[redacted]ORIO

Industria y Comercio
SUPERINTENDENCIA

02 088271 00

SUPERINDUSTRIA Y COMERCIO
Radicacion : 02088271 00000000 Folios: 238
Fecha (AMD): 2002-10-01 15:18:04
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

(1) SOLICITUD DE:

☒ Patente de Invención ☐ Patente de Modelo de Utilidad

☐ Capítulo I. ☒ Capítulo II.

(2) SOLICITANTE (71)

Nombre: ASTRAZENECA AB

Dirección: S-151 85 Södertälje (SE).

Nacionalidad o Domicilio: Södertälje, Suecia

Lugar de Constitución: Suecia

Teléfono: 3264270 Fax: 6069701

E-mail: jllcco@lloredacamacho.com

IDENTIFICACION

C.C. ☐ NIT ☐
C.E. ☐ Otro ☐

_____ Cual

Número _____

(3) REPRESENTANTE O APODERADO

Nombre: JOSE ANTONIO LLOREDA

Dirección: Calle 72 No. 5-83 Piso 5o.

Teléfono: 3264270 Fax: 6069701

E-mail: jllcco@lloredacamacho.com

C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual _____

Número 17.159.681 TP 10.784

(4) INVENTOR(ES) (72)

Nombre: BROWN, William; WALPOLE Christopher.

Dirección: (CA/CA); AstraZeneca R & D Montreal, 7171 Frederick-Banting, St. Laurent, Quebec H4S 1Z9 (CA); (GA/CA). AstraZeneca R & D Montreal, 7171 Frederick-Banting, St. Laurent, Quebec H4S 1Z9 (CA).

Nacionalidad o Domicilio: Quebec, Canada

(5) PCT (86)

Solicitud Internacional No. PCT/SE01/00708 Fecha: Marzo 30, 2001

Publicación Internacional No. WO 01/74806 A1 Fecha: Octubre 11, 2001

(6) Título (54) " DERIVADOS DE QUINOLINIL-PIPERIDIN-4-ILIDEN-METIL-BENZAMIDA PARA EL TRATAMIENTO DEL DOLOR"

(7) Clasificación Internacional (51) C07D 401/14 , A61K 31/4523

(8) Prioridad	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI ☒ NO ☐	SE	Abril 04, 2000	0001208-8

(9) Comprobante de Pago No. 02-82,618 **Fecha:** Septiembre 19, 2002

(10) **ANEXOS**

- [X] Comprobante de pago de la tasa de presentación de la solicitud.
- [X] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [X] Documento de Representación Legal.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones
- [ ] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [X] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [X] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [X] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [X] Arte Final 12X12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionados parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros: reporte de Búsqueda Internacional, su traducción,documentos citados en el Reporte de búsqueda y Publicación con sus traducciones.

(11) **FIGURA CARACTERISTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: JOSE ANTONIO LLOREDA

FIRMA:

C.C. 17.159.681 Bta. T.P. 10.784

Industria y Com rcio

SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Radicacion : 02008271 00000000 Folios: 236
Fecha (AMD): 2002-10-01 16:18:04
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 0020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 02 - 62,618
FECHA : SEPTIEMBRE 19 DE 2002

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

DEPENDIENTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LLOREDA Y CIA S. A	CONSIGNACION	BANCO POPULAR	050-00110-6	3036794	19/09/2002	13,453,000.00

C O N C E P T O

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	378,000.00
		TOTAL : $	378,000.00

SON: TRESCIENTOS SETENTA Y OCHO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador 382 0840
Fax 350 5220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

ANEXO

El documento que acredita la calidad de REPRESENTANTES LEGALES en Bogotá de los doctores **JOSE ANTONIO LLOREDA y/o GUSTAVO TAMAYO y/o ANGELA MARIA RESTREPO y/o ALICIA LLOREDA RICAURTE** para TODOS LOS ASUNTOS RELACIONADOS CON LA PROPIEDAD INDUSTRIAL de la sociedad peticionaria, que faculta a cada uno de dichos abogados para actuar individualmente, se está presentando con esta solicitud. En consecuencia, ruego a usted reconocer la personería de cada uno de dichos Representantes Legales para actuar dentro del presente expediente, a fin de que cualquiera de ellos pueda intervenir en cualquier tiempo respecto de la solicitud en él contenida.

JOSE ANTONIO LLOREDA
T.P. No. 10.784
Código 231

TRADUCCION OFICIAL No. 135

LEGALIZACION de un documento presentado simultáneamente en inglés y español. PODER de representación legal otorgado a JOSÉ LLOREDA CAMACHO y/o JOSE ANTONIO LLOREDA y/o AURA DUEÑAS RODRIGUEZ y/o GUSTAVO TAMAYO y/o ANGELA MARIA RESTREPO y/o ALICIA LLOREDA por ***AstraZeneca Aktiebolag.***

Dado y firmado: marzo 23, 2000

Firmado: **Susan Margaret Evans**
Director, Jefe de Marcas

CERTIFICADO NOTARIAL (SOCIEDAD) SIMULTANEAMENTE EN INGLES Y ESPAÑOL.

Firmado: (firma ilegible)
Notario Público

ANGELA SALAMANCA DE ABREU
TRADUCTORA OFICIAL
DECRETO 1142 DE 1978

EL SUSCRITO NOTARIO SESENTA Y SIETE (67) DEL CIRCULO DE BOGOTA, HACE CONSTAR QUE LA FOTOCOPIA CORRESPONDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

03 SET 2002

PABLO MENDEZ BARAJAS
NOTARIO (E)

5

REIN UNID DE GRAN BRETAÑA E IRLANDA DEL NORTE

No. D 617801

Fecha: mayo 15, 2000

Este documento lleva la firma/sello de

J.B. Hodgson

Quien actúa en su condición de **Notario Público**

Firmado por: **B. Amarteifio**
(firma ilegible)
Principal Secretario de Estado de su Majestad para Asuntos Extranjeros y del Commonwealth

Hay sello en altorrelieve y plano de la Foreign and Commonwealth Office de Londres.

CERTIFICACION DEL CONSULADO GENERAL DE COLOMBIA EN LONDRES EN ESPAÑOL.

Firmado: **Jaime Lozada Perdomo**
Cónsul General

Sello del Consulado General de Colombia en Londres

COMO NOTARIO SEXTO (E) DEL ... DE BOGOTA, NADA CONSTAR QUE LA ... FOTOCOPIA CORRESPONDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
03 SET 2002
PABLO MENDEZ BARAJAS
NOTARIO (E)

JAIME SALAMANCA DE ABREU
TRADUCTORA DE ...
RES MINJUSTICIA ...

CERTIFICACION EN ESPAÑOL DEL CONSULADO GENERAL DE COLOMBIA EN LONDRES.

Firmado: **JAIME LOZADA PERDOMO**

Cónsul General

MINISTERIO DE RELACIONES EXTERIORES

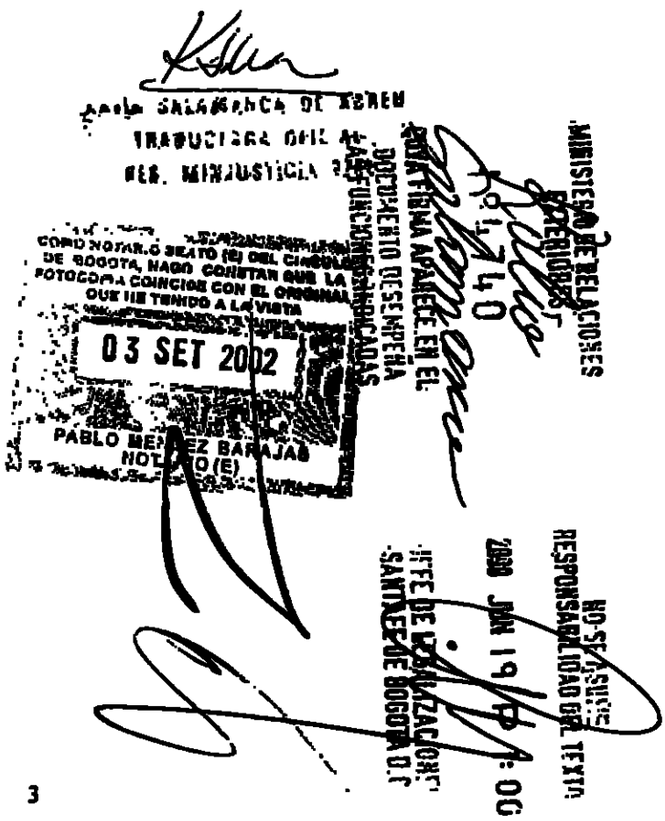
SANTA FE DE BOGOTA

CERTIFICA la firma y el cargo del funcionario consular JAIME LOZADA, bajo el número 182199 el día junio 14, 2000.

(Firma llegible)

JEFE DE LEGALIZACIONES

Santafé de Bogotá, D.C.



CONSULADO GENERAL DE COLOMBIA
3RD FLOOR, 15-19 GREAT TITCHFIELD STREET, LONDON W1P 7FB
TELEPHONE 020-7637 9893 • TELEFAX 020-7637 5804
E-MAIL consulco@consulco.demon.co.uk

El suscrito Cónsul General de Colombia en Londres, vistos los documentos presentados ante este Despacho,

CERTIFICA

Que, **J. B. HODGSON**, Notario Público de Macclesfield, Inglaterra, Gran Bretaña, autenticó la firma del Documento precedente y su firma se encuentra certificada por **B. AMARTEIFIO**, Oficial del Ministerio de Relaciones Exteriores Británico, firma que a su vez se encuentra registrada en este Consulado General.

Que, **ASTRAZENECA AKTIEBOLAG**, es una Sociedad constituida y existente en Sodertalje, Suecia, y que cumple con su objeto social de conformidad con las leyes de ese país.

Que, **SUSAN MARGARET EVANS**, en su calidad de Directora de la mencionada Sociedad, debidamente autorizada otorga el Documento precedente y su firma se encuentra autenticada por **J. B. HODGSON**, Notario Público de Macclesfield, Inglaterra, Gran Bretaña.

El Cónsul General no asume responsabilidad por el contenido del mencionado documento.

Dado en Londres, Inglaterra, Gran Bretaña, a los diecisiete (17) días del mes de Mayo de 2000.

Certificación No. 05/0681
Derechos: U$ 106,00 CANCELADOS

JAIME LOZADA PERDOMO
Cónsul General

IH

EL SUSCRITO NOTARIO DEL CIRCULO DE MACCLESFIELD CERTIFICA QUE LA FOTOCOPIA CONCUERDA CON EL ORIGINAL QUE HE TENIDO A LA VISTA
13 SET 2002
PABLO MENDEZ BARAJAS
NOTARIO (E)

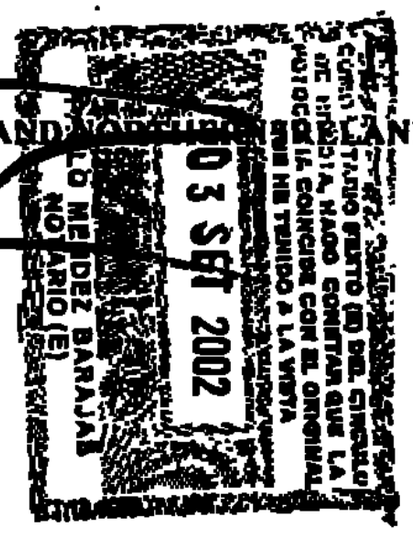
MINISTERIO DE RELACIONES EXTERIORES
19 MAY 2000
LA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

CONSULADO GENERAL DE COLOMBIA
LONDRES

NO SE ASUME RESPONSABILIDAD DEL TEXTO
2000 JUN 14 P 2:40
JEFE DE LEGALIZACIONES SANTAFE DE BOGOTA D.C.

8

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND



No. **D617801**

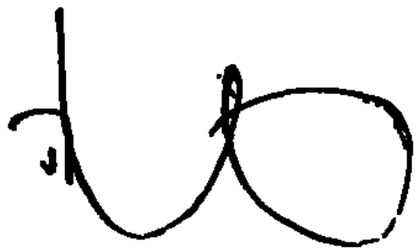
Date **15 May, 2000**

This document bears
the signature / seal of **J B Hodgson**

Acting in the capacity of **Notary Public**



Signed by: **B. Amarteifio**



For Her Majesty's Principal Secretary of State
For Foreign and Commonwealth Affairs

Los abajo firmados, AstraZeneca Aktiebolag, una sociedad organizada y existente de conformidad con las leyes de Suecia,

con domicilio en

Sodertalje, Suecia,

nombramos por el presente a JOSE LLOREDA CAMACHO, y/o JOSE ANTONIO LLOREDA, y/o AURA DUEÑAS RODRIGUEZ, y/o GUSTAVO TAMAYO, y/o ANGELA MARIA RESTREPO y/o ALICIA LLOREDA, domiciliados en Bogotá, Colombia, con oficinas en dicha ciudad, Calle 72 No. 5-83, piso 6o., nuestros representantes legales y verdaderos en Bogotá,con facultades para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales, con el fin de dar cumplimiento al parágrafo 1o. del artículo 543 del decreto 410 de 1971.

Los doctores JOSE LLOREDA CAMACHO, y/o JOSE ANTONIO LLOREDA, y/o AURA DUEÑAS RODRIGUEZ, y/o GUSTAVO TAMAYO, y/o ANGELA MARIA RESTREPO y/o ALICIA LLOREDA, o los apoderados que cualquiera de ellos designe, quedan especialmente facultados para representarnos ante las autoridades colombianas, administrativas, judiciales o de policía, en todos los trámites relativos a la propiedad industrial, a cuyo efecto les facultamos para dar ante dichas autoridades todos los pasos necesarios al objeto indicado; elevar solicitudes, declaraciones y reclamos; formular descripciones, enmiendas, oposiciones y apelaciones; instaurar cancelaciones y amparos administrativos; abonar todos los impuestos y cuotas y efectuar todo otro pago determinado por la ley; recibir todos los documentos y valores, dando el descargo respectivo; llenar cualesquiera otros requisitos y tomar, en fin, todas las medidas que creyeren conducentes al resguardo de nuestros intereses; y en caso de producirse oposición, pasando los antecedentes a los tribunales, quedan facultados para tomar intervención como demandantes o demandados ante los jueces que sean competentes, pudiendo transar, someter a árbitros, desistir, percibir y apelar, con todas las demás facultades que resulten necesarias; y por el presente declaramos desde ahora válido y bueno cuanto dichos representantes y/o los apoderados que cualquiera de ellos nombre hicieren en nuestro beneficio.

Asimismo, facultamos a los doctores JOSE LLOREDA CAMACHO, y/o JOSE ANTONIO LLOREDA, y/o AURA DUEÑAS RODRIGUEZ, y/o GUSTAVO TAMAYO, y/o ANGELA MARIA RESTREPO y/o ALICIA LLOREDA, para solicitar en la Oficina de Propiedad Industrial la protocolización de este documento y de cualquier poder que cualquiera de ellos otorgue a nombre nuestro, así como para sustituir el presente.

Dado y firmado el 23 de Marzo de 2000

The undersigned, AstraZeneca Aktiebolag, a corporation organized and existing under the laws of Sweden,

of

Sodertalje, Sweden,

hereby appoint JOSE LLOREDA CAMACHO, and/or JOSE ANTONIO LLOREDA, and/or AURA DUEÑAS RODRIGUEZ, and/or GUSTAVO TAMAYO, and/or ANGELA MARIA RESTREPO and/or ALICIA LLOREDA, of Bogotá, Colombia, with offices in said town, Calle 72 No. 5-83, Sixth Floor, our true and legal representatives in Bogotá, with power to receive notifications and to appoint judicial or extrajudicial agents, so as to comply with paragraph 1 of article 543 of decree 410 of 1971.

Doctors JOSE LLOREDA CAMACHO, and/or JOSE ANTONIO LLOREDA, and/or AURA DUEÑAS RODRIGUEZ, and/or GUSTAVO TAMAYO, and/or ANGELA MARIA RESTREPO and/or ALICIA LLOREDA, or the agents by any one of them appointed, are especially empowered to represent us before the administrative, judicial or police authorities of Colombia, in all proceedings pertaining to industrial property, for which purpose we authorize them to take before the said authorities all the necessary steps to the said end; to file petitions, declarations, claims, cancellations and administrative injunction proceedings; to draw up specifications; to make amendments, oppositions and appeals, to pay all installments and effect all other payments prescribed by law; to receive proper receipts to comply with all other requirements and, in short, to take all such measures which they may deem fit for the protection of our interests; and in case of opposition, where the proceedings be passed over to the courts, we authorize said agents to act on our behalf, as complainants as well as defendants, before the competent judges, with full powers to make, to compromise, to submit to arbitrators, to desist, to collect, to appeal and, in short, with all such further powers as may be required; and we hereby declare from now on valid and good all that said representatives and/or the agents by any one of them appointed may do for our benefit.

We also authorize doctors JOSE LLOREDA CAMACHO, and/or JOSE ANTONIO LLOREDA, and/or AURA DUEÑAS RODRIGUEZ, and/or GUSTAVO TAMAYO, and/or ANGELA MARIA RESTREPO and/or ALICIA LLOREDA, to apply for protocolization of this document and of any power of attorney by any one of them conferred in our name, before the Office of Industrial Property, as well as to substitute these presents.

Given and signed this 23rd Day of MARCH 2000

SUSAN MARGARET EVANS

NOTARY SHOULD EXECUTE OTHER SIDE

ESCRITO NOTARIO SEXTO (6) DEL CIRCULO DE BOGOTA
FOTOCOPIA CONCUERDA CON EL ORIGINAL
03 SET 2002
PABLO MENDEZ BARRIAL

0810

CERTIFICADO NOTARIAL (INDIVIDUO)

Estados Unidos de América
Estado de {ss
Condado de
A los días del mes de de 19
comparecí personalmente ante mí, Notario Público en y por el condado antes citado,

a quien doy fe de conocer y me consta que es/son la persona descrita y firmante del documento que precede, declarando ante mí que otorga el mismo para los fines y propósitos que en él se expresan.

Notary Public (Notario Público).

CERTIFICADO NOTARIAL (INDIVIDUO)

Estados Unidos de América
Estado de
Condado de
A los días del mes de de 19
comparecí personalmente ante mí, Notario Público en y por el condado antes citado,

a quien PARA MAYOR IDENTIFICACIÓN doy fe de conocer y me consta que es/son la persona descrita y firmante del documento que precede, declarando ante mí que otorga el mismo para los fines y propósitos que en él se expresan.

Notary Public (Notario Público).

CERTIFICADO NOTARIAL (SOCIEDAD)

~~Estados Unidos de América~~
Estado de {ss
~~Condado de~~
Hoy 23 de Marzo de 2000, compareció Susan Margaret Evans, a quien conozco y de quien me consta que firmó el anterior documento, y quien debidamente juramentado declaró y dijo que él es Director, Jefe de Marcas de AstraZeneca Aktiebolag
la compañía nombrada en el documento, que antecede, una sociedad debidamente organizada y existente conforme a las leyes de ~~Estados~~ Suecia, ~~Estados Unidos de América~~, domiciliada en la ciudad de Sodertalje, ~~Condado de~~ Suecia, ~~Estado~~ y legalmente constituída para un período de duración que aún no ha determinado; que el declarante está autorizado por dicha Compañía para conferir este poder; que el sello estampado por él al pie de tal poder, en nombre y en representación de la expresada Compañía, es el sello oficial de ella; y que el objeto para el cual se confiere este instrumento está comprendido dentro del de la sociedad.

El suscrito Notario ha visto los Estatutos de incorporación firmados en ~~Estados~~, con fecha, y certifica que de conformidad con la legislación de dicho Estado la anterior declaración juramentada es prueba suficiente de que los hechos sobre que ella versa son ciertos o verdaderos, de lo cual da fe.

Notary Public (Notario Público)

NOTARIAL CERTIFICATE (INDIVIDUAL)

United States of America
State of {ss.
County of
On this day of ,19 ,personally appeared before me, a Notary Public, in and for the above mentioned county,

to me known to be the person described in and who executed the foregoing document, and who duly acknowledged to me that executed same for the uses and purposes therein expressed.

NOTARIAL CERTIFICATE (INDIVIDUAL)

United States of America
State of {ss.
County of
On this day of , 19 , personally appeared before me, a Notary Public, in and for the above mentioned county,

to me known to be the person described in and who executed the foregoing document, and who duly acknowledged to me that executed same for the uses and purposes therein expressed.

NOTARIAL CERTIFICATE (CORPORATION)

~~UNITED STATES OF AMERICA~~
~~State of~~
~~County of~~ {ss.
On this 23 day of March of 2000, ~~BE~~, personally came SUSAN MARGARET EVANS, to me known, and known to me to be the person who signed the foregoing instrument, who being by me duly sworn did depose and say that he is the DIRECTOR, HEAD OF TRADE MARKS of AstraZeneca Aktiebolag, the company named within, a a Corporation organized and existing under the laws of ~~the~~ ~~State of~~ Sweden, ~~United States of America~~, domiciled at the City of Sodertalje, Sweden ~~County of~~, ~~State of~~, and legally constituted for a period of tenure not yet expired; that the deponent is authorized by said Company to confer this power of attorney; that the seal affixed hereunto by the deponent in the name and on behalf of said Corporation is the corporate seal thereof; and that the purpose for which this instrument is granted is included within the corporate purposes of the Company.

The undersigned Notary Public has seen the articles of Incorporation of said Corporation executed at ~~State of~~, under date of, and hereby certifies that under the laws of said State the foregoing acknowledment is sufficient proof that the facts therein contained are true, which he attests.

FORMATO DE DIGITALIZACION
RELACION DE ANEXOS

Royal Technologies S.A.

10

Item	Expediente No	No de unidades	No de Folio √
1	CD		
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA	1	
8	SOBRE BLANCO TAMAÑO CARTA		
9	SOBRE BLANCO TAMAÑO OFICIO		
10	OTROS:		

Observaciones: Dct Final

Industria y Comercio
SUPERINTENDENCIA

EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCION

(21) No. SOLICITUD: PCT/SE01/00708

(22) FECHA DE PRESENTACIÓN: 01/10/02

(30) PRIORIDAD: 0001208-8

(31) No. DE SOLICITUD:

(32) FECHA DE PRESENTACIÓN: 04-04-2000

(33) PAÍS: SE

(51) INT. CL.: C07D 401/14

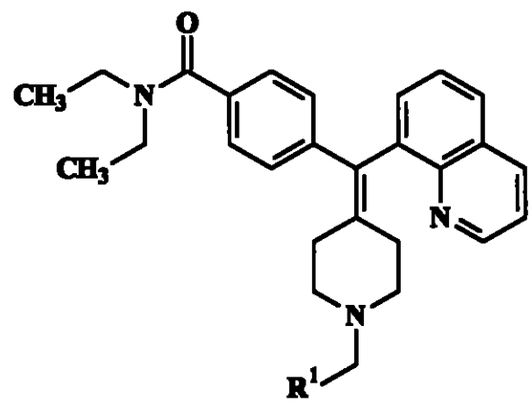
(71) SOLICITANTE: ASTRAZENECA AB

(72) INVENTOR(ES): BROWN, William; WALPOLE, Christopher.

(74) REPRESENTANTE LEGAL: JOSE ANTONIO LLOREDA

(54) TÍTULO:
"DERIVADOS DE QUINOLINIL-PIPERIDIN-4-ILIDEN-METIL-BENZAMIDA PARA EL TRATAMIENTO DEL DOLOR"

(57) RESUMEN:



(I)

(57) **Resumen:** Se revelan y reivindican en la presente solicitud compuestos de fórmula general (I), en donde R^1 se selecciona de cualquiera de fenil, piridinil, tienil, furanil, imidazolil y triazolil; en donde cada anillo fenilo R^1 y cada anillo heteroaromático R^1 puede estar además substituido opcional e independientemente con 1, 2 o 3 substituyentes seleccionados de alquilo C_1-C_6 de cadena recta y ramificada, NO_2, CF_3, alcoxi C_1-C_6, cloro, flúor, bromo y yodo, en donde las substituciones sobre el anillo fenilo y el anillo heteroaromático pueden tener lugar en cualquier posición sobre dichos sistemas de anillo, como también sus sales farmacéuticamente aceptables y composiciones farmacéuticas que comprenden los novedosos compuestos y su uso en terapia, en particular en el manejo del dolor.

12

(FORMA P-104)

EXTRACTO

21	Solicitud Internacional No. PCT/SE01/00708
22	01-10-02
31	0001208-8
32	04-04-2000
33	SE

Dibujo Característico se puede pegar aquí

6 cms. X 6 cms.

Título No. 57)

Fecha

51 C07D 401/14

74 JOSE ANTONIO LLOREDA

72 BROWN, William (CA/CA); AstraZeneca R & D Montreal, 7171 Frederick-Banting, St. Laurent, Quebec H4S 1Z9 (CA). WALPOLE, Christopher (GA/CA); AstraZeneca R & D Montreal, 7171 Frederick-Banting, St. Laurent, Quebec H4S 1Z9 (CA).

Continúa al respaldo

71 ASTRAZENECA AB

Södertälje, Suecia

51 TITULO "DERIVADOS DE QUINOLINIL-PIPERIDIN-4-ILIDEN-METIL-BENZAMIDA PARA EL TRATAMIENT DE L DOLOR"

12

PATENTE ☒ MODELO DE UTILIDAD ☐ DISEÑO INDUSTRIAL ☐

SOLICITANTES, RAZON SOCIAL O APELLIDOS Y NOMBRES ASTRAZENECA AB

SOLICITUD INTERNACIONAL NUMERO PCT/SE01/00708

DOMICILIO Södertälje, Suecia

Representante Legal JOSE ANTONIO LLOREDA

TITULO "DERIVADOS DE QUINOLINIL-PIPERIDIN-4-ILIDEN-METIL-BENZAMIDA PARA EL TRATAMIENTO DEL DOLOR"

CLASIFICACION C07D 401/14

EXPEDIENTE No. _____ FECHA DE SOLICITUD 01/10/02 ROLLO MICROFILM _____

CERTIFICADO No. _____ FECHA DE CONCESION _____ VIGENCIA DESDE _____ HASTA _____

PRORROGA _____ CAMBIO DE NOMBRE _____

TRASPASO A _____

INVENTORES BROWN, William; WALPOLE Christopher.

OTROS _____

TRATADO DE COOPERACION DE PATENTES
PCT
REPORTE DE BUSQUEDA INTERNACIONAL

(PCT Artículo 18 y Reglas 43 y 44)

Registro de referencia del solicitante o agente	PARA FUTURAS ACCIONES ver Notificación o Transmisión del Reporte de Búsqueda Internacional (Forma PCT/ISA/220) así como, donde aplique, el ítem 5 a continuación.	
Solicitud internacional No. PCT/SE 01/00708	Fecha de registro internacional *(día/mes/año)* Marzo 30, 2001	Fecha de Prioridad (Primera) *(día/mes/año)* Abril 4 2000
Solicitante AstraZeneca AB et al		

Este Reporte de Búsqueda Internacional ha sido preparado por esta Autoridad de Búsqueda Internacional y es transmitido al solicitante Según el Artículo 18. Una copia será transmitida a la Oficina Internacional.

Este Reporte de Búsqueda Internacional consta de un total de _5_ hojas.

☒ También está acompañado de una copia de cada documento técnico anterior citado en este reporte.

1. Bases del reporte

a. Respecto al lenguaje, la búsqueda internacional se llevó a cabo según la solicitud internacional en el lenguaje en el cual se presentó, a menos que se indique de otro modo en este ítem.

☐ la búsqueda internacional se llevó a cabo según la traducción de la solicitud internacional proporcionada a esta Autoridad (Regla 23.1(b)).

b. Respecto a una secuencia de ácido nucleótido y/o amino revelado en la solicitud internacional, la búsqueda internacional se llevó a cabo según la lista de la secuencia:

☐ contenido en la solicitud internacional en forma escrita.

☐ presentada junto con la solicitud internacional en forma legible por computador.

☐ proporcionada subsiguientemente a esta Autoridad en forma escrita.

☐ proporcionada subsiguientemente a esta Autoridad en forma legible por computador.

☐ se ha proporcionado la afirmación de que el listado de secuencias escrito proporcionado subsiguientemente no va más allá de la revelación en la solicitud internacional según se presentó.

☐ se ha proporcionado la afirmación de que la información registrada en forma legible por computador es idéntica al listado de la secuencia escrita.

2. ☒ Ciertas reivindicaciones no pudieron localizarse (Ver Casilla I).

3. ☐ Falta unidad de invención (ver Casilla II).

4. Respecto al título,

☒ El texto es aprobado según lo presenta el solicitante.

☐ Esta Autoridad ha establecido que el texto se lea así:

5. Respecto al resumen,

☒ El texto es aprobado según lo presenta el solicitante.

☐ Esta Autoridad ha establecido el texto de acuerdo con la Norma 38.2(b), según aparece en el Recuadro III. El solicitante puede, un mes después de la fecha de haber enviado por correo este reporte de búsqueda internacional, presentar comentarios a esta Autoridad.

6. La figura de los dibujos que se publicará con el resumen es la Figura No.

☐ como lo sugirió el solicitante.

☐ porque el solicitante no sugirió una figura.

☐ porque esta figura caracteriza mejor a la invención.

☐ Ninguna de las figuras.

REPORTE DE BUSQUEDA INTERNACIONAL

Solicitud Internacional No.
PCT/ SE 01/00708

A. CLASIFICACION DE MATERIA

IPC7: C07D 401/14, C07D 405/14, C07D 409/14, C07D 211/68, A61K 31/4523, A61P 25/04, A61P 25/00

Según la Clasificación de Patentes Internacional (CPI) o según la clasificación nacional y la CPI

B. CAMPOS BUSCADOS

Documentación mínima buscada (sistema de clasificación seguido de símbolos de clasificación)

IPC7: C07D, A61K

Documentación buscada fuera de documentación mínima hasta donde dichos documentos se incluyan en los campos buscados

SE, DK, FI, NO clases como arriba

Base de datos electrónica consultada durante la búsqueda internacional (nombre de la base de datos y, donde sea práctico, buscar términos usados)

C. DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría *	Citación de documento, con indicación, donde sea apropiado, de los textos relevantes	Relevante a la reivindicación No.
X	WO 9828275 A1 (ASTRA PHARMA INC.), Julio 2, 1998 (02.07.98), las reivindicaciones, ejemplos y compuesto 52 (página 55 y 58)	1-18
X	WO 9723466 A1 (ASTRA PHARMA INC.), Julio 3, 1997 (03.07.97), las reivindicaciones, ejemplos	1-6,8-17
X	WO 9933806 A1 (ORTHO-MCNEIL PHARMACEUTICAL, INC.), Julio 8, 1999 (08.07.99), las reivindicaciones, ejemplos	1-6,8-17

☒ En el recuadro C se enumeran más documentos.

☒ En el anexo se enumeran miembros de la familia de patentes.

* Categorías especiales de documentos citados:

'A' documento que define el estado general de la técnica el cual no se considera de relevancia particular

'E' documento anterior pero publicado en o después de la fecha de presentación internacional

'L' documento que puede arrojar dudas sobre reivindicaciones de prioridad o que se cita para establecer la fecha de publicación de otra citación u otra razón especial (según se especifica)

'O' documento que se refiere a una revelación oral, uso, exhibición u otros medios

'P' documento publicado antes de la fecha de presentación internacional pero después de la fecha de prioridad reivindicada

'T' documento posterior publicado después de la fecha de presentación internacional o fecha de prioridad y que no está en conflicto con la solicitud pero citado para entender el principio o teoría que sustenta la invención

'X' documento de relevancia particular; la invención reivindicada no puede considerarse nueva o no puede considerarse que comprende un paso inventivo cuando el documento se toma solo

'Y' documento de relevancia particular; la invención reivindicada no puede considerarse que comprende un paso inventivo cuando el documento se combina con uno o más documentos, siendo dicha combinación obvia para una persona experta en la técnica

'&' documento miembro de la misma familia de patentes

Fecha de la terminación real de la búsqueda internacional	Fecha de envío por correo del reporte de búsqueda internacional
Julio 30, 2001	31-07-2001
Nombre y dirección de correo de ISA Swedish Patent Office Box 5055. S-102 42 STOCKHOLM Facsimile No. +468 666 02 86	**Funcionario autorizado** Solveig Gustavsson /BS Tel. No. +468 782 25 00

Forma PCT ISA 210 (segunda hoja) (Julio 1998)

REPORTE DE BUSQUEDA INTERNACIONAL

Solicitud Internacional No.
PCT/SE 01/00708

C. (Continuación) DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría *	Citación de documento, con indicación, donde sea apropiado, de los textos relevantes	Relevante a la reivindicación No.
X	J. Med. Chem., Volumen 42, 1999 Xiaoyan Zhang "Pruebas para Fenómeno Mediado por Receptor Narcótico. 26.1-3 Síntesis y Evaluación Biológica de Diarilmetilpiperazinas y Diarilmetilpiperidinas como Ligandos Receptores Novedosos, No-Peptídicos y Opioides" página 5455 - página 5463	1-6,8-17
X	J. Med. Chem., Volumen 43, 2000, Zhong-Yong Wei et al, "N,N-Dietil -4 -(fenilpiperidin -4-iliden metil) benzamida: Un Novedoso Excepcionalmente Selectivo, Potente y Receptor Agonista Opioide con Biodisponibilidad Oral y sus Análogos", página 3895 - página 3905, página 3897, compuesto 8 y esquema 3	7,18

REPORTE DE BUSQUEDA INTERNACIONAL

Solicitud Internacional No.
PCT/SE 01/00708

Casilla I Observaciones donde ciertas reivindicaciones fueron inescrutables (Continuación del Item 1 de la primera hoja)

Este reporte de búsqueda internacional no ha sido establecido respecto a ciertas reivindicaciones bajo el Artículo 17(2)(a) por las siguientes razones:

1. ☒ Reivindicaciones Nos.: 15-17

porque se relacionan con un asunto que no es necesario que esta Autoridad busque, a saber:

Ver próxima hoja

2. ☐ Reivindicaciones Nos.:
porque se relacionan con partes de la solicitud internacional que no cumplen con los requisitos prescritos hasta tal grado que no se puede llevar a cabo una búsqueda internacional significativa, específicamente:

3. ☐ Reivindicaciones No.:
porque son reivindicaciones dependientes y no están diseñadas de acuerdo con la segunda y tercera oración de la Norma 6.4(a).

Casilla II Observaciones donde falta unidad de invención (Continuación del Item 2 de la primera hoja)

Esta Autoridad de Búsqueda Internacional encontró invenciones múltiples en esta solicitud internacional, así:

1. ☐ Puesto que todos los derechos de búsqueda adicionales requeridos fueron pagados oportunamente por el solicitante, este informe de búsqueda internacional cubre todas las reivindicaciones investigables.

2. ☐ Puesto que todas las reivindicaciones investigables pudieron investigarse sin esfuerzo que justifique derechos adicionales, esta Autoridad no solicitó pago de derechos adicionales.

3. ☐ Puesto que sólo algunos de los derechos de búsqueda adicionales fueron pagados oportunamente por el solicitante, este informe de búsqueda internacional cubre únicamente aquellas reivindicaciones para las cuales se pagaron derechos, específicamente las reivindicaciones Nos.:

4. ☐ El solicitante no pagó oportunamente los derechos de búsqueda adicionales requeridos. Por consiguiente, este informe de búsqueda internacional se restringe a la primera invención mencionada en las reivindicaciones; está cubierto por las reivindicaciones Nos.:

Comentario sobre Protesta

☐ Los derechos de búsqueda adicionales estuvieron acompañados por la protesta del solicitante.

☐ El pago de los derechos de búsqueda adicionales no estuvo acompañado por una protesta.

REPORTE DE BUSQUEDA INTERNACIONAL	Solicitud Internacional No. PCT/SE 01/00708

Las reivindicaciones 15-17 relacionan metodos de tratamiento del cuerpo humano o animal por métodos de cirugía o de terapia / diagnóstico practicados en el cuerpo humano o animal / Regla 39.1. (iv). Sin embargo, una búsqueda ha sido ejecutada para estas reivindicaciones. La búsqueda ha sido basada en los efectos allegados de los compuestos/composiciones.

REPORTE DE BUSQUEDA INTERNACIONAL

Informe sobre miembros de familia de patentes

Solicitud Internacional No.
PCT/SE 01/00708

Documento de patente citado en el reporte de búsqueda	Fecha de publicación	Miembro(s) de la familia de patentes	Fecha de publicación
WO 9828275 A1	02/07/98	AU 5351298 A	17/07/98
		BR 9714055 A	09/05/00
		CN 1246111 A	01/03/00
		CZ 9902199 A	17/11/99
		EP 0946511 A	06/10/99
		IL 130535 D	00/00/00
		NO 993022 A	20/08/99
		PL 334374 A	28/02/00
		SE 9604785 D	00/00/00
		SK 76299 A	08/11/99
		TR 9901417 T	00/00/00
		US 6187792 B	13/02/01
		HU 0000610 A	28/09/00
		SE 9702535 D	00/00/00
WO 9723466 A1	03/07/97	AU 715547 B	03/02/00
		AU 1216297 A	17/07/97
		BR 9612204 A	13/07/99
		CN 1209124 A	24/02/99
		CZ 9801768 A	16/09/98
		EP 0915855 A	19/05/99
		HU 9901304 A	30/08/99
		IL 124996 D	00/000/00
		JP 2000502679 T	07/03/00
		NO 982807 A	19/08/98
		PL 327403 A	07/12/98
		SE 9504661 D	00/00/00
		SK 82298 A	04/11/98
		TR 9801180 T	00/00/00
		US 6130222 A	10/10/00
WO 9933806 A1	08/07/99	AU 2009799 A	19/07/99
		EP 1049676 A	08/11/00

20

CH

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:

Global Intellectual Property
AstraZeneca AB
151 85 Södertälje

RECEIVED
AUG - 7 2001
ASTRAZENECA
GLOBAL INTELLECTUAL PROPERTY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *(day/month/year)* 31-07-2001
Applicant's or agent's file reference 100002-1 WO	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/SE01/00708	International filing date *(day/month/year)* 30-03-2001
Applicant AstraZeneca AB et al	

1. [X] The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46)

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report: however, for more details, see the notes on the accompanying sheet.

Where? To the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see notes on the accompanying sheet.

CODE | DATE | NTD
ANKOM 02 AUG 2001 SIPS
DATA ENTERED
FINAL CHECK

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest: the applicant will be notified as soon as a decision is made.

4. Further action(s): The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/ Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667 72 86 Telex 17978 PATOREG-S	Authorized officer Anne Vilval Telephone No. 08-782 25 00

Form PCT/ISA/220 (January 1994) *(See notes on accompanying sheet)*

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 100002-1 WO	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/SE 01/00708	International filing date *(day/month/year)* 30 March 2001	(Earliest) Priority Date *(day/month/year)* 4 April 2000
Applicant AstraZeneca AB et al		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

[x] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b) With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readable form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. [x] Certain claims were found unsearchable (See Box I).

3. [ ] Unity of invention is lacking (See Box II).

4. With regard to the title,

   [x] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the abstract,

   [x] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. -

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/00708

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 401/14, C07D 405/14, C07D 409/14, C07D 211/68, A61K 31/4523, A61P 25/04, A61P 25/00

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)

IPC7: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9828275 A1 (ASTRA PHARMA INC.), 2 July 1998 (02.07.98), the claims, examples and compound 52 (page 55 and 58) --	1-18
X	WO 9723466 A1 (ASTRA PHARMA INC.), 3 July 1997 (03.07.97), the claims, examples --	1-6,8-17
X	WO 9933806 A1 (ORTHO-MCNEIL PHARMACEUTICAL, INC.), 8 July 1999 (08.07.99), the claims, examples --	1-6,8-17

[X] Further documents are listed in the continuation of Box C. [X] 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	Date of mailing of the international search report
30 July 2001	31-07-2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Solveig Gustavsson/BS Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/00708

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. Med. Chem., Volume 42, 1999, Xiaoyan Zhang et al, "Probes for Narcotic Receptor Mediated Phenomena. 26.1-3 Synthesis and Biological Evaluation of Diarylmethylpiperazines and Diarylmethylpiperidines as Novel, Nonpeptidic & Opioid Receptor Ligands" page 5455 - page 5463 --	1-6,8-17
X	J. Med. Chem., Volume 43,.2000, Zhong-Yong Wei et al, "N,N-Diethyl -4- (phenylpiperidin -4 -ylidenemethyl) benzamide: A Novel, Exceptionally Selective, Potent & Opioid Receptor Agonist with Oral Bioavailability and Its Analogues", page 3895 - page 3905, page 3897, compound 8 and scheme 3 --	7,18

INTERNATI NAL SEARCH REPORT

International application No.
PCT/SE01/00708

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 15-17
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/00708

Claims 15-17 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised n the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/07/01

International application No.
PCT/SE 01/00708

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9828275 A1	02/07/98	AU 5351298 A	17/07/98
		BR 9714055 A	09/05/00
		CN 1246111 A	01/03/00
		CZ 9902199 A	17/11/99
		EP 0946511 A	06/10/99
		IL 130535 D	00/00/00
		NO 993022 A	20/08/99
		PL 334374 A	28/02/00
		SE 9604785 D	00/00/00
		SK 76299 A	08/11/99
		TR 9901417 T	00/00/00
		US 6187792 B	13/02/01
		HU 0000610 A	28/09/00
		SE 9702535 D	00/00/00
WO 9723466 A1	03/07/97	AU 715547 B	03/02/00
		AU 1216297 A	17/07/97
		BR 9612204 A	13/07/99
		CN 1209124 A	24/02/99
		CZ 9801768 A	16/09/98
		EP 0915855 A	19/05/99
		HU 9901304 A	30/08/99
		IL 124996 D	00/00/00
		JP 2000502679 T	07/03/00
		NO 982807 A	19/08/98
		PL 327403 A	07/12/98
		SE 9504661 D	00/00/00
		SK 82298 A	04/11/98
		TR 9801180 T	00/00/00
		US 6130222 A	10/10/00
WO 9933806 A1	08/07/99	AU 2009799 A	19/07/99
		EP 1049676 A	08/11/00

Probes for Narcotic Receptor Mediated Phenomena. 26.[1–3] Synthesis and Biological Evaluation of Diarylmethylpiperazines and Diarylmethylpiperidines as Novel, Nonpeptidic δ Opioid Receptor Ligands

Xiaoyan Zhang,[†,‡] Kenner C. Rice,*[,†] Silvia N. Calderon,[†,⊥] Hiroshi Kayakiri,[†,▽] Larren Smith,[†] Andrew Coop,[†,#] Arthur E. Jacobson,[†] Richard B. Rothman,[‖] Peg Davis,[§] Christina M. Dersch,[‖] and Frank Porreca[§]

Laboratory of Medicinal Chemistry, Building 8, Room B1-23, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20892, and Clinical Psychopharmacology Section, National Institute on Drug Abuse, Addiction Research Center, Baltimore, Maryland 21224, and Department of Pharmacology, College of Medicine, The University of Arizona, Tucson, Arizona 85724

Received August 2, 1999

We recently reported (+)-4-[(α*R*)-α-{(2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl}-3-methoxybenzyl]-*N*,*N*-diethylbenzamide (1b, SNC80) as a novel nonpeptidic δ receptor agonist and explored the structure–activity relationships (SAR) of a series of related derivatives. We have found that δ binding activities and selectivity showed little change when the 3-methoxy group in 1b was removed or replaced by the other substituents, whereas the *N*,*N*-diethylbenzamide group is important for interaction with the δ receptor. Extensive modification of the piperazine nucleus led to the synthesis of a new series of *N*,*N*-diethyl(α-piperazinylbenzyl)benzamides (2, 3a–e), *N*,*N*-diethyl(α-piperidinyl or piperidinylidenebenzyl)benzamides (4a, 5a–c, 6a–b), and related derivatives (4b, 7a–c). Several compounds (2, 3a, 3e, 6a) strongly bound to the δ receptor with K_i values in the low nanomolar range. On the other hand, the binding affinities of these compounds for the μ and κ receptors were negligible, indicating excellent δ opioid receptor subtype selectivity. The two nitrogen atoms on the piperazine nucleus showed different SAR in the interaction of this series of compounds at the δ receptor. Nitrogen N^4 appears to be an important structural element and is essential for electrostatic interaction, while N^1 seems to be unnecessary for recognition at the δ receptor.

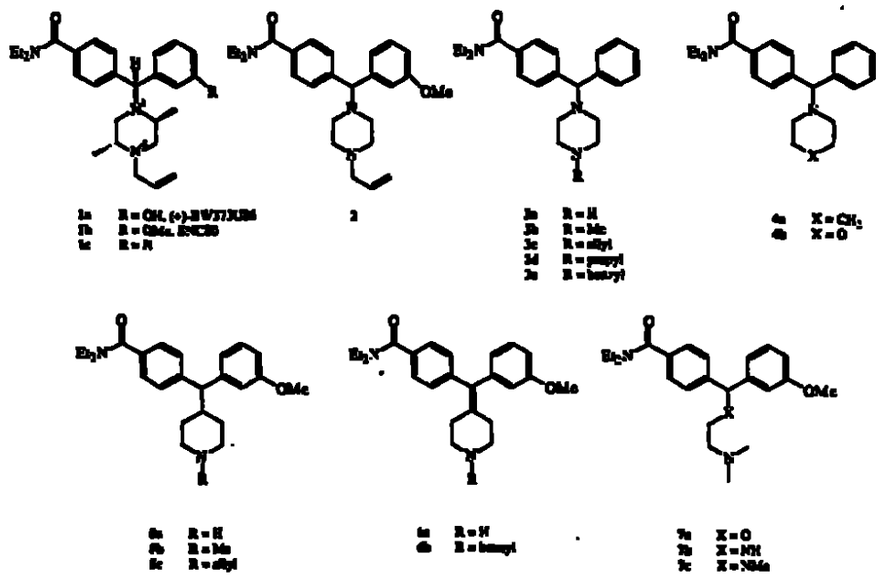
Classification of opioid receptors into mu (μ), delta (δ), and kappa (κ) is widely accepted, and they have been identified by molecular cloning and pharmacological means.[4–6] Recent advances in the understanding of the physiological functions of the δ opioid receptors have highlighted the important role of this receptor in the regulation of pain,[7–10] and the search for δ receptor agonists has been pursued in numerous laboratories. A number of selective δ agonists, such as DPDPE and [D-Ala^2]deltorphin II, have been developed for probing the function of the δ receptor.[10] Despite their δ agonist activity, their therapeutic use is limited due to their peptidic structure. The discovery and identification of (±)-4-[(α*R*)-α-(2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]-*N*,*N*-diethylbenzamide ((±)-BW373U86, (±)-1a) as a selective and nonpeptidic δ receptor agonist was a major advance in this area.[11–13] This compound has been described as the first systemically active, nonpeptide δ agonist and has proven useful in the characterization of the behavioral effects mediated by central δ receptors in primates.[14,15]

Recently, we reported the synthesis and absolute configuration of the optically pure enantiomers of the nonpeptide δ opioid agonist, (±)-1a, its benzylic epimers, and their methyl ethers.[1,2] Among this series, we have found that replacement of the phenolic hydroxyl group in 1a with either a methoxyl group ((+)-4-[(α*R*)-α-(2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide, 1b, SNC80) or a hydrogen atom (1c) gave ligands which retained the potent δ activities and significantly increased the μ/δ selectivity in both opioid receptor binding and in vitro functional assays (Chart 1). Subsequent studies included an investigation of the role of the amide functional group of 1b–c at the opioid receptors.[3] We found that the *N*,*N*-*p*-disubstituted amide functional group is important for the interaction of this series of compounds at the δ receptor. Furthermore, from the above studies we also learned that the spatial orientation of the α-benzylic position dramatically influenced the activity and selectivity of these molecules at δ opioid receptors. The pharmacological profile of compound 1b is similar to (±)-1a in mice, both producing antinociception and mild transient convulsions at the same dose range.[16] However, compound 1b produces greater antinociceptive activity in assays of thermal nociception without convulsant activity in the rhesus monkey, suggesting that

[†] National Institute of Diabetes and Digestive and Kidney Diseases.
[‡] National Institute on Drug Abuse.
[§] The University of Arizona.
[#] Present address: Neuregen Inc., 35 NE Industrial Road, Branford, CT.
[⊥] Present address: Division of Anesthetic, Critical Care and Abuse Drug Products, HFD 170, Food and Drug Administration, 8600 Fishers Lane, Rockville, MD 20857.
[▽] Present address: Fujisawa Pharmaceutical Co., Ltd., Medicinal Chemistry Research Laboratories, 2-1-6, Kashima, Yodogawa-ku, Osaka 532-8514, Japan.
[‖] Present address: Department of Pharmaceutical Sciences, University of Maryland School of Pharmacy, 20 North Pine St., Baltimore, MD 21201.

10.1021/jm9903885 CCC: $18.00 © 1999 American Chemical Society
Published on Web 12/10/1999

Chart 1. Structures of δ Opioid Receptor Selective Ligands



1b and related nonpeptidic δ agonists may be promising candidates for development as safe and effective clinical analgesics.[17] Extensive chemical modifications of this compound enabled us to further refine the basic framework for the interaction of this series of compounds at the δ receptor.

Most of the nonpeptidic δ opioid ligands (such as naltrindole and 17-(cyclopropylmethyl)-4,5-α-epoxy-7(*E*)-(1-naphthylidene)-3,14-dihydroxymorphinan (BNTX)) contain only one basic nitrogen atom. Site-directed mutagenesis experiments and molecular modeling studies have suggested that a basic nitrogen in δ opioid ligands is an essential structural element for receptor recognition, although there is conflicting evidence as to which receptor residue is important for that recognition.[18-21] Compound 1b has a carbon−nitrogen skeleton that is very different from the well-known fused-ring opioids, such as naltrindole and BNTX, and thus any structure−activity relationships dependent upon the better-known fused-ring opioids may not pertain to this new structure. Herein, we report our continuing structure−activity relationship studies of 1b focused on the investigation of the role of the two basic nitrogen atoms (N^1 and N^4) and the influence of substituents on N^4. We initially examined the effects of the *trans*-dimethyl groups on the piperazine ring of 1b and found that piperazine derivative 2, lacking the ring methyl groups of 1b, retained reasonable δ binding affinity and μ/δ selectivity. Furthermore, we found that the desmethoxy analogue 3c shows a similar δ opioid receptor binding profile as the methoxy analogue 1b. We then prepared a series of piperazine derivatives with various substituents on N^4 (3a−e). The influence of the two nitrogens was studied by replacement of one of the nitrogen atoms (N^1 or N^4) with carbon (4a, 5a−c, 6a−b) or oxygen (4b, 7a). Diarylmethyldiamines (7b−c) were also prepared to compare the δ activity of 7a. The synthesis and the structure−activity relationships of these new compounds on the opioid receptors are reported herein. The newly synthesized analogues were tested as racemates in order to evaluate the broad effect of the modification. During this work, similar modifications were published with comparable results.[22-28]

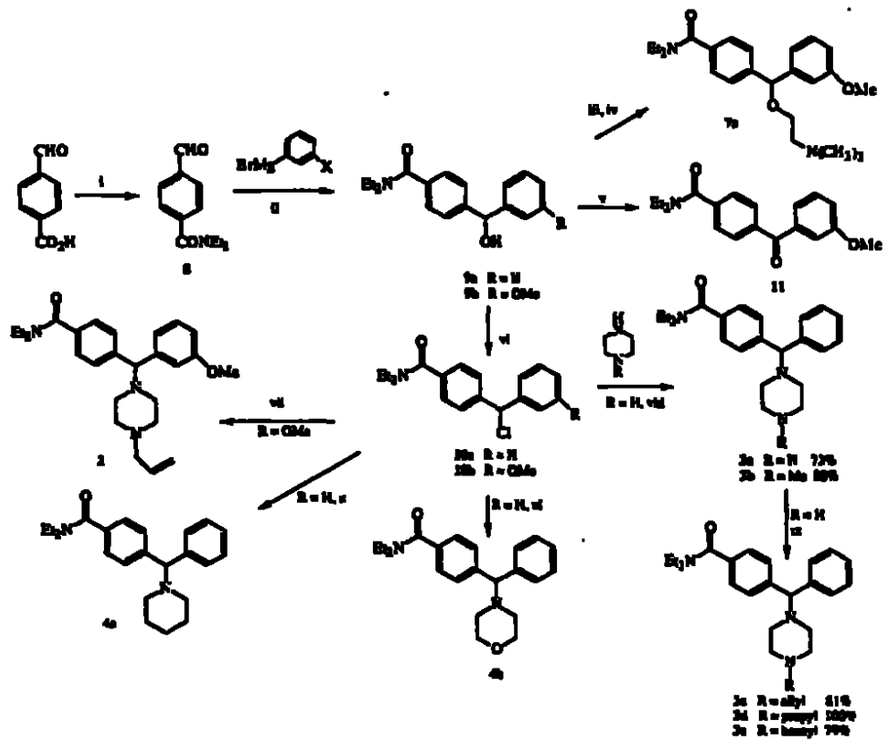
Chemistry

The synthetic intermediates 9−11 were prepared according to the previously reported method[2] or an alternative pathway[26,27] (Scheme 1) more applicable to the synthesis of these intermediates on a large scale. Condensation of 4-formylbenzoic acid with diethylamine in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) gave 4-formyl-*N*,*N*-diethylbenzamide (8).[25] The Grignard reaction of aldehyde 8 with (3-methoxyphenyl)magnesium bromide provided benzhydryl alcohol 9b.[2,26] Oxidation of the alcohol 9b with MnO_2 gave the corresponding benzoylbenzamide 11,[2,26] while treatment of 9b with concentrated hydrochloric acid generated the corresponding chloride 8b[2] in quantitative yield. This newer approach[26,27] of preparing intermediates 9a and 9b offered significant advantages over the previous one[2] in terms of fewer steps, higher yields, and the easier isolation of the products.

Treatment of the benzhydryl chloride 10a[2] or 10b[2] with the appropriate amine yielded the corresponding analogues 2,[23,27] 3a−b,[27] and 4a−b, as shown in Scheme 1. N-Alkylation of 3a afforded analogues 3c−e.[22,25] Compound 7a was synthesized in two steps from benzhydryl alcohol 9b[2,26] with chloroethanol, followed by the displacement of the chloride atom with dimethylamine.

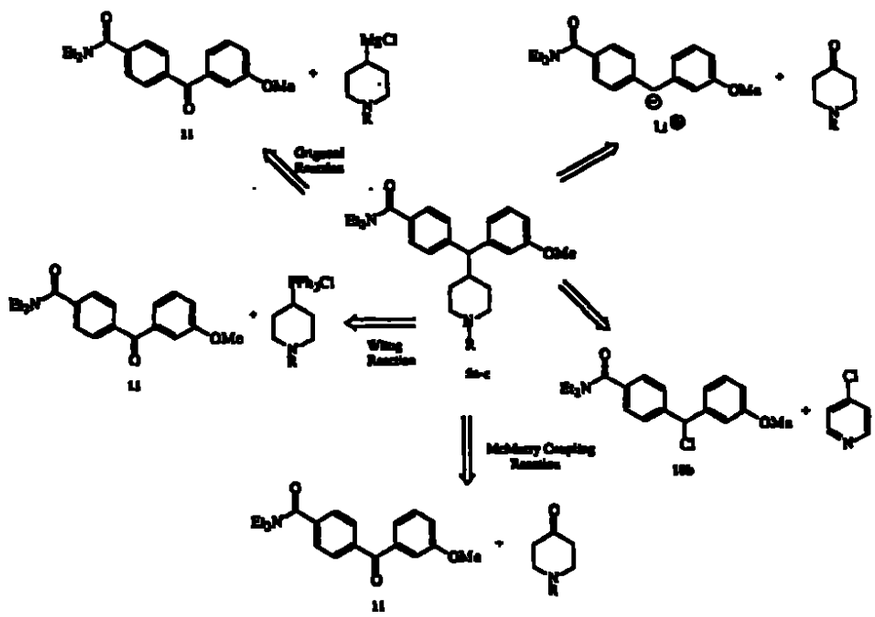
Several approaches different from that of Delorme et al.[24] were examined to construct the diarylmethylpiperidines 5[29,30] (Scheme 2), and only the McMurry coupling reaction[31] of 11[2,26] with *N*-benzyl-1-piperidone gave the desired intermediate 6b[24] in reasonable yield (Scheme 3). Hydrogenation of 6b with a catalytic

Scheme 1[a]



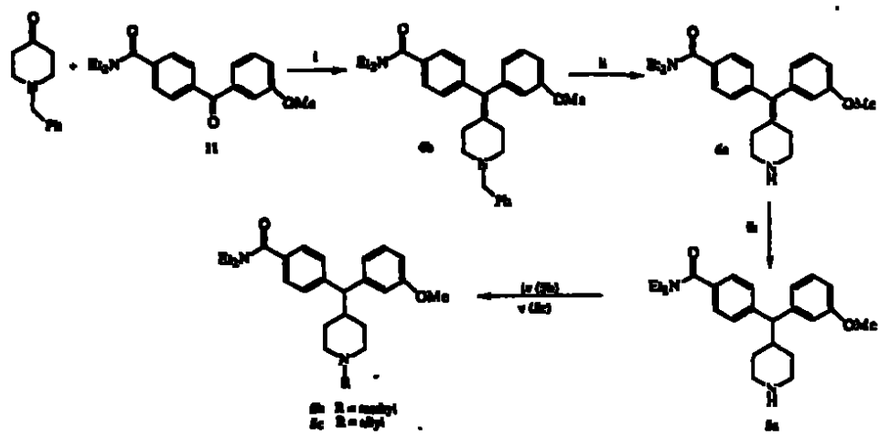
[a] Conditions: (i) EDCI, Et_2NH, CH_2Cl_2, rt, 87%; (ii) THF, rt, 91%; (iii) H^+, 2-chloroethanol, $PhCH_3$, reflux; (iv) $HNMe_2$, K_2CO_3, KI, THF, 60−65 °C, sealed, 72%; (v) MnO_2, CH_2Cl_2, 100%; (vi) HCl (conc), $CHCl_3$, 100%; (vii) *N*-allylpiperazine, K_2CO_3, CH_3CN, 66%; (viii) K_2CO_3, CH_3CN; (ix) alkyl halide, K_2CO_3, CH_3CN; (x) piperidine, K_2CO_3, CH_3CN, 38%; (xi) morpholine, K_2CO_3, CH_3CN, 78%.

Scheme 2



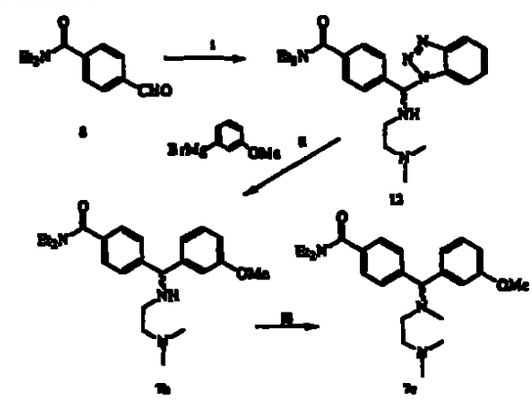
amount of Pd/C (10%) in acetic acid yielded a partially reduced intermediate 6a,[24] which was further reduced with an equal amount of Pd/C (30%) to give diarylmethylpiperidines 5a. Eschweiler−Clarke reaction of 5a afforded *N*-methyl analogue 5b, while alkylation of 5a with allyl bromide provided *N*-allyl derivative 5c.

Scheme 3[a]



[a] Conditions: (i) Zn, $TiCl_4$, DME, reflux; (ii) H_2 (80 psi), AcOH, Pd/C (10%); (iii) H_2 (80 psi), AcOH, Pd/C (30%); (iv) H_2CO, HCO_2H; (v) allyl bromide, K_2CO_3, THF.

Scheme 4[a]



[a] Conditions: (i) 2-(diaminomethyl)ethylamine, benzotriazole, PhH, reflux; (ii) THF, rt; (iii) H_2CO, HCO_2H.

The modified Katritzky tertiary amine method[32,33] yielded diarylmethyldiamine derivative 7b in a yield of 59%, as illustrated in Scheme 4. Eschweiler–Clarke reaction of 7b afforded analogue 7c.

Results and Discussion

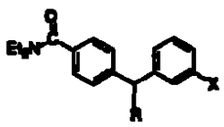
All compounds were tested for inhibition of specific binding of [^{3}H]DAMGO (Tyr-D-Ala-Gly-(Me)-Phe-Gly-ol)[34] to μ receptors and [^{3}H]DADLE (Tyr-D-Ala-Gly-Phe-D-Leu)[35] to δ receptors at rat brain membranes as previously reported.[1-3] The affinity of these derivatives for κ receptors was determined by inhibition of binding of [^{3}H]U69,593[36] at guinea pig brain membranes. The values for the μ, δ, and κ receptors are listed in Table 1.

All compounds displayed low affinity at μ and κ receptors, thus the most δ selective compounds are the ligands with the greatest δ affinity. The simple didemethylpiperazine derivative 2 had about one-seventh of the δ receptor affinity (δ K_i = 27 nM) of its *trans*-dimethyl relative 1b. The affinity of 2 indicates that *trans*-dimethyl groups on the piperazine ring are not critical for recognition at the δ receptor, a finding consistent with that of Morphy.[22,23] Furthermore, in accord with our findings that the aromatic methoxyl group of 1b is not essential (its demethoxylated relative 1c had very high affinity for the δ receptor), replacement of the aromatic methoxyl of 2 with a proton in 3c increased δ affinity (K_i = 10.5 nM). Thus, the influence of the N^4 substitution was investigated using this simplified carbon–nitrogen skeleton. It was shown that replacement of the *N*-allyl group with an alkyl moiety (3b,d) somewhat reduced affinity at the δ receptor. However, the *N*-benzyl derivative 3e had very high affinity for the δ receptor (K_i = 1.5 nM), more than twice the affinity of 1b, in accord with the binding data of Delorme et al. (1.2 nM).[25] It would appear that an electron rich substituent on N^4 leads to increased δ receptor affinity.

