydroxyaralkyl piperazine derivatives and the uses as anti-depression medicine thereof

FIELD OF INVENTION

[01] The present invention relates to 1-butyl-2-hydroxyaralkyl piperazine derivatives and their use as broad-spectrum antidepressants.

BACKGROUND OF THE INVENTION

[02] Depression is a syndrome characterized by significant and lasting low mood, which mainly manifests as affective disorder. The symptoms include low mood, less speech, slow mentality and motion, and even suicide attempt. Depression, as a chronic mental disease, has become a fiendish problem which bothers the medical health service in China, due to long treatment course, slow effect onset and higher rate of relapse, disability and suicide. According to "World Health Reports" announced by World Health Organization (WHO), depression has become the fourth largest disease in the world, and depression might become the second largest illness after heart disease in 2020, and thus become a serious problem to human health.

[03] So far, the action mechanism of antidepressant has not been clearly demonstrated. Drugs having definite effect substantially act on synapses of the nerve ending, and exert their curative effects by adjusting the level of neurotransmitters in synaptic cleft. The biochemistry study on etiology indicated that depression relates mainly to five types of neurotransmitters, i.e., central 5-hydroxytryptamine (5-HT), noradrenaline (NA), dopamine (DA), acetylcholine (Ach), and γ -aminobutyric acid (GABA).

[04] Antidepressant can be divided into two categories: early non-selective antidepressants and novel selective reuptake inhibitors. Non-selective antidepressants mainly include monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs); selective reuptake inhibitors mainly comprise selective 5-hydroxytryptamine (5-HT) reuptake inhibitors (SSRIs), noradrenaline (NA) reuptake inhibitors (NRIs), noradrenergic and specific 5-HT reuptake inhibitors (NDRIs), 5-HT and NA dual reuptake inhibitors (SNRIs), 5-HT re-absorption enhancers, and the like.

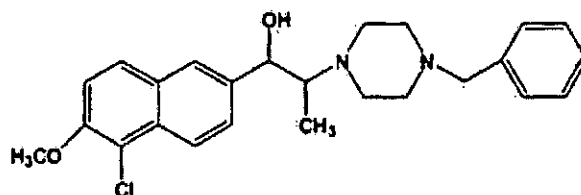
[05] Early monoamine oxidase inhibitors and tricyclic antidepressants have serious adverse reactions; as for the subsequent selective NA reuptake inhibitors and selective 5-HT reuptake inhibitors, although they have less adverse reactions, disadvantages such as slow onset, indefinite efficacy and the like, still exist. Therefore, the effects of

all kinds of drugs above in treating depression are not satisfactory. So far, the existing antidepressants still can not meet the demand of clinical treatment.

[06] Venlafaxine, the first 5-HT and NA dual reuptake inhibitor marketed in American in 1997, and duloxetine marketed in 2004 have advantages of rapid onset of action, compared with selective 5-hydroxytryptamine reuptake inhibitors such as fluoxetine, and noradrenaline reuptake inhibitors such as reboxetine, and have significant effects on both serious depression and refractory depression. From venlafaxine on, development on the novel antidepressants that have 5-HT and NA dual action routes, faster onset, fewer side effects and stronger effect, becomes the research emphasis and an important development direction.

[07] At present, many studies indicate that the addition of DA reuptake inhibitors in dual reuptake inhibitors can obtain better antidepression effect. 5-HT, NA and DA triple selective reuptake inhibitors(also known as "broad-spectrum" antidepressants), developed based on dual reuptake inhibitors, are now still in clinical research phase. For example, triple selective reuptake inhibitor DOV-216303 developed by DOV Pharmaceutical Inc. is in phase III clinical trial; NS-2359 developed jointly by GlaxoSmithKline and NeuroSearch Inc. is now in phase II clinical trial of antidepressant. These monoamine transmitter triple selective reuptake inhibitors possess advantages of high effectiveness and fast onset and are becoming hot points in the antidepressants development.

[08] The applicant has disclosed aryl alkanol piperazine derivatives and their use in preparation of antidepressants in Chinese patent ZL02111934.1. A preferred compound therein, N¹-benzyl-N⁴-[1-methyl-2-(5'-chloro-6'-methoxy-2'-naphthyl)hydroxyethyl]piperazine (IV-19, SIPIyy24, see formula A below), has a dual inhibition effect on the reuptake of 5-HT and NA, and has a strong antidepression biologic activity on animals. But a further research finds that the antidepression effect thereof is still not so satisfactory and adverse reaction thereof is obvious.



Formula A

[09] Subsequently, the applicant disclosed the optical isomers of compound SIPIyy24

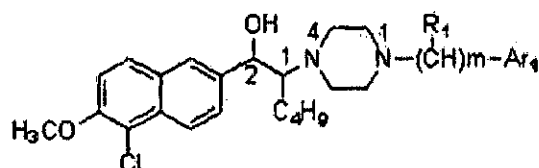
and the use thereof in Chinese patent ZL 200510030354.1. Study shows that the (1S,2R) optical isomer of SIPlly24 (code SIPI5286) has an inhibition effect on the reuptake of the three kinds of monoamine transmitters, i.e. 5-HT, NA and DA. It is a novel triple reuptake inhibitor, and has better antidepressant activity and safety than that of the racemate, and is worthy of being a novel antidepressant. However, it is found through further studies that, the half life of SIPI5286 is too short, and thus not suitable to be formulated into a medicament.

DESCRIPTION OF THE INVENTION

[10] One of the technical problems to be resolved in the present invention is to disclose a 1-butyl-2-hydroxyl aralkyl piperazine derivative to overcome the defects in the prior art, i.e., low efficacy, prominent side effects and slow onset, and thus resolve the clinical problem and meet the requirements of clinical application.

[11] Another technical problem to be resolved in the present invention is to disclose the use of above mentioned derivative in the preparation of antidepressants.

[12] The 1-butyl-2-hydroxyl aralkyl piperazine derivative mentioned in the present invention is the free alkali or its salt of compound of formula (1), or the free alkali or its salt of the optical isomers of compound of formula (1):



(1)

wherein:

Ar₁ represents benzene; substituted phenyl; a 5-member or 6-member aromatic heterocycle containing N, O or S, or cinnamyl, wherein the substituted phenyl is a phenyl containing one to four (1, 2, 3 or 4) substituents on the benzene ring, wherein the substituents are halogen, hydroxyl, alkyl, nitro, alkoxy or amino;

m is an integer of 0-5, preferably 0 or 1;

R₁ represents hydrogen, C₁-C₃ alkyl (preferably C₁-C₃ alkyl and more preferably methyl), C₅ or C₆ alicyclic ring, benzene, substituted phenyl, hydroxyl,

amino, substituted amino, C₁-C₄ alkoxy, C₁-C₄ acyl, halogen, carboxylic acid or carboxylic ester, wherein, the substituted amino is an amino substituted by C₁-C₄ alkyl, C₅ or C₆ alicyclic ring, benzene or substituted phenyl; the substituted phenyl is a phenyl with one to four substituents on the benzene ring, the substituent being halogen (preferably chloro), hydroxyl, alkyl (preferably C₁-C₃ alkyl and more preferably C₁-C₃ linear chain alkyl), nitro, alkoxy or amino; the C₁-C₅ alkyl (preferably C₁-C₃ alkyl) and the alkyl moiety in C₁-C₄ alkoxy, C₁-C₄ acyl and C₅ or C₆ alicyclic ring is preferably linear chain alkyl which can be optionally substituted by 1~3 fluorine atoms;

[13] The asymmetric carbon atoms in the structure are achiral or chiral carbon atoms; For chiral carbon atoms, the configuration of C₁ and C₂ are respectively (1S,2R), (1S,2S), (1R,2S) or (1R,2R); wherein, the (1SR,2RS) isomer is an erythro isomer and (1SR,2SR) isomer is a threo isomer.

[14] Where the compound of formula (1) is a free alkali, they can form various salts with various inorganic acids or organic acids.

[15] In one embodiment, the salt is a salt containing a pharmaceutically acceptable anions, for example, hydrochloride, hydrobromide, hydriodide, nitrate, sulfate or hydrosulfate, phosphate or acid phosphate, acetate, lactate, citrate, tartrate, malcate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, methanesulfonate, ethanesulfonate, benzene sulfonate or p-toluenesulfonate, and preferably hydrochloride, hydrobromide, sulfate, trifluoroacetate and methanesulfonate.

[16] In another embodiment, the salt contains 0.5~4 molecules of crystal water.

[17] Preferably, the 1-butyl-2-hydroxyl aralkyl piperazine derivatives are selected from the group consisting of:

VIII-1 (1SR,2RS)-N¹-p-methoxyphenyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl) hydroxyethyl]piperazine,

VIII-2 (1SR,2SR)-N¹-p-methoxyphenyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl) hydroxyethyl]piperazine,

VIII-3 (1SR,2RS)-N¹-o-methoxyphenyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,

VIII-4 (1SR,2SR)-N¹-o-methoxyphenyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl] piperazine,

- VIII-5 (1SR,2RS)-N¹-m-chlorophenyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,
- VIII-6 (1SR,2SR)-N¹-m-chlorophenyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,
- VIII-7 (1SR,2RS)-N¹-(2,3-dimethylphenyl)-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,
- VIII-8 (1SR,2SR)-N¹-(2,3-dimethylphenyl)-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,
- VIII-9 (1SR,2RS)-N¹-benzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,
- VIII-10 (1SR,2SR)-N¹-benzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,
- VIII-11 (1SR,2RS)-N¹-p-nitrobenzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,
- VIII-12 (1SR,2SR)-N¹-p-nitrobenzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,
- VIII-13 (1SR,2RS)-N¹-p-aminobenzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,
- VIII-14 (1SR,2SR)-N¹-p-aminobenzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,
- VIII-15 (1SR,2RS)-N¹-(3',4',5'-trimethoxybenzyl)-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,
- VIII-16 (1SR,2SR)-N¹-(3',4',5'-trimethoxybenzyl)-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,
- VIII-17 (1SR,2RS)-N¹-α-phenemyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,
- VIII-18 (1SR,2SR)-N¹-α-phenemyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,
- VIII-19 (1SR,2RS)-N¹-benzhydryl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-Naphthyl)hydroxyethyl]piperazine,

VIII-20 (1SR,2SR)-N¹-benzhydryl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-Naphthyl)hydroxyethyl]piperazine,

VIII-21 (1SR,2RS)-N¹-cinnamyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-Naphthyl)hydroxyethyl]piperazine,

VIII-22 (1SR,2SR)-N¹-cinnamyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,

IX-23 (1S,2R)-N¹-benzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl] piperazine,

IX-24 (1S,2S)-N¹-benzyl-N⁴-[1-butyl -2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,

IX-25 (1R,2S)-N¹-benzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine, and

IX-26 (1R,2R)-N¹-benzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine.

[18] Most preferred are:

VIII-9 (1SR,2RS)-N¹-benzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,

VIII-10 (1SR,2SR)-N¹-benzyl -N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,

IX-23 (1S,2R)-N¹-benzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,

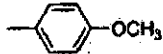
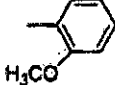
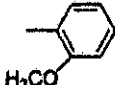
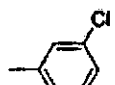
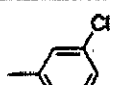
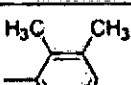
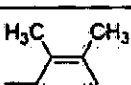
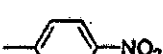
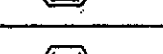
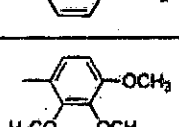
IX-24 (1S,2S)-N¹-benzyl-N⁴-[1-butyl -2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,

IX-25 (1R,2S)-N¹-benzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine, and

IX-26 (1S,2R)-N¹-benzyl-N⁴-[1-butyl -2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine.

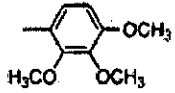
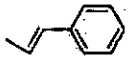
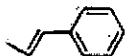
[19] The structures of the compounds are shown in Table 1.

Table 1 the structures of the compounds

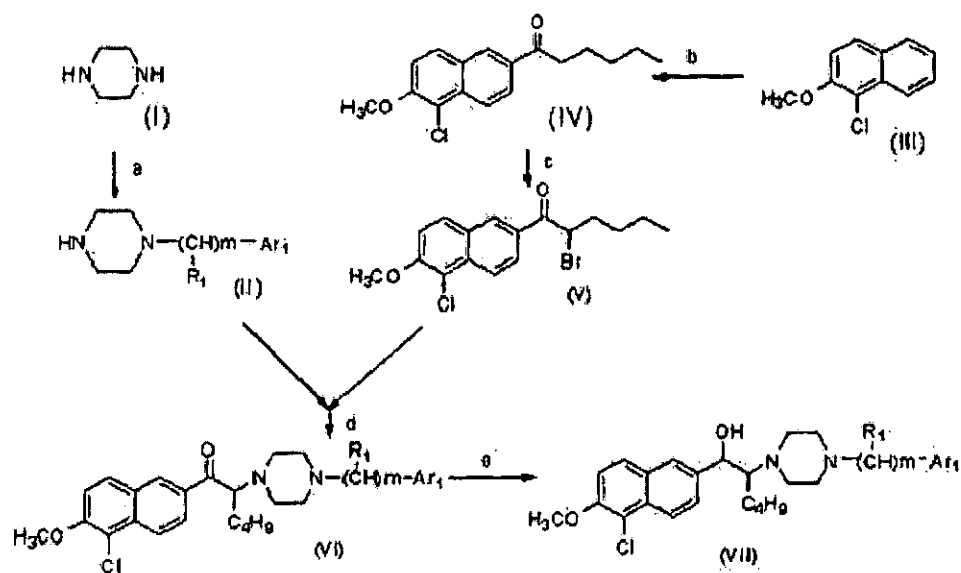
Code	Configuration	Ar ₁	R ₁	m
VIII-1	(1SR,2RS)		H	0
VIII-2	(1SR,2SR)		H	0
VIII-3	(1SR,2RS)		H	0
VIII-4	(1SR,2SR)		H	0
VIII-5	(1SR,2RS)		H	0
VIII-6	(1SR,2SR)		H	0
VIII-7	(1SR,2RS)		H	0
VIII-8	(1SR,2SR)		H	0
VIII-9	(1SR,2RS)	Ph	H	1
VIII-10	(1SR,2SR)	Ph	H	1
VIII-11	(1SR,2RS)		H	1
VIII-12	(1SR,2SR)		H	1
VIII-13	(1SR,2RS)		H	1
VIII-14	(1SR,2SR)		H	1
VIII-15	(1SR,2RS)		H	1

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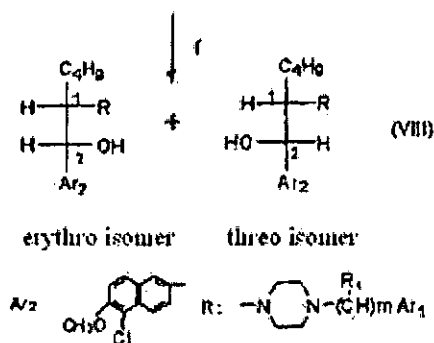
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VIII-16	(1SR,2SR)		H	1
VIII-17	(1SR,2RS)	Ph	CH ₃	1
VIII-18	(1SR,2SR)	Ph	CH ₃	1
VIII-19	(1SR,2RS)	Ph	Ph	1
VIII-20	(1SR,2SR)	Ph	Ph	1
VIII-21	(1SR,2RS)		H	1
VIII-22	(1SR,2SR)		H	1
IX-23	(1S,2R)	Ph	H	1
IX-24	(1S,2S)	Ph	H	1
IX-25	(1R,2S)	Ph	H	1
IX-26	(1R,2R)	Ph	H	1

[20] In one embodiment, the compounds of VIII-1~VIII-22, which are erythro or threo isomer, can be synthesized according to the method below:



- a: $Ar_1 (CH)_m X$, KOH, CTBA, Ph/H₂O
- b: $X-C(=O)-C_6H_{11}$, AlCl₃, CH₂Cl₂
- c: CuBr₂, CHCl₃, EtOAc
- d: K₂CO₃, KI, CH₃COCH₃
- e: NaBH₄, CH₃OH/Al(OiPr)₃, 1-PrOH
- f: separation



[21] Piperazine is used as the starting material. Firstly a nucleophilic substitution reaction with a corresponding halogenated arylalkane is performed to obtain N-monoalkylated compound (II). This reaction is carried out under phase transfer catalytic condition. N-monoalkylation of piperazine may be carried out by reaction with KOH in a reaction media of benzene/water using cetyl trimethylammonium bromide (CTAB) as the phase transfer catalyst, and the yield may be up to 86%. The phase transfer catalyst is the catalyst as reported in Chinese patent ZL02111934.1.

[22] Compound (III) is reacted with corresponding acyl chloride to carry out a Friedel-Crafts reaction to obtain aryl alkanone (IV). This reaction is performed at room temperature, using dichloromethane as the solvent and anhydrous aluminum chloride as the catalyst. The yield is about 80%.

[23] Compound (IV) is bromized to give halogenated aryl alkanone (V). This reaction is performed by heating under refluxing, using CuBr₂ as brominating agent and a mixed solution of chloroform and ethyl acetate as the solvent. The yield is about 85%.

[24] Compound (II) can be reacted with compound (V) to conduct N⁴-alkylation reaction, thereby providing aryl alkanone piperazine compound (VI). The reaction is performed under refluxing for 8-24 hours using K₂CO₃/acetone as reaction system. The yield is 80%.

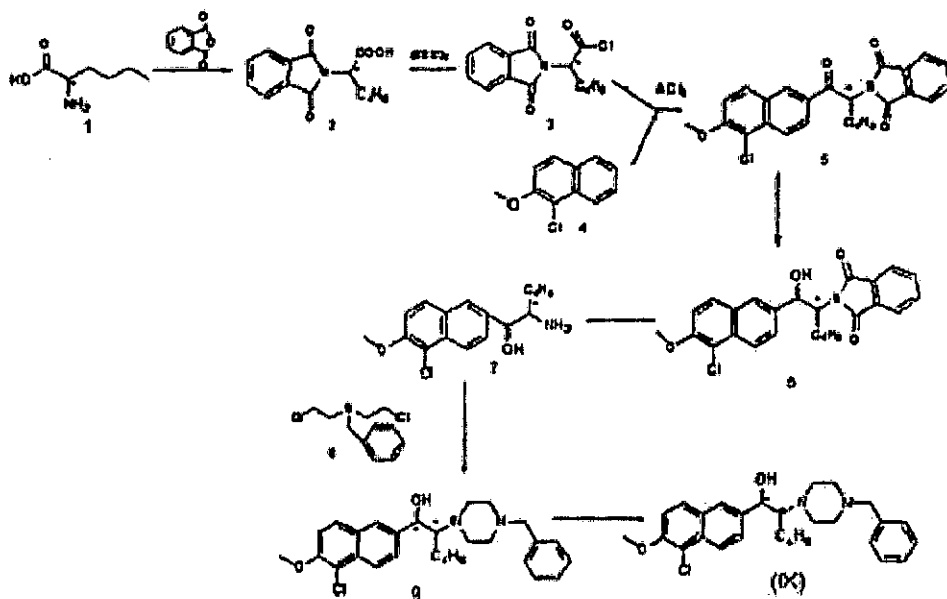
[25] Compound (VI) is reacted with NaBH₄ in methanol at room temperature for 0.5-1 hours, or with aluminium isopropoxide in isopropanol at 60-65°C for 24-48 hours, to reduce carbonyl group, thereby obtaining corresponding aryl alkanol piperazine compound (VII).

[26] The compound (VII) is separated by column chromatography, and the erythro and threo isomers (VIII) of corresponding 1-butyl-2-hydroxyl aralkyl piperazine derivatives are obtained. Compounds VIII-1~VIII-22 of interest can be obtained using the procedures above.

[27] Haloarylalkane compounds in step a, and acyl chloride compound and Compound III in step b are all commercial available, or can be prepared by the conventional methods reported in literatures.

[28] For the optical isomers of Compounds IX-23~IX-26, they can be synthesized by the method below:

[29] Compound 3 is obtained by starting from chiral norleucine 1, protecting amino group with phthaloyl and acylating carboxyl group with oxalyl chloride; then Compound 3 is reacted with Compound 4 to carry out Friedel-Crafts reaction, thereby obtaining compound 5. Compound 5 is reduced by aluminium isopropoxide, and then hydrolyzed to obtain Compound 7. Compound 7 is condensed with Compound 8 to obtain Compound 9, then the optical pure product of interest (IX) is obtained by column chromatography separation. The detailed synthesis scheme is shown as below:



[30] The present invention uses the prochiral method to synthesize the four optical isomers of compound N¹-benzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl) hydroxyethyl]piperazine:

[31] A mixture of (1S,2R) isomer and (1S,2S) isomer is synthesized using

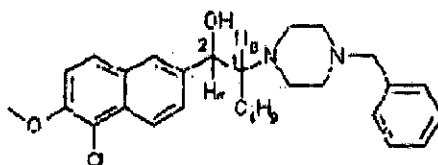
L-norleucine as starting material, then separated by column chromatography with silica gel or alumina as carrier and the solution of methylene chloride and methanol with a volume ratio of 200:1 as eluant, to obtain (1S,2S)-N¹-benzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine (IX-24) and (1S,2R)-N¹-benzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine (IX-23). If D-norleucine is used as starting material, according to the same method, (1S,2S)-N¹-benzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine (IX-25) and (1S,2R)-N¹-benzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine (IX-26) are obtained.

[32] For the synthesis method above, the materials are available, the products need not resolution and are obtained with a high optical purity and a high overall yield. The purity of four optical isomers are determined by high performance liquid chromatography with a chiral column, and enantiomeric excess (ee) thereof are all more than 99%. [Detective condition: OJ-H chiral column (from Daicel industries.Co. Ltd., JP) 4.6 × 250mm; mobile phase: n-hexane:ethanol: diethylamine = 40:60:0.1(v/v/v); ultraviolet wavelength:UV220nm; column temperature:35°C]

[33] The configurations of the four optical isomers can be presumed by the configuration of the starting material and the coupling constant of the product. In the course of reaction, the bonds connecting to the chiral center do not break and the relative size of the groups connected do not change, therefore, the configuration of C1 connecting to N in the final product is the same as that of the starting material norleucine. Furthermore, the configuration of C2 can be presumed by the coupling constant between H_α and H_β connecting to the chiral center. Specifically, the lower coupling constant J_{αβ} represents erythro form, and corresponding configuration of which is (1S,2R) or (1R,2S); the higher coupling constant J_{αβ} represents threo form, and corresponding configuration thereof is (1S,2S) or (1R,2R). The detail is shown in table 2.

[34] The (1S,2R) and (1S,2S) isomers are prepared using L-norleucine as the starting material; and the (1R,2S) and (1R,2R) isomers are prepared using D-norleucine as the starting material.

Table 2 the configurations presumed of the four optical isomers



compound	configuration of norleucine	configuration of C ₁	coupling constant J _{αβ} /Hz	Erythro / Threo	configuration of C ₂	configuration of product
IX-23	L	S	2.0	Erythro	R	1S, 2R
IX-24	L	S	9.6	Threo	S	1S, 2S
IX-25	D	R	2.0	Erythro	S	1R, 2S
IX-26	D	R	9.6	Threo	R	1R, 2R

[35] Monoamine transmitter reuptake inhibition experiment in vitro shows that the 1-butyl-2-hydroxyl aralkyl piperazine derivatives and the optical isomers thereof of the present invention are triple reuptake inhibitors, which has quite strong inhibition effect in vitro on the reuptake of monoamine transmitters DA, NE and 5-HT. The preferred compound VIII-10 has an equivalent in vitro inhibition effect on the reuptake for 5-HT and NA as compared with venlafaxine and SIPIyy24, and has a stronger inhibition activity on the reuptake for DA as compared with venlafaxine, SIPIyy24 and SIPI5286; Compound VIII-9 had a stronger inhibition activity on the reuptake of all the three monoamine transmitters as compared with venlafaxine, SIPIyy24 and SIPI5286.

[36] In vivo antidepressant activity studies in animals shows that: Compound VIII-9 has an equivalent in vivo antidepressant activity as compared with venlafaxine and SIPI5286, and has a significant difference compared with the blank group; and the antidepressant activity in vivo of Compound VIII-10 is stronger than that of venlafaxine and SIPI5286.

[37] Acute toxicity study shows that LD₅₀ (95% confidence limit) of the preferred compound VIII-10 is 1048.5 (751.33~1433.7) mg/kg, MLD(minimum lethal dosage) of VIII-9 is more than 2844.7 mg/kg. Their acute toxicity are less than that of SIPIyy24 (a preferred compound in China Patent ZL02111934.1) and SIPI5286 (a preferred compound in Chinese patent ZL200510030354.1)

[40] The amount administrated is 5-30 mg/kg body weight (oral) or 1-10 mg/kg body weight (injection). The derivatives of the present invention showed OP0011-26-0137.

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[38] Pharmacokinetics study shows that half life of Compound VIII-10 oral administrated is 16.41 hours, which is longer than that of VIII-9 (5.89 hours) and SIP15286 (5.71 hours). The bioavailability of Compound VIII-10 oral administrated is 63.78%, which is higher than that of VIII-9 (16.32%) and SIP15286 (31.63%). Therefore, Compound VIII-10 is of good drugability.

[39] The 1-butyl-2-hydroxyl aralkyl piperazine derivatives of the present invention have triple-inhibition effect on reuptake of 5-HT, NA and DA, and can be used to prepare antidepressants.

[40] The derivatives of the present invention can be administrated to patients in need thereof in the form of composition by the route of oral administration, injection and the like.

[41] The present invention also relates to a method for treating a patient with depression, comprising administering a therapeutically effective amount of derivatives of the invention or the composition containing the same to the patient. The administration route may be oral administration or injection.

[42] The composition contains therapeutically effective amount of derivatives of the present invention as active ingredient, together with one or more pharmaceutically acceptable carriers.

[43] The carrier means conventional carriers in pharmaceutical field, for example, diluents, excipients such as water; adhesive such as cellulose derivatives, gelatin, polyvinylpyrrolidone and the like; fillers such as starch and the like; disintegrating agents such as calcium carbonate, sodium bicarbonate and the like; in addition, other adjuvants such as flavoring agents and sweeteners may be added into the composition.

[44] For oral administration, it may be formulated into conventional solid preparations such as tablet, powder or capsule; for injection administration, it may be formulated into injection solution.

[45] Various preparations of the composition according to the present invention can be prepared using conventional methods in pharmaceutical field, wherein the content of active ingredient is 0.1% to 99.5% (by weight).

[46] The amount administrated in the present invention may vary according to route of administration, age and weight of the patient, type and severity of the disease being treated, and the like, and the daily dose is 5-30 mg/kg body weight (oral) or 1-10 mg/kg body weight (injection). The derivatives of the present invention showed

antagonism against depression in animal trials.

[47] In order to overcome the defect of SIPI5286, structure modification is carried out using SIPI5286 as the lead compound. The present inventor found that, when the substituent group of C1 is fatty hydrocarbon, with the increase of carbon chain from 1 to 4, the erythro and threo isomers of the compounds show better inhibition on reuptake of 5-HT, NA and DA, comparable with SIPIyy24 and the positive control venlafaxine. When the substituent is butyl, that is 1-butyl-2-hydroxyl aralkyl piperazine derivatives of the present invention, the inhibition activity on reuptake of 5-HT, NA and DA of the erythro and threo isomers thereof reach the maximum, higher than that of SIPIyy24, SIPI5286 and the positive control venlafaxine. However, when the substituent of C1 is pentyl, the inhibition activity decreases sharply. When structure qualification was carried out on other compounds in ZL02111934.1, the present inventor found that when the substituent of C1 is butyl, the inhibition activity on reuptake of 5-HT, NA and DA reached the maximum value for all. Therefore, the present inventor considered that 1-butyl-2-hydroxyl aralkyl piperazine derivatives have the strongest activity in the aryl alkanol piperazine derivatives.

[48] The subsequent in vivo study on animals also shows that, compared with aryl alkanol piperazine derivatives disclosed in Chinese patent ZL02111934.1 and the optical isomer disclosed in Chinese patent ZL200510030354.1, the 1-butyl-2-hydroxyl aralkyl piperazine derivatives of the present invention have advantages in stronger activity in antidepression, lower toxicity, higher bioavailability, longer half life and better druggability.

[49] In conclusion, the 1-butyl-2-hydroxyl aralkyl piperazine derivatives in the present invention, compared with current clinically used dual targets depressants (for example, venlafaxine) may have stronger potency, broader indications, lower toxicity and less neurotoxic side reactions. The derivatives have the advantages of stronger activity in antidepression, lower toxicity, higher bioavailability, longer half life and better druggability, compared with aryl alkanol piperazine derivatives disclosed in Chinese patent ZL02111934.1 and optical isomers disclosed in Chinese patent ZL200510030354.1.

Specific Modes for Carrying Out the Invention

general method 1:synthesis of N-aralkyl piperazine hydrochloride(II)

[50] Piperazine hexahydrate (350mmol, from Shanghai chemical reagent station), solid KOH (100mmol) and CTAB(Hexadecyl Trimethylammonium Bromide, 1mmol)

were added to 18 ml water and heated to dissolve. 140 ml solution of aralkyl chloride (100mmol, commercial available) in benzene was added dropwise at the temperature of 70°C. After dropping the reactant was refluxed for 1.5 hours, and allowed to stand and demix, then the organic phase was washed with 50ml water and 50ml saturated NaCl solution respectively, dried with MgSO_4 and filtered. The solvent was evaporated to dryness under reduced pressure, and the concentrate was then dissolved in 50ml absolute alcohol and adjusted to pH of 3 by dropping the solution of $\text{HCl}/\text{C}_2\text{H}_5\text{OH}$. Then solid precipitated and was filtered and dried. N-aralkyl piperazine hydrochloride was obtained by recrystallization in ethanol. The yield was 80%-86%.

general method 2: synthesis of 2-hexanone-5-chloro-6-methoxynaphthalene(IV)

[51] Compound (III) (28.4mmol) was dissolved in dichloromethane (30ml). AlCl_3 (30.8mmol) was added, the reactant was stirred for 1 hour at room temperature. With AlCl_3 dissolving gradually, the color of the solution became darker to light brown. Hexanoyl chloride(23.7mmol) was added dropwise slowly to the mixture, with the temperature controlled below 10°C. After dropping, the reactant was warmed naturally to room temperature and stirred for 1h. The color of the reaction solution became darker to brown. The reaction solution was poured into a mixture of hydrochloric acid (20ml)/crashed ice (50g) under stirring, and the color of organic phase turned lighter to be light yellow to yellow. The organic phase was separated, washed with water (20ml×3) till the aqueous phase being neutral and dried with anhydrous Na_2SO_4 overnight. The desiccant was filtered, the residue was washed with a small amount of dichloromethane. Then the solvent of the filtrate was evaporated, and light yellow oily substance was obtained. The product IV was separated as a light yellow oily product by column chromatography (ethyl acetate: petroleum ether=1:400~1:60), allowed to stand and solidified. The yield was about 80%.

general method 3:

synthesis of 2-(α -bromo-hexanone)-5-chloro-6-methoxynaphthalene(V)

[52] Compound (IV) (21mmol) was dissolved in the mixture of ethyl acetate (50ml) and chloroform (50ml), then CuBr_2 (40.2mmol) was added, the reaction was performed under refluxing for 3 hours. CuBr produced was filtered. The filtrate was washed with water (20ml×3), and dried with anhydrous Na_2SO_4 overnight. The desiccant was filtered, with the residue washed with a small amount of ethyl acetate. The solvent of the filtrate was evaporated. Light yellow crystalline solid was obtained by recrystallization with ethanol. The yield was about 85%.

general method 4:**synthesis of N¹-aralkyl-N⁴-[1-(5'-chloro-6'-methoxyl-2'-naphthoyl)pentyl]****piperazine hydrochloride(VI)**

[53] N-aralkyl piperazine hydrochloride (II) (10mmol), 2-(α -bromo-hexanone)-5-chloro-6-methoxynaphthalene (V) (12mmol), potassium iodide (1mmol) and anhydrous K₂CO₃ (35mmol) were placed into acetone (50ml). The reaction was performed by stirring under refluxing for 8 to 12 hours. After filtered, the solvent was evaporated to dryness under reduced pressure. 50ml water was added, the reactant was extracted with EtOAc (100ml $\times$ 3). The ester layers were pooled and washed with 20ml water and 30ml saturated NaCl solution successively, then dried with MgSO₄. After filtration, the solvent was evaporated. The concentrate was dissolved by adding 30ml of ethanol, and adjusted to a pH of 2 with HCl/C₂H₅OH (5N). The precipitated solid was filtered and recrystallized in ethanol/water or methanol to obtain Compound (VI) in a yield of 60%~85%.

general method 5:**synthesis of N¹-aralkyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)****hydroxyethyl] piperazine hydrochloride(VII)**

[54] Aluminium isopropoxide (35mmol) was dissolved in 80ml of isopropanol, and anhydrous AlCl₃ (3.5mmol) was added. After heated to 45-50°C, the mixture was stirred for 30min until clear, the solution of N¹-aralkyl-N⁴-aralkylacyl alkylpiperazine(10mmol) in isopropanol was added. The temperature was increased to 60-65°C, the reaction was performed until the material spot disappeared (TLC detected, 6-48 hours). Then, 15% of NaOH solution (by weight) was added to adjust to a pH of about 7. Extraction was performed with dichloromethane or ethyl acetate and the extract was washed with saturated NaCl solution (20ml), dried with MgSO₄. After filtration, the solvent of filtrate was evaporated under reduced pressure. The residue was dissolved in 20ml of ethanol, and adjusted to a pH of 2 with HCl/C₂H₅OH. The solid precipitated and was filtered in a yield of 85%~95%.

Example 1

VIII-1 (1SR,2RS)-N¹-p-methoxyphenyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine (erythro form)

[55] 4.2g of N¹-p-methoxyphenyl-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxy naphthalene-2-yl)]ethylpiperazine hydrochloride was synthesized using N¹-p-

methoxyphenylpiperazine (10mmol) and 2-(α -bromo-hexanone)-5-chloro-6-methoxynaphthalene (10mmol), according to general method 2 to general method 4, in a yield of 79%, m.p.=231.5-233.6°C(dec). Then the reduction of carbonyl was performed upon N¹-p-methoxyphenyl-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine according to general method 5, and 3.78g of N¹-p-methoxyphenyl-N⁴-[1-butyl-2-hydroxy-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine hydrochloride was obtained in a yield of 90%. The compound produced was transformed to free alkali thereof and separated by column chromatography to obtain the erythro form, then was dissolved in ethanol, and adjusted to a pH of 2 with HCl/C₂H₅OH(5N). The precipitated solid was filtered, and compound (VIII-1) was obtained by recrystallization in ethanol/water or methanol. Element analysis of the compound showed that 0.5 molecule of crystal water was contained in the compound.

m.p.=221.6-223.2°C(dec). MS : m/z 483 (M⁺).

¹HNMR(DMSO-d₆): δ 0.73-1.66(m, 9H, CH₂CH₂CH₂CH₃), 2.65-2.91(m, 9H, CH+piperazine-H), 3.76(s, 3H, OCH₃), 3.87(s, 3H, OCH₃), 5.0 (d, 1H, CH, J=4.0), 5.17(d, 1H, OH), 6.84-8.04(m,9H, Ar-H)

Example 2

VIII-2 (1SR,2SR)-N¹-p-methoxyphenyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine (threo form)

[56] 4.2g of N¹-p-methoxyphenyl-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine hydrochloride was synthesized using N¹-p-methoxyphenylpiperazine (10mmol) and 2-(α -bromo-hexanone)-5-chloro-6-methoxynaphthalene (10mmol), according to general method 2 to general method 4, in a yield of 79%, m.p.=231.5-233.6°C(dec). Then the reduction of carbonyl was performed upon N¹-p-methoxyphenyl-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine according to general method 5, and 3.78g of N¹-p-methoxyphenyl-N⁴-[1-butyl-2-hydroxy-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine hydrochloride was obtained in a yield of 90%. The compound produced was transformed to free alkali thereof and separated by column chromatography. The threo form was obtained and dissolved in ethanol, and adjusted to a pH of 2 with HCl/C₂H₅OH(5N). The precipitated solid was filtered, and Compound VIII-2 was obtained by recrystallization in ethanol/water or methanol.

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Element analysis of the compound showed that 2 molecules of crystal water were contained in the compound.

m.p=220.4-222.8°C(dec). MS: m/z 483 (M⁺)

¹HNMR(DMSO-d₆): δ 0.65-1.51(m, 9H, CH₂CH₂CH₂CH₃), 2.49-2.97(m, 9H, CH+piperazine-H), 3.78(s, 3H, OCH₃), 3.87(s, 3H, OCH₃), 4.6 (d, 1H, CH, J=8.0), 5.14(d, 1H, OH), 6.86-8.06(m, 9H, Ar-H).

Example 3

VIII-3 (1SR,2RS)-N¹-o-methoxyphenyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine (erythro form)

[57] 4.03g of N¹-o-methoxyphenyl-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxy naphthalene-2-yl)]ethylpiperazine hydrochloride was synthesized using N¹-o-methoxyphenylpiperazine (10mmol) and 2-(α-bromo-hexanone)-5-chloro-6-methoxynaphthalene (10mmol), according to general method 2 to general method 4, in a yield of 78%, m.p=232.4-234.1°C(dec).

[58] Then the reduction of carbonyl was performed upon N¹-o-methoxyphenyl-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxy naphthalene-2-yl)]ethylpiperazine according to general method 5, and 3.58g of N¹-o-methoxyphenyl-N⁴-[1-butyl-2-hydroxy-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine hydrochloride was obtained in a yield of 89%. The compound produced was transformed to free alkali thereof and separated by column chromatography. The erythro form was obtained and dissolved in ethanol, and adjusted to a pH of 2 with HCl/C₂H₅OH(5N). The precipitated solid was filtered, and Compound VIII-3 was obtained by recrystallization in ethanol/water or methanol. Element analysis of the compound showed that 2 molecules of crystal water were contained in the compound.

m.p=227.3-229.1°C(dec). MS: m/z 483 (M⁺).

¹HNMR(DMSO-d₆): δ 0.73-1.66(m, 9H, CH₂CH₂CH₂CH₃), 2.65-2.91(m, 9H, CH+ piperazine-H), 3.76(s, 3H, OCH₃), 3.98(s, 3H, OCH₃), 5.0 (d, 1H, CH, J=4.0), 5.17(d, 1H, OH), 6.84-8.04(m, 9H, Ar-H)

Example 4

VIII-4 (1SR,2SR)-N¹-o-methoxyphenyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-

naphthyl) hydroxyethyl]piperazine (threo form)

[59] 4.03g of N¹-o-methoxyphenyl-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxy naphthalene-2-yl)]ethylpiperazine hydrochloride was synthesized using N¹-o-methoxyphenylpiperazine (10mmol) and 2-(α -bromo-hexanone)-5-chloro-6-methoxynaphthalene(10mmol), according to general method 2 to general method 4, in a yield of 78%, m.p=232.4-234.1°C(dec).

[60] Then the reduction of carbonyl was performed upon N¹-o-methoxyphenyl-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxy naphthalene-2-yl)]ethylpiperazine according to general method 5, and 3.58g of N¹-o-methoxyphenyl-N⁴-[1-butyl-2-hydroxy-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine hydrochloride was obtained in a yield of 89%. The compound produced was transformed to free alkali thereof and separated by column chromatography. The threo form was obtained and dissolved in ethanol, and adjusted to a pH of 2 with HCl/C₂H₅OH(5N). The precipitated solid was filtered, and Compound VIII-4 was obtained by recrystallization in ethanol/water or methanol. Element analysis of the compound showed that 2 molecules of crystal water were contained in the compound.

m.p=223.5-225.0°C(dec). MS: m/z 483 (M⁺).

¹HNMR(DMSO-d₆): δ 0.65-1.51(m, 9H, CH₂CH₂CH₂CH₃), 2.49-2.97(m, 9H, CH+ piperazine-H), 3.78(s, 3H, OCH₃), 3.98(s, 3H, OCH₃), 4.6 (d, 1H, CH, J=8.0), 5.14(d, 1H, OH), 6.86-8.06(m, 9H, Ar-H).

Example 5

VIII-5 (1SR,2RS)-N¹-m-chlorophenyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl) hydroxyethyl]piperazine(crythro form)

[61] 4.20g of N¹-m-chlorophenyl-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxy naphthalene-2-yl)]ethylpiperazine hydrochloride was synthesized using N¹-m-chlorophenylpiperazine (10mmol) and 2-(α -bromo-hexanone)-5-chloro-6-methoxynaphthalene (10mmol), according to general method 2 to general method 4, in a yield of 79%, m.p=231.5-233.6°C(dec).

[62] Then the reduction of carbonyl was performed upon N¹-m-chlorophenyl-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxy naphthalene-2-yl)]ethylpiperazine according to general method 5, and 3.78g of

N^1 -m-chlorophenyl- N^4 -[1-butyl-2-hydroxy-2-(5-chloro-6-methoxynaphthalene-2-yl)] ethylpiperazine hydrochloride was obtained in a yield of 90%. The compound produced was transformed to free alkali thereof and separated by column chromatography. The erythro form was obtained, and then dissolved in ethanol, and adjusted to a pH of 2 with HCl/C₂H₅OH(5N). The precipitated solid was filtered, and Compound VIII-5 was obtained by recrystallization in ethanol/water or methanol.

m.p=224.2-226.8°C(dec). MS: m/z 487 (M⁺).

¹HNMR(DMSO-d₆): δ 0.73-1.66(m, 9H, CH₂CH₂CH₂CH₃), 2.65-2.91(m, 9H, CH+ piperazine-H), 3.76(s, 3H, OCH₃), 5.0 (d, 1H, CH, J=4.0), 5.17(d, 1H, OH), 6.84-8.04(m, 9H, Ar-H)

Example 6

VIII-6 (1SR,2SR)- N^1 -m-chlorophenyl- N^4 -[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine (threo form)

[63] 4.20g of N^1 -m-chlorophenyl- N^4 -[1-butyl-2-carbonyl-2-(5-chloro-6-methoxy naphthalene-2-yl)]ethylpiperazine hydrochloride was synthesized using N^1 -m-chlorophenylpiperazine (10mmol) and 2-(α-bromo-hexanone)-5-chloro-6-methoxynaphthalene(10mmol) according to general method 2 to general method 4, in a yield of 79%, m.p=231.5-233.6°C(dec).

[64] Then the reduction of carbonyl was performed upon N^1 -m-chlorophenyl- N^4 -[1-butyl-2-carbonyl-2-(5-chloro-6-methoxynaphthalene-2-yl)] ethylpiperazine according to general method 5, and 3.78g of N^1 -m-chlorophenyl- N^4 -[1-butyl-2-hydroxy-2-(5-chloro-6-methoxynaphthalene-2-yl)] ethylpiperazine hydrochloride was obtained in a yield of 90%. The compound produced was transformed to free alkali thereof and separated by column chromatography. The threo form was obtained and dissolved in ethanol, and adjusted to a pH of 2 with HCl/C₂H₅OH (5N). The precipitated solid was filtered, and Compound VIII-6 was obtained by recrystallization in ethanol/water or methanol.

m.p=220.4-222.8°C(dec). MS: m/z 487 (M⁺).

¹HNMR(DMSO-d₆): δ 0.65-1.51(m, 9H, CH₂CH₂CH₂CH₃), 2.49-2.97(m, 9H, CH+ piperazine-H), 3.78(s, 3H, OCH₃), 4.6 (d, 1H, CH, J=8.0), 5.14(d, 1H, OH), 6.86-8.06(m, 9H, Ar-H).

Example 7

VIII-7 (1SR,2RS)-N¹-(2,3-dimethylphenyl)-N⁴-[1-butyl-2-(5'-chloro-6'-methoxy-2'-naphthyl)hydroxyethyl]piperazine (erythro form)

[65] 3.80g of N¹-(2,3-dimethylphenyl)-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine hydrochloride was synthesized using N¹-(2,3-dimethylphenyl)piperazine (10mmol) and 2-(α -bromo-hexanone)-5-chloro-6-methoxynaphthalene (10mmol), according to general method 2 to general method 4, in a yield of 80%, m.p.=232.5-235.6°C(dec).

[66] Then the reduction of carbonyl was performed upon N¹-(2,3-dimethylphenyl)-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine according to general method 5, and 3.34g of N¹-(2,3-dimethylphenyl)-N⁴-[1-butyl-2-hydroxy-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine hydrochloride was obtained in a yield of 88%. The compound produced was transformed to free alkali thereof and separated by column chromatography. The erythro form was obtained and dissolved in ethanol, and adjusted to a pH of 2 with HCl/C₂H₅OH(5N). The precipitated solid was filtered, and Compound VIII-7 was obtained by recrystallization in ethanol/water or methanol.

m.p.=218.5-220.8°C(dec). MS: m/z 481 (M⁺).

¹HNMR(DMSO-d₆): δ 0.74-0.77(m, 3H, CH₂CH₂CH₃), 1.13-2.11(m, 6H, CH₂CH₂CH₂CH₃), 2.15 (s, 3H, CH₃), 2.20(s, 3H, CH₃), 2.50-2.87(m, 9H, piperazine-CH), 3.99(s, 3H, OCH₃), 5.06-5.07(m, 1H, CH, J=4.0), 5.18-5.19(d, 1H, OH), 6.83-8.05(m, 8H, Ar-H).

Example 8

VIII-8 (1SR,2SR)-N¹-(2,3-dimethylphenyl)-N⁴-[1-butyl-2-(5'-chloro-6'-methoxy-2'-naphthyl)hydroxyethyl]piperazine (threo form)

[67] 3.80g of N¹-(2,3-dimethylphenyl)-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxy naphthalene-2-yl)]ethylpiperazine hydrochloride was synthesized using N¹-(2,3-dimethylphenyl)piperazine (10mmol) and 2-(α -bromo-hexanone)-5-chloro-6-methoxynaphthalene (10mmol), according to general method 2 to general method 4, in a yield of 80%, m.p.=232.5-235.6°C(dec).

[68] Then the reduction of carbonyl was performed upon

N^1 -(2,3-dimethylphenyl)- N^4 -[1-butyl-2-carbonyl-2-(5-chloro-6-methoxy naphthalene-2-yl)]ethylpiperazine according to general method 5, and 3.34g of N^1 -(2,3-dimethylphenyl)- N^4 -[1-butyl-2-hydroxy-2-(5-chloro-6-methoxy naphthalene-2-yl)]ethylpiperazine hydrochloride was obtained in a yield of 88%. The compound produced was transformed to free alkali thereof and separated by column chromatography. The threo form was obtained and dissolved in ethanol, and adjusted to a pH of 2 with HCl/C₂H₅OH(5N). The precipitated solid was filtered, and Compound VIII-8 was obtained by recrystallization in ethanol/water or methanol.

m.p.=220.4-222.8°C(dec). MS: m/z 481 (M⁺).

¹HNMR(DMSO-d₆): δ 0.66-0.69(m, 3H, CH₂CH₂CH₃), 0.96-1.53(m, 6H, CH₂CH₂CH₂CH₃), 2.17(s, 3H, CH₃), 2.21(s, 3H, CH₃), 2.80-2.96(m, 9H, piperazine -CH), 3.99(s, 3H, OCH₃), 4.59-4.61(m, 1H, CH, J=8.4), 5.14 (d, 1H, OH), 6.83-8.05(m, 8H, Ar-H).

Example 9

VIII-9 (1SR,2RS)- N^1 -benzyl- N^4 -[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine (erythro form)

[69] 4.20g of N^1 -benzyl- N^4 -[1-butyl-2-carbonyl-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine hydrochloride was synthesized using N^1 -benzylpiperazine (10mmol) and 2-(α-bromo-hexanone)-5-chloro-6-methoxynaphthalene (10mmol), according to general method 2 to general method 4, in a yield of 78%, m.p.=241.7-243.3°C (dec). Then the reduction of carbonyl was performed upon N^1 -benzyl- N^4 -[1-butyl-2-carbonyl-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine according to general method 5, and 3.73g of N^1 -benzyl- N^4 -[1-butyl-2-hydroxy-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine hydrochloride was obtained in a yield of 89%. The compound produced was transformed to free alkali thereof and separated by column chromatography. The erythro form was obtained and dissolved in ethanol, and adjusted to a pH of 2 with HCl/C₂H₅OH(5N). The precipitated solid was filtered, and Compound VIII-9 was obtained by recrystallization in ethanol/water or methanol. Element analysis of the compound showed that 2 molecules of crystal water were contained in the compound.

m.p.=225.0-225.8°C(dec). MS: m/z 467 (M⁺).

¹HNMR(DMSO-d₆): δ 0.72-1.60(m, 9H, CH₂CH₂CH₂CH₃), 2.27-2.70(m, 9H,

CH+ piperazine -H), 3.40(s, 2H, CH₂ Ph), 3.98(s, 3H, OCH₃), 5.0 (d, 1H, CH, J=4.4), 5.10(s, 1H, OH), 7.20-8.02(m, 10H, Ar-H).

Example 10

VIII-10 (1SR,2SR)-N¹-benzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine(threo form)

[70] 4.20g of N¹-benzyl-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine hydrochloride was synthesized using N¹-benzylpiperazine (10mmol) and 2-(α -bromo-hexanone)-5-chloro-6-methoxyl naphthalene (10mmol), according to general method 2 to general method 4, in a yield of 78%, m.p.=241.7-243.3 °C(dec). Then the reduction of carbonyl was performed upon N¹-benzyl-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine according to general method 5, and 3.73g of N¹-benzyl-N⁴-[1-butyl-2-hydroxy-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine hydrochloride was obtained in a yield of 89%. The compound produced was transformed to free alkali thereof and separated by column chromatography. The threo form was obtained and dissolved in ethanol, and adjusted to a pH of 2 with HCl/C₂H₅OH(5N). The precipitated solid was filtered, and Compound VIII-10 was obtained by recrystallization in ethanol/water or methanol. Element analysis showed that 2 molecules of crystal water were contained in the compound.

m.p.=223.1-224.3 °C(dec).MS: m/z 467 (M⁺).

¹HNMR(DMSO-d₆): δ 0.66-1.50(m, 9H, CH₂CH₂CH₂CH₃), 2.42-2.84(m, 9H, CH+ piperazine -H), 3.49(s, 2H, CH₂ Ph), 4.02(s, 3H, OCH₃), 4.5(d, 1H, CH, J=8.8), 5.10(s, 1H, OH), 7.26-8.08(m, 10H, Ar-H).

Example 11

VIII-11 (1SR,2RS)-N¹-p-nitrobenzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine (erythro form)

[71] 3.94g of N¹-p-nitrobenzyl-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine hydrochloride was synthesized using N¹-p-nitrobenzylpiperazine (10mmol) and 2-(α -bromo-hexanone)-5-chloro-6-methoxynaphthalene (10mmol), according to general method 2 to general method 4, in a yield of 77%, m.p.=233.5-235.7 °C(dec).

[72] Then the reduction of carbonyl was performed upon N¹-p-nitrobenzyl-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine according to general method 5, and 3.47g of N¹-p-nitrobenzyl-N⁴-[1-butyl-2-hydroxy-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine hydrochloride was obtained in a yield of 88%. The compound produced was transformed to free alkali thereof and separated by column chromatography. The erythro form was obtained and dissolved in ethanol, and adjusted to a pH of 2 with HCl/C₂H₅OH(5N). The precipitated solid was filtered, and Compound VIII-11 was obtained by recrystallization in ethanol/water or methanol.

m.p=228.7-221.0°C(dec). MS: m/z 512 (M⁺).

¹HNMR(DMSO-d₆): δ 0.72-1.60(m, 9H, CH₂CH₂CH₂CH₃), 2.27-2.70(m, 9H, CH+ piperazine -H), 3.40(s, 2H, CH₂ Ph), 3.98(s, 3H, OCH₃), 5.0 (d, 1H, CH, J=4.4), 5.10(s, 1H, OH), 7.20-8.02(m, 9H, Ar-H).

Example 12

VIII-12 (1SR,2SR)-N¹-p-nitrobenzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine (threo form)

[73] 3.94g of N¹-p-nitrobenzyl-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxy naphthalene-2-yl)]ethylpiperazine hydrochloride was synthesized using N¹-p-nitrobenzylpiperazine (10mmol) and 2-(α-bromo-hexanone)-5-chloro-6-methoxyl naphthaline (10mmol), according to general method 2 to general method 4, in a yield of 77%, m.p=233.5-235.7°C(dec).

[74] Then the reduction of carbonyl was performed upon N¹-p-nitrobenzyl-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine according to general method 5. 3.47g of N¹-p-nitrobenzyl-N⁴-[1-butyl-2-hydroxy-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine hydrochloride was obtained in a yield of 88%. The compound produced was transformed to free alkali thereof and separated by column chromatography. The threo form was obtained and dissolved in ethanol, and adjusted to a pH of 2 with HCl/C₂H₅OH(5N). The precipitated solid was filtered, and Compound VIII-12 was obtained by recrystallization in ethanol/water or methanol.

m.p=226.8-229.0°C(dec). MS: m/z 512 (M⁺).

¹HNMR(DMSO-d₆): δ 0.65-1.51(m, 9H, CH₂CH₂CH₂CH₃), 2.49-2.97(m, 9H,

CH+ piperazine -H), 3.78(s, 3H, OCH₃), 4.6 (d, 1H, CH, J=8.0), 5.14(d, 1H, OH), 6.96-8.16(m, 9H, Ar-H).

Example 13

VIII-13 (1SR,2RS)-N¹-p-aminobenzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine (erythro form)

[75] 3.76g of N¹-p-aminobenzyl-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxy naphthalene-2-yl)]ethylpiperazine hydrochloride was synthesized using N¹-p-aminobenzylpiperazine (10mmol) and 2-(α -bromo-hexanone)-5-chloro-6-methoxynaphthalene (10mmol), according to general method 2 to general method 4, in a yield of 78%, m.p.=233.6-235.9°C(dec).