The high affinity of 3e for the δ receptor in this series is in marked contrast to the observed decrease in affinity that is obtained when an *N*-benzyl group is introduced in naltrindole-like molecules. Thus, 3e, a highly δ-selective ligand (μ/δ = >4500, Table 1), was found to have >70 times higher affinity at the δ receptor than *N*-benzyl-substituted oxymorphindole, 17-benzylnoroxymorphindole.[37] The differences in the δ receptor affinity between *N*-substituted naltrindole-like molecules and compounds similar to 1b could be ascribed to the distinctively different three-dimensional spatial orientation of the lone-pair electrons on the nitrogen atom which have been found in these compounds.[38]

Piperidine analogue 4a and morpholine analogue 4b showed little or no affinity for the three opioid receptor subtypes. In contrast, piperidine analogues 5a and 5c exhibited moderate binding affinity at the δ receptor. This observed structure–activity relationship suggests that the basic nitrogen N^4 is an important structural element in the interaction of this series of compounds at the δ receptor whereas the N^1 nitrogen could be modified while retaining reasonable interaction with the δ receptor. It should noted that ligands 5a and 5c possess a methoxy-substituted aromatic ring, whereas 4a and 4b do not, however the SAR above suggest that this aromatic substituent would not affect affinity to the extent observed. The poor affinity of 5b is consistent

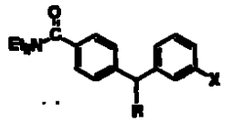
Table 1. Binding Affinities of Diarylmethylpiperazines and Diarylmethylpiperidines for μ, δ, and κ Receptors



compd	R	X	mp (°C)	formula[b]	K_i (nM ± SEM) μ binding[c]	δ binding[d]	κ binding[e]	K_i ratio μ/δ
1b[f]	*trans*-2,5,5*R*-dimethyl-*N*-allyl-1-piperazinyl	OCH_3			3970 ± 170	4 ± 0.18	11700 ± 630	990
1c[g]	*trans*-2,5,5*R*-dimethyl-*N*-allyl-1-piperazinyl	H			3000 (1840)[h]	0.5 ± 0.05	3000 (1900)[h]	>3600
2	*N*-allyl-1-piperazinyl	OCH_3	125–127	$C_{28}H_{38}N_2O_3 \cdot C_2H_2O_4$	10000 (8300)[h]	27 ± 2	10000 (8000)[h]	>230
3a	*N*-piperazinyl	H	188–189	$C_{25}H_{28}N_2O$	10000 (8800)[h]	4.85 ± 0.51	ND	>1400
3b	*N*-methyl-1-piperazinyl	H	182[a]	$C_{26}H_{30}N_2O \cdot HCl \cdot 2H_2O$	10000 (5800)[h]	43.2 ± 3	10000 (7000)[h]	>130
3c	*N*-allyl-1-piperazinyl	H	150[a]	$C_{28}H_{32}N_2O \cdot HCl \cdot 2.5H_2O$	10000 (8800)[h]	10.5 ± 0.8	ND	>800
3d	*N*-propyl-1-piperazinyl	H	170–172	$C_{28}H_{34}N_2O \cdot C_2H_2O_4$	10000 (8800)[h]	44.2 ± 3.9	10000 (7000)[h]	>150
3e	*N*-benzyl-1-piperazinyl	H	153–155	$C_{32}H_{32}N_2O \cdot C_2H_2O_4 \cdot 0.25H_2O$	10000 (8800)[h]	1.48 ± 0.6	2000 (1400)[h]	>4500
4a	*N*–1-piperidinyl	H	125–127	$C_{25}H_{29}NO \cdot 0.5H_2O$	10000 (8800)[h]	3000 (1700)[h]	10000 (7000)[h]	>4
4b	*N*-morpholinyl	H	98–100	$C_{24}H_{27}NO_2$	10000 (8800)[h]	3000 (1700)[h]	10000 (7000)[h]	>4
5a	4-piperidinyl	OCH_3	99[a]	$C_{26}H_{31}NO_2 \cdot HCl \cdot H_2O$	10000 (8300)[h]	20 ± 2	10000 (8000)[h]	>300
5b	*N*-methyl-4-piperidinyl	OCH_3	59[a]	$C_{27}H_{33}NO_2 \cdot HCl \cdot 1.75H_2O$	10000 (8300)[h]	328 ± 21	10000 (8000)[h]	>15
5c	*N*-allyl-4-piperidinyl	OCH_3	75[a]	$C_{29}H_{33}NO_2 \cdot HCl \cdot 0.5H_2O$	10000 (8300)[h]	27 ± 2	10000 (8000)[h]	>200
6a	4-piperidinylidene	OCH_3	83–85	$C_{26}H_{29}NO_2 \cdot HCl \cdot 0.5H_2O$	10000 (8300)[h]	5 ± 0.3	10000 (8000)[h]	>1200
6b	*N*-benzyl-4-piperidinylidene	OCH_3	92–95	$C_{33}H_{33}NO_2 \cdot HCl \cdot 0.5H_2O$	10000 (8300)[h]	12 ± 1	7650 ± 429	>500
7a	2-(*N*,*N*-dimethylamino)ethoxy	OCH_3	91[a]	$C_{28}H_{36}N_2O_2 \cdot C_2H_2O_4$	10000 (8300)[h]	258 ± 30	10000 (8000)[h]	>20
7b	2-(*N*,*N*-dimethylamino)ethamino	OCH_3	92–94	$C_{31}H_{41}N_3O_{16}$	10000 (8300)[h]	622 ± 42	10000 (8000)[h]	>10
7c	2-(*N*,*N*-dimethylaminoal-*N*-methylethylamino	OCH_3	95–97	$C_{34}H_{48}N_2O_2 \cdot 2HCl \cdot 1.5H_2O$	10000 (8300)[h]	248 ± 26	10000 (8000)[h]	>20

[a] Amorphous powder. [b] Analyses for C, H, and N were within ±0.4% of the theoretical values. [c] Inhibitory effect to [^{3}H]DAMGO in rat brain membranes. [d] Inhibitory effect to [^{3}H]DADAL in rat brain membranes. [e] Inhibitory effect to [^{3}H]U69,593 in guinea pig brain membrane. [f] See refs 1 and 2. [g] See ref 2. [h] No exact number could be given. The highest concentration tested (nM) is given with the maximum binding affinity (nM) in parentheses.

Table 2. Agonist Activity of Selected Compounds in the Mouse Vas Deferens (MVD) and Guinea Pig Ileum (GPI) Bioassay



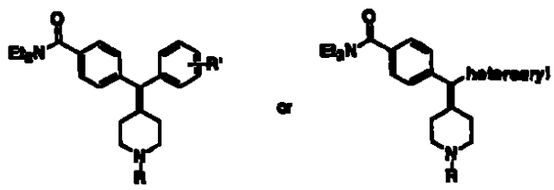
compd	R	X	IC_{50} (nM ± SEM) GPI (μ)	MVD (δ)	μ/δ ratio
1b[a]	*trans*-2,5,5*R*-dimethyl-*N*-allyl-1-piperazinyl	OCH_3	5450 ± 2050	2.73 ± 0.48	2000
1c[a]	*trans*-2,5,5*R*-dimethyl-*N*-allyl-1-piperazinyl	H	6580 ± 1300	10.5 ± 0.4	813
2	*N*-allyl-1-piperazinyl	OCH_3	20300 ± 1300	33.1 ± 3.0	610
3e	*N*-benzyl-1-piperazinyl	H	9850 ± 1050	25.7 ± 6.5	382
6a	4-piperidinylidene	OCH_3	27700 ± 900	125 ± 28	220

[a] Data from ref 2.

with the findings above that an N^4-substituent should be an electron rich system. When the relative orientation of the three rings were partially restricted by a double bond, piperidine **6a** exhibited 4-fold higher affinity at the δ receptor (K_i = 5 nM) than the unrestricted piperidine **5a**. Replacement of N^1 and N^4 with oxygen led to an ether linked ring-opened analogue **7a**, which showed decreased affinity at the δ receptor. As comparison, diarylmethyldiamines **7b** and **7c** also showed a considerable loss of affinity at the δ receptor, indicating that a cyclic amine is required for recognition at the receptor.

Compounds **2**, **3e**, and **6a**, which possessed good δ affinity and therefore the greatest δ selectivity in this series, were evaluated for opioid agonist activity in the mouse vas deferens (MVD) and guinea pig ileum (GPI) preparations (Table 2).[39] The agonism displayed by these ligands in the MVD was inhibited by the δ antagonist, ICI 174,864. Though the current ligands were less potent δ agonists than the parent compound

Chart 2. Structures of δ Opioid Receptor Selective Piperidines



13

1b, all three ligands showed high δ selectivity (GPI/MVD), which is consistant with the studies in the binding assays.

Conclusions

We have investigated a series of *N,N*-diethyl(α-piperazinylaryl)benzamides, *N,N*-diethyl(α-piperidinyl or piperidinylidenearyl)benzamides, and related derivatives as novel δ opioid receptor ligands. All of these compounds showed low binding affinity at μ and κ receptors, and several displayed high binding affinity at the δ receptor. Two important structure–activity relationships were observed from this present data: (1) the alkyl substituent pattern on the nitrogen N^4 decreased δ binding, and an electron rich substituent aids interaction with the δ receptor; (2) the nitrogen N^4 of the piperazine is sufficient to provide an essential electrostatic interaction with the δ receptor; N^1 is relatively unnecessary for binding to the δ receptor.

Recently, it has been reported that a series of *N,N*-diethyl(α-piperidinylidenearyl)benzamides 13 (Chart 2), structurally related analogues of 6a–b, display δ selective agonism, though the biological activities of these new compounds were not disclosed.[24] Thus, the *N,N*-diethyl(α-piperidinylidene-3-methoxybenzyl)benzamides 6a–b could be used as a valuable template for the development of new nonpeptidic ligands for the δ receptor.

Experimental Section.

Chemistry. Melting points were determined on a MEL-TEMP II capillary melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) were recorded in $CDCl_3$ (unless otherwise noted) with tetramethylsilane (TMS) as the internal standard on a Varian Gemini-300 spectrometer. Mass spectra (MS) were recorded on a VG 7070E spectrometer or a Finnigan 4600 spectrometer in the chemical ionization mode (MS, CI–NH_3). Thin-layer chromatography (TLC) was performed on Analtech silica gel GHLF 0.25 mm plates. Flash column chromatography was performed with Fluka silica gel 60 (mesh 220–240). Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA, and the results were within ±0.4% of the theoretical values unless otherwise indicated. Unless specifically indicated otherwise, amine salts were obtained and purified by the following standard procedures: (a) hydrochlorides: by the dropwise addition of 1.0 M HCl/Et_2O solution to a solution of the amine in acetone, until the resulting mixture was acidic to moist pH paper; (b) maleates and oxalates: by the dropwise addition of a molar equivalent solution of maleic acid or oxalic acid in anhydrous Et_2O to a solution of the amine in absolute methanol.

4-Formyl-*N,N*-diethylbenzamide (8).[25] 1-(3-Dimethylaminopropyl)-3-ethylcarbodimide hydrochloride (30.0 g, 157 mmol) was added portionwise to a cold solution (0 °C) of 4-formylbenzoic acid (21.36 g, 142 mmol), diethylamine (10.41 g, 142 mmol), and triethylamine (20 mL) in 350 mL of anhydrous CH_2Cl_2. The mixture was stirred at 0 °C for 30 min and warmed to the room temperature under Ar. After 4 h, the reaction was quenched by the addition of 200 mL of saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organics were washed successively with water, aqueous hydrochloric acid (5%), water, and brine, then dried over Na_2SO_4, and concentrated. The product 8 (27.2 g, 93%) was purified by high vacuum distillation: bp 113–116 °C/0.1 mmHg; ^{1}H NMR δ 1.12 (bs, 3H, CH_3), 1.27 (bs, 3H, CH_3), 3.22 (bd, J = 6.84 Hz, 2H, NCH_2), 3.57 (bd, J = 6.84 Hz, 2H, NCH_2), 7.53 (d, J = 8.14 Hz, 2H), 7.83 (d, J = 8.03 Hz, 2H), 10.05 (s, 1H, CHO); ^{13}C NMR δ 192 (CHO); MS (CI–NH_3) *m/z* 206 (MH^+).

4-[Hydroxy(3-methoxyphenyl)methyl]-*N,N*-diethylbenzamide (9b).[2,26] A solution of 3-(methoxyphenyl)magnesium bromide was prepared by stirring 3-bromoanisole (11.22 g, 60 mmol) in 120 mL of anhydrous THF with 1.8 g of magnesium turnings and refluxing for 1 h. The Grignard solution was cooled, and the clear supernate was transferred into a 500 mL round-bottom flask equipped with a mechanical stirrer and reflux condenser via a double-end needle under an atmosphere of Ar. A solution of 8 (6.15 g, 30 mmol) in 25 mL of anhydrous THF was added to the Grignard solution via syringe. The resulting mixture was stirred vigorously for 1 h, and the reaction was quenched by the addition of 100 mL of saturated aqueous NH_4Cl. The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organics were dried over $MgSO_4$ and concentrated. The crude product was crystallized from EtOAc/hexane to yield 8.55 g (91%) of 9b as white crystals: mp 90–91.5 °C (lit.[2] mp 89–90 °C); ^{1}H NMR δ 1.10–1.25 (m, 6H, $2CH_3$), 2.37 (d, J = 3.8 Hz, 1H, OH), 3.24 (bs, 2H, NCH_2), 3.51 (bs, 2H, NCH_2), 3.79 (s, 3H, OCH_3), 5.82 (d, J = 3.26 Hz, 1H, CH), 6.80–6.84 (m, 1H), 6.93–6.95 (m, 2H), 7.23–7.42 (m, 5H).

4-(3-Methoxybenzoyl)-*N,N*-diethylbenzamide (11).[2,26] To a solution of 9b (10.6 g, 34 mmol) in 200 mL of anhydrous CH_2Cl_2 was added activated manganese (IV) oxide (14.8 g, 5 equiv). The resulting mixture was heated at reflux for 3 h under Ar and then filtered through Celite. The filtrate was concentrated to give 10.5 g (100%) of 11 as a white solid: mp 88–89.5 °C (lit.[2] mp 88–89 °C); ^{1}H NMR δ 1.13–1.28 (bd, 6H), 3.26 (bs, 2H, NCH_2), 3.58 (bs, 2H, NCH_2), 3.87 (s, 3H, OCH_3), 7.15 (dd, J = 1.96, 8.46 Hz, 1H), 7.27–7.50 (m, 5H), 7.84 (d, J = 7.92 Hz, 2H).

4-[(4-Allyl-1-piperazinyl)-3-methoxybenzyl]-*N,N*-diethylbenzamide (2).[22,27] A mixture of 10b[2] (1.38 g, 4.13 mmol), *N*-allyl-piperazine (0.65 g, 5.15 mmol) and K_2CO_3 (1.70 g, 12.39 mmol) in 20 mL of anhydrous acetonitrile was heated to reflux overnight under Ar. The reaction mixture was poured into a mixture of EtOAc and water. The organic layer was washed with water, saturated aqueous solution of sodium carbonate twice and brine, dried over Na_2SO_4 and evaporated in a vacuum to give 2 as a colorless oil (1.13 g, 66%): ^{1}H NMR δ 1.12–1.21 (m, 6H), 2.30–2.55 (bs, 8H), 2.90 (d, J = 6.51 Hz, 2H), 3.21 (bs, 2H), 3.50 (bs, 2H), 3.78 (s, 3H, OCH_3), 4.20 (s, 1H, CHN), 5.11–5.20 (m, 2H, C=CH_2), 5.75–5.90 (m, 1H, C=CH), 6.74–6.75 (m, 1H), 6.97–7.00 (m, 2H), 7.19 (t, J = 8.1 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H); MS (CI–NH_3) *m/e* 422 (MH^+). Compound 2·oxalate: mp 125–127 °C; Anal. ($C_{28}H_{39}N_3O_3 \cdot C_2H_2O_4$) C, H, N.

4-(1-Piperazinylbenzyl)-*N,N*-diethylbenzamide (3a).[27] A mixture of 10a[2] (1.85 g, 6.13 mmol), piperazine (1.58 g, 18.3 mmol), K_2CO_3 (4.24 g, 30.7 mmol), and anhydrous acetonitrile (100 mL) was treated in a manner similar to that described above for the preparation of 2. This gave 1.55 g (72%) of 3a as colorless crystals: mp 168–169 °C (lit.[27] 157–169 °C); ^{1}H NMR δ 1.10 (bs, 3H), 1.20 (bs, 3H), 2.33 (bs, 4H), 2.88 (t, J = 5 Hz, 4H), 3.25 (bs, 2H), 3.51 (bs, 2H), 4.23 (s, 1H, CHN), 7.18–7.32 (m, 5H), 7.40 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H); MS (CI–NH_3) *m/e* 352 (MH^+). Anal. ($C_{22}H_{29}N_3O$) C, H, N.

4-[(4-Methyl-1-piperazinyl)benzyl]-*N,N*-diethylbenzamide (3b). A mixture of **10a**[2] (0.51 g, 1.88 mmol), *N*-methylpiperazine (0.19 g, 1.85 mmol), K_2CO_3 (0.70 g, 5.04 mmol), and anhydrous acetonitrile (5 mL) was treated in a manner similar to that described above for the preparation of **2**. This gave 0.54 g (88%) of **3b** as a colorless oil: ^{1}H NMR δ 1.10 (bs, 3H), 1.20 (bs, 3H), 2.28 (s, 3H, NCH_3), 2.43 (bs, 8H), 3.24 (bs, 2H), 3.51 (bs, 2H), 4.22 (s, 1H, CHN), 7.17–7.32 (m, 5H), 7.40 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H); MS (CI–NH_3) *m/e* 366 (MH^+). Compound **3b**·HCl: mp 182 °C (soften). Anal. ($C_{23}H_{31}N_3O$·HCl·$2H_2O$) C, H, N.

4-[(4-Allyl-1-piperazinyl)benzyl]-*N,N*-diethylbenzamide (3c).[22,27] A mixture of **3a** (0.21 g, 0.80 mmol), allyl bromide (0.09 g, 0.72 mmol), K_2CO_3 (0.17 g, 1.20 mmol), and anhydrous acetonitrile (8 mL) was treated in a manner similar to that described above for the preparation of **2**. This gave 0.19 g (81%) of **3c** as a colorless oil: ^{1}H NMR δ 1.10 (bs, 3H), 1.20 (bs, 3H), 2.46 (bs, 8H), 3.00 (d, J = 7.0 Hz, 2H), 3.23 (bs, 2H), 3.51 (bs, 2H), 4.23 (s, 1H), 5.10–5.22 (m, 3H), 5.85–5.87 (m, 1H), 7.19 (dd, J = 10.0, 7.0 Hz, 1H), 7.24–7.31 (m, 4H), 7.40 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H); MS *m/e* calcd for $C_{25}H_{33}N_3O$: 391.2624, found 391.2611. Compound **3c**·HCl: mp 150 °C (soften). Anal. ($C_{25}H_{33}N_3O$·HCl·$2.5H_2O$) C, H, N.

4-[(4-Propyl-1-piperazinyl)benzyl]-*N,N*-diethylbenzamide (3d).[22] A mixture of **3a** (0.35 g, 1 mmol), propyl iodide (0.2 mL, 2 mmol), K_2CO_3 (0.28 g, 2 mmol), and anhydrous acetonitrile (20 mL) was treated in a manner similar to that described above for the preparation of **2**. This gave 0.39 g (100%) of **3d** as a colorless oil: ^{1}H NMR δ 0.89 (t, J = 7.8 Hz, 3H), 1.10–1.20 (m, 6H), 1.46–1.90 (m, 4H), 2.28–2.45 (m, 8H), 3.24 (bs, 2H), 3.51 (bs, 2H), 4.24 (s, 1H, CHN), 7.19–7.28 (m, 5H), 7.38–7.45 (m, 4H); MS (CI–NH_3) *m/e* 394 (MH^+). Compound **3d**·oxalate: mp 170–172 °C. Anal. ($C_{25}H_{35}N_3O$·$C_2H_2O_4$) C, H, N.

4-[(4-Benzyl-1-piperazinyl)benzyl]-*N,N*-diethylbenzamide (3e).[28] A mixture of **3a** (0.20 g, 0.57 mmol), benzyl chloride (0.13 mL, 1.14 mmol), K_2CO_3 (0.16 g, 1.14 mmol), and anhydrous acetonitrile (8 mL) was treated in a manner similar to that described above for the preparation of **2**. This gave 0.20 g (79%) of **3e** as a colorless oil: ^{1}H NMR δ 1.00–1.25 (bd, 6H), 2.43–2.48 (m, 8H), 3.24 (bs, 2H), 3.51 (bs, 4H), 4.24 (s, 1H, CHN), 7.18–7.29 (m, 10H), 7.37–7.44 (m, 4H); MS (CI–NH_3) *m/e* 442 (MH^+). Compound **3e**·oxalate: mp 153–155 °C. Anal. ($C_{29}H_{35}N_3O$·$C_2H_2O_4$·$0.25H_2O$) C, H, N.

4-[(1-Piperidinyl)benzyl]-*N,N*-diethylbenzamide (4a). A mixture of **10a** (0.50 g, 1.88 mmol), morpholine (0.4 mL, 4.15 mmol), K_2CO_3 (0.70 g, 5.04 mmol), and anhydrous acetonitrile (10 mL) was treated in a manner similar to that described above for the preparation of **2**. This gave 0.22 g (38%) of **4a** as colorless crystals: mp 125–127 °C; ^{1}H NMR δ 1.12–1.25 (m, 6H), 1.42–1.58 (m, 6H, $3CH_2$), 2.31 (bs, 4H, $2NCH_2$), 3.28 (bs, 2H, $CONCH_2$), 3.49 (bs, 2H, $CONCH_2$), 4.24 (s, 1H, CHN), 7.18–7.30 (m, 5H), 7–7.44 (m, 4H); MS (CI–NH_3) *m/e* 351 (MH^+). Anal. ($C_{24}H_{30}N_2O$·$0.5H_2O$) C, H, N.

4-[(4-Morpholinyl)benzyl]-*N,N*-diethylbenzamide (4b). A mixture of **10a** (0.50 g, 1.88 mmol), morpholine (0.4 mL, 4.15 mmol), K_2CO_3 (0.70 g, 5.04 mmol), and anhydrous acetonitrile (10 mL) was treated in a manner similar to that described above for the preparation of **2**. This gave 0.45 g (78%) of **4b** as colorless crystals: mp 98–100 °C; ^{1}H NMR δ 1.10–1.25 (m, 6H), 2.36–2.39 (m, 4H, $2NH_2$), 3.21 (bs, 2H, $CONCH_2$), 3.52 (bs, 2H, $CONCH_2$), 3.69–3.72 (m, 4H, $2OCH_2$), 4.22 (s, CHN), 7.22–7.31 (m, 5H), 7.40–7.47 (m, 4H); MS (CI–NH_3) *m/e* 353 (MH^+). Anal. ($C_{23}H_{28}N_2O_2$) C, H, N.

4-[(1-Benzyl-4-piperidinylidene)-3-methoxybenzyl]-*N,N*-diethylbenzamide (6b).[24] Titanium (IV) chloride (2.85 g, 15 mmol) was added to a mechanically stirred suspension of zinc powder (1.96 g) in dry dimethoxyethane (75 mL) at −10 °C under Ar. When the addition was complete, the mixture was warmed to room temperature and then refluxed for 2 h. A mixture of **11** (1.58 g, 5 mmol) and *N*-benzylpiperidone (0.95 g, 5 mmol) in 25 mL of dimethoxyethane was added to the cooled suspension of the titanium reagent. The mixture was refluxed for 4 h, cooled, and poured into 10% aqueous K_2CO_3 (300 mL). After the mixture was stirred overnight, the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined ether extracts were dried over Na_2SO_4 and concentrated. The crude product was purified by acid–base extraction, followed by chromatography, to yield 1.53 g (65%) of **6b** as a light yellow powder: ^{1}H NMR δ 1.12–1.25 (m, 6H, $2CH_3$), 2.48 (m, 4H), 2.49 (m, 4H), 3.27 (bs, $CONCH_2$), 3.49–3.54 (m, 4H, $CONCH_2$, NCH_2Ph), 3.78 (s, 3H, OCH_3), 6.65–6.78 (m, 3H), 7.13–7.33 (m, 5H); MS *m/e* calcd for $C_{31}H_{36}N_2O_2$: 468.2777, found 468.2763. Compound **6b**·HCl, lyophilizate, mp 92–95 °C (lit.[24] 100–110 °C. Anal. ($C_{31}H_{36}N_2O_2$·HCl·$0.5H_2O$) C, H, N.

4-[(4-Piperidinylidene)-3-methoxybenzyl]-*N,N*-diethylbenzamide (8a).[24] To a solution of **6b** (0.70 g, 1.5 mmol) in acetic acid (15 mL) was added 70 mg of 10% Pd/C under Ar. The mixture was subjected to 60 psi of H_2 for 24 h. The mixture was filtered through Celite, and the solvent was evaporated. The residue was partitioned between 40 mL of saturated $NaHCO_3$ and 25 mL of CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organics were dried over Na_2SO_4 and concentrated. The crude product was filtered through a short silica column, eluting with $CHCl_3$:CH_3OH:NH_4OH (100:8:1) to give 0.40 g (70%) of **8a** as a glass: ^{1}H NMR δ 1.21–1.33 (m, 6H, $2CH_3$), 2.37–2.41 (m, 4H), 2.98–3.00 (m, 4H), 3.36 (bs, 2H, $CONCH_2$), 3.81 (bs, 2H, $CONCH_2$), 3.85 (s, 3H, OCH_3), 6.74–6.87 (m, 3H), 7.22–7.39 (m, 5H); ^{13}C NMR δ 12.77 (CH_3), 14.08 (CH_3), 33.32, 33.47, 39.12 ($CONCH_2$), 43.28 ($CONCH_2$), 48.44, 55.12 (OCH_3), 111.63, 115.76, 122.44, 126.26, 129.09, 129.79, 135.04, 135.16, 137.07, 143.32, 143.63, 159.44, 171.43 (CON); MS (CI–NH_3) *m/z* 379 (MH^+). Compound **8a**·HCl, lyophilizate, mp 83–85 °C (lit.[24] mp >90 °C (dec)). Anal. ($C_{24}H_{30}N_2O_2$·HCl·$0.5H_2O$) C, H, N.

4-[(4-Piperidinyl)-3-methoxybenzyl]-*N,N*-diethylbenzamide (5a). To a solution of **8a**[24] (1.87 g, 4.0 mmol) in acetic acid (30 mL) was added 1.87 g of 30% Pd/C under Ar. The mixture was subjected to 60 psi of H_2 for 10 h. The mixture was filtered through Celite, and the solvent was evaporated. The residue was partitioned between 40 mL of saturated $NaHCO_3$ and 40 mL of CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (40 mL × 3) and the combined organics were dried over Na_2SO_4 and concentrated. The crude product was filtered through a short silica column, eluting with $CHCl_3$:CH_3OH:NH_4OH (100:15:1) to give 1.25 g (82%) of **5a** as a glass: ^{1}H NMR δ 1.10–1.34 (m, 9H), 1.83 (t, J = 15.8 Hz, 2H), 2.20–2.27 (m, 2H), 2.61–2.71 (m, 2H), 3.17–3.21 (m, 2H), 3.50–3.54 (m, 3H), 3.79 (s, 3H, OCH_3), 6.72–6.75 (m, 1H), 6.82–6.89 (m, 2H), 7.19–7.30 (m, 5H); MS *m/e* calcd for $C_{25}H_{34}N_2O_2$: 380.2464, found 380.2467. Compound **5a**·HCl, mp 98 °C (soften). Anal. ($C_{24}H_{30}N_2O_2$·HCl·H_2O) C, H, N.

4-[(1-Methyl-4-piperidinyl)-3-methoxybenzyl]-*N,N*-diethylbenzamide (5b). A solution of **5a** (0.38 g, 1 mmol) in 1 mL of formic acid (98%) was treated with 1.5 mL of formaldehyde aqueous solution (37%) and stirred at 70–80 °C overnight. The reaction mixture was cooled and basified with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ (3 × 10 mL), and the combined organics were dried over Na_2SO_4 and concentrated. The crude product was filtered through a short silica column, eluting with $CHCl_3$:CH_3OH:NH_4OH (100:10:1) to give 0.34 g (86%) of **5b** as a colorless oil: ^{1}H NMR δ 1.11–1.29 (m, 9H), 1.58 (t, J = 13.7 Hz, 2H), 1.84–1.89 (m, 1H), 1.90–2.06 (m, 1H), 2.24 (s, 3H, NCH_3), 2.79 (d, J = 10.7 Hz, 2H), 3.25 (bs, 2H), 3.45–3.60 (m, 3H), 3.79 (s, 3H, OCH_3), 6.70–6.74 (m, 1H), 6.83–6.90 (m, 2H), 7.18–7.32 (m, 5H); MS *m/e* calcd for $C_{26}H_{36}N_2O_2$: 394.2820, found 394.2837. Compound **5b**·HCl: lyophilizate, mp 59 °C (soften). Anal. ($C_{26}H_{36}N_2O_2$·HCl·$1.75H_2O$) C, H, N.

4-[(1-Allyl-4-piperidinyl)-3-methoxybenzyl]-*N,N*-diethylbenzamide (5c). To a solution of **5a** (0.40 g, 1.1 mmol) in 10 mL of anhydrous THF were added allyl bromide (0.1 mL, 1.15 mmol) and K_2CO_3 (0.18 g, 1.3 mmol). The resulting mixture was stirred at room temperature under Ar. After 4 h, TLC analysis ($CHCl_3$:CH_3OH:NH_4OH 90:8:1) showed that no **5a** remained. The reaction suspension was filtered, and the filter cake was washed with CH_2Cl_2. The filtrate was evaporated and filtered through a short silica column, eluting with $CHCl_3$:CH_3OH:NH_4OH (100:3:0.5). The appropriate fractions were collected and dried under high vacuum to give 0.40 g (91%) of **5c** as a colorless oil: ^{1}H NMR δ 1.12–1.29 (m, 9H),

1.56 (t, J = 14.6 Hz, 2H), 1.88–2.09 (m, 2H), 2.86 (d, J = 11.7 Hz, 2H), 2.97 (d, J = 6.9 Hz, 2H), 3.25 (bs, 2H, $CONCH_2$), 3.46–3.60 (m, 3H), 3.79 (s, 3H, OCH_3), 5.10–5.18 (m, 2H, C=CH_2), 5.81–5.91 (m, 1H, C=CH), 6.70–6.74 (m, 1H), 6.82–6.89 (m, 2H), 7.18–7.29 (m, 5H); MS *m/e* calcd for $C_{25}H_{32}NO_2$: 420.2777, found 420.2772. Compound 5c·HCl: mp 75 °C (soften). Anal. ($C_{25}H_{32}NO_2$·HCl·0.5H_2O) C, H, N.

4-[(2,2-Dimethylaminoethoxy)-3-methoxybenzyl]-*N,N*-diethylbenzamide (7a). The benzhydrol 6b was placed in 20 mL of toluene and heated to solution. The solution was transferred into acidic chloroethanol in 10 mL of toluene and brought to reflux for 4 h. The reaction was cooled and treated with 20 mL of saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic were dried over $MgSO_4$ and concentrated to yield 2.11 g (99%) of 4-[(2-chloroethoxy)-3-methoxybenzyl]-*N,N*-diethylbenzamide as a colorless oil: ^1H NMR δ 1.13–1.28 (bd, 6H, $2CH_3$), 3.27 (bs, 3H, NCH_2), 3.54 (bs, 3H, NCH_2), 3.67–3.77 (m, 4H), 3.80 (s, 3H, OCH_3),.5.41 (s, 1H, OCH), 6.81–6.84 (m, 1H), 6.91–6.94 (m, 2H), 7.23–7.29 (m, 1H), 7.32–7.41 (m, 4H); MS (CI–NH_3) *m/z* 376 (MH^+). This material was used in the next step.

To a 2.0 M solution of dimethylamine (6 mL, 12 mmol) in THF were added the chloride from above (0.75 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol), and KI (0.332 g, 2 mmol). The resulting mixture was stirred in a sealed tube at 60–65 °C overnight. The reaction mixture was then cooled and poured into 30 mL of saturated aqueous $NaHCO_3$ and Et_2O (20 mL). The aqueous layer was extracted with Et_2O (2 × 20 mL), and the combined organics were dried over Na_2SO_4 and concentrated. The crude product was filtered through a short silica column, eluting with $CHCl_3$:CH_3OH:NH_4OH (100:3:1) to yield 0.554 g (72%) of 7a as colorless oil: ^1H NMR δ 1.11–1.22 (bd, 6H), 2.27 (s, 6H), 2.60 (t, J = 5.8 Hz, 2H), 3.25–3.59 (m, 4H), 3.79 (s, 3H, OCH_3), 5.35 (s, 1H, OCH), 6.78–6.82 (m, 1H), 6.91–6.93 (m, 2H), 7.21–7.39 (m, 5H); MS (CI–NH_3) *m/z* 385 (MH^+). The free base was converted to the oxalate salt (7a·oxalate): mp 51 °C (soften). Anal. ($C_{23}H_{32}N_2O_7$·$C_2H_2O_4$) C, H, N.

4-[(2,2-Dimethylaminoethylamino)-3-methoxybenzyl]-*N,N*-diethylbenzamide (7b). This material was prepared by the modified Katritzky tertiary amine method.[22,23] A solution of 3-(methoxyphenyl)magnesium bromide was prepared by stirring 3-bromoanisole (5 mL, 40 mmol) in 40 mL of anhydrous THF with 1 g of magnesium turnings and refluxing for 4 h. The imine adduct 12 was prepared by refluxing *N,N*-dimethylethylamine (0.93 g, 10 mmol) and 8 (2.28 g, 10 mmol) in 30 mL of benzene with a Dean–Stark trap attached to remove water. After being refluxed for 3 h, the cold solution of 12 was added dropwise to the Grignard solution, and the resulting mixture was stirred vigorously under Ar. The reaction mixture was quenched with HCl (10%, 100 mL) at 0 °C. The acidic aqueous layer was washed (Et_2O, 100 mL) and then carefully basified with aqueous NaOH to pH ~ 12 at 0 °C. The basic aqueous layer was extracted with $CHCl_3$ (3 × 100 mL), and the combined $CHCl_3$ layers were dried over Na_2SO_4 and concentrated. The crude product was purified by chromatography (silica: $CHCl_3$:CH_3OH:NH_4OH (100:3:1)) to yield 2.26 g (59%) of 7b as a glass: ^1H NMR δ 1.17–1.22 (bd, 6H), 1.87 (bs, 1H, NH), 1.74 (s, 6H), 2.44 (t, J = 5.97 Hz, 2H, NCH_2), 2.64 (t, J = 6.30 Hz, 2H, NCH_2), 3.25 (bs, 2H, $CONCH_2$), 3.52 (bs, 2H, $CONCH_2$), 3.79 (s, 3H, OCH_3), 4.78 (s, 1H, CH), 6.75 (dd, J = 2.71, 8.04 Hz, 1H), 6.97 (d, J = 6.51 Hz, 2H), 7.19–7.31 (m, 3H), 7.42 (d, J = 8.03 Hz, 2H); MS (CIMS) *m/e* 384 (MH^+). The free base was converted to the maleate salt (7b·maleate): mp 92–94 °C. Anal. ($C_{31}H_{41}N_3O_{10}$) C, H, N.

4-[(2,2-Dimethylamino-1-methylethylamino)-3-methoxybenzyl]-*N,N*-diethylbenzamide (7c). A solution of 7b (0.4 g, 1 mmol) in 1 mL of formic acid (96%) was treated with 1.5 mL of formaldehyde aqueous solution (37%) and stirred at 70–80 °C overnight. The reaction mixture was cooled and basified with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ (3 × 10 mL), and the combined organics were dried over Na_2SO_4 and concentrated. The crude product was filtered through a short silica column, eluting with $CHCl_3$:CH_3OH:NH_4OH (100:6:1) to give 0.25 g (61%) of 7c as a glass: ^1H NMR δ 1.11–1.25 (bd, 6H), 2.16 (s, 6H, $2NCH_3$), 2.17 (s, 3H, NCH_3), 2.44–2.48 (m, 4H, $2NCH_2$), 3.25 (bs, 2H, $CONCH_2$), 3.51 (bs, 2H, $CONCH_2$), 3.78 (s, 3H, OCH_3), 4.35 (s, 1H, NCH), 6.73–6.75 (m, 1H), 6.97–6.99 (m, 2H), 7.19 (t, J = 7.8 Hz, 1H), 7.28 (d, J = 10.8 Hz, 2H), 7.44 (d, J = 7.8 Hz, 2H); MS (CI–NH_3) *m/e* 398 (MH^+). Compound 7c·HCl, lyophilizate, mp 95–97 °C. Anal. ($C_{24}H_{39}N_3O_2$·2HCl·1.5H_2O) C, H, N.

Biological Assays. Radioligand Binding Assays for μ, δ, and κ Receptors. μ-Binding sites were labeled using [^{3}H]-DAMGO (2 nM) and rat brain membranes as previously described[24] with several modifications. Rat membranes were prepared daily, using a partially thawed frozen rat brain which was polytroned in 10 mL/brain of ice-cold 10 mM Tris-HCl, pH 7.0. Membranes were then centrifuged twice, each at 30000*g* for 10 min. After the second centrifugation, the membranes were resuspended in 50 mM Tris-HCl, pH 7.4 (50 mL/brain), at 25 °C. Incubations proceeded for 2 h at 25 °C in 50 mM Tris-HCl, pH 7.4, along with a protease inhibitor cocktail (PIC). The nonspecific binding was determined using 20 μM levallorphan. δ-Binding sites were labeled using [^{3}H]-DADLE (2 nM) and rat brain membranes as previously described[24] with several modifications. Rat membranes were prepared daily as with the μ-binding sites, above, except that incubations proceeded for 2 h at 25 °C in 50 mM Tris-HCl, pH 7.4, containing 100 mM choline chloride, 3 mM $MnCl_2$, and 100 mM DAMGO to block binding to μ sites, and PIC. Nonspecific binding was determined using 20 μM levallorphan. κ_1-Binding sites were labeled using [^{3}H]U69,593 (2 nM) as previously described[25] with several modifications. Guinea pig brain membranes were prepared daily, using partially thawed guinea pig brain which was polytroned in 10 mL/brain of ice cold 10 mM Tris-HCl, pH 7.0. Membranes were then centrifuged twice, each at 30000*g* for 10 min. After the second centrifugation, the membranes were resuspended in 50 mM Tris-HCl, pH 7.4 (75 mL/brain), at 25 °C. Incubations proceeded for 2 h at 25 °C in 50 mM Tris-HCl, pH 7.4, containing PIC and 1 μg/mL of captopril. Nonspecific binding was determined using 1 μM U69,593. Each [^{3}H] ligand was displaced by 10 concentrations of test drug, two times. All drug dilutions were done in 10 mM Tris-HCl, pH 7.4, containing 1 mg/mL bovine serum albumin. All washes were done with ice-cold 10 mM Tris-HCl, pH 7.4. The IC_{50} and slope factor (N) were obtained by using the program MLAB-PC (Civilized Software, Bethesda, MD). K_i values were calculated according to the equation $K_i = IC_{50}/(1 + [L]/K_d)$.

GPI and MVD Bioassays.[26] Electrically induced smooth muscle contraction of mouse vas deferens and strips of guinea pig ileum longitudinal muscle myenteric plexus were used. Tissues came from male ICR mice weighing 25–40 g and male Hartley guinea pigs weighing 250–500 g. The tissues were tied to gold chain with suture silk, suspended in 20 mL baths containing 37 °C oxygenated (95% O_2, 5% CO_2) Krebs bicarbonate solution (magnesium free for the MVD), and allowed to equilibrate for 15 min. The tissues were then stretched to an optimal length previously determined to be 1 g tension (0.5 g for MVD) and allowed to equilibrate for 15 min. The tissues were stimulated transmurally between platinum wire electrodes at 0.1 Hz, 0.4 ms pulses (2 ms pulses for MVD), and supramaximal voltage. Drugs were added to the baths in 14–60 mM volumes. The agonists remained in contact with the tissue until maximum inhibition was reached before the addition of the next cumulative dose. Percent inhibition was calculated by using the average contraction height for 1 min preceding the addition of the agonist divided by the contraction height at maximal inhibition after exposure to the dose of agonist. IC_{50} estimates and their associated standard errors were determined by using a computerized nonlinear least-squares method.[49] Sensitivity to the antagonist ICI-174,864 was tested by adding a 1 μM concentration of the antagonist to the tissue bath at the completion of the agonist dose–response curve. Partial or complete restoration of contraction height on addition of the antagonist was used as an indicator of the agonistic action at the δ receptor in the case of ICI-174,864.

Acknowledgment. We thank Noel Whittaker and Wesley White of the Laboratory of Analytical Chemistry for spectral data. We also acknowledge the National Institute of Drug Abuse for partial financial support.

References

(1) Calderon, S. N.; Rothman, R. B.; Porreca, F.; Flippen-Anderson, J. L.; McNutt, R. W.; Xu, H.; Smith, L. E.; Bilsky, E. J.; Davis, P.; Rice, K. C. Probes for Narcotic Receptor Mediated Phenomena. 19. Synthesis of (+)-4-[(αR)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide (SNC80): A Highly Selective Nonpeptide δ Opioid Receptor Agonist. *J. Med. Chem.* **1994**, *37*, 2125−2128.

(2) Calderon, S. N.; Rice, K. C.; Rothman, R. B.; Porreca, F.; Flippen-Anderson, J. L.; Kayakiri, H.; Xu, H.; Becketts, K.; Smith, L. E.; Bilsky, E. J.; Davis, P.; Horvath, R. Probes for Narcotic Receptor Mediated Phenomena. 23. Synthesis, Opioid Receptor Binding, and Bioassay of the Highly Selective δ Agonist (+)-4-[(α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide (SNC 80) and Related Novel Nonpeptide δ Opioid Receptor Ligands. *J. Med. Chem.* **1997**, *40*, 695−704.

(3) Katsura, Y.; Zhang, X. Y.; Homma, K.; Rice, K. C.; Calderon, S. N.; Rothman, R. B.; Yamamura, H. I.; Davis, P.; Flippen-Anderson, J. L.; Xu, H.; Becketts, K.; Fultz, E. J.; Porreca, F. Probes for Narcotic Receptor Mediated Phenomena. 25. Synthesis and Evaluation of *N*-Alkyl-substituted (α-Piperazinylbenzyl)-benzamides as Novel, Highly Selective δ Opioid Receptor Agonists. *J. Med. Chem.* **1997**, *40*, 2936−2947.

(4) Simon, E. J.; Hiller, J. M.; Edelman, I. Stereospecific Binding of the Potent Narcotic Analgesic [^{3}H]Etorphine to Rat-brain Homogenate. *Proc. Natl. Acad. Sci. U.S.A.* **1973**, *70*, 1947−1949.

(5) Lord, J.; Waterfield, A.; Hughes, J.; Kosterlitz, H. Endogenous Opioid Peptides: Multiple Agonists and Receptors. *Nature* **1977**, *267*, 495−499.

(6) Herz, A. The Multiplicity of Opioid Receptors and their Functional Significance. In *Trends in Medicinal Chemistry: Proceedings of the 8th International Symposium on Medicinal Chemistry*; Mutschler, E., Winterfeldt, E., Eds.; VCH Verlagsgesellschaft: Berlin, 1987; pp 337−350.

(7) Jiang, Q.; Mosberg, H. I.; Porreca, F. Selective Modulation of Morphine Antinociception, but Not Development of Tolerance, by δ Receptor Antagonists. *Eur. J. Pharmacol.* **1990**, *186*, 137−141.

(8) Heron, P.; Tafferida, R. J.; Hasseth, R. C.; Matsunaga, T. O.; Hruby, V. L.; Porreca, F. Antinociceptive Interactions of Opioid Delta Receptor Agonists with Morphine in Mice: Supra- and Sub-Additivity. *Life Sci.* **1992**, *50*, 1535−1541.

(9) Porreca, F.; Takemori, A. E.; Sultana, M.; Portoghese, P. S.; Bowen, W. D.; Mosberg, H. I. Modulation of Mu-Mediated Antinociception in the Mouse Involves Opioid Delta-2 Receptors. *J. Pharmacol. Exp. Ther.* **1992**, *263*, 147−152.

(10) Hammond, D. L. In *Current and Emerging Issues in Cancer Pain: Research and Practice*; Chapman, C. R., Foley, K. M., Eds.; Raven Press Ltd.: New York, 1993; pp 175−193.

(11) Chang, K. J.; Boswell, G. E.; Bubacz, D. G.; Collins, M. A.; Davis, A. O.; McNutt, R. W. Analgesic Diarylmethyl Piperazine and Piperidines. International Patent Application 1993, WO 93/15082.

(12) Chang, K. J.; Rigdon, G. C.; Howard, J. L.; McNutt, R. W. A Novel, Potent and Selective Nonpeptidic Delta Opioid Receptor Agonist BW373U86. *J. Pharmacol. Exp. Ther.* **1993**, *267*, 852−857.

(13) Wild, K. D.; McCormick, J.; Bilsky, E. J.; Vanderah, T.; McNutt, R. W.; Chang, K. J.; Porreca, F. Antinociceptive Actions of BW373U86 in the Mouse. *J. Pharmacol. Exp. Ther.* **1993**, *267*, 858−865.

(14) Negus, S. S.; Butelman, E. R.; Chang, K. J.; DeCosta, B.; Winger, G.; Woods, J. H. Behavioral Effects of the Systemically Active δ Opioid Agonist BW373U86 in Rhesus Monkeys. *J. Pharmacol. Exp. Ther.* **1994**, *270*, 1025−1034.

(15) Negus, S. S.; Picker, M. J. BW373U86: A Non-Peptidic Systemically-Active δ Opioid Agonist. *CNS Drug Rev.* **1996**, *2*, 53−74.

(16) Hong, E. J.; Rice, K. C.; Calderon, S.; Woods, J. H.; Traynor, J. R. Convulsive Behavior of Nonpeptide δ-Opioid Ligands: Comparison of SNC80 and BW373U86 in Mice. *Analgesia* **1996**, *2*, 269−278.

(17) Negus, S. S.; Gatch, M. B.; Mello, N. K.; Zhang, X. Y.; Rice, K. Behavioral Effects of the Delta-Selective Opioid Agonist SNC80 and Related Compounds in Rhesus Monkeys. *J. Pharmacol. Exp. Ther.* **1998**, *286*, 362−375.

(18) Kong, H.; Raynor, K.; Yasuda, K.; Moe, S. T.; Portoghese, P. S.; Bell, G. I.; Reisine, T. A Single Residue, Aspartic Acid 95, in the δ Opioid Receptor Specifies Selective High Affinity Agonist Binding. *J. Biol. Chem.* **1993**, *268*, 23055−23058.

(19) Huang, P.; Kim, S.; Loew, G. Development of a Common 3D Pharmacophore for δ Opioid Recognition from Peptides and Nonpeptidic Using a Novel Computer Program. *J. Comput.-Aided Mol. Des.* **1997**, *11*, 21−28.

(20) Befort, K.; Tabbara, L.; Bausch, S.; Chavkin, C.; Evans, C.; Kieffer, B. The Conserved Aspartate Residue in the Third Putative Transmembrane Domain of the δ-Opioid Receptor is not the Anionic Counterpart for Cationic Opiate Binding but is a Constituent of the Receptor Binding Site. *Mol. Pharm.* **1996**, *48*, 216−223.

(21) Pasa, G.; Malgret, B. Computer Modeling of δ Opioid Receptor and Interaction with Ligands. *Lett. Pept. Sci.* **1998**, *5*, 193−197.

(22) Barn, D. R.; Bom, A.; Cotmey, J.; Caulfield, W. I.; Murphy, J. R. Synthesis of Novel Analogues of the Delta Opioid Ligand SNC-80 Using AlCl$_3$-Promoted Aminolysis. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1329−1334.

(23) Cotmey, J.; Ramkovic, Z.; Murphy, J. R. Synthesis of Novel Analogues of the Delta Opioid Ligand SNC-80 Using REM Resin. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1323−1328.

(24) Delorme, D.; Roberts, E.; Wei, Z. Preparation of 4-[Diaryl or (Arylheteroaryl)methylene]piperidine Derivatives with Analgesic Effect. International Patent Application 1998, WO 98/28275.

(25) Delorme, D.; Barthelette, C.; Lavoie, R.; Roberts, E. Asymmetric Synthesis of Diarylmethylamines: Preparation of Selective Opioid Delta Receptor Ligands. *Tetrahedron: Asymmetry* **1998**, *9*, 3963−3966.

(26) Roberts, E.; Wahlestedt, C. Preparation of Homopiperazine Derivatives as Analgesics. International Patent Application 1997, WO 97/23467.

(27) Roberts, E.; Plebeck, N.; Wahlestedt, C. Preparation of N-Diarylmethylpiperazines as Analgesics. International Patent Application 1997, WO 97/23486.

(28) Dondio, G.; Bonsord, S. Preparation of Diarylalkenylamines as Selective Delta Opioid Agonists and Antagonists. International Patent Application 1997, WO 97/10230.

(29) Nagai, Y.; Una, H. Studies of Psychotropic Agent V. Synthesis of 1-Substituted Spiro[dibenz[*b*,*f*]oxepin-11,4′-piperidine]-10-(11*H*)-one and Related Compound. *Chem. Pharm. Bull.* **1979**, *27*, 2056−2064.

(30) Teng, L. C.; Walsh, D. A.; James R. Shanklin, J. Preparation of N−Phenoxyalkyl(aralkyl)piperidines and Related Compounds as Cardiovascular, Antihistaminic, Antisecretory and Antiallergy Agents. US Patent 5070087, 1991.

(31) Cox, P. L.; Scriven, C. E. Crossed Coupling of Functionalized Ketones by Low Valent Titanium (The McMurry Reaction): A New Stereoselective Synthesis of Tamoxifen. *J. Chem. Soc., Perkin Trans. 1* **1998**, 475−477.

(32) Bishop, M. J.; McNutt, R. W. An Efficient Synthesis of the Benzhydrylpiperazine Delta Opioid Agonist (+)-BW373U86. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1311−1314.

(33) Zhang, X.; Calderon, S. N.; Rice, K. C. An Improved Synthesis of SNC80, A Highly Selective Delta Opioid Receptor Agonist. In *Problems of Drug Dependence 1998*; Harris, L. S., Ed.; NIDA Research Monograph 174; Washington, DC, 1998; p 101.

(34) Rothman, R. B.; Xu, H.; Seggal, M.; Jacobson, A. E.; Rice, K. C.; Brine, G. A.; Carroll, F. I. An Analogue of (+)-*cis*-3-Methylfentanyl with a 27,000-fold Binding Selectivity for Mu Versus Delta Binding Sites. *Life Sci.* **1991**, *48*, PL111−PL116.

(35) Rothman, R. B.; Bykov, V.; Ofri, D.; Rice, K. C. LY164929: A Highly Selective Ligand for the Lower Affinity [^{3}H][D-Ala^2-D-Leu^5]-enkephalin Binding Sites. *Neuropeptides* **1988**, *11*, 13−15.

(36) Rothman, R. B.; da Costa, B. R.; Bykov, V.; Jacobson, A. E.; Rice, K. C.; Brady, L. S. Interaction of Endogenous Opioid Peptides and Other Drugs with Four Kappa Opioid Binding Sites in Guinea Pig Brain. *Peptides* **1990**, *11*, 311−331.

(37) May, E. L.; Jacobson, A. E.; Martson, M. V.; Camp, A.; Aceto, M. D.; Bowman, E. R.; Traynor, J. R.; Woods, J. H.; Harris, L. S. Synthesis, In Vitro, and In Vivo Activity of *N*-*p*-Substituted-Benzyl- (−)- and (+)-N-Normetazocines, (−)- and (+)-N-Normorphinans, N-Norketobemidones, and (−)-N-Nor-4,5-Epoxymorphinans. *Med. Chem. Res.* **1998**, *8*, 311−321.

(38) Camp, A.; Jacobson, A. E. The LMC Delta Opioid Recognition Pharmacophore: Comparison of SNC80 and Oxymorphindole. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 357−362.

(39) Kramer, T. H.; Davis, P.; Hruby, V. J.; Burks, T. F.; Porreca, F. In vitro Potency, Affinity and Agonist Efficacy of Highly Selective Delta Opioid Receptor Ligands. *J. Pharmacol. Exp. Ther.* **1993**, *265*, 577−584.

(40) MINSQ Least Squares Parameter Estimation, version 3.05; MicroMath, Inc., 1989.

JM9903895

J. Med. Chem. 2000, *43*, 3895−3905

N,N-Diethyl-4-(phenylpiperidin-4-ylidenemethyl)benzamide: A Novel, Exceptionally Selective, Potent δ Opioid Receptor Agonist with Oral Bioavailability and Its Analogues

Zhong-Yong Wei,* William Brown, Bryan Takasaki, Niklas Plobeck, Daniel Delorme,‡ Fei Zhou, Hua Yang, Paul Jones, Lars Gawell, Helene Gagnon, Ralf Schmidt, Shi-Yi Yue, Chris Walpole, Kemal Payza,# Stephane St-Onge,# Maryse Labarre,# Claude Godbout,# Andrea Jakob,# Joanne Butterworth,# Augustus Kamassah,# Pierre-Emmanuel Morin,# Denis Projean,# Julie Ducharme,# and Edward Roberts†

Departments of Chemistry and Pharmacology, AstraZeneca R&D Montreal, 7171 Frederick-Banting, Saint-Laurent, Quebec, Canada H4S 1Z9

Received May 30, 2000

The design, synthesis, and pharmacological evaluation of a novel class of δ opioid receptor agonists, *N,N*-diethyl-4-(phenylpiperidin-4-ylidenemethyl)benzamide (6a) and its analogues, are described. These compounds, formally derived from SNC-80 (2) by replacing the piperazine ring with a piperidine ring containing an exocyclic carbon carbon double bond, were found to bind with high affinity and exhibit excellent selectivity for the δ opioid receptor as full agonists. 6a, the simplest structure in the class, exhibited an IC_{50} = 0.87 nM for the δ opioid receptors and extremely high selectivity over the μ receptors (μ/δ = 4370) and the κ receptors (κ/δ = 8590). Rat liver microsome studies on a selected number of compounds show these olefinic piperidine compounds (6) to be considerably more stable than SNC-80. This novel series of compounds appear to interact with δ opioid receptors in a similar way to SNC-80 since they demonstrate similar SAR. Two general approaches have been established for the synthesis of these compounds, based on dehydration of benzhydryl alcohols (7) and Suzuki coupling reactions of vinyl bromide (8), and are herewith reported.

Introduction

Studies have indicated the existence of three main opioid receptor subtypes, μ, δ, and κ, that all appear to be present in both the central and peripheral nervous systems of many species including humans.[1−3] Agonists of all three receptor subtypes have been shown to produce analgesia.[4] Recently, increasing evidence[5−10] has accumulated to support the hypothesis that a selective δ opioid agonist will be an effective analgesic devoid of the side-effect liability associated with μ opioid agonists such as morphine (e.g., respiratory depression, dependence liability, and inhibition of gastrointestinal motility) or the clinically limiting side effects from κ opioid agonists such as CI977 (e.g., dysphoria, diuresis, and locomotor impairment). This has provided the impetus for the development of selective nonpeptide δ opioid agonists. Two major advances in the area of δ-selective agonists were the discoveries of diarylpiperazine derivative (±)-BW373U86 (1)[11] and morphinan derivative (−)-TAN-67 (3) (Figure 1).[12] Both compounds exhibit a high affinity for the δ opioid receptor with moderate selectivity with respect to the μ opioid receptor. An analogue of (+)-BW373U86, SNC-80 (2),[13] demonstrated an improved selectivity while retaining potent δ receptor agonist activity.

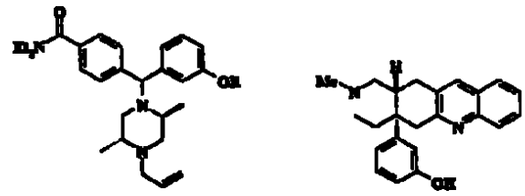


Figure 1. Structures of compounds 1−3.

Due to the presence of three asymmetric carbon atoms, (+)-4-[(α*R*)-α-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-*N,N*-diethylbenzamide (SNC-80, 2) has seven possible stereoisomers, which should exhibit different pharmacological profiles. As described in the first paper in the series,[14] we aimed to find a simple substructure of SNC-80 that retains δ receptor agonist activity and improves the selectivity of δ against μ or κ. Initial SAR studies[15] around SNC-80 indicated that the 4-*N,N*-diethylaminocarbonyl group is a key structural feature, but neither the methoxy group, the allyl group, nor the two methyl groups on the piperazine were essential for high affinity at the δ opioid receptor or for selectivity over the μ or κ opioid receptors. Compared to SNC-80, compound 4 displayed a limited decrease in δ binding affinity but improved selectivity. These observations are consistent with recent reports by Calderon et al.[16−18] and Cottney et al.[19] Further studies also indicated that nitrogen N^1 of the piperazine was not involved in binding to the δ opioid receptor. For

* To whom correspondence should be addressed. Tel: 514-832-3200, ext 2402. Fax: 514-832-3232. E-mail: john.wei@astrazeneca.com.
Department of Pharmacology.
‡ Present address: Methylgene Inc., 7220 Frederick-Banting, Saint-Laurent, Quebec, Canada H4S 2A1.
† Present address: F. Hoffmann-La Roche Ltd., Pharmaceuticals Division, PRBC, Bldg 013/203, CH-4070 Basel, Switzerland.

10.1021/jm000229p CCC: $19.00 © 2000 American Chemical Society
Published on Web 09/19/2000

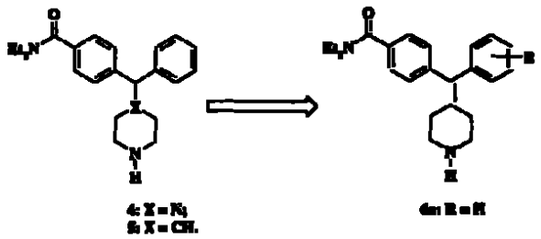


Figure 2. Structures of compounds 4, 5, and 6a.

example, piperidine derivative 5 (IC_{50} = 8.8 nM) exhibited an almost identical δ binding affinity to compound 4 (IC_{50} = 11.3 nM) (Figure 2).

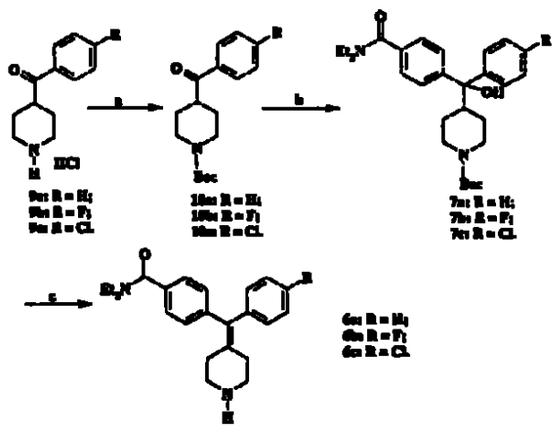
Introduction of conformational constraints in biologically active compounds is a well-established approach for enhancing receptor binding affinity and selectivity. On the basis of the above assumption, incorporation of an exocyclic carbon–carbon double bond into the piperidine ring of 5 became the most logical modification[20] on SNC-80. The resulting compound, 6a, has displayed a 9-fold increase in binding affinity for the δ receptor (IC_{50} = 0.87 nM) and extremely high selectivity over the μ receptor (μ/δ = 4370) and the κ receptor (κ/δ = 8590). In this paper, we investigate the δ receptor binding effects of the substitution pattern on the aromatic ring of 6a and the effect of *N*-substitution of the piperidine. All compounds were examined for their affinity for all three human opioid receptor subtypes, and their δ agonist activity was determined using the GTP[γ-^{35}S] binding assay.

Chemistry

Diarylmethylenepiperidines have been well-known as antihistamine drugs in the treatment of allergic diseases. The synthesis of these compounds has been achieved by several approaches such as Wittig–Horner reaction[21] and McMurry coupling reaction.[22] In our opinion, however, more efficient procedures were required to prepare compounds 6 with modified aromatic groups (Figure 3). Thus, novel approaches have been explored, including the methodology based on the Suzuki coupling reaction of compound 8 with different arylboronic acids and the procedure based on dehydration of compounds 7, which were easily prepared by reacting a 4-benzoylpiperidine with an aryllithium or an arylmagnesium halide.

Synthesis of compounds 6a–6c is described in Scheme 1. Thus 4-benzoylpiperidine hydrochloride (9a) was transformed to its N-Boc derivative 10a in 98% yield under basic conditions. 4-Iodo-*N*,*N*-diethylbenzamide[23] was subjected to metal–halogen exchange with *t*-BuLi

Scheme 1[a]



[a] Reagents: (a) Boc_2O; (b) 4-iodo-*N*,*N*-diethylbenzamide/BuLi, −78 °C; (c) TFA.

in THF at −78 °C followed by the addition of 10a, to furnish compound 7a in 94% yield. Subsequent dehydration of the benzhydryl alcohol 7a was performed in methylene chloride in the presence of trifluoroacetic acid to provide compound 6a in 91% yield. Similarly compounds 6b and 6c were prepared from commercially available 4-benzoylpiperidines 9b and 9c.

A more efficient strategy based on the dehydration approach would react 10d with a number of different arylmagnesium halides or aryllithiums. Thus as shown in Scheme 2, 4-(4′-*N*,*N*-diethylaminocarbonyl)benzoylpiperidine was prepared from ethyl isonipecotate (11) in 28% yield by a three-step procedure. Benzhydryl alcohols 7d–7g were then obtained from reacting 10d with a variety of aryllithium reagents. Dehydration under the same conditions as for 6a provided the desired compounds 6d–6g.