[76] Then the reduction of carbonyl was performed upon N¹-p-aminobenzyl-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxy naphthalene-2-yl)]ethylpiperazine according to general method 5, and 3.27g of N¹-p-aminobenzyl-N⁴-[1-butyl-2-hydroxy-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine hydrochloride was obtained in a yield of 87%. The compound produced was transformed to free alkali thereof and separated by column chromatography. The erythro form was obtained and dissolved in ethanol, and adjusted to a pH of 2 with HCl/C₂H₅OH(5N). The precipitated solid was filtered, and Compound VIII-13 was obtained by recrystallization in ethanol/water or methanol.

m.p.=219.4-221.0°C(dec). MS: m/z 482 (M⁺).

¹HNMR(DMSO-d₆): δ 0.72-1.60(m, 9H, CH₂CH₂CH₂CH₃), 2.27-2.70(m, 9H, CH+ piperazine -H), 3.40(s, 2H, CH₂ Ph), 3.98(s, 3H, OCH₃), 4.0(m, 2H, NH₂), 5.0 (d, 1H, CH, J=4.4), 5.10(s, 1H, OH), 7.20-8.02(m, 9H, Ar-H).

Example 14

VIII-14 (1SR,2SR)-N¹-p-aminobenzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine (threo form)

[77] 3.76g of N¹-p-aminobenzyl-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxy naphthalene-2-yl)]ethylpiperazine hydrochloride was synthesized using N¹-p-aminobenzylpiperazine (10mmol) and 2-(α -bromo-hexanone)-5-chloro-6-methoxynaphthalene (10mmol), according to general method 2 to general method 4, in a yield of 78%, m.p.=233.6-235.9°C(dec).

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[78] Then the reduction of carbonyl was performed upon N¹-p-aminobenzyl-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxy naphthalene-2-yl)] ethylpiperazine according to general method 5, and 3.27g of N¹-p-aminobenzyl-N⁴-[1-butyl-2-hydroxy-2-(5-chloro-6-methoxynaphthalene-2-yl)] ethylpiperazine hydrochloride was obtained in a yield of 87%. The compound produced was transformed to free alkali thereof and separated by column chromatography. The threo form was obtained and dissolved in ethanol, and adjusted to a pH of 2 with HCl/C₂H₅OH(5N). The precipitated solid was filtered, and Compound VIII-14 was obtained by recrystallization in ethanol/water or methanol.

m.p=215.2-218.0°C(dec). MS: m/z 482 (M⁺).

¹HNMR(DMSO-d₆): δ 0.65-1.51(m, 9H, CH₂CH₂CH₂CH₃), 2.49-2.97(m, 9H, CH+ piperazine -H), 3.78(s, 3H, OCH₃), 3.87(s, 3H, OCH₃), 4.0(m, 2H, NH₂), 4.6 (d, 1H, CH, J=8.0), 5.14(d, 1H, OH), 6.86-8.06(m, 9H, Ar-H).

Example 15

VIII-15 (1SR,2RS)-N¹-(3',4',5'-trimethoxybenzyl)-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'- naphthyl)hydroxyethyl]piperazine (erythro form)

[79] 4.18g of N¹-(3',4',5'-trimethoxybenzyl)-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine hydrochloride was synthesized using N¹-(3',4',5'-trimethoxybenzyl)piperazine (10mmol) and 2-(α-bromo-hexanone)-5-chloro-6-methoxynaphthalene (10mmol), according to general method 2 to general method 4, in a yield of 75%, m.p=235.5-238.6°C(dec).

[80] Then the reduction of carbonyl was performed upon N¹-(3',4',5'-trimethoxybenzyl)-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine according to general method 5, and 3.63g of N¹-(3',4',5'- trimethoxybenzyl)-N⁴-[1-butyl-2-hydroxy-2-(5-chloro-6-methoxynaphthalene-2-yl)] ethylpiperazine hydrochloride was obtained in a yield of 87%. The compound produced was transformed to free alkali thereof and separated by column chromatography. The erythro form was obtained and dissolved in ethanol, and adjusted to a pH of 2 with HCl/C₂H₅OH(5N). The precipitated solid was filtered, and Compound VIII-15 was obtained by recrystallization in ethanol/water or methanol.

m.p=221.3-223.6°C(dec). MS: m/z 557 (M⁺).

¹HNMR(DMSO-d₆): δ 0.72-1.60(m, 9H, CH₂CH₂CH₂CH₃), 2.27-2.70(m, 9H,

CH+ piperazine -H), 3.40(s, 2H, CH₂ Ph), 3.70(m, 9H, OCH₃), 3.98(s, 3H, OCH₃), 4.0(m, 2H, NH₂), 5.0 (d, 1H, CH, J=4.4), 5.10(s, 1H, OH), 7.20-8.02(m, 7H, Ar-H).

Example 16

VIII-16 (1SR,2SR)-N¹-(3',4',5'-trimethoxybenzyl)-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine (threo form)

[81] 4.18g of N¹-(3',4',5'-trimethoxybenzyl)-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine hydrochloride was synthesized using N1-(3',4',5'-trimethoxybenzyl)piperazine (10mmol) and 2-(α-bromo-hexanone)-5-chloro-6-methoxynaphthalene (10mmol), according to general method 2 to general method 4, in a yield of 75%, m.p=235.5-238.6°C(dec).

[82] Then the reduction of carbonyl was performed upon N¹-(3',4',5'-trimethoxybenzyl)-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine according to general method 5, and 3.63g of N¹-(3',4',5'-trimethoxybenzyl)-N⁴-[1-butyl-2-hydroxy-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine hydrochloride was obtained in a yield of 87%. The compound produced was transformed to free alkali thereof and separated by column chromatography. The threo form was obtained and dissolved in ethanol, and adjusted to a pH of 2 with HCl/C₂H₅OH(5N). The precipitated solid was filtered, and Compound VIII-16 was obtained by recrystallization in ethanol/water or methanol.

m.p=226.5-228.8°C(dec). MS: m/z 557 (M⁺).

¹HNMR(DMSO-d₆): δ 0.65-1.51(m, 9H, CH₂CH₂CH₂CH₃), 2.49-2.97(m, 9H, CH+ piperazine -H), 3.70(m, 9H, OCH₃), 3.78(s, 3H, OCH₃), 3.87(s, 3H, OCH₃), 4.6 (d, 1H, CH, J=8.0), 5.14(d, 1H, OH), 6.86-8.06(m, 7H, Ar-H).

Example 17

VIII-17 (1SR,2RS)-N¹-α-phenemyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine (erythro form)

[83] 4.22g of N¹-α-phenemyl-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine hydrochloride was synthesized using N¹-α-phenemyl piperazine (10mmol) and 2-(α-bromo-hexanone)-5-chloro-6-methoxynaphthalene (10mmol), according to general method 2 to general method 4, in a yield of 78%, m.p=241.7-243.3°C(dec).

[84] Then the reduction of carbonyl was performed upon N¹- α -phenemyl-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine according to general method 5, and 3.75g of N¹- α -phenemyl-N⁴-[1-butyl-2-hydroxy-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine hydrochloride was obtained in a yield of 89%. The compound produced was transformed to free alkali thereof and separated by column chromatography. The erythro form was obtained and dissolved in ethanol, and adjusted to a pH of 2 with HCl/C₂H₅OH(5N). The precipitated solid was filtered, and Compound VIII-17 was obtained by recrystallization in ethanol/water or methanol.

m.p=235.0-237.6°C (dec). MS: m/z 481.1 (M⁺).

¹HNMR(DMSO-d₆): δ 0.54-0.63(m, 3H, CH₂CH₂CH₃), 0.78-1.24(m, 6H, CH₂CH₂CH₂CH₃), 1.57-1.75(m, 3H, CHCH₃), 1.83-1.86(m, 2H, CH₂CH₂CH₂CH₃), 3.44-3.59(m, 8H, piperazine -H), 3.99(s, 3H, OCH₃), 4.57(m, 1H, CH₃-CH-Ph), 4.57(m, 1H, CH), 5.66-5.67(d, 1H, CH, J=4.8), 7.48-8.11(m, 10H, Ar-H).

Example 18

VIII-18 (1SR,2SR)-N¹- α -phenemyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine (threo form)

[85] 4.22g of N¹- α -phenemyl-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine hydrochloride was synthesized using N¹- α -phenemylpiperazine (10mmol) and 2-(α -bromo-hexanone)-5-chloro-6-methoxynaphthalene(10mmol), according to general method 2 to general method 4, in a yield of 78%, m.p=241.7-243.3°C(dec).

[86] Then the reduction of carbonyl was performed upon N¹- α -phenemyl-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine according to general method 5, and 3.75g of N¹- α -phenemyl-N⁴-[1-butyl-2-hydroxy-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine hydrochloride was obtained in a yield of 89%. The compound produced was transformed to free alkali thereof and separated by column chromatography. The threo form was obtained and dissolved in ethanol, and adjusted to a pH of 2 with HCl/C₂H₅OH(5N) The precipitated solid was filtered, and Compound VIII-18 was obtained by recrystallization in ethanol/water or methanol. m.p=224.0-226.1°C. MS: m/z 481 (M⁺).

^1H NMR(DMSO- d_6): δ 0.61-0.65(m, 3H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.88-1.06(m, 6H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.28-1.29(m, 3H, CHCH_3), 2.33-2.76(m, 8H, piperazine), 2.50-2.510(m, 1H, CH-N), 3.25-3.39(m, 1H, $\text{CH}_3\text{-CH-Ph}$), 3.99(s, 3H, OCH_3), 4.47-4.51(m, 1H, CH, $J=8.4$), 5.05(d, 1H, OH), 7.23-8.03(m, 10H, Ar-H).

Example 19

VIII-19 (1SR,2RS)- N^1 -benzhydryl- N^4 -[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine (erythro form)

[87] 4.68g of N^1 -benzhydryl- N^4 -[1-butyl-2-carbonyl-2-(5-chloro-6-methoxy naphthalene-2-yl)]ethylpiperazine hydrochloride was synthesized using N^1 -benzhydryl piperazine (10mmol) and 2-(α -bromo-hexanone)-5-chloro-6-methoxyl naphthalene (10mmol), according to general method 2 to general method 4, in a yield of 76%, m.p.=212.9-215.2 $^\circ\text{C}$ (dec).

[88] Then the reduction of carbonyl was performed upon N^1 -benzhydryl- N^4 -[1-butyl-2-carbonyl-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethyl piperazine according to general method 5, and 4.83g of N^1 -benzhydryl- N^4 -[1-butyl-2-hydroxy-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine hydrochloride was obtained in a yield of 85%. The compound produced was transformed to free alkali thereof and separated by column chromatography. The erythro form was obtained and dissolved in ethanol, and adjusted to a pH of 2 with $\text{HCl}/\text{C}_2\text{H}_5\text{OH}(5\text{N})$. The precipitated solid was filtered, and Compound VIII-19 was obtained by recrystallization in ethanol/water or methanol. m.p.=183.0-184.6 $^\circ\text{C}$ (dec). MS : m/z 543 (M^+).

^1H NMR(DMSO- d_6): δ 0.71-1.60(m, 9H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2.24-2.74(m, 9H, CH+ piperazine -H), 4.22(s, 1H, CH Ph_2), 3.98(s, 3H, OCH_3), 5.0 (d, 1H, CH, $J=3.6$), 5.11(d, 1H, OH), 7.14-8.01(m, 15H, Ar-H).

Example 20

VIII-20 (1SR,2SR)- N^1 -benzhydryl- N^4 -[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine (threo form)

[89] 4.68g of N^1 -benzhydryl- N^4 -[1-butyl-2-carbonyl-2-(5-chloro-6-methoxy naphthalene-2-yl)]ethylpiperazine hydrochloride was synthesized using N^1 -benzhydryl piperazine (10mmol) and 2-(α -bromo-hexanone)-5-chloro-6-methoxyl

naphthalene (10mmol), according to general method 2 to general method 4, in a yield of 76%, m.p.=212.9-215.2°C(dec).

[90] Then the reduction of carbonyl was performed upon N¹-benzhydryl-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine according to general method 5, and 4.13g of N¹-benzhydryl-N⁴-[1-butyl-2-hydroxy-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine hydrochloride was obtained in a yield of 85%. The compound produced was transformed to free alkali thereof and separated by column chromatography. the threo form was obtained and dissolved in ethanol, and adjusted to a pH of 2 with HCl/C₂H₅OH(5N).The precipitated solid was filtered, and Compound VIII-20 was obtained by recrystallization in ethanol/water or methanol. m.p.=179.3-181.1°C(dec). MS: m/z 543 (M⁺).

¹HNMR(DMSO-d₆): δ 0.63-1.46(m, 9H, CH₂CH₂CH₂CH₃), 2.33-2.82(m, 9H, CH+ piperazine -H), 4.28(s, 1H, CH Ph₂), 3.98(s, 3H, OCH₃), 4.5 (d, 1H, CH, J=8.4), 5.06(s, 1H, OH), 7.16-8.03(m, 15H, Ar-H).

Example 21

VIII-21 (1SR,2RS)-N¹-cinnamyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine (erythro form)

[91] 4.61g of N¹-cinnamyl-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine hydrochloride was synthesized using N¹-cinnamylpiperazine (10mmol) and 2-(α-bromo-hexanone)-5-chloro-6-methoxynaphthalene (10mmol), according to general method 2 to general method 4, in a yield of 82%, m.p.=232.2-234.0°C(dec).

[92] Then the reduction of carbonyl was performed upon N¹-cinnamyl-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine according to general method 5, and 4.19g of N¹-cinnamyl-N⁴-[1-butyl-2-hydroxy-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine hydrochloride was obtained in a yield of 91%. The compound produced was transformed to free alkali thereof and separated by column chromatography. The erythro form was obtained and dissolved in ethanol, and adjusted to a pH of 2 with HCl/C₂H₅OH(5N). The precipitated solid was filtered, and Compound VIII-21 was obtained by recrystallization in ethanol/water or methanol. m.p.=228.8-230.1°C(dec).MS : m/z 493 (M⁺).

¹HNMR(DMSO-d₆): 0.73-1.60(m, 9H, CH₂CH₂CH₂CH₃), 2.31-3.04(m, 11H, CH+ CH₂+ piperazine -H), 3.98(s, 3H, OCH₃), 4.9 (d, 1H, CH, J=4.0), 5.11(d, 1H, OH), 6.23-6.52(m, 2H, CH=CH), 7.22-8.02(m, 10H, Ar-H).

Example 22

VIII-22 (1SR,2SR)-N¹-cinnamyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine (threo form)

[93] 4.61g of N¹-cinnamyl-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine hydrochloride was synthesized using N¹-cinnamyl piperazine (10mmol) and 2-(α-bromo-hexanone)-5-chloro-6-methoxynaphthalene (10mmol), according to general method 2 to general method 4, in a yield of 82%, m.p=232.2-234.0°C(dec).

[94] Then the reduction of carbonyl was performed upon N¹-cinnamyl-N⁴-[1-butyl-2-carbonyl-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethyl piperazine according to general method 5, and 4.19g of N¹-cinnamyl-N⁴-[1-butyl-2-hydroxy-2-(5-chloro-6-methoxynaphthalene-2-yl)]ethylpiperazine hydrochloride was obtained in a yield of 91%. The compound produced was transformed to free alkali thereof and separated by column chromatography. The threo form was obtained and dissolved in ethanol, and adjusted to a pH of 2 with HCl/C₂H₅OH(5N). The precipitated solid was filtered, and Compound VIII-22 was obtained by recrystallization in ethanol/water or methanol. m.p=194.1-195.6°C(dec). MS : m/z 493 (M⁺).

¹HNMR(DMSO-d₆): δ 0.36-1.49(m, 9H, CH₂CH₂CH₂CH₃), 2.43-3.27(m, 11H, CH+ CH₂+ piperazine -H), 3.98(s, 3H, OCH₃), 4.5 (d, 1H, CH, J=8.0), 5.18(s, 1H, OH), 6.24-6.55(m, 2H, CH=CH), 7.21-8.05(m, 10H, Ar-H).

Example 23

Synthesis of (S)-2-(1,3-dicarbonylisoindole)hexanoic acid (2)

[95] 6.55g of L-norleucine(0.05mol), 7.40g of phthalic anhydride (0.05mol), 0.8ml of triethylamine were added into 150ml of toluene under stirring at 110°C. After reaction by refluxing for 24 hours, the reaction was complete. The solvent was evaporated after standing to cool down, and 50ml of water was added. Extraction was performed

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with ethyl acetate(50ml×3), and the ethyl acetate layer was washed with saturated NaCl solution, dried by anhydrous MgSO_4 . The solvent of the filtrate was evaporated after filtrating the mixture, and 12.28g of white solid was obtained in a yield of 90.3%. MS: m/z 262(M^+). ^1H NMR(DMSO- d_6): δ 0.86-1.37(m, 9H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 4.46(m, 1H, CH), 7.25-7.86(m, 4H, Ar-H).

Example 24

[96] Preparation of (R)-2-(1,3-dicarbonylisoindole)hexanoic acid was same as that of (S)-2-(1,3-dicarbonylisoindole)hexanoic acid (2). The yield was 87.6%.

MS: m/z 262(M^+). ^1H NMR(DMSO- d_6): δ 0.90-1.25(m, 9H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 4.68(m, 1H, CH), 7.42-7.91(m, 4H, Ar-H).

Example 25

Synthesis of (S)-2-[2-(1,3-dicarbonylisoindole)hexanoyl]-5-chloro-6-methoxynaphthalene (5)

[97] 10.45g of Compound 2 (0.04mol) was dissolved in 100ml of dichloromethane at 0°C , and 8.15ml (0.1mol) of oxalyl chloride was added dropwise in ice-bath. After dropping, 8 drops of pyridine was added. The temperature increased slowly to room temperature and the mixture was stirred for 20 hours. Superfluous acyl chloride and solvent was evaporated by rotary evaporation at 35°C , the concentrate was dissolved in 100ml of dichloromethane. 9.25g of Compound 4 (0.048mol) and 6.41g of anhydrous AlCl_3 (0.048mol) were added to react for 30 hours at room temperature. The reactant was pooled slowly into the mixture of 1N HCl(100ml)/ice/dichloromethane (100ml), stirred and stood to allow layers separated. The aqueous layer was extracted with dichloromethane(100ml × 2). The dichloromethane layers were pooled, then washed with saturated NaCl solution, dried by anhydrous MgSO_4 . The solvent of the filtrate was evaporated after filtration. Dark brown oily substance was obtained, and separated by column chromatography (neutral alumina, petroleum ether:ethyl acetate=3:1). 4.68g of light yellow oily substance was obtained in a yield of 26.8%. MS: m/z 438(M^+). ^1H NMR(DMSO- d_6): δ 0.96-1.77(m, 9H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 3.73(s, 3H, OCH_3), 5.09(m, 1H, CH), 7.64-8.34(m, 9H, Ar-H).

Example 26

[98] Preparation of (R)-2-[2-(1,3-dicarbonylisoindole)hexanoyl]-5-chloro-6-methoxynaphthalene

naphthalene was same as that of (S)-2-[2-(1,3-dicarbonylisoindole)hexanoyl]-5-chloro-6-methoxynaphthalene(5) in a yield of 28.4%. MS: m/z 438(M⁺). ¹HNMR(DMSO-d₆): δ 1.03-1.62(m, 9H, CH₂CH₂CH₂CH₃), 3.10(s, 3H, OCH₃), 5.14 (m, 1H, CH), 7.35-8.11 (m, 9H, Ar-H).

Example 27

Synthesis of (2S)-2-[1-hydroxy-2-(1,3-dicarbonylisoindole)hexyl]-5-chloro-6-methoxynaphthalene (6)

[99] 4.36 g of Compound 5(0.01mol) was dissolved in the mixture of 19.2ml of toluene and 12.6ml of isopropanol, then 10.2g (0.05mol) of aluminium isopropoxide was added to react at 100°C for 4 hours. After the reaction was complete, the mixture was cooled down, the solvent was evaporated, and 1N of HCl (50ml) was added. Extraction was performed with ethyl acetate (50ml × 3). The ethyl acetate layer was washed with a small amount of water and saturated NaCl solution, dried by anhydrous MgSO₄. The solvent was evaporated after filtration, and 4.32g of light yellow solid was obtained in a yield of 98.6%. MS: m/z 439(M⁺). ¹HNMR(DMSO-d₆): δ 0.96-1.58(m, 9H, CH₂CH₂CH₂CH₃), 3.73(s, 3H, OCH₃), 4.05(m, 1H, CHN), 5.12 (m, 1H, CHOH), 7.34-8.08 (m, 9H, Ar-H).

Example 28

[100] Preparation of (2R)-2-[1-hydroxy-2-(1,3-dicarbonylisoindole)hexyl]-5-chloro-6-methoxynaphthalene was same as that of (2S)-2-[1-hydroxy-2-(1,3-dicarbonylisoindole)hexyl]-5-chloro-6-methoxynaphthalene (6) in a yield of 97.4%. MS: m/z 439(M⁺). ¹HNMR(DMSO-d₆): δ 0.89-1.44 (m, 9H, CH₂CH₂CH₂CH₃), 3.70(s, 3H, OCH₃), 4.19(m, 1H, CHN), 5.07 (m, 1H, CHOH), 7.12-8.00 (m, 9H, Ar-H).

Example 29

Synthesis of (1S)-2-(5-chloro-6-methoxynaphthalene)-2-hydroxy-1-butyl ethylamine (7)

[101] 2.15g of Compound 6(0.005mol) was dissolved in 15ml of methanol, 5ml of hydrazine hydrate (0.01mol) was added. The mixture was stirred for 3 hours at room temperature and white solid was produced. After filtration, the solvent of filtrate was evaporated, and extraction was performed with water(20ml)/dichloromethane(20ml × 3). The pooled dichloromethane layer was washed with saturated NaCl solution, dried

with anhydrous MgSO_4 . After filtration, the solvent of filtrate was evaporated, and 1.13g of white solid was obtained in a yield of 73.4%. MS: m/z 309 (M^+). ^1H NMR(DMSO- d_6): δ 0.93-1.54(m, 9H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 3.08(m, 1H, CHN), 3.77(s, 3H, OCH_3), 4.75 (m, 1H, CHOH), 7.50-8.17 (m, 5H, Ar-H).

Example 30

[102] Preparation of (1R)-2-(5-chloro-6-methoxynaphthalene)-2-hydroxy-1-butylethyl amine was same as that of (1S)-2-(5-chloro-6-methoxynaphthalene)-2-hydroxy-1-butylethylamine (7) in a yield of 70.1%. MS: m/z 309 (M^+). ^1H NMR(DMSO- d_6): δ 1.11-1.77(m, 9H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 3.14(m, 1H, CHN), 3.58(s, 3H, OCH_3), 4.69 (m, 1H, CHOH), 7.75-8.29 (m, 5H, Ar-H).

Example 31

Preparation of (1S,2R)- N^1 -benzyl- N^4 -[1-butyl-2-hydroxy-2-(5'-chloro-6'-methoxyl-2')-naphthylethyl]piperazine hydrochloride (IX-23) and (1S,2S)- N^1 -benzyl- N^4 -[1-butyl-2-hydroxy-2-(5'-chloro-6'-methoxyl-2')-naphthylethyl]piperazine hydrochloride (IX-24).

[103] To 0.924g of compound 7(0.003mol) were added 10ml of acetonitrile, 2ml of triethylamine and 1.624g of compound 8(0.007mol, prepared c.f. patent US4748726), the mixture was heated and refluxed for 20 hours till the reaction was complete detected by TLC. Acetonitrile was evaporated, extraction was performed with chloroform(50ml $\times$ 3) and water. The chloroform layers was pooled and dried by MgSO_4 . Chloroform was evaporated, and yellow oily substance was obtained, which was the mixture of two isomers (9). MS: m/z 465(M^+).

[104] The mixture (9) was separated by silica gel column chromatography with dichloromethane: methanol=200:1 as the eluant. 0.47g of yellow oily (1S,2S) isomer (yield:34%) was firstly eluted and dissolved in 20ml of methanol. Hydrochloric acid/ethanol was used to adjust the pH to 2. White solid precipitated, and 0.25g of white product was obtained by filtration.

[105] 0.12g of yellow oily (1S,2R) isomer (yield:8.5%) was eluted later and dissolved in 10ml of methanol. Hydrochloric acid/ethanol was used to adjust the pH to 2. Light yellow solid precipitated, and 0.05g of yellow product was obtained by filtration and heating to dryness.

IX-23: mp: 225.0 ~ 225.8 $^\circ\text{C}$ (dec); MS: m/z 467 (M^+); ^1H NMR(DMSO- d_6): δ

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0.36-1.86(m, 9H, CH₂CH₂CH₂CH₃), 3.54-3.80(m, 9H, CH+piperazine-H), 3.96(s, 2H, CH₂-Ph), 4.42(s, 3H, OCH₃), 5.519-5.524 (d, 1H, CH, J=2.0), 7.43-8.14(m, 10H, Ar-H).

IX-24: mp: 223.1 ~ 224.3 °C(dec); MS: m/z 467 (M⁺); ¹HNMR(DMSO-d₆): δ 0.33-1.58(m, 9H, CH₂CH₂CH₂CH₃), 3.62-3.79(m, 9H, CH+ piperazine-H), 3.95(s, 2H, CH₂-Ph), 4.42(s, 3H, OCH₃), 4.913-4.937(d, 1H, CH, J=9.6), 7.43-8.17(m, 10H, Ar-H).

Example 32

[106] Preparation of (1S,2S)-N¹-benzyl-N⁴-[1-butyl-2-hydroxy-2-(5'-chloro-6'-methoxyl-2')-naphthylethyl]piperazine hydrochloride (IX-25) and (1S,2R)-N¹-benzyl-N⁴-[1-butyl-2-hydroxy-2-(5'-chloro-6'-methoxyl-2')-naphthylethyl]piperazine hydrochloride(IX-26) were same as Example31.

IX-25: mp: 225.0 ~ 225.8 °C(dec); MS: m/z 467 (M⁺); ¹HNMR(DMSO-d₆): δ 0.36-1.86(m, 9H, CH₂CH₂CH₂CH₃), 3.54-3.80(m, 9H, CH+ piperazine-H), 3.96(s, 2H, CH₂-Ph), 4.42(s, 3H, OCH₃), 5.519-5.524 (d, 1H, CH, J=2.0), 7.43-8.14(m, 10H, Ar-H).

IX-26: mp: 223.1 ~ 224.3 °C(dec); MS: m/z 467 (M⁺); ¹HNMR(DMSO-d₆): δ 0.33-1.58(m, 9H, CH₂CH₂CH₂CH₃), 3.62-3.79(m, 9H, CH+ piperazine-H), 3.95(s, 2H, CH₂-Ph), 4.42(s, 3H, OCH₃), 4.913-4.937(d, 1H, CH, J=9.6), 7.43-8.17(m, 10H, Ar-H).

Example 33

Tablet:

derivative of the present invention	10mg
sucrose	150mg
corn starch	38mg
calcium stearate	2mg

[107] Preparation: the active ingredient was mixed with sucrose and corn starch, then the mixture was wetted by adding water, stirred evenly, dried, crushed and screened, then calcium stearate was added. The mixture obtained was stirred evenly and then pressed into tablets. The tablet weight was 200mg per tablet, containing 10mg of active ingredient.

Example 34

Injection:

Derivative of the present invention	20mg
water for injection	80mg

[108] Preparation: the active ingredient was dissolved and mixed evenly with water for injection, then filtered. The mixture obtained was distributed into ampoules under sterile conditions. The weight was 10mg ampoule per ampoule, containing 2mg of active ingredient.

Example 35

Inhibition effect of the compounds on the reuptake of 5-HT, NA and DA by brain synaptosomes

[109] Studies on the reuptake of monoamine neurotransmitters by brain synaptosomes was performed, which is a currently important mean adopted in the worldwide in pharmacological studies of central nervous. This method can not only be used to study the action mechanism of a drug, but also be used for screening new drugs acting by this mechanism. In the present invention, studies on the inhibition effect of the compounds on the reuptake of 5-HT, NA and DA by brain synaptosomes was performed, using venlafaxine (an effective dual inhibitor on the reuptake of 5-HT and NA) and 6-hydroxy DA as the positive controls.

1. Preparation of rat brain synaptosomes

[110] Male SD rats were sacrificed by cervical dislocation and then the brains thereof were taken out rapidly by decollation and placed on ice. Related brain tissues (for [^{3} H]5-HT and [^{3} H]NA reuptake experiment, prefrontal cortex was taken; for [^{3} H]DA reuptake experiment, striatum was taken) were separated and weighed. 10 times (V/W) of 0.32mol/L ice-cold sucrose solution was added and was homogenized electrically with glass-teflon. The homogenate was centrifugated at 4 °C at 1000g×10min. Then the supernatant was taken and centrifugated at 4 °C at 17000g×20min. The precipitation was suspended in 30 volume of KRH Buffer (125mM NaCl, 4.8mM KCl, 1.2mM CaCl₂, 1.2mM MgSO₄, 1.0mM KH₂PO₄, 22mM NaHCO₃, 25mM HEPES, 10mM Glucose, 10 μM Pargyline, 0.2mg/ml Ascorbic Acid) and then was preserved in an ice bath for use. (for NA reuptake experiment, the cortex needed was suspended in 20 volume of KRH Buffer)

2. [^{3} H]5-HT/NA/DA reuptake experiments

[111] Stock solution of the test substance was thawed immediately before use and diluted with KBH Buffer to 100 μ mol/L. 50 μ l thereof was added in 500 μ l of total reaction system, and the final concentration was 10 μ mol/L. Then 50 μ l suspended synaptic prepared above was added and mixed evenly, incubated in water bath for 30min at 37°C. Then 10nmol/L [^{3} H] 5-HT (50nmol/L [^{3} H]DA or 60nmol/L [^{3} H]NA) was added. After incubated at 37°C for 10min, the reaction system was immediately taken out and the reaction was stopped by adding 2ml of ice-cold 150mmol/L Tris-HCl buffer solution. The samples were collected on the circular fiberglass membrane by vacuum filtration, and the membrane was washed 3 times with 3ml of ice-cold Tris-HCl buffer solution. The filtration membrane was removed, baked for 15min in a far-infrared oven and placed into an EP tube. 1.5ml scintillation fluid was added overnight and was tested by liquid scintillation counter. For the solvent control total binding tube and the non-specific binding tube, no test substance was added; for the total binding tube, 50 μ l solvent was added.

3. Results:

[112] Taking the inhibitory rate of 0.1mM of venlafaxine and 6-hydroxy DA on reuptake of monoamine as 100%, the inhibitory intensity of the compounds, compared with venlafaxine and 6-hydroxy DA was shown in Table 3.

Table 3 inhibitory percent (%) on reuptake of 5-HT, NA and DA by brain synaptosomes

compounds	Inhibition on the reuptake of 5-HT(%)	Inhibition on the reuptake of NA(%)	Inhibition on the reuptake of DA(%)
venlafaxine	100	100	/
6-hydroxy DA	/	/	100
VIII-3	65.1	144	96
VIII-4	23	146.5	68
VIII-9	125	155.2	117
VIII-10	136	145	133
VIII-19	73.4	103.6	95
VIII-20	0	78	57

VIII-21	81	87.5	90
VIII-22	82.3	78.9	94

4. Conclusion

[113] The 1-butyl-2-hydroxy aralkyl piperazine derivatives of the present invention, were triple reuptake inhibitors, which have strong in vitro inhibition on the reuptake of monoamine transmitters DA, NE and 5-HT. The triple reuptake-inhibition activity of preferred compounds VIII-9 and VIII-10 were stronger than that of the positive control venlafaxine.

Example 36

determination of IC_{50} of preferred compounds VIII-9 and VIII-10 for inhibiting reuptake of 5-HT, NA and DA by brain synaptosomes

1. Preparation of rat brain synaptosomes (the same as Example 35)

2. Research on reuptake inhibition (IC_{50}) on [^3H]5-HT/NA/DA

[114] The compounds were used for the studies on inhibition effect (IC_{50}) on reuptake of [^3H]5-HT/NA/DA. At least 5 concentrations each time were settled for each test compound. Each concentration was determined by the average of double twin tubes and the test was repeated for more than 3 times. A series of concentrations of the compounds were prepared by gradient dilution before use. 50 μ l thereof was added in total reaction system. Then 50 μ l suspended synaptic membrane was added and mixed evenly, incubated in water bath at 37°C for 30min. Then 10nmol/L [^3H] 5-HT (or 50nmol/L [^3H]DA or 40nmol/L [^3H]NA) was added and incubated in water bath at 37°C for 10min (for [^3H]NA, incubated for 5min). For the [^3H]5-HT reuptake experiment, 50 μ L of fluoxetine (100 μ mol/L) was added to the non-specific binding tube; for the [^3H]DA reuptake experiment, 50 μ L of cocaine (600 μ mol/L) was added to the non-specific binding tube; for the [^3H]NA reuptake experiment, 50 μ L of desipramine (100 μ mol/L) was added to the non-specific binding tube; for the solvent control, solvent was added to the total binding tube, but no test compound added.

3. Data processing

[115] specific binding CPM value for each test sample tube = total binding CPM value for each test sample tube - non-specific binding CPM value for each test sample tube; inhibition rate of the compound (%) on the reuptake of [^3H]5-HT/NA/DA by prefrontal cortex and striatum = 100% - specific binding for each test sample tube (CPM value)/solvent specific binding (CPM value) $\times$ 100%. Sigmoidal curve fitting

was performed for the data obtained from all of the test drugs by Origin 6.1, and the IC_{50} value was calculated.

4. IC_{50} determination results

[116] Inhibition of the compounds (IC_{50}) on the reuptake of 5-HT, NA and DA by prefrontal cortex and striatum was shown in Table 4.

Table 4 inhibition effect of the compounds on the reuptake of [^3H]5-HT/NA/DA
 IC_{50} (mean $\pm$ SE, n=3-4)

compounds	IC_{50} (nmol/L)		
	[^3H]5-HT	[^3H]NA	[^3H]DA
venlafaxine	145	1420	3070
SIPIyy24	200	1000	No activity detected
SIP15286	12	185	1150
VIII-9	73.28	2.8	2.1
VIII-10	271.51	4726.1	165.4

note: Compound SIPIyy24 was the preferred compound in Patent ZL02111934.1;

Compound SIP15286 was the preferred compound in Patent ZL200510030354.1.

5. Conclusion

[117] Compound VIII-10 had a comparable in vitro inhibition activity on the reuptake of 5-HT and NA, compared with venlafaxine and SIPIyy24, and had a stronger inhibition activity on the reuptake of DA, compared with venlafaxine, SIPIyy24 and SIP15286; Compound VIII-9 had a stronger inhibition activity on the reuptake of the three kinds of monoamine transmitters, compared with venlafaxine, SIPIyy24 and SIP15286.

Example 37

In vitro inhibition effect of the four optical isomers IX-23~IX-26 on the reuptake of the three monoamine transmitters

1. Experiment materials and methods

experiments	materials	control	Methods (references)
NE reuptake	Rat hypothalamus synaptosome	protriptyline	Perovic and Muller W.E.G. Pharmacological profile of hypericum extract on serotonin uptake by postsynaptic receptors. <i>Arzneim-Forsch. Drug Res.</i> , 1995, 45:1145-1148.
DA reuptake	Rat striatum synaptosome	GBR 12909	Janowsky; Berger, P.; Vocci, F.; Labarca, R., Skolnick, P.; Paul, S.M. Characterization of sodium-dependent[3H]GBR-12935 binding in brain: a radioligand for selective labelling of the dopamine transport complex. <i>J. Neurochem.</i> , 1986, 46:1272-1276.
5-HT reuptake	Rat brain synaptosome	imipramine	Perovic and Muller W.E.G. Pharmacological profile of hypericum extract on serotonin uptake by postsynaptic receptors. <i>Arzneim-Forsch. Drug Res.</i> , 1995, 45:1145-1148.

2. Experiment conditions

experiments	label	incubation	reaction product	detection method
NE reuptake	[3H]NE(μ 0.2Ci/ml)	20min./37°C	[3H]NE binding synaptosome	scintiscouting
DA reuptake	[3H] DA (μ 0.2Ci/ml)	15min./37°C	[3H] DA binding synaptosome	scintiscouting
5-HT reuptake	[3H] 5-HT (μ 0.2Ci/ml)	15min./37°C	[3H] 5-HT binding synaptosome	scintiscouting

3. Experiment results (IC₅₀ value was obtained by nonlinear regression analysis of inhibition rate/concentration response curve)

Compounds	configuration	IC ₅₀ (nM)		
		5-HT	NE	DA
1X-23	(1S,2R)	1900	2100	1000
1X-24	(1S,2S)	3100	1400	1100

IX-25	(1R,2S)	830	140	670
IX-26	(1R,2R)	1200	1200	1100

4. Conclusion

[118] The four optical isomers IX-23~IX-26 had strong *in vitro* inhibition activity on the reuptake of the three monoamine transmitters DA, NE and 5-HT, and belonged to triple reuptake inhibitors.

Example 38

Studies on the *in vivo* antidepressant activity in animals of preferred compounds VIII-9 and VIII-10.

[119] Studies was carried out on the *in vivo* antidepressant effect of compounds VIII-9 and VII-10 using the mice Forced Swimming Test in Learned Helplessness Experiment (Zhang Juntian, Modern Pharmacological Experiments Methods (first volume). Beijing Medical University and Peking Union Medical University Joint Publishing House, 1998:1064-1066), with venlafaxine as the positive control.

Table 5 effect of single oral administration on swimming test for ICR mice ($n=12, \bar{x} \pm s$)

groups	dosage	swimming test: immobility time(s)
blank control	N.S	109.4 ± 66.19
venlafaxine	50mg/kg	$46.5 \pm 25.14^{**}$
VIII-9	48mg/kg	104.3 ± 75.81
	28.8mg/kg	77.4 ± 53.81
	17.3mg/kg	119.4 ± 28.02
	10.4mg/kg	74.3 ± 46.63
VIII-10	48mg/kg	64.4 ± 43.01
	28.8mg/kg	$40.8 \pm 40.24^{**}$

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	17.3mg/kg	43.4±35.41**
	10.4mg/kg	81.8±39.34
SIPI5286	48mg/kg	90.1±26.02**
	28.8mg/kg	92.1±23.11**
	17.3mg/kg	105.4±33.11
	10.4mg/kg	107.9±37.19

* $p < 0.05$, ** $p < 0.01$ compared with blank control group

[120] The results of swimming test for ICR mice of single oral administration showed that Compounds VIII-9 and VIII-10 had an equivalent *in vivo* antidepressant activity compared with venlafaxine and SIPI5286, and had a significant difference compared the blank control group. ED_{50} of VIII-9 was 34.3mg/kg, ED_{50} of VIII-10 was 11.8mg/kg and ED_{50} of SIPI5286 was 28.9mg/kg. VIII-10 had the strongest *in vivo* antidepressant activity.

Table 6 effect of one week oral administration on swimming test of ICR mice
($n=12$, $\bar{x} \pm s$)

groups	dosage	swimming test: immobility time(s)
Blank control	N.S	133.2±35.88
venlafaxine	50mg/kg	83.5±29.0**
VIII-9	48mg/kg	91.5±58.14**
	28.8mg/kg	87.2±40.07**
	17.3mg/kg	82.1±44.06**
	10.4mg/kg	93.4±26.71**
VIII-10	48mg/kg	68.3±34.01**
	28.8mg/kg	51.9±51.23**
	17.3mg/kg	78.2±25.63**

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	10.4mg/kg	77.6±24.69**
SIPI5286	48mg/kg	95.5±27.0**
	28.8mg/kg	97.2±28.33**
	17.3mg/kg	102.9±37.94
	10.4mg/kg	123.8±21.68

* $p < 0.05$, ** $p < 0.01$ compared with blank control group

[121] The results of swimming test of one week continuous oral administration for ICR mice also showed that Compound VIII-9 had an equivalent *in vivo* antidepressant activity compared with venlafaxine and SIPI5286, and had a significant difference compared the blank control group. The *in vivo* antidepressant activity of Compound VIII-10 was stronger than that of venlafaxine and SIPI5286.

Example 39

Studies on the acute toxicity of Compound VIII-9 and VIII-10

[122] Studies on the oral administration acute toxicity in mice of Compound VIII-9 and VIII-10 were performed (Zhang Juntian, Modern Pharmacological Experiments Methods (last volume), Beijing Medical University and Peking Union Medical University Joint Publishing House, 1998:1818-1821). The results were shown as below:

gender	dosage mg/kg	logarithmic dosage	animal number	Death distribution of animals (day)								number of died animals	mortality (%)	regression rate	LD ₅₀ (95%con fidential limit) mg/kg
				1h	2h	4h	1	4	7	10	14				
male & female	2844.7	3.454	6	0	0	0	0	0	0	0	0	0	0		MLD> 2844.7 mg/kg
VIII-9	1849.1	3.267	5	0	0	0	0	0	0	0	0	0	0		
	1201.9	3.0799	6	0	0	0	0	0	0	0	0	0	0		
	781.2	2.8928	6	0	0	0	0	0	0	0	0	0	0		

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	507.8	2.7057	6	0	0	0	0	0	0	0	0	0	0		
male & female	2844.7	3.454	6	0	0	0	6	0	0	0	0	6	100	7.2765	1048.5 (751.33~1433.7)
VIII-10	1849.1	3.267	6	0	0	0	5	0	0	0	0	5	83.3	6,2940	
	1201.9	3.0799	6	0	0	0	4	0	0	0	0	4	66.7	5,3113	
	781.2	2.8928	6	0	0	0	2	0	0	0	0	2	33.3	4,3286	
	507.8	2.7057	6	0	0	0	0	0	0	0	0	0	0.00	3,3461	

[123] Result: After statistically treated by Bliss method, LD₅₀ of VIII-10 (95% confidential limit) was 1048.5(751.33~1433.7) mg/kg, minimum lethal dosage (MLD) of VIII-9 was more than 2844.7mg/kg. The acute toxicity thereof was lower than that of the preferred compound SIPlly24 in patent ZL02111934.1 and of the preferred compound SIPI5286 in patent ZL200510030354.1)

Example 40

Studies on pharmacokinetics of Compound VIII-9 and VIII-10

1. Purpose of test

[124] To study the pharmacokinetics parameters and the bioavailability of VIII-9, VIII-10 and SIPI5286 when single i.v. and oral administration in SD rat

2. Test method:

[125] Eighteen male rats were randomized into 6 groups and were administrated with the three compounds via i.v. and oral route, respectively. The dosage was 10mg/kg (IV) and 50mg/kg (PO). The test substance was dissolved in the solution of 5%DMSO/95%HP- β -CD aqueous solution(30%), and were administrated to the animal via i.v. and oral route. Blood plasma was collected at a serial of time points after i.v. and oral administration, and the blood drug concentrations were determined by LC/MS/MS. Then the pharmacokinetics parameters and the bioavailability were calculated based on the blood drug concentrations.

2. test results:

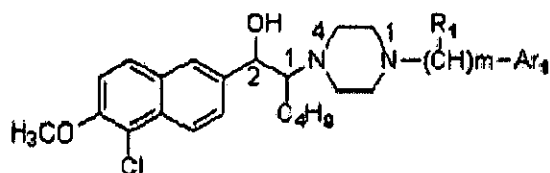
compounds	mode of administration	dosage mg/kg	C _{max} (µg/L)	T _{max}	AUC(0-t) (hr ⁴ µg/L)	half life (T _{1/2}) (hr)	bioavailability
VIII-9	i.v.	10	2640.94 (5min)		4060.59	7.83	
	oral	50	352.27	1.50 hr	3345.73	5.89 hr	16.32%
VIII-10	i.v.	10	2998.49 (5min)		2932.05	9.06 hr	
	oral	50	727.20	1.67 hr	5552.24	16.41 hr	63.78%
SIP15286	i.v.	10	13876.57 (5min)		12564.22	3.41 hr	
	oral	50	6856.69	0.50 hr	30255.45	5.71 hr	51.63%

4. Conclusion

[126] Half life for oral administration of Compound VIII-10 was 16.41 hours, which was longer than that of Compound VIII-9(5.89 hours) and SIP15286(5.71hours). The bioavailability for oral administration of Compound VIII-10 was 63.78%, which was higher than that of Compound VIII-9(16.32%) and SIP15286 (51.63%). Compound VIII-10 has a quite good druggability.

What is claimed is:

1. A 1-butyl-2-hydroxyl aralkyl piperazine derivative, characterized in that, the derivative is the free alkali or its salt of compound of formula (1), or the free alkali or its salt of the optical isomers of compound of formula (1):



(1)

wherein,

Ar₁ represents benzene, substituted phenyl, a 5-member or 6-member aromatic heterocycle containing N, O or S, or cinnameryl;

m is an integer of 0-5;

R₁ represents hydrogen, C₁-C₅ alkyl, C₅ or C₆ alicyclic ring, benzene, substituted phenyl, hydroxyl, amino, substituted amino, C₁-C₄ alkoxy, C₁-C₄ acyl, halogen, carboxylic acid or carboxylic ester.

2. The 1-butyl-2-hydroxyl aralkyl piperazine derivative according to claim 1, characterized in that, Ar₁ represents a substituted phenyl wherein the benzene ring contains one to four substituents and the substituents are halogen, hydroxyl, alkyl, nitro, alkoxy or amino.

3. The 1-butyl-2-hydroxyl aralkyl piperazine derivative according to claim 1, characterized in that, R₁ represents a substituted amino wherein the amino contains C₁-C₄ alkyl, C₅ or C₆ alicyclic ring, benzene or substituted phenyl as the substituents; wherein the substituted phenyl is a phenyl that contains one to four substituents on the benzene ring, and the substituents are halogen, hydroxyl, alkoxy or amino group.

4. The 1-butyl-2-hydroxyl aralkyl piperazine derivative according to claim 3, characterized in that, the alkyl moiety in C₁-C₅ alkyl, C₁-C₄ alkoxy, C₁-C₄ acyl and C₅

or C₆ alicyclic ring can be optionally substituted by 1~3 fluorine atoms.

5. The 1-butyl-2-hydroxyl aralkyl piperazine derivative according to claim 1, characterized in that, asymmetric carbon atoms in the structure are achiral or chiral carbon atoms; for chiral carbon atoms, the configuration of chiral carbon atom C₁ and C₂ are respectively (1S,2R), (1S,2S), (1R,2S) or (1R,2R); wherein, (1SR,2RS) is an erythro isomer and (1SR,2SR) is a threo isomer.

6. The 1-butyl-2-hydroxyl aralkyl piperazine derivative according to claim 1, characterized in that, the salt is a salt containing the pharmaceutically acceptable anions.

7. The 1-butyl-2-hydroxyl aralkyl piperazine derivative according to claim 6, characterized in that, the salt is hydrochloride, hydrobromide, sulfate, trifluoroacetate or methanesulfonate.

8. The 1-butyl-2-hydroxyl aralkyl piperazine derivative according to claim 1, characterized in that, 0.5~4 molecules of crystal water are contained in the salt.

9. The 1-butyl-2-hydroxyl aralkyl piperazine derivative according to any one of claims 1~8, which is selected from the group consisting of:

VIII-1 (1SR,2RS)-N¹-p-methoxyphenyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl) hydroxyethyl]piperazine,

VIII-2 (1SR,2SR)-N¹-p-methoxyphenyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl) hydroxyethyl]piperazine,

VIII-3 (1SR,2RS)-N¹-o-methoxyphenyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,

VIII-4 (1SR,2SR)-N¹-o-methoxyphenyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,

VIII-5 (1SR,2RS)-N¹-m-chlorophenyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,

VIII-6 (1SR,2SR)-N¹-m-chlorophenyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,

- VIII-7 (1SR,2RS)-N¹-(2,3-dimethylphenyl)-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,
- VIII-8 (1SR,2SR)-N¹-(2,3-dimethylphenyl)-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,
- VIII-9 (1SR,2RS)-N¹-benzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,
- VIII-10 (1SR,2SR)-N¹-benzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,
- VIII-11 (1SR,2RS)-N¹-p-nitrobenzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,
- VIII-12 (1SR,2SR)-N¹-p-nitrobenzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,
- VIII-13 (1SR,2RS)-N¹-p-aminobenzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,
- VIII-14 (1SR,2SR)-N¹-p-aminobenzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,
- VIII-15 (1SR,2RS)-N¹-(3',4',5'-trimethoxybenzyl)-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,
- VIII-16 (1SR,2SR)-N¹-(3',4',5'-trimethoxybenzyl)-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,
- VIII-17 (1SR,2RS)-N¹-α-phenemyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,
- VIII-18 (1SR,2SR)-N¹-α-phenemyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,
- VIII-19 (1SR,2RS)-N¹-benzhydryl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-Naphthyl)hydroxyethyl]piperazine,
- VIII-20 (1SR,2SR)-N¹-benzhydryl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-Naphthyl)hydroxyethyl]piperazine,
- VIII-21 (1SR,2RS)-N¹-cinnamyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-Naphthyl)hydroxyethyl]piperazine,

VIII-22 (1S,2SR)-N¹-cinnamyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,

IX-23 (1S,2R)-N¹-benzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,

IX-24 (1S,2S)-N¹-benzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,

IX-25 (1R,2S)-N¹-benzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine,

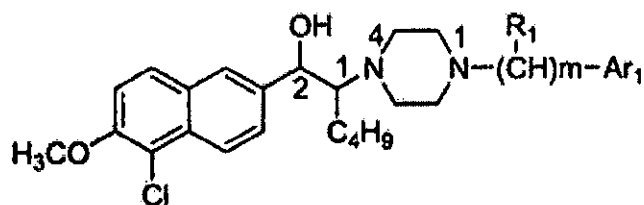
IX-26 (1R,2R)-N¹-benzyl-N⁴-[1-butyl-2-(5'-chloro-6'-methoxyl-2'-naphthyl)hydroxyethyl]piperazine.

10. A pharmaceutical composition comprising therapeutically effective amount of 1-butyl-2-hydroxyl aralkyl piperazine derivatives according to any one of claims 1-9, together with pharmaceutically acceptable carriers.

11. Use of the 1-butyl-2-hydroxyl aralkyl piperazine derivatives according to any one of claims 1-9 in the manufacture of an antidepressant.

ABSTRACT

The invention discloses 1-butyl-2-hydroxyl aralkyl piperazine derivatives and their use as antidepressants. The derivatives of the present invention have triple inhibition effect on the reuptake of 5-HT, NA and DA, and can be administrated to the patients in need thereof in form of composition by route of oral administration, injection and the like. Compared with clinically currently used dual targets antidepressants (such as venlafaxine), said derivatives may have stronger antidepressant effect, broader indications, faster onset and lower neurotoxicity and side reaction; and said derivatives have stronger antidepressant activity, lower toxicity, higher bioavailability, longer half life and better druggability, compared with aryl alkanol piperazine derivatives and optical isomers thereof disclosed in prior art. The 1-butyl-2-hydroxyl aralkyl piperazine derivative is the free alkali or its salt of a compound of formula below:



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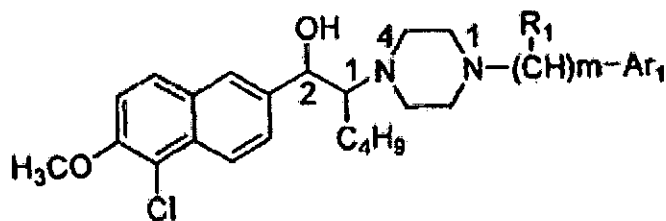
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— 包括国际检索报告 (条约第 21 条(3))。

(54) Title: THE 1-BUTYL-2-HYDROXYARALKYL PIPERAZINE DERIVATIVES AND THE USES AS ANTI-DEPRESSION
MEDICINE THEREOF

(54) 发明名称: 1-丁基-2-羟基芳烷基哌嗪衍生物及作为抗抑郁剂的应用



(57) Abstract: The 1-butyl-2-hydroxyaralkyl piperazine derivatives and the uses as anti-depression medicine thereof. The deriva-
tives have three inhibiting effects on the re-uptaking of 5-HT, NA and DA. The derivatives may be orally taken by or injected to
the patient needing the said treatment. Compared with available depression treating medicine with double effect in clinics, such as
Venlafaxine, the derivatives may have more availability, more widely uses, faster effect, lower toxicity and less nerve side-effect.
Compared with the aralkyl alcohol piperazine compounds of the prior disclosure and optical isomer thereof, the present com-
pounds may have more availability on the anti-depression, lower toxicity, higher bioavailability, longer half-life, more easy for
making medicine. The 1-butyl-2-hydroxyaralkyl piperazine derivatives are the free bases or salts of the following compounds of
general formula.