The synthetic approach based on Suzuki coupling reaction is shown in Scheme 3. The key intermediate 8 was prepared in five steps from compound 13. Thus, methyl 4-(bromomethyl)benzoate was refluxed for 5 h in trimethyl phosphite to provide compound 14 in quantitative yield. Wittig–Horner olefination of *N*-*tert*-butoxycarbonyl-4-piperidone with compound 14 was performed in the presence of LDA. Addition of bromine to a solution of 15 in dichloromethane afforded compound 16 in 78% yield, which was then treated with aqueous NaOH in methanol at 40 °C to provide compound 17. *N*,*N*-Diethylbenzamide (8) was then prepared in 73% yield from 17 by the mixed anhydride approach. The Suzuki coupling reaction of vinyl bromide 8 with a variety of arylboronic acids was performed in the

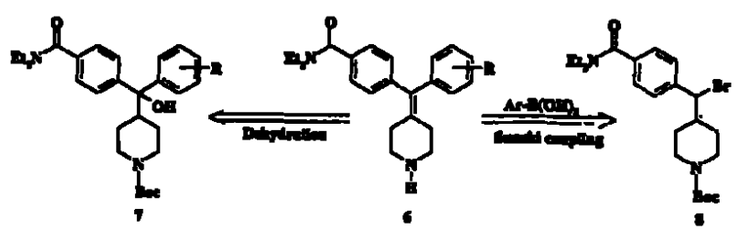
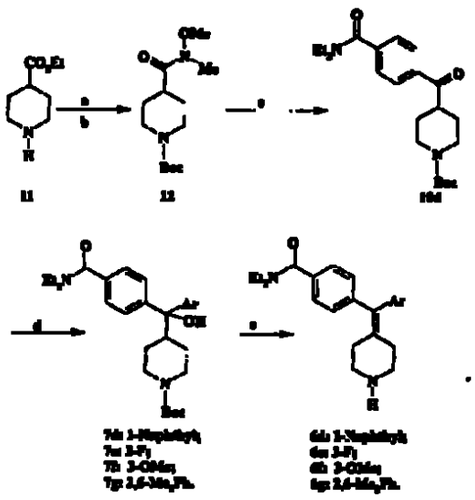


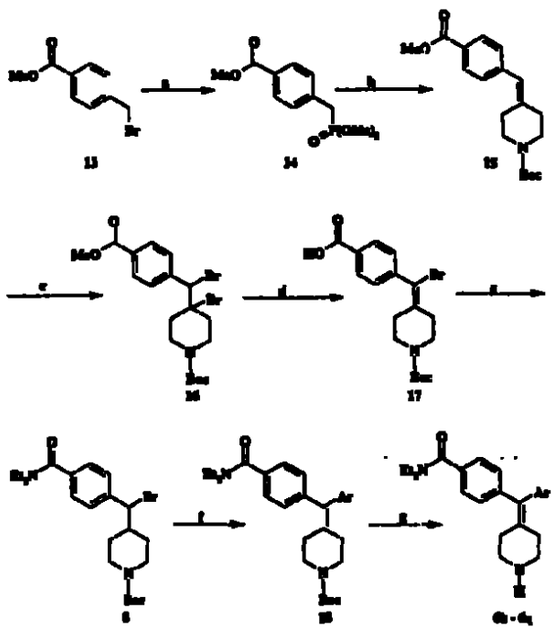
Figure 3. Reactions to prepare compound 6.

Scheme 2[a]



[a] Reagents: (a) Boc_2O; (b) Me(MeO)NH, *i*-PrMgCl; (c) 4-Iodo-*N*,*N*-diethylbenzamide/BuLi, −78 °C; (d) Ar-Li; (e) TFA.

Scheme 3[a]

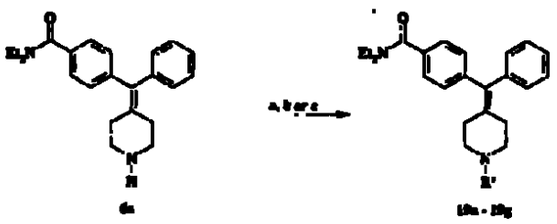


[a] Reagents: (a) $P(OMe)_3$; (b) LDA, *N*-*tert*-butoxycarbonyl-4-piperidone; (c) Br_2; (d) NaOH; (e) $(COCl)_2$/Et_3N, Et_2NH; (f) Ar-$B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3; (g) 4 N HCl.

presence of tetrakis(triphenylphosphine)palladium (0) using 2 M Na_2CO_3 as base. Subsequent cleavage of the Boc group was achieved with 4 N HCl in dioxane providing the final compounds **6h**−**6q**.

Compounds **19a**−**19g** representing different *N*-substituted analogues of **6a** were prepared as described in Scheme 4. Compounds **19a**−**19e** were obtained by treatment of **6a** with the corresponding alkyl halides in the presence of potassium carbonate in acetonitrile at room temperature. The *N*-cyclohexyl derivative **19f** was provided by reductive amination from **6a** and

Scheme 4[a]



[a] Reagents: (a) R′-X, K_2CO_3; (b) $R^1R^2C{=}O$, $NaBH_4$; or (c) Ph-Br, $Pd(dba)_2$, BINAP, NaO-*t*-Bu.

cyclohexanone. Finally the *N*-phenyl analogue **19g** was obtained by palladium catalyzed *N*-arylation[24] of **6a**.

Results and Discussion

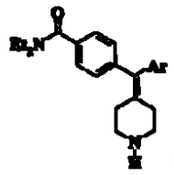
In Vitro Pharmacology. The binding affinities (IC_{50}) of all compounds were determined using cloned human δ, μ, and κ opioid receptors, and the δ agonist potency (EC_{50}) was measured with the GTP[γ-^{35}S] binding assay.

The opioid receptor binding affinity, selectivity, and agonist potency of the target compounds **6** are listed in Table 1, and those of SNC-80, diarylmethylpiperazine **4**, and diarylmethylpiperidine **5** are also included for comparison. As compared to SNC-80 [δ IC_{50} = 1.31 nM; μ/δ = 245; κ/δ = 1890 (K_i = 4 nM; μ/δ = 990 on rat brain membranes)[18]], compound **6f** displayed similar binding affinity [IC_{50} = 1.56 nM (K_i = 5 nM; μ/δ > 1200 on rat brain membranes)[18]] on δ receptors but an improved selectivity over μ and κ receptors (μ/δ = 3370; κ/δ > 6410). **6a**, a derivative of **6f** without the 3-MeO group on the phenyl ring, even further increased selectivity as a result of improved δ-affinity (IC_{50} = 0.87 nM; μ/δ = 4370; κ/δ = 8590). Considerable variation is possible in the nature of the substitution on the phenyl ring, and this can lead to some highly potent δ agonists. For example, compounds **6e** (EC_{50} = 4.6 nM) and **6h** (EC_{50} = 3.18 nM) exhibited improved agonist activities at δ receptors compared to the "parent" structure (**6a**, EC_{50} = 7.2 nM). The position of a substituent on the phenyl ring is important for both binding affinity and agonist activity. Substitution at the *para*-position of the phenyl ring appeared to be detrimental (**6b** vs **6e**, **6l**; **6p** vs **6f**, **6q**), presumably reflecting steric constraints in this region. The 2,6-dimethylphenyl analogue **6g** exhibited a dramatically reduced δ binding affinity as compared to the parent compound **6a**, suggesting that the steric constraints imposed by the two methyl groups may alter the conformation of the dimethylphenyl ring in a manner which is deleterious to activity. On the other hand, the phenyl group can be replaced by heteroaryl or other aryl groups. For example, 1-naphthyl (**6d**) and 2-thiophenyl (**6m**) analogues still retain potent δ affinity and high selectivity over μ and κ receptors.

In general, this entire series of compounds displayed extremely high affinity to δ opioid receptors (low nanomolar to subnanomolar range) and very high selectivity over μ or κ opioid receptors (>1000 in most cases). All compounds exhibited full δ agonism at the cloned human δ receptor as determined in GTP[γ-^{35}S] binding assay.

To examine the effect on biological activity of *N*-alkyl substitution on the piperidine nitrogen of **6a**, *N*-Me,

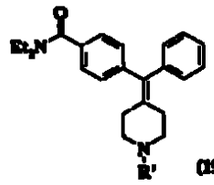
Table 1. Binding Affinities and Agonist Activities of Compounds 6



(6)

		IC_{50} (nM)			selectivity ratio		δ	
compd	Ar	δ	μ	κ	μ/δ	κ/δ	EC_{50}(nM)	E_{max} (%)
SNC-80		1.31 ± 0.17	320 ± 58	2480 ± 378	245	1890	3.67 ± 0.70	100± (REF)
4		11.3 ± 2.3	8150±373	>10000	741	>909	36.5 ± 5.9	105 ± 5
5		8.77 ± 0.89	n/a	n/a	n/a	n/a	121 ± 15	97 ± 3
6a		0.87 ± 0.23	3800 ± 172	7470 ± 606	4370	8590	7.2 ± 0.9	110 ± 3
6b		15.0 ± 2.4	>10000	>10000	>667	>667	98.1 ± 11.4	96 ± 7
6c		4.17 ± 1.20	5050 ± 272	8340 ± 1710	1210	2000	25.5 ± 4.1	111 ± 2
6d		1.23 ± 0.07	817 ± 77	1660 ± 268	664	1350	5.9 ± 1.8	107 ± 4
6e		0.74 ± 0.14	3570 ± 444	>10000	4820	>13500	4.6 ± 0.5	112 ± 6
6f		1.56 ± 0.26	5250 ± 445	>10000	3370	>6410	13.7 ± 3.2	109 ± 7
6g		167 ± 15.4	1020 ± 66	2610 ± 515	5.5	14	n/a	n/a
6h		0.63 ± 0.11	1510 ± 161	5350 ± 648	2400	8490	3.18 ± 0.56	110 ± 1
6i		2.31 ± 0.24	2590 ± 749	3870 ± 162	1120	1680	8.96 ± 2.19	104 ± 2
6j		0.86 ± 0.15	3290 ± 535	>10000	3820	>10000	10.6 ± 2.4	110 ± 1
6k		1.10 ± 0.32	2740 ± 304	>10000	2490	>9090	8.6 ± 2.5	98 ± 2
6l		1.04 ± 0.11	2980 ± 647	>10000	2860	>9620	15.9 ± 4.5	112 ± 5
6m		2.85 ± 0.21	5440 ± 656	>10000	1910	>3510	30.6 ± 6.3	99 ± 6
6n		2.09 ± 0.36	6760 ± 926	>10000	3240	>4790	23.4 ± 5.7	98 ± 5
6o		2.57 ± 0.23	5980 ± 1060	>10000	2330	>3890	20.5 ± 2.9	96 ± 4
6p		2.04 ± 0.22	5440 ± 1270	>10000	2670	>4900	12.1 ± 3.8	109 ± 2
6q		0.97 ± 0.08	3480 ± 579	>10000	3590	>10300	5.9 ± 0.4	104 ± 1

Table 2. Binding Affinities and Agonist Activities of 6a Analogues (19)



(19)

		IC_{50} (nM)			selectivity ratio		δ	
compd	R'	δ	μ	κ	μ/δ	κ/δ	EC_{50}(nM)	E_{max} (%)
6a	H	0.87 ± 0.23	3800 ± 172	7470 ± 606	4370	8590	7.2 ± 0.9	110 ± 3
19a	Me	27.0 ± 2.2	>10000	>8900	>370	>330	161 ± 12	85 ± 6
19b		3.00 ± 0.69	3330 ± 275	2290 ± 369	1110	763	28.3 ± 2.1	98 ± 3
19c		2.09 ± 0.11	1030 ± 100	982 ± 90	493	470	14.1 ± 1.8	106 ± 3
19e		9.35 ± 1.93	3390 ± 748	6140 ± 1060	362	657	42.3 ± 8.2	108 ± 4
19d		6.53 ± 1.25	4130 ± 884	4270 ± 1120	632	654	46 ± 3.9	111 ± 2
19f		35.5 ± 5.9	597 ± 164	1330 ± 135	16.8	37.4	n/a	n/a
19g		736 ± 145	>10000	3160 ± 602	>13.6	4.3	n/a	n/a

N-allyl, *N*-3,3-dimethylallyl, *N*-cyclopropylmethyl, *N*-butyl, *N*-cyclohexyl, and *N*-phenyl substituents were introduced (Table 2). None of these compounds bind to δ opioid receptors with as high affinity as the "parent" compound 6a: compounds 19b and 19c with allyl substituents, which are known to be tolerated in piperazine series such as SNC-80, exhibited slightly decreased affinities relative to 6a, while 19a and 19f showed more than 30-fold decreased δ receptor affinities. The *N*-phenyl derivative 19g almost completely lost its ability to bind to the δ receptors, presumably because of the decreased basicity of the nitrogen (calculated pK_a values are 5.32 for compound 19g and 9.68 for compound 6a by ACD pK_a from Advanced Chemistry Development Inc., Toronto, Canada), which is an essential pharmacophore point to have an electrostatic interaction at an anionic receptor site. The butyl and cyclopropylmethyl derivatives (19d, 19e) showed similar binding affinity and identical agonist activity in the δ receptor assay probably due to their similarity in size. In general, the *N*-alkyl compounds are also comparably weak ligands for μ and κ opioid receptors with respect to the parent compound 6a, while 19f exhibited somewhat increased μ receptor affinity.

In Vitro Metabolism. Selected compounds were examined in rat liver microsomes (Table 3). While SNC-80 is unstable in rat liver microsomes, most of the compound being degraded in 1 h at both concentrations, most olefinic analogues 6 were found to be significantly more stable. Major metabolites were *N*-deethylated analogues (M − 28), while minor metabolites included hydroxylated derivatives (M + 16).

Table 3. Microsomal Incubation Analysis[a]

	% parent remaining at	
compd	10 μM	100 μM
SNC-80	1 ± 1 (*n* = 5)	24 ± 6 (*n* = 5)
6a	77 ± 7 (*n* = 7)	95 ± 6 (*n* = 7)
6e	55 ± 14 (*n* = 3)	94 ± 6 (*n* = 3)
6f	1 (*n* = 2)	58 ± 3 (*n* = 2)
6h	75 ± 2 (*n* = 3)	95 ± 3 (*n* = 3)
6l	83 ± 17 (*n* = 2)	91 ± 9 (*n* = 3)
6k	80 ± 1 (*n* = 2)	100 (*n* = 2)
6q	55 (*n* = 2)	90 ± 1 (*n* = 2)

[a] After 1-h incubations in rat liver microsomes.

In agreement with the metabolic profiling data obtained for SNC-80 in rat liver microsomes,[14] the methoxy analogue 6f was less stable than other compounds, being extensively metabolized into an *O*-demethylated derivative. The olefin 6a is markedly more stable, being virtually undegraded at 100 μM, in sharp contrast to SNC-80. As could be predicted by the improved metabolic stability of 6a, together with the low molecular weight and conformity with Lipinski's rules,[25] 6a has exceptional oral bioavailability, approaching 100%.

Proposed Common Binding Mode of 2 (SNC-80) and 6a. The essential elements of the δ agonist pharmacophore (described in more detail in the previous paper in this series[14]) are the basic nitrogen, the 'right-

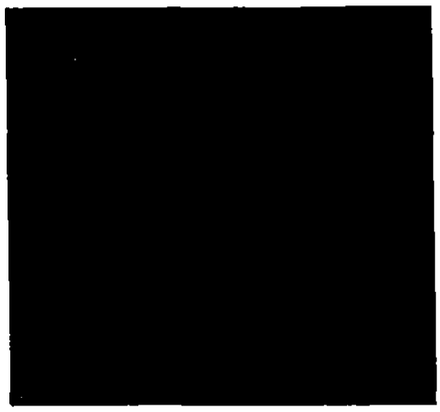


Figure 4. Superpositions of 64 conformers of SNC-80, generated from conformational search. Carbon atoms are in light green, nitrogen atoms in blue, and oxygen atoms in red.

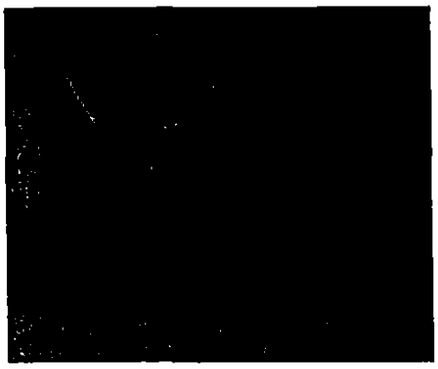


Figure 5. Superpositions of 4 conformers of 6a, generated from conformational search with the same color coding as in Figure 4.

hand' (oxygenated in the case of SNC-80, unsubstituted in the case of 6a) phenyl ring, and the diethylamide carbonyl group. To compare the pharmacophore groups in the two molecules, SNC-80 and 6a, an extensive conformational search was performed and the correspondence of these key groups (the carbonyl carbon atom was taken to represent the amide pharmacophore to reduce the complexity of the conformational search) in low energy conformers was examined (Figures 4 and 5). This comparison of the two compounds showed that compound 6a only partially covers the conformational space available to SNC 80, while key pharmacophores are closely superimposed in 6a and a population of SNC-80 conformers. The first interpretation of this conformational comparison is that compound 6a can efficiently bind to and activate the δ opioid receptor but has improved selectivity compared to SNC-80, since it does not intrude into conformational space which might be attributed to recognition of the other opioid receptor subtypes.

Figure 6 shows a superposition of the crystallographic structures of SNC-80 and compound 6a. The three-dimensional coordinates of SNC-80 were built according to its absolute stereochemistry.[13] The basic nitrogen, the two centroid phenyl rings, and the carbon atom of the carbonyl group were used for the superposition (rms = 0.36). It is interesting to notice that, while the C atoms

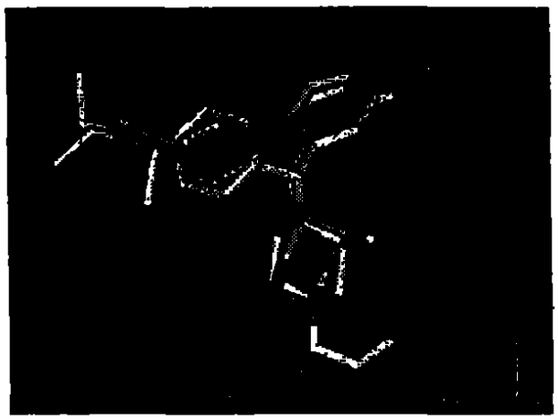


Figure 6. Superposition of the crystal structures between SNC-80 (carbon atoms in light green) and compound 6a (carbon atoms in gold).

of the piperidine ring in 6a and the piperazine ring of SNC-80 do not overlay well in the superposition, the basic N atoms are disposed very closely in space. The same phenomenon was also observed in the conformational search, suggesting that this part of the ring structure only serves as a spacer to connect the basic nitrogen and the two aromatic rings containing the other two pharmacophore groups. A recent publication[28] also experimentally proved this observation. The superposition of the amide carbonyl groups in the two molecules is excellent, despite the different orientations of the intervening phenyl rings. The 'right-hand' phenyl ring is well-overlaid in the two structures.

Conclusion

A novel class of exceptionally selective, potent δ opioid receptor ligands was identified as a result of replacing the piperazine N atom in the progenitor series of agonists with an olefinic C atom, resulting in 6a, the simplest structure in the series which exhibited an $IC_{50} = 0.87$ nM for δ opioid receptors and exceptional selectivity over μ receptors ($\mu/\delta = 4370$) and κ receptors ($\kappa/\delta = 8590$). This compound and its analogues presented here have the highest selectivity in the human opioid receptors assay of any comparator compounds we have tested: 14 out of the 17 compounds showed δ affinity less than 3 nM, while 5 of these compounds had subnanomolar affinity. The majority of these compounds displayed a ratio of >1000 with respect to μ or κ opioid receptors. Furthermore evaluation of a number of compounds in rat liver microsomes showed these compounds (including 6a) to be much more stable than the parent compound SNC-80. 6a was subsequently found to have excellent oral availability[27] ($F = 90-100\%$ in the rat).

These *N,N*-diethyl 4 (piperidin 4-ylidenemethyl)benzamides are the most selective δ opioid receptor agonists described so far. They do not contain any chiral centers and can easily be prepared by established synthetic approaches. These important chemical features coupled with their excellent pharmacological profile and oral bioavailability make these compounds ideal for further investigation and development.

Experimental Section

Synthesis. Melting points were taken in a capillary tube by using a Thomas-Hoover melting point apparatus and are uncorrected. For the HCl salts of many final compounds, melting points were not measured because they were not crystalline due to the fractional amounts of HCl present from combustion analyses. IR spectra were determined with a Perkin-Elmer Pragon 100 FT-IR spectrometer. NMR spectra were recorded on a Varian Unity Plus 400 MHz spectrometer; chemical shifts were recorded in parts per million downfield from Me_4Si. Elemental analyses were performed by Canadian Microanalytical Service Ltd., Delta, British Columbia. Flash column chromatography was performed with silica gel 60 (70–230 mesh). Dry THF was distilled from sodium benzophenone prior to use. Other anhydrous solvents over molecular sieves were obtained from Fluka.

4-Benzoyl-*N*-*tert*-butoxycarbonylpiperidine (10a). A mixture of **9a** (6.77 g, 30.0 mmol), di-*tert*-butyl dicarbonate (7.2 g, 33.0 mmol) and Na_2CO_3 (6.36 g, 60 mmol) was refluxed in H_2O–THF (50/20 mL) for 1 h. The reaction mixture was then cooled and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to give **10a** (8.54 g, 98%): mp 95–96 °C (Et_2O); ^1H NMR ($CDCl_3$) δ 1.47 (s, 9H), 1.70 (m, 2H), 1.83 (m, 2H), 2.91 (m, 2H), 3.42 (m, 1H), 4.18 (brs, 2H), 7.46 (m, 2H), 7.58 (m, 1H), 7.93 (m, 2H).

4-(4-Fluorobenzoyl)-*N*-*tert*-butoxycarbonylpiperidine (10b). Following the same method as used to prepare **10a** but starting with **9b** (2.44 g, 10 mmol) led to **10b** as a solid (2.27 g, 74%): mp 80–83 °C (CH_2Cl_2); IR (KBr) 1680, 1597 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9H), 1.69 (m, 2H), 1.79 (m, 2H), 2.87 (m, 2H), 3.34 (m, 1H), 4.13 (brs, 2H), 7.12 (m, 2H), 7.95 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 27.4, 28.4, 43.2, 43.4, 79.6, 115.8, 115.9, 130.8, 130.9, 132.2, 154.8, 164.4, 166.9, 200.4.

4-(4-Chlorobenzoyl)-*N*-*tert*-butoxycarbonylpiperidine (10c). Following the same method as used to prepare **10a** but starting with **9c** (2.60 g, 10 mmol) led to **10c** as a solid (2.75 g, 85%): mp 122–125 °C (CH_2Cl_2); IR (KBr) 1680, 1592 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47(s, 9H), 1.69 (m, 2H), 1.81 (m, 2H), 2.90 (m, 2H), 3.36 (m, 1H), 4.18 (brs, 2H), 7.44 (m, 2H), 7.88 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 28.3, 28.4, 43.2, 43.4, 79.8, 129.0, 129.8, 134.1, 139.4, 154.6, 200.7.

4-(α-Hydroxy-α-(4-*N*-*tert*-butoxycarbonylpiperidinyl)-benzyl)-*N*,*N*-diethylbenzamide (7a). To a solution of 4-iodo-*N*,*N*-diethylbenzamide (6.67 g, 22.0 mmol) in dry THF (70 mL) was added *tert*-butyllithium (18.0 mL, 2.5 M, 45.0 mmol) at −78 °C. After 10 min, **10a** (4.34 g, 15.0 mmol) in THF (5 mL) was dropwise added. The reaction mixture was warmed to room temperature and then quenched with aqueous NH_4Cl solution and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Removal of solvents gave a crude product, which was purified by flash chromatography eluting with MeOH–CH_2Cl_2 (0:100 → 5:95) to provide **7a** (6.58 g, 94%): mp 100–103 °C (CH_2Cl_2); IR (KBr) 3426, 1687, 1618 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (brs, 3H), 1.20 (brs, 3H), 1.30 (m, 4H), 1.41 (s, 9H), 2.50 (t, J = 11.2 Hz, 1H), 2.66 (m, 2H), 2.86 (s, OH), 3.22 (brs, 2H), 3.50 (brs, 2H), 4.09 (brs, 2H), 7.18 (m, 1H), 7.26 (m, 4H), 7.45 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 12.8, 14.1, 26.2, 28.3, 39.1, 43.2, 44.3, 53.3, 79.2, 79.4, 125.75, 125.79, 126.2, 126.6, 128.1, 135.1, 145.3, 146.8, 154.6, 171.0.

4-(α-Hydroxy-α-(4-*N*-*tert*-butoxycarbonylpiperidinyl)-4-fluorobenzyl)-*N*,*N*-diethylbenzamide (7b). Method as described for **7a**, but starting with **10b** (1.54 g, 5.0 mmol) led to **7b** as a solid (1.14 g, 47%): mp 84–86 °C (CH_2Cl_2); IR (KBr) 3421, 1685, 1612 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (brs, 3H), 1.23 (brs, 3H), 1.32 (m, 4H), 1.44 (s, 9H), 2.48 (m, 1H), 2.68 (brs, 2H), 3.26 (brs, 2H), 3.54 (brs, 2H), 3.57 (s, 1H), 4.11 (brs, 2H), 6.96 (m, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.44 (m, 2H), 7.47 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.9, 14.0, 26.2, 28.2, 39.1, 43.2, 43.6, 44.3, 78.9, 79.1, 114.5, 114.7, 125.7, 126.1, 127.5, 127.6, 135.0, 141.2, 148.9, 154.5, 160.0, 162.5, 170.9.

4-(α-Hydroxy-α-(4-*N*-*tert*-butoxycarbonylpiperidinyl)-4-chlorobenzyl)-*N*,*N*-diethylbenzamide (7c). Method as described for **7a**, but starting with **10c** (1.62 g, 5.0 mmol) led to **7c** as a solid (1.58 g, 63%): mp 100–105 °C (CH_2Cl_2); IR (KBr) 3411, 1685, 1617 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (brs, 3H), 1.20 (brs, 3H), 1.33 (m, 4H), 1.41 (s, 9H), 2.44 (m, 1H), 2.83 (brs, 2H), 3.22 (brs, 2H), 3.49 (brs, 2H), 3.99 (s, 1H), 4.05 (m, 2H), 7.20 (m, 4H), 7.39 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.5, 13.9, 25.9, 28.1, 39.0, 43.0, 44.1, 78.7, 79.0, 125.6, 126.0, 127.2, 127.6, 131.9, 134.8, 144.1, 146.6, 154.3, 170.7.

***N*,*N*-Diethyl-4-(phenylpiperidin-4-ylidenemethyl)benzamide (8a).** To a solution of **7a** (932 mg, 2.0 mmol) in dry dichloromethane (10 mL) was added trifluoroacetic acid (10.0 mL) at room temperature. The reaction mixture was stirred overnight and then concentrated. The residue was then dissolved in CH_2Cl_2 (100 mL), washed with 1 N NaOH, brine, and dried over $MgSO_4$. Removal of solvents gave a crude product, which was purified by flash chromatography eluting with MeOH–CH_2Cl_2 (20:80) to provide **8a** (632 mg, 91%): ^1H NMR ($CDCl_3$) δ 1.08 (brs, 3H), 1.17 (brs, 3H), 2.29 (m, 4H), 2.86 (m, 4H), 2.94 (brs, 1H), 3.24 (brs, 2H), 3.47 (brs, 2H), 7.09 (m, 4H), 7.15 (m, 1H), 7.24 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 12.8, 14.1, 32.7, 32.8, 39.1, 43.2, 47.9, 126.0, 126.4, 127.9, 129.6, 134.9, 135.4, 135.9, 141.7, 143.2, 171.1. HCl salt: mp 110–120 °C (CH_2Cl_2); IR (KBr) 3440, 1617. Anal. ($C_{23}H_{30}N_2O$·2.1HCl) C, H, N.

***N*,*N*-Diethyl-4-(4-fluorophenylpiperidin-4-ylidenemethyl)benzamide (8b).** Method as described for **8a**, but starting with **7b** led to **8b** in quantitative yield: ^1H NMR ($CDCl_3$) δ 1.12 (brm, 3 H, CH_3CH_2-), 1.24 (brm, 3 H, CH_3CH_2-), 2.32 (m, 4 H, piperidine CH_2), 2.54 (brm, 1 H, NH), 2.91 (m, 4 H, piperidine CH_2-), 3.27 (brm, 2 H, CH_2N-), 3.52 (brm, 2 H, CH_2N-), 7.00 (m, 2 H, ArH), 7.09 (m, 2 H, ArH), 7.11 (d, J = 8.0 Hz, 2H, ArH), 7.29 (d, J = 8.0 Hz, 2 H, ArH). Anal. ($C_{23}H_{27}FN_2O$·1.5HCl) C, H, N.

***N*,*N*-Diethyl-4-(4-chlorophenylpiperidin-4-ylidenemethyl)benzamide (8c).** Method as described for **8a**, but starting with **7c** led to **8c** in quantitative yield: ^1H NMR ($CDCl_3$) δ 1.13 (brm, 3 H, CH_3CH_2-), 1.22 (brm, 3 H, CH_3CH_2-), 2.02 (brm, 1 H, NH), 2.30 (m, 4 H, piperidine CH_2), 2.90 (m, 4 H, piperidine CH_2-), 3.28 (brm, 2 H, CH_2N-), 3.53 (brm, 2 H, CH_2N-), 7.04 (d, J = 8.0 Hz, 2 H, ArH), 7.11 (d, J = 8.0 Hz, 2 H, ArH), 7.25 (d, J = 8.0 Hz, 2 H, ArH), 7.30 (d, J = 8.0 Hz, 2 H, ArH). HCl salt: mp 115–120 °C (CH_2Cl_2); IR (KBr) 3337, 1618 cm^{-1}. Anal. ($C_{23}H_{27}ClN_2O$·1.6HCl) C, H, N.

***N*-*tert*-Butoxycarbonyl-*N*-methyl-*N*-methoxyisonipecotamide (12).** Method as described for **10a**, but starting with ethyl isonipecotate (**11**; 4.71 g, 30.0 mmol) led to *N*-*tert*-butoxylcarbonyl ethyl isonipecotate (7.67 g): ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 3H), 1.45 (s, 9H), 1.62 (m, 2H), 1.87 (m, 2H), 2.43 (m, 1H), 2.84 (m, 2H), 4.02 (m, 2H), 4.13 (q, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0, 27.8, 28.2, 40.9, 42.9, 60.2, 79.2, 154.4, 174.2.

To a mixture of the above product and NHMe(OMe) HCl (4.39 g, 45.0 mmol) in dry THF was added *i*-PrMgCl (2.0 M in THF, 45 mL, 90 mmol) at −20 °C. The resulting solution was stirred for 1 h at −5 °C, then quenched with aqueous NH_4Cl solution and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Removal of solvents gave **12** (8.0 g, 98%): ^1H NMR ($CDCl_3$) δ 1.30 (s, 9H), 1.54 (m, 4H), 2.65 (m, 3H), 3.02 (s, 3H), 3.58 (s, 3H), 3.99 (brs, 2H); ^{13}C NMR ($CDCl_3$) δ 27.7, 28.1, 32.0, 37.8, 43.1, 61.3, 79.1, 154.4, 176.0.

4-(4′-*N*,*N*-Diethylaminocarbonylbenzoyl)-*N*-*tert*-butoxycarbonylpiperidine (10d). To a solution of 4-iodo-*N*,*N*-diethylbenzamide (9.09 g, 30.0 mmol) and TMEDA (8.96 g, 60.0 mmol) in dry THF (60 mL) was added *tert*-butyllithium (35.0 mL, 1.7 M, 60.0 mmol) at −78 °C. After 30 min, **12** (6.0 g, 29.4 mmol) in THF (10 mL) was dropwise added. The reaction mixture was warmed to room temperature, then quenched with aqueous NH_4Cl solution, acidified with hydrochloric acid (concentrated, 20 mL) at 0 °C, and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with

brine and dried over $MgSO_4$. Removal of solvents gave a crude product, which was purified by flash chromatography eluting with MeOH–CH_2Cl_2 (2:98) to provide 10d (3.15 g, 28%): ^1H NMR ($CDCl_3$) δ 1.08 (brs, 3H), 1.23 (brs, 3H), 1.43 (s, 9H), 1.61 (m, 2H), 1.80 (m, 2H), 2.89 (m, 2H), 3.20 (brs, 2H), 3.40 (m, 1H), 3.53 (brs, 2H), 4.11 (brs, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.94 (d, J = 8.0 Hz, 2H).

4-(α-Hydroxy-α-(4-*N*-*tert*-butoxycarbonylpiperidinyl)-α-(1-naphthyl)methyl)-*N*,*N*-diethylbenzamide (7d). To a solution of 1-bromonaphthalene (0.52 g, 2.5 mmol) in dry THF (10 mL) was added *n*-butyllithium (1.1 mL, 2.5 M, 2.75 mmol) at −78 °C. After 30 min, 10d (776 mg, 2.0 mmol) in THF (2 mL) was dropwise added. The reaction mixture was warmed to room temperature, quenched with aqueous NH_4Cl solution, and extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Removal of solvents gave a crude product, which was purified by flash chromatography eluting with MeOH–CH_2Cl_2 (0.5:99.5 → 5:95) to provide 7d (760 mg, 74%): mp 121–124 °C (CH_2Cl_2); IR (KBr) 3402, 1685, 1626 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (brs, 3H), 1.16 (brs, 3H), 1.18–1.35 (m, 3H), 1.95 (m, 1H), 2.60 (m, 2H), 2.75 (brs, 2H), 3.15 (brs, 2H), 3.42 (brs, 2H), 4.10 (brs, 2H), 7.10–7.50 (m, 7H), 7.75 (m, 3H), 8.27 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 12.8, 14.1, 27.1, 27.2, 28.4, 38.2, 43.3, 45.4, 79.3, 80.4, 124.1, 124.9, 125.2, 125.3, 126.0, 127.3, 128.8, 129.2, 131.4, 135.0, 135.2, 139.4, 146.5, 154.8, 171.0. Anal. ($C_{36}H_{42}N_2O_4$·0.5H_2O) C, H, N.

***N*,*N*-Diethyl-4-[(*N*-*tert*-butoxycarbonylpiperidin-4-yl)-3-fluorophenylhydroxymethyl]benzamide (7e).** Method as for 7d using 3-bromofluorobenzene provided 7e (282 mg, 27%): ^1H NMR ($CDCl_3$) δ 1.03 (br, 3H, CH_3CH$_2$N-), 1.15 (br, 3H, CH_3CH$_2$N-), 1.19–1.29 (m, 4H, piperidine CH_2), 1.35 (s, 9H, CH_3C), 2.39 (m, 1H, piperidine CH), 2.59 (br, 2H, piperidine CH), 3.17 (br, 2H, CH$_3$CH_2N-), 3.28 (s, 1H, OH), 3.45 (br, 2H, CH$_3$CH_2N-), 4.02 (br, 2H, piperidine CH), 6.80 (m, 1H, ArH), 7.15 (m, 3H, ArH), 7.18 (d, J = 8.0 Hz, 2H, ArH), 7.39 (d, J = 8.0 Hz, 2H, ArH).

***N*,*N*-Diethyl-4-[(*N*-*tert*-butoxycarbonylpiperidin-4-yl)-3-methoxyphenylhydroxymethyl]benzamide (7f).** Method as for 7d using 3-bromoanisole provided 7f (228 mg, 23%): mp 95–103 °C (CH_2Cl_2); IR (NaCl) 3422, 1684, 1614 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (br, 3H, CH_3CH$_2$N-), 1.19 (br, 3H, CH_3CH$_2$N-), 1.31 (m, 4H, piperidine CH$_2$), 1.41 (s, 9H, CH_3C), 2.48 (m, 1H, piperidine CH), 2.64 (br, 2H, piperidine CH), 3.22 (br, 2H, CH$_3$CH_2N-), 3.49 (br, 2H, CH$_3$CH_2N-), 3.65 (s, 1H, OH), 3.72 (s, 3H, OCH$_3$), 4.06 (br, 2H, piperidine CH), 6.69 (m, 1H, ArH), 7.01 (d, J = 7.8 Hz, 1H, ArH), 7.08 (s, 1H, ArH), 7.17 (d, J = 8.0 Hz, 1H, ArH), 7.21 (d, J = 8.0 Hz, 2H, ArH), 7.48 (d, J = 8.0 Hz, 2H, ArH). Anal. ($C_{36}H_{44}N_2O_5$·0.5H_2O) C, H, N.

4-(α-Hydroxy-α-(4-*N*-*tert*-butoxycarbonylpiperidinyl)-2,6-dimethylbenzyl)-*N*,*N*-diethylbenzamide (7g). Method as described for 7d, but using 2-bromo-*m*-xylene led to 7g (752 mg, 78%): mp 92–96 °C (CH_2Cl_2); IR (KBr) 3451, 1680, 1631 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (brs, 3H), 1.21 (brs, 3H), 1.32 (m, 2H), 1.43 (s, 9H), 1.69 (m, 1H), 1.77 (m, 1H), 2.32 (s, 6H), 2.47 (s, 1H), 2.75 (m, 3H), 3.25 (brs, 2H), 3.51 (brs, 2H), 4.13 (brs, 2H), 6.91 (m, 2H), 7.00 (m, 1H), 7.26 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.6, 14.0, 25.0, 27.7, 28.2, 39.1, 42.9, 43.1, 44.4, 53.3, 79.1, 83.0, 125.8, 126.3, 127.2, 131.2, 135.3, 136.7, 142.9, 147.8, 154.5, 170.7. Anal. ($C_{30}H_{42}N_2O_4$·0.5H_2O) C, H, N.

***N*,*N*-Diethyl-4-(1-naphthylpiperidin-4-ylidenemethyl)-benzamide (6d).** Method as described for 6a, but starting with 7d (517 mg, 1.0 mmol) led to 6d (283 mg, 71%): mp 80–85 °C (CH_2Cl_2); IR (KBr) 1628 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (brs, 3H), 1.16 (brs, 3H), 2.00 (m, 2H), 2.53 (m, 2H), 2.64 (brs, NH), 2.77 (m, 2H), 2.97 (m, 2H), 3.20 (brs, 2H), 3.47 (brs, 2H), 7.26 (m, 5H), 7.43 (m, 3H), 7.74 (m, 2H), 8.0 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 12.8, 14.1, 32.6, 33.5, 39.1, 43.2, 47.9, 48.2, 125.5, 125.7, 125.8, 126.1, 127.1, 127.2, 129.1, 131.9, 132.5, 133.8, 135.1, 138.3, 139.8, 142.8, 171.1. Anal. ($C_{27}H_{32}N_2O$·0.4HCl) C, H, N.

***N*,*N*-Diethyl-4-(3-fluorophenylpiperidin-4-ylidenemethyl)benzamide (6e).** Method as described for 6a, but starting with 7e (242 mg, 0.5 mmol) led to 6e (159 mg, 87%): ^1H NMR ($CDCl_3$) δ 1.08 (br, 3H, CH_3CH$_2$N-), 1.19 (br, 3H, CH_3CH$_2$N-), 2.09 (s, 1H, NH), 2.25 (m, 4H, piperidine CH), 2.84 (br, 4H, piperidine CH), 3.23 (br, 2H, CH$_3$CH_2N-), 3.47 (br, 2H, CH$_3$CH_2N-), 6.74 (m, 1H, ArH), 6.86 (m, 2H, ArH), 7.06 (d, J = 8.0 Hz, 2H, ArH), 7.18 (m, 1H, ArH), 7.24 (d, J = 8.0 Hz, 2H, ArH). HCl salt: mp ≥ 70 °C dec; IR (NaCl) 1605 cm^{-1}. Anal. ($C_{24}H_{29}FN_2O$·2.2HCl) C, H, N.

***N*,*N*-Diethyl-4-(3-methoxyphenylpiperidin-4-ylidenemethyl)benzamide (6f).** Method as described for 6a, but starting with 7f (199 mg, 0.4 mmol) led to 6f[18] (148 mg, 98%). Anal. ($C_{24}H_{30}N_2O_2$·1.8HCl) C, H, N.

***N*,*N*-Diethyl-4-(2,6-dimethylphenylpiperidin-4-ylidenemethyl)benzamide (6g).** Method as described for 6a, but starting with 7g (485 mg, 1.0 mmol) led to 6g (301 mg, 80%): ^1H NMR ($CDCl_3$) δ 1.10 (brs, 3H), 1.21 (brs, 3H), 2.08 (m, 4H), 2.21 (s, 6H), 2.84 (m, 2H), 3.00 (m, 2H), 3.20 (brs, 1H), 3.25 (brs, 2H), 3.46 (brs, 2H), 6.94 (m, 1H), 7.00 (m, 2H), 7.04 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H). HCl salt: dec ≥ 115 °C (CH_2Cl_2); IR (KBr) 1590 cm^{-1}. Anal. ($C_{26}H_{34}N_2O$·2.2HCl) C, H, N.

4-(4-Methoxycarbonylbenzylidene)piperidine-1-carboxylic Acid *tert*-Butyl Ester (15). A mixture of 13 (11.2 g, 49 mmol) and trimethyl phosphite (25 mL) was refluxed under N_2 for 5 h. Excess trimethyl phosphite was removed by codistillation with toluene to give 14 in quantitative yield: ^1H NMR ($CDCl_3$) δ 3.20 (d, 2H, J = 22 Hz), 3.68 (d, 3H, 10.8 Hz), 3.78 (d, 3H, 11.2 Hz), 3.91 (s, 3H), 7.38 (m, 2H), 8.00 (d, 2H, J = 8 Hz).

To a solution of the above product (14) in dry THF (200 mL) was added dropwise lithium diisopropylamide (32.7 mL, 1.5 M in hexanes, 49 mmol) at −78 °C. The reaction mixture was then allowed to warm to room temperature prior to addition of *N*-*tert*-butoxycarbonyl-4-piperidone (9.78 g, 49 mmol in 100 mL dry THF). After 12 h, the reaction mixture was quenched with water (300 mL) and extracted with ethyl acetate (3 × 300 mL). The combined organic phases were dried over $MgSO_4$ and evaporated to give a crude product, which was purified by flash chromatography (0–33% ethyl acetate in hexanes) to provide 15 as a white solid (5.64 g, 35%): IR (NaCl) 1718, 1688, 1606 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 1H), 2.31 (t, J = 5.5 Hz, 2H), 2.42 (t, J = 5.5 Hz, 2H), 3.37 (t, J = 5.5 Hz, 2H), 3.48 (t, J = 5.5 Hz, 2H), 3.87 (s, 3H), 6.33 (s, 1H), 7.20 (d J = 8.7 Hz, 2H), 7.94 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 28.3, 29.2, 36.18, 51.9, 123.7, 127.8, 128.7, 129.4, 140.5, 142.1, 154.6, 166.6. Anal. ($C_{19}H_{25}NO_4$) C, H, N.

4-Bromo-4-[bromo(4-methoxycarbonylphenyl)methyl]-piperidine-1-carboxylic Acid *tert*-Butyl Ester (16). To a mixture of 15 (5.2 g, 16 mmol) and K_2CO_3 (1.0 g) in dry dichloromethane (200 mL) was added a solution of bromine (2.9 g, 18 mmol) in 30 mL CH_2Cl_2 at 0 °C. after 1.5 h at room temperature, the solution after filtration of K_2CO_3 was concentrated. The residue was then dissolved in ethyl acetate (200 mL), washed with water (200 mL), 0.5 M HCl (200 mL) and brine (200 mL), and dried over $MgSO_4$. Removal of solvents provided a crude product, which was recrystallized from methanol to give 16 as a white solid (6.07 g, 78%): IR (NaCl) 1725, 1669 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (s, 9H), 1.75 (m, 2H), 1.90 (m, 2H), 2.1 (m, 4H), 3.08 (br, 4H), 3.90 (s, 3H), 4.08 (br, 4H), 5.14 (s, 1H), 7.57 (d, J = 8.4 Hz, 2H) 7.98 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 28.3, 36.6, 38.3, 40.3, 52.1, 63.2, 72.9, 129.0, 130.3, 130.4, 141.9, 154.4, 166.3. Anal. ($C_{19}H_{25}Br_2NO_4$) C, H, N.

4-[Bromo(4-carboxyphenyl)methylene]piperidine-1-carboxylic Acid *tert*-Butyl Ester (17). A solution of 16 (5.4 g 11 mmol) in methanol (300 mL) and 2.0 M NaOH (100 mL) was heated at 40 °C for 3 h. The solid was collected by filtration and dried overnight under vacuum. The dry salt was dissolved in 40% acetonitrile/water and was adjusted to pH 2 using concentrated HCl. The desired product (17; 3.8 g, 87%) was isolated as a white powder by filtration: ^1H NMR ($CDCl_3$) δ 1.45 (s, 9H), 2.22 (dd, J = 5.5 Hz, 6.1 Hz, 2H), 2.64 (dd, J =

5.5 Hz, 6.1 Hz, 2H), 3.34 (dd, J = 5.5 Hz, 6.1 Hz, 2H), 3.54 (dd, J = 5.5 Hz, 6.1 Hz, 2H), 7.35 (d, J = 6.7 Hz, 2H), 8.08 (d, J = 6.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 28.3, 31.5, 34.2, 44.0, 115.3, 128.7, 129.4, 130.2, 137.7, 145.2, 154.8, 170.3. Anal. ($C_{15}H_{23}BrNO_4$) C, H, N.

4-[Bromo(4-diethylcarbamoylphenyl)methylene]piperidine-1-carboxylic Acid *tert*-Butyl Ester (8). To a solution of 17 (1.0 g, 2.5 mmol) in dry dichloromethane (10 mL) at −20 °C was added isobutyl chloroformate (450 mg, 3.3 mmol). After 20 min at −20 °C diethylamine (4 mL) was added and the reaction was allowed to warm to room temperature. After 1.5 h the solvents were evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was washed with brine and dried over $MgSO_4$. Removal of solvents provided a crude product, which was purified by flash chromatography (0−80% ethyl acetate in heptanes) to give 8 as white needles (800 mg, 73%): ^{1}H NMR ($CDCl_3$) δ 1.13 (br, 3H), 1.22 (br, 3H), 1.44 (s, 9H), 2.22 (t, J = 5.5 Hz, 2H), 2.62 (t, J = 5.5 Hz, 2H), 3.31 (t, J = 5.5 Hz, 2H), 3.52 (t, J = 5.5 Hz, 2H), 7.27 (d, J = 7.9 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.71, 14.13, 28.3, 31.5, 34.2, 39.1, 43.2, 79.7, 115.9, 128.3, 129.3, 138.8, 137.1, 140.6, 154.8, 170.5. Anal. ($C_{20}H_{31}BrN_2O_3$) C, H, N.

***N,N*-Diethyl-4-[piperidin-4-ylidene(3-trifluoromethylphenyl)methyl]benzamide (9h).** A mixture of 8 (500 mg, 1.1 mmol), 3-trifluoromethylphenylboronic acid (500 mg, 2.6 mmol), 2 M Na_2CO_3 (3 mL), and tetrakis(triphenylphosphine)-palladium(0) (20 mg) in toluene (degassed, 5 mL) and ethanol (degassed, 5 mL) was refluxed at 85 °C for 5 h under N_2. The reaction mixture was then cooled to room temperature and extracted with ethyl acetate (2 × 100 mL). The combined organic phases were dried over $MgSO_4$ and evaporated to give a crude product (18a).

The above product (18a) was treated with 4.0 M HCl in dioxane at room temperature for 2 h. After evaporation, the residue was dissolved in 1 M HCl (100 mL) and impurities were extracted with diethyl ether (3 × 100 mL). The aqueous phase was basified with NH_4OH and extracted with dichloromethane (3 × 100 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and evaporated to give 9h (291 mg, 64%): ^{1}H NMR ($CDCl_3$) δ 1.13 (brm, 3 H, CH_3-CH_2-), 1.22 (brm, 3 H, CH_3CH_2-), 1.96 (s, 1 H, NH), 2.28 (m, 2 H, piperidine CH-), 2.33 (m, 2 H, piperidine CH-), 2.92 (m, 4 H, piperidine CH-), 3.29 (brm, 2 H, CH_3CH_2N-), 3.54 (brm, 2 H, CH_3CH_2N-), 7.13 (d, J = 8.0 Hz, 2 H, ArH), 7.28−7.48 (m, 6 H, ArH). HCl salt: mp > 85 °C dec; IR (NaCl) 3409, 1620 cm^{-1}. Anal. ($C_{24}H_{27}F_3N_2O$·1.3HCl) C, H, N.

***N,N*-Diethyl-4-(3,4-dichlorophenylpiperidin-4-ylidenemethyl)benzamide (9i).** Method as for 9h using 8 (500 mg, 1.3 mmol) and 3,4-dichlorophenylboronic acid (500 mg, 2.6 mmol) provided 9i (437 mg, 79%): ^{1}H NMR ($CDCl_3$) δ 1.12 (br, 3H), 1.20 (br, 3H), 2.28 (t, J = 5.6 Hz, 4H), 2.89 (m, 4H), 3.27 (br, 2H), 3.52 (br, 2H), 6.8−7.4 (m, 7H). Anal. ($C_{23}H_{24}Cl_2N_2O$·1.5HCl) C, H, N.

***N,N*-Diethyl-4-(3-acetylphenylpiperidin-4-ylidenemethyl)benzamide (9j).** Method as for 9h using 8 (500 mg, 1.1 mmol) and 3-acetylphenylboronic acid (500 mg, 3.0 mmol) provided 9j (401 mg, 93%): ^{1}H NMR ($CDCl_3$) δ 1.11 (br, 3H), 1.20 (br, 3H), 2.08 (brs, 1H), 2.28 (m, 2H), 2.34 (m, 2H), 2.55 (s, 3H), 2.92 (m, 4H), 3.26 (br, 2H), 3.51 (br, 2H), 7.15 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 7.2 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.74 (s, 1H), 7.81 (d, J = 7.2 Hz, 1H). Anal. ($C_{25}H_{30}N_2O_2$·1.8HCl) C, H, N.

***N,N*-Diethyl-4-(3-nitrophenylpiperidin-4-ylidenemethyl)benzamide (9k).** Method as for 9h but using 3-nitrophenylboronic acid provided 9k in quantitative yield: ^{1}H NMR ($CDCl_3$) δ 1.11 (br, 3H), 1.21 (br, 3H), 2.27−2.34 (m, 4H), 2.92 (t, J = 6.0 Hz, 4H), 3.26 (br, 2H), 3.52 (br, 2H), 7.10 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.40−7.50 (m, 2H), 7.95−8.08 (m, 2H). Anal. ($C_{23}H_{27}N_3O_3$·1.4HCl) C, H, N.

***N,N*-Diethyl-4-(2-fluorophenylpiperidin-4-ylidenemethyl)benzamide (9l).** Method as for 9h but using 2-fluorophenylboronic acid provided 9l in quantitative yield: ^{1}H NMR ($CDCl_3$) δ 1.11 (br, 3H), 1.15 (br, 3H), 2.10 (t, J = 5.2 Hz, 2H), 2.27 (t, J = 5.2 Hz, 2H), 2.83(m, 4H), 3.20 (br, 2H), 3.45 (br, 2H), 6.94−7.03 (m, 3H), 7.10−7.23 (m, 5H). Anal. ($C_{23}H_{27}FN_2O$·1.5HCl) C, H, N.

***N,N*-Diethyl-4-(2-thiophenylpiperidin-4-ylidenemethyl)benzamide (9m).** Method as for 9h but using 2-thiophenylboronic acid provided 9m in quantitative yield: ^{1}H NMR ($CDCl_3$) δ 1.12 (br, 3H), 1.20 (br, 3H), 2.24 (t, J = 5.2 Hz, 2H), 2.50 (t, J = 5.2 Hz, 2H), 2.85 (t, J = 5.8 Hz, 2H), 2.92 (t, J = 5.8 Hz, 2H), 3.27 (br, 2H), 3.51 (br, 2H), 6.75 (d, J = 3.6 Hz, 1H), 6.93 (t, J = 3.6 Hz, 1H), 7.16 (d, J = 7.2 Hz, 2H), 7.21 (d, J = 3.6 Hz, 1H), 7.30 (d, J = 7.2 Hz, 2H). Anal. ($C_{21}H_{26}N_2OS$·1.5HCl) C, H, N.

***N,N*-Diethyl-4-(4-methylthiophenylpiperidin-4-ylidenemethyl)benzamide (9n).** Method as for 9h but using 4-methylthiophenylboronic acid provided 9n in quantitative yield: ^{1}H NMR ($CDCl_3$) δ 1.11 (br, 3H), 1.20 (br, 3H), 2.32−2.75 (m, 4H), 2.45 (s, 3H), 2.90−2.87 (m, 4H), 3.26 (br, 2H), 3.51 (br, 2H), 7.01 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 6.8 Hz, 2H). Anal. ($C_{24}H_{30}N_2OS$·2.5HCl) C, H, N.

***N,N*-Diethyl-4-(3-aminophenylpiperidin-4-ylidenemethyl)benzamide (9o).** Method as for 9h but using 3-aminophenylboronic acid provided 9o in quantitative yield: ^{1}H NMR ($CDCl_3$) δ 1.11 (br, 3H), 1.20 (br, 3H), 2.27−2.33 (m, 4H), 2.86−2.90 (m, 4H), 3.27 (br, 2H), 3.51 (br, 2H), 3.57 (br, 2H), 3.68 (s, 1H), 6.39 (s, 1H), 6.52 (dd, J = 1.8 Hz, J = 7.8 Hz, 2H), 7.06 (t, J = 8.0 Hz, 1H), 7.12 (d, J = 6.4 Hz, 2H), 7.26 (d, J = 6.4 Hz, 2H). Anal. ($C_{23}H_{29}N_3O$·1.2HCl) C, H, N.

***N,N*-Diethyl-4-(4-methoxyphenylpiperidin-4-ylidenemethyl)benzamide (9p).** Method as for 9h but using 4-methoxyphenylboronic acid provided 9p in quantitative yield: ^{1}H NMR ($CDCl_3$) δ 1.12 (br, 3H), 1.19 (br, 3H), 2.29 (m, 4H), 2.87 (m, 4H), 3.27 (br, 2H), 3.51 (br, 2H), 3.77 (s, 3H), 6.80 (m, 2H), 7.00 (m, 2H), 7.10 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz). Anal. ($C_{24}H_{30}N_2O_2$·1.95HCl) C, H, N.

***N,N*-Diethyl-4-(2-methoxyphenylpiperidin-4-ylidenemethyl)benzamide (9q).** Method as for 9h but using 2-methoxyphenylboronic acid provided 9q in quantitative yield: ^{1}H NMR ($CDCl_3$) δ 1.09 (br, 3H), 1.18 (br, 3H), 2.10 (q, J = 4.8 Hz, 2H), 2.31 (q, J = 4.8 Hz, 2H), 2.8−2.9 (m, 4H), 3.25 (br, 2H), 3.50 (br, 2H), 3.68 (s, 3H), 6.83−6.90 (m, 2H), 7.0 (d, 1H), 7.15−7.25 (m, 5H). Anal. ($C_{24}H_{30}N_2O_2$·1.5HCl) C, H, N.

***N,N*-Diethyl-4-[(1-methylpiperidin-4-ylidene)phenylmethyl]benzamide (10a).** *N,N*-Diethyl-4-[(piperidin-4-ylidene)phenylmethyl]benzamide (6a: 0.35 g, 1.0 mmol) was dissolved in acetonitrile (5 mL). Potassium carbonate (0.14 g, 1.0 mmol) and methyl iodide (63 μL, 1.0 mmol) were added with stirring at 25 °C. After 30 min, the reaction mixture was evaporated and put onto silica gel for purification by chromatography using 0 to 10% MeOH (10% NH_4OH) in CH_2Cl_2 to give 48 mg of the final product (28% of converted starting material), which was converted to the hydrochloride salt by treatment with HCl in ether: ^{1}H NMR ($CDCl_3$) δ 1.1 (m, 6H, amide-Me), 2.40 (s, 3H, MeN), 2.40, 2.60 (2m, 8H, piperazine-H), 3.40 (m, 4H, amide-CH_2) 7.08−7.34 (m, 9H, Ar−H). HCl salt: mp ≥ 110 °C dec; IR (KBr) 1695 cm^{-1}. Anal. ($C_{24}H_{30}N_2O$·3.2HCl) C, H, N.

***N,N*-Diethyl-4-(phenyl-*N*-allylpiperidin-4-ylidenemethyl)benzamide (10b).** Method as described for compound 10a, using allyl bromide as the alkylating reagent provided 10b (88%): ^{1}H NMR ($CDCl_3$) δ 1.12 (brs, 3H), 1.21 (brs, 3H), 2.43 (m, 4H), 2.55 (m, 4H), 3.08 (d, J = 6.8 Hz, 2H), 3.25 (brs, 2H), 3.53 (brs, 2H), 5.18 (m, 2H), 5.86 (m, 1H), 7.12 (m, 4H), 7.20 (m, 1H), 7.27 (m, 4H). HCl salt: mp 85−95 °C (CH_2Cl_2); IR (KBr) 1624 cm^{-1}. Anal. ($C_{26}H_{32}N_2O$·1.8HCl) C, H, N.

***N,N*-Diethyl-4-[*N*-(3-methyl-2-butenyl)phenylpiperidin-4-ylidenemethyl]benzamide (10c).** Method as described for compound 10a, using 1-bromo-3-methyl-2-butene as the alkylating reagent provided 10c (71%): ^{1}H NMR ($CDCl_3$) δ 1.10−1.30 (br, 6 H, OCNCH$_2$CH_3), 1.64 (s, 3 H, =CCH_3), 1.73 (s, 3 H, =CCH_3), 2.40 (m, 4 H, NCH_2CH$_2$), 2.52 (m, 4 H, =CCH_2), 3.0 (d, J = 7.6 Hz, 2 H, NCH_2CH=C), 3.20−3.60 (br, 4 H,

H_2CH_3), 5.28 (m, 1 H, NCH_2CH=C), 7.16–7.45(m, 9 H, ...l salt: IR (NaCl) 1623 cm^{-1}. Anal. ($C_{28}H_{38}N_2O \cdot 1.8HCl$) ...l.

Diethyl-4-(*N*-butylphenylpiperidin-4-ylidenemeth-...zamide (19d). Method as described for compound 19a. ...l-iodobutane as the alkylating reagent provided 19d (^1H NMR ($CDCl_3$) δ 0.92 (t, J = 7.2 Hz, 3 H, CH_2CH_2), ...28 (br, 6 H, $OCNCH_2CH_2$), 1.32 (m, 2 H, $CH_2CH_2CH_3$), 1.53 ..., $CH_2CH_2CH_3$), 2.42 (m, 6 H, NCH_2), 2.55 (m, 4 H, ... 3.20–3.60 (br, 4 H, $OCNCH_2CH_3$), 7.10–7.31 (m, 9 H, ...l salt: IR (NaCl) 1622 cm^{-1}. Anal. ($C_{27}H_{36}N_2O \cdot 1.8HCl$) ...l.

...Diethyl-4-(1-cyclopropylmethylphenylpiperidin-...nemethyl)benzamide (19e). Method as described for ...nd 19a, using compound 6 and cyclopropylmethyl ...le provided 19e (86%): ^1H NMR ($CDCl_3$) δ 0.20 (m, 2H), ..., 2H), 1.04 (m, 1H), 1.14 (brs, 3H), 1.24 (brs, 3H), 2.48 ... 6.4 Hz, 2H), 2.58 (brs, 4H), 2.80 (brs, 4H), 3.29 (brs, ...53 (brs, 2H), 7.14 (m, 4H), 7.22 (m, 1H), 7.27 (m, 4H); ...R ($CDCl_3$) δ 4.18, 7.3, 12.8, 14.1, 30.3, 39.2, 43.2, 54.3, ...126.2, 128.6, 128.0, 129.5, 129.8, 134.1, 135.3, 136.3, ...142.8, 171.0. HCl salt: dec ≥ 100 °C (CH_2Cl_2): IR (KBr) ...cm^{-1}. Anal. ($C_{27}H_{36}N_2O \cdot 2.3HCl$) C, H, N.

...1-Cyclohexylpiperidin-4-ylidene)phenylmethyl]-...diethylbenzamide (19f). A mixture of 6a (100 mg, 0.29 ..., cyclohexanone (39 uL, 0.35 mmol) and Ti(OPr-i)$_4$ (0.17 ...58 mmol) was ultrasonicated for 1 h and then stirred ...m temperature overnight under a nitrogen atmosphere. ...ixture was diluted with ethanol (5 mL) followed by ...on of $NaBH_4$ (33 mg, 0.87 mmol). The resulting mixture ...irred for 12 h at room temperature. 2 N $NH_3 \cdot H_2O$ was ...to quench the reaction and the mixture filtered through ... The filtrate was extracted with ethyl acetate several ... and the combined organic phases were washed with ... and brine and dried over Na_2SO_4. Concentration in ... and MPLC purification (0:100 to 100:0 EtOAc:heptane ...g on silica gel 60) gave the title compound 11f (24 mg, ...^1H NMR ($CDCl_3$) δ 1.00–1.25 (m, 19H), 1.60 (m, 1H), ...1H, m), 1.80 (m, 1H), 2.30 (m, 3H), 2.60 (m, 2H), 3.20 ...H), 3.50 (bs, 2H), 7.00–7.30 (m, 9H); ^{13}C NMR ($CDCl_3$) δ ...14.1, 25.9, 28.7, 32.0, 39.1, 43.2, 50.7, 50.8, 63.6, 126.0, ..., 127.9, 128.7, 128.8, 134.7, 134.9, 136.9, 142.0, 143.4, ...: mp (HCl salt) 105–109 °C. Anal. ($C_{28}H_{38}N_2O \cdot 2.0HCl$) ...N.

...(1-Phenylpiperidin-4-ylidene)phenylmethyl]-*N,N*-...ylbenzamide (19g). A mixture of 6a (44 mg, 0.13 mmol), ...*i* bromide (20 uL, 0.19 mmol), $Pd(dba)_2$ (1 mg, 0.0017 ...), BINAP (2.5 mg, 0.004 mmol) and sodium *tert*-butoxide ...g, 0.20 mmol) in 2 mL toluene was heated at 80–90 °C ...2 h, under a nitrogen atmosphere. The solvent was ...ved in vacuo and the residue purified by MPLC (0 to ... of EtOAc in heptane on silica gel) to give the desired ...ompound 19g (30 mg, 58%): ^1H NMR ($CDCl_3$) δ 1.0–1.4 ...H), 2.45 (m, 4H), 3.1–3.7 (m, 8H), 6.8–7.5 (m, 14H); ^{13}C ...(CD... 12.77, 13.97, 31.29, 39.10, 43.21, 51.03, 116.23, ...1, 12..., 126.49, 127.98, 128.98, 129.66, 129.72, 135.13, ...3, 135.73, 141.81, 143.15, 151.00, 171.09; IR (HCl salt) ...cm^{-1}. Anal. ($C_{28}H_{32}N_2O \cdot 1.7HCl$) C, H, N.

...ological Assays. 1. Cell Culture and Membrane ...aration. Human HEK-293S cells were subject to stable ...fection with cDNA encoding the human μ, δ, and κ ...tors. Clones were chosen for high receptor expression and ...n in suspension culture. Cells were harvested and P2 ...brane preparations were produced.

Receptor Binding Assays. Membranes were combined ... test compounds and approximately 0.07 nM of the ...opriate radioligand [^{125}I][D-Ala^2]deltorphin II (K_d = 0.93 ...*δ*), [^{125}I]FK33824 (K_d = 1.14 nM at *μ*), and [^{125}I]-D-Pro^{10}-...rphin A[1–11] (K_d = 0.16 nM at *κ*) in 50 mM Tris, 3 mM ...l_2, 1 mg/mL BSA, pH 7.4. The amounts of bound radio-...ity were determined at equilibrium by filtration. The ...pecific (NS) binding was defined in the presence of 10 μM ...zone. The IC_{50} values of test compounds were determined from 2-parameter logistic curve fits of percent specific binding vs log(molar ligand), solving for IC_{50} and Hill slope.