(见续页)

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(57) 摘要:

本发明公开了一种 1-丁基-2-羟基芳烷哌嗪衍生物及作为抗抑郁剂的应用。本发明所衍生物对 5-HT、NA 及 DA 的再摄取具有三重抑制作用，该衍生物可以组合物的形式通过口服、注射等方式施用于需要这种治疗的患者。该衍生物的抗抑郁作用比目前临床上使用的双重作用靶点的抗抑郁药，如文拉法辛可能作用更强、适应症更广、起效更快、神经毒副作用更小；比现有技术中公开的芳烷醇哌嗪类化合物及光学异构体抗抑郁作用强、毒性低、生物利用度高、半衰期长、成药性更好。该 1-丁基-2-羟基芳烷哌嗪衍生物为具有以下结构通式化合物的游离碱或盐：

1-丁基-2-羟基芳烷哌嗪衍生物及作为抗抑郁剂的应用

技术领域

本发明涉及一种 1-丁基-2-羟基芳烷哌嗪衍生物,以及该衍生物作为广谱抗抑郁症药物
5 的应用。

背景技术

抑郁症是一种以情感性精神障碍为主要表现类型,显著而持久的心境低落为主要特
征的综合症。主要表现为情绪低落,言语减少,精神、运动迟缓,甚至企图自杀等症状。
10 抑郁症作为一种慢性精神疾病,因治疗的疗程长,显效慢,且复发率,致残率及自杀率
较高,已成为困扰我国医疗卫生事业的一大难题。根据世界卫生组织(WHO)发表的
《世界卫生报告》,抑郁症目前已成为世界第四大疾患,到 2020 年抑郁症可能成为仅次
于心脏病的第二大疾病,成为影响人类健康的严重问题。

目前,抗抑郁药物的作用机制尚未完全阐明。有明确疗效的药物基本作用于神经末
15 梢突触部位,通过调节突触间隙神经递质的水平而发挥治疗作用。其病因学的生化研究
表明抑郁症主要与中枢 5-羟色胺(5-HT)、去甲肾上腺素(NA)、多巴胺(DA)、乙酰
胆碱(Ach)和 γ -氨基丁酸(GABA)等五种神经递质相关。

抗抑郁药可以分为早期的非选择性抗抑郁药和新型选择性再摄取抑制剂两大类。非
选择性抗抑郁药主要包括:单胺氧化酶抑制剂(MAOIs)和三环类抗抑郁药(TCAs);
20 选择性再摄取抑制剂主要有:选择性 5-羟色胺(5-HT)再摄取抑制剂(SSRIs)、去甲肾
上腺素(NA)再摄取抑制剂(NRIs)、去甲肾上腺素能和特异性 5-HT 再摄取抑制剂
(NDRIs)、5-HT 和 NA 双重再摄取抑制剂(SNRIs)、5-HT 再吸收促进剂等。

早期的单胺氧化酶抑制剂和三环类抗抑郁药,存在着严重的不良反应;随后的选择

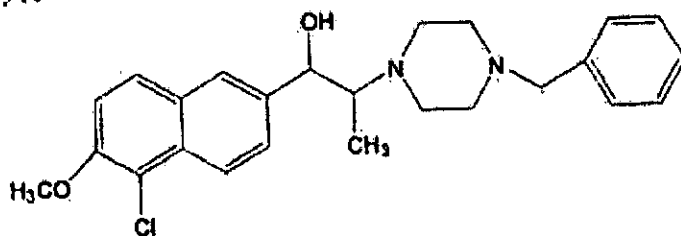
性 NA 再摄取抑制剂和选择性 5-HT 再摄取抑制剂虽然不良反应较少,但仍存在起效慢、疗效不确切等缺陷,因此,以上的几类药物用于治疗抑郁症的效果均不理想。到目前为止,现有的抗抑郁药物仍不能满足临床治疗需要。

1997 年英国推出了第一个能同时抑制 5-HT 和 NA 再摄取的双重抑制剂文拉法辛及 2004 年上市的度洛西汀,它们较氟西汀等选择性五羟色胺再摄取抑制剂及瑞波西汀等去甲肾上腺素再摄取抑制剂具有起效快的特点,对重症抑郁症和难治性抑郁症均有明显疗效。从文拉法辛开始,开发对 5-HT 及 NA 双重作用途径、起效快、副作用小、作用强的新型抗抑郁药成了研发的重点和重要发展方向。

目前,已有多方研究表示在双重再摄取抑制剂中加入对多巴胺作用后,对于治疗抑郁症可取得更好的效果。在双重再摄取抑制剂基础上发展起来的 5-HT、NA、DA 选择性三重再摄取抑制剂(也称“广谱”抗抑郁剂)目前还处于临床研究阶段。如由 DOV Pharmaceutical 公司研发的重三重再摄取抑制剂 DOV-216303 处于 III 期临床;葛兰素史克公司与 NeuroSearch 公司共同开发的 NS-2359 目前正处于抗抑郁 II 期临床。这些单胺递质三重再摄取抗抑郁剂具备疗效强、起效迅速等优势,正成为抗抑郁药研发领域关注的重点。

申请人中国专利 ZL 02111934.1 中公开了一种芳烷醇哌嗪衍生物及其在制备抗抑郁症药物中的应用,其中优选化合物 N¹-苄基-N⁴-(1-甲基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基)哌嗪(IV-19, SIPlly24, 结构式见下式 A)对 5-HT 和 NA 的再摄取具有双重抑制作用,动物体内具有较强的抗抑郁生物活性。但进一步研究发现,其抗抑郁效果还不够

理想、副作用较大。



式 A

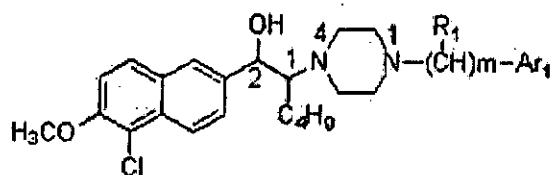
随后, 申请人在中国专利 ZL 200510030354.1 中公开了化合物 SIPIyy24 的光学异构体及应用, 研究表明: 其 (1S, 2R) 光学异构体 (代号 SIPI5286) 对三种单胺递质 5-HT, NA 与 DA 的再摄取都有抑制作用, 是新型三重再摄取抗抑郁剂, 其抗抑郁活性和安全性均优于消旋体, 更具有作为新型抗抑郁药的价值。但进一步研究发现, SIPI5286 半衰期短, 成药性不好。

发明内容

本发明需要解决的技术问题之一是公开一种 1-丁基-2-羟基芳烷哌嗪衍生物, 以克服现有技术存在的疗效差、毒副反应大、起效慢的缺陷, 以解决临床难题和满足临床用药需求;

本发明需要解决的技术问题之二是公开上述衍生物在制备治疗抗抑郁症药物中的应用。

本发明所说的 1-丁基-2-羟基芳烷哌嗪衍生物为具有如结构通式 (1) 所示的化合物及其光学异构体的游离碱或盐:



(1)

通式 (1) 中:

Ar₁ 代表: 苯、取代苯基、含 N、O 或 S 的五或六元芳香杂环或苯乙烯基, 其中,

所述取代苯基为苯环上含有 1 至 4 个 (1、2、3 或 4 个) 取代基的苯基, 所述取代基是卤素、羟基、烷基、硝基、烷氧基或氨基;

m 为 0~5 的整数, 优选 0 或 1;

R_1 代表: 氢、 C_1 - C_3 的烷基 (优选 C_1 - C_3 的烷基, 更优选甲基)、 C_5 或 C_6 的脂肪环、
 5 苯、取代苯基、羟基、氨基、取代氨基、 C_1 - C_4 烷氧基、 C_1 - C_4 酰基、卤素、羧酸或羧酸
 酯, 其中, 所述取代氨基为氨基上含 C_1 - C_4 的烷基、 C_5 或 C_6 的脂肪环、苯或取代苯基
 的氨基; 所述取代苯基为苯环上含有 1 至 4 个取代基的苯基, 所述取代基是卤素 (优选
 氟)、羟基、烷基 (优选 C_1 - C_3 的烷基, 更优选 C_1 - C_3 的直链烷基)、硝基、烷氧基或氨
 基基团; 其中所述 C_1 - C_3 的烷基 (优选 C_1 - C_3 的烷基)、 C_1 - C_4 烷氧基、 C_1 - C_4 酰基、 C_5
 10 或 C_6 的脂肪环上的烷基部分优选为直链烷基, 并且可以任选被 1-3 个氟原子取代;

结构中的不对称碳为非手性或手性碳原子; 若为手性碳原子, C_1 和 C_2 两个手性碳
 原子的构型分别为: (1S, 2R), (1S, 2S), (1R, 2S), (1R, 2R); 其中 (1SR, 2RS)
 为赤式消旋异构体, (1SR, 2SR) 为苏式消旋异构体。

在通式 (1) 的化合物为游离碱的情况下, 它们均能够与各种无机酸或有机酸形成
 15 各种不同的盐;

在一个实施方案中, 所述的盐为含有药物上可接受的阴离子的盐, 诸如盐酸盐、氢
 溴酸盐、氢碘酸盐、硝酸盐、硫酸盐或硫酸氢盐、磷酸盐或酸式磷酸盐、乙酸盐、乳酸
 盐、柠檬酸盐、酒石酸盐、马来酸盐、富马酸盐、葡萄糖酸盐、糖二酸盐、苯甲酸盐、甲
 磺酸盐、乙磺酸盐、苯磺酸盐或对甲苯磺酸盐, 优选为盐酸盐、氢溴酸盐、硫酸盐、三
 20 氟硼酸盐或甲磺酸盐;

在一个实施方案中, 所说的盐含 0.5-4 分子的结晶水;

优选的, 所述 1-丁基-2-羟基芳烷哌嗪衍生物包括:

VIII-1 (1SR, 2RS)- N^1 -对甲氧基苯基- N^4 -[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪、

- VIII-2 (1SR,2SR)-N¹-对甲氧基苄基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪、
- VIII-3 (1SR,2RS)-N¹-邻甲氧基苄基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪、
- VIII-4 (1SR,2SR)-N¹-邻甲氧基苄基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪、
- VIII-5 (1SR,2RS)-N¹-间氯苄基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪、
- 5 VIII-6 (1SR,2SR)-N¹-间氯苄基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪、
- VIII-7 (1SR,2RS)-N¹-(2,3-二甲基苄基)-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪、
- VIII-8 (1SR,2SR)-N¹-(2,3-二甲基苄基)-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪、
- 10 VIII-9 (1SR,2RS)-N¹-苄基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪、
- VIII-10 (1SR,2SR)-N¹-苄基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪、
- VIII-11 (1SR,2RS)-N¹-对硝基苄基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪、
- VIII-12 (1SR,2SR)-N¹-对硝基苄基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪、
- VIII-13 (1SR,2RS)-N¹-对氨基苄基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪、
- 15 VIII-14 (1SR,2SR)-N¹-对氨基苄基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪、
- VIII-15 (1SR,2RS)-N¹-(3',4',5'-三甲氧基苄基)-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪、
- VIII-16 (1SR,2SR)-N¹-(3',4',5'-三甲氧基苄基)-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪、
- VIII-17 (1SR,2RS)-N¹- α -苄乙基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪、
- VIII-18 (1SR,2SR)-N¹- α -苄乙基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪、
- 20 VIII-19 (1SR,2RS)-N¹-二苯甲基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪、
- VIII-20 (1SR,2SR)-N¹-二苯甲基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪、
- VIII-21 (1SR,2RS)-N¹-肉桂基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪、
- VIII-22 (1SR,2SR)-N¹-肉桂基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪、
- IX-23 (1S,2R)-N¹-苄基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪、
- 25 IX-24 (1S,2S)-N¹-苄基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪、
- IX-25 (1R,2S)-N¹-苄基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪或

IX-26 (1R,2R)-N¹-苄基-N⁴-(1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基)哌嗪。

最优选的为：

VIII-9 (1SR,2RS)-N¹-苄基-N⁴-(1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基)哌嗪、

5 VIII-10 (1SR,2SR)-N¹-苄基-N⁴-(1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基)哌嗪、

IX-23 (1S,2R)-N¹-苄基-N⁴-(1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基)哌嗪、

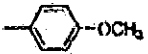
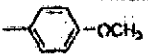
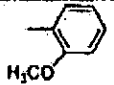
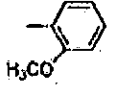
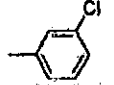
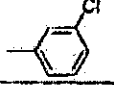
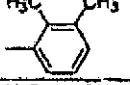
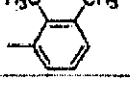
IX-24 (1S,2S)-N¹-苄基-N⁴-(1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基)哌嗪、

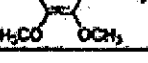
IX-25 (1R,2S)-N¹-苄基-N⁴-(1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基)哌嗪、

IX-26 (1R,2R)-N¹-苄基-N⁴-(1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基)哌嗪。

10 化合物的结构式见表 1。

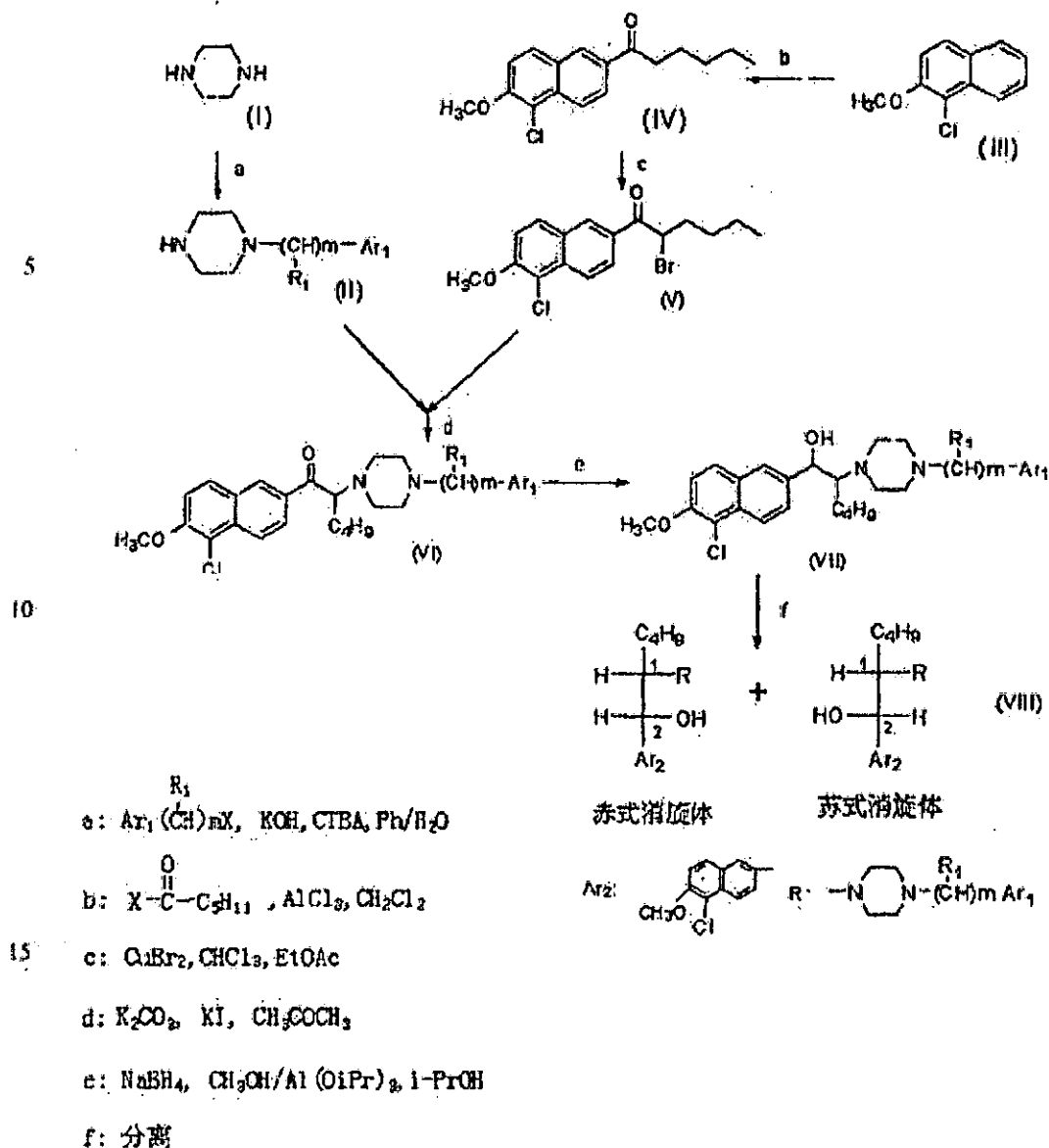
表 1 化合物结构列表

代号	构型	Ar ₁	R ₁	m
VIII-1	(1SR,2RS)		H	0
VIII-2	(1SR,2SR)		H	0
VIII-3	(1SR,2RS)		H	0
VIII-4	(1SR,2SR)		H	0
VIII-5	(1SR,2RS)		H	0
VIII-6	(1SR,2SR)		H	0
VIII-7	(1SR,2RS)		H	0
VIII-8	(1SR,2SR)		H	0
VIII-9	(1SR,2RS)	Ph	H	1
VIII-10	(1SR,2SR)	Ph	H	1

VIII-11	(1SR,2RS)		H	1
VIII-12	(1SR,2SR)		H	1
VIII-13	(1SR,2RS)		H	1
VIII-14	(1SR,2SR)		H	1
VIII-15	(1SR,2RS)		H	1
VIII-16	(1SR,2SR)		H	1
VIII-17	(1SR,2RS)	Ph	CH ₃	1
VIII-18	(1SR,2SR)	Ph	CH ₃	1
VIII-19	(1SR,2RS)	Ph	Ph	1
VIII-20	(1SR,2SR)	Ph	Ph	1
VIII-21	(1SR,2RS)		H	1
VIII-22	(1SR,2SR)		H	1
IX-23	(1S,2R)	Ph	H	1
IX-24	(1S,2S)	Ph	H	1
IX-25	(1R,2S)	Ph	H	1
IX-26	(1R,2R)	Ph	H	1

在一个实施方案中，化合物 VIII-1~VIII-22 为苏式和赤式消旋体，可采用如下的

5 方法进行合成：



以哌嗪为起始原料，首先与相应卤代芳烷烃进行亲核取代反应，得到 N-单烷基化
 20 化合物(II)。该反应在相转移催化条件下进行，以十六烷基三甲基溴化胺(CTAB)为相转移
 催化剂，苯/水系统为反应溶媒，在 KOH 作用下可进行哌嗪的 N-单烷基化，收率可达
 86%。所述相转移催化剂如中国专利 ZL 02111934.1 报道的催化剂。

化合物 (III) 与相应的酰氯进行傅-克反应，得到芳烷酮 (IV)。该反应以无水三氯

化铝为催化剂，二氯甲烷为溶剂，在室温下进行，收率达 80%左右。

化合物 (IV) 经溴化得到卤代的芳烷酮(V)，采用 CuBr_2 为溴化试剂，氯仿与乙酸乙酯的混合溶液作为溶剂，加热回流，收率达 85%左右。

化合物 (II) 与化合物 (V) 进行 N^4 的烷基化反应得到芳烷酮哌嗪化合物(VI)。采用 K_2CO_3 /丙酮为反应系统，回流反应 8~24 小时，收率达 80%。

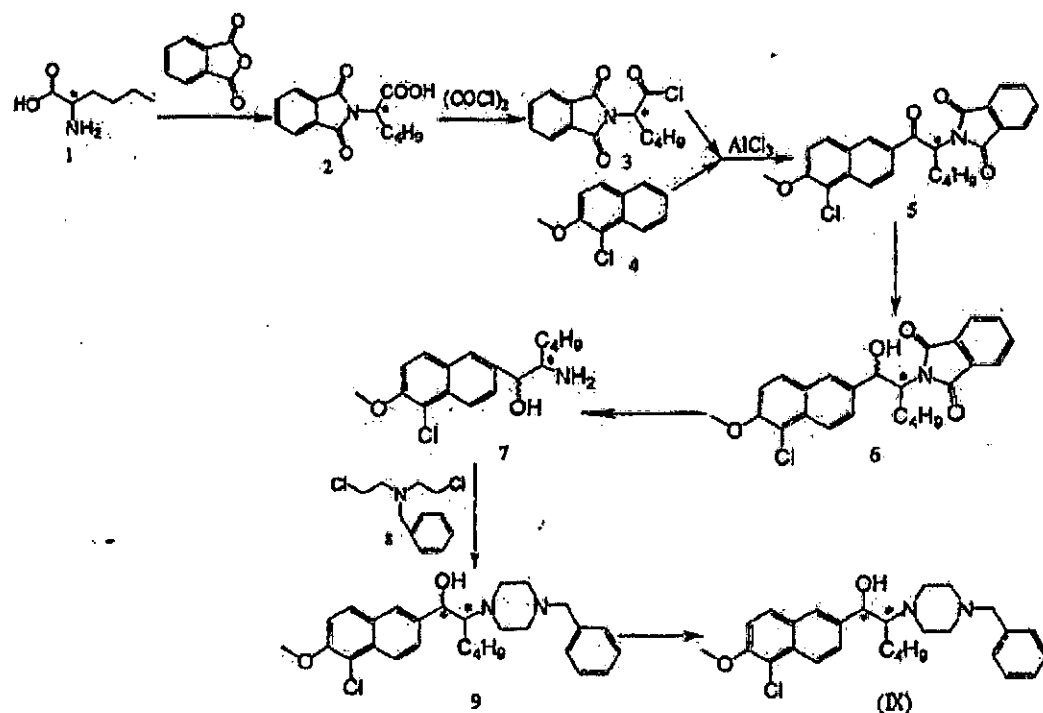
化合物(VI)经 NaBH_4 在甲醇中室温反应 0.5~1 小时，或经异丙醇铝在异丙醇中 60-65 $^\circ\text{C}$ 反应 24~48 小时，还原羰基得到相应芳烷醇哌嗪化合物(VII)。

化合物(VII)经柱分离得到相应 1-丁基-2-羟基芳烷醇哌嗪衍生物的赤式体和苏式体 (VIII)，采用上述步骤，可获得目标化合物 VIII-1 至 VIII-22。

10 a 中的卤代芳烷烃化合物, b 中的酰氯化合物及化合物 III 均可以通过商业渠道购买, 亦可采用文献报道的常规方法制备。

化合物 IX-23~IX-26 为光学异构体时, 可采用如下的方法进行合成:

以手性正亮氨酸 1 为原料, 氨基经邻苯二甲酰基保护, 羧基经草酰氯酰化, 生成化合物 3, 再与化合物 4 通过傅-克反应生成化合物 5, 化合物 5 经异丙醇铝还原、水解得
15 到化合物 7, 化合物 7 与化合物 8 缩合得到化合物 9, 再经柱层析分离得到光学纯的目标产物 (IX)。具体合成路线见下:



本发明采用前手性的方法合成化合物 N^1 -苄基- N^4 -[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪的四个光学异构体:

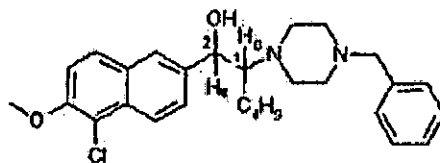
以 L-正亮氨酸为原料先合成出 (1S,2R) 异构体和 (1S,2S) 异构体的混合物,再以硅胶或者氧化铝为载体,二氯甲烷:甲醇=200:1 为洗脱剂,对其进行柱层分离,得到 (1S,2S)- N^1 -苄基- N^4 -[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪 (IX-24) 和 (1S,2R)- N^1 -苄基- N^4 -[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪 (IX-23);若以 D-正亮氨酸为原料,按同样方法,可制备 (1R,2S)- N^1 -苄基- N^4 -[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪 (IX-25) 和 (1R,2R)- N^1 -苄基- N^4 -[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪 (IX-26)。

上述的合成方法,原料易得,所得产物不需拆分,光学纯度好,总收率高。四个光学异构体的纯度通过高效液相手性柱色谱进行检测,其 ee 值均大于 99%。[分析条件: OJ-H 手性柱 (从日本大冢药有限公司购买) 4.6×250mm; 流动相: 正己烷:乙醇:二乙胺=40:60:0.1 (v/v/v); 紫外波长: UV 220 nm; 柱温: 35℃]

四个光学异构体的构型可以根据起始原料的构型以及目标产物的耦合常数进行推定, 在反应过程中, 与手性中心相连的键不发生断裂, 所连基团的相对大小也没有改变, 所以最终产物中与 N 相连的 C_1 的构型与起始手性原料正亮氨酸的构型相同; C_2 的构型可通过与手性中心相连的 H_a 和 H_b 之间的耦合常数来推定, 耦合常数 J_{ab} 较小的为赤式异构体, 其相应的构型为 (1S, 2R) 或 (1R, 2S); 耦合常数 J_{ab} 较大的为苏式异构体, 其相应的构型为 (1S, 2S) 或 (1R, 2R), 具体见表 2。

以 L-正亮氨酸为起始原料制得 (1S, 2R) 和 (1S, 2S) 异构体; 以 D-正亮氨酸为起始原料制得 (1R, 2S) 和 (1R, 2R) 异构体。

表 2 四个光学异构体的构型推定



化合物	正亮氨酸的构型	C_1 的构型	耦合常数 J_{ab}/Hz	赤式/苏式 (Erythro/Threo)	C_2 构型	产物构型
IX-23	L	S	2.0	Erythro-	R	1S, 2R
IX-24	L	S	9.6	Threo-	S	1S, 2S
IX-25	D	R	2.0	Erythro-	S	1R, 2S
IX-26	D	R	9.6	Threo-	R	1R, 2R

体外单胺递质再摄取抑制试验表明: 本发明所述 1-丁基-2-羟基芳烷哌啶衍生物及其光学异构体属三重再摄取抑制剂, 体外具有较强的 DA、NE、5-HT 三种单胺递质再摄取剂作用。优选化合物 VIII-10 体外 5-HT、NA 再摄取抑制活性与文拉法辛、SIPlly24 相当, 对 DA 的再摄取抑制活性强于文拉法辛、SIPlly24 和 SIPI5286; 化合物 VIII-9 对三种单胺递质的再摄取抑制活性均强于文拉法辛、SIPlly24 和 SIPI5286。

动物体内抗抑郁活性研究表明: 优选化合物 VIII-9 的体内抗抑郁活性与文拉法辛、

SIP15286 相当, 与空白对照组相比具有显著差异; 化合物 VIII-10 的体内抗抑郁活性则强于文拉法辛及 SIP15286。

急性毒性研究表明: 优选化合物 VIII-10 的 LD_{50} (95%可信限) 为 1048.5 (751.33~1433.7) mg/kg, VIII-9 的最小致死剂量大于 2844.7 mg/kg。其急性毒性小于专利 ZL 02111934.1 的优选化合物 SIP15286 和专利 ZL 200510030354.1 的优选化合物 SIP15286。

药代动力学研究表明: 化合物 VIII-10 口服给药的半衰期为 16.41 小时, 长于化合物 VIII-9 (5.89 小时) 和 SIP15286 (5.71 小时); 化合物 VIII-10 的口服生物利用度为 63.78%, 高于化合物 VIII-9 (16.32%) 及 SIP15286 (51.63%)。由此可见, 化合物 VIII-10 具有很好的成药性。

10 本发明所述 1-丁基-2-羟基芳烷哌啶衍生物对 5-HT、NA 和 DA 再摄取有三重抑制作用, 可用于制备抗抑郁症药物。

本发明的衍生物可以组合物的形式通过口服或注射等方式施用于需要这种治疗的患者。

本发明还涉及一种治疗患有抑郁症的患者的方法, 该方法包括: 向所述患者施用治疗有效量的本发明的衍生物或含有其的药物组合物。施用途径可以是口服或注射。

所述组合物以含有治疗有效量的本发明的衍生物为活性成分, 并含有一种或多种药学上可接受的载体。

所述及的载体是指药学领域常规的载体, 例如: 稀释剂、赋形剂如水等; 粘合剂如纤维素衍生物、明胶、聚乙烯吡咯烷酮等; 填充剂如淀粉等; 崩裂剂如碳酸钙、碳酸氢钠; 另外, 还可以在组合物中加入其他辅助剂如香味剂和甜味剂。