3. GTP[γ-^{35}S] Binding Assays. Membranes expressing 10 pmol of hDOR/mg protein were combined with test compounds and approximately 0.2 nM GTP[γ-^{35}S] in 50 mM Hepes, 20 mM NaOH, pH 7.4, 5 mM $MgCl_2$, 100 mM NaCl, 1 mM EDTA, 1 mM DTT, 0.1% BSA, 15 μM GDP. The bound radioactivity was determined after 1 h by filtration. Control and stimulated binding were determined in the absence and presence of 3 μM SNC-80, respectively. Values of EC_{50} and E_{max} for ligands were obtained from 3-parameter logistic curve fits of percent stimulated GTP[γ-^{35}S] binding vs log(molar ligand), solving for EC_{50}, Hill slope, and $\%E_{max}$.

4. In Vitro Metabolic Studies. Incubation conditions: All incubations [rat liver microsomes (0.4 mg/mL protein; Xenotech LLC, Kansas City, KS), substrate at 10 or 100 nmol/L, 1 mM NADPH, 100 mM phosphate buffer at pH 7.4] were performed in duplicate in disposable 96-well plates on a gently shaking platform maintained at 37 °C. Control incubations were carried out by incubating the same substrate concentrations in phosphate buffer without rat liver microsomes or NADPH. The final assay volume was 500 μL, containing 1% DMSO (test article stock solutions were prepared at 10 mM in DMSO).

Incubations were started by the addition of NADPH (or buffer for NADPH-free controls) and were stopped after 0 and 60 min by the addition of 500 μL of ice-cold acetonitrile. The precipitated proteins were removed following a 10-min centrifugation at 8500*g* and the supernatants were analyzed for parent drug by a benchtop LC–MSD system.

Analytical conditions: Aliquots (5 μL) of the supernatants were directly injected onto a Zorbax Eclipse XDB C18 column (4.6 × 30 mm, 3.5-μm particles) using a micro plate sampler (HP220, Hewlett-Packard, Kirkland, Quebec, Canada). The mobile phase consisted of a mixture of acetonitrile, methanol and 0.04% formic acid in water (60–80:0–15:15–30, v/v). The flow rate was 1.0 mL/min. The LC system (HP1100, Hewlett-Packard) was equipped with a quaternary pump (Hewlett-Packard) and linked to a mass selective detector (MSD) with an electrospray interface (Hewlett-Packard). The MSD was operated in selected ion monitoring mode (the selected *m/z* being that of the parent compound). Nebulizer pressure was 60 psi, while the drying gas (nitrogen) was delivered at 13 L/min. The capillary voltage was 3500 V, and the fragmentor (collision-induced dissociation cell) was set at 70 eV.

5. Results (parent drug disappearance from the incubation medium). The parent drug peak area in the 0-min incubation sample was considered to be the 100% value, and parent drug levels were expressed as percent (%) parent remaining.

6. Molecular Modeling Studies. Models of compound 6a and SNC-80 were constructed with standard parameters in Sybyl 6.2 (Tripos Inc., 1699 South Hanley Rd., St. Louis, MO 63144) using a SGI workstation (Indigo 2). The random conformational search and energy minimization were performed using the Tripos force field. An energy window of 5 kcal/mol ($E_i - E_{min}$) was used to collect low-energy conformers. The rotatable bonds with an interval of 30° were further used to classify the low-energy conformers. There were 12 different conformers for 6a and 159 for SNC-80. The representative conformers were then compared between the two compounds. The superposition of the conformers was carried out with the piperazine ring (for SNC-80) or piperidine ring (for 6a) and the right-hand phenyl rings. The superposition of X-ray structures of 6a and SNC-80 was carried out between five points: the two nitrogen atoms of the piperazine ring, the centroid points of the two phenyl rings, and the carbon atom of the carbonyl group.

References

(1) Hughes, J.; Smith, T. W.; Kosterlitz, H. W.; Fothergill, L. A.; Morgan, B. A.; Morris, H. R. Identification of two Related Peptides From The Brain With Potent Opiate Agonistic Activity. *Nature* **1975**, *258*, 577–579.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 96/01635

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 241/04, C07D 295/04, A61K 31/495, A61K 51/04
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)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9315062 A1 (THE WELLCOME FOUNDATION LIMITED), 5 August 1993 (05.08.93) --	1-17
X	FR 2696744 A1 (LABORATOIRES JACQUES LOGEAIS), 15 April 1994 (15.04.94) --	1-14,16-17
X	DE 2431178 A1 (CERMOL S.A.), 16 January 1975 (16.01.75) --	1-14,16-17
X	WO 9504051 A1 (THE WELLCOME FOUNDATION LIMITED), 9 February 1995 (09.02.95) --	1-14,15-16

[X] Further documents are listed in the continuation of Box C. [X] 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 document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 April 1997	09 -04- 1997
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	**Authorized officer** Solveig Gustavsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 96/01635

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0133323 A1 (THE WELLCOME FOUNDATION LIMITED), 20 February 1985 (20.02.85) --	1-14,16-17
X	EP 0289227 A1 (SYNTEX PHARMACEUTICALS LTD), 2 November 1988 (02.11.88) --	1-14,16-17
X	GB 2076403 A (SELVI & C. S.P.A.), 2 December 1981 (02.12.81) --	1-14,16-17
X	DE 2900810 A1 (CASSELLA AG), 24 July 1980 (24.07.80) --	1-14,16-17
X	GB 2210366 A (AMERICAN HOME PRODUCTS CORPORATION), 7 June 1989 (07.06.89) --	1-14,16-17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 96/01635

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 18
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

04/03/97

International application No.
PCT/SE 96/01635

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9315062 A1	05/08/93	AU 3457393 A	01/09/93
		EP 0649414 A	26/04/95
		EP 0650536 A	03/05/95
		JP 7501583 T	16/02/95
		JP 7503247 T	06/04/95
		NZ 246916 A	27/08/96
		US 5492737 A	20/02/96
		US 5574159 A	12/11/96
		ZA 9300717 A	02/08/94
FR 2696744 A1	15/04/94	NONE	
DE 2431178 A1	16/01/75	AR 203031 A	08/08/75
		AT 340932 B	10/01/78
		BE 816984 A	16/10/74
		CA 1025452 A	31/01/78
		CH 583713 A	14/01/77
		CH 585209 A	28/02/77
		FR 2234898 A,B	24/01/75
		GB 1461689 A	19/01/77
		JP 1311667 C	11/04/86
		JP 50036480 A	05/04/75
		JP 60037095 B	24/08/85
		NL 184682 B,C	01/05/89
		NL 7408507 A	31/12/74
		SE 7408344 A	30/12/74
		US 3940386 A	24/02/76
WO 9504051 A1	09/02/95	AU 7235194 A	28/02/95
		CA 2168432 A	09/02/95
		CN 1133593 A	16/10/96
		EP 0711289 A	15/05/96
		HU 72893 A	28/06/96
		HU 9501982 D	00/00/00
		IL 110512 D	00/00/00
		US 5552404 A	03/09/96
		US 5574159 A	12/11/96
		ZA 9405669 A	29/01/96
EP 0133323 A1	20/02/85	DE 3469173 A	10/03/88
		JP 1727360 C	19/01/93
		JP 4015786 B	19/03/92
		JP 60056973 A	02/04/85
		US 4757074 A	12/07/88

INTERNATIONAL SEARCH REPORT

Information on patent family members

04/03/97

International application No.
PCT/SE 96/01635

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0289227 A1	02/11/88	SE 0289227 T3	
		AU 614282 B	29/08/91
		AU 1510288 A	27/10/88
		CA 1320199 A	13/07/93
		DE 3869821 A	14/05/92
		FI 93104 B,C	15/11/94
		HU 210720 B	28/06/95
		HU 9500079 A	28/04/95
		IE 62106 B	14/12/94
		JP 7037451 B	26/04/95
		JP 63280081 A	17/11/88
		KR 9607524 B	05/06/96
		US 4829065 A	09/05/89
		US 4935417 A	19/06/90
		US 5010075 A	23/04/91
		US 5043447 A	27/08/91
		US 5091428 A	25/02/92
		US 5252736 A	12/10/93
		US 5276034 A	04/01/94
		US 5514800 A	07/05/96
GB 2076403 A	02/12/81	BE 888811 A	28/08/81
		DE 3118162 A,C	18/02/82
		FR 2482965 A,B	27/11/81
		JP 1368134 C	11/03/87
		JP 57031678 A	20/02/82
		JP 61035189 B	12/08/86
		NL 8102361 A	16/12/81
DE 2900810 A1	24/07/80	NONE	
GB 2210366 A	07/06/89	AU 2215588 A	06/04/89
		CA 1301757 A	26/05/92
		DE 3887614 D,T	11/05/94
		EP 0310268 A,B	05/04/89
		SE 0310268 T3	
		ES 2061670 T	16/12/94
		IE 60916 B	24/08/94
		JP 1121281 A	12/05/89
		US 4826844 A	02/05/89

D1

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 211/70, 307/81, A61K 31/445 — A1

(11) International Publication Number: WO 98/28275

(43) International Publication Date: 2 July 1998 (02.07.98)

(21) International Application Number: PCT/SE97/02050

(22) International Filing Date: 9 December 1997 (09.12.97)

(30) Priority Data:

9604785-7	20 December 1996 (20.12.96)	SE
9702535-7	1 July 1997 (01.07.97)	SE

(71) Applicant *(for all designated States except MG US)*: ASTRA PHARMA INC. [CA/CA]; 1004 Middlegate Road, Mississauga, Ontario L4Y 1M4 (CA).

(71) Applicant *(for MG only)*: ASTRA AKTIEBOLAG (publ) [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

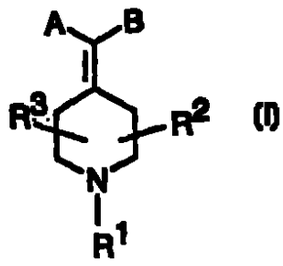
(75) Inventors/Applicants *(for US only)*: DELORME, Daniel [CA/CA]; 793 Charbonneau, St. Lazare, Quebec J7T 2B2 (CA). ROBERTS, Edward [GB/CA]; 2541 Chestnut Circle, St. Lazare de Vaudreuil, Quebec J7T 2A1 (CA). WEI, Zhongyong [CA/CA]; 17750 Antoine-Faucon, Pierrefonds, Quebec H9J 3N2 (CA).

(74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: NOVEL COMPOUNDS WITH ANALGESIC EFFECT



(I)

(57) Abstract

Compounds of general formula (I) are disclosed and claimed in the present application, as well as their pharmaceutically acceptable salts, pharmaceutical compositions comprising the novel compounds and their use in therapy, in particular in the management of pain.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

NOVEL COMPOUNDS WITH ANALGESIC EFFECT

Field of the invention

The present invention is related to novel compounds, to a process for their preparation, their use and pharmaceutical compositions comprising the novel compounds. The novel compounds are useful in therapy, and in particular for the treatment of pain.

Background and prior art

The δ receptor has been identified as having a role in many bodily functions such as circulatory and pain systems. Ligands for the δ receptor may therefore find potential use as analgesics, and/or as antihypertensive agents. Ligands for the δ receptor have also been shown to possess immunomodulatory activities.

The identification of at least three different populations of opioid receptors (μ, δ and κ) is now well established and all three are apparent in both central and peripheral nervous systems of many species including man. Analgesia has been observed in various animal models when one or more of these receptors has been activated.

With few exceptions, currently available selective opioid δ ligands are peptidic in nature and are unsuitable for administration by systemic routes. Some non-peptidic δ antagonists have been available for some time (see Takemori and Portoghese, 1992, Ann. Rev. Pharmacol. Tox., 32: 239-269. for review). These compounds, e.g. naltrindole, suffer from rather poor (i.e., < 10-fold) selectivity for the δ receptor vs. μ receptor binding and exhibit no analgesic activity, a fact which underscores the need for the development of highly selective non-peptidic δ-ligands.

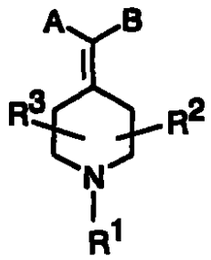
Thus, the problem underlying the present invention was to find new compounds having improved analgesic effects, but also with an improved side-effect profile over current μ agonists and potential oral efficacy.

Analgesics that have been identified and are existing in the prior art have many disadvantages such as that they suffer from poor pharmacokinetics and are not analgesic when administered by systemic routes. Also, it has been documented that preferred compounds, described within the prior art, show significant convulsive effects when administered systemically.

The problem mentioned above has been solved by developing novel compounds which possess a piperidine ring with an exocyclic double bond, as will be described below.

Outline of the invention

The novel compounds according to the present invention are defined by the general formula (I)



(I)

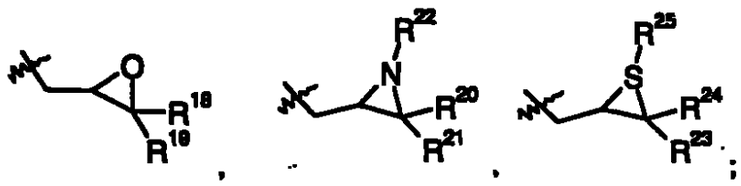
wherein

R^1 is selected from

hydrogen, a branched or straight C_1-C_6 alkyl, C_1-C_6 alkenyl, C_3-C_8 cycloalkyl, C_4-C_8(alkyl-cycloalkyl) wherein alkyl is C_1-C_2 alkyl and cycloalkyl is C_3-C_6 cycloalkyl;

C_6-C_{10} aryl; or heteroaryl having from 5 to 10 atoms selected from any of C, S, N and O; wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents independently selected from any of hydrogen, CH_3, $-(CH_2)_pCF_3$, halogen, $-CONR^5R^4$, $-COOR^5$, $-COR^5$, $-(CH_2)_pNR^5R^4$, $-(CH_2)_pCH_3(CH_2)_pSOR^5R^4$, $-(CH_2)_pSO_2R^5$, and $-(CH_2)_pSO_2NR^5$, wherein R^4 and R^5 is each and independently as defined for R^1 above and p is 0, 1 or 2;

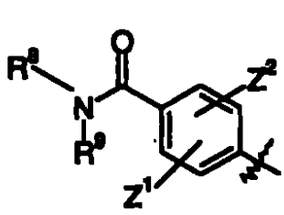
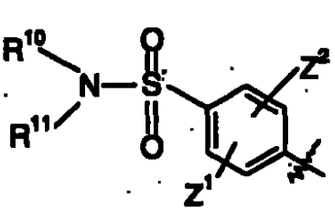
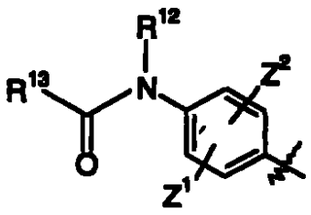
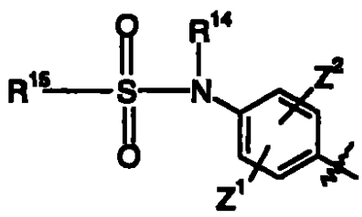
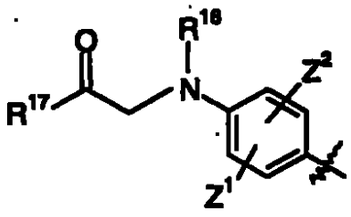
(C_1-C_2 alkyl)-(C_6-C_{10} aryl); or (C_1-C_2 alkyl)heteroaryl, the heteroaryl moieties having from 5 to 10 atoms selected from any of C, S, N and O, and where the aryl or heteroaryl may optionally and independently be substituted by 1 or 2 substituents independently selected from any of hydrogen, CH_3, $-(CH_2)_qCF_3$, halogen, $-CONR^5R^4$, $-COOR^5$, $-COR^5$, $-(CH_2)_qNR^5R^4$, $-(CH_2)_qCH_3(CH_2)_qSOR^5R^4$, $-(CH_2)_qSO_2R^5$, $-(CH_2)_qSO_2NR^5$ and $-(CH_2)_pOR^5$, wherein R^4 and R^5 is each and independently as defined for R^1 above and q is 0, 1 or 2; and

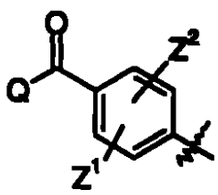


wherein R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24} and R^{25} is each and independently hydrogen, C_1-C_6 alkyl or C_1-C_6 alkenyl;

R^2 and R^3 is each and independently hydrogen or C_1-C_6 alkyl;

A is selected from






, and


;

wherein R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} is each and independently as defined for R^1 above, and wherein the phenyl ring of each A substituent may be optionally and independently substituted at any position of the phenyl ring by 1 or 2 substituents Z^1 and Z^2 which are each and independently selected from hydrogen, CH_3, —$(CH_2)_qCF_3$, halogen, —$CONR^6R^7$, —COOR6, —COR^6, —$(CH_2)_rNR^6R^7$, —$(CH_2)_rCH_3(CH_2)_rSOR^6$, —$(CH_2)_rSO_2R^6$ and —$(CH_2)_rSO_2NR^6R^7$ wherein R^6 and R^7 is each and independently as defined for R^1 above and r is 0, 1, or 2;

Q is C_5-C_6 hydroaryl or heterohydroaromatic having 5 or 6 atoms selected from anyone of C, S, N and O; C_5 -C_6 cykloalkyl, or heterocycloalkyl having 5 or 6 atoms selected from

anyone of C, N, O and S; and where each Q may optionally be substituted by a substituent Z^1 and Z^2 as defined above;

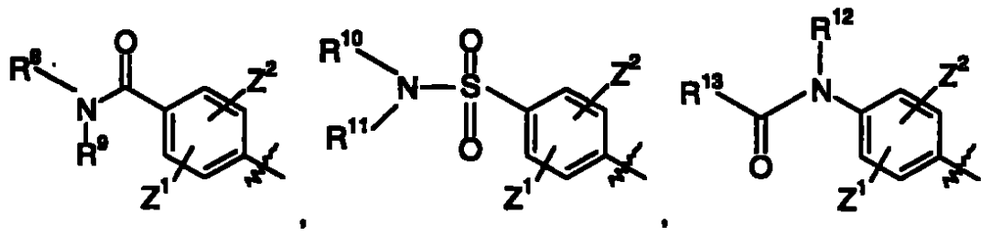
B is a substituted or unsubstituted aromatic, heteroaromatic, hydroaromatic or heterohydroaromatic moiety having from 5 to 10 atoms selected from any of C, S, N and O, optionally and independently substituted by 1 or 2 substituents independently selected from hydrogen, CH_3, $-(CH_2)_tCF_3$, halogen, $-(CH_2)_tCONR^5R^4$, $-(CH_2)_tNR^5R^4$, $-(CH_2)_tCOR^5$, $-(CH_2)_tCOOR^5$, $-OR^5$, $-(CH_2)_tSOR^5$, $-(CH_2)_tSO_2R^5$, and $-(CH_2)tSO_2NR^5R^4$, wherein R^4 and R^5 is each and independently as defined for R^1 above, and t is 0, 1, 2 or 3; and

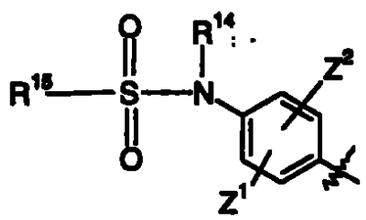
R^4 and R^5 is each and independently as defined for R^1 above.

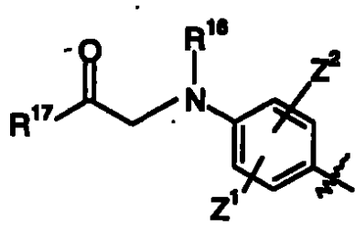
Within the scope of the invention are also pharmaceutically acceptable salts of the compounds of the formula (I), as well as isomers, hydrates, isoforms and prodrugs thereof.

Preferred compounds according to the invention are compounds of the formula (I) wherein

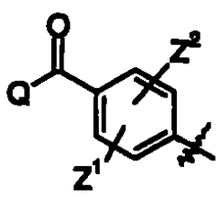
A is selected from







; and



;

wherein R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} is each and independently as defined for R^1 above, and wherein the phenyl ring of each A substituent may be optionally and independently substituted at any position of the phenyl ring by 1 or 2 substituents Z^1 and Z^2 which are each and independently selected from hydrogen, CH_3, $-(CH_2)_qCF_3$, halogen, $-CONR^6R^7$, $-COOR^6$, $-COR^6$, $-(CH_2)_rNR^6R^7$, $-(CH_2)_rCH_3(CH_2)_rSOR^6$, $-(CH_2)_rSO_2R^6$ and $-(CH_2)_rSO_2NR^6R^7$ wherein R^6 and R^7 is each and independently as defined for R^1 above, and r is 0, 1, or 2;

Q is selected from morpholine, piperidine and pyrrolidine;

R^1, R^4, and R^5 is each and independently selected from hydrogen, a branched or straight C_1-C_4 alkyl, C_3-C_5 cycloalkyl, C_4-C_8 (alkyl-cycloalkyl) wherein alkyl is C_1-C_2 alkyl and cycloalkyl is C_3-C_6 cycloalkyl; C_6-C_{10} aryl; and heteroaryl having from 5 to 6 atoms selected from any of C, S, N and O; and where the aryl or heteroaryl may optionally and independently be substituted by 1 or 2 substituents independently selected from any of hydrogen, CH_3, $-(CH_2)_pCF_3$, halogen, $-CONR^5R^4$, $-COOR^5$, $-COR^5$, $-(CH_2)_pNR^5R^4$, $-(CH_2)_pCH_3(CH_2)_pSOR^5R^4$, $-(CH_2)_pSO_2R^5$, and

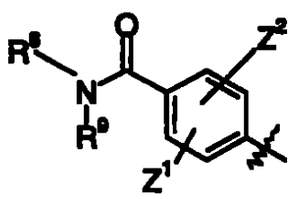
—$(CH_2)_pSO_2NR^5$, wherein R^4 and R^5 is each and independently as defined for R^1 above and p is 0, 1 or 2;

B is selected from phenyl, naphthyl, indolyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl, pyrryl, furanyl, quinolinyl, isoquinolinyl, cyclohexyl, cyclohexenyl, cyclopentyl, cyclopentenyl, indanyl, indenyl, tetrahydronaphthyl, tetrahydroquinyl, tetrahydroisoquinolinyl, tetrahydrofuranyl, pyrrolidinyl, and indazolinyl, each optionally and independently substituted by 1 or 2 substituents independently selected from hydrogen, CH_3, CF_3, halogen, —$(CH_2)_qCONR^5R^4$, —$(CH_2)_qNR^5R^4$, —$(CH_2)_qCOR^5$, —$(CH_2)_qCO_2R^5$, and —OR^5, wherein q is 0 or 1, and wherein R^4 and R^5 are as defined above;

R^2 and R^3 is each and independently hydrogen or methyl.

Especially preferred compounds according to the invention are compounds of the formula (I) wherein

A is



wherein R^8 and R^9 are both ethyl, and where the phenyl ring optionally and independently may be substituted at any position of the phenyl ring by 1 or 2 substituents Z^1 and Z^2 which are each and independently selected from hydrogen, CH_3, —$(CH_2)_qCF_3$, halogen, —$CONR^6R^7$, —$COOR^6$, —COR^6, —$(CH_2)_rNR^6R^7$, —$(CH_2)_rCH_3(CH_2)_rSOR^6$, —$(CH_2)_rSO_2R^6$ and —$(CH_2)_rSO_2NR^6R^7$ wherein R^6 and R^7 is each and independently as defined for R^1 above and r is 0, 1, or 2;

R^1 is selected from hydrogen, methyl, ethyl, $—CH_2CH=CH_2$, $—CH_2$-cyclopropyl, $—CH_2—$aryl, or $CH_2—$heteroaryl, the heteroaryl moieties having from 5 to 6 atoms selected from any of C, S, N and O;

B is selected from phenyl, naphthyl, indolyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl, furanyl, quinolinyl, isoquinolinyl, cyclohexyl, cyclohexenyl, cyclopentyl, cyclopentenyl, indanyl, indenyl, tetrahydronaphthyl, tetrahydroquinyl, tetrahydroisoquinolinyl, tetrahydrofuranyl, and indazolinyl, each optionally and independently substituted by 1 or 2 substituents independently selected from hydrogen, CH_3, CF_3, halogen, $—(CH_2)_qCONR^5R^4$, $—(CH_2)_qNR^5R^4$, $—(CH_2)_qCOR^5$, $—(CH_2)_qCO_2R^5$, and $—OR^5$, wherein q is 0 or 1, and wherein R^4 and R^5 are as defined above;

R^2 and R^3 is each and independently hydrogen or methyl.

The substituents A and B respectively, may optionally be substituted at any position of the ring.

By "halogen" we mean chloro, fluoro, bromo and iodo.

By "aryl" we mean an aromatic ring having from 6 to 10 carbon atoms, such as phenyl and naphtyl.

By "heteroaryl" we mean an aromatic ring in which one or more of the from 5-10 atoms in the ring are elements other than carbon, such as N, S and O.

By "hydroaromatic" we mean a partly or fully saturated aromatic ring structure having 5-10 carbon atoms in the ring.

By "heterohydroaromatic" we mean a partly or fully saturated aromatic ring structure in which one or more of the 5-10 atoms in the ring are elements other than carbon, such as N, S and O.

By "isomers" we mean compounds of the formula (I), which differ by the position of their functional group and/or orientation. By "orientation" we mean stereoisomers, diastereoisomers, regioisomers and enantiomers.

By "isoforms" we mean compounds of the formula (I) which differ by their crystal lattice, such as crystalline compound and amorphous compounds.

By "prodrug" we mean pharmacologically acceptable derivatives, e.g. esters and amides, such that the resulting biotransformation product of the derivative is the active drug. The reference by Goodman and Gilmans, The Pharmacological basis of Therapeutics, 8th ed., McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs, p. 13-15, describing prodrugs generally, is hereby incorporated.

The novel compounds of the present invention are useful in therapy, especially for the treatment of various pain conditions such as chronic pain, acute pain, cancer pain, pain caused by rheumatoid arthritis, migraine, visceral pain etc. This list should however not be interpreted as exhaustive.

Compounds of the invention are useful as immunomodulators, especially for autoimmune diseases, such as arthritis, for skin grafts, organ transplants and similar surgical needs, for collagen diseases, various allergies, for use as anti-tumour agents and anti viral agents.

Compounds of the invention are useful in disease states where degeneration or dysfunction of opioid receptors is present or implicated in that paradigm. This may involve the use of

isotopically labelled versions of the compounds of the invention in diagnostic techniques and imaging applications such as positron emission tomography (PET).

Compounds of the invention are useful for the treatment of diarrhoea, depression, urinary incontinence, various mental illnesses, cough, lung oedema, various gastro-intestinal disorders, spinal injury and drug addiction, including the treatment of alcohol, nicotine, opioid and other drug abuse and for disorders of the sympathetic nervous system for example hypertension.

Compounds of the invention are useful as an analgesic agent for use during general anaesthesia and monitored anaesthesia care. Combinations of agents with different properties are often used to achieve a balance of effects needed to maintain the anaesthetic state (eg. Amnesia, analgesia, muscle relaxation and sedation). Included in this combination are inhaled anaesthetics, hypnotica, anxiolytics, neuromuscular blockers and opioids.

The compounds of the present invention in isotopically labelled form are useful as a diagnostic agent.

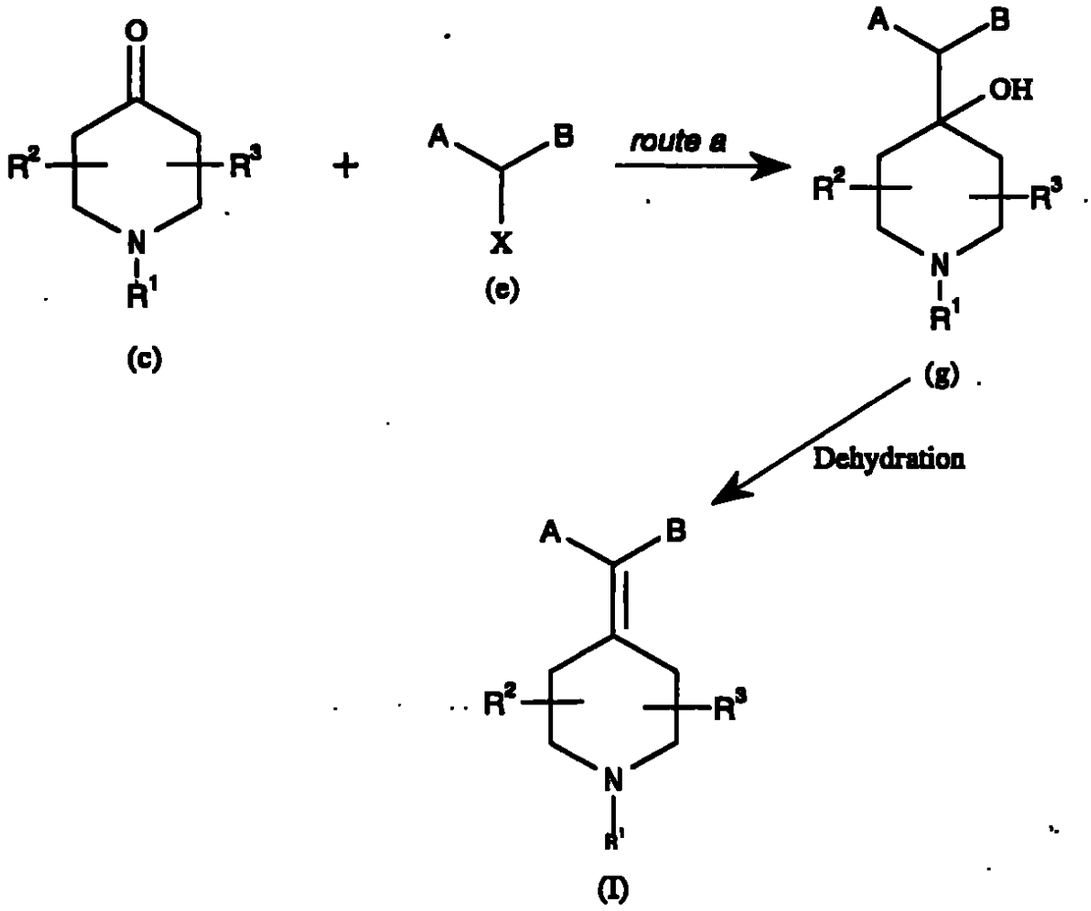
Also within the scope of the invention is the use of any of the compounds according to the formula (I) above, for the manufacture of a medicament for the treatment of any of the conditions discussed above.

A further aspect of the invention is a method for the treatment of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the formula (I) above, is administered to a patient in need of such treatment.

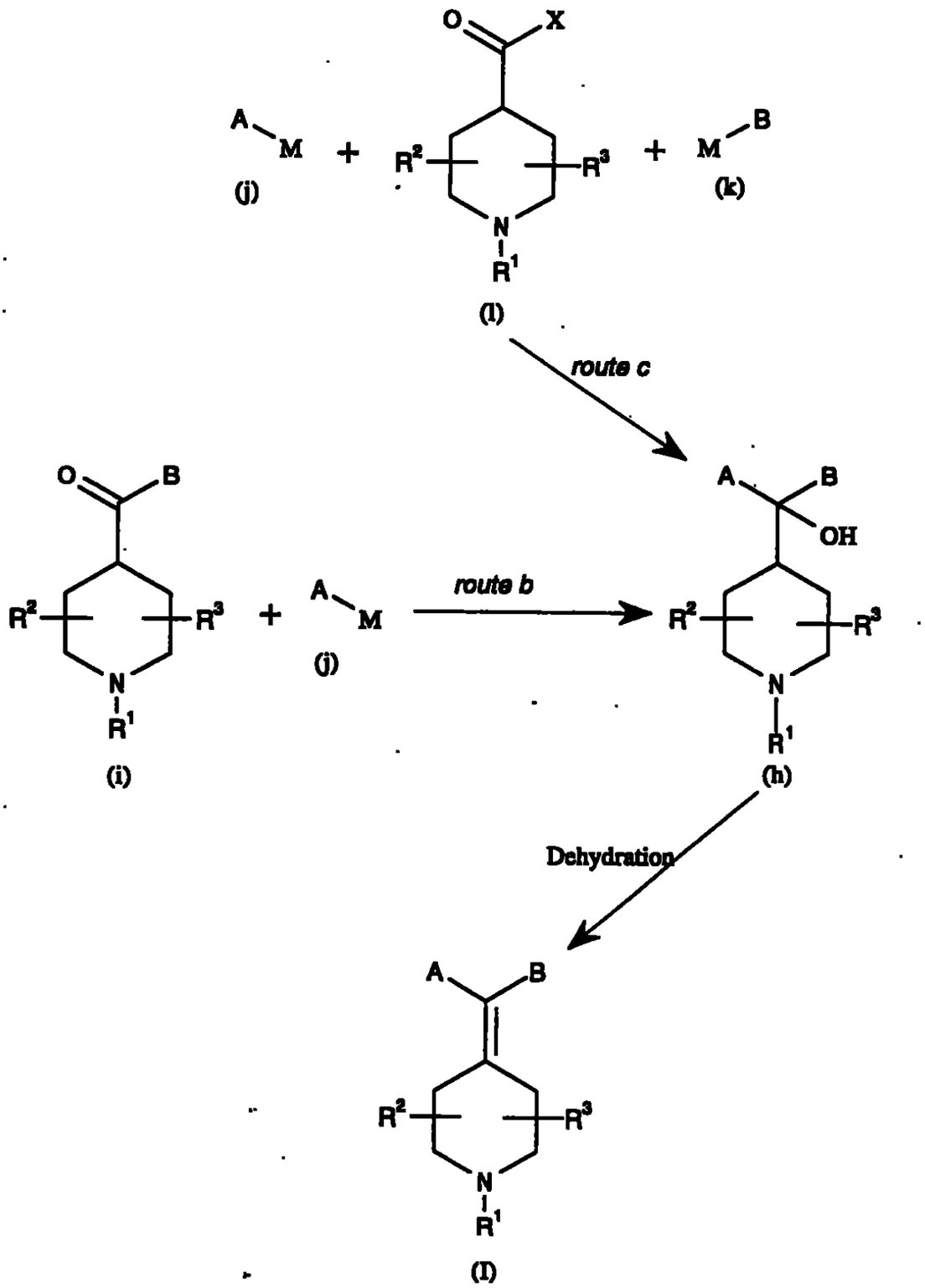
Methods of preparation

The compounds of the present invention may be prepared as described in the following.

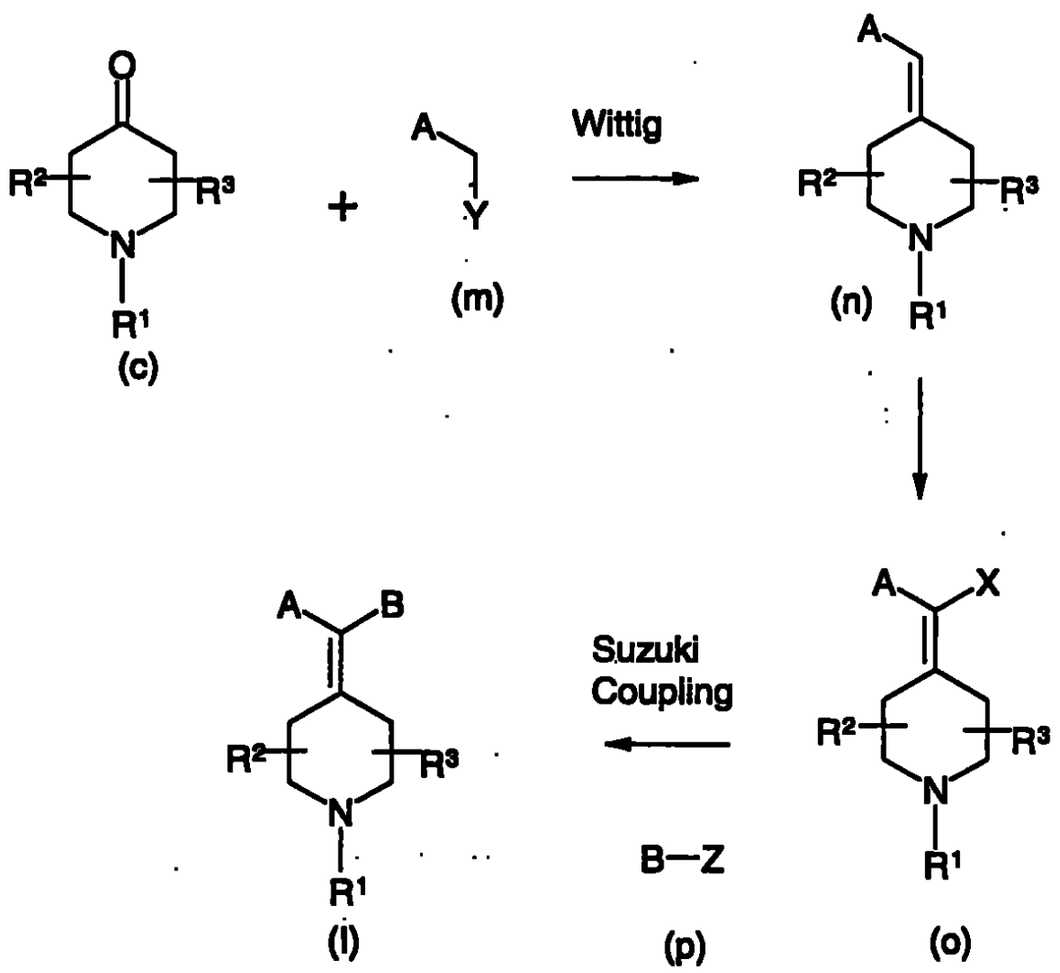
SCHEME I



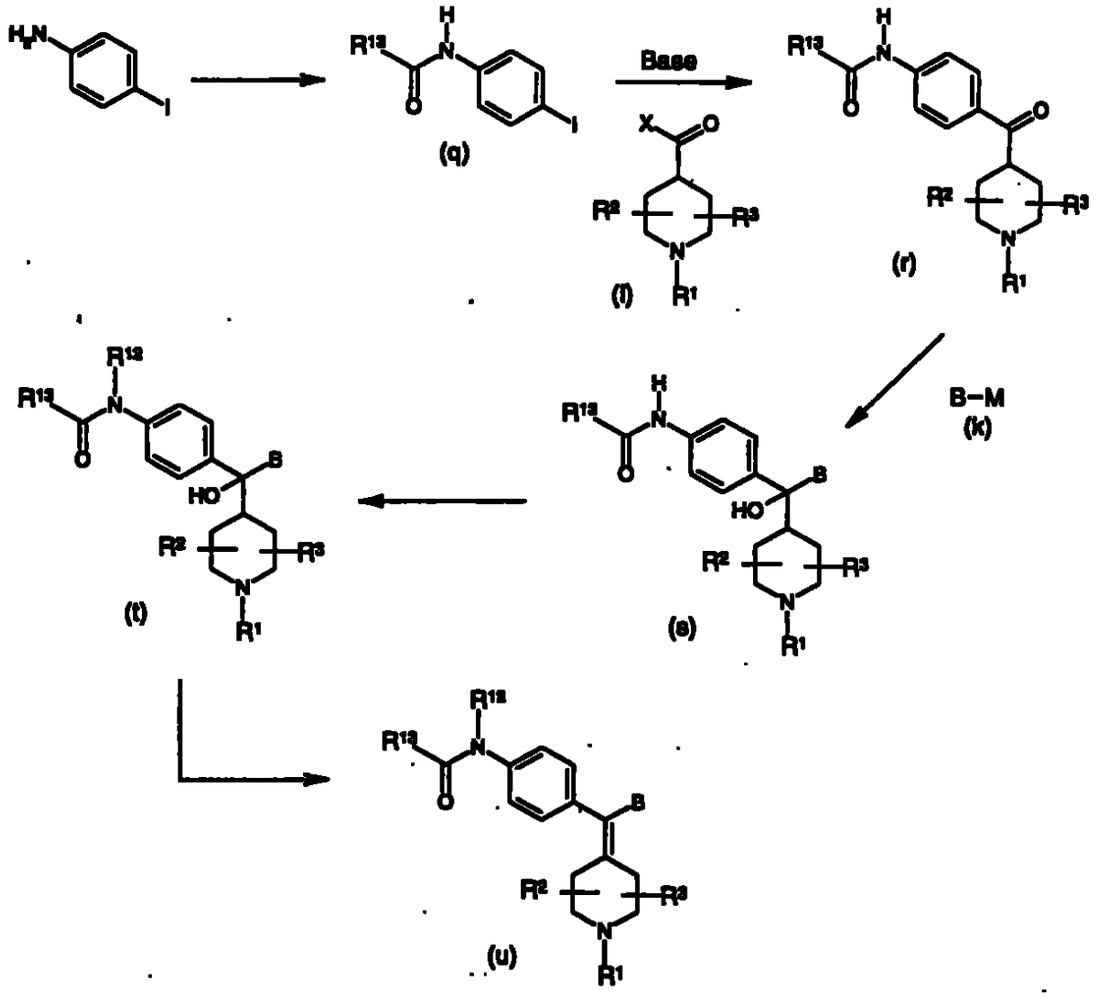
SCHEME II


O
X
A
M
(j)
R2
R3
N
R1
(l)
M
B
(k)
route c
O
B
R2
R3
N
R1
(i)
A
M
(j)
route b
A
B
OH
R2
R3
N
R1
(h)
Dehydration
A
B
R2
R3
N
R1
(I)

SCHEME III


O
R2
R3
N
R1
(c)
A
Y
(m)
Wittig
A
R2
R3
N
R1
(n)
A
X
R2
R3
N
R1
(o)
Suzuki
Coupling
B—Z
(p)
A
B
R2
R3
N
R1
(I)

SCHEME IV



As shown in SCHEME I & II above, compounds of the formula (I) above, may be obtained by dehydration of hydroxy compounds (g) or (h), wherein R^1, R^2, R^3, A and B are as defined in formula (I) above. Subsequent dehydration of hydroxyl compounds (g) or (h), wherein R^1, R^2, R^3, A and B are as defined in formula (I), may be performed without solvents or in a solvent such as water, alcohols, esters, HMPA, dichloromethane, toluene, ethers, ketones, carboxylic acids or in a solvent mixture in the presence of Brønstedt or Lewis acids such as sulphuric acid, hydrochloric acid, trifluoroacetic acid, aluminium trichloride, $ZnCl_2$ or the like, or in the presence of metallic oxides such as Al_2O_3, Cr_2O_3, TiO_2, WO_3, P_2O_5 or the like, or in the presence of other dehydrating agents such as I_2, dimethyl sulfoxide, $KHSO_4$, $CuSO_4$, phthalic anhydride or the like.

The substituents R^1, R^2 and R^3 and the substituents on A and B of compound (I), as defined above, may be modified by methods known in the art and exemplfied in the literature, see e.g. *Protecting groups* by Green, or *Modern Synthetic Reactions* by House, which are well known to a person skilled in the art, after or during the preparation of (I) from (g) and (h).

As shown the *route a* of SCHEME I, compounds of formula (g), as described above, may be obtained by a reaction between a ketone of formula (c) wherein R^1, R^2 and R^3 are as defined in formula (I), and a compound of formula (e) wherein A and B are as defined in formula (I), and X is a suitable group such as H, Cl, Br, I, OSO_2R or the like

The reaction may be performed without solvents, or in an organic solvent such as THF, toluene, ethers, dimethylsulfoxide, or in solvent mixtures by treatment with an appropriate metal such as magnesium, lithium, zinc, copper, cerium or the like, or by treatment with a metal halide such as SmI_2, $CrCl_2$ or the like, or by treatment with an organometallic agents such as alkylmagnesium halides, alkyllithium or the like.

R^1, R^2 and R^3 and the substituents on A and B of compounds (g), as defined above, may be modified, by methods known in the art, after or during the organometallic reactions (March, J., *Advanced Organic Chemistry*, 4th Ed, John Wiley & Sons, 1992).

Compounds of formula (c) and (e) may be commercially available, or prepared by methods known in the art (March, J., *Advanced Organic Chemistry*, 4th Ed, John Wiley & Sons, 1992).

As shown in *route b* of SCHEME II, compounds of formula (h), as described above, may be obtained by a reaction between a ketone of formula (i) wherein R^1, R^2 and R^3, and B are as defined in formula (I), and an organometallic reagent of formula (j) wherein A is as defined in formula (I), and M is an appropriate metal group such as magnesium, lithium, zinc, copper, cerium or the like. The reaction may be performed without solvents, or in an organic solvent such as THF, toluene, ethers, dimethylsulfoxide, or in solvent mixtures.

As shown in *route c* of SCHEME II, compounds of formula (h) may also be obtained by reactions among a carbonyl compound of formula (l), wherein R^1, R^2 and R^3 are as defined in formula (I), and X is an appropriate leaving group such as Cl, Br, OH, OR, SR, NR_2, N(OR')R or the like, and organometallic reagents of formula (j) and (k), wherein A and B are as defined in formula (I), and M is an appropriate metal group such as magnesium, lithium, zinc, copper, cerium or the like. The reactions may be performed without solvents or in solvents such as THF, toluene, ethers, dimethyl formamide, dioxane, dimethylsulfoxide, or in solvent mixtures.

R^1, R^2 and R^3 and the substituents on A and B of compounds (h), as defined above, may be modified, by methods known in the art and exemplified in the literature, see e.g. *Protecting groups* by Green, or *Modern Synthetic Reactions* by House, which are well known to a person skilled in the art, after or during the organometallic reactions.

Compounds of formula (i), (j), (k) and (l) may be commercially available, or prepared by methods known in the art (March, J., *Advanced Organic Chemistry*, 4th Ed, John Wiley & Sons, 1992).

As shown in SCHEME III above, compounds of the formula (I) above, may be obtained from the Suzuki coupling of vinylic halide (o) (X= Br, I) with a boronic acid, boronate ester (p), in the presence of a base such as Na_2CO_3, K_2CO_3, K_3PO_4, triethylamine, CsF, NaOH or alkoxides and palladium catalyst such as $(PPh_3)_4Pd$, Bis(dibenzylideneacetone)Pd(0), Pd on carbon with PPh_3; Pd(II) species may also be used as a catalyst including: $(PPh_3)_2PdCl_2$, 1,4-Bis(diphenylphosphinobutane)palladium(II) chloride, Palladium acetate, Bis(acetonitrile)palladium(II) chloride, dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium(II) and palladium acetate-tri(0-tolyl)phosphine, wherein R^1, R^2, R^3, A and B are as defined in formula (I) above. The Suzuki coupling may be performed in toluene, xylene, anisole, DMF, THF, alcohols, ethers, water or in a solvent mixture.

Compounds or formula (p), where B is as defined in formula (I) and Z is $B(OH)_2$, may be commercially available or prepared from the hydrolysis of a boronate ester. Compounds or formula (p), where B is as defined in formula (I) and Z is $B(OR)_2$ (R=Me, Et), may be prepared from the reaction of a compound of formula B-M and $B(OR)_3$ where R=Me or Et, and M is an appropriate metal group such as lithium or magnesium or the like. Compounds of formula (p) where B is as defined in formula (I) and Z is 9-borabicyclo[3.3.1]nonane (9-BBN) may be prepared from the reaction of an alk-1-yne with borabicyclo[3.3.1]nonane.

The substituents R^1, R^2, R^3 and the substituents on A and B of compound (I) as defined above, may be modified by methods known in the art and exemplified in the literature, see e.g. *Protecting groups* by Green or *Modern Synthetic Reactions* by House, which are well known to a person skilled in the art, after or during the preparation of (I) from (o) and (p).

As shown in SCHEME III, compounds of formula (o) wherein X is Br or I, may be prepared from the halogenation and elimination of an alkene of formula (n) wherein R^1, R^2, R^3 and A are as defined in formula (I). The halogenation may be performed in a solvent such as dichloromethane, chloroform, carbon tetrachloride, dichloroethane, or acetic acid using molecular bromine or iodine as halogenation agent. The subsequent elimination step is accomplished in a solvent such as water, alcohols, DMF, or ethers using a base such as sodium hydroxide, potassium hydroxide, metal alkoxides, or triethylamine.

As shown in SCHEME III, compounds of formula (n), as described above, may be prepared from the Wittig reaction of a ketone of formula (c), where R^1, R^2 and R^3 are as defined in formula (I), and a reagent of formula (m) where A is as defined in formula (I) and Y is an appropriate phosphonate or phosphonium salt. The Wittig reaction may be carried out under a variety of conditions known in the art and exemplified in the literature (March, J., *Advanced Organic Chemistry*, 4th Ed., John Wiley & Sons, 1992).

Reagents of formula (c) and (m) may be commercially available, or prepared by methods known in the art (March, J., *Advanced Organic Chemistry*, 4th Ed., John Wiley & Sons, 1992).

As shown in SCHEME IV above, compounds of formula (u) may be obtained by dehydration of hydroxy compound (t) wherein R^1,R^2,R^3,R^{12},R^{13} and B are as defined above. Dehydration step may be performed without solvent or in a solvent such as water, alcohols, esters, HMPA, dichloromethane, toluene, ethers, ketones, carboxylic acids, or in a solvent mixture in the presence of Bronstedt or Lewis acids such as sulfuric acid, hydrochloric acid, trifluoroacetic acid, aluminium trichloride, $ZnCl_2$, or the like, or in the presence of metallic oxides such as Al_2O_3, Cr_2O_3, TiO_2, WO_3, P_2O_5 or the like, or in the presence of other dehydrating agents such as I_2, dimethylsulfoxide, $KHSO_4$, $CuSo_4$, phthalic anhydride or the like.

The substituents R^1,R^2 and R^3 and the substituent B of compound (u) as defined above may be modified by methods known in the art and exemplified in the literature, see e.g. *Protecting Groups* by Green, or *Modern Synthetic Reactions* by House, which are well known to a person skilled in the art, after or during the preparation of (u) from (t).

As shown in SCHEME IV above, compounds of formula (t) may be obtained from compound (s) wherein R^1,R^2,R^3,R^{13} and B are as defined above using alkylation reaction with alkyl halide such as MeI in presence of a base such as sodium hydroxide and a phase transfer agent such as Bu_4NHSO_4. Compounds of formula (s) may be prepared by a reaction between a ketone of formula (r) wherein R^1,R^2,R^3,R^{13} are as defined above and an organometallic reagent of formula (k) wherein B is defined in formula (I) and M is an appropriate metal group such as magnesium, lithium, zinc, copper, cerium, or the like. The reaction may be performed without solvent or in solvents such as THF, toluene, ethers, dimethylformamide, dioxane, dimethylsufoxide, or in solvent mixtures.

The substituents R^1,R^2,R^3,R^{13} of compound (s) as defined above may be modified by methods known in the art and exemplified in the literature, see e.g. *Protecting Groups* by Green, or *Modern Synthetic Reactions* by House, which are well known to a person skilled in the art, after or during the preparation of (s) from (r) and (k).

As shown in SCHEME IV, a compound of formula (r) may be obtained by reactions among a carbonyl compound of formula (l) wherein R^1, R^2 and R^3 are as defined in formula (I) and X is an appropriate leaving group such as Cl, Br, OH, OR, SR, NR_2, $N(OR^1)R$ or the like and organometallic reagent obtained by first base treatment such as NaH on compound (q) wherein R^{13} is as defined above followed by subsequent transmetallation using alkyl lithium such as BuLi. The reaction may be performed in solvents such as THF, toluene, ethers, dimethylformamide, dioxane, or in solvent mixtures. The substituents R^1,R^2,R^3,R^{13} of compound (r) as defined above may be modified by methods known in the art and exemplified in the literature, see e.g. *Protecting Groups* by Green, or *Modern Synthetic*

Reactions by House, which are well known to a person skilled in the art, after or during the preparation of (r) from (q) and (l).

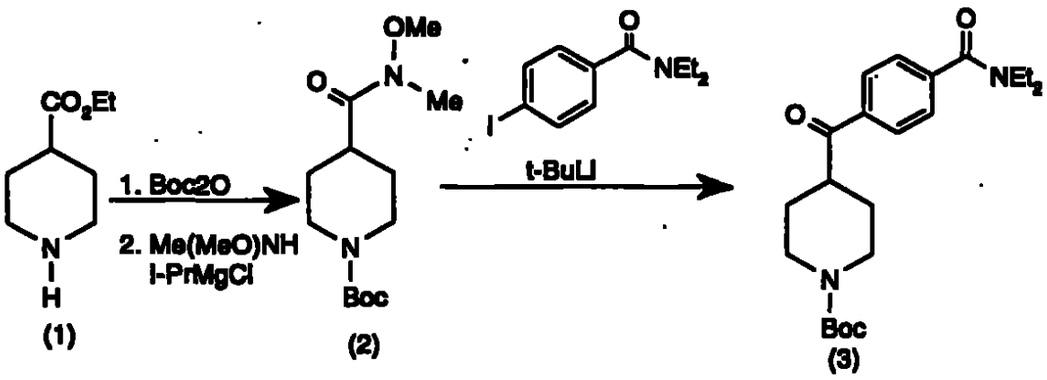
As shown in SCHEME IV, compounds of formula (q) may be obtained by acylation of 4-iodoaniline using either acylanhydride or acylchloride in an organic solvent such as dichloromethane. The substituent R^{13} of compound (q) is as defined above.

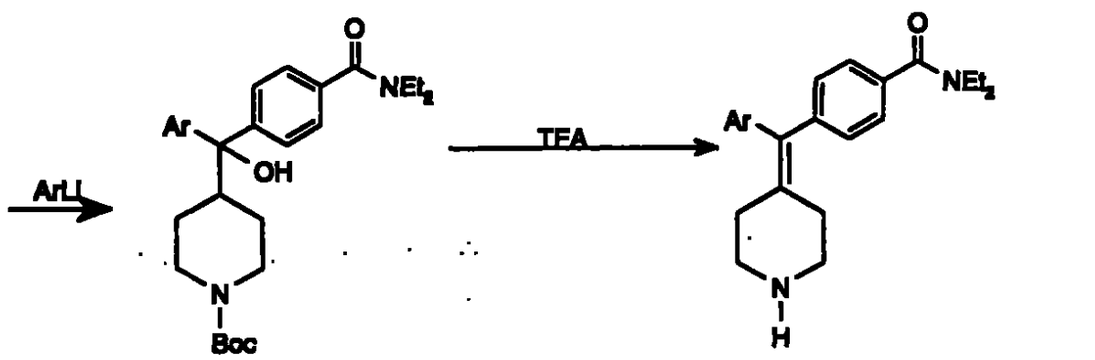
The invention will now be described in more detail by way of the following Examples, which are not to be construed as limiting the invention in any way.

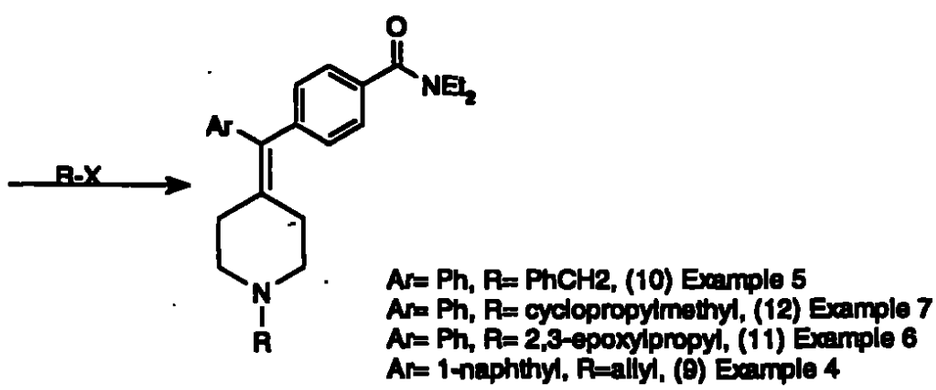
A) Synthetic scheme for the preparation of the compounds of Examples 1-7

The compounds of Examples 1-7 were prepared by following the procedure as is shown in Scheme 1 below.

Scheme 1







(i) Preparation of N-t-Butoxylcarbonyl N'-methyl-N'-methoxyl-isonipecotamide (compound 2)

A mixture of ethyl isonipecotate (compound 1) (4.71 g, 30.0 mmol), di-tert-butyl dicarbonate (6.55 g, 30.0 mmol) and Na_2CO_3 (4.77 g, 45 mmol) in H_2O-THF (90/10 mL) was refluxed for 2h. The reaction mixture was extracted with ethyl acetate (150 mL). The organic layer was washed with brine, dried over $MgSO_4$. Removal of solvents gave N-t-butoxylcarbonyl ethyl isonipecotate (7.67 g):

δ_H (400 MHz, $CDCl_3$) 1.25 (t, J=7.2 Hz, 3H), 1.45 (s, 9H), 1.62 (m, 2H), 1.87 (m, 2H), 2.43 (m, 1H), 2.84 (m, 2H), 4.02 (m, 2H), 4.13 (q, J=7.2 Hz, 2H); δ_{C-13} (100 MHz, $CDCl_3$) δ: 14.0, 27.8, 28.2, 40.9, 42.9, 60.2, 79.2, 154.4, 174.2.

The above N-t-butoxylcarbonyl ethyl isonipecotate was dissolved in dry THF (60 mL) and mixed with NHMe(OMe) HCl (4.39 g, 45.0 mmol). The mixture was treated with i-PrMgCl (2.0 M in THF, 45 ml, 90 mmol) at -20 C and the resulting solution was stirred for 1 hr at -5 °C and then quenched with aqueous NH_4Cl solution and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$. Removal of solvents gave N-t-butoxylcarbonyl N'-methyl-N'-methoxyl-isonipecotamide (compound 2) (8.0 g, 98%):

δ_H (400 MHz, $CDCl_3$) 1.30 (s, 9H), 1.54 (m, 4H), 2.65 (m, 3H), 3.02 (s, 3H), 3.56 (s, 3H), 3.99 (brs, 2H); δ_{C-13} (100 MHz, $CDCl_3$) δ: 27.7, 28.1, 32.0, 37.8, 43.1, 61.3, 79.1, 154.4, 176.0.

(ii) Preperation of 4-(4'-N',N'-Diethylaminocarbonylbenzoyl)-N-t-butoxylcarbonylpiperidine (compound 3)

To a solution of 4-iodo-N,N-diethylbenzamide (9.09 g, 30.0 mmol) and TMEDA (6.96 g, 60.0 mmol) in dry THF (60 mL) was added t-butyllithium (35.0 mL, 1.7 M, 60.0 mmol) at -78 ^{0}C. After 30 min, N-t-butoxylcarbonyl N'-methyl-N'-methoxyl-isonipecotamide (compound 2) (8.0 g, 29.4 mmol) in THF (10 mL) was dropwise added. The reaction mixture was warmed to r.t. and then quenched with aqueous NH_4Cl solution, neutralized with hydrochloric acid (concentrated, 20 mL) at ^{0}C, and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$. Removal of solvents gave a crude product, which was purified by silica gel column eluting with MeOH-CH_2Cl_2 (2 : 98) to provide 4-(4'-N',N'-diethylaminocarbonylbenzoyl)-N-t-butoxylcarbonylpiperidine (compound 3) (3.15 g, 28 %):

δ_H (400 MHz, $CDCl_3$) 1.08 (brs, 3H), 1.23 (brs, 3H), 1.43 (s, 9H), 1.61 (m, 2H), 1.80 (m, 2H), 2.89 (m, 2H), 3.20 (brs, 2H), 3.40 (m, 1H), 3.53 (brs, 2H), 4.11 (brs, 2H), 7.44 (d, J=8.0 Hz, 2H), 7.94 (d, J=8.0 Hz, 2H).

(iii) Preparation of 4-(α-Hydroxyl-α-(4-N-t-butoxylcarbonylpiperidinyl)-α-(1-naphthyl)-methyl)-N,N-diethylbenzamide (compound 4)

To a solution of 1-bromonaphthalene (0.52 g, 2.5 mmol) in dry THF (10 mL) was added n-butyllithium (1.1 mL, 2.5 M, 2.75 mmol) at -78 ^{0}C. After 30 min, 4-(4'-N',N'-diethylaminocarbonylbenzoyl)-N-t-butoxylcarbonylpiperidine (compound 3)-(776 mg, 2.0 mmol) in THF (2 mL) was dropwise added. The reaction mixture was warmed to r.t. and then quenched with aqueous NH_4Cl solution, and extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$. Removal of solvents gave a crude product, which was purified by silica gel column eluting with MeOH-CH_2Cl_2 (0.5 : 99.5 → 5 : 95) to provide 4-(α-hydroxyl-α-(4-N-t-

butoxylcarbonylpiperidinyl)-α-(1-naphthyl)-methyl)-N,N-diethylbenzamide (compound 4) (760 mg, 74 %):

m.p. 121-124 ^{0}C (CH_2Cl_2);

ν_{max} (KBr) cm^{-1} 3402, 2960, 1685, 1626, 1425, 1283, 1160;

Anal.Calcd.for $C_{32}H_{40}N_2O_4$. 0.50H_2O: C, 73.11; H, 7.86; N, 5.33.

Found: C, 72.86; H, 7.64; N, 5.26; δ_H (400 MHz, $CDCl_3$) 1.03 (brs, 3H), 1.16 (brs, 3H), 1.18-1.35 (m, 3H), 1.95 (m, 1H), 2.60 (m, 2H), 2.75 (brs, 2H), 3.15 (brs, 2H); 3.42 (brs, 2H), 4:10 (brs, 2H), 7.10-7.50 (m, 7H), 7.75 (m, 3H), 8.27 (brs, 1H); δ_{C-13} (100 MHz, $CDCl_3$) δ: 12.8, 14.1, 27.1, 27.2, 28.4, 39.2, 43.3, 45.4, 79.3, 80.4, 124.1, 124.9, 125.2, 125.3, 126.0, 127.3, 128.8, 129.2, 131.4, 135.0, 135.2, 139.4, 146.5, 154.6, 171.0.

(iv) Preparation of 4-(α-Hydroxyl-α-(4-N-t-butoxylcarbonylpiperidinyl)-2,6-dimethylbenzyl)-N,N-diethylbenzamide (compound 5)

Method as described for compound 4, except using 2-bromo-*m*-xylene; (749 mg, 76 %):

m.p. 92-96 ^{0}C (CH_2Cl_2);

ν_{max} (KBr) cm^{-1} 3451, 2970, 1690, 1631, 1425, 1165;

Anal.Calcd.for $C_{30}H_{42}N_2O_4$. 0.50H_2O: C, 71.54; H, 8.61; N, 5.56.

Found: C, 71.70; H, 8.34; N, 5.62; δ_H (400 MHz, $CDCl_3$) 1.10 (brs, 3H), 1.21 (brs, 3H), 1.32 (m, 2H), 1.43 (s, 9H), 1.69 (m, 1H), 1.77 (m, 1H), 2.32 (s, 6H), 2.47 (s, 1H), 2.75 (m, 3H), 3.25 (brs, 2H), 3.51 (brs, 2H), 4.13 (brs, 2H), 6.91 (m, 2H), 7.00 (m, 1H), 7.26 (d, J=8.4 Hz, 2H), 7.39 (d, J=8.4 Hz, 2H); δ_{C-13} (100 MHz, $CDCl_3$) δ: 12.6, 14.0, 25.0, 27.7, 28.2, 39.1, 42.9, 43.1, 44.4, 53.3, 79.1, 83.0, 125.8, 126.3, 127.2, 131.2, 135.3, 136.7, 142.9, 147.8, 154.5, 170.7.

EXAMPLE 1

Preparation of N,N-Diethyl-4-(phenyl-piperidin-4-ylidene-methyl)-benzamide (compound 6)

To a solution of 4-(α-hydroxyl-α-(4-N-t-butoxylcarbonylpiperidinyl)-benzyl)-N,N-diethylbenzamide (932 mg, 2.0 mmol) in dry dichloromethane (10 mL) was added trifluoroacetic acid (10.0 mL) at r.t. The reaction mixture was stirred for 16 h at r.t., and then condensed. The residue was dissolved in AcOEt (100 ml). The resulting solution was washed with 1 N NaOH solution, aqueous NH_4Cl solution and brine, dried over $MgSO_4$. Removal of solvents gave a crude product, which was purified by silica gel column eluting with MeOH-CH_2Cl_2 (20 : 80) to provide (α-phenyl-α-(4-N',N'-diethylaminocarbonylphenyl))-4-methylene-piperidine (compound 6), (632 mg, 91 %):

δ_H (400 MHz, $CDCl_3$) 1.08 (brs, 3H), 1.17 (brs, 3H), 2.29 (m, 4H), 2.86 (m, 4H), 2.94 (brs, 1H), 3.24 (brs, 2H), 3.47 (brs, 2H), 7.09 (m, 4H), 7.15 (m, 1H), 7.24 (m, 4H); δ_{C-13} (100 MHz, $CDCl_3$) δ: 12.6, 14.1, 32.7, 32.8, 39.1, 43.2, 47.9, 126.0, 126.4, 127.9, 129.6, 134.9, 135.4, 135.9, 141.7, 143.2, 171.1.

HCl salt: m.p. 110-120 ^{0}C(AcOEt-Ether-CH_2Cl_2);

ν_{max} (KBr) cm^{-1} 3440, 2970, 1617, 1438, 1289;

Anal.Calcd.for $C_{23}H_{28}N_2O$. 1.0 HCl. 0.50CH_2Cl_2. 0.25H_2O: C, 65.35; H, 7.12; N, 6.49. Found: C, 65.14; H, 7.08; N, 6.55.

EXAMPLE 2

Preparation of N,N-Diethyl-4-(1-naphtyl-piperidin-4-ylidene-methyl)-benzamide (compound 7)

Method as described for Example 1, using compound 4;(226 mg, 71 %):

m.p. 80-85 ^{0}C (MeOH-CH_2Cl_2);

ν_{max} (KBr) cm^{-1} 3052, 2970, 1628, 1431, 1286;

Anal.Calcd.for $C_{27}H_{30}N_2O$. $0.20CH_2Cl_2$: C, 78.62; H, 7.37; N, 6.74.

Found: C, 78.63; H, 7.07; N, 6.54; δ_H (400 MHz, $CDCl_3$) 1.06 (brs, 3H), 1.16 (brs, 3H), 2.00 (m, 2H), 2.53 (m, 2H), 2.64 (brs, NH), 2.77 (m, 2H), 2.97 (m, 2H), 3.20 (brs, 2H), 3.47 (brs, 2H), 7.26 (m, 5H), 7.43 (m, 3H), 7.74 (m, 2H), 8.0 (m, 1H); δ_{C-13} (100 MHz, $CDCl_3$) δ: 12.8, 14.1, 32.6, 33.5, 39.1, 43.2, 47.9, 48.2, 125.5, 125.7, 125.8, 126.1, 127.1, 127.2, 129.1, 131.9, 132.5, 133.8, 135.1, 138.3, 139.8, 142.6, 171.1

EXAMPLE 3

Preparation of N,N-Diethyl-4-(2,6-dimethylphenyl-piperidin-4-ylidene-methyl)-benzamide (compound 8)

Method as described for Example 1, using compound 5 (242 mg, 80 %).

Its HCl salt: Dec. ≥ 115 ^{0}C (AcOEt-Ether-CH_2Cl_2);

ν_{max} (KBr) cm^{-1} 2970, 2725, 1590, 1464, 1290, 1101;

Anal.Calcd.for $C_{25}H_{32}N_2O$. 1.0 HCl. $0.50CH_2Cl_2$. $0.5H_2O$: C, 65.94; H, 7.60; N, 6.03.

Found: C, 65.98; H, 7.37; N, 5.81.

EXAMPLE 4

Preparation of N,N-Diethyl-4-(1-naphtyl-N-allyl-piperidin-4-ylidene-methyl)-benzamide (compound 9)

A mixture of (α-(1-Naphthyl)-α-(4-N',N'-diethylaminocarbonylphenyl))-4-methylene-piperidine (compound 7) (125 mg), allyl bromide (90 mg) and K_2CO_3 (138 mg) in MeCN (10 mL) was stirred for 14 hr at r.t., and then quenched with 1 N NH_4OH solution, extracted with AcOEt (100 ml). The organic phase was washed with aqueous NH_4Cl solution and brine, dried over $MgSO_4$. Removal of solvents gave a crude product, which was purified by silica gel column eluting with MeOH-CH_2Cl_2 (2 : 98) to provide (α-(1-

naphthyl)-α-(4-N',N'-diethylaminocarbonylphenyl))-4-methylene-N-allylpiperidine (50 mg, 36 %):

δ_H (400 MHz, $CDCl_3$) 1.08 (brs, 3H), 1.19 (brs, 3H), 2.08 (m, 2H), 2.39 (m, 2H), 2.61 (m, 4H), 3.01 (m, 2H), 3.24 (brs, 2H), 3.52 (brs, 2H), 5.13 (m, 2H), 5.90 (m, 1H), 7.27 (m, 5H), 7.45 (m, 3H), 7.80 (m, 2H), 8.04 (m, 1H); δ_{C-13} (100 MHz, $CDCl_3$) δ: 12.8, 14.1, 30.9, 32.0, 39.1, 43.2, 54.7, 54.9, 61.5, 117.8, 125.4, 125.6, 125.8, 126.0, 127.1, 128.2, 129.1, 131.8, 132.4, 133.7, 135.0, 138.0, 139.8, 142.6, 171.1.

Its HCl salt: m.p. 110-120 ^{0}C (AcOEt-Ether-CH_2Cl_2);
ν_{max} (KBr) cm^{-1} 3416, 2961, 1620, 1430, 1288;
Anal.Calcd.for $C_{30}H_{34}N_2O$. 1.0 HCl. 0.50CH_2Cl_2. 0.25H_2O: C, 70.17; H, 7.05; N, 5.37.
Found: C, 70.15; H, 6.92; N, 5.24.

EXAMPLE 5

Preparation of N,N-Diethyl-4-(phenyl-N-benzyl-piperidin-4-ylidene-methyl)-benzamide (compound 10)

Method as described for Example 4, using compound 6 and benzyl bromide (215 mg, 98):

δ_H (400 MHz, $CDCl_3$) 1.09 (brs, 3H), 1.19 (brs, 3H), 2.37 (m, 4H), 2.47 (m, 4H), 3.25 (brs, 2H), 3.50 (brs, 4H), 7.0-7.30 (m, 14 H); δ_{C-13} (100 MHz, $CDCl_3$) δ: 12.7, 14.0, 31.6, 39.1, 43.1, 54.9, 55.0, 62.8, 125.9, 126.2, 126.8, 127.8, 128.0, 128.9, 129.6, 129.7, 134.9, 135.0, 136.3, 138.2, 141.9, 143.3, 171.0.

Its HCl salt: m.p. 230-245 ^{0}C (AcOEt-Ether-CH_2Cl_2);
ν_{max} (KBr) cm^{-1} 3423, 2976, 1624, 1434, 1288;
Anal.Calcd.for $C_{30}H_{34}N_2O$. 1.0 HCl. 0.25CH_2Cl_2. 0.25H_2O: C, 72.55; H, 7.25; N, 5.59.
Found: C, 72.38; H, 7.16; N, 5.50.

EXAMPLE 6

Preparation of N,N-Diethyl-4-(N-2,3-epoxypropyl-phenyl-piperidin-4-ylidene-methyl)-benzamide (compound 11)

Method as described for Example 4, using compound 6 and epibromohydrin (102 mg, 84 %):

δ_H (400 MHz, $CDCl_3$) 1.10 (brs, 3H), 1.20 (brs, 3H), 2.28 (m, 1H), 2.39 (m, 4H), 2.45 (m, 1H), 2.54 (m, 2H), 2.61 (m, 2H), 2.74 (m, 2H), 3.09 (m, 1H), 3.26 (brs, 2H), 3.50 (brs, 2H), 7.10 (m, 4H), 7.15 (m, 1H), 7.25 (m, 4H); δ_{C-13} (100 MHz, $CDCl_3$) δ: 12.8, 14.1, 31.4, 39.1, 43.2, 44.9, 50.1, 55.5, 60.8, 126.0, 126.4, 127.9, 129.6, 129.7, 135.0, 135.3, 135.7, 141.8, 143.2, 171.1.

EXAMPLE 7

Preparation of N,N-Diethyl-4-(1-cyclopropylmethyl-phenyl-piperidin-4-ylidene-methyl)-benzamide (compound 12)

Method as described for Example 4, using compound 6 and cyclopropylmethyl chloride (104 mg, 86 %):

δ_H (400 MHz, $CDCl_3$) 0.20 (m, 2H), 0.59 (m, 2H), 1.04 (m, 1H), 1.14 (brs, 3H), 1.24 (brs, 3H), 2.48 (d, J=6.4 Hz, 2H), 2.56 (brs, 4H), 2.80 (brs, 4H), 3.29 (brs, 2H), 3.53 (brs, 2H), 7.14 (m, 4H), 7.22 (m, 1H), 7.27 (m, 4H); δ_{C-13} (100 MHz, $CDCl_3$) δ: 4.18, 7.3, 12.8, 14.1, 30.3, 39.2, 43.2, 54.3, 62.7, 126.2, 126.6, 128.0, 129.5, 129.6, 134.1, 135.3, 136.3, 141.5, 142.9, 171.0.

Its HCl salt: Dec. ≥ 100 ^{0}C(AcOEt-Ether-CH_2Cl_2);

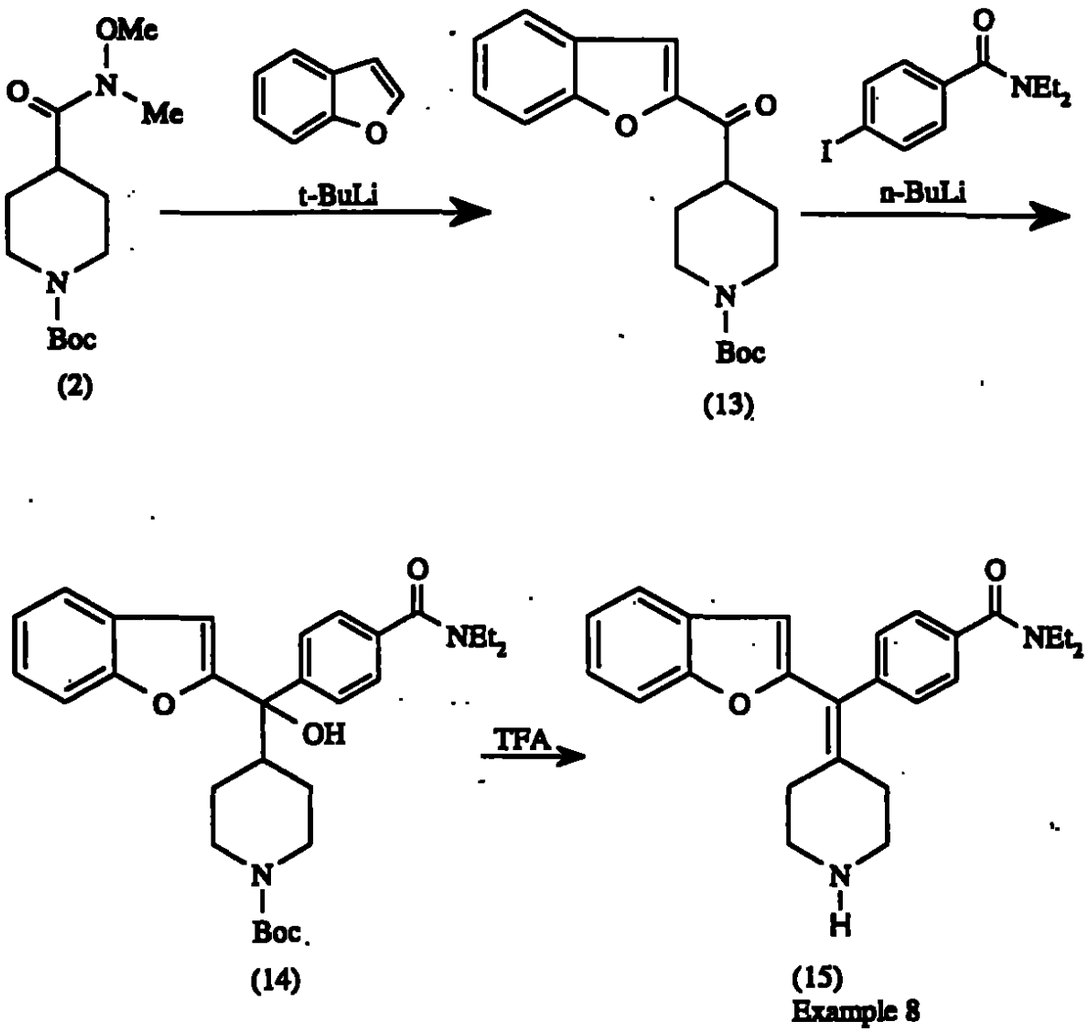
ν_{max} (KBr) cm^{-1} 3027, 2359, 1620, 1439, 958;

Anal.Calcd.for $C_{27}H_{34}N_2O$. 1.0 HCl. 0.50CH_2Cl_2. 0.75H_2O: C, 66.73; H, 7.64; N, 5.66. Found: C, 66.60; H, 7.45; N, 5.78.

B) Synthetic scheme for the preparation of the compound of Example 8

The compound of Example 8 was prepared by following the procedure as is shown in Scheme 2 below.

Scheme 2



(i) Preparation of 4-(2-Benzofuroyl)-N-t-butoxylcarbonylpiperidine (compound13)

To a solution of 2,3-benzofuran (295 mg, 2.5 mmol) in dry THF (10 mL) was added t-butyllithium (1.5 mL, 1.7 M, 2.5 mmol) at -78 ^{0}C. After 30 min, N-t-butoxylcarbonyl N-methyl-N-methoxyl-isonipecotamide (544 mg, 2.0 mmol) in THF (2 mL) was dropwise added. the reaction mixture was warmed to r.t. and then quenched with aqueous NH_4Cl solution, and extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$. Removal of solvents gave a crude product, which was purified by silica gel column eluting with MeOH-CH_2Cl_2 (5 : 95) to provide 4-(2-benzofuroyl)-N-t-butoxylcarbonylpiperidine (13) (456 mg, 69 %):

δ_H (400 MHz, $CDCl_3$) 1.46 (s, 9H), 1.75 (m, 2H), 1.91 (m, 2H), 2.91 (m, 2H), 3.37 (m, 1H), 4.20 (brs, 2H), 7.29 (m, 1H), 7.46 (m, 1H), 7.53 (s, 1H), 7.56 (m, 1H), 7.69 (m, 1H); δ_{C-13} (100 MHz, $CDCl_3$) δ: 27.8, 28.3, 43.1, 44.4, 79.5, 112.3, 112.9, 123.1, 123.8, 126.9, 128.2, 151.8, 154.5, 155.5, 192.8.

(ii) Preparation of 4-(α-Hydroxy-α-(4-N-t-butoxylcarbonylpiperidinyl)-2-benzofuryl)-N,N-diethylbenzamide (compound 14)

Method as described for compound 4, using 4-iodo-N,N-diethylbenzamide (425 mg, 61):

m.p. 102-106 ^{0}C (CH_2Cl_2);
ν_{max} (KBr) cm^{-1} 3362, 2970, 1690, 1617, 1425, 1288, 1160; δ_H (400 MHz, $CDCl_3$) 1.06 (brs, 3H), 1.20 (brs, 3H), 1.24 (m, 2H), 1.46 (m, 11 H), 2.42 (m, 1H), 2.58 (brs, 2H), 3.20 (brs, 2H), 3.50 (brs, 2H), 4.05 (brs, 2H), 4.37 (s, 1H), 6.70 (s, 1H), 7.16 (m, 2H), 7.23 (d, J=8.0 Hz, 2H), 7.41 (d, J=7.6 Hz, 1H), 7.47 (d, J=7.6 Hz, 1H), 7.58 (d, J=8.0 Hz, 2H); δ_{C-13} (100 MHz, $CDCl_3$) δ: 12.6, 13.9, 25.5, 26.3, 28.2, 39.0, 43.1, 44.9, 77.3, 79.0, 103.3, 110.9, 120.6, 122.5, 123.5, 125.6, 125.8, 127.9, 135.3, 144.0, 154.4, 154.5, 160.5, 170.9.

EXAMPLE 8

Preparation of N,N-Diethyl-4-(2-benzofuryl-piperidin-4-ylidene-methyl)-benzamide (compound 15)

Method as described for Example 1, using compound 14 (135 mg, 88 %):

δ_H (400 MHz, $CDCl_3$) 1.20 (brs, 3H), 1.24 (brs, 3H), 2.36 (brs, 2H), 3.00 (brs, 4H), 3.15 (brs, 2H), 3.33 (brs, 2H), 3.56 (brs, 2H), 4.45 (brs, 1H), 6.25 (s, 1H), 7.24 (m, 4H), 7.41 (m, 4H); δ_{C-13} (100 MHz, $CDCl_3$) δ: 12.9, 14.2, 29.6, 32.0, 32.4, 39.3, 43.4, 47.2, 107.4, 111.0, 120.7, 122.7, 124.2, 126.0, 126.5, 128.2, 129.9, 136.1, 139.5, 140.5, 154.4, 156.2, 171.0.

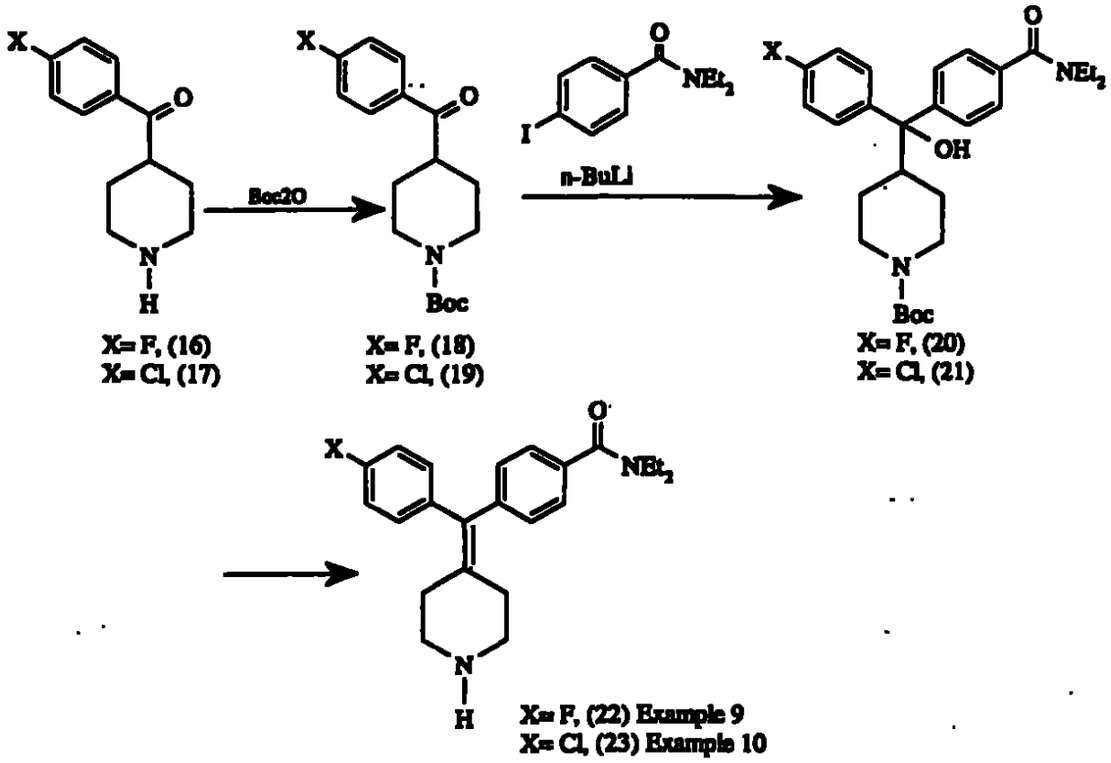
Its HCl salt: Dec. ≥ 120 ^{0}C(AcOEt-Ether-CH_2Cl_2);

ν_{max} (KBr) cm^{-1} 2977, 2801, 1586, 1449, 1257.

C) Synthetic scheme for the preparation of the compounds of Examples 9-10

The compounds of Examples 9 and 10 were prepared by following the procedure of Scheme 3 below.

Scheme 3



(i) Preparation of 4-(4-Fluorobenzoyl)-N-t-butoxylcarbonylpiperidine (compound 18)

A mixture of 4-(4-fluorobenzoyl)piperidine hydrochloride (compound 16) (2.44 g, 10.0 mmol), Di-tert-butyl dicarbonate (2.18 g, 10.0 mmol) and Na_2CO_3 (1.59 g, 15 mmol) in H2O-THF (50/5 mL) was refluxed for 1h. The reaction mixture was extracted with ethyl

acetate (2 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$. Removal of solvents gave 4-(4-fluorobenzoyl)-N-t-butoxylcarbonylpiperidine (OB 701-31, 2.28 g, 74 %);

m.p. 80-83 ^{0}C (CH_2Cl_2);
ν_{max} (KBr) cm^{-1} 2980, 2842, 1680, 1587, 1416, 1160;
δ_H (400 MHz, $CDCl_3$) 1.44 (s, 9H), 1.69 (m, 2H), 1.79 (m, 2H), 2.87 (m, 2H), 3.34 (m, 1H), 4.13 (brs, 2H), 7.12 (m, 2H), 7.95 (m, 2H); δ_{C-13} (100 MHz, $CDCl_3$) δ: 27.4, 28.4, 43.2, 43.4, 79.6, 115.8, 115.9, 130.8, 130.9, 132.2, 154.6, 164.4, 166.9, 200.4.

(ii) Preparation of 4-(4-Chlorobenzoyl)-N-t-butoxylcarbonylpiperidine (compound 19)

Method as described for compound 18, using compound 17 (1.23 g, 85 %):

m.p. 122-125 ^{0}C (CH_2Cl_2);
ν_{max} (KBr) cm^{-1} 2970, 2842, 1680, 1582, 1420, 1200;
δ_H (400 MHz, $CDCl_3$) 1.47(s, 9H), 1.69 (m, 2H), 1.81 (m, 2H), 2.90 (m, 2H), 3.36 (m, 1H), 4.18 (brs, 2H), 7.44 (m, 2H), 7.88 (m, 2H); δ_{C-13} (100 MHz, $CDCl_3$) δ: 28.3, 28.4, 43.2, 43.4, 79.6, 129.0, 129.6, 134.1, 139.4, 154.6, 200.7.

(iii) Preparation of 4-(α-Hydroxy-α-(4-N-t-butoxylcarbonylpiperidinyl)-4-fluorobenzyl)-N,N-diethylbenzamide (compound 20)

Method as described for compound 4, using compound 18 and 4-iodo-N,N-diethylbenzamide (454 mg, 47 %):

m.p. 84-86 ^{0}C (CH_2Cl_2);
ν_{max} (KBr) cm^{-1} 3421, 2970, 1685, 1612, 1430, 1288, 1165;
δ_H (400 MHz, $CDCl_3$) 1.13 (brs, 3H), 1.23 (brs, 3H), 1.32 (m, 4H), 1.44 (s, 9H), 2.48 (m, 1H), 2.68 (brs, 2H), 3.26 (brs, 2H), 3.54 (brs, 2H), 3.57 (s, 1H), 4.11 (brs, 2H), 6.96 (m,

2H), 7.27 (d, J=8.0 Hz, 2H), 7.44 (m, 2H), 7.47 (d, J=8.0 Hz, 2H); δ_{C-13} (100 MHz, $CDCl_3$) δ: 12.9, 14.0, 26.2, 28.2, 39.1, 43.2, 43.6, 44.3, 78.9, 79.1, 114.5, 114.7, 125.7, 126.1, 127.5, 127.6, 135.0, 141.2, 146.9, 154.5, 160.0, 162.5, 170.9.

(iv) Preparation of 4-(α-Hydroxy-α-(4-N-t-butoxylcarbonylpiperidinyl)-4-chlorobenzyl)-N,N-diethylbenzamide (compound 21)

Method as described for compound 4, using compound 19 and 4-iodo-N,N-diethylbenzamide (626 mg, 63 %):

m.p. 100-105 ^{0}C (CH_2Cl_2);
ν_{max} (KBr) cm^{-1} 3411, 2970, 1685, 1617, 1425, 1288, 1165, 1092;
δ_H (400 MHz, $CDCl_3$) 1.08 (brs, 3H), 1.20 (brs, 3H), 1.33 (m, 4H), 1.41 (s, 9H), 2.44 (m, 1H), 2.63 (brs, 2H), 3.22 (brs, 2H), 3.49 (brs, 2H), 3.99 (s, 1H), 4.05 (m, 2H), 7.20 (m, 4H), 7.39 (d, J=8.0 Hz, 2H), 7.44 (d, J=8.0 Hz, 2H); δ_{C-13} (100 MHz, $CDCl_3$) δ: 12.5, 13.9, 25.9, 28.1, 39.0, 43.0, 44.1, 78.7, 79.0, 125.6, 126.0, 127.2, 127.8, 131.9, 134.8, 144.1, 146.6, 154.3, 170.7.

EXAMPLE 9

Preparation of N,N-Diethyl-4-(4-fluorophenyl-piperidin-4-ylidene-methyl)-benzamide (compound 22)

Method as described for Example 1 (compound 6), using compound 20.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.12 (3 H, br m, CH_3CH_2-), 1.24 (3 H, br m, CH_3CH_2-), 2.32 (4 H, m, piperidine CH-), 2.54 (1 H, br m, NH), 2.91 (4 H, m. piperidine CH-), 3.27 (2 H, br m, CH_2N-), 3.52 (2 H, br m, CH_2N-), 7.00 (2 H, m, ArH), 7.09 (2 H, m, ArH), 7.11 (2 H, d, J = 8.0 Hz, ArH), 7.29 (2 H, d, J = 8.0 Hz, ArH).

EXAMPLE 10

Preparation of N,N-Diethyl-4-(4-chlorophenyl-piperidin-4-ylidene-methyl)-benzamide (compound 23)

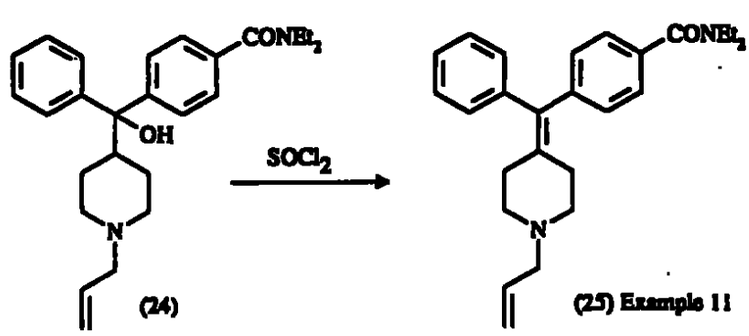
Method as described for Example 1 (compound 6), using compound 21.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.13 (3 H, br m, CH_3CH_2-), 1.22 (3 H, br m, CH_3CH_2-), 2.02 (1 H, br m, NH), 2.30 (4 H, m, piperidine CH-), 2.90 (4 H, m, piperidine CH-), 3.28 (2 H, br m, CH_2N-), 3.53 (2 H, br m, CH_2N-), 7.04 (2 H, d, J = 8.0 Hz, ArH), 7.11 (2 H, d, J = 8.0 Hz, ArH), 7.25 (2 H, d, J = 8.0 Hz, ArH), 7.30 (2 H, d, J = 8.0 Hz, ArH).

Its HCl salt: m.p. 115-120°C (H_2O-CH_2Cl_2);
IR (KBr) 3337, 2973, 1618, 1431, 1290, 1092 cm^{-1};
Anal. Calcd. for $C_{23}H_{27}ClN_2O.1.0HCl.1.20H_2O$: C, 62.64%; H, 6.95%; N, 6.35%;
Found: C, 62.53%; H, 6.91%; N, 6.30%.

D) Synthetic scheme for the preparation of the compound of Example 11

Scheme 4



(24) (25) Example 11

EXAMPLE 11

Preparation of N,N-Diethyl-4-(phenyl-N-allyl-piperidin-4-ylidene-methyl)-benzamide (compound 25)

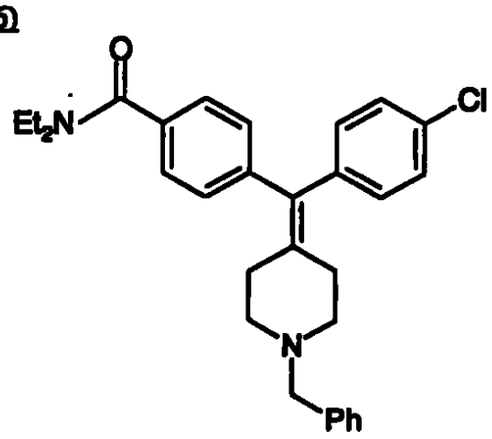
4-(α-hydroxy-α-(4-N-allylpiperidinyl)-benzyl)-N,N-diethylbenzamide (compound 24) (81mg) was dissolved in CH_2Cl_2 (10 ml) and was treated with thionyl chloride (2 ml) at r.t. The reaction mixture was refluxed for 2 hrs, and then condensed. The residue was dissolved in ethyl acetate (50 mL) and the resulting solution was washed with NH_4OH (1 N), aqueous NH_4Cl solution and brine, dried over $MgSO_4$. Removal of solvents gave a crude product, which was purified by silica gel column eluting with MeOH-CH_2Cl_2 (1 : 99 → 5 : 95) to provide (α-phenyl-α-(4-N',N'-diethylaminocarbonylphenyl))-4-methylene-N-allylpiperidine (compound 25; Example 11)
(32 mg, 40 %):

δ_H (400 MHz, $CDCl_3$) 1.12 (brs, 3H), 1.21 (brs, 3H), 2.43 (m, 4H), 2.55 (m, 4H), 3.08 (d, J=6.8 Hz, 2H), 3.25 (brs, 2H), 3.53 (brs, 2H), 5.18 (m, 2H), 5.86 (m, 1H), 7.12 (m, 4H), 7.20 (m, 1H), 7.27 (m, 4H).

Its HCl salt: m.p. 85-95 ^{0}C (AcOEt-CH_2Cl_2);
ν_{max} (KBr) cm^{-1} 3491, 2971, 1624, 1428, 1289, 1096;
Anal.Calcd.for $C_{26}H_{32}N_2O.HCl$. 0.25 H_2O . 0.25CH_2Cl_2: C, 69.95; H, 7.60; N, 6.21.
Found: C, 70.00; H, 7.73; N, 6.07.

EXAMPLE 12

Preparation of N,N-Diethyl-4-(4-chlorophenyl-N-benzyl-piperidin-4-ylidene-methyl)-benzamide (compound 26)



(26)

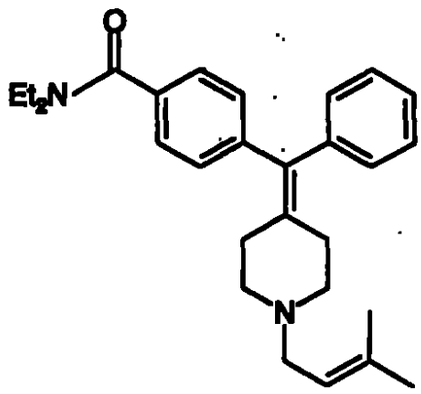
Method as described for Example 4, using compound 23 (96 mg) and benzyl bromide (43 mg) provided N,N-diethyl-4-(4-chlorophenyl-N-benzyl-piperidin-4-ylidene-methyl)-benzamide (110 mg, 93%):

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.13 (3 H, br m, CH_3CH_2-), 1.23 (3 H, br m, CH_3CH_2-), 2.37 (4 H, m, piperidine CH-), 2.49 (4 H, m, piperidine CH-), 3.28 (2 H, br m, CH_3CH_2N-), 3.53 (4 H, br m, $PhCH_2N$ and CH_3CH_2N-), 7.04 (2 H, d, J = 8.0 Hz, ArH), 7.11 (2 H, d, J = 8.0 Hz, ArH), 7.25 (2 H, d, J = 8.0 Hz, ArH), 7.29 (7 H, m, ArH).

Its $(CHOHCO_2H)_2$ salt: m.p. 100-110 ^{0}C (MeOH);
IR (KBr) 3368, 2977, 1728, 1603, 1433, 1290, 1087 cm^{-1};
Anal.Calcd.for $C_{34}H_{39}ClN_2O_7.1.50H_2O$: C, 62.81%; H, 6.51%; N, 4.31%;
Found: C, 62.85%; H, 6.17%; N, 4.21%.

EXAMPLE 13

Preparation of N,N-Diethyl-4-[(N-3-methyl-2-butenyl)-phenyl-piperidin-4-ylidene-methyl]-benzamide (compound 27)



(27)

Method as described for example 4, using 1-Bromo-3-methyl-2-butene as the alkylating reagent.

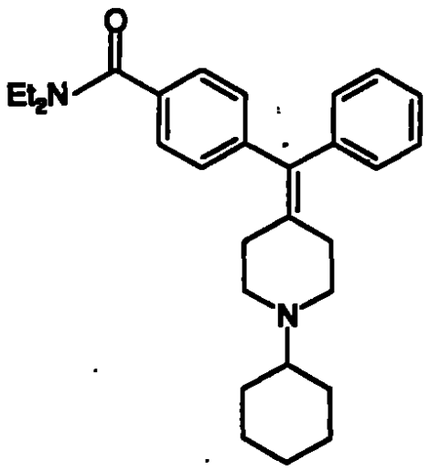
IR (NaCl Film): HCl salt ν =3432, 2976, 1623, 1434, cm^{-1}.

^1H NMR: (Base) ($CDCl_3$, TMS) δ: 1.10–1.30 (6H, br, $OCNCH_2CH_3$), 1.64 (3H, s, $=CCH_3$), 1.73 (3H, s, $=CCH_3$), 2.40 (4H, m, NCH_2CH_2), 2.52 (4H, m, $=CCH_2$), 3.0 (2H, d, J=7.6Hz, $NCH_2CH=C$), 3.20–3.60 (4H, br, $OCNCH_2CH_3$),. 5.28 (1H, m, $NCH_2CH=C$), 7.16–7.45(9H, m, Ar)ppm.

ANALYSIS: (%) *Anal.* Calcd.for:: $C_{28}H_{36}N_2O$. 1.8HCl: C, 69.74; H, 7.90; N, 5.81. Found: C, 69.71; H, 7.48; N, 5.58.

EXAMPLE 14

Preparation of N,N-diethyl-4-[(1-Cyclohexyl-piperidin-4-ylidene)-phenyl-methyl]-benzamide (compound 28)



(28)

A mixture of compound 6 (100 mg, 0.29 mmol), cyclohexanone (36 ul, 0.35 mmol) and $Ti(OPr\text{-}i)_4$ (0.17 ml, 0.58 mmol) was ultrasonicated for 1 hr and then stirred at rt overnight under a nitrogen atmosphere. The mixture was diluted with ethanol (5 ml) and followed by addition of $NaBH_4$ (33 mg, .87 mmol). The resulting mixture was stirred for 12 hr at rt. 2N $NH_3.H_2O$ was added to quench the reaction and the mixture filtered through celite. The filtrate was extracted with ethyl acetate several times and the combined organic phases washed with water and brine, and dried over Na_2SO_4. Concentration in vacuo and MPLC purification (0::100 to 100:0 EtOAc:Heptane eluting on silcal gel 60) gave the title compound (24 mg, 20%).

m.p. (HCl salt): 105-109 °C

IR (HCl salt, film) ν: 3394 (NH), 1620 ($CONEt_2$)cm^{-1}.

^1H NMR (free amine, 400 MHz, $CDCl_3$) δ: 1.00-1.25 (17H, m, NCH$\underline{CH_2CH_2CH_2CH_2CH_2}$, 2x$\underline{CH_3}$ and $\underline{CH}$(CH)C=C), 1.60 (1H, m, $\underline{CH}$(CH)C=C), 1.75 (1H, m, $\underline{CH}$(CH)C=C), 1.80

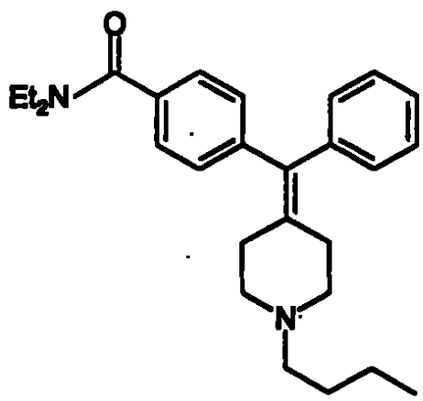
(1H, m, CH(CH)C=C), 2.30 (3H, m, NCH$_2$ and NCH), 2.60 (2H, m, NCH$_2$), 3.20 (2H, bs, NCH$_2$CH$_3$), 3.50 (2H, bs, NCH$_2$CH$_3$), 7.00-7.30 (9H, m, Ar).

^{13}C NMR (free amine, 100 MHz, $CDCl_3$) δ: 12.7, 14.1, 25.9, 28.7, 32.0, 39.1, 43.2, 50.7, 50.8, 63.6, 126.0, 126.3, 127.9, 129.7, 129.8, 134.7, 134.9, 136.9, 142.0, 143.4, 171.2.

Elemental analysis: Calcd.for $C_{29}H_{40}N_2OCl_2$: C, 69.17; H, 8.01; N, 5.56. Found: C, 69.17; H, 7.82; N, 5.18.

EXAMPLE 15

Preparation of N,N-Diethyl-4-[(N-butyl)-phenyl-piperidin-4-ylidene-methyl]-benzamide (compound 29)



(29)

Method as described for Example 4, using 1-Iodobutane as the alkylating reagent.

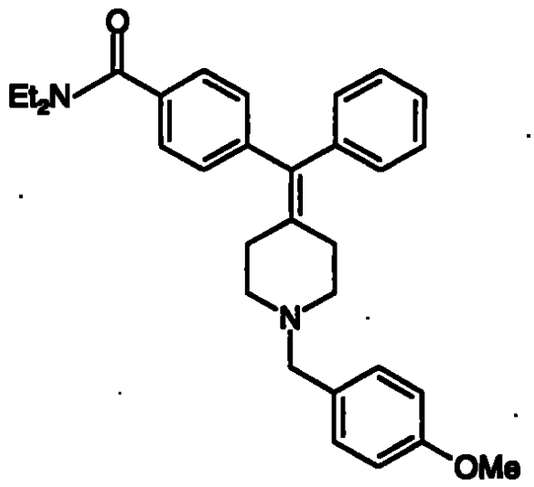
IR (NaCl Film):(HCl salt) ν =3430, 2967, 2499, 1622, 1433cm^{-1}

^{1}H NMR: ($CDCl_3$, TMS) δ: 0.92 (3H, t, *J*=7.2Hz, CH_2CH_3), 1.10–1.26 (6H, br, OCNCH$_2$CH$_3$), 1.32 (2H, m, CH2CH3), 1.53 (2H, m, CH2CH2CH2), 2.42 (6H, m, NCH2), 2.55 (4H, m, =CCH2), 3.20–3.60 (4H, br, OCNCH$_2$CH$_3$), 7.10–7.31 (9H, m,

Ar)ppm. ANALYSIS: (%) *Anal.*Calcd.for : $C_{27}H_{36}N_2O \bullet HCl \bullet 0.4CH_2Cl_2 \bullet 0.4H_2O$: C, 68.24; H, 8.07; N, 5.81. Found: C, 68.24; H, 8.12; N, 5.89.

EXAMPLE 16

Preparation of N,N-Diethyl-4-[(N-4-methoxybenzyl)-phenyl-piperidin-4-ylidene-methyl]-benzamide (compound 30)



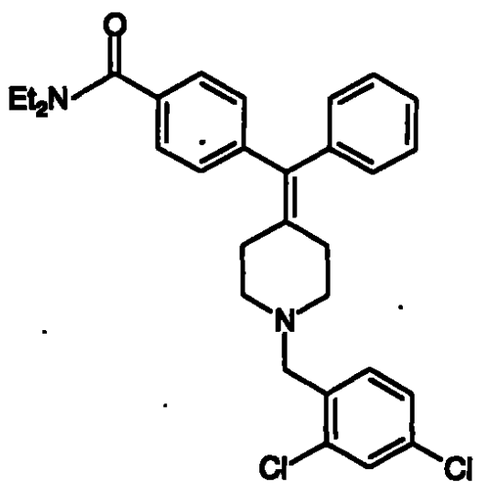
Method as described for Example 4, using compound 6 (174 mg) and 4-methoxybenzyl chloride (78 mg) provided N,N-diethyl-4-[(N-4-methoxybenzyl)-phenyl-piperidin-4-ylidene-methyl]-benzamide (160 mg, 68 %):

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.11 (3 H, br, CH_3CH_2N-), 1.20 (3 H, br, CH_3CH_2N-), 2.38 (4 H, m, CCH_2C), 2.46 (4 H, m, NCH_2-), 3.26 (2 H, m, NCH_2-), 3.47 (2H, s, CH_2N-), 3.49 (2 H, br, CH_3CH_2N-), 3.77 (3H, s, OCH_3), 6.83 (2H, d, J = 8.0 Hz, ArH), 7.05-7.30 (11 H, m, ArH).

Its HCl salt: m.p. 100-110 ^{0}C (CH_2Cl_2);
IR (KBr) 3425, 2974, 1618, 1515, 1434, 1255 cm^{-1};
Anal.Calcd.for $C_{31}H_{36}N_2O_2.1.0HCl\ 0.35CH_2Cl_2$: C, 70.41%; H, 7.11%; N, 5.24%;
Found: C, 70.46%; H, 7.10%; N, 5.21 .

EXAMPLE 17

Preparation of N,N-Diethyl-4-[(N-2,4-dichlorobenzyl)-phenyl-piperidin-4-ylidene-methyl]-benzamide (compound 31)



(31)

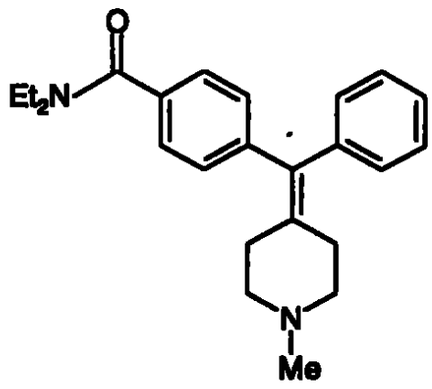
Method as described for Example 4, using compound 6 (174 mg) and α,2,4-trichlorotoluene(98 mg) provided N,N-diethyl-4-[(N-2,4-dichlorobenzyl)-phenyl-piperidin-4-ylidene-methyl]-benzamide (206 mg, 81 %):

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.12 (3 H, br, CH_3CH_2N-), 1.21 (3 H, br, CH_3CH_2N-), 2.39 (4 H, m, CCH_2C), 2.52 (4 H, m, NCH_2-), 3.28 (2 H, m, NCH_2-), 3.53 (2 H, br, CH_3CH_2N-), 3.57 (2 H, m, NCH_2-), 7.05-7.48 (12 H, m, ArH).

Its HCl salt: m.p. 95-110 ^{0}C (CH_2Cl_2);
IR (KBr) 3408, 2976, 1620, 1472, 1436, 1288, 1101 cm^{-1};
Anal.Calcd.for $C_{30}H_{32}N_2OCl_2.1.0HCl\ 0.30CH_2Cl_2$: C, 63.91%; H, 5.95%; N, 4.92%;
Found: C, 63.81%; H, 6.03%; N, 4.84%.

EXAMPLE 18

Preparation of N,N-Diethyl-4-[(1-methyl-piperidin-4-ylidene)-phenyl-methyl]-benzamide (compound 32)



(32)

N,N-Diethyl-4-[(piperidin-4-ylidene)-phenyl-methyl]-benzamide (0.34g, 1.0mmol) was disolved in acetonitrile (5mL). Potassium carbonate (0.14g, 1.0mmol) and methyl iodide (63µL, 1.0mmol) was added with stirring at 25 °C. After 30 min., the reaction mixture was evaporated and put onto silica gel for purification by chromatography using 0 to 10% MeOH(10% NH_4OH) in CH_2Cl_2 to give 48 mg of the final product (28% of converted starting material), which was converted to the hydrochloride salt by treatment with HCl in ether.

Mp: 110 °C (dec.).

IR (KBr) (cm-1): 2361, 1695, 1487, 1289.

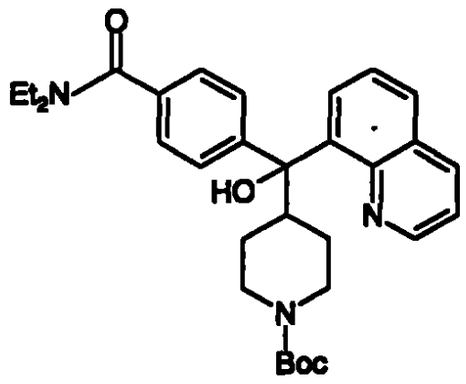
MS(free amine): 362, 318, 219, 189, 165, 144.

^1H NMR: (amine, $CDCl_3$): δ = 1.1(m, 6H, amide-Me), 2.40 (s, 3H, MeN), 2.49, 2.60 (2m, 8H, piperazine-H), 3.40 (m, 4H, amide-CH_2) 7.08 -7.34 (m, 9H, Ar-H). $C_{24}H_{30}N_2O$ x0.1 H_2O x3.1 HCl, requires: C:60.39, H:7.03 , N:5.87.

Found C:60.43, H:6.84, N:5.45.

EXAMPLE 19

Preparation of N,N-Diethyl-4-[(N-tert-butoxycarbonyl-piperidin-4-yl)-8-quinolinyl-hydroxy-methyl]-benzamide (compound 33)



(33)

To a solution of 4-iodo-N,N-diethylbenzamide (1.52 g, 5.0 mmol) and 8-bromoquinoline (1.0 g) in dry THF (30 mL) was added n-butyllithium (7.0 mL, 2.5 M, 17.5 mmol) at -78 °C. After 10 min, N-t-butoxylcarbonyl ethyl isonipecotate (2) (0.77 g, 3.0 mmol) in THF (5 mL) was dropwise added. The reaction mixture was warmed to °C, and then quenched with aqueous NH_4Cl solution, and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$. Removal of solvents gave a crude product, which was purified by silica gel column eluting with MeOH-CH_2Cl_2 (2 : 98) to MTL 0599 (145 mg, 9 %):

m.p. 100-105 °C;

IR (NaCl) 2971, 1686, 1625, 1426, 1167 cm^{-1};

Anal.Calcd.for $C_{31}H_{39}N_3O_4.0.20H_2O$: C, 71.43 %; H, 7.62 %.

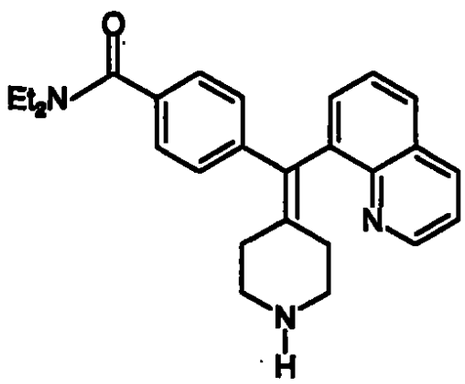
Found: C, 71.50 %; H, 7.75 %; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.07 (3 H, br, CH_3CH_2N-), 1.19 (3 H, br, CH_3CH_2N-), 1.24 (1 H, m, piperidine CH-), 1.43 (9 H, s, CH_3C), 1.65 (1 H, m, piperidine CH-), 1.89 (2 H, m, piperidine CH-), 2.52 (1 H, m, piperidine CH-), 2.64 (1 H, br, piperidine CH-), 2.78

(1 H, br, piperidine CH-), 3.22 (2 H, br, CH_3CH_2N-), 3.49 (2 H, br, CH_3CH_2N-), 4.16 (2 H, br, piperidine CH-), 7.24 (2 H, d, J = 8.0 Hz, ArH), 7.35 (1 H, dd, J = 8.0, 4.4 Hz, ArH), 7.55 (2 H, d,

J = 8.0 Hz, ArH), 7.58 (1 H, d, J = 8.0 Hz, ArH), 7.71 (1 H, d, J = 8.0 Hz, ArH), 7.80 (1 H, d, J = 8.0 Hz, ArH), 8.14 (1 H, d, J = 8.0 Hz, ArH), 8.69 (1 H, m, ArH), 9.80 (1H, s, OH).

EXAMPLE 20

Preparation of N,N-Diethyl-4-(8-quinolinyl-piperidin-4-ylidene-methyl)-benzamide (compound 34)



(34)

A mixture of the compound of Example 19 (45 mg), trifluoroacetic acid (1.0 mL) and trifluoromethanesulforic acid (1 mL) was refluxed for 8 hrs., and then condensed. The residue was dissolved in AcOEt (50 ml). The resulting solution was washed with 1 N NaOH solution, aqueous NH_4Cl solution and brine, dried over Na_2SO_4. Removal of solvents gave a crude product, which was purified by silica gel column eluting with NH_4OH (1N)-MeOH-CH_2Cl_2 (2.5 : 17.5 : 80) to provide N,N-diethyl-4-(8-quinolinyl-piperidin-4-ylidene-methyl)-benzamide (29 mg, 84 %):

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.07 (3 H, br m, CH_3CH_2-), 1.20 (3 H, br m, CH_3CH_2-), 2.00 (2 H, m, piperidine CH-), 2.46 (1H, s, NH), 2.52 (2 H, m, piperidine CH-), 2.75 (1H, m, piperidine CH-), 2.92 (2 H, m, piperidine CH-), 3.05 (1 H, m, piperidine CH-), 3.22 (2 H, m, CH_2N-), 3.49 (2 H, m, CH_2N-), 7.23 (2 H, m, ArH), 7.32 (2 H, m, ArH), 7.36 (1 H, m, ArH), 7.49 (2 H, m, ArH), 7.72 (1 H, dd, J = 6.4, 3.2 Hz, ArH), 8.11 (1 H, dd, J = 8.4, 1.6 Hz, ArH), 8.91 (1 H, dd, J = 4.0, 1.6 Hz, ArH).

Its HCl salt: m.p. > 170 °C (Dec.);

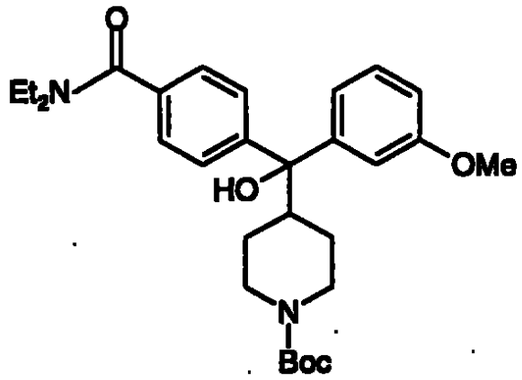
IR (KBr) 3410, 2973, 1614, 1551, 1436, 1284 cm^{-1};

Anal.Calcd.for $C_{26}H_{29}N_3O$. 2.0 HCl. 0.50 CH_2Cl_2. 0.75 H_2O: C, 60.23 %; H, 6.39 %;

Found: C, 60.27 %; H, 6.42 %.

EXAMPLE 21

Preparation of N,N-Diethyl-4-[(N-tert-butoxycarbonyl-piperidin-4-yl)-3-methoxyphenyl-hydroxy-methyl]-benzamide (compound 35)



(35)

Method as for Example 19 using 3-bromoanisole provided the title compound (226 mg, 23 %):

m.p. 95-103 °C;

IR (NaCl) 3422, 2973, 1684, 1614, 1429, 1289 cm^{-1};

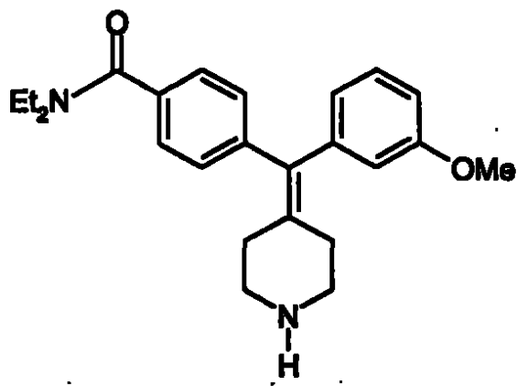
Anal.Calcd.for $C_{29}H_{40}N_2O_5$.0.60H_2O: C, 68.64 %; H, 8.18 %; N, 5.52 %.

Found: C, 68.66 %; H, 7.98 %; N, 5.64 %; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.07 (3 H, br, CH_3CH_2N-), 1.19 (3 H, br, CH_3CH_2N-), 1.31 (4 H, m, piperidine CH-), 1.41 (9 H, s, CH_3C), 2.46 (1 H, m, piperidine CH-), 2.64 (2 H, br, piperidine CH-), 3.22 (2 H, br, CH_3CH_2N-), 3.49 (2 H, br, CH_3CH_2N-), 3.65 (1H, s, OH), 3.72 (3H, s, OCH_3), 4.06 (2 H, br, piperidine CH-), 6.69 (1 H, m,

ArH), 7.01 (1H, d, J = 7.6 Hz, ArH), 7.08 (1 H, s, ArH), 7.17 (1H, d, J = 8.0 Hz, ArH), 7.21 (2 H, d, J = 8.0 Hz, ArH), 7.48 (2 H, d, J = 8.0 Hz, ArH).

EXAMPLE 22

Preparation of N,N-Diethyl-4-(3-methoxyphenyl-piperidin-4-ylidene-methyl)-benzamide (compound 36)



(36)

Method as described for Example 1, using the compound of Example 21 (100 mg) provided N,N-diethyl-4-(3-methoxyphenyl-piperidin-4-ylidene-methyl)-benzamide (75 mg, 98 %):

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.12 (3 H, br, CH_3CH_2N-), 1.23 (3 H, br, CH_3CH_2N-), 2.34 (4 H, m, piperidine CH-), 2.91 (4 H, br, piperidine CH-), 3.17 (1H, s, NH), 3.27 (2 H, br, CH_3CH_2N-), 3.52 (2 H, br, CH_3CH_2N-), 3.76 (3H, s, OCH_3), 6.64 (1 H, s, ArH), 6.70 (1H, d, J = 8.0 Hz, ArH), 6.76 (1H, d, J = 7.6 Hz, ArH), 7.15 (2 H, d, J = 8.0 Hz, ArH), 7.22 (1H, m, ArH), 7.29 (2 H, d, J = 8.0 Hz, ArH).

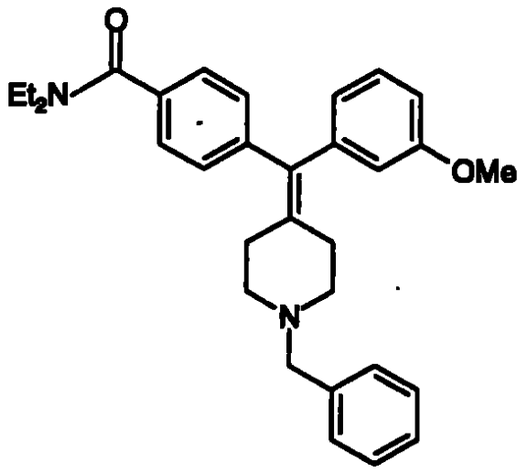
Its HCl salt: m.p. > 90 °C (Dec); IR (NaCl) 2970, 1621, 1430, 1287 cm^{-1};

Anal.Calcd.for $C_{24}H_{30}N_2O_2.HCl.1.70H_2O$: C, 64.69 %; H, 7.78 %; N, 6.29 %;

Found: C, 64.82 %; H, 7.60 %; N, 6.08 %.

EXAMPLE 23

Preparation of N,N-Diethyl-4-[(N-benzyl)-3-methoxyphenyl-piperidin-4-ylidene-methyl]-benzamide (compound 37)



(37)

Method as for Example 4, using the compound of Example 22 (38 mg) provided N,N-diethyl-4-[(N-benzyl)-3-methoxyphenyl-piperidin-4-ylidene-methyl]-benzamide (46 mg, 98 %):

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.12 (3 H, br, CH_3CH_2N-), 1.25 (3 H, br, CH_3CH_2N-), 2.38 (4 H, m, piperidine CH_2-), 2.48 (4 H, br, piperidine CH_2-), 3.27 (2 H, br, CH_3CH_2N-), 3.52 (2H, s, Ph CH_2N), 3.53 (2 H, br, CH_3CH_2N-), 3.75 (3H, s, OCH_3), 6.65 (1 H, s, ArH), 6.69 (1H, d, J = 8.0 Hz, ArH), 6.74 (1H, d, J = 7.6 Hz, ArH), 7.13 (2 H, d, J = 8.0 Hz, ArH), 7.13-7.32 (8H, m, ArH).

Its HCl salt: m.p. 100-110 ^{0}C (CH_2Cl_2);

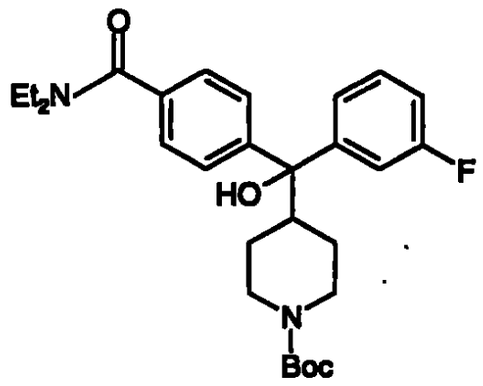
IR (NaCl) 3421, 2972, 1619, 1430, 1287 cm^{-1};

Anal.Calcd.for $C_{31}H_{36}N_2O_2.HCl.0.40CH_2Cl_2$: C, 69.96 %; H, 7.07 %; N, 5.20 %;

Found: C, 69.94 %; H, 7.06 %; N, 5.15 %.

EXAMPLE 24

Preparation of N,N-Diethyl-4-[(N-tert-butoxycarbonyl-piperidin-4-yl)-3-fluorophenyl-hydroxy-methyl]-benzamide (compound 38)



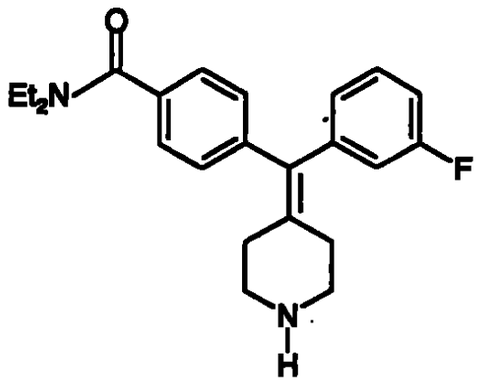
(38)

Method as for Example 19 using 3-bromofluorobenzene provided the title compound (257 mg, 27 %):

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.03 (3 H, br, CH_3CH_2N-), 1.15 (3 H, br, CH_3CH_2N-), 1.19-1.29 (4 H, m, piperidine CH-), 1.35 (9 H, s, CH_3C), 2.39 (1 H, m, piperidine CH-), 2.59 (2 H, br, piperidine CH-), 3.17 (2 H, br, CH_3CH_2N-), 3.28 (1H, s, OH), 3.45 (2 H, br, CH_3CH_2N-), 4.02 (2 H, br, piperidine CH-), 6.80 (1 H, m, ArH), 7.15 (3 H, m, ArH), 7.18 (2H, d, J = 8.0 Hz, ArH), 7.39 (2 H, d, J = 8.0 Hz, ArH).