20 用于口服时, 可将其制备成常规的固体制剂如片剂、粉剂或胶囊等; 用于注射时, 可将其制备成注射液。

本发明的组合物的各种剂型可以采用药学领域常规的方法进行制备, 其中活性成分

的含量为 0.1%~99.5%(重量比)。

本发明的施用量可根据用药途径、患者的年龄、体重、所治疗的疾病的类型和严重程度等进行变化，其日剂量为 5~30mg/kg 体重(口服)或 1~10mg/kg 体重(注射)。本发明的衍生物在动物试验中显示出对抑郁症的拮抗作用。

5 本发明为了克服 SIPI5286 的缺陷，以 SIPIyy24 为先导化合物，在对其进行结构修饰的过程中发现：当 C1 上的取代基为脂肪烃取代时，随着碳链 1~4 的增长，化合物的赤式和苏式异构体对 5-HT、NA 及 DA 的再摄取都有较好的抑制作用，可以和 SIPIyy24 以及阳性对照文拉法辛相媲美。当取代基为丁基时，即为本发明所述的 1-丁基-2-羟基芳烷哌啶衍生物时，其赤式和苏式异构体对 5-HT、NA 及 DA 三种单胺递质的再摄取抑
10 制活性均达到最大值，高于 SIPIyy24、SIPI5286 及阳性对照文拉法辛。但是，当 C1 上的取代基为戊基时，其抑制活性大幅度下降。申请人对 ZL 02111934.1 中的其它化合物进行结构修饰时发现，当 C1 上取代基为丁基时，化合物对 5-HT、NA 及 DA 的再摄取抑制活性均达到最大值。因此申请人认为 1-丁基-2-羟基芳烷哌啶衍生物为此类芳烷醇哌啶衍生物中活性最强结构。

15 随后的动物体内研究亦表明：本发明所述的 1-丁基-2-羟基芳烷哌啶衍生物较专利 ZL 02111934.1 中公开的芳烷醇哌啶类化合物及专利 ZL 200510030354.1 中公开的光学异构体，抗抑郁作用强、毒性低、生物利用度高、半衰期长、成药性更好。

综上所述，本发明所述 1-丁基-2-羟基芳烷哌啶衍生物抗抑郁作用比目前临床上使用的双重作用靶点抗抑郁药，如文拉法辛可能作用更强、适应症更广、神经毒副反应更
20 小。该衍生物比专利 ZL 02111934.1 中公开的芳烷醇哌啶类化合物及专利 ZL 200510030354.1 中公开的光学异构体抗抑郁作用更强、毒性更低、生物利用度更高、半衰期更长、成药性更好。

具体实施方式

通法一：N-芳烷基哌嗪盐酸盐(II)合成：

将六水哌嗪(350mmol, 上海化学试剂站售), 固体 KOH (100mmol), CTAB(Hexadecyl Trimethylammonium Bromide, 1mmol), 置于 18ml 水中, 加热溶解, 在 70℃ 下滴加含
 5 有芳烷基氯(100mmol, 市售)的 140 ml 苯溶液, 滴加完毕后, 回流反应 1.5 小时, 静置分
 层, 有机相分别用 50 ml 水和 50ml 饱和 NaCl 溶液洗涤, 用 $MgSO_4$ 干燥, 过滤, 减压
 蒸干溶剂, 用 50ml 无水乙醇溶解, 滴加 HCl/ C_2H_5OH 溶液, 使溶液 pH 为 3, 析出固
 体, 过滤, 干燥, 乙醇重结晶得 N-芳烷基哌嗪盐酸盐备用, 收率 80%~86%。

通法二：2-己酮-5-氯-6-甲氧基萘(IV)合成：

10 将化合物 III(28.4mmol)溶于二氯甲烷(30ml)中, 加入 $AlCl_3$ (30.8mmol), 室温下搅拌
 1h, $AlCl_3$ 逐渐溶解, 溶液颜色加深至浅棕色。控温 $< 10^\circ C$, 缓慢滴入正己酰氯
 (23.7mmol), 滴毕, 自然升至室温, 搅拌反应 1h, 反应液颜色加深, 呈棕色。搅拌下将
 反应液倒入盐酸(20ml)/碎冰(50g)混合物中, 有机相颜色褪去, 呈淡黄色至黄色。分出有
 15 机相, 水洗(20ml $\times$ 3)至水相中性, 无水 Na_2SO_4 干燥过夜。滤去干燥剂, 少量二氯甲烷
 冲洗滤渣, 滤液蒸去溶剂, 得淡黄色油状物。柱层析分得产物 IV(乙酸乙酯: 石油醚=1:
 400-1: 60)为淡黄色油状物, 放置后固化, 收率 80%左右。

通法三：2-(α -溴-己酮)-5-氯-6-甲氧基萘(V)合成：

将化合物(IV)(21mmol)溶于乙酸乙酯(50ml)和氯仿(50ml)中, 加入 $CuBr_2$ (40.2mmol),
 回流反应 3h, 过滤除去生成的 $CuBr$, 滤液水洗(20ml $\times$ 3), 无水 Na_2SO_4 干燥过夜, 滤去
 20 干燥剂, 少量乙酸乙酯冲洗滤渣。滤液蒸去溶剂, 乙醇重结晶, 得淡黄色结晶性固体,
 收率 85%左右。

通法四：N¹-芳烷基-N¹-[1-(5'-氯-6'-甲氧基-2'-萘甲酰基)戊基]哌嗪盐酸盐(VI)合成：

将 N-芳烷基哌嗪盐酸盐(II)(10mmol), 2-(α -溴-己酮)-5-氯-6-甲氧基萘(V)

(12mmol), 碘化钾 (1mmol) 和无水 K_2CO_3 (35mmol) 置于丙酮(50ml)中, 加热回流搅拌反应 8~12 小时, 过滤, 减压蒸干溶剂, 加水 50ml, 用 AcOEt(100ml×3)提取, 合并酯层, 依次用水 20ml, 饱和 NaCl 溶液 30ml 洗, $MgSO_4$ 干燥, 过滤, 蒸去溶剂, 加乙醇 30 ml 溶解, 用 HCl/ C_2H_5OH (5N)调 pH=2; 过滤析出的固体, 乙醇/水或甲醇重结晶,

5 得化合物(VI), 收率 60%~85%。

通法五: N^1 -芳烷基- N^4 -[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪盐酸盐(VII) 合成:

将异丙醇铝 (35mmol) 溶解于 80ml 异丙醇中, 加入无水 $AlCl_3$ (3.5mmol), 加热至 45-50℃, 搅拌 30min 至溶液澄清, 加入游离态的 N^1 -芳(芳烷基)基- N^4 -芳烷酰烷基哌嗪 (10mmol) 的异丙醇溶液, 升温至 60-65℃, 反应至原料点消失 (TLC 检测, 6-48 小
10 时)。反应毕, 加入重量浓度 15% 的 NaOH 溶液调 pH=7 左右, 二氯甲烷或乙酸乙酯萃取, 用饱和 NaCl 20 ml 洗, $MgSO_4$ 干燥, 过滤, 减压蒸干溶剂, 残留物溶于乙醇 20 ml 中, 用 HCl/ C_2H_5OH 调 pH=2, 析出固体, 过滤, 收率 85%~95%。

15

实施例 1

VIII-1 (1SR,2RS)- N^1 -对甲氧基苯基- N^4 -[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪 (赤式体)

将 N^1 -对甲氧基苯基哌嗪 (10mmol) 和 2-(α -溴-己酮)-5-氯-6-甲氧基萘 (10mmol), 按通法二~通法四合成 N^1 -对甲氧基苯基- N^4 -[1-丁基-2-羰基-2-(5-氯-6-甲氧基萘-2-基)]乙基哌嗪盐酸盐 4.20g, 收率 79%, m.p.=231.5-233.6℃(dec)。将 N^1 -对甲氧基苯基- N^4 -[1-丁基-2-羰基-2-(5-氯-6-甲氧基萘-2-基)]乙基哌嗪按通法五进行羰基的还原反应, 得 N^1 -对甲氧基苯基- N^4 -[1-丁基-2-羟基-2-(5-氯-6-甲氧基萘-2-基)]乙基哌嗪盐酸盐 3.78g, 收率 90%。将其游离后, 柱层析分离得其赤式体产物, 加乙醇溶解, 用

HCl/C₂H₅OH (5N)调 pH=2, 过滤析出的固体, 乙醇/水或甲醇重结晶, 得化合物(VIII-1), 对该化合物进行元素分析结果显示化合物含有 0.5 分子结晶水。

m.p=221.6-223.2°C(dec). MS: m/z 483 (M⁺).

¹HNMR(DMSO-d₆): δ 0.73-1.66(m, 9H, CH₂CH₂CH₂CH₃), 2.65-2.91(m, 9H, CH+哌嗪
s -H), 3.76(s, 3H, OCH₃), 3.87(s, 3H, OCH₃), 5.0 (d, 1H, CH, J=4.0), 5.17(d, 1H, OH),
6.84-8.04(m, 9H, Ar-H).

实施例 2

VIII-2 (1SR,2SR)-N¹-对甲氧基苯基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪 (苏式体)

10 将 N¹-对甲氧基苯基哌嗪 (10mmol) 和 2-(6-溴-己酮)-5-氯-6-甲氧基蔡 (10mmol), 按通法二~通法四合成 N¹-对甲氧基苯基-N⁴-[1-丁基-2-羰基-2-(5-氯-6-甲氧基蔡-2-基)]乙基哌嗪盐酸盐 4.20g, 收率 79%, m.p=231.5-233.6°C(dec).

将 N¹-对甲氧基苯基-N⁴-[1-丁基-2-羰基-2-(5-氯-6-甲氧基蔡-2-基)]乙基哌嗪按通法
五进行羰基的还原反应, 得 N¹-对甲氧基苯基-N⁴-[1-丁基-2-羟基-2-(5-氯-6-甲氧基蔡
15 -2-基)]乙基哌嗪盐酸盐 3.78g, 收率 90%. 将其游离后, 柱层析分离得其苏式体产物, 加乙醇溶解, 用 HCl/C₂H₅OH (5N)调 pH=2, 过滤析出的固体, 乙醇/水或甲醇重结晶, 得化合物(VIII-2), 对该化合物进行元素分析结果显示化合物含有 2 分子结晶水。

m.p=220.4-222.8°C(dec). MS: m/z 483 (M⁺).

¹HNMR(DMSO-d₆): δ 0.65-1.51(m, 9H, CH₂CH₂CH₂CH₃), 2.49-2.97(m, 9H, CH+哌嗪
20 -H), 3.78(s, 3H, OCH₃), 3.87(s, 3H, OCH₃), 4.6 (d, 1H, CH, J=8.0), 5.14(d, 1H, OH),
6.86-8.06(m, 9H, Ar-H).

实施例 3

VIII-3 (1SR,2RS)-N¹-邻甲氧基苯基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌

嗪(赤式体)

将 N¹-邻甲氧基苯基哌嗪(10mmol)和 2-(α -溴-己酮)-5-氯-6-甲氧基蔡(10mmol), 按通法二~通法四合成 N¹-邻甲氧基苯基-N⁴-[1-丁基-2-羰基-2-(5-氯-6-甲氧基蔡-2-基)]乙基哌嗪盐酸盐 4.03g, 收率 78%, m.p=232.4-234.1℃(dec).

- 5 将 N¹-邻甲氧基苯基-N⁴-[1-丁基-2-羰基-2-(5-氯-6-甲氧基蔡-2-基)]乙基哌嗪按通法五进行羰基的还原反应, 得 N¹-邻甲氧基苯基-N⁴-[1-丁基-2-羟基-2-(5-氯-6-甲氧基蔡-2-基)]乙基哌嗪盐酸盐 3.58g, 收率 89%。将其游离后, 柱层析分离得其赤式体产物, 加乙醇溶解, 用 HCl/C₂H₅OH (5N)调 pH=2, 过滤析出的固体, 乙醇/水或甲醇重结晶, 得化合物(VIII-3), 对该化合物进行元素分析结果显示化合物含有 2 分子结晶水。

10 m.p=227.3-229.1℃(dec). MS: m/z 483 (M⁺).

¹HNMR(DMSO-d₆): δ 0.73-1.66(m, 9H, CH₂CH₂CH₂CH₃), 2.65-2.91(m, 9H, CH+哌嗪-H), 3.76(s, 3H, OCH₃), 3.98(s, 3H, OCH₃), 5.0 (d, 1H, CH, J=4.0), 5.17(d, 1H, OH), 6.84-8.04(m, 9H, Ar-H).

实施例 4

- 15 VIII-4 (1SR,2SR)-N¹-邻甲氧基苯基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)]羟乙基]哌嗪(苏式体)

将 N¹-邻甲氧基苯基哌嗪(10mmol)和 2-(α -溴-己酮)-5-氯-6-甲氧基蔡(10mmol), 按通法二~通法四合成 N¹-邻甲氧基苯基-N⁴-[1-丁基-2-羰基-2-(5-氯-6-甲氧基蔡-2-基)]乙基哌嗪盐酸盐 4.03g, 收率 78%, m.p=232.4-234.1℃(dec).

- 20 将 N¹-邻甲氧基苯基-N⁴-[1-丁基-2-羰基-2-(5-氯-6-甲氧基蔡-2-基)]乙基哌嗪按通法五进行羰基的还原反应, 得 N¹-邻甲氧基苯基-N⁴-[1-丁基-2-羟基-2-(5-氯-6-甲氧基蔡-2-基)]乙基哌嗪盐酸盐 3.58g, 收率 89%。将其游离后, 柱层析分离得其苏式体产物, 加乙醇溶解, 用 HCl/C₂H₅OH (5N)调 pH=2, 过滤析出的固体, 乙醇/水或甲醇重结晶

品, 得化合物(VIII-4), 对该化合物进行元素分析结果显示化合物含有 2 分子结晶水。

m.p.=223.5-225.0°C(dec). MS: m/z 483 (M^+).

$^1\text{H NMR}$ (DMSO- d_6): δ 0.65-1.51(m, 9H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2.49-2.97(m, 9H, CH+咪唑-H), 3.78(s, 3H, OCH_3), 3.98(s, 3H, OCH_3), 4.6 (d, 1H, CH, $J=8.0$), 5.14(d, 1H, OH),

5 6.86-8.06(m, 9H, Ar-H).

实施例 5

VIII-5 (1*SR*,2*RS*)- N^1 -间氯苯基- N^4 -[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]咪唑 (赤式体)

10 将 N^1 -间氯苯基咪唑 (10mmol) 和 2-(α -溴-己酮)-5-氯-6-甲氧基萘 (10mmol), 按通法二~通法四合成 N^1 -间氯苯基- N^4 -[1-丁基-2-羧基-2-(5-氯-6-甲氧基萘-2-基)]乙基咪唑盐酸盐 4.20g, 收率 79%, m.p.=231.5-233.6°C(dec).

15 将 N^1 -间氯苯基- N^4 -[1-丁基-2-羧基-2-(5-氯-6-甲氧基萘-2-基)]乙基咪唑按通法五进行羧基的还原反应, 得 N^1 -间氯苯基- N^4 -[1-丁基-2-羟基-2-(5-氯-6-甲氧基萘-2-基)]乙基咪唑盐酸盐 3.78g, 收率 90%。将其游离后, 柱层析分离得其赤式体产物, 加乙醇溶解, 用 $\text{HCl}/\text{C}_2\text{H}_5\text{OH}$ (5*N*)调 pH=2, 过滤析出的固体, 乙醇/水或甲醇重结晶, 得化合物 (VIII-5), m.p.=224.2-226.8°C(dec). MS: m/z 487 (M^+).

$^1\text{H NMR}$ (DMSO- d_6): δ 0.73-1.66(m, 9H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2.65-2.91(m, 9H, CH+咪唑-H), 3.76(s, 3H, OCH_3), 5.0 (d, 1H, CH, $J=4.0$), 5.17(d, 1H, OH), 6.84-8.04(m, 9H, Ar-H).

实施例 6

20 VIII-6 (1*SR*,2*SR*)- N^1 -间氯苯基- N^4 -[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]咪唑 (苏式体)

将 N^1 -间氯苯基咪唑 (10mmol) 和 2-(α -溴-己酮)-5-氯-6-甲氧基萘 (10mmol), 按通法二~通法四合成 N^1 -间氯苯基- N^4 -[1-丁基-2-羧基-2-(5-氯-6-甲氧基萘-2-基)]乙基咪唑

基哌嗪盐酸盐 4.20g, 收率 79%, m.p.=231.5-233.6°C(dec).

将 N¹-间氯苯基-N⁴-[1-丁基-2-羧基-2-(5-氯-6-甲氧基苯-2-基)]乙基哌嗪按通法五进行羧基的还原反应, 得 N¹-间氯苯基-N⁴-[1-丁基-2-羧基-2-(5-氯-6-甲氧基苯-2-基)]乙基哌嗪盐酸盐 3.78g, 收率 90%。将其游离后, 柱层析分离得其苏式体产物, 加乙醇溶解, 用 HCl/C₂H₅OH (5N) 调 pH=2, 过滤析出的固体, 乙醇/水或甲醇重结晶, 得化合物 (VIII-6), m.p.=220.4-222.8°C(dec). MS: m/z 487 (M⁺).

¹HNMR(DMSO-d₆): δ 0.65-1.51(m, 9H, CH₂CH₂CH₂CH₃), 2.49-2.97(m, 9H, CH+哌嗪-H), 3.78(s, 3H, OCH₃), 4.6(d, 1H, CH, J=8.0), 5.14(d, 1H, OH), 6.86-8.06(m, 9H, Ar-H).

实施例 7

10 VIII-7 (1SR,2RS)-N¹-(2,3-二甲基苯基)-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)]乙基哌嗪 (赤式体)

将 N¹-(2,3-二甲基苯基)哌嗪 (10mmol) 和 2-(α-没-己酮)-5-氯-6-甲氧基萘 (10mmol), 按通法二~通法四合成 N¹-(2,3-二甲基苯基)-N⁴-[1-丁基-2-羧基-2-(5-氯-6-甲氧基萘-2-基)]乙基哌嗪盐酸盐 3.80g, 收率 80%, m.p.=232.5-235.6°C(dec).

15 将 N¹-(2,3-二甲基苯基)-N⁴-[1-丁基-2-羧基-2-(5-氯-6-甲氧基萘-2-基)]乙基哌嗪按通法五进行羧基的还原反应, 得 N¹-(2,3-二甲基苯基)-N⁴-[1-丁基-2-羧基-2-(5-氯-6-甲氧基萘-2-基)]乙基哌嗪盐酸盐 3.34g, 收率 88%。将其游离后, 柱层析分离得其赤式体产物, 加乙醇溶解, 用 HCl/C₂H₅OH (5N) 调 pH=2, 过滤析出的固体, 乙醇/水或甲醇重结晶, 得化合物(VIII-7), m.p.=218.5-220.8°C(dec). MS: m/z 481 (M⁺).

20 ¹HNMR(DMSO-d₆): δ 0.74-0.77(m, 3H, CH₂CH₂CH₃), 1.13-2.11(m, 6H, CH₂CH₂CH₂CH₃), 2.15(s, 3H, CH₃), 2.20(s, 3H, CH₃), 2.50-2.87(m, 9H, 哌嗪-CH), 3.99(s, 3H, OCH₃), 5.06-5.07(m, 1H, CH, J=4.0), 5.18-5.19(d, 1H, OH), 6.83-8.05(m, 8H, Ar-H).

实施例 8

VIII-8 (1SR,2SR)-N¹-(2,3-二甲基苯基)-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪(苏式体)

将 N¹-(2,3-二甲基苯基)哌嗪(10mmol)和 2-(α -溴-己酮)-5-氯-6-甲氧基萘(10mmol),按通法二~通法四合成 N¹-(2,3-二甲基苯基)-N⁴-[1-丁基-2-羰基-2-(5-氯-6-甲氧基萘-2-基)]乙基哌嗪盐酸盐 3.80g,收率 80%, m.p.=232.5-235.6°C(dec).

将 N¹-(2,3-二甲基苯基)-N⁴-[1-丁基-2-羰基-2-(5-氯-6-甲氧基萘-2-基)]乙基哌嗪按通法五进行羰基的还原反应,得 N¹-(2,3-二甲基苯基)-N⁴-[1-丁基-2-羟基-2-(5-氯-6-甲氧基萘-2-基)]乙基哌嗪盐酸盐 3.34g,收率 88%。将其游离后,柱层析分离得其苏式体产物,加乙醇溶解,用 HCl/C₂H₅OH (5N)调 pH=2,过滤析出的固体,乙醇/水或
10 甲醇重结晶,得化合物(VIII-8), m.p.=220.4-222.8°C(dec). MS: m/z 481 (M⁺).

¹HNMR(DMSO-d₆): δ 0.66-0.69(m, 3H, CH₂CH₂CH₃), 0.96-1.53(m, 6H, CH₂CH₂CH₂CH₃), 2.17(s, 3H, CH₃), 2.21(s, 3H, CH₃), 2.80-2.96(m, 9H, 哌嗪-CH), 3.99(s, 3H, OCH₃), 4.59-4.61(m, 1H, CH, J=8.4), 5.14 (d, 1H, OH), 6.83-8.05(m, 8H, Ar-H).

实施例 9

15 VIII-9 (1SR,2RS)-N¹-苄基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪(赤式体)

将 N¹-苄基哌嗪(10mmol)和 2-(α -溴-己酮)-5-氯-6-甲氧基萘(10mmol),按通法二~通法四合成 N¹-苄基-N⁴-[1-丁基-2-羰基-2-(5-氯-6-甲氧基萘-2-基)]乙基哌嗪盐酸盐 4.20g,收率 78%, m.p.=241.7-243.3°C(dec).

20 将 N¹-苄基-N⁴-[1-丁基-2-羰基-2-(5-氯-6-甲氧基萘-2-基)]乙基哌嗪按通法五进行羰基的还原反应,得 N¹-苄基-N⁴-[1-丁基-2-羟基-2-(5-氯-6-甲氧基萘-2-基)]乙基哌嗪盐酸盐 3.73g,收率 89%。将其游离后,柱层析分离得其赤式体产物,加乙醇溶解,用 HCl/C₂H₅OH (5N)调 pH=2,过滤析出的固体,乙醇/水或甲醇重结晶,得化合物(VIII-9),对该化合

物进行元素分析结果显示化合物含有 2 分子结晶水。

m.p.=225.0-225.8°C(dec). MS: m/z 467 (M^+).

^1H NMR(DMSO- d_6): δ 0.72-1.60(m, 9H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2.27-2.70(m, 9H, CH+哌嗪-H), 3.40(s, 2H, CH_2 Ph), 3.98(s, 3H, OCH_3), 5.0 (d, 1H, CH, $J=4.4$), 5.10(s, 1H, OH),
5 7.20-8.02(m, 10H, Ar-H).

实施例 10

VIII-10 (1SR,2SR)- N^1 -苄基- N^4 -[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪 (苏式体)

将 N^1 -苄基哌嗪 (10mmol) 和 2-(α -溴-己酮)-5-氯-6-甲氧基萘 (10mmol), 按通
10 法二~通法四合成 N^1 -苄基- N^4 -[1-丁基-2-羰基-2-(5-氯-6-甲氧基萘-2-基)]乙基哌嗪盐
酸盐 4.20g, 收率 78%, m.p.=241.7-243.3°C(dec).
将 N^1 -苄基- N^4 -[1-丁基-2-羰基-2-(5-氯-6-甲氧基萘-2-基)]乙基哌嗪按通法五进行羰基
的还原反应, 得 N^1 -苄基- N^4 -[1-丁基-2-羟基-2-(5-氯-6-甲氧基萘-2-基)]乙基哌嗪盐
酸盐 3.73g, 收率 89%。将其游离后, 柱层析分离得其苏式体产物, 加乙醇溶解, 用 $\text{HCl}/\text{C}_2\text{H}_5\text{OH}$
15 (5N)调 pH=2, 过滤析出的固体, 乙醇/水或甲醇重结晶, 得化合物(VIII-10), 对该化
合物进行元素分析结果显示化合物含有 2 分子结晶水。

m.p.=223.1-224.3°C(dec). MS: m/z 467 (M^+).

^1H NMR(DMSO- d_6): δ 0.66-1.50(m, 9H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2.42-2.84(m, 9H, CH+哌嗪-H), 3.49(s, 2H, CH_2 Ph), 4.02(s, 3H, OCH_3), 4.5(d, 1H, CH, $J=8.8$), 5.10(s, 1H, OH),
20 7.26-8.08(m, 10H, Ar-H).

实施例 11

VIII-11 (1SR,2RS)- N^1 -对硝基苄基- N^4 -[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪
(苏式体)

将 N'-对硝基苄基哌嗪 (10mmol) 和 2-(α -溴-己酮)-5-氯-6-甲氧基萘 (10mmol),
按通法二~通法四合成 N'-对硝基苄基-N'-[1-丁基-2-羧基-2-(5-氯-6-甲氧基萘-2-基)]
乙基哌嗪盐酸盐 3.94g, 收率 77%, m.p=233.5-235.7°C(dec).

将 N'-对硝基苄基-N'-[1-丁基-2-羧基-2-(5-氯-6-甲氧基萘-2-基)]乙基哌嗪按通
5 法五进行羧基的还原反应, 得 N'-对硝基苄基-N'-[1-丁基-2-羟基-2-(5-氯-6-甲氧基萘
-2-基)]乙基哌嗪盐酸盐 3.47g, 收率 88%. 将其游离后, 柱层析分离得其赤式体产物,
加乙醇溶解, 用 HCl/C₂H₅OH (5N) 调 pH=2, 过滤析出的固体, 乙醇/水或甲醇重结晶,
得化合物(VIII-11), m.p=228.7-221.0°C(dec). MS: m/z 512 (M⁺).

¹HNMR(DMSO-d₆): δ 0.72-1.60(m, 9H, CH₂CH₂CH₂CH₃), 2.27-2.70(m, 9H, CH+哌嗪
10 -H), 3.40(s, 2H, CH₂-Ph), 3.98(s, 3H, OCH₃), 5.0 (d, 1H, CH, J=4.4), 5.10(s, 1H, OH),
7.20-8.02(m, 9H, Ar-H).

实施例 12

VIII-12 (1SR,2SR)-N'-对硝基苄基-N'-[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪
(苏式体)

15 将 N'-对硝基苄基哌嗪 (10mmol) 和 2-(α -溴-己酮)-5-氯-6-甲氧基萘 (10mmol),
按通法二~通法四合成 N'-对硝基苄基-N'-[1-丁基-2-羧基-2-(5-氯-6-甲氧基萘-2-基)]
乙基哌嗪盐酸盐 3.94g, 收率 77%, m.p=233.5-235.7°C(dec).

将 N'-对硝基苄基-N'-[1-丁基-2-羧基-2-(5-氯-6-甲氧基萘-2-基)]乙基哌嗪按通
法五进行羧基的还原反应, 得 N'-对硝基苄基-N'-[1-丁基-2-羟基-2-(5-氯-6-甲氧基萘
20 -2-基)]乙基哌嗪盐酸盐 3.47g, 收率 88%. 将其游离后, 柱层析分离得其苏式体产物,
加乙醇溶解, 用 HCl/C₂H₅OH (5N) 调 pH=2, 过滤析出的固体, 乙醇/水或甲醇重结晶,
得化合物(VIII-12), m.p=226.8-229.0°C(dec). MS: m/z 512 (M⁺).