EXAMPLE 25

Preparation of N,N-Diethyl-4-(3-fluorophenyl-piperidin-4-ylidene-methyl)-benzamide (compound 39)



(39)

Method as for Example 20 using the compound of Example 24 (165 mg) provided N,N-Diethyl-4-(3-fluorophenyl-piperidin-4-ylidene-methyl)-benzamide (108 mg, 87 %):

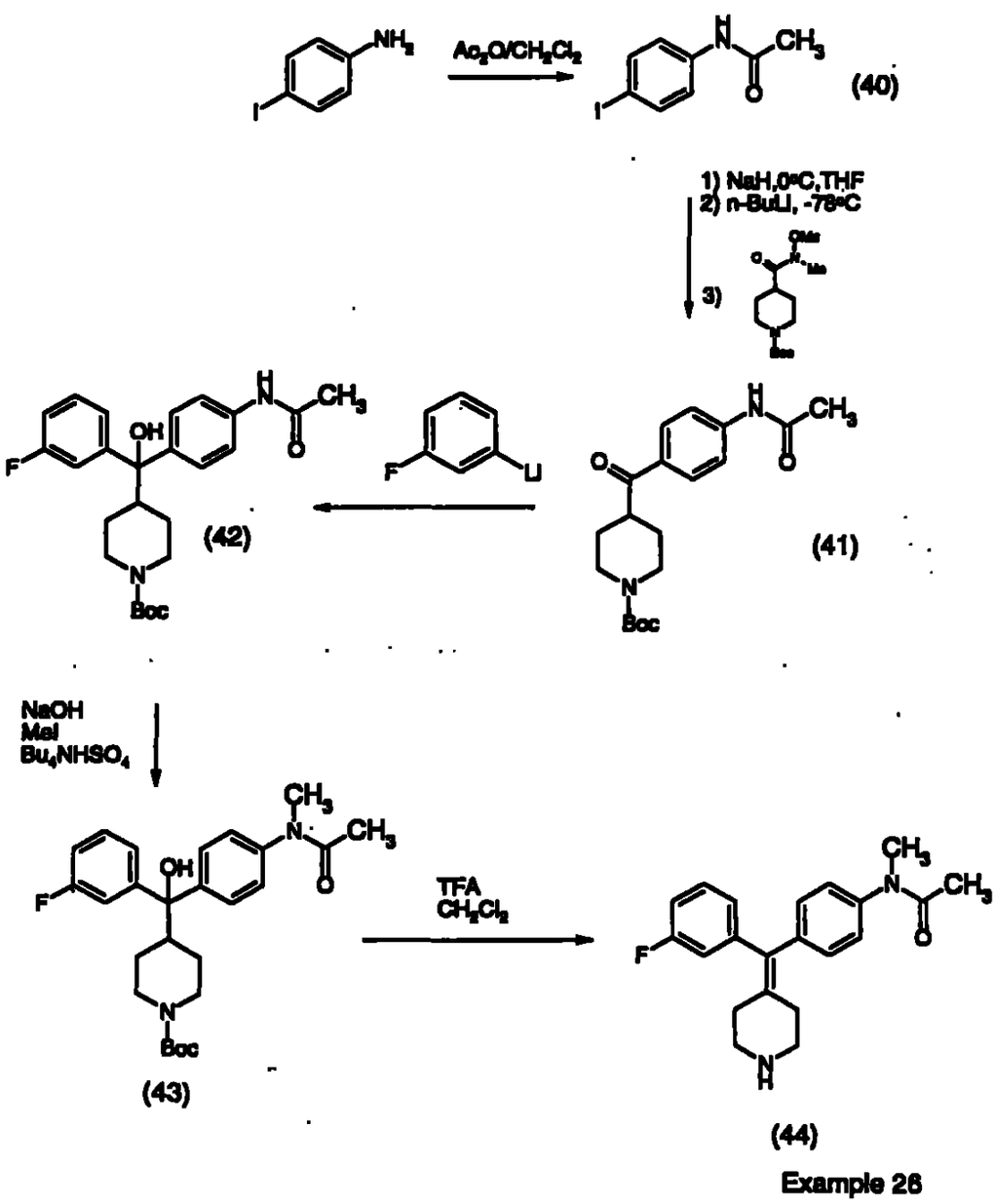
^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.08 (3 H, br, CH_3CH_2N-), 1.19 (3 H, br, CH_3CH_2N-), 2.09 (1H, s, NH), 2.25 (4 H, m, piperidine CH-), 2.84 (4 H, br, piperidine CH-), 3.23 (2 H, br, CH_3CH_2N-), 3.47 (2 H, br, CH_3CH_2N-), 6.74 (1 H, m, ArH), 6.86 (2H, m, ArH), 7.06 (2 H, d, J = 8.0 Hz, ArH), 7.18 (1H, m, ArH), 7.24 (2 H, d, J = 8.0 Hz, ArH).

Its HCl salt: m.p. > 70 °C (Dec.);
IR (NaCl) 2978, 1605, 1478, 1432, 1290 cm^{-1};
Anal.Calcd.for $C_{23}H_{27}N_2OF.HCl.0.25\ CH_2Cl_2.1.50\ H_2O$: C, 61.89 %; H, 7.04 %; N, 6.21 %;
Found: C, 61.97 %; H, 6.95 %; N, 6.22 %.

B) Synthetic Scheme for the preparation of the compound of Example 26

The compound of Example 26 was prepared by following the procedure as is shown in Scheme 5 below.

Scheme 5



Example 26

(i) Preparation of Preparation of 4'-Iodo-acetanilide (compound 40)

To a solution of 4-Iodo-aniline (15 g, 69 mmol) in dry CH_2Cl_2 (100 ml) was added acetic anhydride(14.09 g, 138 mmol) at room temperature, the reaction mixture was then stirred for 2 hr. The gray color precipitate formed during the reaction was filtered, washed with ether and collected, the mother solution was concentrated to dryness and AcOEt was added, the resulting precipitate was filtered, washed with ether and combined with the previous solid as the desired product (15.95 g, 88.7%).

^{1}H NMR: ($CDCl_3$) δ: 2.19 (3H, s, $COCH_3$), 7.2 (1H, s, br, -NH), 7.23 (2H, m, Ar), 7.61 (2H, m, Ar)

(ii) Preparation of 4-(4-acetamidobenzoyl)-N-t-butoxylcarbonylpiperidine (compound 41)

To a solution of 4'-iodo-acetanilide (11.7 g, 45 mmol) in dry THF (200 ml) was added NaH (1.62g, 67.5 mmol) at 0°C, the reaction mixture was stirred for 30 min while temperature was warming up to room temperature, following by the slow addition of n-BuLi (1.6 M in Heptane, 54 mmol) at -78°C. The mixture was stirred for 15 min then N-t-Butoxylcarbonyl N'-methyl-N'methoxyl-isonipecotamide(6.15 g, 30 mmol) in THF (10 ml) was added dropwise via syringe. The reaction mixture was warmed up to r.t. and then quenched with aqueous NH_4Cl solution, and extracted with ethyl acetate (2x100 ml) The organic layer was washed with saturated (aq)NH_4Cl, brine, dried over $MgSO_4$ and concentrated to give a crude product, which was further purified by silica gel column chromatography using MeOH-CH_2Cl_2 (0 : 100 ~ 5 : 95) to provide the desired product (9.02 g, 87%).

^{1}H NMR: ($CDCl_3$) δ: 1.47 (9H, s $(CH_3)_3$), 1.6-1.8 (4H, m, piperidine), 2.21 (3H, s, $COCH_3$), 2.9 (2H, m, piperidine), 3.37 (1H, m, COCH-), 4.15 (2H, m, piperidine), 7.64 (2H, m, Ar), 7.86 (1H, s, br, -CONH), 7.91 (2H, m, Ar)

(iii) Preparation of 4-(α-Hydroxy-α-(4-N-t-butoxylcarbonylpiperidinyl)-3-Fluorobenzyl) acetanilide (compound 42)

Method as described for the preparation of compound 4 but substituting 3-fluoro-1-iodobenzene for 1-bromonaphthalene to give the title compound. (93%)

^{1}H NMR: (DMSO-D_6) δ: 1.2-1.3 (4H, m, piperidine), 1.37 (9H, s, $(CH_3)_3$), 2.0 (3H, s, $COCH_3$), 2.65 (3H, br, piperidine), 3.95 (2H, m, piperidine), 6.98 (1H, m, Ar), 7.21-7.50 (7H, m, Ar), 9.85 (1H, s, OC-NH)

(iv) Preparation of N-methyl-4-(α-Hydroxy-α-(4-N-t-butoxylcarbonylpiperidinyl)-3-Fluorobenzyl) acetanilide (compound 43)

To a 2M (aq)NaOH solution (10 ml), tetrabutylammonium hydrogen sulphate(1.35 g, 3.97 mmol) was added, followed by the addition of 4-(α-Hydroxy-α-(4-N-t-butoxylcarbonylpiperidinyl)-3-fluorobenzyl)acetanilide (825 mg, 1.86 mmol) and methyl iodide (769 mg, 5.4 mmol) in 10ml of dichloromethane. The reaction mixture was then refluxed for 1 hr, cooled down to r.t.. The dichloromethane layer was collected and evaporated to ~1ml. Ethyl acetate was added and the precipitate was filtered out. The organic phase was washed with brine and dried over MgSO4, concentrated to give a solid which was further purified by MPLC using MeOH-CH_2Cl_2 (5:95) as to give the pure titled compound (770 mg, 93%).

^{1}H NMR: ($CDCl_3$) δ:1.2-1.5 (4H, m, piperidin), 1.42 (9H, s, $(CH_3)_3$), 1.83 (3H, s, $COCH_3$), 2.52 (1H, m, -CH-C-OH), 2.70 (2H, m, piperidine), 2.86 (1H, s, br, -OH), 3.21 (3H, s, NCH_3), 4.15 (2H, s, br, piperidine), 6.90 (1H, m, Ar), 7.12-7.60 (7H, m, Ar)

EXAMPLE 26

Preparation of N-methyl-4-(3-Fluorophenyl-piperidin-4-ylidenemethyl)acetanilide (compound 44)

To a solution of N-methyl-4-(α-Hydroxy-α-(4-N-t-butoxylcarbonylpiperidinyl)-3-fluorobenzyl) acetanilide (300 mg, 0.657 mmol) in dry dichloromethane (5 mL) was added trifluoroacetic acid (5.0 mL) at r.t. The reaction mixture was refluxed for 4 hr., and then condensed. The residue was dissolved in AcOEt (50 ml). The resulting solution was washed with 2 N (aq)NaOH, (aq) NH_4Cl and brine, dried over $MgSO_4$. Removal of solvents gave a crude product, which was purified by MPLC eluting with MeOH-CH_2Cl_2-NH_4OH (5 : 95 : 1) to provide the pure product (176 mg, 79%).

mp. 235~237 °C dec.

IR (NaCl Film): (HCl salt) ν(max.) =2961, 2722, 2480, 1658, 1608, 1580, 1507, 1429, 1381cm^{-1}.

^{1}H NMR: ($CDCl_3$) δ: 1.89 (3H, s, $COCH_3$), 1.95 (1H, s, -NH), 2.32(4H, m, piperazine), 2.92 (4H, m, piperazine), 3.26 (3H, s, $N-CH_3$), 6.81-7.28 (8H, m, Ar)

^{13}C NMR:($CDCl_3$) δ: 22.4, 33.2, 33.3, 37.0, 48.3, 113.3(m, C-F), 116.5(m, C-F), 125.4, 126.6, 129.5, 129.6, 130.9, 133.7, 137.7, 141.2, 142.8, 144.2, 161.3, 163.8, 170.4..

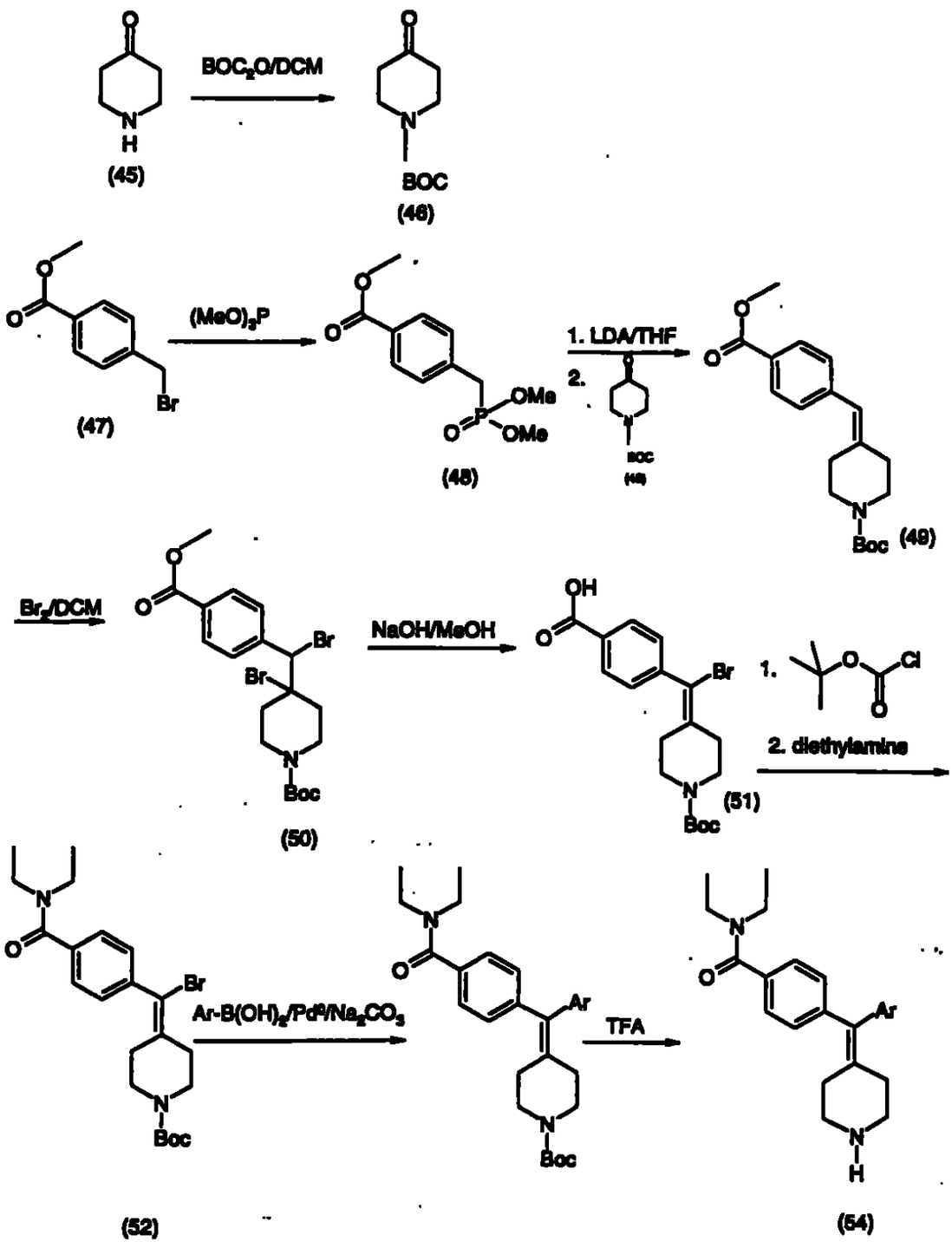
ANALYSIS: (%)

*Anal.*Calcd.for: $C_{21}H_{23}N_2FO \cdot HCl$: C, 67.28; H, 6.45; N, 7.47. Found: C, 66.88; H, 6.44; N, 7.16.

F) Synthetic Scheme for the preparation of the compound of Example 27

The compound of Example 27 was prepared by following the procedure as is shown in Scheme 6 below.

Scheme 6



Example 27

(i) Preparation of N-*tert*-Butoxylcarbonyl-4-piperidone (compound 46)

A mixture of compound 45 (50 g, 0.325 mol) and di-*tert*-butyl dicarbonate (71 g, 0.325 mol) in 300 mL of dichloromethane were stirred at 0 °C while triethylamine (133 g, 1.32 mol) was added dropwise. The mixture was allowed to warm to room temperature and was stirred for 12 hrs. The solvent was evaporated and the crude product was partitioned between water (400 mL) and diethyl ether (400 mL). The aqueous phase was washed with an additional portion of diethyl ether (400 mL). The combined ether was washed with water (400 mL) and brine (400 mL) dried over $MgSO_4$. Removal of solvent gave compound 46 as a pale yellow solid. (55.3 g, 85%):

δ_H(400 MHz, $CDCl_3$) 1.50 (s, 9H), 2.45 (t, 4H, J=6.1 Hz), 3.72 (t, 4H, J=6.1 Hz)

(ii) Preparation of 4-(4-Methoxycarbonyl-benzylidene)-piperidine-1-carboxylic acid *tert*-butyl ester (compound 49)

Methyl 4-(bromomethyl) benzoate (compound 47) (11.2 g, 49 mmol) was dissolved in 25 mL trimethyl phosphite and refluxed under N_2 for 5 hrs. Excess trimethyl phosphite was removed by co-distillation with toluene to give crude 4-(Dimethoxy-phosphorylmethyl)-benzoic acid methyl ester (compound 48).

δ_H(400 MHz, $CDCl_3$) 3.20 (d, 2H, J=22 Hz), 3.68 (d, 3H 10.8 Hz), 3.78 (d, 3H, 11.2 Hz), 3.91 (s, 3H), 7.38 (m, 2H), 8.00 (d, 2H, J=8 Hz.

The crude product (compound 48) was dissolved in dry THF (200 mL) under N_2 and cooled to -78 °C. Lithium diisopropylamide (32.7 mL 1.5 M in hexanes, 49 mmol) was added dropwise. The solution was allowed to warm to room temperature. A solution of compound 46 (9.76 g, 49 mmol in 100 mL dry THF) was added to the reaction dropwise and was stirred under N_2 for 12 hrs. Water (300 mL) and ethyl acetate (300 mL) were added to the reaction mixture and extracted. The aqueous phase was washed with ethyl acetate (2 x 300 mL). The combined ethyl acetate was dried over $MgSO_4$ and evaporated to

give a crude product, which was purified by silica gel chromatography (0-33% ethyl acetate in hexanes) to provide compound 49 as a white solid (5.64 g, 35%).

δ_H(400 MHz, $CDCl_3$) 1.44 (s, 1H), 2.31 (t, *J*=5.5 Hz, 2H), 2.42 (t, *J*=5.5 Hz, 2H), 3.37 (t, *J*=5.5 Hz, 2H), 3.48 (t, *J*=5.5 Hz, 2H), 3.87(s, 3H), 6.33 (s, 1H), 7.20 (d *J*=6.7 Hz, 2H), 7.94 (d, *J*=6.7 Hz, 2H). δ_{C-13} ($CDCl_3$) 28.3, 29.2, 36.19, 51.9, 123.7, 127.8, 128.7, 129.4, 140.5, 142.1, 154.6, 166.8 ppm. ν_{max} (NaCl) cm^{-1} 3424, 2974, 2855, 1718, 1 688, 1606, 1427, 1362, 1276.

Analysis calculated for $C_{19}H_{25}NO_4$: C 68.86%, H 7.60%, N 4.23%; actual: C 69.1%, H7.69%, N 4.25%.

(iii) Preparation of 4-Bromo-4-[bromo-(4-methoxycarbonyl-phenyl)-methyll-piperidine-1-carboxylic acid *tert*-butyl ester (compound 50)

To a solution of compound 49 (5.2 g, 16 mmol) in dry dichloromethane (200 mL) was added K_2CO_3 (1.0 g). A bromine solution (2.9 g, 18 mmol in 30 mL DCM) was then added dropwise at 0 °C and stirred for 1.5 hrs at room temperature. The K_2CO_3 was removed by filtration and the solvent was evaporated to dryness. The crude product was dissolved in ethyl acetate (200 mL) and washed with water (200 mL), 0.5 M HC1 (200 mL) and brine (200 mL), dried over $MgSO_4$. The solvent was evaporated to give crude product which was recrystallized from methanol to give compound 50 as a white solid (6.07 g, 78%).

δ_H (400 MHz, $CDCl_3$) 1.28 (s, 9H), 1.75 (m, 2H), 1.90 (m, 2H), 2.1 (m, 4H), 3.08 (br, 4H), 3.90 (s, 3H), 4.08 (br, 4H), 5.14 (s, 1H), 7.57 (d, J=8.4 Hz, 2H) 7.98 (d, J=8.4 Hz, 2H). δ_{C-13} (400 MHz, $CDCl_3$) 28.3, 36.6, 38.3, 40.3, 52.1, 63.2, 72.9, 129.0, 130.3, 130.4, 141.9, 154.4, 166.3 ppm. ν_{max} (NaCl) cm^{-1} 3425, 2969, 1725, 1669, 1426, 1365, 1279, 1243.

Analysis calculated for: $C_{19}H_{25}Br_2NO_4$: V46.6%, H 5.13%, N 2.85%; actual: 46.64%, H 5.16%, N 2.89%.

(iv) Preparation of 4-[Bromo-(4-caboxy-phenyl)-methylene]-piperidine-1-carboxylic acid *tert*-butyl ester (compound 51)

To a solution of compound 50 (5.4g 11 mmol) in methanol (300 mL) at 40 °C was added 2.0 M NaOH (100 mL). The reaction was stirred for 3 hrs at 40 °C. The crude salt was isolated by filtration. The solid was dried overnight *en vacuo*. The dry salt was dissolved in 40% acetonitrile/water and the pH was adjusted to 2 using concentrated HCl. The desired product (7) (3.8 g, 87%) was isolated as a white powder by filtration.

δ_H (400 MHz, $CDCl_3$) 1.45 (s, 9H), 2.22 (dd, J=5.5 Hz, 6.1 Hz, 2H), 2.64 (dd, J=5.5 Hz, 6.1 Hz, 2H), 3.34 (dd, J=5.5 Hz, 6.1 Hz, 2H), 3.54 (dd, J=5.5 Hz, 6.1 Hz, 2H), 7.35 (d, J=6.7 Hz, 2H), 8.08 (d, J=6.7 Hz, 2H). δ_{c-13} (400 MHz, $CDCl_3$) 28.3, 31.5, 34.2, 44.0, 115.3, 128.7, 129.4, 130.2, 137.7, 145.2, 154.6, 170.3.

Analysis calculated for: $C_{18}H_{22}BrNO_4$: C 54.56%, H 5.60%, N 3.53%; actual: C 54.66%, H 5.68%, N 3.59%.

(v) Preparation of 4-[Bromo-(4-diethylcarbamoyl-phenyl)-methylene]-piperidine-1-carboxylic acid *tert*-butyl ester (compound 52)

To a solution of compound 51 (1.0 g, 2.5 mmol) in dry dichloromethane (10 mL) at - 20 °C was added *iso*-butylchloroformate (450 mg, 3.3 mmol). After 20 min at -20 °C diethylamine (4 mL) was added and the reaction was allowed to warm to room temperature. After 1.5 hrs the solvent was evaporated and the reaction mixture was partitioned between ethyl acetate and water. The ethyl acetate was washed with water and brine and dried over $MgSO_4$ and removed by evaporation. The crude product was purified by silica gel chromatography (0-60% ethyl acetate in heptanes) to give the product (compound 52) as white needles (800 mg, 73%).

δ_H(400 MHz, CDC13) 1.13 (br, 3H), 1.22 (br, 3H), 1.44 (s, 9H), 2.22 (t, J=5.5 Hz, 2H), 2.62 (t, J=5.5 Hz, 2H), 3.31 (t, J=5.5 Hz, 2H), 3.52 (t, J=5.5 Hz, 2H), 7.27 (d, J=7.9 Hz,

2H), 7.33 (d, J=7.9 Hz, 2H). δ_{C-13} (400 MHz, $CDCl_3$) 12.71, 14.13, 28.3, 31.5, 34.2, 39.1, 43.2, 79.7, 115.9, 126.3, 129.3, 136.8, 137.1, 140.6, 154.6, 170.5.

Analysis calculated for: $C_{22}H_{31}BrN_2O_3$: C 58.3%, H 6.92%, N6.21%; actual: C 58.62%, 6.89%, 6.21%.

EXAMPLE 27

Preparation of *N,N*-Diethyl-4-[piperidin-4-ylidene(3-trifluoromethyl-phenyl)-methyl]-benzamide (compound 54, Ar=3-Trifluoromethylphenyl)(general procedure)

The Suzuki coupling of compound 52 with a variety of boronic acids and the subsequent deprotection were performed on a small scale in parallel. The reactions and liquid-liquid extractions were carried out in 25 x 150 mm culture tubes. The protocol for a typical reaction is outlined below.

To a solution of compound 52 (25 mg, 57 µmol) and Tetrakis(triphenyl phosphine) palladium(0) (5 mg, 4.3 µmol) in xylenes (degassed, 0.5 mL) was added 3-Trifluorophenyl boronic acid (28.5 mg, 150 µmol) in ethanol (degassed, 0.5 mL) followed by 150 µL of 2M Na_2CO_3 (aq) (300 µmol). The reaction was allowed to procede at 80 °C for 1.5 hrs under Ar. The reaction was diluted with water (1 mL) and diethyl ether (1 mL) and vortexed. The organic phase was isolated and evaporated to give a crude product (compound 9, Ar = 3-Trifluoromethylphenyl).

The Boc group was removed by treating the crude product with 1 mL of TFA. After 30 minutes at room temperature the TFA was evaporated to give the crude TFA salt. The salt was neutralized with 1 M NH_4OH(1.0M) and extracted into diethyl ether (2 x 1 mL). The ether phase was acidified with 4.0 M HCl in dioxane (200 µL) and the HCl salt was extracted into water (2 x 1 mL). The aqueous salt solution was washed with diethyl ether (2

x 1 mL) and lyophilized to yield the product (compound 54, Ar = 3-Trifluoromethylphenyl) as a white powder (10 mg, 39%).

^{1}H NMR ($CDCl_3$) (base) δ 1.11 (br, 3H), 1.20 (br, 3H), 2.26 (t, J=5.6 Hz, 2H), 2.31 (t, J=5.6 Hz, 2H), 2.88-2.91 (m, 4H), 3.27 (br, 2H), 3.52 (br, 2H), 7.10-7.47 (m, *H).

Analysis calculated for: $C_{24}H_{28}N_2OF_3Cl$ x 1.80 H_2O: C, 59.39; H, 6.56; N, 5.77; Actual: C, 59.39; H, 5.90; N, 5.77.

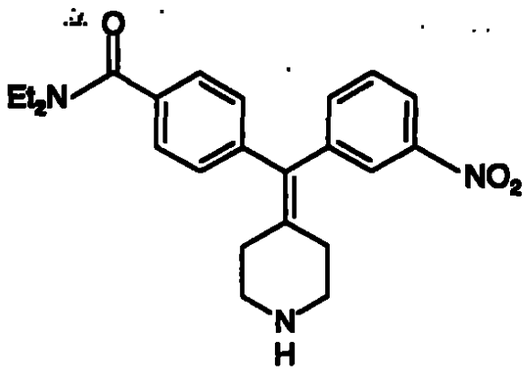
EXAMPLES 28-52

By following the same procedure as described for compound 54 of Example 27 but substituting the respective boronic acids for 3-trifluoromethylphenylboronic acid, the following compounds were also prepared.

EXAMPLE 28

N,N-Diethyl-4-(3-nitrophenyl-piperidin-4-ylidene-methyl)-benzamide (compound 55)

3-nitrophenylboronic acid was used.



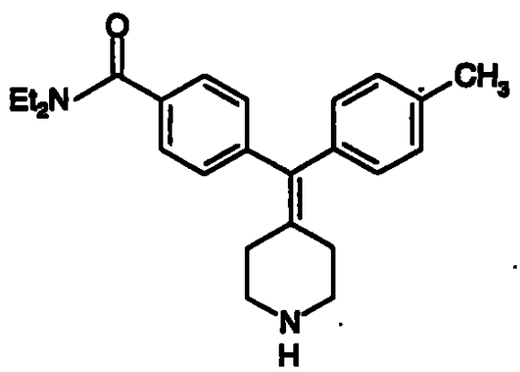
(55)

1H NMR (CDCl3) (base) δ 1.11 (br, 3H), 1.21 (br, 3H), 2.27-2.34 (m, 4H), 2.92 (t, *J*=6.0 Hz, 4H), 3.26 (br, 2H), 3.52 (br, 2H), 7.10 (d, *J*=8.4 Hz, 2H), 7.31 (d, *J*=8.4 Hz, 2H), 7.40-7.50 (m, 2H), 7.95-8.08 (m, 2H)

EXAMPLE 29

N,N-Diethyl-4-(4-toluyl-piperidin-4-ylidene-methyl)-benzamide (compound 56)

p-toluylboronic acid was used.



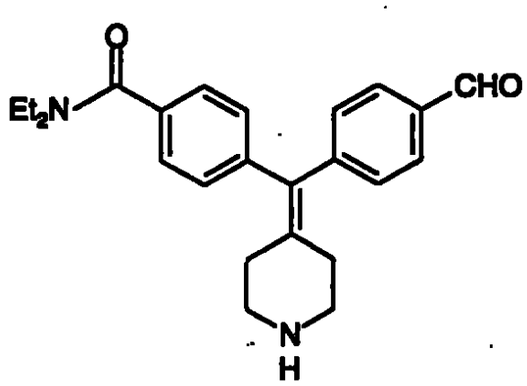
(56)

1H NMR (CDCl3) (base) δ 1.10 (br, 3H), 1.19 (br, 3H), 2.29 (s, 3H), 2.26-2.31 (m, 4H), 2.86-2.88 (m, 4H), 3.25 (br, 2H), 3.49 (br, 2H), 6.95-7.28 (m, 8H)

EXAMPLE 30

N,N-Diethyl-4-(4-formylphenyl-piperidin-4-ylidene-methyl)-benzamide (compound 57)

4-formylphenylboronic acid was used.



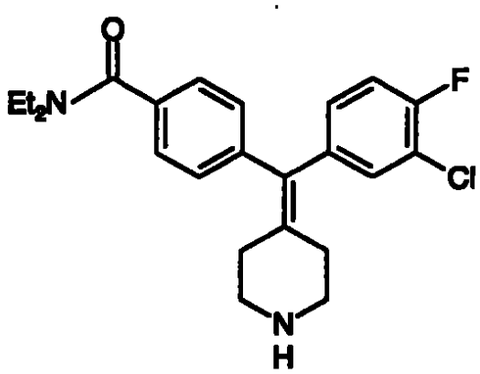
(57)

1H NMR (CDCl3) (base) δ 1.10 (br, 3H), 1.20 (br, 3H), 2.28-2.33 (m, 4H), 2.89-2.92 (m, 4H), 3.25 (br, 2H), 3.50 (br, 2H), 7.08-7.79 (m, 8H), 9.95 (s, 1H)

EXAMPLE 31

N,N-Diethyl-4-(3-chloro-4-fluorophenyl-piperidin-4-ylidene-methyl)-benzamide (compound 58)

3-chloro-4-fluorophenylboronic acid was used.



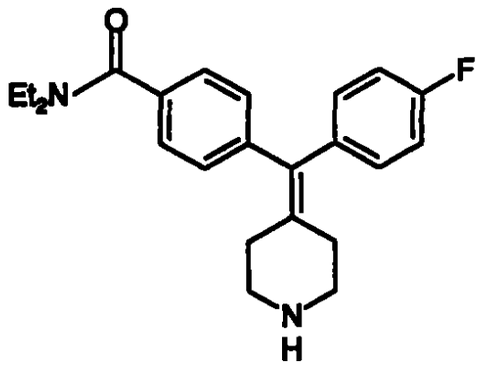
(58)

1H NMR (CDCl3) (base) δ 1.10 (br, 3H), 1.20 (br, 3H), 2.26-2.30 (m, 4H), 2.86-2.91 (m, 4H), 3.25 (br, 2H), 3.50 (br, 2H), 6.93-7.30 (m, 7H)

EXAMPLE 32

N,N-Diethyl-4-(4-fluorophenyl-piperidin-4-ylidene-methyl)-benzamide (compound 59)

4-fluorophenylboronic acid was used.



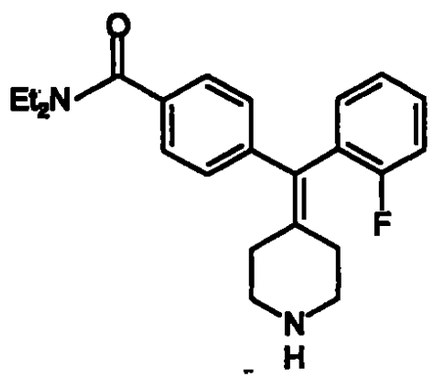
(59)

1 HNMR (CDCl3) (base) δ 1.11 (br, 3H), 1.16 (br, 3H), 2.25 (s, 4H), 2.84 (s, 4H), 3.20 (br, 2H), 3.47 (br, 2H), 6.92 (m, 2H), 7.01 (m, 4H), 7.23 (d, *J*=8.8 Hz, 2H)

EXAMPLE 33

N,N-Diethyl-4-(2-fluorophenyl-piperidin-4-ylidene-methyl)-benzamide (compound 60)

2-fluorophenylboronic acid was used.



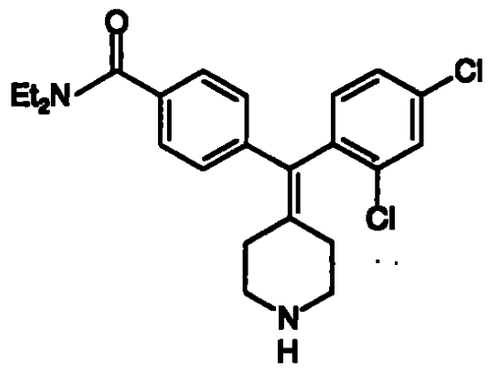
(60)

1H NMR (CDCl3) (base) δ 1.11 (br, 3H), 1.15 (br, 3H), 2.10 (t, *J*=5.2 Hz, 2H), 2.27 (t, *J*=5.2 Hz, 2H), 2.83(m, 4H), 3.20 (br, 2H), 3.45 (br, 2H), 6.94-7.03 (m, 3H), 7.10-7.23 (m, 5H)

EXAMPLE 34

N,N-Diethyl-4-(2,4-dichlorophenyl-piperidin-4-ylidene-methyl)-benzamide (compound 61)

2,4-dichlorophenylboronic acid was used.



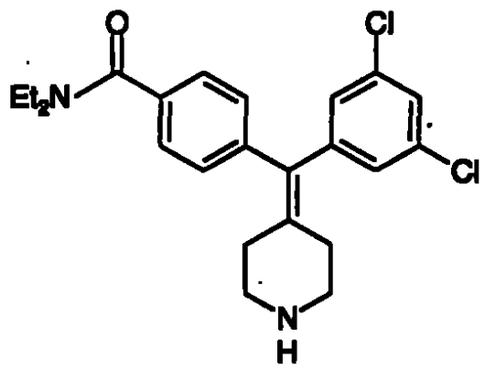
(61)

1H NMR (DMSO) (HCl salt) δ 1.07 (br, 6H), 2.24 (t, 2H), 2.50 (t, 2H), 3.10 (t, 2H), 3.30 (t, 2H), 3.31 (br, 2H), 3.43 (br, 2H), 7.25 (d, *J*=8.4 Hz, 2H), 7.32 (d, *J*=8.4 Hz, 2H), 7.43 (d, *J*=8.0 Hz, 1H), 7.47 (d, *J*=8.0 Hz, 1H), 7.68 (s, 1H), 9.20 (br, 2H)

EXAMPLE 35

N,N-Diethyl-4-(3,5-dichlorophenyl-piperidin-4-ylidene-methyl)-benzamide (compound 62)

3,5-dichlorophenylboronic acid was used.



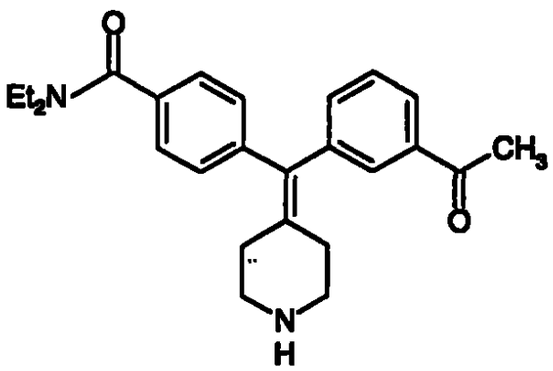
(62)

1H NMR (DMSO) (HCl salt) δ 1.03 (br, 6H), 2.36-2.38 (m, 4H), 3.0-3.2 (m, 4H), 3.2 (br, 2H), 3.38 (br, 2H), 7.19 (s, 1H), 7.21 (d, *J*=8.0 Hz, 2H), 7.29 (d, *J*=8.0 Hz, 2H), 7.49 (s, 2H), 9.10 (br, 2H)

EXAMPLE 36

N,N-Diethyl-4-(3-acetylphenyl-piperidin-4-ylidene-methyl)-benzamide (compound 63)

3-acetylphenylboronic acid was used.



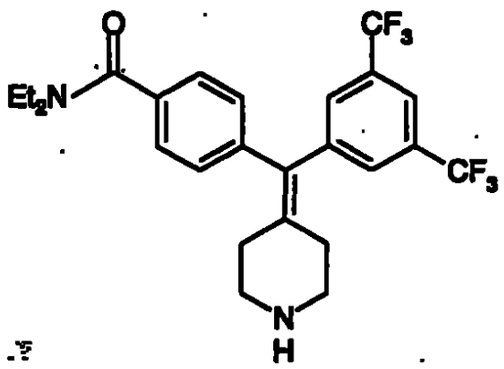
(63)

1H NMR (CDCl3) (base) δ 1.11 (br, 3H), 1.20 (br, 3H), 2.26 (t, *J*=5.6 Hz, 2H), 2.32 (t, *J*=5.6 Hz, 2H), 2.55 (s, 3H), 2.92-2.88 (m, 4H), 3.26 (br, 2H), 3.51 (br, 2H), 7.11 (d, *J*=8.0 Hz, 2H), 7.29 (d, *J*=8.0 Hz, 2H), 7.29 (d, *J*=7.2 Hz, 1H), 7.37 (t, *J*=8.0 Hz, 1H), 7.70 (s, 1H), 7.79 (d, *J*=7.2Hz, 1H)

EXAMPLE 37

N,N-Diethyl-4-(3,5-trifluoromethylphenyl-piperidin-4-ylidene-methyl)-benzamide (compound 64)

3,5-trifluoromethylphenylboronic acid was used.



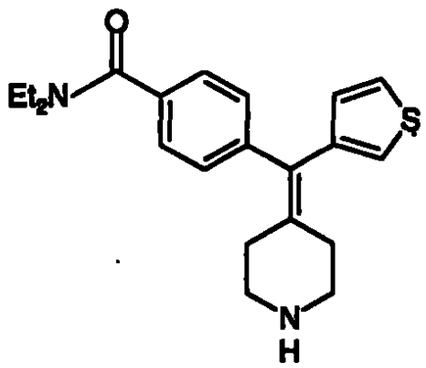
(64)

1H NMR (DMSO) (HCl salt) δ 1.06 (br, 3H), 1.08 (br, 3H), 2.33 (br, 2H), 2.41 (br, 2H), 3.12 (br, 6H), 3.38 (br, 2H), 7.24 (d, *J*=7.6 Hz, 2H), 7.30 (d, *J*=7.6 Hz, 2H), 7.84 (s, 2H), 8.00 (s, 2H), 8.9 (br, 2H)

EXAMPLE 38

N,N-Diethyl-4-(3-thiophenyl-piperidin-4-ylidene-methyl)-benzamide (compound 65)

3-thiophenylboronic acid was used.



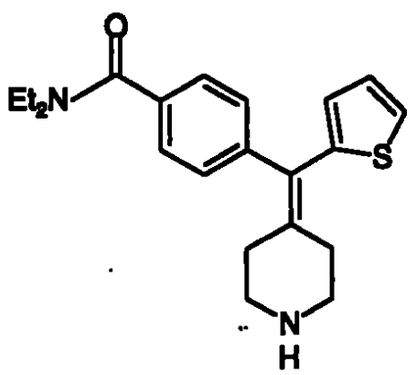
(65)

1 HNMR (DMSO) (HCl salt) δ 1.10 (br, 6H), 2.44 (t, 2H), 2.58 (t, 2H), 3.10-3.15 (m, 4H), 3.21 (br, 2H), 3.44 (br, 2H), 6.86 (d, *J*=4.8 Hz, 1H), 7.20 (d, *J*=8.0 Hz, 2H), 7.32 (d, *J*=8.0 Hz, 2H), 7.33 (s, 1H), 7.52 (d, *J*=4.8 Hz, 1H)

EXAMPLE 39

N,N-Diethyl-4-(2-thiophenyl-piperidin-4-ylidene-methyl)-benzamide (compound 66)

2-thiophenylboronic acid was used.



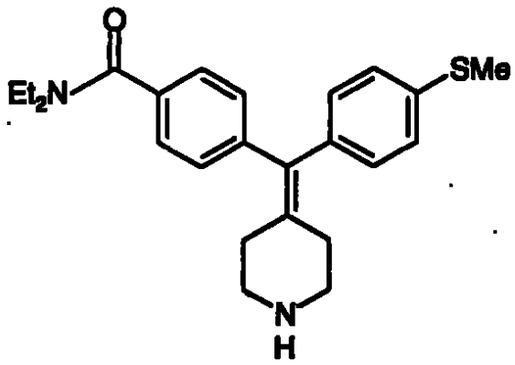
(66)

1H NMR (CDCl3) (base) δ 1.12 (br, 3H), 1.20 (br, 3H), 2.24 (t, *J*=5.2 Hz, 2H), 2.50 (t, *J*=5.2 Hz, 2H), 2.85 (t, *J*=5.6 Hz, 2H), 2.92 (t, *J*=5.6 Hz, 2H), 3.27 (br, 2H), 3.51 (br, 2H), 6.75 (d, *J*=3.6 Hz, 1H), 6.93 (t, J=3.6 Hz, 1H), 7.16 (d, *J*=7.2 Hz, 2H), 7.21 (d, *J*=3.6 Hz, 1H), 7.30 (d, *J*=7.2 Hz, 2H)

EXAMPLE 40

N,N-Diethyl-4-(4-methylthiophenyl-piperidin-4-ylidene-methyl)-benzamide (compound 67)

4-methylthiophenylboronic acid was used.



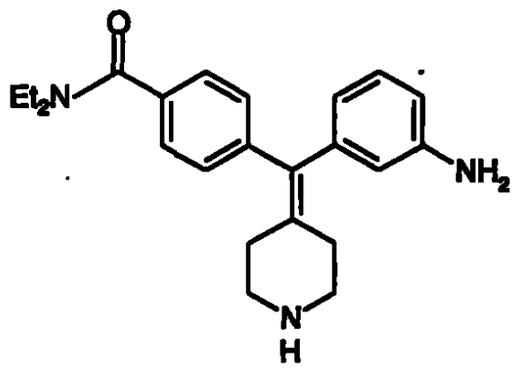
(67)

1H NMR (CDCl3) (base) δ 1.11 (br, 3H), 1.20 (br, 3H), 2.32-2.75 (m, 4H), 2.45 (s, 3H), 2.90-2.87 (m, 4H), 3.26 (br, 2H), 3.51 (br, 2H), 7.01 (d, *J*=6.0 Hz, 2H), 7,10 (d, *J*=6.0 Hz, 2H), 7.15 (d, *J*=6.8Hz, 2H), 7.27 (d, *J*=6.8 Hz, 2H)

EXAMPLE 41

N,N-Diethyl-4-(3-aminophenyl-piperidin-4-ylidene-methyl)-benzamide (compound 68)

3-aminophenylboronic acid was used.



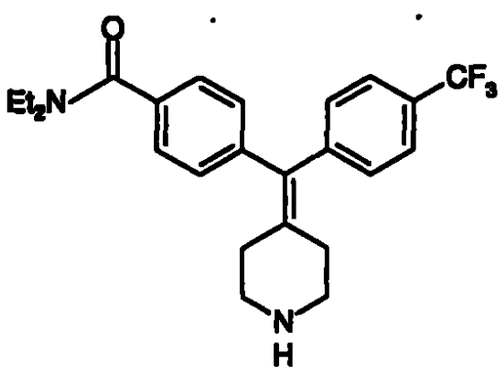
(68)

1H NMR (CDCl3) (base) δ 1.11 (br, 3H), 1.20 (br, 3H), 2.27-2.33 (m, 4H), 2.86-2.90 (m, 4H), 3.27 (br, 2H), 3.51 (br, 2H), 3.57 (br, 2H), 3.68 (s, 1H), 6.39 (s, 1H), 6.52 (dd, *J*=1.6 Hz, *J*=7.6 Hz, 2H), 7.06 (t, *J*=8.0 Hz, 1H), 7.12 (d, *J*=6.4 Hz, 2H), 7.26 (d, *J*=6.4 Hz, 2H)

EXAMPLE 42

N,N-Diethyl-4-(4-trifluoromethylphenyl-piperidin-4-ylidene-methyl)-benzamide (compound 69)

4-trifluoromethylphenylboronic acid was used.



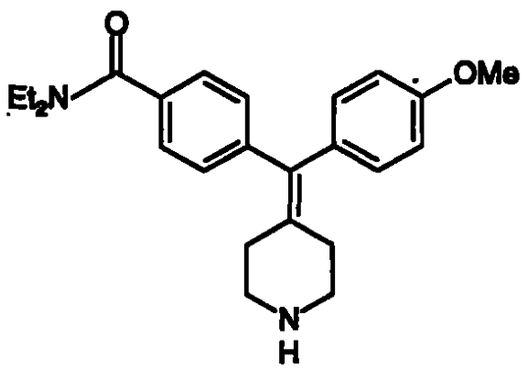
(69)

1H NMR (DMSO) (HCl salt) δ 1.05 (br, 6H), 2.35 (t, 2H), 2.40 (t, 2H), 3.09 (m, 6H), 3.35 (br, 2H), 7.17 (d, *J*=8.0 Hz, 2H), 7.28 (d, *J*=8.0 Hz, 2H), 7.35 (d, *J*=8.0 Hz, 2H), 7.67 (d, *J*=8.0 Hz, 2H), 8.71 (br, 2H)

EXAMPLE 43

N,N-Diethyl-4-(4-methoxyphenyl-piperidin-4-ylidene-methyl)-benzamide (compound 70)

4-methoxyphenylboronic acid was used.



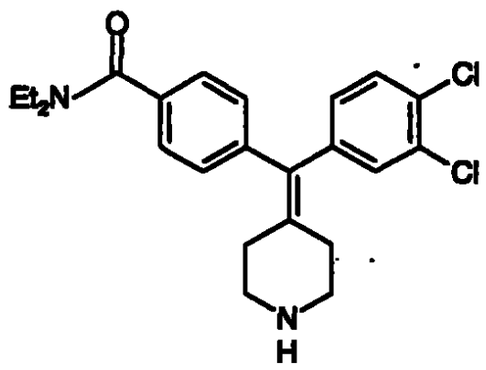
(70)

1H NMR (CDCl3) (base) δ 1.12 (br, 3H), 1.19 (br, 3H), 2.29 (m, 4H), 2.87 (m, 4H), 3.27 (br, 2H), 3.51 (br, 2H), 3.77 (s, 3H), 6.80 (m, 2H), 7.00 (m, 2H), 7.10 (d, *J*=8.4 Hz, 2H), 7.26 (d, *J*=8.4 Hz)

EXAMPLE 44

N,N-Diethyl-4-(3,4-dichlorophenyl-piperidin-4-ylidene-methyl)-benzamide (compound 71)

3,4-dichlorophenylboronic acid was used.



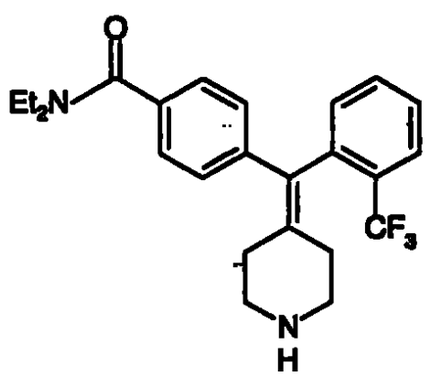
(71)

1H NMR (CDCl3) (base) δ 1.12 (br, 3H), 1.20 (br, 3H), 2.28 (t, *J*=5.6 Hz, 4H), 2.89 (m, 4H), 3.27 (br, 2H), 3.52 (br, 2H), 6.8-7.4 (m, 7H)

EXAMPLE 45

N,N-Diethyl-4-(2-trifluoromethylphenyl-piperidin-4-ylidene-methyl)-benzamide (compound 72)

2-trifluoromethylphenylboronic acid was used.



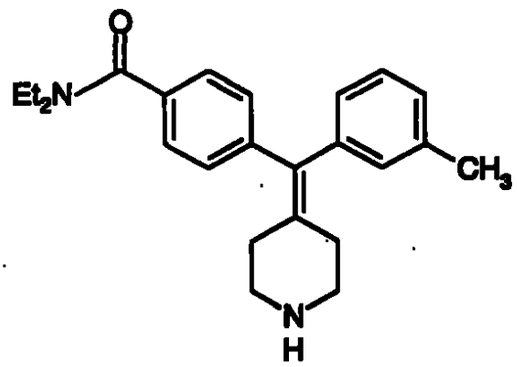
(72)

1H NMR (CDCl3) (base) δ 1.05 (br, 3H), 1.16 (br, 3H), 1.95 (m, 2H), 2.35-2.41 (m, 2H), 2.7-2.9 (m, 4H), 3.20 (br, 2H), 3.48 (br, 2H), 7.2-7.6 (m, 8H)

EXAMPLE 46

N,N-Diethyl-4-(3-toluyl-piperidin-4-ylidene-methyl)-benzamide (compound 73)

m-tolylboronic acid was used.



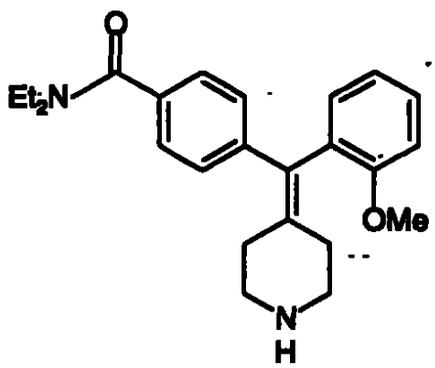
(73)

1H NMR (CDCl3) (base) δ 1.11 (br, 3H), 1.19 (br, 3H), 2.28 (s, 3H), 2.29 (m, 4H), 2.89 (m, 4H), 3.27 (br, 2H), 3.51 (br, 2H), 6.8-7.3 (m, 8H)

EXAMPLE 47

N,N-Diethyl-4-(2-methoxyphenyl-piperidin-4-ylidene-methyl)-benzamide (compound 74)

2-methoxyphenylboronic acid was used.



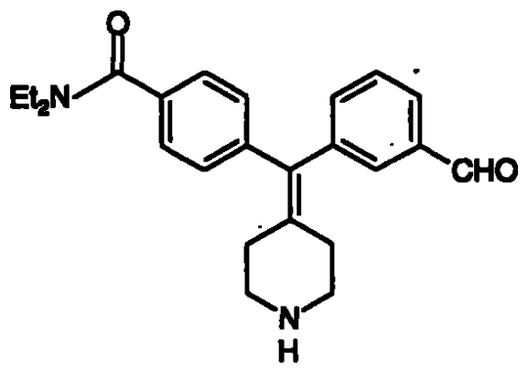
(74)

1H NMR (CDCl3) (base) δ 1.09 (br, 3H), 1.18 (br, 3H), 2.10 (q, *J*=4.8 Hz, 2H), 2.31 (q, *J*=4.8 Hz, 2H), 2.8-2.9 (m, 4H), 3.25 (br, 2H), 3.50 (br, 2H), 3.68 (s, 3H), 6.83-6.90 (m, 2H), 7.0 (d, 1H), 7.15-7.25 (m, 5H)

EXAMPLE 48

N,N-Diethyl-4-(3-formylphenyl-piperidin-4-ylidene-methyl)-benzamide (compound 75)

3-formylphenylboronic acid was used.



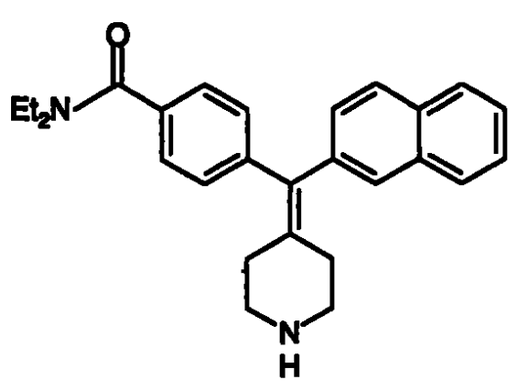
(75)

1H NMR (CDCl3) (base) δ 1.15 (br, 3H), 1.20 (br, 3H), 2.26-2.34 (m, 4H), 2.90-2.92 (m, 4H), 3.28 (br, 2H), 3.2 (br, 2H), 7.11-7.31 (m, 8H), 9.96 (s, 1H)

EXAMPLE 49

N,N-Diethyl-4-(2-naphtyl-piperidin-4-ylidene-methyl)-benzamide (compound 76)

2-naphtylboronic acid was used.



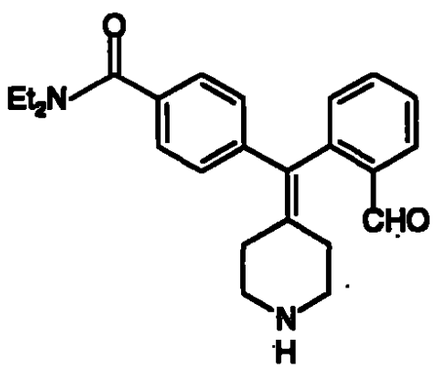
(76)

1H NMR (CDCl3) (base) δ 1.11 (br, 3H), 1.20 (br, 3H), 2.35-2.39 (m, 4H), 2.91-2.96 (m, 4H), 3.27 (br, 2H), 3.51 (br, 2H), 7.16-7.40 (m, 5H), 7.42-7.44 (m, 2H), 7.57 (s, 1H), 7.72-7.79 (m, 2H)

EXAMPLE 50

N,N-Diethyl-4-(2-formylphenyl-piperidin-4-ylidene-methyl)-benzamide (compound 77)

2-formylphenylboronic acid was used.



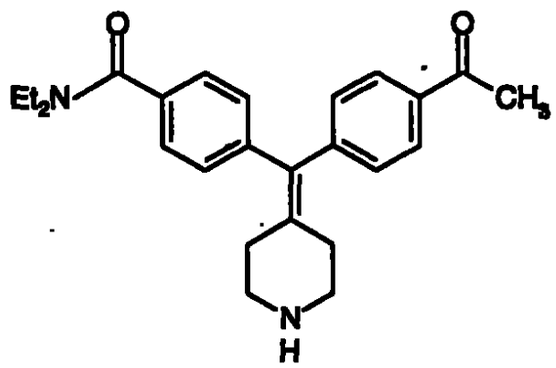
(77)

1H NMR (CDCl3) (base) δ 1.09 (br, 3H), 1.18 (br, 3H), 1.70-2.10 (m, 2H), 2.40-2.49 (m, 2H), 2.76-2.84 (m, 2H), 2.85-2.97 (m, 2H), 3.23 (br, 2H), 3.48 (br, 2H), 7.13-7.40 (m, 6H), 7.53-7.55 (m, 1H), 7.90 (d, *J*=7.6 Hz,1H), 10.27 (s, 1H)

EXAMPLE 51

N,N-Diethyl-4-(4-acetylphenyl-piperidin-4-ylidene-methyl)-benzamide (compound 78)

4-acetylphenylboronic acid was used.



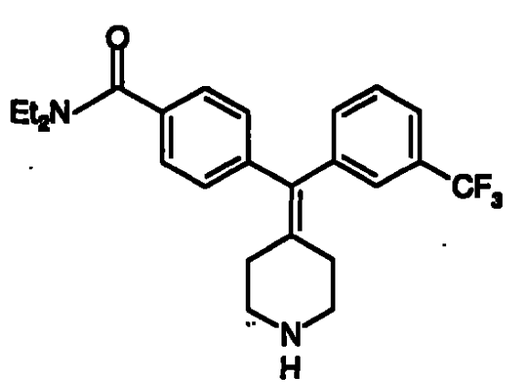
(78)

1H NMR (CDCl3) (base) δ 1.11 (br, 3H), 1.20 (br, 3H), 2.30-2.35 (m, 4H), 2.56 (s, 3H), 2.92 (m, 4H), 3.27 (br, 2H), 3.52 (br, 2H), 7.10-7.30 (m, 6H), 7.87 (d, *J*=7.2 Hz, 2H)

EXAMPLE 52

N,N-Diethyl-4-(3-trifluoromethylphenyl-piperidin-4-ylidene-methyl)-benzamide (compound 79)

3-trifluoromethylphenylboronic acid was used.

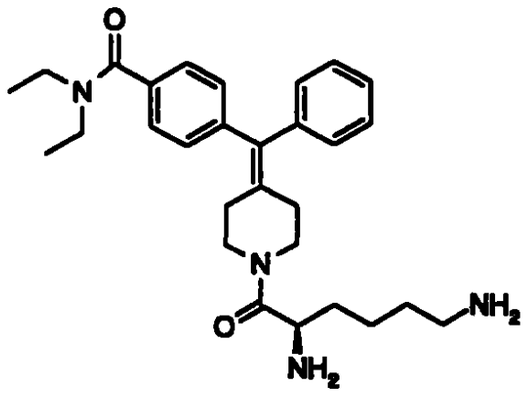


(79)

1H NMR (CDCl3) (base) δ 1.11 (br, 3H), 1.20 (br, 3H), 2.26 (t, *J*=5.6 Hz, 2H), 2.31 (t, *J*=5.6 Hz, 2H), 2.88-2.91 (m, 4H), 3.27 (br, 2H), 3.52 (br, 2H), 7.10-7.47 (m, 8H)

EXAMPLE 53

Preparation of *N,N*-Diethyl-4-([1-(2,6-Diamino-hexanoyl)-piperidin-4-ylidene]-phenyl-methyl) -benzamide (compound 80).



(80)

L-Boc-Lysine(Cbz) (0.38g, 1.0mmol) was dissolved in dry tetrahydrofuran (5mL) under nitrogen at -15 °C. N-Methylmorpholine (0.11mL, 1.0mmol) then isobutyl chloroformate (0.13mL, 1mmol) was added. After stirring 10 minutes, N,N-Diethyl-4-(phenyl-piperidin-4-ylidene-methyl)-benzamide (compound 6) (0.35g, 1.0mmol) was added in tetrahydrofuran (1mL) and the temperature was allowed to rise to 25 °C for 2h. The reaction mixture was evaporated onto silica gel. MPLC on silica gel (0 to 100% ethyl acetate in heptane) gave 0.4g.

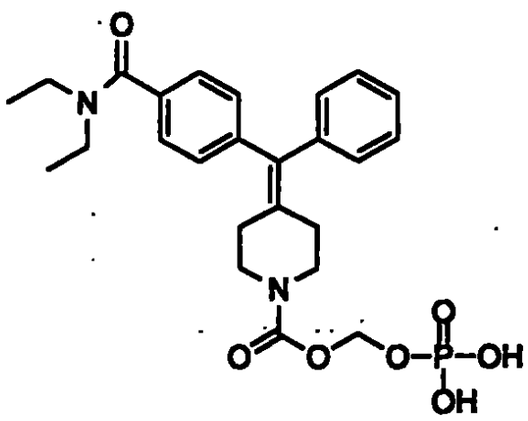
The product (0.40g, 0.56mmol) was dissolved in methylene chloride (10mL) and treated with trifluoroacetic acid (3mL) for 30min, then the volatiles were evaporated. The residue was dissolved in acetic acid (25mL) and subjected to hydrogenolysis 1.5h with hydrogen (1atm) over palladium on carbon (10%, 0.10g). The solvent was evaporated and the residue purified by chromatography on a short reverse phase (RP-18) column, eluting with 0 to 30 % acetonitrile in water. The free amine was extracted with 5% potassium carbonate/

methylene chloride to give 123mg and then treated with two equivalents of hydrochloric acid in methanol/ water. Lyophilization gave the dihydrochloride salt.

^{1}H NMR: (free amine, CD_3OD): δ = 1.0-1.7(m, 16H, amide-Me, piperidine-H, lysine-H), 2.3-2.7 and 3.0-4.5 (m, 11H, amide-H, piperidine-H, lysine-H),4.8 (s, 4H, 2 NH_2), 7.10 - 7.50 (m, 9H, Ar-H). $C_{29}H_{40}N_4O_2$ x2.4 H_2O x2 HCl, requires: C:58.76, H:7.96 , N:9.43. Found C:58.70, H:7.51, N:9.33.

EXAMPLE 54

Preparation of 4-[(4-Diethylcarbamoyl-phenyl)-phenyl-methylene]-piperidine-1-carboxylic acid phosphono-oxymethyl ester Compound 81)



(81)

N,N-Diethyl-4-(phenyl-piperidin-4-ylidene-methyl)-benzamide (compound 6) (0.62g, 1.8mmol) was dissolved in methylene chloride (10mL) and 1,8-bisdiaminonaphtalene (0.42g, 2.0mmol) was added. The solution was cooled to 0 °C and chloromethyl chloroformate (0.25g, 2.0mmol) added dropwise in methylene chloride (1mL). After 2h at 25 °C, a further portion of first 1,8-bisdiaminonaphtalene (0.21g, 1.0mmol), then chloromethyl chloroformate (0.12g,1.0mmol) was added. After a total of 4 hours, the solution was washed with 1 M HCl, brine and dried ($MgSO_4$) and evaporation gave 0.62g. The residue was dissolved in toluene (25mL) , silver dibenzylphosphate (0.81g, 2.1mmol)

was added and the mixture was heated 3h at 80 °C. The solution was filtered, then washed with 5% potassium carbonate solution, brine, dried (K_2CO_3) and evaporated. MPLC on silica gel (0 to 100% ethyl acetate in heptane) gave 0.66g (0.96mmol, 54%).

The residue was dissolved in ethyl acetate (50mL) and subjected to hydrogenolysis (1 atm hydrogen) with palladium on carbon (10%, 0.3g) for 2h. After filtration and evaporation of the solvent, the product was treated with two equivalents of sodium hydroxide in methanol/ water. Lyophilization gave the disodium salt of the product as a white solid.

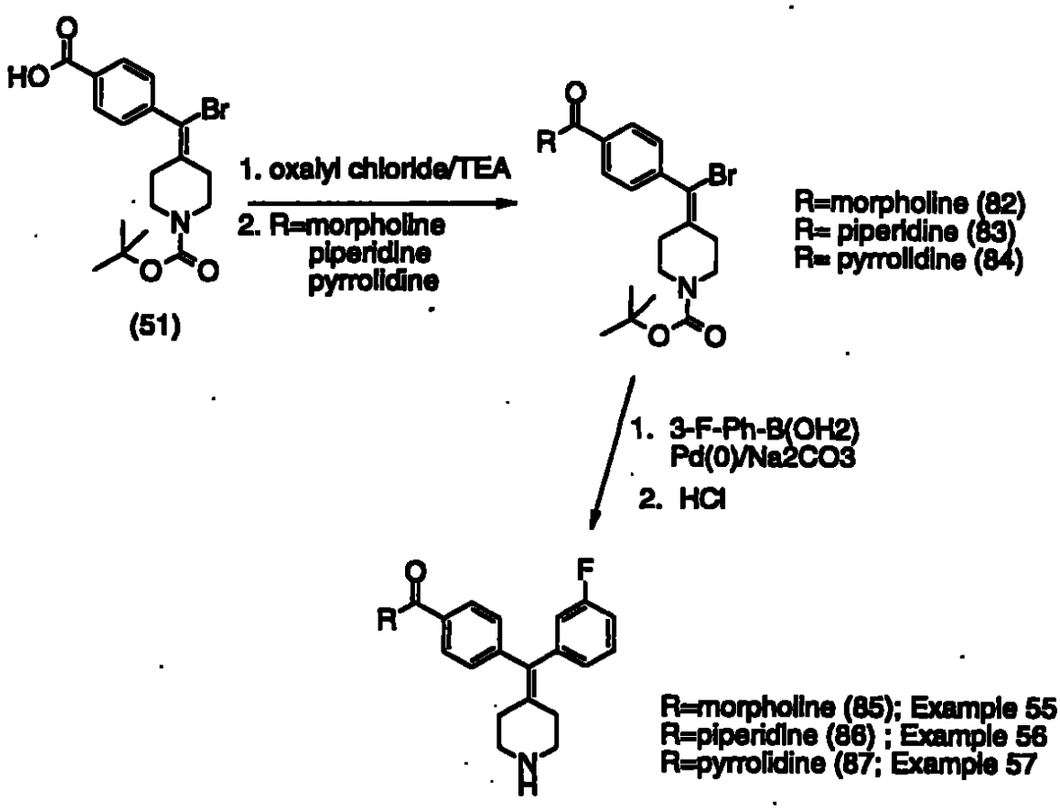
^{1}H NMR: (D_2O): δ = 1.03, 1.20 (2m, 6H, amide-Me), 2.34 (m, 4H, piperidine-H), 3.19-3.61 (m, 8H, amide-CH_2, piperidine-H), 5.44 (d, *J*=13Hz, 2H, OCH_2O), 7.18-7.36 (m, 9H, Ar-H).