¹HNMR(DMSO-d₆): δ 0.65-1.51(m, 9H, CH₂CH₂CH₂CH₃), 2.49-2.97(m, 9H, CH+哌嗪

-H), 3.78(s, 3H, OCH₃), 4.6(d, 1H, CH, J=8.0), 5.14(d, 1H, OH), 6.96-8.16(m, 9H, Ar-H).

实施例 13

VIII-13 (1SR,2RS)-N¹-对氨基苄基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-巯基)羟乙基]哌嗪
(赤式体)

5 将 N¹-对氨基苄基哌嗪 (10mmol) 和 2-(α-溴-己酮)-5-氯-6-甲氧基苯 (10mmol), 按通法二~通法四合成 N¹-对氨基苄基-N⁴-[1-丁基-2-巯基-2-(5-氯-6-甲氧基苯-2-基)]乙基哌嗪盐酸盐 3.76g, 收率 78%, m.p=233.6-235.9℃(dec).

将 N¹-对氨基苄基-N⁴-[1-丁基-2-巯基-2-(5-氯-6-甲氧基苯-2-基)]乙基哌嗪按通法
五进行巯基的还原反应, 得 N¹-对氨基苄基-N⁴-[1-丁基-2-羟基-2-(5-氯-6-甲氧基苯-2-
10 基)]乙基哌嗪盐酸盐 3.27g, 收率 87%. 将其游离后, 柱层析分离得其赤式体产物, 加
乙醇溶解, 用 HCl/C₂H₅OH (5N) 调 pH=2, 过滤析出的固体, 乙醇/水或甲醇重结晶, 得
化合物(VIII-13), m.p=219.4-221.0℃(dec). MS: m/z 482 (M⁺).

¹HNMR(DMSO-d₆): δ 0.72-1.60(m, 9H, CH₂CH₂CH₂CH₃), 2.27-2.70(m, 9H, CH+哌嗪
-H), 3.40(s, 2H, CH₂Ph), 3.98(s, 3H, OCH₃), 4.0(m, 2H, NH₂), 5.0(d, 1H, CH, J=4.4), 5.10(s,
15 1H, OH), 7.20-8.02(m, 9H, Ar-H).

实施例 14

VIII-14 (1SR,2SR)-N¹-对氨基苄基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-巯基)羟乙基]哌嗪
(苏式体)

将 N¹-对氨基苄基哌嗪 (10mmol) 和 2-(α-溴-己酮)-5-氯-6-甲氧基苯 (10mmol),
20 按通法二~通法四合成 N¹-对氨基苄基-N⁴-[1-丁基-2-巯基-2-(5-氯-6-甲氧基苯-2-基)]
乙基哌嗪盐酸盐 3.76g, 收率 78%, m.p=233.6-235.9℃(dec).

将 N¹-对氨基苄基-N⁴-[1-丁基-2-巯基-2-(5-氯-6-甲氧基苯-2-基)]乙基哌嗪按通法
五进行巯基的还原反应, 得 N¹-对氨基苄基-N⁴-[1-丁基-2-羟基-2-(5-氯-6-甲氧基苯-2-

基)]乙基哌嗪盐酸盐 3.27g, 收率 87%。将其游离后, 柱层析分离得其苏式体产物。加乙醇溶解, 用 HCl/C₂H₅OH (5N) 调 pH=2, 过滤析出的固体, 乙醇/水或甲醇重结晶, 得化合物(VIII-14), m.p=215.2-218.0°C(dec)。MS : m/z 482 (M⁺)。

¹H NMR(DMSO-d₆): δ 0.65-1.51(m, 9H, CH₂CH₂CH₂CH₃), 2.49-2.97(m, 9H, CH+哌嗪-H), 3.78(s, 3H, OCH₃), 3.87(s, 3H, OCH₃), 4.0(m, 2H, NH₂), 4.6 (d, 1H, CH, J=8.0), 5.14(d, 1H, OH), 6.86-8.06(m, 9H, Ar-H)。

实施例 15

VIII-15 (1SR,2RS)-N¹-(3',4',5'-三甲氧基苄基)-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪 (苏式体)

10 将 N¹-(3',4',5'-三甲氧基苄基)哌嗪 (10mmol) 和 2-(α-溴-己酮)-5-氯-6-甲氧基萘 (10mmol), 按通法二~通法四合成 N¹-(3',4',5'-三甲氧基苄基)-N⁴-[1-丁基-2-羰基-2-(5-氯-6-甲氧基萘-2-基)]乙基哌嗪盐酸盐 4.18g, 收率 75%, m.p=235.5-238.6°C(dec)。

将 N¹-(3',4',5'-三甲氧基苄基)-N⁴-[1-丁基-2-羰基-2-(5-氯-6-甲氧基萘-2-基)]乙基哌嗪按通法五进行羰基的还原反应, 得 N¹-(3',4',5'-三甲氧基苄基)-N⁴-[1-丁基-2-羟基-2-(5-氯-6-甲氧基萘-2-基)]乙基哌嗪盐酸盐 3.63g, 收率 87%。将其游离后, 柱层析分离得其苏式体产物, 加乙醇溶解, 用 HCl/C₂H₅OH (5N) 调 pH=2, 过滤析出的固体, 乙醇/水或甲醇重结晶, 得化合物(VIII-15), m.p=221.3-223.6°C(dec)。MS : m/z 557 (M⁺)。

15 ¹H NMR(DMSO-d₆): δ 0.72-1.60(m, 9H, CH₂CH₂CH₂CH₃), 2.27-2.70(m, 9H, CH+哌嗪-H), 3.40(s, 2H, CH₂ Ph), 3.70(m, 9H, OCH₃), 3.98(s, 3H, OCH₃), 4.0(m, 2H, NH₂), 5.0 (d, 1H, CH, J=4.4), 5.10(s, 1H, OH), 7.20-8.02(m, 7H, Ar-H)。

实施例 16

VIII-16 (1SR,2SR)-N¹-(3',4',5'-三甲氧基苄基)-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪 (苏式体)

将 N¹-(3',4',5'-三甲氧基苄基)哌嗪 (10mmol) 和 2-(α -溴-己酮)-5-氯-6-甲氧基蔡 (10mmol), 按通法二~通法四合成 N¹-(3',4',5'-三甲氧基苄基)-N⁴-[1-丁基-2-羧基-2-(5-氯-6-甲氧基蔡-2-基)]乙基哌嗪盐酸盐 4.18g, 收率 75%, m.p.=235.5-238.6°C(dcc).

将 N¹-(3',4',5'-三甲氧基苄基)-N⁴-[1-丁基-2-羧基-2-(5-氯-6-甲氧基蔡-2-基)]乙基哌嗪按通法五进行羧基的还原反应, 得 N¹-(3',4',5'-三甲氧基苄基)-N⁴-[1-丁基-2-羟基-2-(5-氯-6-甲氧基蔡-2-基)]乙基哌嗪盐酸盐 3.63g, 收率 87%. 将其游离后, 柱层析分离得其苏式体产物, 加乙醇溶解, 用 HCl/C₂H₅OH (5N)调 pH=2, 过滤析出的固体, 乙醇/水或甲醇重结晶, 得化合物(VIII-16), m.p.=226.5-228.8°C(dec). MS: m/z 557 (M⁺).

¹HNMR(DMSO-d₆): δ 0.65-1.51(m, 9H, CH₂CH₂CH₂CH₃), 2.49-2.97(m, 9H, CH-哌嗪-H), 3.70(m, 9H, OCH₃), 3.78(s, 3H, OCH₃), 3.87(s, 3H, OCH₃), 4.6 (d, 1H, CH, J=8.0), 5.14(d, 1H, OH), 6.86-8.06(m, 7H, Ar-H).

实施例 17

VIII-17 (1SR,2RS)-N¹- α -苄基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪 (赤式体)

将 N¹- α -苄基哌嗪 (10mmol) 和 2-(α -溴-己酮)-5-氯-6-甲氧基蔡 (10mmol), 按通法二~通法四合成 N¹- α -苄基-N⁴-[1-丁基-2-羧基-2-(5-氯-6-甲氧基蔡-2-基)]乙基哌嗪盐酸盐 4.22g, 收率 78%, m.p.=241.7-243.3°C(dcc).

将 N¹-苄基-N⁴-[1-丁基-2-羧基-2-(5-氯-6-甲氧基蔡-2-基)]乙基哌嗪按通法五进行羧基的还原反应, 得 N¹-苄基-N⁴-[1-丁基-2-羟基-2-(5-氯-6-甲氧基蔡-2-基)]乙基哌嗪盐酸盐 3.75g, 收率 89%. 将其游离后, 柱层析分离得其赤式体产物, 加乙醇溶解, 用 HCl/C₂H₅OH (5N)调 pH=2, 过滤析出的固体, 乙醇/水或甲醇重结晶, 得化合物(VIII-17), m.p.=235.0-237.6°C(dcc). MS: m/z 481.1 (M⁺).

¹HNMR(DMSO-d₆): δ 0.54-0.63(m, 3H, CH₂CH₂CH₃), 0.78-1.24(m, 6H,

$\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.57-1.75(m, 3H, CHCH_3), 1.83-1.86(m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 3.44-3.59(m, 8H, 咪唑-H), 3.99(s, 3H, OCH_3), 4.57(m, 1H, $\text{CH}_3\text{-CH-Ph}$), 4.57(m, 1H, CH), 5.66-5.67(d, 1H, CH, $J=4.8$), 7.48-8.11(m, 10H, Ar-H)。

实施例 18

- 5 VIII-18 (1SR,2SR)- N^1 - α -苄乙基- N^4 -[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪 (苏式体)

将 N^1 - α -苄乙基哌嗪 (10mmol) 和 2-(α -溴-己酮)-5-氯-6-甲氧基萘 (10mmol), 按通法二~通法四合成 N^1 - α -苄乙基- N^4 -[1-丁基-2-羰基-2-(5-氯-6-甲氧基萘-2-基)]乙基哌嗪盐酸盐 4.22g, 收率 78%, $m.p.=241.7-243.3^\circ\text{C}(\text{dec})$ 。

- 10 将 N^1 -苄基- N^4 -[1-丁基-2-羰基-2-(5-氯-6-甲氧基萘-2-基)]乙基哌嗪按通法五进行羰基的还原反应, 得 N^1 -苄基- N^4 -[1-丁基-2-羟基-2-(5-氯-6-甲氧基萘-2-基)]乙基哌嗪盐酸盐 3.75g, 收率 89%。将其游离后, 柱层析分离得其苏式体产物, 加乙醇溶解, 用 $\text{HCl}/\text{C}_2\text{H}_5\text{OH}$ (5N) 调 $\text{pH}=2$, 过滤析出的固体, 乙醇/水或甲醇重结晶, 得化合物(VIII-18), $m.p.=224.0-226.1^\circ\text{C}$, $\text{MS}: m/z$ 481 (M^+)。

- 15 ^1H NMR(DMSO- d_6): δ 0.61-0.65(m, 3H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.88-1.06(m, 6H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.28-1.29(m, 3H, CHCH_3), 2.33-2.76(m, 8H, 咪唑), 2.50-2.510(m, 1H, CH-N), 3.25-3.39(m, 1H, $\text{CH}_3\text{-CH-Ph}$), 3.99(s, 3H, OCH_3), 4.47-4.51(m, 1H, CH, $J=8.4$), 5.05(d, 1H, OH), 7.23-8.03(m, 10H, Ar-H)。

实施例 19

- 20 VIII-19 (1SR,2RS)- N^1 -二苯甲基- N^4 -[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪 (苏式体)

将 N^1 -二苯甲基哌嗪 (10mmol) 和 2-(α -溴-己酮)-5-氯-6-甲氧基萘 (10mmol), 按通法二~通法四合成 N^1 -二苯甲基- N^4 -[1-丁基-2-羰基-2-(5-氯-6-甲氧基萘-2-基)]乙基哌嗪

基哌嗪盐酸盐 4.68g, 收率 76%, m.p=212.9-215.2°C(dec).

将 N¹-二苯甲基-N⁴-[1-丁基-2-羧基-2-(5-氯-6-甲氧基苯-2-基)]乙基哌嗪按通法五进行羧基的还原反应, 得 N¹-二苯甲基-N⁴-[1-丁基-2-羟基-2-(5-氯-6-甲氧基苯-2-基)]乙基哌嗪盐酸盐 4.83g, 收率 85%。将其游离后, 柱层析分离得其赤式体产物, 加乙醇溶解, 用 HCl/C₂H₅OH (5N)调 pH=2, 过滤析出的固体, 乙醇/水或甲醇重结晶, 得化合物(VIII-19), m.p=183.0-184.6°C(dec). MS: m/z 543 (M⁺).

¹HNMR(DMSO-d₆): δ 0.71-1.60(m, 9H, CH₂CH₂CH₂CH₃), 2.24-2.74(m, 9H, CH+哌嗪-H), 4.22(s, 1H, CH Ph₂), 3.98(s, 3H, OCH₃), 5.0 (d, 1H, CH, J=3.6), 5.11(d, 1H, OH), 7.14-8.01(m, 15H, Ar-H).

实施例 20

VIII-20 (1SR,2SR)-N¹-二苯甲基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪 (苏式体)

将 N¹-二苯甲基哌嗪 (10mmol) 和 2-(α-溴-己酮)-5-氯-6-甲氧基苯 (10mmol), 按通法二~通法四合成 N¹-二苯甲基-N⁴-[1-丁基-2-羧基-2-(5-氯-6-甲氧基苯-2-基)]乙基哌嗪盐酸盐 4.68g, 收率 76%, m.p=212.9-215.2°C(dec).

将 N¹-二苯甲基-N⁴-[1-丁基-2-羧基-2-(5-氯-6-甲氧基苯-2-基)]乙基哌嗪按通法五进行羧基的还原反应, 得 N¹-二苯甲基-N⁴-[1-丁基-2-羟基-2-(5-氯-6-甲氧基苯-2-基)]乙基哌嗪盐酸盐 4.13g, 收率 85%。将其游离后, 柱层析分离得其苏式体产物, 加乙醇溶解, 用 HCl/C₂H₅OH (5N)调 pH=2, 过滤析出的固体, 乙醇/水或甲醇重结晶, 得化合物(VIII-20), m.p=179.3-181.1°C(dec). MS: m/z 543 (M⁺).

¹HNMR(DMSO-d₆): δ 0.63-1.46(m, 9H, CH₂CH₂CH₂CH₃), 2.33-2.82(m, 9H, CH+哌嗪-H), 4.28(s, 1H, CH Ph₂), 3.98(s, 3H, OCH₃), 4.5 (d, 1H, CH, J=8.4), 5.06(s, 1H, OH), 7.16-8.03(m, 15H, Ar-H).

实施例 21

VIII-21 (1SR,2RS)-N¹-肉桂基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪
(赤式体)。

将 N¹-肉桂基哌嗪 (10mmol) 和 2-(α -溴-己酮)-5-氯-6-甲氧基萘 (10mmol), 按
5 通法二~通法四合成 N¹-肉桂基-N⁴-[1-丁基-2-羰基-2-(5-氯-6-甲氧基萘-2-基)]乙基哌
嗪盐酸盐 4.61g, 收率 82%, m.p=232.2-234.0°C(dec)。

将 N¹-肉桂基-N⁴-[1-丁基-2-羰基-2-(5-氯-6-甲氧基萘-2-基)]乙基哌嗪按通法五进
行羰基的还原反应, 得 N¹-肉桂基-N⁴-[1-丁基-2-羟基-2-(5-氯-6-甲氧基萘-2-基)]乙基哌
嗪盐酸盐 4.19g, 收率 91%。将其游离后, 柱层析分离得其赤式体产物, 加乙醇溶解,
10 用 HCVC₂H₅OH (5N) 调 pH=2, 过滤析出的固体, 乙醇/水或甲醇重结晶, 得化合物
(VIII-21), m.p=228.8-230.1°C(dec)。MS: m/z 493 (M⁺)。

¹HNMR(DMSO-d₆): 0.73-1.60(m, 9H, CH₂CH₂CH₂CH₃), 2.31-3.04(m, 11H, CH+
CH₂+哌嗪-H), 3.98(s, 3H, OCH₃), 4.9 (d, 1H, CH, J=4.0), 5.11(d, 1H, OH), 6.23-6.52(m, 2H,
CH=CH), 7.22-8.02(m, 10H, Ar-H)。

实施例 22

15

VIII-22 (1SR,2SR)-N¹-肉桂基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪
(苏式体)

将 N¹-肉桂基哌嗪 (10mmol) 和 2-(α -溴-己酮)-5-氯-6-甲氧基萘 (10mmol),
按通法二~通法四合成 N¹-肉桂基-N⁴-[1-丁基-2-羰基-2-(5-氯-6-甲氧基萘-2-基)]乙基
20 哌嗪盐酸盐 4.61g, 收率 82%, m.p=232.2-234.0°C(dec)。

将 N¹-肉桂基-N⁴-[1-丁基-2-羰基-2-(5-氯-6-甲氧基萘-2-基)]乙基哌嗪按通法五进
行羰基的还原反应, 得 N¹-肉桂基-N⁴-[1-丁基-2-羟基-2-(5-氯-6-甲氧基萘-2-基)]乙基哌
嗪盐酸盐 4.19g, 收率 91%。将其游离后, 柱层析分离得其苏式体产物, 加乙醇溶解,

用 $\text{HCl}/\text{C}_2\text{H}_5\text{OH}$ (5N) 调 $\text{pH}=2$, 过滤析出的固体, 乙醇/水或甲醇重结晶, 得化合物 (VIII-22), $\text{m.p.}=194.1-195.6^\circ\text{C}(\text{dec})$. MS: m/z 493 (M^+).

^1H NMR(DMSO- d_6): δ 0.36-1.49(m, 9H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2.43-3.27(m, 11H, $\text{CH}+\text{CH}_2$ +咪唑-H), 3.98(s, 3H, OCH_3), 4.5 (d, 1H, CH , $J=8.0$), 5.18(s, 1H, OH), 6.24-6.55(m, 2H, $\text{CH}=\text{CH}$), 7.21-8.05(m, 10H, Ar-H).

实施例 23

(S)-2-(1,3-二巯基异吲哚)己酸 (2) 的合成

甲苯 150ml 搅拌下加入 L-正亮氨酸 6.55g (0.05mol), 邻苯二甲酸酐 7.40g (0.05mol), 三乙胺 0.8ml, 外温 110°C , 回流反应 24 小时后, 反应完全。放冷, 蒸除溶剂, 加入水 (50ml), 乙酸乙酯萃取 (50ml $\times$ 3), 乙酸乙酯层经饱和食盐水洗, 无水 MgSO_4 干燥, 过滤后, 滤液蒸除溶剂, 得白色固体 12.28g, 收率为 90.3%。MS: m/z 262 (M^+). ^1H NMR(DMSO- d_6): δ 0.86-1.37(m, 9H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 4.46 (m, 1H, CH), 7.25-7.86 (m, 4H, Ar-H).

实施例 24

(R)-2-(1,3-二巯基异吲哚)己酸的制备方法同 (S)-2-(1,3-二巯基异吲哚)己酸 (2), 收率为 87.6%。MS: m/z 262 (M^+). ^1H NMR(DMSO- d_6): δ 0.90-1.25(m, 9H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 4.68 (m, 1H, CH), 7.42-7.91 (m, 4H, Ar-H).

实施例 25

(S)-2-[2-(1,3-二巯基异吲哚)己酰基]-5-氯-6-甲氧基苯 (5) 的合成。

0°C 条件下, 化合物 2 10.45 g (0.04mol), 溶于 100ml 二氯甲烷中。冰浴下缓慢滴加草酰氯 8.15ml (0.1mol), 滴毕, 加入吡啶 8 滴, 缓慢升至室温, 继续搅拌 20 小时。在 35°C 下将过量的酰氯与溶剂旋蒸去除, 溶解于二氯甲烷 100ml, 加入化合物 4 9.25g (0.048mol), 无水三氯化铝 6.41g (0.048mol), 室温反应 30 小时。将反应液缓慢倒入 1N

的 HCl (100ml) /冰/二氯甲烷 (100ml) 混合液中, 搅拌, 静置分层, 水层用二氯甲烷 (100ml×2) 萃取, 合并二氯甲烷层, 经饱和食盐水洗, 无水 MgSO_4 干燥, 过滤, 滤液蒸除溶剂, 得深棕色油状物, 柱层析 (中性氧化铝, 石油醚: 乙酸乙酯=3:1), 得浅黄色油状物 4.68g, 收率为 26.8%。MS: m/z 438(M^+)。 ^1H NMR(DMSO- d_6): δ 0.96-1.77(m, 9H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 3.73(s, 3H, OCH_3), 5.09 (m, 1H, CH), 7.64-8.34 (m, 9H, Ar-H)。

实施例 26

(R)-2-[2-(1,3-二巯基异吲哚)己酰基]-5-氯-6-甲氧基苯的制备方法同(S)-2-[2-(1,3-二巯基异吲哚)己酰基]-5-氯-6-甲氧基苯 (5)。收率为 28.4%。MS: m/z 438(M^+)。 ^1H NMR(DMSO- d_6): δ 1.03-1.62(m, 9H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 3.10(s, 3H, OCH_3), 5.14 (m, 1H, CH), 7.35-8.11 (m, 9H, Ar-H)。

实施例 27

(2S)-2-[1-羟基-2-(1,3-二巯基异吲哚)己基]-5-氯-6-甲氧基苯 (6) 的合成。

化合物 5 4.36 g(0.01mol)溶解于甲苯 19.2ml 和异丙醇 12.6ml, 加入异丙醇铝 10.2g(0.05mol), 100℃加热反应 4 小时。反应完全后, 放冷, 蒸除溶剂, 加入 1N 的 HCl (50ml), 乙酸乙酯萃取 (50ml×3), 乙酸乙酯层经少量水洗, 饱和食盐水洗, 无水 MgSO_4 干燥, 过滤, 滤液蒸干, 得浅黄色固体 4.32g, 收率为 98.6%。MS: m/z 439(M^+)。 ^1H NMR(DMSO- d_6): δ 0.96-1.58(m, 9H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 3.73(s, 3H, OCH_3), 4.05(m, 1H, CHN), 5.12 (m, 1H, CHOH), 7.34-8.08 (m, 9H, Ar-H)。

实施例 28

(2R)-2-[1-羟基-2-(1,3-二巯基异吲哚)己基]-5-氯-6-甲氧基苯的制备方法同 (2S)-2-[1-羟基-2-(1,3-二巯基异吲哚)己基]-5-氯-6-甲氧基苯 (6)。收率为 97.4%。MS: m/z 439(M^+)。 ^1H NMR(DMSO- d_6): δ 0.89-1.44(m, 9H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 3.70(s, 3H, OCH_3), 4.19(m, 1H, CHN), 5.07 (m, 1H, CHOH), 7.12-8.00 (m, 9H, Ar-H)。

实施例 29

(1S)-2-(5-氯-6-甲氧基萘)-2-羟基-1-丁基乙胺(7)的合成

化合物 6 2.15g (0.005mol) 溶解于甲醇 15ml 中, 加入水合肼 5ml(0.01mol), 室温搅拌约 3 小时, 有白色固体生成。过滤, 滤液蒸除溶剂, 加入水 (20ml)/二氯甲烷 (20ml × 3) 萃取, 合并二氯甲烷层, 经饱和食盐水洗, 无水 $MgSO_4$ 干燥。过滤, 滤液蒸除溶
 5 剂, 得白色固体 1.13g, 收率为 73.4%。MS : m/z 309 (M^+)。 ^1H NMR(DMSO- d_6): δ 0.93-1.54(m, 9H, $CH_2CH_2CH_2CH_3$), 3.08(m, 1H, CHN), 3.77(s, 3H, OCH_3), 4.75 (m, 1H, CHOH), 7.50-8.17 (m, 5H, Ar-H)。

实施例 30

10 (1R)-2-(5-氯-6-甲氧基萘)-2-羟基-1-丁基乙胺的制备方法同(1S)-2-(5-氯-6-甲氧基萘)-2-羟基-1-丁基乙胺(7)。收率为 70.1%。MS : m/z 309 (M^+)。 ^1H NMR(DMSO- d_6): δ 1.11-1.77(m, 9H, $CH_2CH_2CH_2CH_3$), 3.14(m, 1H, CHN), 3.58(s, 3H, OCH_3), 4.69 (m, 1H, CHOH), 7.75-8.29 (m, 5H, Ar-H)。

实施例 31

15 (1S, 2R)- N^1 -苄基- N^4 -[1-丁基-2-羟基-2-(5'-氯-6'-甲氧基-2')-萘基乙基]哌嗪盐酸盐 (IX-23) 和 (1S, 2S)- N^1 -苄基- N^4 -[1-丁基-2-羟基-2-(5'-氯-6'-甲氧基-2')-萘基乙基]哌嗪盐酸盐 (IX-24) 的制备。

化合物 7 0.924g (0.003mol), 加入乙腈 10ml, 三乙胺 2ml, 化合物 8 (参照专利 US4748726 制备) 1.624g (0.007mol) 加热至回流, 回流反应 20 小时, TLC 检测, 反应
 20 完全。蒸除乙腈, 加入氯仿 (50ml × 3)、水萃取, 合并氯仿层, 硫酸镁干燥, 蒸除氯仿, 得黄色油状物, 为两个异构体的混和物 (9)。MS : m/z 465 (M^+)。

对混和物 9 进行硅胶柱层分离, 洗脱剂二氯甲烷: 甲醇 = 200:1, 先出柱的 (1S, 2S) 异构体为黄色油状物 0.47 克 (收率 34%), 加入甲醇 20ml 溶解, 加入盐酸/乙醇调节 pH

=2, 有白色固体析出, 过滤得白色产物 0.25 克。

后出柱的 (1S,2R) 异构体为黄色油状物 0.12 克 (收率 8.5%), 加入甲醇 10ml 溶解。

加入盐酸/乙醇调节 PH=2, 有淡黄色固体析出, 过滤后烘干得黄色产物 0.05 克。

IX-23: mp: 225.0~225.8°C (dec); MS: m/z 467 (M+); ¹HNMR(DMSO-d₆): δ 0.36-1.86(m, 9H, CH₂CH₂CH₂CH₃), 3.54-3.80(m, 9H, CH+咪唑-H), 3.96(s, 2H, CH₂-Ph), 4.42(s, 3H, OCH₃), 5.519-5.524 (d, 1H, CH, J=2.0), 7.43-8.14(m, 10H, Ar-H)。

IX-24: mp: 223.1~224.3°C (dec); MS: m/z 467 (M+); ¹HNMR(DMSO-d₆): δ 0.33-1.58(m, 9H, CH₂CH₂CH₂CH₃), 3.62-3.79(m, 9H, CH+咪唑-H), 3.95(s, 2H, CH₂-Ph), 4.42(s, 3H, OCH₃), 4.913-4.937(d, 1H, CH, J=9.6), 7.43-8.17(m, 10H, Ar-H)。