Compounds 80 and 81 respectively, are suitable prodrugs of the compounds of the general formula (I).

G) Synthetic scheme for the preparation of the compounds of Examples 55-57

The compounds of Examples 55, 56 and 57 were prepared by following the procedure of Scheme 7 below.

Scheme 7



(i) Preparation of tert-butyl-4-[bromo[4-(morpholinocarbonyl)phenyl]methylene]-1-piperidinecarboxylate (compound 82)

To a solution of compound 51, prepared according to scheme 6, (0.25 g, 0.625 mmole) and freshly distilled triethylamine (0.5 mL)in dichloromethane (12 mL), was added oxalyl chloride (0.38 mL 2.0 M, 0.75 mmole) dropwise at room temperature. The solution was stirred for 10 minutes at room temperature and the solvent and excess reagents were removed *in vacuo* to give the acid chloride as a crude product which was used in the next step without further purification.

Morpholine (56 mg , 0.65 mmole) was added to a solution of the acid chloride (0.65 mmole) and triethylamine (0.5 mL) in dichloromethane (5mL). The reaction was allowed to proceed for one hour at room temperature. The solvent was then removed *in vacuo*. The crude product was partitioned between ethyl acetate (25 mL) and water (25 mL). The

water was washed with ethyl acetate and the combined ethyl acetate was washed with 2M NaOH (2 x 25 mL), (2M HCl (2 x 25 mL), brine (1 x 25 mL) and dried over magnesium sulfate. The solvent was removed *in vacuo* to give the product (compound 82) (294 mg, 97% yield).

^{1}H-nmr $CDCl_3$ (400 MHz) 1.44 (s, 9H), 2.21 (t, J=5.6 Hz, 2H), 2.62 (t, J=5.6 Hz, 2H), 3.31 (t, J=5.6 Hz, 2H), 3.52 (t, J=5.6 Hz, 2H), 3.69 (br, 8H), 7.31 (d, J=6.4 Hz, 2H), 7.37 (d, J=6.4 Hz, 2H).

(ii) Preparation of tert-butyl-4-{bromo[4-(piperidinocarbonyl)phenyl]methylene}-1-piperidinecarboxylate (compound 83)

Same procedure as described for the preparation of compound 82, but using piperidine in place of morpholine.

^{1}H nmr $CDCl_3$ (400 MHz) 1.44 (s, 9H), 1.51 (br, 2H), 1.66 (br, 4H), 2.21 (t, J=5.6 Hz, 2H), 2.62 (t, J=5.6 Hz, 2H), 3.31 (t, J=5.6 Hz, 2H), 3.33(br, 2H), 3.52 (t, J=5.6 Hz, 2H), 3.68 (br, 2H), 7.26 (d, J=8.4 Hz, 2H), 7.35 (d, J=8.4 Hz, 2H)

(iii) Preparation of tert-butyl-4-{bromo[4-(tetrahydro-1H-1-pyrrolylcarbonyl)phenyl]methylene}-1-piperidinecarboxylate (compound 84)

Same procedure as described for the preparation of compound 82, but using pyrrolidine in place of morpholine.

^{1}H nmr $CDCl_3$ (400 MHz) 1.44 (s, 9H), 1.87 (q, J=6.8 Hz, 2H), 1.95 (q, J=6.8 Hz, 2H), 2.20 (t, J=5.6 Hz, 2H), 2.62 (t, J=5.6 Hz, 2H), 3.31 (t, J=5.6 Hz, 2H), 3.43 (t, J=6.8 Hz, 2H), 3.52 (t, J=5.6 Hz, 2H), 3.63 (t, J=6.8 Hz, 2H), 7.27 (d, J=8.0 Hz, 2H), 7.47 (d, J=8.0 Hz, 2H)

EXAMPLE 55

Preparation of 4-[(3-fluorophenyl)-piperidin-4-yl-methyl]-phenyl-morpholin-4-yl-methanone (compound 85)

To a solution of compound 82 (37 mg, 0.082 mmol) and tetrakis(triphenyl phosphine) palladium(0) (5 mg, 0.0043 mmol) in xylenes (degassed, 0.5 mL) was added 3-fluorophenyl boronic acid (25 mg, 0.18 mmol) in ethanol (degassed, 0.5 mL) followed by 150 µL 2M Na_2CO_3 (aq) (300 µmol). The reaction was allowed to proceed at 80 °C for 2 hrs under argon. The reaction was diluted with water (1 mL) and diethyl ether (1 mL) and vortexed. The organic phase was isolated and evaporated to give a crude product which was used without further purification.

The Boc group was removed by treating the crude product with 1 mL of TFA. After 30 minutes at room temperature the TFA was evaporated to give the crude TFA salt. The salt was neutralized with 1 M NH_4OH (1.0 M) and extracted into diethyl ether (2 x 1mL). The ether phase was acidified with 4.0 M HCl in dioxane (200 µL) and the HCl salt was extracted into water (2 x 1mL). The aqueous salt solution was washed with diethyl ether (2 x 1 mL) and lyophilized to yield the product as a white powder.

^{1}H NMR $CDCl_3$ (400 MHz) δ 2.67 (m, 4H), 3.19 (m, 4H), 3.45 (br, 2H), 3.68 (br, 6H), 6.75 (d, J=9.6 Hz, 1H), 6.85 (d, J=8.0 Hz, 1H), 6.95 (m, 1H), 7.11 (d, J=7.6 Hz, 2H), 7.25 (s, 1H), 7.35 (d, J=7.6 Hz, 2H).

EXAMPLE 56

Preparation of 4-[(3-fluorophenyl)-piperidin-4-yl-methyl]-phenyl-piperidin-1-yl-methanone (compound 86)

Same procedure as described for the preparation of compound 85, but using compound 83 as starting material.

^{1}H NMR $CDCl_3$ (400 MHz) δ 1.51 (br, 2H), 1.65 (br, 4H), 2.60 (br, 4H), 3.14 (br, 4H), 3.33 (br, 2H), 3.68 (br, 2H), 6.76 (d, J=8.0 Hz, 1H), 6.86 (d, J=8.0 Hz, 1H), 6.93 (t, J=8.0 Hz, 1H), 7.08 (d, J=8.4 Hz, 2H), 7.25 (s, 1H), 7.32 (d, J= 8.4 Hz, 2H).

EXAMPLE 57

Preparation of 4-[(3-fluorophenyl)-piperidin-4-yl-methyl]-phenyl-pyrolidin-1-yl-methanone (compound 87)

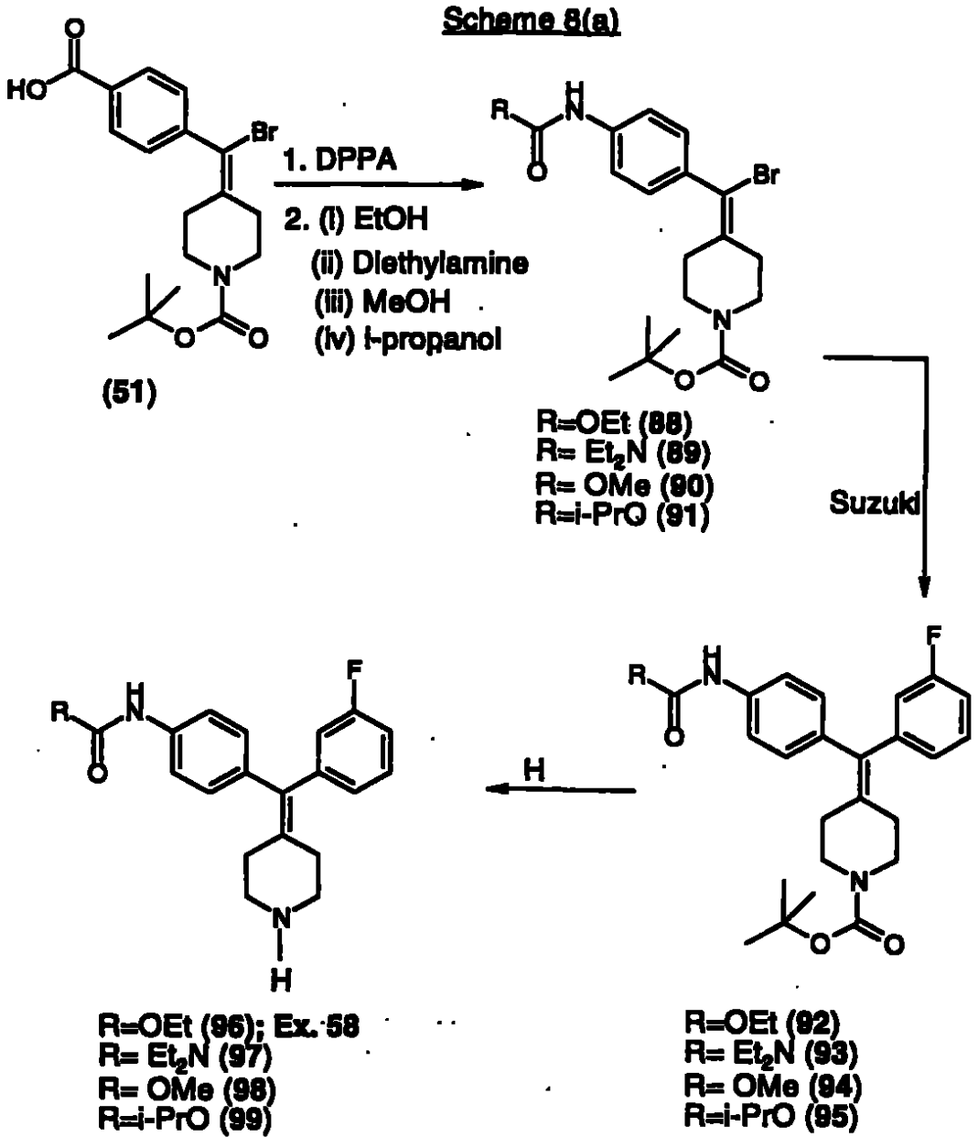
Same procedure as for the preparation of compound 85, but using compound 84 as starting material.

^{1}H NMR $CDCl_3$ (400 MHz) δ 1.84-1.89 (m, 2H), 1.90-1.98 (m, 2H), 2.60-2.63 (m, 4H), 3.13-3.17 (m, 4H), 3.41 (t, J=6.8 Hz, 2H), 3.62 (t, J=6.8 Hz), 6.73 (d, J=8.8 Hz, 1H), 6.86 (d, J=7.2 Hz, 1H), 6.93 (m, 1H), 7.10 (d, J=8.0 Hz, 2H), 7.25 (s, 1H), 7.45 (d, J=8.0 Hz, 2H).

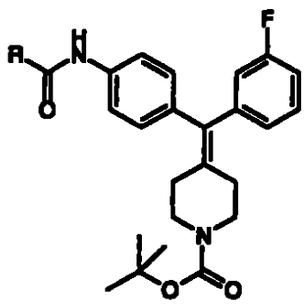
H) Synthetic scheme for the preparation of the compounds of Examples 58-68

The compounds of Examples 58-68 were prepared by following the procedure of Scheme 8 (a) -(c) below.

Scheme 8(a)


HO
O
Br
1. DPPA
2. (i) EtOH
(ii) Diethylamine
(iii) MeOH
(iv) i-propanol
(51)
R
H
N
O
Br
R=OEt (88)
R= Et2N (89)
R= OMe (90)
R=i-PrO (91)
Suzuki
F
H
R=OEt (96); Ex. 58
R= Et2N (97)
R= OMe (98)
R=i-PrO (99)
R=OEt (92)
R= Et2N (93)
R= OMe (94)
R=i-PrO (95)

Scheme 8(b)

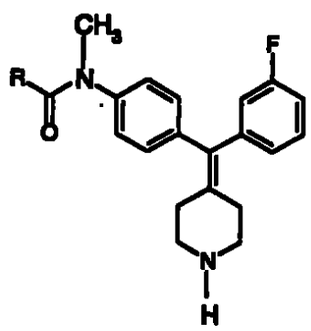


R=OEt (92)
R= Et_2N (93)
R= OMe (94)
R=i-PrO (95)

1. (I) CH_3I/ NaOH
(II) C_2H_5I/ NaOH

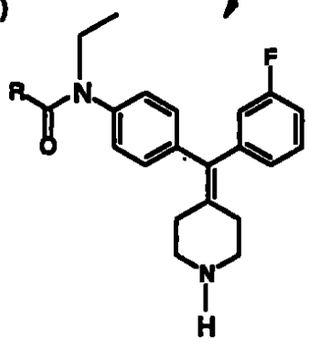
2. HCl

(I)



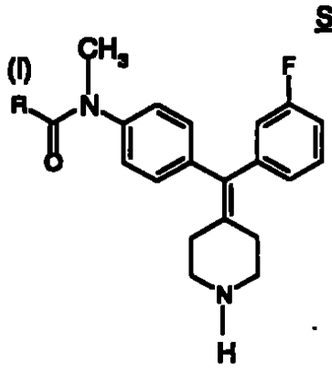
R=OEt (100) Ex. 59
R= Et_2N (101)
R= OMe (102); Ex. 64
R=i-PrO(103); Ex. 62

(II)



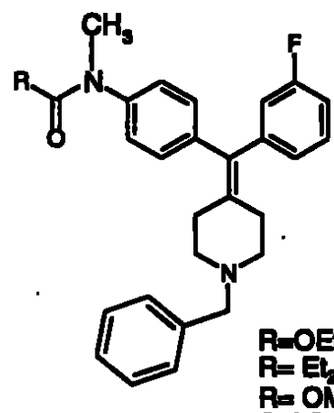
R=OEt (104); Ex. 66
R= Et_2N (105)
R= OMe (106); Ex.65
R=i-PrO (107); Ex. 63

Scheme 8(c)

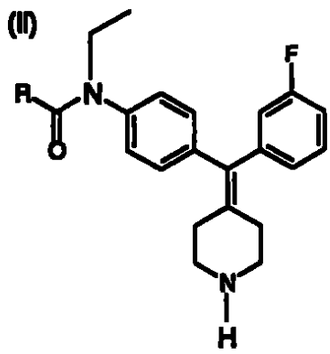


R=OEt (100) Ex. 59
R= Et_2N (101)
R= OMe (102)
R=i-PrO (103)

BnBr/TEA

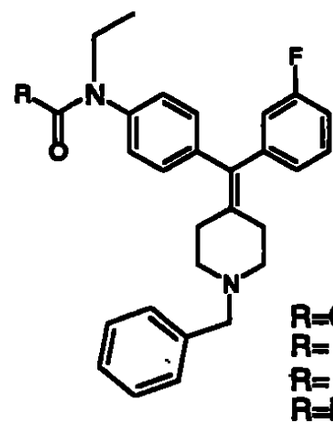


R=OEt (108); Ex. 61
R= Et_2N (109)
R= OMe (110)
R=i-PrO (111)

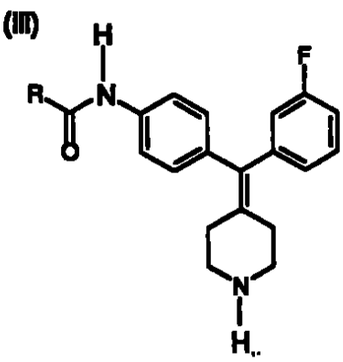


R=OEt (104); Ex. 66
R= Et_2N (105)
R= OMe (106); Ex. 65
R=i-PrO (107)

BnBr/TEA

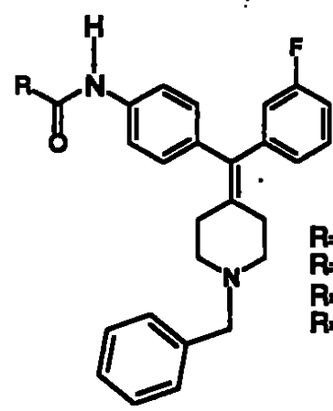


R=OEt (112))
R= Et_2N (113)
R= OMe (114)
R=i-PrO (115)



R=OEt (96)
R= Et_2N (97)
R= OMe (98)
R=i-PrO (99); Ex. 67

BnBr/TEA



R=OEt (116); Ex. 60
R= Et_2N (117)
R= OMe (118)
R=i-PrO (119)

(i) Preparation of 4-[Bromo-(4-ethoxycarbonylamino-phenyl)-methyl]-piperidine-1-carboxylic acid *tert*-butyl ester (compound 88)

To a mixture of compound 51, prepared according to Scheme 6, (0.25 g, 0.625 mmole) in toluene (5 mL), was added diphenylphosphorylazide (0.192 g, 0.70 mmole) and triethylamine (0.1 mL, 0.7 mmole). After stirring the mixture under argon at 95 °C for two hours an excess of anhydrous ethanol (2 mL) and triethylamine (0.1 mL) were added and the solution was stirred at 95 °C for an additional 5 hours. After cooling to room temperature the reaction mixture was partitioned between water and diethyl ether. The ether was washed with water, dried over magnesium sulfate and removed *in vacuo* to give the product (compound 88) as a tan foam (300 mg, 99% yield).

^{1}H NMR (400 MHz) ($CDCl_3$) 1.30 (t, J=7.2 Hz, 3H), 1.44 (s, 9H), 2.22 (t, J=6.0 Hz, 2H), 2.60 (t, J=6.0 Hz, 2H), 3.31 (t, J= 6.0 Hz, 2H), 3.51 (t, J=6.0 Hz, 2H), 4.21 (q, J=7.2 Hz, 2H), 6.58 (s, 1H), 7.19 (d, J=8.4 Hz, 2H), 7.33 (d, J=8.4 Hz, 2H).

(ii) Preparation of 4-[(4-ethoxycarbonylaminophenyl)-(3-fluorophenyl)-methyl]-piperidine-1-carboxylic acid *tert*-butyl ester (compound 92)

The Suzuki coupling of the four vinyl bromides (compounds 88-91) with 3-fluorophenyl boronic acid was performed in parallel. The reactions and liquid-liquid extractions were carried out in 25 mm x 150 mm culture tubes. The protocol for a typical reaction is outlined below.

To a solution of compound 88 (0.30 g, 0.625 mmoles) and tetrakis(triphenyl phosphine), palladium(0) (50 mg) in toluene (degassed, 5 mL) was added 3-fluorophenyl boronic acid (0.182 g, 1.3 mmoles) in ethanol (degassed, 5 mL) followed by 0.75 mL 2M Na_2CO_3 (aq) (1.5 mmoles). The reaction was allowed to proceed at 80 °C for 3 hrs under argon. The reaction was diluted with water and diethyl ether and vortexed. The organic phase was isolated and evaporated to give a crude product. The crude product was purified by silica

gel chromatography (0-50% EtOAc in hexanes) to give the product (compound 92) as a white powder (0.166 g, 58% yield).

^{1}H NMR (400 MHz) ($CDCl_3$) δ 1.25 (t, J=7.2 Hz, 3H), 1.44 (s, 9H), 2.27-2.33 (m, 4H), 3.41-3.44 (m, 4H), 4.20 (q, J=7.2 Hz, 2H), 6.52 (s, 1H), 6.76 (d, J=10 Hz, 2H), 6.85-6.89 (m, 2H), 7.01 (d, J=8.8 Hz, 2H), 7.19-7.23 (m, 1H), 7.28 (d, J=8.8 Hz, 2H)

EXAMPLE 58

Preparation of 4-[(3-fluorophenyl)-piperidin-4-yl-methyll-phenyl-carbamic acid ethyl ester (compound 96)

The removal of the BOC protecting group was performed on a small scale in parallel in test tubes (13 mm x100 mm). A typical procedure is described below.

The BOC group was removed by treating compound 92 (50 mg, 0.11 mmole) with HCl in dioxane (4.0 M, 2 mL). The mixture was stirred at room temperature for 30 minutes. The solvent and HCl were removed *in vacuo* to yield the product compound 96 as a white powder after lyophilization (40 mg, 99% yield).

^{1}H NMR (400 MHz) ($CDCl_3$) δ 1.28 (t, J=7.2 Hz, 3H), 2.27-2.31 (m, 4H), 2.85-2.91 (m, 4H), 4.19 (q, J=7.2 Hz, 2H), 6.50 (s, 1H), 6.76 d, J=10 Hz, 1H), 6.85-6.89 (m, 2H), 7.01 (d, J=8.8 Hz, 2H), 7.19-7.23 (m, 1H), 7.28 (d, J=8.8 Hz, 2H).

EXAMPLE 59

Preparation of 4-[(3-fluorophenyl)-piperidin-4-yl-methyll-phenyl-methyl carbamic acid ethyl ester (compound 100)

The alkylation of the amide nitrogen was performed on a small scale in parallel in test tubes (13 mm x 100 mm). A typical procedure is outline below.

To a solution of compound 92 (50 mg, 0.11 mmoles) in dichloromethane (1.5 mL) was added methyl iodide (31 mg, 0.22 mmoles), aqueous sodium hydroxide (1.0 mL, 2M) and tetrabutylammonium sulfate (44 mg, 0.13 mmoles). The solution was refluxed for one hour. After cooling to room temperature the dichloromethane was separated and evaporated. Ether was added to the residue and the white tetrabutylammonium iodide was removed by filtration. The ether was removed *in vacuo* to give the crude product compound 100 as a clear oil. The BOC group was removed by treatment with HCl in dioxane as described above to give the product as a white powder after lyophilization (17 mg, 42% yield).

^{1}H NMR (400 MHz) ($CDCl_3$) δ 1.23 (t, J=7.2 Hz, 3H), 2.27-2.33 (m, 4H), 2.85-2.91 (m, 4H), 3.26 (s, 3H), 4.15 (q, J=7.2 Hz, 2H), 6.78 (d, J=10 Hz, 1H), 6.85-6.89 (m, 2H), 7.05 (d, J=8.0 Hz, 2H), 7.14 (d, J=8.0 Hz, 2H) 7.19-7.23 (m, 1H).

EXAMPLE 60

Preparation of 4-[(1-benzylpiperidin-4-yl)-(3-fluorophenyl)-methyl]-phenyl-carbamic acid ethyl ester (compound 116)

The benzylation of compound 100 was performed on a small scale in parallel in test tubes (13 mm x 100 mm). A typical procedure is outline below.

The free base form of compound 100 was obtained by addition of ammonium hydroxide (1M, 0.5 mL) to an aqueous solution of compound 100 (0.046 mmoles) and extracted into ether. The ether was removed *in vacuo* to give an oil which was dissolved in dichloromethane and treated with benzyl bromide (0.14 mL of 0. 5 M in dichloromethane) and triethylamine (0.05 mL). The solution was stirred at room temperature for 5 hours. The solvent was removed *in vacuo*. The product was dissolved in water/acetonitrile/HCl (2:1:0.5 M) and lyophilized to give the product compound 108 as a white powder.

^{1}H NMR (400 MHz) ($CDCl_3$) δ 1.28 (t, J=7.2 Hz, 3H), 2.33-2.36 (m, 4H), 2.38-2.46 (m, 4H), 3.51 (s, 2H), 4.19 (q, J=7.2 Hz, 2H), 6.50 (s, 1H), 6.78 d, J=10 Hz, 1H), 6.85-6.89 (m, 2H), 7.05 (d, J=8.0 Hz, 2H), 7.19-7.30 (m, 7H).

EXAMPLES 61-68

The following compounds were also made by following the synthesis routes described in Schemes 8 (a)-(c).

Table 1

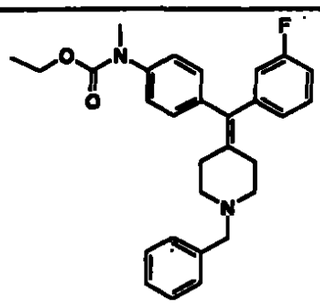
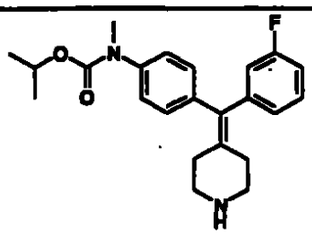
Example	*Compound*	*Chemical structure*	*Characterization data [^{1}H NMR; 400 MHz ($CDCl_3$)]*	*Scheme*
61	108		δ 1.17 (t, J=7.6 Hz, 3H), 2.28-2.35 (m, 4H), 2.40-2.45 (m, 4H), 3.21 (s, 3H), 3.50 (s, 2H), 4.10 (q, J=7.2 Hz, 2H), 6.73 (d, J=8.7 Hz, 1H), 6.85 (m, 2H), 7.01 (d, J=8.8 Hz, 2H), 7.2-7.3 (m, 8H)	8 (c)
62	103		δ 1.21 (d, J=6.8 Hz, 6H), 2.28 (t, J=5.6 Hz, 2H), 2.31 (t, J=5.6 Hz, 2H), 2.88 (t, J=5.6 Hz, 4H), 3.25 (s, 3H), 4.93 (quin, J=6.0 Hz, 1H), 6.78 (d, 1H), 6.87 (d, 2H), 7.04 (d, 2H), 7.14 (d, 2H), 7.15-7.29 (m, 2H)	8 (b)

Table 1 (contd)

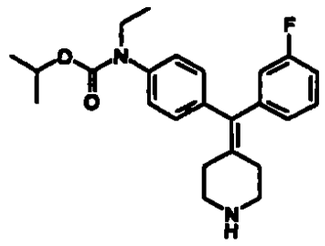
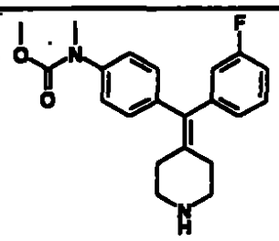
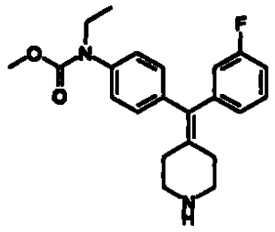
Example	*Compound*	*Chemical structure*	*Characterization data [^{1}H NMR; 400 MHz ($CDCl_3$)]*	*Scheme*
63	107		δ 1.14 (t, J=7.2 Hz, 3H), 1.20 (d, J=6.4 Hz, 6H), 2.92 (t, J=5.2 Hz, 2H), 2.33 (t, J=5.2 Hz, 2H), 2.90 (t, J=5.2 Hz, 4H), 3.66 (q, J=7.6 Hz, 2H), 4.93 (quin, J=6.0 Hz, 1H), 6.79 (d, 1H), 6.88 (d, 2H), 7.02 (d, 2H), 7.15 (d, 2H), 7.18-7.25 (m, 2H)	8 (b)
64	102		δ 2.27-2.33 (m, 4H), 2.88-2.90 (m, 4H), 3.27 (s, 3H), 3.70 (s, 3H), 6.79 (d, 10 Hz, 1H), 6.88-6.90 (m, 2H), 7.06 (d, J=8.4 Hz, 2H), 7.13 (d, J=8.4 Hz, 2H), 7.20-7.25 (m, 1H)	8 (b)
65	106		δ 1.13 (t, J=6.8 Hz, 3H), 2.27-2.33 (m, 4H), 2.88-2.90 (m, 4H), 3.67 (s, 3H), 3.68 (q, J=6.8 Hz, 2H), 6.79 (d, 10 Hz, 1H), 6.88-6.90 (m, 2H), 7.06 (d, J=8.4 Hz, 2H), 7.13 (d, J=8.4 Hz, 2H), 7.20-7.25 (m, 1H)	8 (b)

Table 1 (contd)

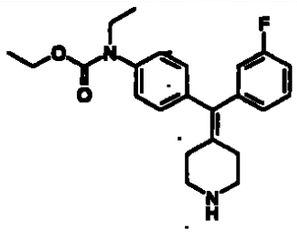
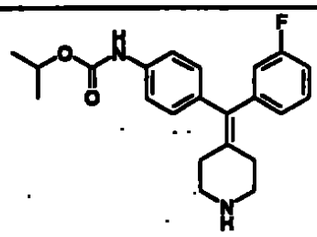
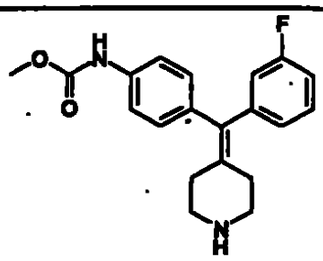
Example	*Compound*	*Chemical structure*	*Characterization data [^{1}H NMR; 400 MHz ($CDCl_3$)]*	*Scheme*
66	104		δ 1.13 (t, J=6.8 Hz, 3H), 1.21 (t, J=7.2 Hz, 3H), 2.30-2.36 (m, 4H), 2.91-2.93 (m, 4H), 3.67 (q, J=6.8 Hz, 2H), 4.13 (q, J=6.8 Hz, 2H), 6.79 (d, 10 Hz, 1H), 6.88-6.90 (m, 2H), 7.06 (d, J=8.4 Hz, 2H), 7.13 (d, J=8.4 Hz, 2H), 7.20-7.25 (m, 1H)	8 (b)
67	99		δ 1.26 (d, J=6.0 Hz, 6H), 2.27-2.32 (m, 4H), 2.87-2.89 (m, 4H), 4.95-5.02 (m, 1H), 6.56 (s, 1H), 6.79 (d, 10 Hz, 1H), 6.88-6.90 (m, 2H), 7.01 (d, J=8.4 Hz, 2H), 7.20-7.25 (m, 1H), 7.27 (d, J=8.4 Hz, 2H)	8 (b)

Table 1 (cont)

Example	*Compound*	*Chemical structure*	*Characterization data [^{1}H NMR; 400 MHz ($CDCl_3$)]*	*Scheme*
68	98		δ 2.27-2.31 (m, 4H), 2.86-2.89 (m, 4H), 3.75 (s, 3H), 6.64 (s, 1H), 6.76-6.80 (m, 1H), 6.85-7.00 (m, 2H), 7.02 (d, J=8.8 Hz, 2H), 7.18-7.22 (m, 1H), 7.28 (d, J=8.8 Hz, 2H)	8 (b)

The best mode of performing the invention known at present, is to use the compounds 6, 7, 9, 10, 12, 26. 27, 34, 39, 44, 58, 59, 62, 69, 71, 104, 106, and 109.

Pharmaceutical compositions

The novel compounds according to the present invention may be administered orally, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracially, intravenously, epidurally, intrathecally, intracerebroventricularly and by injection into the joints.

A preferred route of administration is orally, intravenously or intramuscularly.

The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician,

when determining the individual regimen and dosage level at the most appropriate for a particular patient.

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized molds and allowed to cool and solidify.

Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

Pharmaceutically acceptable salts are acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium acetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, glucaptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate,

maleate, mandelate mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclate, triethiodide, benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminium, calcium, lithium, magnesium, potassium, sodium, and zinc.

Preferred pharmaceutically acceptable salts are the hydrochlorides and citrates.

The term composition is intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid from compositions include solutions, suspensions, and emulsions. Sterile water or water-propylene glycol solutions of the active compounds may be mentioned as an example of liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Preferably the pharmaceutical compositions is in unit dosage form. In such form, the composition is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparations, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

BIOLOGICAL EVALUATION

A) IN VITRO MODEL

Cell culture

Human 293S cells expressing cloned human μ, δ, and κ receptors and neomycin resistance were grown in suspension at 37°C and 5% CO_2 in shaker flasks containing calcium-free DMEM 10% FBS, 5% BCS, 0.1% Pluronic F-68, and 600 μg/ml geneticin.

Membrane preparation

Cells were pelleted and resuspended in lysis buffer (50 mM Tris, pH 7.0, 2.5 mM EDTA, with PMSF added just prior to use to 0.1 mM from a 0.1 M stock in ethanol), incubated on ice for 15 min, then homogenized with a polytron for 30 sec. The suspension was spun at 1000g (max) for 10 min at 4°C. The supernatant was saved on ice and the pellets resuspended and spun as before. The supernatants from both spins were combined and spun at 46,000 g(max) for 30 min. The pellets were resuspended in cold Tris buffer (50 mM Tris/Cl, pH 7.0) and spun again. The final pellets were resuspended in membrane buffer (50 mM Tris, 0.32 M sucrose, pH 7.0). Aliquots (1 ml) in polypropylene tubes were frozen in dry ice/ethanol and stored at -70°C until use. The protein concentrations were determined by a modified Lowry assay with SDS.

Binding assays

Membranes were thawed at 37°C, cooled on ice, passed 3 times through a 25-gauge needle, and diluted into binding buffer (50 mM Tris, 3 mM $MgCl_2$, 1 mg/ml BSA (Sigma A-7888), pH 7.4, which was stored at 4°C after filtration through a 0.22 m filter, and to which had been freshly added 5 µg/ml aprotinin, 10 µM bestatin, 10 µM diprotin A, no DTT). Aliquots of 100 µl (for µg protein, see Table 1) were added to iced 12x75 mm polypropylene tubes containing 100 µl of the appropriate radioligand (see Table 1) and 100 µl of test peptides at various concentrations. Total (TB) and nonspecific (NS) binding were determined in the absence and presence of 10 µM naloxone respectively. The tubes were vortexed and incubated at 25°C for 60-75 min, after which time the contents are rapidly vacuum-filtered and washed with about 12 ml/tube iced wash buffer (50 mM Tris, pH 7.0, 3 mM $MgCl_2$) through GF/B filters (Whatman) presoaked for at least 2h in 0.1% polyethyleneimine. The radioactivity (dpm) retained on the filters was measured with a beta counter after soaking the filters for at least 12h in minivials containing 6-7 ml scintillation fluid. If the assay is set up in 96-place deep well plates, the filtration is over 96-place PEI-soaked unifilters, which were washed with 3 x 1 ml wash buffer, and dried in an oven at 55°C for 2h. The filter plates were counted in a TopCount (Packard) after adding 50 µl MS-20 scintillation fluid/well.

Data analysis

The specific binding (SB) was calculated as TB-NS, and the SB in the presence of various test peptides was expressed as percentage of control SB. Values of IC_{50} and Hill coefficient (n_H) for ligands in displacing specifically bound radioligand were calculated from logit plots or curve fitting programs such as Ligand, GraphPad Prism, SigmaPlot, or ReceptorFit. Values of K_i were calculated from the Cheng-Prussoff equation. Mean ± S.E.M. values of IC_{50}, K_i and n_H were reported for ligands tested in at least three displacement curves.

Receptor saturation experiments

Radioligand K_s values were determined by performing the binding assays on cell membranes with the appropriate radioligands at concentrations ranging from 0.2 to 5 times the estimated K_s (up to 10 times if amounts of radioligand required are feasable). The specific radioligand binding was expressed as pmole/mg membrane protein. Values of K_s and B_{max} from individual experiments were obtained from nonlinear fits of specifically bound (B) vs. nM free (F) radioligand from individual according to a one-site model.

B) BIOLOGICAL MODEL (IN VIVO MODEL)

FREUND'S COMPLETE ADJUVANT (FCA), AND SCIATIC NERVE CUFF INDUCED MECHANO-ALLODYNIA IN RAT

Animals

Male Sprague-Dawley rats (Charles River, St-Constant, Canada) weighing 175-200g at the time of surgery were used. They were housed in groups of three in rooms thermostatically maintained at 20° C with a 12:12 hr light/dark cycle, and with free access to food and water. After arrival, the animals were allowed to acclimatize for at least 2 days before surgery. The experiments were approved by the appropriate Medical Ethical Committee for animal studies.

EXPERIMENTAL PROCEDURE

FREUND'S COMPLETE ADJUVANT

The rats were first anesthetized in a Halothane chamber after which 10µl of FCA was injected s.c. into the dorsal region of the left foot, between the second and third external digits. The animals were then allowed to recover from anesthesia under observation in their home cage.

SCIATIC NERVE CUFF

The animals were prepared according to the method described by Mosconi and Kruger (1996). Rats were anesthetized with a mixture of Ketamine / Xylazine i.p. (2ml/kg) and placed on their right side and an incision made over, and along the axis of, the lateral aspect of the left femur. The muscles of the upper quadriceps were teased apart to reveal the sciatic nerve on which a plastic cuff (PE-60 tubing, 2mm long) was placed around. The wound was then closed in two layers with 3-0 vicryl and silk sutures.

DETERMINATION OF MECHANO-ALLODYNIA USING VON FREY TESTING

Testing was performed between 08:00 and 16:00h using the method described by Chaplan et al. (1994). Rats were placed in Plexiglas cages on top of a wire mesh bottom which allowed access to the paw, and were left to habituate for 10-15 min. The area tested was the mid-plantar left hind paw, avoiding the less sensitive foot pads. The paw was touched with a series of 8 Von Frey hairs with logarithmically incremental stiffness (0.41, 0.69, 1.20, 2.04, 3.63, 5.50, 8.51, and 15.14 grams; Stoelting, Ill, USA). The von Frey hair was applied from underneath the mesh floor perpendicular to the plantar surface with sufficient force to cause a slight buckling against the paw, and held for approximately 6-8 seconds. A positive response was noted if the paw was sharply withdrawn. Flinching immediately upon removal of the hair was also considered a positive response. Ambulation was considered an ambiguous response, and in such cases the stimulus was repeated.

TESTING PROTOCOL

The animals were tested on postoperative day 1 for the FCA-treated group and on post-operative day 7 for the Sciatic Nerve Cuff group. The 50% withdrawal threshold was determined using the up-down method of Dixon (1980). Testing was started with the 2.04 g hair, in the middle of the series. Stimuli were always presented in a consecutive way, whether ascending or descending. In the absence of a paw withdrawal response to the initially selected hair, a stronger stimulus was presented; in the event of paw withdrawal, the next weaker stimulus was chosen. Optimal threshold calculation by this method

requires 6 responses in the immediate vicinity of the 50% threshold, and counting of these 6 responses began when the first change in response occurred, e.g. the threshold was first crossed. In cases where thresholds fell outside the range of stimuli, values of 15.14 (normal sensitivity) or 0.41 (maximally allodynic) were respectively assigned. The resulting pattern of positive and negative responses was tabulated using the convention, X = no withdrawal; O = withdrawal, and the 50% withdrawal threshold was interpolated using the formula:

$$50\%\ \text{g threshold} = 10^{(Xf + k\delta)} / 10{,}000$$

where Xf = value of the last von Frey hair used (log units); k = tabular value (from Chaplan et al. (1994)) for the pattern of positive / negative responses; and δ = mean difference between stimuli (log units). Here $\delta = 0.224$.

Von Frey thresholds were converted to percent of maximum possible effect (% MPE), according to Chaplan et al. 1994. The following equation was used to compute % MPE:

$$\%\ \text{MPE} = \frac{\text{Drug treated threshold (g) - allodynia threshold (g)}}{\text{Control threshold (g) - allodynia threshold (g)}} \times 100$$

ADMINISTRATION OF TEST SUBSTANCE

Rats were injected (subcutaneously, intraperitoneally, or orally) with a test substance prior to von Frey testing, the time between administration of test compound and the von Frey test varied depending upon the nature of the test compound.

Definitions:

The following abbreviations have the indicated meanings:

Ac = acetyl

Ar = aryl

t-BOC = tertiary-butoxycarbonyl

t-Bu = tertiary-butyl

Et = ethyl

iPr = isopropyl

Me = methyl

Ph = phenyl

Pr = propyl

r.t. = room temperature

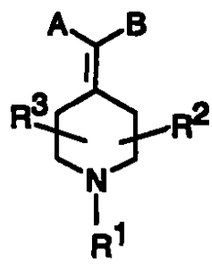
TFA = trifluoroacetic acid

THF = tetrahydrofuran

TMEDA = N,N,N',N'-tetramethylethylenediamine

CLAIMS

1. A compound of the general formula (I)



(I)

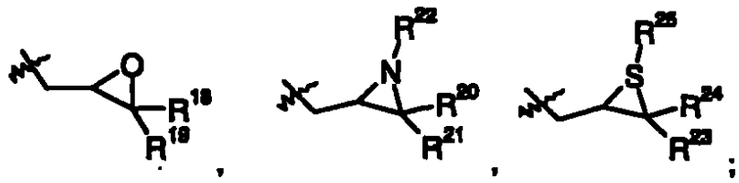
R^1 is selected from

hydrogen, a branched or straight C_1-C_6 alkyl, C_1-C_6 alkenyl, C_3-C_8 cycloalkyl, C_4-C_8(alkyl-cycloalkyl) wherein alkyl is C_1-C_2 alkyl and cycloalkyl is C_3-C_6 cycloalkyl;

C_6-C_{10} aryl; or heteroaryl having from 5 to 10 atoms selected from any of C, S, N and O; wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents independently selected from any of hydrogen, CH_3, $-(CH_2)_pCF_3$, halogen, $-CONR^5R^4$, $-COOR^5$, $-COR^5$, $-(CH_2)_pNR^5R^4$, $-(CH_2)_pCH_3(CH_2)_pSOR^5R^4$, $-(CH_2)_pSO_2R^5$, and $-(CH_2)_pSO_2NR^5$, wherein R^4 and R^5 is each and independently as defined for R^1 above and p is 0, 1 or 2;

(C_1-C_2 alkyl)-(C_6-C_{10} aryl); or (C_1-C_2 alkyl)heteroaryl, the heteroaryl moieties having from 5 to 10 atoms selected from any of C, S, N and O, and where the aryl or heteroaryl may optionally and independently be substituted by 1 or 2 substituents independently selected from any of hydrogen, CH_3, $-(CH_2)_qCF_3$, halogen, $-CONR^5R^4$, $-COOR^5$, $-COR^5$, $-(CH_2)_qNR^5R^4$, $-(CH_2)_qCH_3(CH_2)_qSOR^5R^4$, $-(CH_2)_qSO_2R^5$,

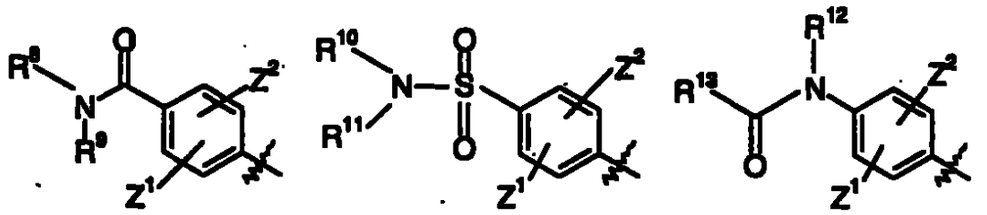
—$(CH_2)_qSO_2NR^5$ and —$(CH_2)_pOR^5$, wherein R^4 and R^5 is each and independently as defined for R^1 above and q is 0, 1 or 2; and

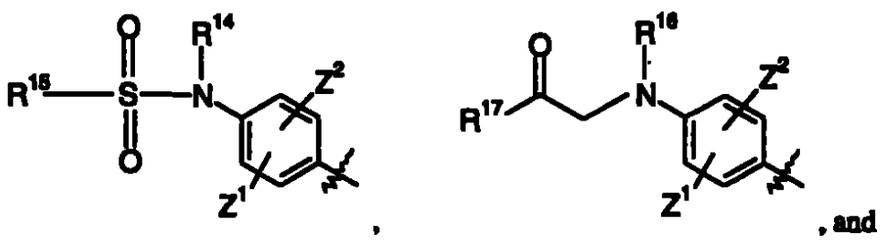


wherein R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24} and R^{25} is each and independently hydrogen, C_1-C_6 alkyl or C_1-C_6 alkenyl;

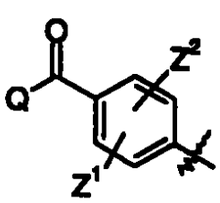
R^2 and R^3 is each and independently hydrogen or C_1-C_6 alkyl;

A is selected from





, and



;

wherein R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} is each and independently as defined for R^1 above, and wherein the phenyl ring of each A substituent may be optionally and independently substituted at any position of the phenyl ring by 1 or 2 substituents Z^1 and Z^2 which are each and independently selected from hydrogen, CH_3, $-(CH_2)_qCF_3$, halogen, $-CONR^6R^7$, $-COOR6$, $-COR^6$, $-(CH_2)_rNR^6R^7$, $-(CH_2)_rCH_3(CH_2)_rSOR^6$, $-(CH_2)_rSO_2R^6$ and $-(CH_2)_rSO_2NR^6R^7$ wherein R^6 and R^7 is each and independently as defined for R^1 above and r is 0, 1, or 2;

Q is C_5-C_6 hydroaryl or heterohydroaromatic having 5 or 6 atoms selected from anyone of C, S, N and O; C_5 -C_6 cykloalkyl, or heterocycloalkyl having 5 or 6 atoms selected from anyone of C, N, O and S; and where each Q may optionally be substituted by a substituent Z^1 and Z^2 as defined above;

B is

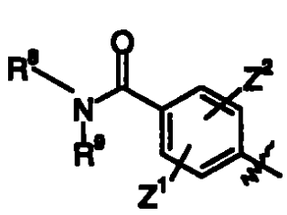
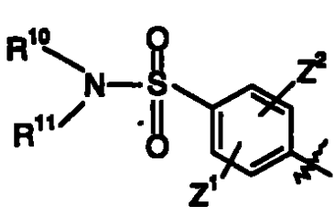
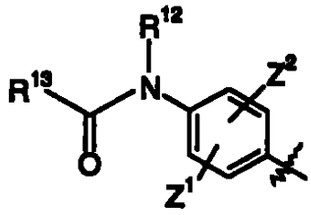
a substituted or unsubstituted aromatic, heteroaromatic, hydroaromatic or heterohydroaromatic moiety having from 5 to 10 atoms selected from any of C, S, N and O, optionally and independently substituted by 1 or 2 substituents independently selected from hydrogen, CH_3, $-(CH_2)_tCF_3$, halogen, $-(CH_2)_tCONR^5R^4$, $-(CH_2)_tNR^5R^4$, $-(CH_2)_tCOR^5$, $-(CH_2)_tCOOR^5$, $-OR^5$, $-(CH_2)_tSOR^5$, $-(CH_2)_tSO_2R^5$, and $-(CH_2)tSO_2NR^5R^4$, wherein R^4 and R^5 is each and independently as defined for R^1 above, and t is 0, 1, 2 or 3;

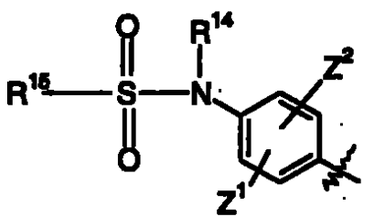
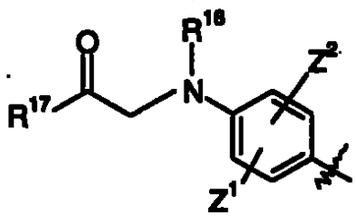
R^4 and R^5 is each and independently as defined for R^1 above;

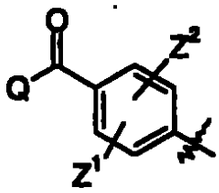
as well as pharmaceutically acceptable salts of the compounds of the formula (I), and isomers, hydrates, isoforms and prodrugs thereof.

2. A compound of the formula (I) according to claim 1, wherein

A is selected from



; and


;

wherein R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} is each and independently as defined for R^1 above, and wherein the phenyl ring of each A substituent may be optionally and independently substituted at any position of the phenyl ring by 1 or 2 substituents Z^1 and Z^2 which are each and independently selected from hydrogen, CH_3, $-(CH_2)_qCF_3$, halogen, $-CONR^6R^7$, $-COOR^6$, $-COR^6$, $-(CH_2)_rNR^6R^7$, $-(CH_2)_rCH_3(CH_2)_rSOR^6$, $-(CH_2)_rSO_2R^6$ and $-(CH_2)_rSO_2NR^6R^7$ wherein R^6 and R^7 is each and independently as defined for R^1 above, and r is 0, 1, or 2;

Q is selected from morpholine, piperidine and pyrrolidine;

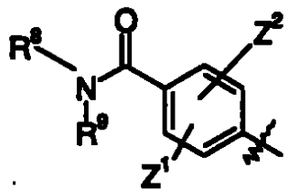
R^1, R^4, and R^5 is each and independently selected from hydrogen, a branched or straight C_1-C_4 alkyl, C_3-C_5 cycloalkyl, C_4-C_8 (alkyl-cycloalkyl) wherein alkyl is C_1-C_2 alkyl and cycloalkyl is C_3-C_6 cycloalkyl; C_6-C_{10} aryl; and heteroaryl having from 5 to 6 atoms selected from any of C, S, N and O; and where the aryl or heteroaryl may optionally and independently be substituted by 1 or 2 substituents independently selected from any of hydrogen, CH_3, $-(CH_2)_pCF_3$, halogen, $-CONR^5R^4$, $-COOR^5$, $-COR^5$, $-(CH_2)_pNR^5R^4$, $-(CH_2)_pCH_3(CH_2)_pSOR^5R^4$, $-(CH_2)_pSO_2R^5$, and $-(CH_2)_pSO_2NR^5$, wherein R^4 and R^5 is each and independently as defined for R^1 above and p is 0, 1 or 2;

B is selected from phenyl, naphthyl, indolyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl, pyrryl, furanyl, quinolinyl, isoquinolinyl, cyclohexyl, cyclohexenyl, cyclopentyl, cyclopentenyl, indanyl, indenyl, tetrahydronaphthyl, tetrahydroquinyl, tetrahydroisoquinolinyl, tetrahydrofuranyl, pyrrolidinyl, and indazolinyl, each optionally and independently substituted by 1 or 2 substituents independently selected from hydrogen, CH_3, CF_3, halogen, $-(CH_2)_qCONR^5R^4$, $-(CH_2)_qNR^5R^4$, $-(CH_2)_qCOR^5$, $-(CH_2)_qCO_2R^5$, and $-OR^5$, wherein q is 0 or 1, and wherein R^4 and R^5 are as defined above;

R^2 and R^3 is each and independently hydrogen or methyl.

3. A compound of the formula (I) according to claim 2, wherein

A is



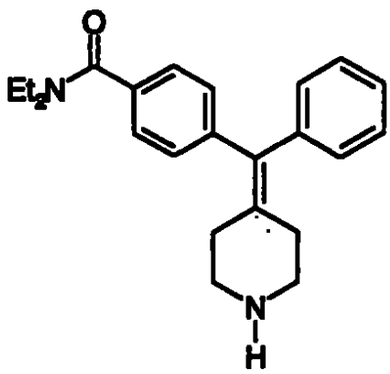
wherein R^8 and R^9 are both ethyl, and where the phenyl ring optionally and independently may be substituted at any position of the phenyl ring by 1 or 2 substituents Z^1 and Z^2 which are each and independently selected from hydrogen, CH_3, $-(CH_2)_qCF_3$, halogen, $-CONR^6R^7$, $-COOR^6$, $-COR^6$, $-(CH_2)_rNR^6R^7$, $-(CH_2)_rCH_3(CH_2)_rSOR^6$, $-(CH_2)_rSO_2R^6$ and $-(CH_2)_rSO_2NR^6R^7$ wherein R^6 and R^7 is each and independently as defined for R^1 above and r is 0, 1, or 2;

R^1 is selected from hydrogen, methyl, ethyl, $-CH_2CH=CH_2$, $-CH_2$-cyclopropyl, $-CH_2-$aryl, or CH_2-heteroaryl, the heteroaryl moieties having from 5 to 6 atoms selected from any of C, S, N and O;

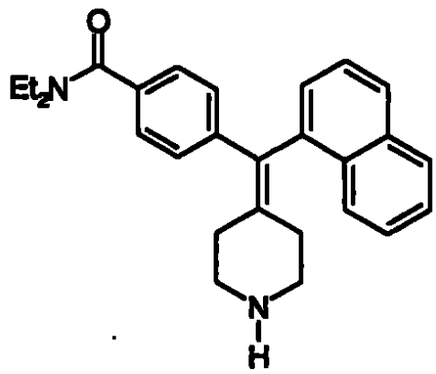
B is selected from phenyl, naphthyl, indolyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl, furanyl, quinolinyl, isoquinolinyl, cyclohexyl, cyclohexenyl, cyclopentyl, cyclopentenyl, indanyl, indenyl, tetrahydronaphthyl, tetrahydroquinyl, tetrahydroisoquinolinyl, tetrahydrofuranyl, and indazolinyl, each optionally and independently substituted by 1 or 2 substituents independently selected from hydrogen, CH_3, CF_3, halogen, $-(CH_2)_qCONR^5R^4$, $-(CH_2)_qNR^5R^4$, $-(CH_2)_qCOR^5$, $-(CH_2)_qCO_2R^5$, and $-OR^5$, wherein q is 0 or 1, and wherein R^4 and R^5 are as defined above; and

R^2 and R^3 is each and independently hydrogen or methyl.

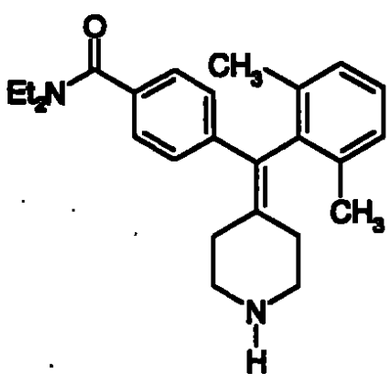
4. A compound of the formula (I) according to claim 1, which compound is any of



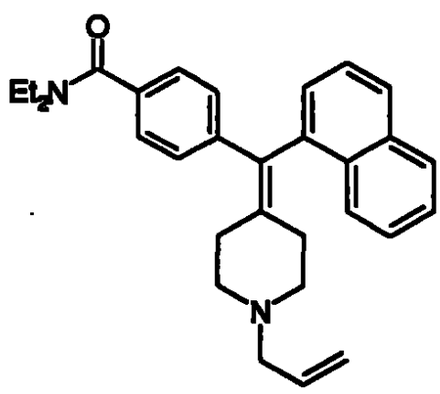
;



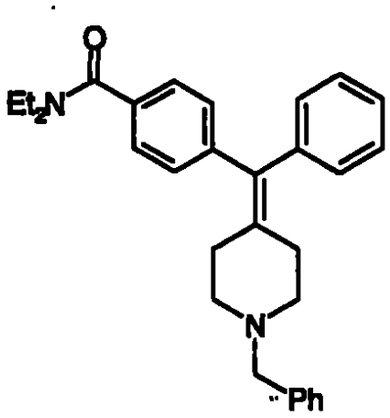
;



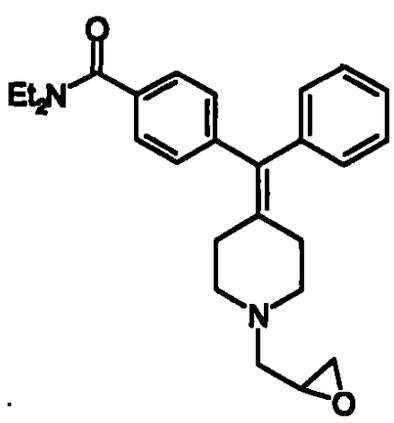
;



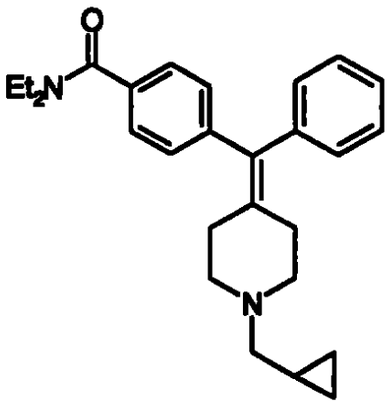
;



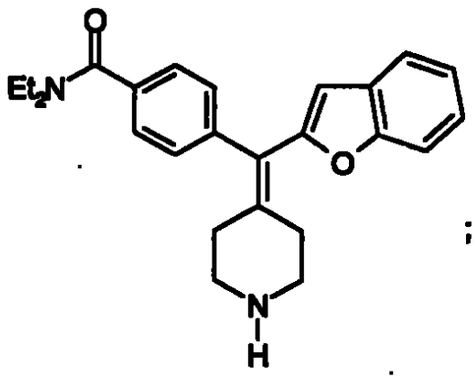
;



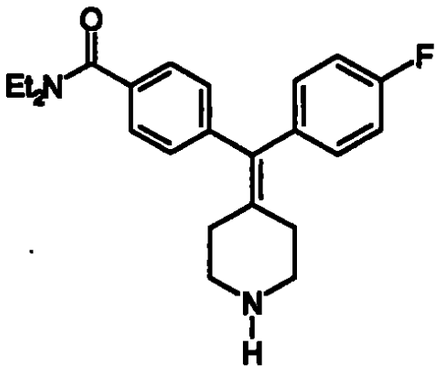
;



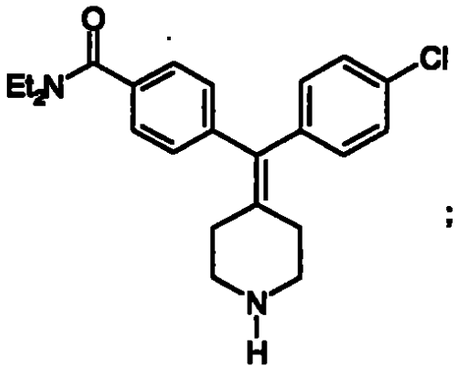
;



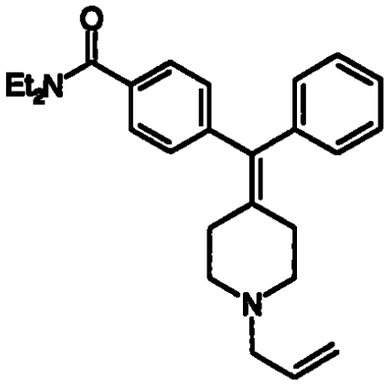
;



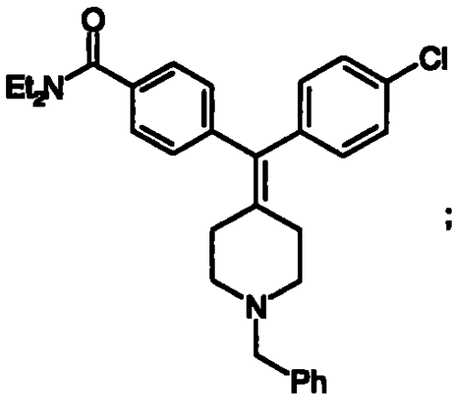
;



;

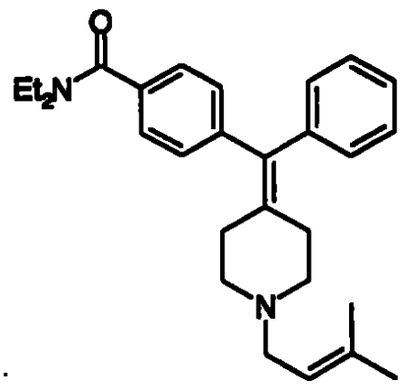


;

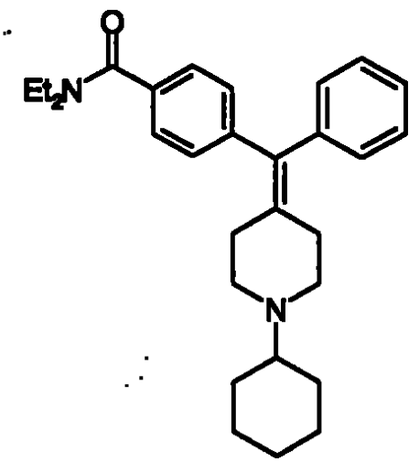


;

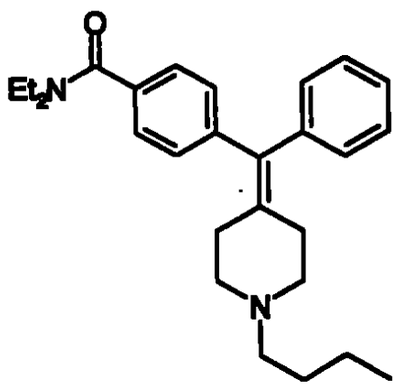
s



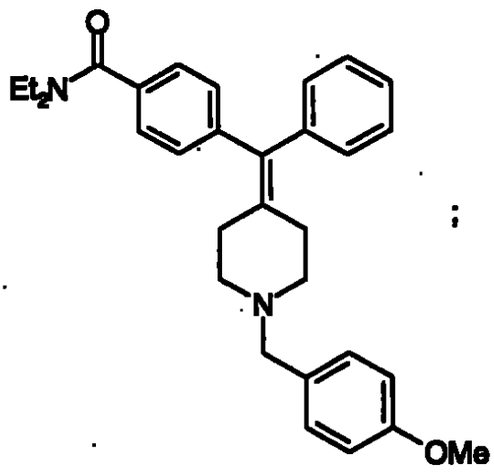
;



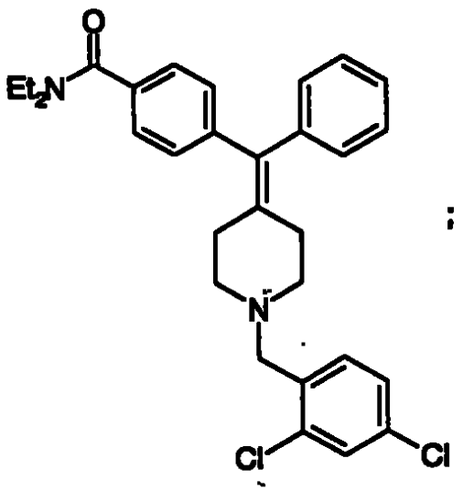
;



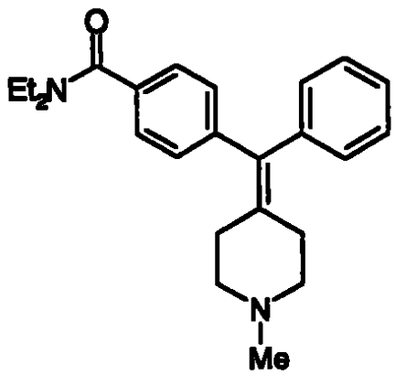
;



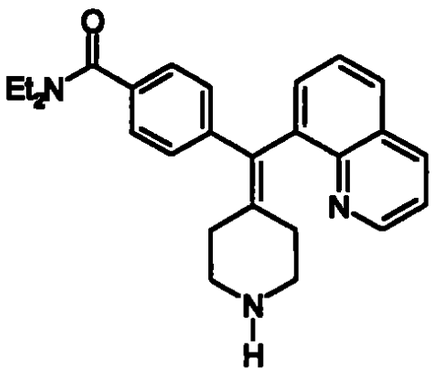
;