实施例 32

10

(1R, 2S) -N¹-苄基-N⁴-[1-丁基-2-羟基-2-(5'-氯-6'-甲氧基-2')-蔡基乙基]咪唑盐酸盐 (IX-25) 和 (1R, 2R) -N¹-苄基-N⁴-[1-丁基-2-羟基-2-(5'-氯-6'-甲氧基-2')-蔡基乙基]咪唑盐酸盐 (IX-26) 的制备方法同实施例 31。

IX-25: mp: 225.0~225.8°C (dec); MS: m/z 467 (M+); ¹HNMR(DMSO-d₆): δ 0.36-1.86(m, 9H, CH₂CH₂CH₂CH₃), 3.54-3.80(m, 9H, CH+咪唑-H), 3.96(s, 2H, CH₂-Ph), 4.42(s, 3H, OCH₃), 5.519-5.524 (d, 1H, CH, J=2.0), 7.43-8.14(m, 10H, Ar-H)。

IX-26: mp: 223.1~224.3°C (dec); MS: m/z 467 (M+); ¹HNMR(DMSO-d₆): δ 0.33-1.58(m, 9H, CH₂CH₂CH₂CH₃), 3.62-3.79(m, 9H, CH+咪唑-H), 3.95(s, 2H, CH₂-Ph), 4.42(s, 3H, OCH₃), 4.913-4.937(d, 1H, CH, J=9.6), 7.43-8.17(m, 10H, Ar-H)。

实施例 33

20

片剂: 本发明的衍生物	10mg
蔗糖	150mg
玉米淀粉	38mg

硬脂酸钙 2mg

制备方法：将活性成分与蔗糖、玉米淀粉混合，加水湿润，搅拌均匀，干燥，粉碎过筛，加入硬脂酸钙，混合均匀，压片。每片重 200 mg，活性成分含量为 10mg。

实施例 34

5 针剂：本发明的衍生物 20mg

注射用水 80mg

制备方法：将活性成分溶解与注射用水，混合均匀，过滤，将所获得的溶液在无菌条件下分装与安瓿瓶中，每瓶 10mg，活性成分含量为 2mg/瓶。

实施例 35

10 化合物对脑突触体再摄取 5-HT、NA 和 DA 的抑制作用：

采用脑突触体对单胺类神经递质再摄取的研究方法，是目前国际上对中枢神经药理研究的重要手段，该方法不仅可以用来研究药物的作用机制，还可以筛选作用于此类环节的新药。本发明采用脑突触体对单胺类神经递质 5-HT、NA 和 DA 再摄取的研究方法，以有效的 5-HT、NA 双重再摄取抑制剂文拉法辛 (Venlafaxine) 和 6-羟 DA 作为阳性对照品，

15 对所发明化合物抑制脑突触体对 5-HT、NA 及 DA 再摄取的作用进行研究。

1、大鼠脑突触体的制备

雄性 SD 大鼠拉颈处死后迅速断头取脑，置于冰上，分离相关脑组织 ($[^3H]$ 5-HT、 $[^3H]$ NA 再摄取试验取前额皮层， $[^3H]$ DA 再摄取试验取纹状体)，称重后，加入 10 倍 (V/W) 冰冷 0.32mol/L 蔗糖液，玻璃-teflon 电动匀浆；匀浆液 4℃ 下 1000g × 10min 离心；
20 取上清，4℃ 下 17000g × 20min 离心；取沉淀，以 30 倍体积 KRH Buffer (125mM NaCl, 4.8mM KCl, 1.2mM $CaCl_2$, 1.2mM $MgSO_4$, 1.0mM KH_2PO_4 , 22mM $NaHCO_3$, 25mM HEPES, 10mM Glucose, 10μM Pargyline, 0.2mg/ml Ascorbic Acid) 悬浮，置于冰浴中备用。
(其中 NA 再摄取试验所需皮层以 20 倍体积悬浮)。

2. [^3H]5-HT/NA/DA 再摄取试验

受试品贮备液临用前取出解冻,以 KRH Buffer 稀释至 $100\mu\text{mol/L}$,取 $50\mu\text{l}$ 加入 $500\mu\text{l}$ 总反应体系中,终浓度即为 $10\mu\text{mol/L}$,再加入 $50\mu\text{l}$ 悬浮的以上制备的突触体,混匀, 37°C 水浴中孵育 30min ;加入 10nmol/L [^3H] 5-HT(50nmol/L [^3H]DA 或 60nmol/L [^3H]NA), 37°C 水浴孵育 10min 后立即取出加入 2ml 冰冷的 150mmol/L Tris-HCl 缓冲液终止反应,真空抽滤收集样品于圆形玻璃纤维膜上,以冰冷的 Tris-HCl 缓冲液 3ml 洗膜三次;取下滤膜,远红外烤箱中烘烤 15min 后置于 EP 管中,加入 1.5ml 闪烁液,过夜后液体闪烁计数器检测。溶剂对照总结合管与非特异性结合管中不加受试物,总结合管中加入 $50\mu\text{l}$ 溶剂。

3. 结果:

以 0.1mM 的文拉法辛、6-羟 DA 对单胺再摄取的抑制率为 100% ,化合物的抑制强度和其进行比较,测定结果见表 3。

表 3 化合物对脑突触体 5-HT、NA、DA 再摄取抑制百分率 (%)

化合物	抑制 5-HT 再摄取 (%)	抑制 NA 再摄取 (%)	抑制 DA 再摄取 (%)
文拉法辛	100	100	/
6-羟 DA	/	/	100
VIII-3	65.1	144	96
VIII-4	23	146.5	68
VIII-9	125	155.2	117
VIII-10	136	145	133
VIII-19	73.4	103.6	95
VIII-20	0	78	57
VIII-21	81	87.5	90
VIII-22	82.3	78.9	94

4. 结论:

本发明所述 1-丁基-2-羟基芳烷哌嗪衍生物属三重再摄取抑制剂,体外具有较强的

DA、NE、5-HT 三种单胺递质再摄取剂作用。优选化合物 VIII-9、VIII-10 体外三重再摄取抑制活性强于阳性对照药文拉法辛。

实施例 36

优选化合物 VIII-9、VIII-10 抑制脑突触体再摄取 5-HT、NA 和 DA 的 IC_{50} 测定

5 1、大鼠脑突触体的制备(同实施例 35)

2、 $[^3H]$ 5-HT/NA/DA 再摄取抑制效应 (IC_{50}) 的研究

化合物用于 $[^3H]$ 5-HT/NA/DA 再摄取抑制效应 (IC_{50}) 的研究, 各试药每次至少设 5 个浓度, 每浓度双复管取均值, 重复试验 3 次以上。化合物临用前以梯度稀释法配成系列浓度, 取 $50 \mu l$ 加入总反应体系中, 再加入 $50 \mu l$ 悬浮的突触体膜, 混匀, $37^\circ C$ 水浴中孵育 30min; 加入 $10nmol/L [^3H]$ 5-HT(或 $50nmol/L [^3H]$ DA 或 $40nmol/L [^3H]$ NA), $37^\circ C$ 水浴孵育 10min ($[^3H]$ NA 孵育 5min); $[^3H]$ 5-HT 再摄取试验的非特异性结合管中加入 $100 \mu mol/L$ 氟西汀 $50 \mu L$, $[^3H]$ DA 再摄取试验的非特异性结合管中加入 $600 \mu mol/L$ 可卡因 $50 \mu L$, $[^3H]$ NA 再摄取试验的非特异性结合管中加入 $100 \mu mol/L$ 地昔帕明 $50 \mu L$, 溶剂对照总结合管中加入溶剂, 不加受试药品。

15 3、数据处理

各试样管特异性结合 CPM 值 = 各试样管总结合 CPM 值 - 非特异性管 CPM 值;
化合物对大鼠前额皮层/纹状体 $[^3H]$ 5-HT/NA/DA 摄取的抑制率 (%) = $100\% - \frac{\text{试药管特异性结合 (CPM 值)}}{\text{溶剂组特异性结合 (CPM 值)}} \times 100\%$; 各试药所得数据应用 Origin 6.1 作 sigmoidal 曲线拟合, 并计算 IC_{50} 值。

20 4、 IC_{50} 测定试验结果

化合物对大鼠前额皮层/纹状体突触体 5-HT、NA、DA 再摄取抑制 IC_{50} 见表 4。

表4 化合物对 5-HT、NA、DA 再摄取抑制效应 IC_{50} (mean $\pm$ SE, n=3~4)

化合物	IC_{50} (nmol/L)		
	[^3H]5-HT	[^3H]NA	[^3H]DA
文拉法辛	145	1420	3070
SIPIyy24	200	1000	测不出活性
SIPI5286	12	185	1150
VIII-9	73.28	2.8	2.1
VIII-10	271.51	4726.1	165.4

注：化合物 SIPIyy24 为专利 ZL 02111934.1 的优选化合物；化合物 SIPI5286 为专利 ZL 200510030354.1 的优选化合物

5、结论：

- 5 化合物 VIII-10 体外 5-HT、NA 再摄取抑制活性与文拉法辛、SIPIyy24 相当，对 DA 的再摄取抑制活性强于文拉法辛、SIPIyy24 和 SIPI5286；化合物 VIII-9 对三种单胺递质的再摄取抑制活性均强于文拉法辛、SIPIyy24 和 SIPI5286。

实施例 37

四个光学异构体 IX-23~IX-26 体外对三种单胺递质再摄取剂作用

10 1、实验材料及方法

实验	材料来源	对照品	方法(参考书目)
NE 再摄取	大鼠下丘脑突触	普罗替林	Perovic and Muller W.E.G. Pharmacological profile of hypericum extract on serotonin uptake by postsynaptic receptors. <i>Arzneim-Forsch. Drug Res.</i> , 1995, 45:1145-1148.
DA 再摄取	大鼠纹状体突触	GBR 12909	Janowsky, Berger, P.; Vocci, F.; Lobarca, R., Skolnick, P.; Paul, S.M. Characterization of sodium-dependent [^3H]GBR-12935 binding in brain: a radioligand for selective labelling of the dopamine transport complex. <i>J. Neurochem.</i> , 1986, 46:1272-1276.
5-HT 再摄取	大鼠脑突触	米帕明	Perovic and Muller W.E.G. Pharmacological profile of hypericum extract on serotonin uptake by postsynaptic receptors. <i>Arzneim-Forsch. Drug Res.</i> , 1995, 45:1145-1148.

2、实验条件

实验	标记物	培养	反应产物	检测方法
NE 再摄取	[3H]NE (μ 0.2Ci/ml)	20min./37°C	[3H]NE 结合突触体	闪烁计数
DA 再摄取	[3H] DA (μ 0.2Ci/ml)	15min./37°C	[3H] DA 结合突触体	闪烁计数
5-HT 再摄取	[3H] 5-HT (μ 0.2Ci/ml)	15min./37°C	[3H] 5-HT 结合突触体	闪烁计数

3、试验结果 (IC₅₀ 值通过对抑制率/浓度响应曲线非线性回归分析得到)

化合物	构型	IC ₅₀ (nM)		
		5-HT	NE	DA
IX-23	(1S,2R)	1900	2100	1000
IX-24	(1S,2S)	3100	1400	1100
IX-25	(1R,2S)	830	140	670
IX-26	(1R,2R)	1200	1200	1100

4、结论:

- 四个光学异构体 IX-23~IX-26 体外具有较强的 DA、NE、5-HT 三种单胺递质再摄取剂作用, 均属三重再摄取抑制剂。

实施例 38

优选化合物 VIII-9、VIII-10 动物体内抗抑郁活性研究:

- 采用“获得性绝望实验”中的鼠强迫游泳“不动”试验 (张均田 主编, 现代药理实验方法 (上册), 北京医科大学中国协和医科大学联合出版社, 1998 年, 第 1064-1066 页), 以文拉法辛为阳性对照药, 对 VIII-9、VIII-10 进行了动物体内抗抑郁作用的研究。

表 5. 单次口服给药对 ICR 小鼠游泳试验的影响 (n=12, $\bar{x} \pm SD$)

组别	药物剂量	游泳试验: 不动时间 (秒)
空白对照	N.S	109.4 $\pm$ 66.19
文拉法辛	50mg/kg	46.5 $\pm$ 25.14**
VIII-9	48mg/kg	104.3 $\pm$ 75.81
	28.8mg/kg	77.4 $\pm$ 53.81
	17.3mg/kg	119.4 $\pm$ 28.02

	10.4mg/kg	74.3±46.63
VIII-10	48mg/kg	64.4±43.01
	28.8mg/kg	40.8±40.24**
	17.3mg/kg	43.4±35.41**
	10.4mg/kg	81.8±39.34
SIP15286	48mg/kg	90.1±26.02**
	28.8mg/kg	92.1±23.11**
	17.3mg/kg	105.4±33.11
	10.4mg/kg	107.9±37.19

* $P < 0.05$, ** $P < 0.01$ 与空白对照组相比

单次口服给药的 ICR 小鼠游泳试验结果表明: 化合物 VIII-9, VIII-10 的体内抗抑郁活性与文拉法辛、SIP15286 相当, 与空白对照组相比具有显著差异。化合物 VIII-9 的 ED_{50} 为 34.3 mg/kg, VIII-10 的 ED_{50} 为 11.8 mg/kg, SIP15286 ED_{50} 为 28.9 mg/kg。VIII-10 体内抗抑郁活性最强。

表 6. 一周口服给药对 ICR 小鼠游泳试验的影响 ($n=12$, $\bar{x} \pm SD$)

组 别	药物剂量	游泳试验: 不动时间 (秒)
空白对照	N.S	133.2±35.88
文拉法辛	50mg/kg	83.5±29.0**
VIII-9	48mg/kg	91.5±58.14**
	28.8mg/kg	87.2±40.07**
	17.3mg/kg	82.1±44.06**
	10.4mg/kg	93.4±26.71**
VIII-10	48mg/kg	68.3±34.01**
	28.8mg/kg	51.9±51.23**
	17.3mg/kg	78.2±25.63**
	10.4mg/kg	77.6±24.69**
SIP15286	48mg/kg	95.5±27.0**
	28.8mg/kg	97.2±28.33**

	17.3mg/kg	102.9±37.94
	10.4mg/kg	123.8±21.68

* $P < 0.05$, ** $P < 0.01$ 与空白对照组相比

连续一周口服给药的 ICR 小鼠游泳试验结果亦显示: 化合物 VIII-9 的体内抗抑郁活性与文拉法辛、SIP15286 相当, 与空白对照组相比具有显著差异; 化合物 VIII-10 的体内抗抑郁活性则强于文拉法辛及 SIP15286。

实施例 39

5

化合物 VIII-9、VIII-10 的急性毒性研究:

对 VIII-9、VIII-10 进行小鼠口服途径急性毒性研究(张均田主编, 现代药理实验方法(下册), 北京医科大学中国协和医科大学联合出版社, 1998 年, 第 1818-1821 页), 结果如下:

性别	剂量 mg/kg	对数 剂量	动物 数	死亡动物分布(天)										死 亡 动物数	死亡率 (%)	回归 机率	LD50 (95%可信 限) mg/kg
				1h	2h	4h	1	4	7	10	14						
雌雄	2844.7	3.454	6	0	0	0	0	0	0	0	0	0	0			MLD> 2844.7 mg/kg	
VIII-9	1849.1	3.267	5	0	0	0	0	0	0	0	0	0	0				
	1201.9	3.0799	6	0	0	0	0	0	0	0	0	0	0				
	781.2	2.8928	6	0	0	0	0	0	0	0	0	0	0				
	507.8	2.7057	6	0	0	0	0	0	0	0	0	0	0				
雌雄	2844.7	3.454	6	0	0	0	6	0	0	0	0	6	100	7.2765		1048.5 (751.33 ~1433.7)	
VIII-10	1849.1	3.267	6	0	0	0	5	0	0	0	0	5	83.3	6.2940			
	1201.9	3.0799	6	0	0	0	4	0	0	0	0	4	66.7	5.3113			
	781.2	2.8928	6	0	0	0	2	0	0	0	0	2	33.3	4.3286			
	507.8	2.7057	6	0	0	0	0	0	0	0	0	0	0.00	3.3461			

10

结果: 经 Bliss 法统计, VIII-10 的 LD_{50} (95%可信限) 为 1048.5 (751.33~1433.7) mg/kg, VIII-9 的最小致死剂量 (MLD) 大于 2844.7 mg/kg。其急性毒性小于专利 ZL 02111934.1 的优选化合物 SIP1yy24 和专利 ZL 200510030354.1 的优选化合物 SIP15286。

实施例 40

化合物 VIII-9、VIII-10 的药代动力学研究:

1、试验的目的:

研究SD 大鼠单次静脉注射和口服给药后, VIII-9、VIII-10 和SIP15286三个化合物的药代参数和生物利用度。

2、试验方法:

十八只雄性大鼠随机分为6 组, 分别进行三个化合物的静脉注射和口服给药, 剂量为10 mg/kg (IV)和50 mg/kg (PO)。受试物溶解在5%DMSO/95% (30%HP- β -CD 水溶液) 中, 通过静脉注射和口服给药给予动物。静脉注射和口服给药后采集一系列时间点的血浆, 用LC/MS/MS 检测血药浓度, 然后根据血药浓度来计算药代参数和生物利用度。

3、试验结果:

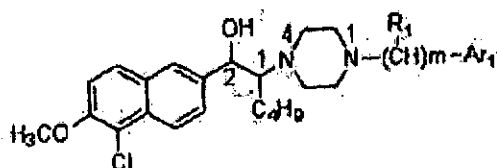
化合物	给药方式	剂量 mg/kg	C _{max} (μ g/L)	T _{max}	AUC(0-4) (hr $\cdot$ μ g/L)	半衰期(T _{1/2}) (hr)	生物利用度
VIII-9	静脉注射	10	2640.94 (5min)		4060.59	7.83	
	口服给药	50	352.27	1.50 hr	3345.73	5.89 hr	16.32%
VIII-10	静脉注射	10	2998.49 (5min)		2932.05	9.06 hr	
	口服给药	50	727.20	1.67 hr	5552.24	16.41 hr	63.78%
SIP15286	静脉注射	10	13876.57 (5min)		12564.22	3.41 hr	
	口服给药	50	6856.69	0.50 hr	30255.45	5.71 hr	51.63%

3、结论:

化合物 VIII-10 口服给药的半衰期为 16.41 小时, 长于化合物 VIII-9 (5.89 小时) 和 SIP15286 (5.71 小时); 化合物 VIII-10 的口服生物利用度为 63.78%, 高于化合物 VIII-9 (16.32%) 及 SIP15286 (51.63%)。化合物 VIII-10 具有很好的成药性。

权 利 要 求

1. 一种 1-丁基-2-羟基芳烷哌嗪衍生物, 其特征在于, 为具有如结构通式 (1) 所示的化合物及其光学异构体的游离碱或盐;



(1)

通式 (1) 中:

Ar_1 代表: 苯、取代苯基、含 N、O 或 S 的五或六元芳香杂环或苯乙烯基;

m 为 0~5 的整数;

R_1 代表: 氢、 C_1 - C_5 的烷基、 C_5 或 C_6 的脂肪环、苯、取代苯基、羟基、氨基、取代氨基、 C_1 - C_4 烷氧基、 C_1 - C_4 酰基、卤素、羧酸或羧酸酯。

2. 根据权利要求 1 所述的 1-丁基-2-羟基芳烷哌嗪衍生物, 其特征在于, Ar_1 代表的取代苯基为苯环上含有 1 至 4 个取代基的苯基, 所述取代基是卤素、羟基、烷基、硝基、烷氧基或氨基。

3. 根据权利要求 1 所述的 1-丁基-2-羟基芳烷哌嗪衍生物, 其特征在于, R_1 代表的取代氨基为氨基上含 C_1 - C_4 的烷基、 C_5 或 C_6 的脂肪环、苯或取代苯基的氨基; 所述取代苯基为苯环上含有 1 至 4 个取代基的苯基, 所述取代基是卤素、羟基、烷氧基或氨基基团。

4. 根据权利要求 3 所述的 1-丁基-2-羟基芳烷哌嗪衍生物, 其特征在于, C_1 - C_5 的烷

基、 C_1 - C_4 烷氧基、 C_1 - C_4 酰基、 C_3 或 C_6 的脂肪环上的烷基部分可以任选被1-3个氟原子取代。

5. 根据权利要求1所述的1-丁基-2-羟基芳烷哌嗪衍生物，其特征在于，结构中的不对称碳为非手性或手性碳原子；若为手性碳原子， C_1 和 C_2 两个手性碳原子的构型分别为：(1S, 2R)，(1S, 2S)，(1R, 2S)，或(1R, 2R)；其中(1SR, 2RS)为赤式消旋异构体，(1SR, 2SR)为苏式消旋异构体。

6. 根据权利要求1所述的1-丁基-2-羟基芳烷哌嗪衍生物，其特征在于，所述的盐为含有药物上可接受的阴离子的盐。

7. 根据权利要求6所述的1-丁基-2-羟基芳烷哌嗪衍生物，其特征在于，所述盐为
10 盐酸盐、氢溴酸盐、硫酸盐、三氟醋酸盐或甲磺酸盐。

8. 根据权利要求1所述的1-丁基-2-羟基芳烷哌嗪衍生物，其特征在于，所述的盐含0.5-4分子的结晶水。

9. 根据权利要求1~8任一项所述的1-丁基-2-羟基芳烷哌嗪衍生物，其特征在于，

包括：

- 15 VIII-1 (1SR,2RS)- N^1 -对甲氧基苄基- N^4 -[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪、
VIII-2 (1SR,2SR)- N^1 -对甲氧基苄基- N^4 -[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪、
VIII-3 (1SR,2RS)- N^1 -邻甲氧基苄基- N^4 -[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪、
VIII-4 (1SR,2SR)- N^1 -邻甲氧基苄基- N^4 -[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪、
VIII-5 (1SR,2RS)- N^1 -间氯苄基- N^4 -[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪、
20 VIII-6 (1SR,2SR)- N^1 -间氯苄基- N^4 -[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]哌嗪、
VIII-7 (1SR,2RS)- N^1 -(2,3-二甲基苄基)- N^4 -[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]
哌嗪、
VIII-8 (1SR,2SR)- N^1 -(2,3-二甲基苄基)- N^4 -[1-丁基-2-(5'-氯-6'-甲氧基-2'-蔡基)羟乙基]

哌嗪、

- VIII-9 (1SR,2RS)-N¹-苄基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪、
 VIII-10 (1SR,2SR)-N¹-苄基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪、
 VIII-11 (1SR,2RS)-N¹-对硝基苄基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪、
 5 VIII-12 (1SR,2SR)-N¹-对硝基苄基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪、
 VIII-13 (1SR,2RS)-N¹-对氨基苄基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪、
 VIII-14 (1SR,2SR)-N¹-对氨基苄基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪、
 VIII-15 (1SR,2RS)-N¹-(3',4',5'-三甲氧基苄基)-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪、
 VIII-16 (1SR,2SR)-N¹-(3',4',5'-三甲氧基苄基)-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪、
 10 VIII-17 (1SR,2RS)-N¹-α-苄乙基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪、
 VIII-18 (1SR,2SR)-N¹-α-苄乙基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪、
 VIII-19 (1SR,2RS)-N¹-二苯甲基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪、
 VIII-20 (1SR,2SR)-N¹-二苯甲基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪、
 VIII-21 (1SR,2RS)-N¹-肉桂基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪、
 15 VIII-22 (1SR,2SR)-N¹-肉桂基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪、
 IX-23 (1S,2R)-N¹-苄基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪、
 IX-24 (1S,2S)-N¹-苄基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪、
 IX-25 (1R,2S)-N¹-苄基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪或
 IX-26 (1R,2R)-N¹-苄基-N⁴-[1-丁基-2-(5'-氯-6'-甲氧基-2'-萘基)羟乙基]哌嗪。
 20 10. 一种药物组合物，包括治疗有效量的权利要求 1-9 任一项所述的 1-丁基-2-羟基芳烷哌嗪衍生物和药学上可接受的载体。

11. 权利要求 1-9 任一项所述的 1-丁基-2-羟基芳烷哌嗪衍生物在制备治疗抗抑郁药物中的应用。

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2009/074314

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CPRS; CNKI; WPI; EPODOC; STN; hydroxy, aralkyl, piperazine, depression, structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CN1948297A(SHANGHAI INSTITUTE OF PHARMACEUTICAL INDUSTRY), 18 Apr. 2007(18.04.2007), Cited in the present application, see the whole document, especially the examples 1 and 6	1-11
A	CN1384102A(SHANGHAI INSTITUTE OF PHARMACEUTICAL INDUSTRY), 11 Dec. 2002(11.12.2002), Cited in the present application, see the whole document, especially the example 19	1-11
A	CN1381448A(SHANGHAI INSTITUTE OF PHARMACEUTICAL INDUSTRY), 27 Nov. 2002(27.11.2002), See the whole document	1-11

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

07 Dec. 2009(07.12.2009)

Date of mailing of the international search report

07 Jan. 2010 (07.01.2010)

Name and mailing address of the ISA/CN

The State Intellectual Property Office, the P.R.China
6 Xueheng Rd., Jimen Bridge, Haidian District, Beijing, China
100088

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No. 11-055206- -00000-0000

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Tra. 2 PATENTES Eve: 1 REGDEPOSITO
Act. 411 PRESENTACION Folios: 209

PATENTE DE INVENCION ☒

MODEL C



Indicación que se solicita una patente.



Datos de identificación del solicitante o de la persona que presenta la solicitud



Descripción de la invención



Dibujos de ser estos pertinentes



Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☒

Incompleta ☐

PATENTE DE INVENCION PCT ☐

MODELO DE UTILIDAD PCT ☐

Art.33 Decisión 486/00, Circular Única



Indicación que se solicita una PCT



Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)



Dibujos de ser estos pertinentes



Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☐

Incompleta ☐

DISEÑO INDUSTRIAL ☐

(Art. 119 Decisión 486/00)



Indicación que se solicita Diseño industrial



Datos de identificación del solicitante o de la persona que presenta la solicitud



Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño



Comprobante de pago de las tasas establecidas

Completa ☐

Incompleta ☐

ESQUEMA DE TRAZADO ☐

(Art. 92 Decisión 486/00)



Indicación que se solicita un esquema de trazado



Datos de identificación del solicitante o de la persona que presenta la solicitud



Representación gráfica de un esquema de trazado



Comprobante de pago de las tasas establecidas

Completa ☐

Incompleta ☐



Bogotá D.C.,
2020

Doctor(a)
PINZON PINZON MAURICIO
Apoderado(a) y/o Representante de
CSPC ZHONGQI PHARMACEUTICAL TECHNOLOGY CO., LTD.

REFERENCIA	Radicación No.	11 055206
	Trámite	2
	Evento	1
	Actuación	430
	Oficio No.	

208842

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que:

1. Debe allegar copia del documento en que consta la cesión del derecho a la patente otorgado por el(los) inventor(s) al(los) solicitante(s) o a su(s) causante(s) (art. 26-k, Dec 486/2000).
2. El solicitante deberá aclarar si la solicitud es via PCT, ya que en la misma se aportan documentos relativos a formularios PCT.
3. El solicitante deberá aportar el título en idioma castellano, tal como lo establece la decisión 486 en el petitorio.

En cumplimiento del artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (c)

02 JUN. 2011

El anterior requerimiento fue notificado por fijación en lista de fecha _____.
adpa11