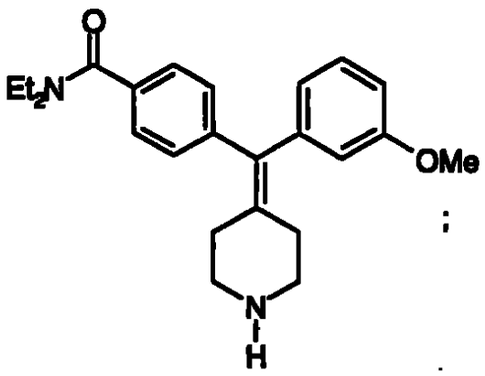
;



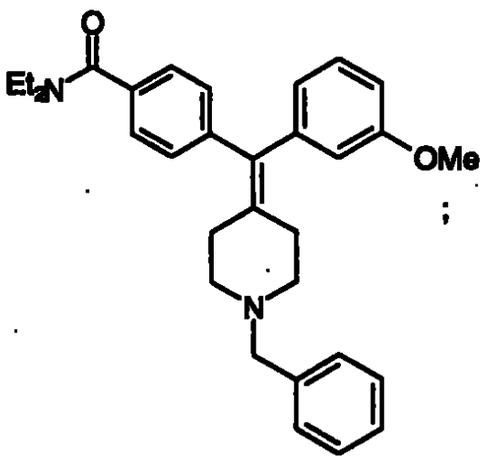
;



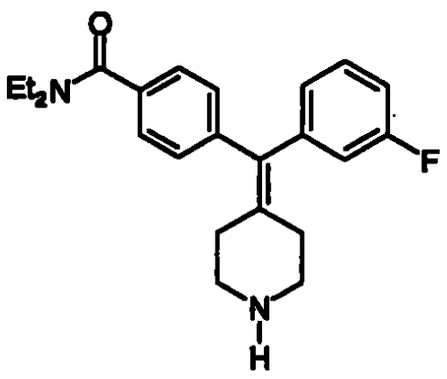
;



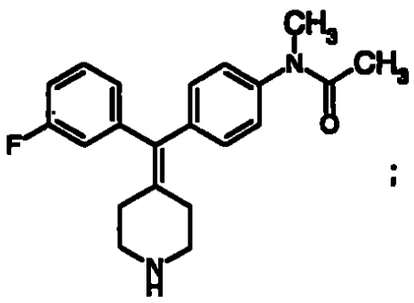
;



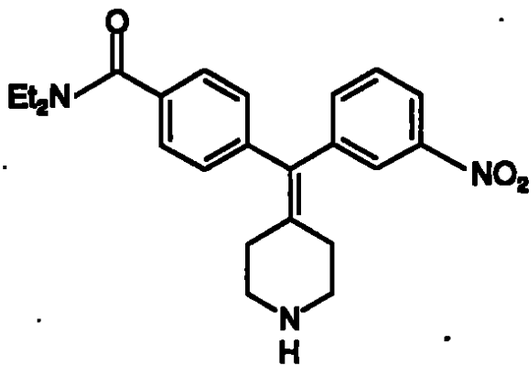
;



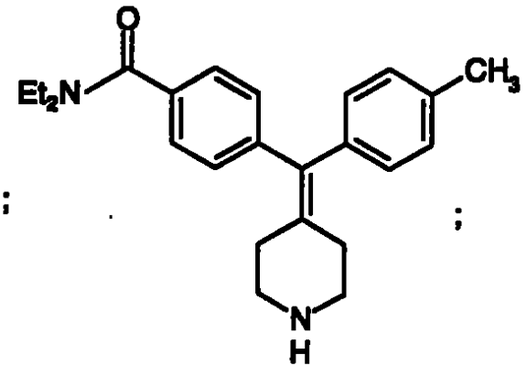
5



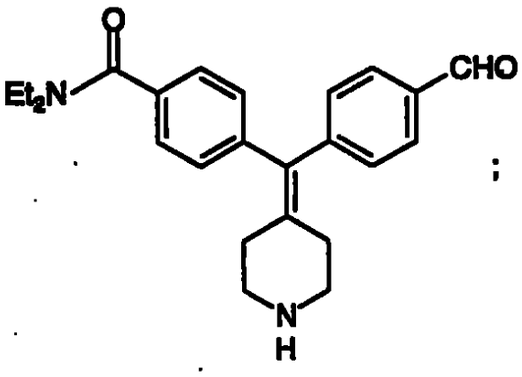
;



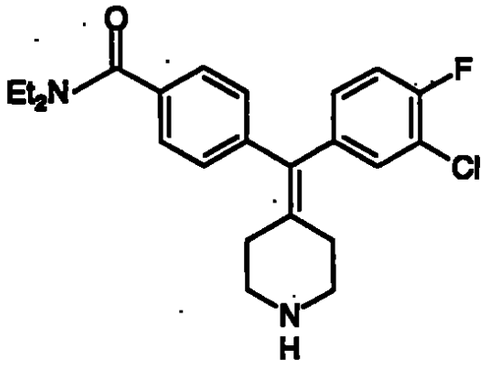
;



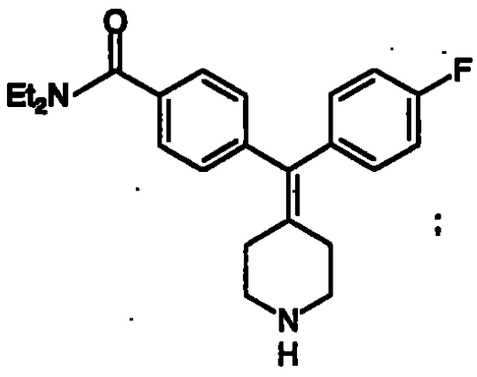
;



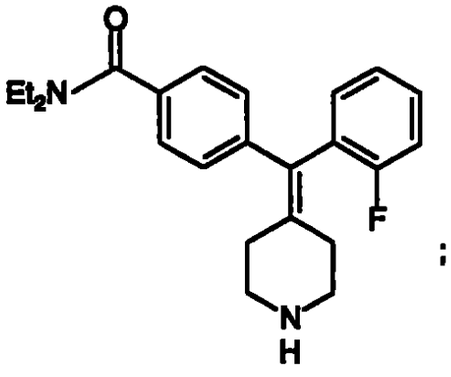
;



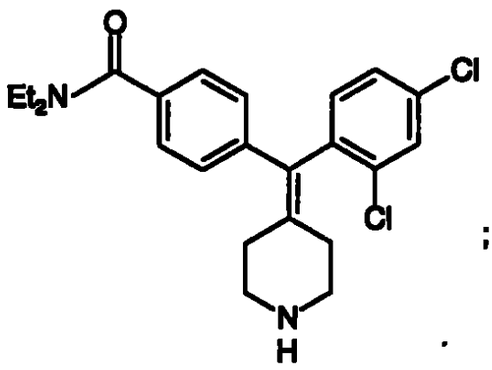
;

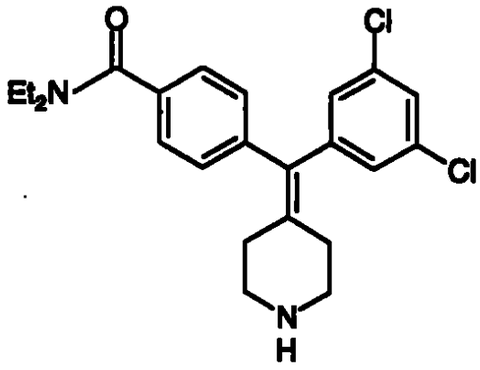


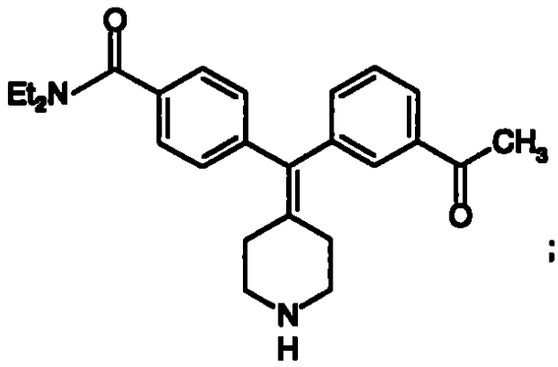
;

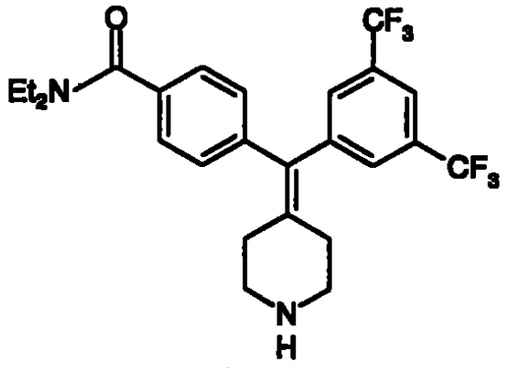


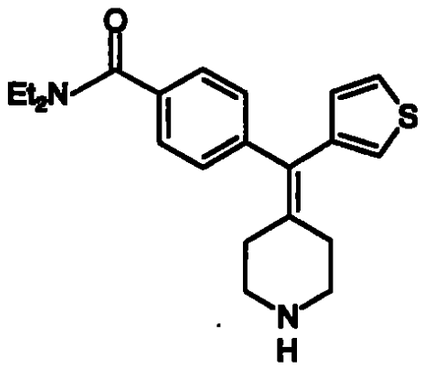
;

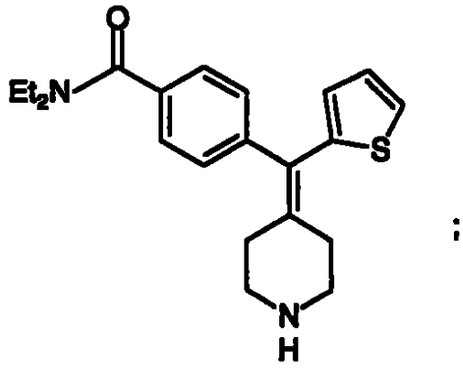

;


;

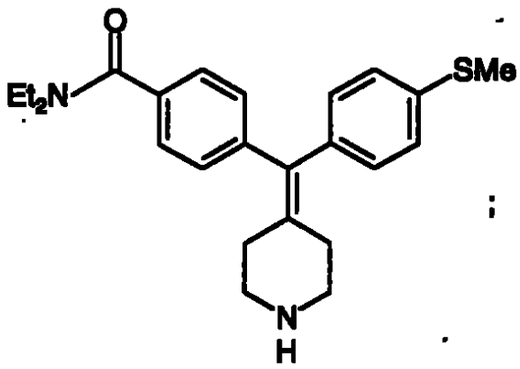

;


;

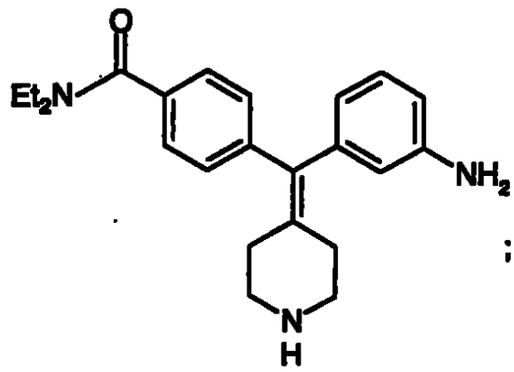

;


;

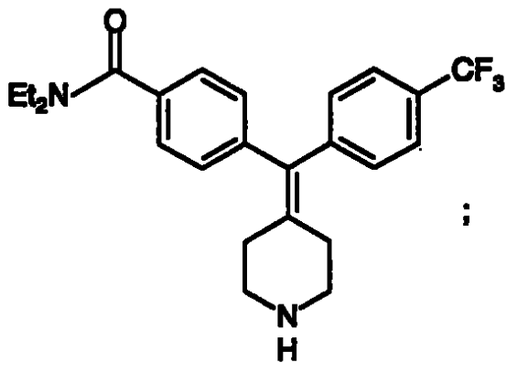
5



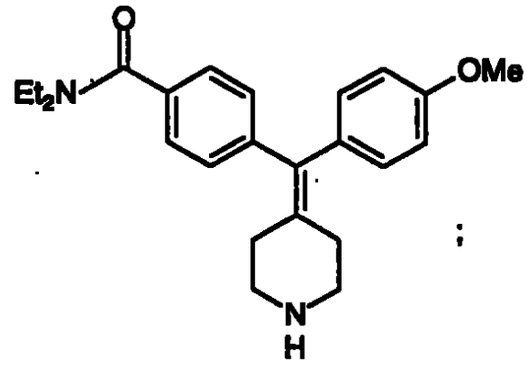
;



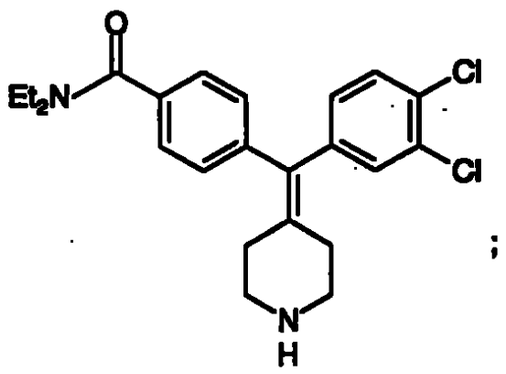
;



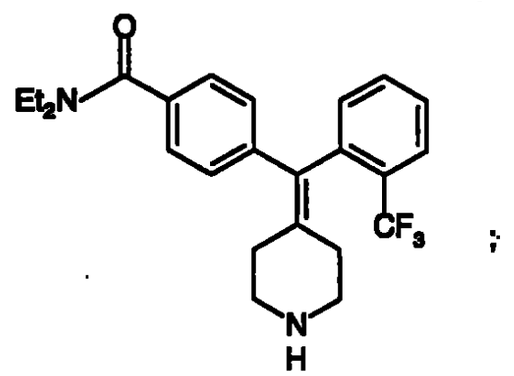
;



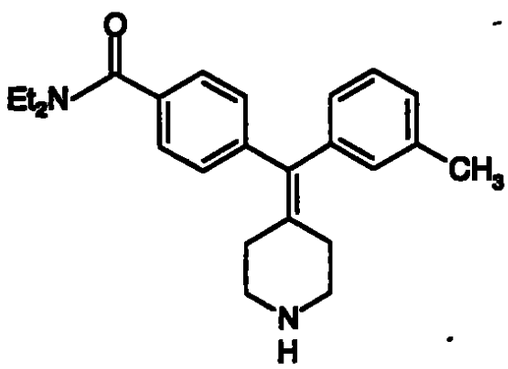
;



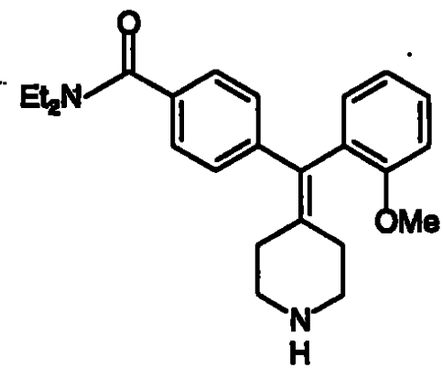
;



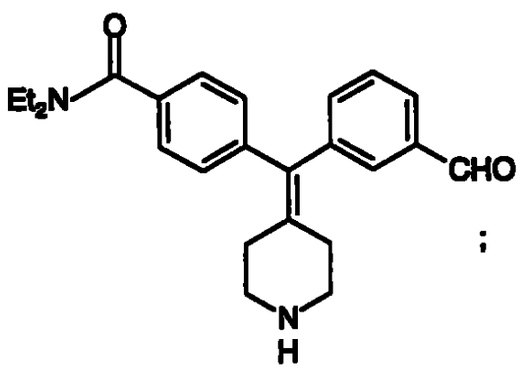
;



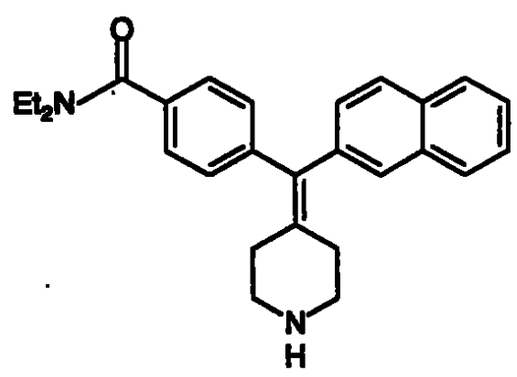
;



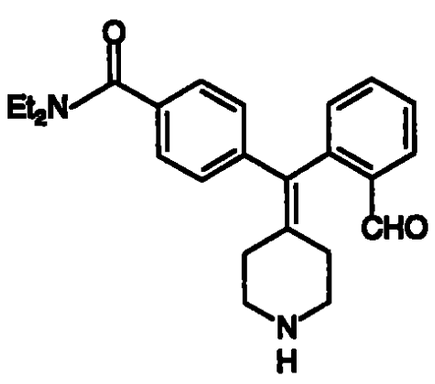
;



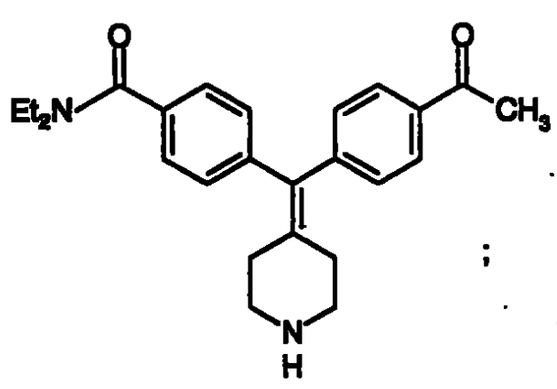
;



;

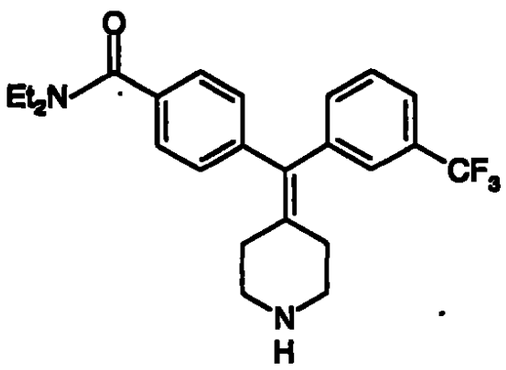


;

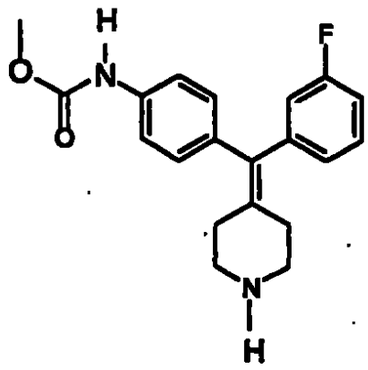


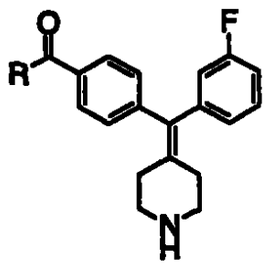
;

5

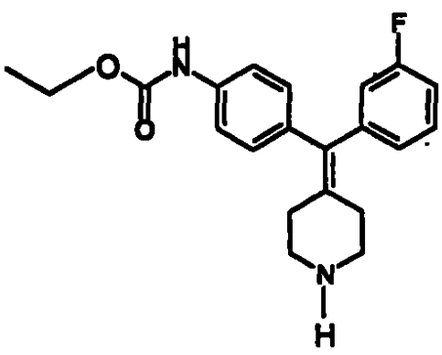


;

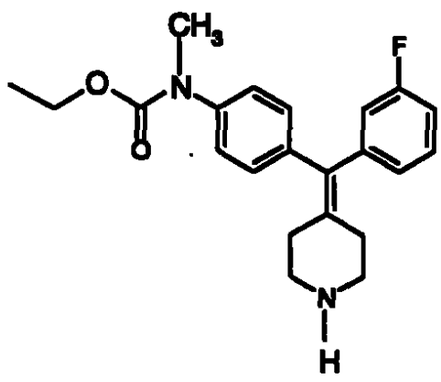




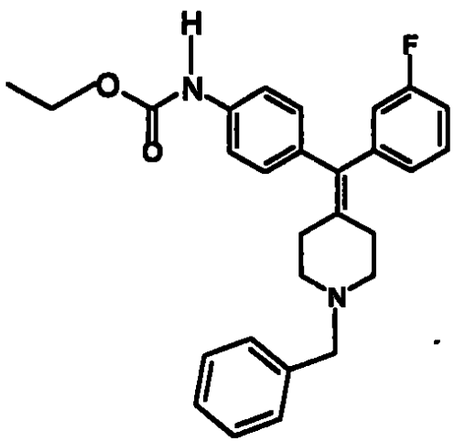
wherein R is morpholine,piperidine or pyrrolidine;

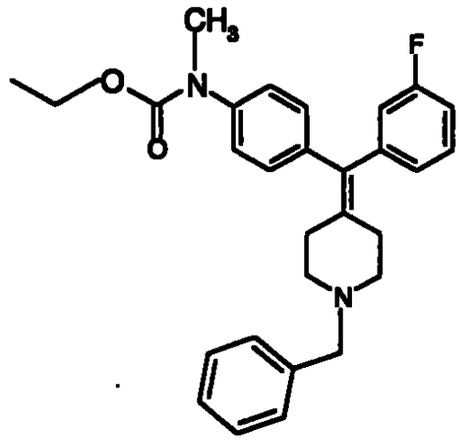


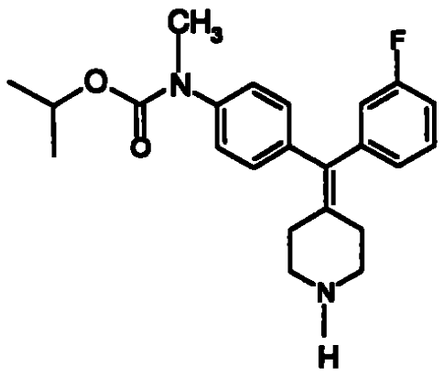
;

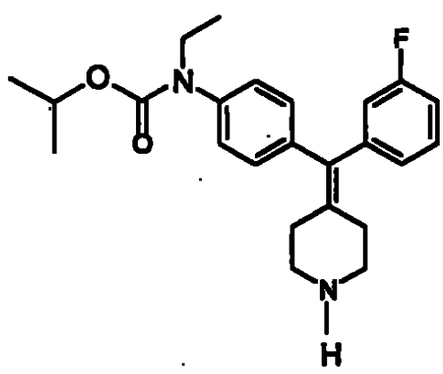


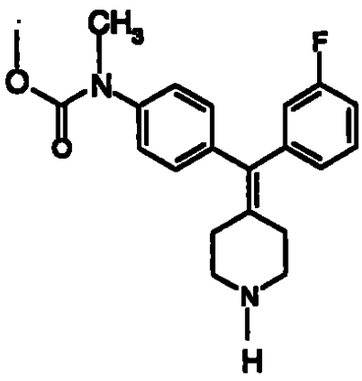
;

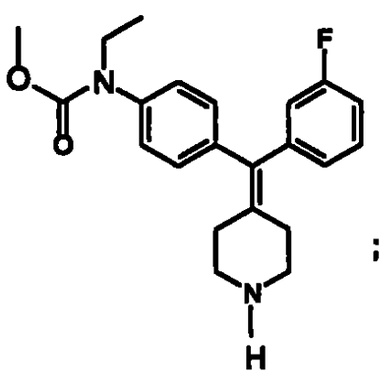

;


;

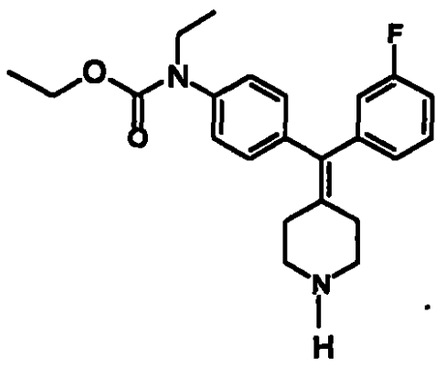

;


;

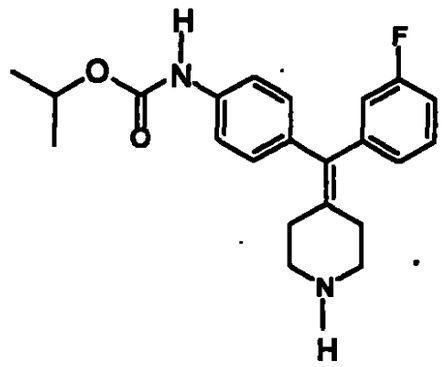

;


;

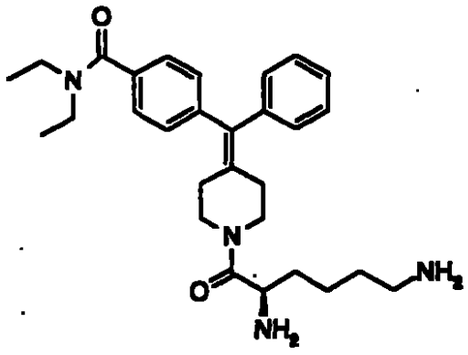
s



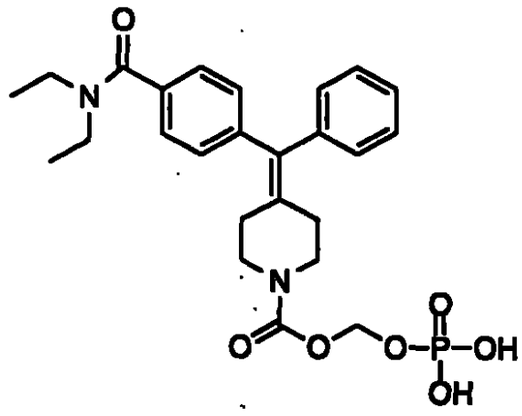
; and



5. A compound according to claim 1, which is selected from



and



6. A compound according to any of the preceding claims, in form of its hydrochloride, sulfate, tartrate or citrate salts.

7. A compound according to any of claims 1-6 for use in therapy.

8. A compound according to claim 7, wherein the therapy is pain management.

9. A compound according to claim 7, wherein the therapy is directed towards gastrointestinal disorders.

10. A compound according to claim 7, wherein the therapy is directed towards spinal injuries.

11. A compound according to claim 7, wherein the therapy is directed to disorders of the sympathetic nervous system.

12. Use of a compound according to formula (I) of claim 1 for the manufacture of a medicament for use in the treatment of pain.

13. Use of a compound according to formula (I) of claim 1 for the manufacture of a medicament for use in the treatment of gastrointestinal disorders.

14. Use of a compound according to formula (I) of claim 1 for the manufacture of a medicament for use in the treatment of spinal injuries.

15. A compound according to any of claim 1-7, further characterised in that it is isotopically labelled.

16. Use of a compound according to claim 15 as a diagnostic agent.

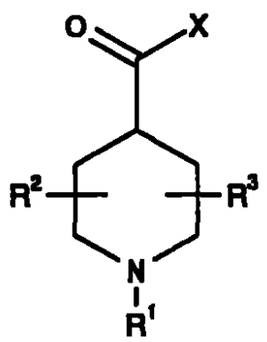
17. An isotopically labelled compound of the formula (I) of claim 1.

18. A diagnostic agent comprising a compound of the formula (I) of claim 1.

19. A pharmaceutical composition comprising a compound of the formula (I) according to claim 1 as an active ingredient, together with a pharmacologically and pharmaceutically acceptable carrier.

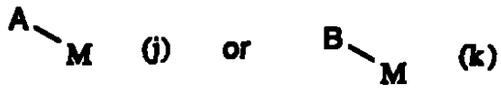
20. A process for the preparation of a compound of the formula (I) according to claim 1, whereby

a) a ketone of the formula (l)



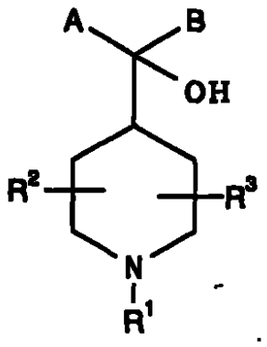
(l)

wherein R^1, R^2 and R^3 are as defined in formula (I) of claim 1, and X is a leaving group, is reacted with an organometallic reagent of the formula (j) or (k)



(j) or (k)

wherein A and B are as defined in formula (I) of claim 1, and M is a metal group; and wherein the reaction is optionally performed in the presence of a solvent, giving a compound of the formula (h)

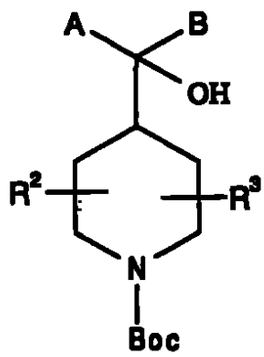


(h)

wherein A, B, R^1, R^2 and R^3 are as defined in formula (I) of claim 1, and wherein R1 also may be tert-butoxycarbonyl.;

b) the compound of the formula (h) is dehydrated, giving a compound of the formula (I) of claim 1.

21. A compound of the formula

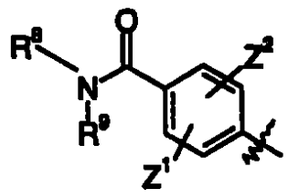


(h)

wherein A, B, R^2 and R^3 are as defined in formula (I) of claim 1.

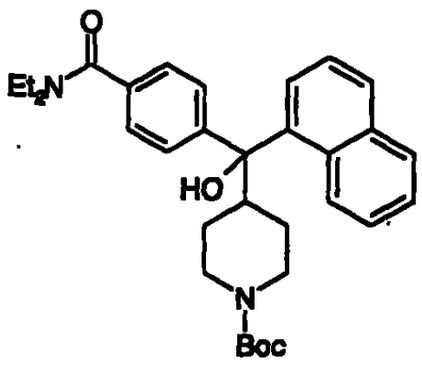
22. A compound of the formula (h) according to step a) of claim 20, wherein

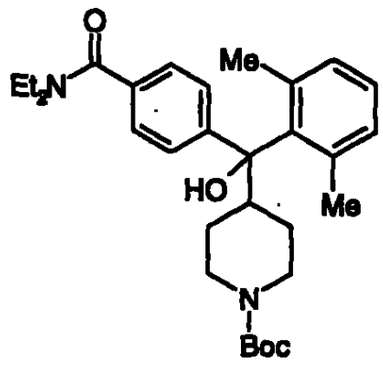
A is



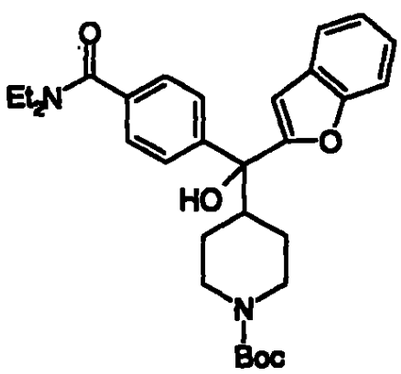
wherein R^8 and R^9 are both an ethyl group, and Z^1 andd Z^2 are as defined in claim 1.

23. A compound according to claim 22, which compound is any of

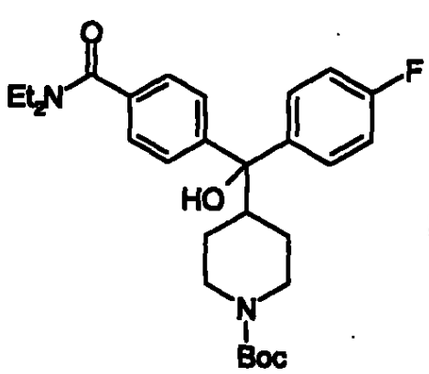




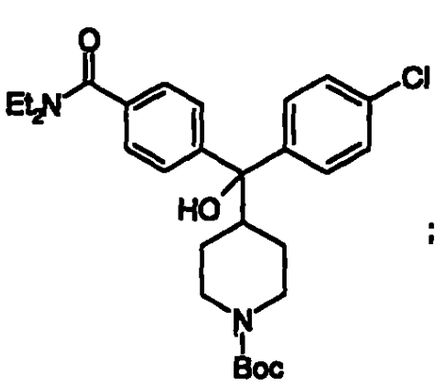
;



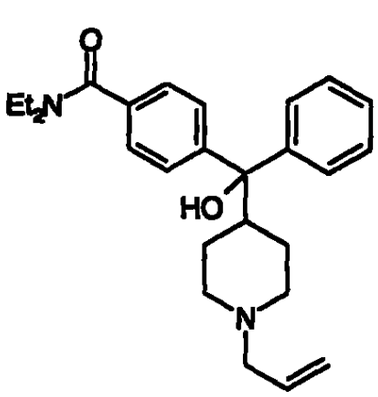
;



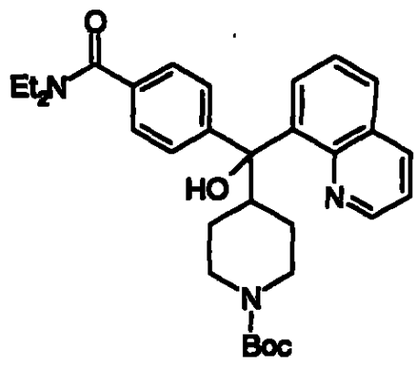
;



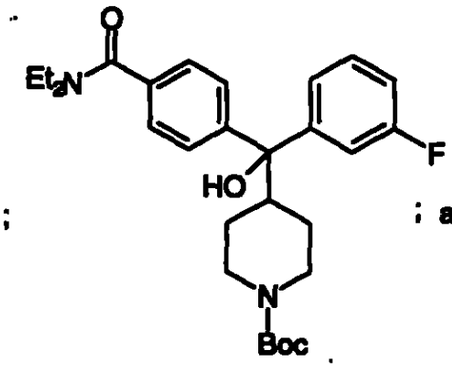
;



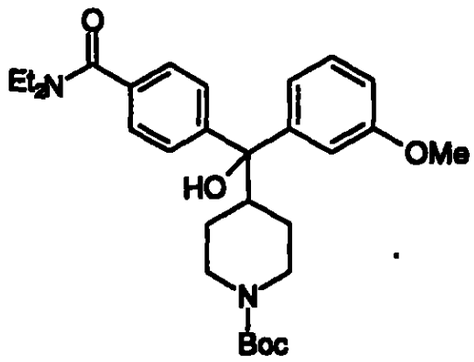
;



;



; and



24. A method for the treatment of pain, whereby an effective amount of a compound of the formula (I) according to claim 1 is administered to a subject in need of pain management.

25. A method for the treatment of gastrointestinal disorders, whereby an effective amount of a compound of the formula (I) according to claim 1, is administered to a subject suffering from said gastrointestinal disorder.

26. A method for the treatment of spinal injuries, whereby an effective amount of a compound of the formula (I) according to claim 1, is administered to a subject suffering from said spinal injury.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 97/02050

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 211/70, C07D 307/81, A61K 31/445
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)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2898339 A (KEITH W. WHEELER ET AL), 4 August 1959 (04.08.59)	1-15,17-23
A	Neuroscience Letters, Volume 99, 1989, Andrew Barber et al, "Antinociceptive effects of the 5-HT2 antagonist ritanserin in rats: evidence for an activation of descending monoaminergic pathways in the spinal cord" page 234 - page 238	1-15,17-23
A	WO 9315062 A1 (THE WELLCOME FOUNDATION LIMITED), 5 August 1993 (05.08.93)	1-15,17-23

☐ 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 document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 March 1998	06 -04- 1998
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE97/02050

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 16 and 24-26
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy as well as diagnostic methods, see rule 39.1

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

03/02/98

International application No.
PCT/SE 97/02050

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2898339 A	04/08/59	NONE	
WO 9315062 A1	05/08/93	AU 675928 B	27/02/97
		AU 3457393 A	01/09/93
		EP 0649414 A	26/04/95
		EP 0650536 A	03/05/95
		JP 7501583 T	16/02/95
		JP 7503247 T	06/04/95
		NZ 246916 A	27/08/96
		US 5492737 A	20/02/96
		US 5574159 A	12/11/96
		US 5658908 A	19/08/97
		US 5681830 A	28/10/97
		ZA 9300717 A	02/08/94

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 211/58, A61K 31/445, C07D 405/12, 405/06, 409/06, 401/06, A61K 31/535 — A1

(11) International Publication Number: **WO 99/33806**

(43) International Publication Date: 8 July 1999 (08.07.99)

(21) International Application Number: PCT/US98/27350

(22) International Filing Date: 23 December 1998 (23.12.98)

(30) Priority Data:
60/068,794 24 December 1997 (24.12.97) US

(71) Applicant *(for all designated States except US)*: ORTHO-McNEIL PHARMACEUTICAL, INC. [US/US]; U.S. Route 202, Raritan, NJ 08869-0602 (US).

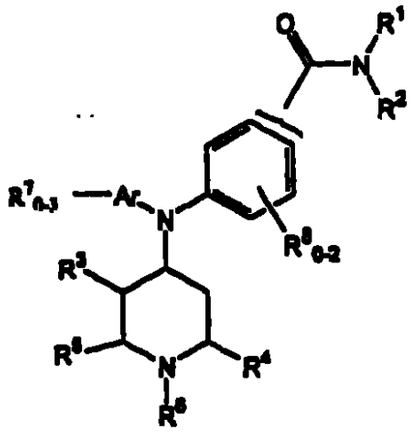
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: CARSON, John, R. [-/US]; 351 Rittenhouse Boulevard, Norristown, PA 19403 (US). CARMOSIN, Richard, J. [-/US]; 122 Woodview Drive, Quakertown, PA 18851 (US). FITZPATRICK, Louis, J. [-/US]; 204 Heatherfield Drive, Souderton, PA 18964 (US). REITZ, Allen, B. [-/US]; 109 Greenbriar Road, Lansdale, PA 19446 (US). JETTER, Michele, C. [-/US]; 3036 Brambling Lane, Norristown, PA 19403 (US).

(74) Agents: CIAMPORCERO, Audley, A., Jr. et al.; Johnson and Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: 4-[ARYL(PIPERIDIN-4-YL)] AMINOBENZAMIDES WHICH BIND TO THE DELTA-OPIOID RECEPTOR



(I)

(57) Abstract

4-[aryl(piperidin-4-yl)] aminobenzamides are delta-opioid receptor agonists/antagonists of formula (I). As delta-opioid receptor agonists, such compounds are useful as analgesics. Depending on their agonist/antagonist effect, such compounds may also be useful immunosuppressants, antiinflammatory agents, agents for the treatment of mental illness, medicaments for drug and alcohol abuse, agents for treating gastritis and diarrhea, cardiovascular agents, and agents for the treatment of respiratory diseases. In formula (I), [Ar is phenyl, 1-naphthyl or 2-naphthyl, each optionally substituted with 1 to 3 R^7; $R^1 - R^8$ are described in the application].

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

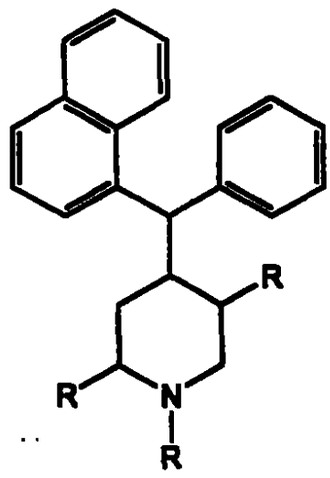
AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

4-[ARYL(PIPERIDIN-4-YL)] AMINOBENZAMIDES WHICH BIND TO THE DELTA-OPIOID RECEPTOR

The present invention relates to delta-opioid receptor agonists/antagonists. More particularly, the present invention relates to 4-[aryl(piperidin-4-yl)]aminobenzamides which are delta-opioid receptor agonists useful as analgesics.

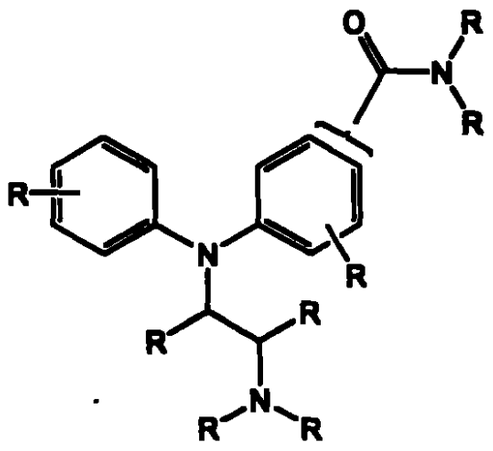
BACKGROUND OF THE INVENTION

WO9723466 to Plobeck N. et al., discloses compounds (approximately) of the formula:



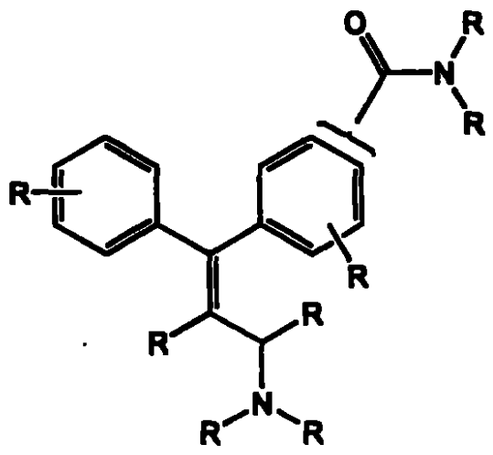
which are mu-opioid antagonists.

WO9636620 to Dondio G., discloses compounds (most relevantly) of the formula:



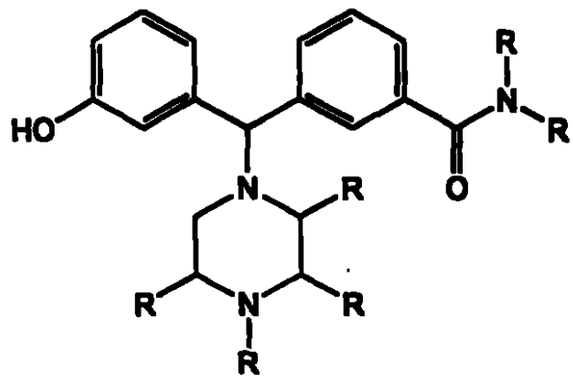
which are delta-opioid agonists/antagonists.

WO9710230 to Dondio G. et al., discloses compounds (most relevantly) of the formula:



which are delta-opioid, kappa-opioid and mu-opioid receptor agonists/antagonists.

WO9315062 to Chang K. et al., discloses compounds (approximately) of the formula:



which are delta-opioid and mu-opioid receptor agonists.

It is an object of the present invention to provide delta-opioid receptor agonists as analgesics.

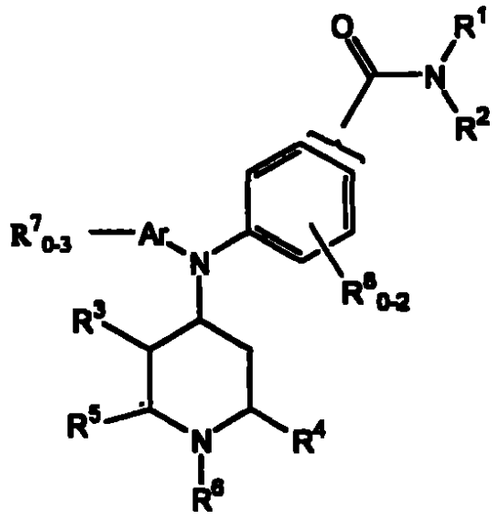
It is another object of the present invention to provide delta-opioid receptor selective agonists as analgesics having reduced side-effects.

It is another object of the present invention to provide delta-opioid receptor agonists/antagonists as immunosuppressants, antiinflammatory agents, agents for the treatment of mental illness, medicaments for drug and alcohol abuse, agents for treating gastritis and diarrhea, cardiovascular agents, and agents for the treatment of respiratory diseases.

It is another object of the present invention to provide delta-opioid receptor selective agonists/antagonists as immunosuppressants, antiinflammatory agents, agents for the treatment of mental illness, medicaments for drug and alcohol abuse, agents for treating gastritis and diarrhea, cardiovascular agents, and agents for the treatment of respiratory diseases, having reduced side-effects.

SUMMARY OF THE INVENTION

There are provided by the present invention delta-opioid receptor agonists/antagonists of the general formula:



I

where

Ar is phenyl, 1-naphthyl or 2-naphthyl, each optionally substituted with 1 to 3 R^7;

R^1 and R^2 are independently selected from the group consisting of hydrogen, C_{1-6}alkyl; phenyl, optionally mono-, di-, or tri-substituted with halo, C_{1-6}alkyl, C_{1-6}alkoxy or trifluoromethyl; or benzyl, optionally mono-, di-, or tri-substituted with halo, C_{1-6}alkyl, C_{1-6}alkoxy or trifluoromethyl, or alternatively, R^1 and R^2 are taken together with their N of attachment to form a ring which is selected from the group consisting of pyrrolidinyl, morpholinyl, piperidinyl and hexamethyleneiminyl, each said ring optionally substituted with 1 to 4 methyl groups;

R^3, R^4 and R^5 are independently selected from hydrogen and C_{1-4}alkyl;

R^6 is selected from the group consisting of hydrogen; C_{1-6}alkyl; C_{3-6}cycloalkylC_{1-3}alkyl, C_{2-6}alkenyl; C_{1-6}alkoxyC_{1-3}alkyl; 4-C_{1-4}alkyl-4,5-dihydro-5-oxo-1H-tretrazol-1-ylC_{1-4}alkyl; thien-2-ylC_{1-4}alkyl; thien-3-ylC_{1-4}alkyl; furan-2-ylC_{1-4}alkyl; furan-3-ylC_{1-4}alkyl; pyrrol-2-ylC_{1-4}alkyl; pyrrol-3-ylC_{1-4}alkyl; pyridin-2-ylC_{1-4}alkyl; pyridin-3-ylC_{1-4}alkyl; pyridin-4-ylC_{1-4}alkyl; pyrazinylC_{1-4}alkyl; pyrimidin-2-ylC_{1-4}alkyl; pyrimidin-4-ylC_{1-4}alkyl; pyrimidin-5-ylC_{1-4}alkyl; thiazol-2-ylC_{1-4}alkyl; thiazol-4-ylC_{1-4}alkyl; thiazol-5-ylC_{1-4}alkyl; oxazol-2-ylC_{1-4}alkyl oxazol-4-ylC_{1-4}alkyl; oxazol-5-ylC_{1-4}alkyl

and phenylC_{1-4}alkyl, where the foregoing thienyl, furanyl, pyrrolyl, thiazolyl and oxazolyl are optionlly mono-, di-, or tri-substituted with a non-fused R^7 and the foregoing pyridinyl, pyrazinyl, pyrimidinyl and phenyl is optionally mono-, di-, or tri-substituted with R^7;

R^7 is independently selected from the group consisting of hydroxy, halo, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}acyl, C_{1-3}acyloxy, cyano, amino, C_{1-3}acylamino, C_{1-3}alkylamino, di(C_{1-3}alkyl)amino, C_{1-3}alkylthio, C_{1-3}alkylsulfonyl, trifluoromethyl and trifluoromethoxy, and two R^7 can together form a single fused moiety selected from the groupconsisting of $-(CH_2)_{3-5}-$ and $-O(CH_2)_{1-3}O-$ attached to adjacent carbon atoms of Ar; and

R^8 is independently selected from the group consisting of halo, C_{1-6}alkyl, C_{1-6}alkoxy and trifluoromethyl.

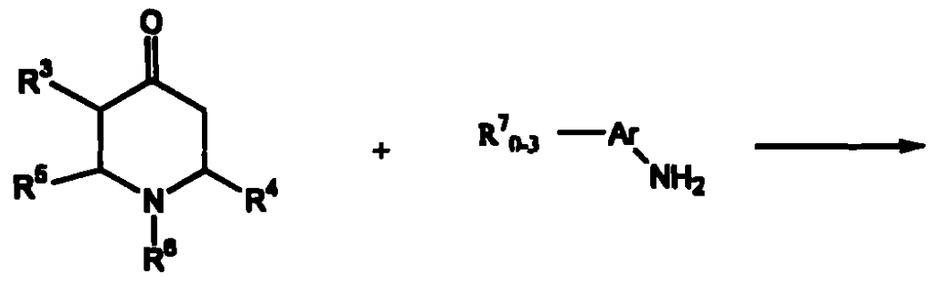
As delta-opioid receptor agonists, such compounds are useful as analgesics. Depending on their agonist/antagonist effect, such compounds may also be useful immunosuppressants, antiiinflammantory agents, agents for treatment of mental illness, medicaments for drug and alcohol abuse, agents for treating gastritis and diarrhea, cardiovascular agents, and agents for the treatment of respiratory diseases.

DETAILED DESCRIPTION OF THE INVENTION

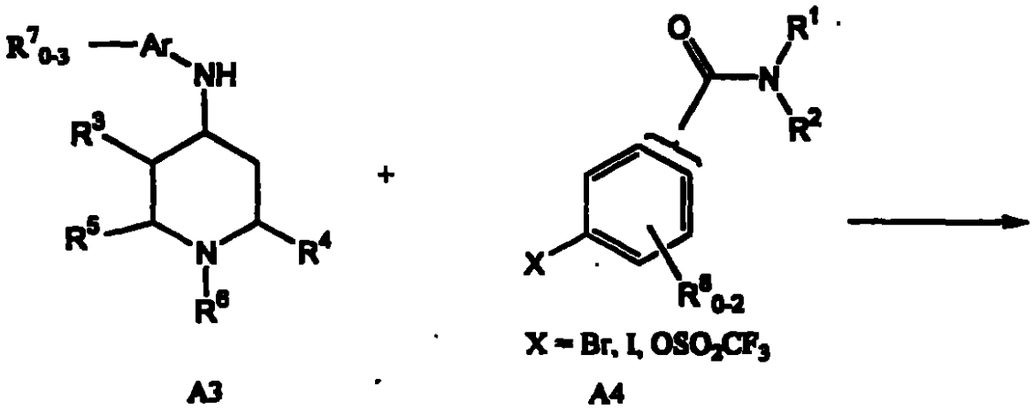
The core structure of the compounds of the present invention can be made in a two step process. This process must be modified as required by the strategy employed to obtain the various substituents. In a first strategy, the starting materials are substituted as desired with the final substituents and, where the substituents or their protected forms are stable to the reaction conditions, the core structure may be subsequently made by the two step process. In a second strategy, the final core structure is obtained and, where the core structure is stable to the modifying reaction conditions, the substituents are modified as desired. Variations might include modifying the substituents on intermdiates or replacing precursor substituents on the finished core structure.

Scheme A generally describes the manufacture of the compounds of the present invention. The first step of Scheme A is a reductive alkylation of piperidone A1 and amine A2 to produce N-aryl-piperidineamine A3. The reductive alkylation is carried out by combining the ketone A1, amine A2, and an appropriate solvent/reducing agent combination to form a reaction mixture which is cooled or heated as necessary. Suitable solvent/reducing agent combinations include 1,2-dichloroethane or acetonitrile/$NaBH(OAc)_3$ + acid catalyst; methanol/$NaBH_3CN$ + acid catalyst; methanol or ethanol or isopropanol/$NaBH_4$; or alcoholic solvent/H_2 + noble metal catalyst. The use of the 1,2-dichloroethane or acetonitrile/$NaBH(OAc)_3$ + acid catalyst combination is further described by Abdel-Magid, A. F., et al., J. Org.Chem., Vol. 61, pp 3849-3862 (1996). In the second step of Scheme A, the N-aryl-piperidineamine A3 is reacted with a bromo, iodo or trifluoromethanesulfonyloxy substituted benzamide A4 in the presence of a palladium catalyst, phosphine ligand and base to give the (N-aryl, N-piperidin-4-yl)aminobenzamide. Preferred palladium catalysts include $PdCl_2$ + phosphine ligand, tris(dibenzylideneacetone)dipalladium(0) which is $Pd_2(dba)_3$ + phosphine ligand, $Pd(OAc)_2$ + phosphine ligand and $Pd(Ph_3P)_4(0)$. Suitable phosphine ligands include BINAP and tri(o-tolyl phosphine). Suitable bases include NaOtBu and Cs_2CO_3. The reaction of the second step is an arylation further described by Buchwald, S. L., J. Org. Chem., Vol. 61, p 1133 (1996). The manufacture of the various starting materials for Scheme A is well within the skill of persons versed in this art.

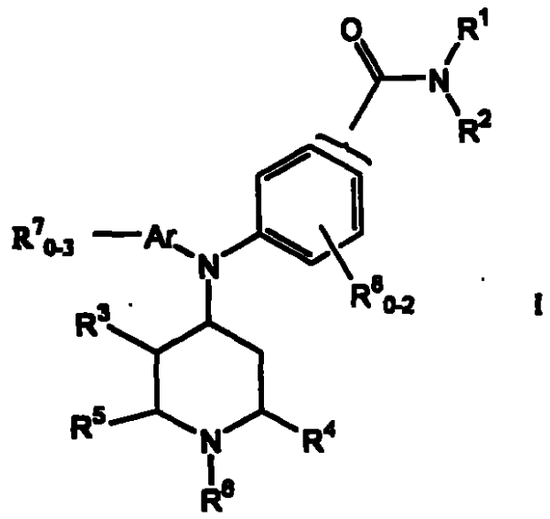
SCHEME A



A1 A2



A3 A4



I

Preferred Ar is phenyl.

Preferred R^1 and R^2 are independently selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, i-butyl, phenyl, p-chlorophenyl, p-fluorophenyl, p-methylphenyl, p-trifluoromethylphenyl, benzyl, p-chlorobenzyl, p-fluorobenzyl, p-methylbenzyl and p-trifluoromethylbenzyl, or alternatively, preferred R^1 and R^2 are taken together with their N of attachment to form a ring which is selected from the group consisting of pyrrolidinyl and piperidinyl.

Preferred R^3, R^4 and R^5 are independently selected from hydrogen, methyl, ethyl, n-propyl, i-propyl and t-butyl.

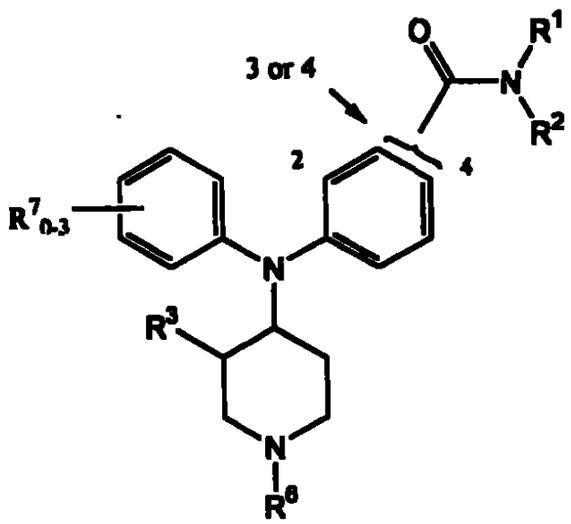
Preferred R^6 are selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, cyclopropylmethyl, ethenyl, allyl, methoxymethyl, benzyl, p-chlorobenzyl, p-fluorobenzyl, p-methylbenzyl,

p-trifluoromethylbenzyl, p-aminobenzyl, thien-2-ylCH_2CH_2-, thian-3-ylCH_2CH_2-, pyridin-3-ylCH_2CH_2-, pyridin-4-ylCH_2CH_2-, thiazol-2-ylCH_2CH_2- and phenylCH_2CH_2-, any of which may be R^7 substituted as taught above. It is a preferred embodiment of R^6, that where it contains a phenyl or heteroaromatic group, that the moiety linking the phenyl or heteroaromatic group to the piperidinyl moiety be at least two carbon atoms long. Thus this linking moiety might be ethyl or propyl which is beta substituted with the phenyl or heteroaromatic group, or propyl, which is gamma substituted.

Preferred R^7 are independently selected from the group consisting of hydroxy, chloro, bromo, fluoro, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, methoxy, ethoxy, formyl, acyl, acetoxy, cyano, amino, methylamido, methylamino, N,N-dimethylamino, methylthio, methylsulfonyl, trifluoromethoxy and trifluoromethyl, and preferred moieties where two R^7 together form a single moiety are selected from the group consisting of propylene, butylene and $-OCH_2O-$.

Preferred R^8 are independently selected from the group consisting of chloro, bromo, fluoro, methyl, ethyl, n-propyl, i-propyl, t-butyl, methoxy, ethoxy and trifluoromethyl.

Preferred compounds of the present invention have the general structure:

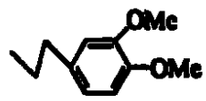
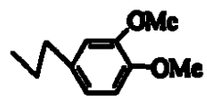
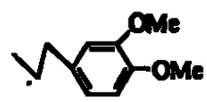
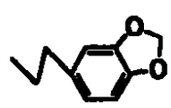
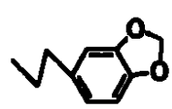
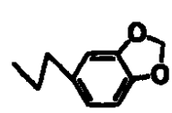
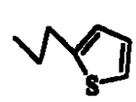
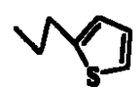
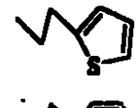
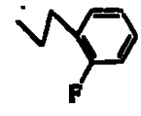
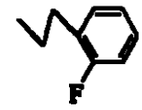
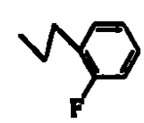
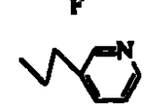


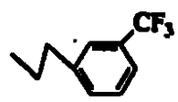
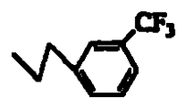
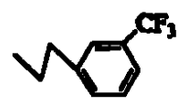
where R^1, R^2, R^3, R^6 and R^7 are dependently selected from the groups consisting of:

Cpd#	R^7	R^6	R^1	R^2	amide subst.	R^3
P1	none	$-CH_2CH=CH_2$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P2	none	$-CH_2-\triangleleft$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P3	3-OH	$-CH_2CH=CH_2$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P4	3-OH	$-CH_2-\triangleleft$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P5	3-OH	$-CH_3$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P6	3-OH	$-CH_2CH_3$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P7	3-OH	$-CH_2CH_2Ph$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P8	3-OH	$-CH_3$	$-nC_3H_7$	$-nC_3H_7$	4	H
P9	3-OH	$-CH_2CH_3$	$-nC_3H_7$	$-nC_3H_7$	4	H
P10	3-OH	$-CH_2CH_2Ph$	$-nC_3H_7$	$-nC_3H_7$	4	H
P11	3-OH	$-CH_3$	$-nC_4H_9$	$-nC_4H_9$	4	H
P12	3-OH	$-CH_2CH_3$	$-nC_4H_9$	$-nC_4H_9$	4	H
P13	3-OH	$-CH_2CH_2Ph$	$-nC_4H_9$	$-nC_4H_9$	4	H
P14	none	$-CH_3$	$-nC_4H_9$	$-nC_4H_9$	4	H
P15	none	$-CH_2CH_3$	$-nC_4H_9$	$-nC_4H_9$	4	H
P16	none	$-CH_2CH_2Ph$	$-nC_4H_9$	$-nC_4H_9$	4	H
P17	3-F	$-CH_3$	$-nC_4H_9$	$-nC_4H_9$	4	H
P18	3-F	$-CH_2CH_3$	$-nC_4H_9$	$-nC_4H_9$	4	H
P19	3-F	$-CH_2CH_2Ph$	$-nC_4H_9$	$-nC_4H_9$	4	H
P20	3-OCH_3	$-CH_3$	$-nC_4H_9$	$-nC_4H_9$	4	H
P21	3-OCH_3	$-CH_2CH_3$	$-nC_4H_9$	$-nC_4H_9$	4	H
P22	3-OCH_3	$-nC_4H_9$	$-nC_4H_9$	$-nC_4H_9$	4	H
P23	3,4-OCH_2O-	$-nC_3H_7$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P24	3,4-OCH_2O-	$-nC_3H_7$	$-nC_3H_7$	$-nC_3H_7$	4	H
P25	3,4-OCH_2O-	$-nC_3H_7$	$2\text{-}C_3H_7$	$2\text{-}C_3H_7$	4	H
P26	3,4-OCH_2O-	$-nC_3H_7$	$-nC_4H_9$	$-nC_4H_9$	4	H
P27	3-$N(CH_3)_2$	$-nC_3H_7$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P28	3-$N(CH_3)_2$	$-nC_3H_7$	$-nC_3H_7$	$-nC_3H_7$	4	H

P29	3-$N(CH_3)_2$	$-nC_3H_7$	$2\text{-}C_3H_7$	$2\text{-}C_3H_7$	4	H
P30	3-$N(CH_3)_2$	$-nC_3H_7$	$-nC_4H_9$	$-nC_4H_9$	4	H
P31	4-F	$-nC_3H_7$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P32	4-F	$-nC_3H_7$	$-nC_3H_7$	$-nC_3H_7$	4	H
P33	4-F	$-nC_3H_7$	$2\text{-}C_3H_7$	$2\text{-}C_3H_7$	4	H
P34	4-F	$-nC_3H_7$	$-nC_4H_9$	$-nC_4H_9$	4	H
P35	2-F	$-nC_3H_7$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P36	2-F	$-nC_3H_7$	$-nC_3H_7$	$-nC_3H_7$	4	H
P37	2-F	$-nC_3H_7$	$2\text{-}C_3H_7$	$2\text{-}C_3H_7$	4	H
P38	2-F	$-nC_3H_7$	$-nC_4H_9$	$-nC_4H_9$	4	H
P39	3-Cl, 4-OCH_3	$-nC_3H_7$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P40	3-Cl, 4-OCH_3	$-nC_3H_7$	$-nC_3H_7$	$-nC_3H_7$	4	H
P41	3-Cl, 4-OCH_3	$-nC_3H_7$	$2\text{-}C_3H_7$	$2\text{-}C_3H_7$	4	H
P42	3-Cl, 4-OCH_3	$-nC_3H_7$	$-nC_4H_9$	$-nC_4H_9$	4	H
P43	3-CF_3	$-nC_3H_7$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P44	3-CF_3	$-nC_3H_7$	$-nC_3H_7$	$-nC_3H_7$	4	H
P45	3-CF_3	$-nC_3H_7$	$2\text{-}C_3H_7$	$2\text{-}C_3H_7$	4	H
P46	3-CF_3	$-nC_3H_7$	$-nC_4H_9$	$-nC_4H_9$	4	H
P47	3-OCH_3, 5-OCH_3	$-nC_3H_7$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P48	3-OCH_3, 5-OCH_3	$-nC_3H_7$	$-nC_3H_7$	$-nC_3H_7$	4	H
P49	3-OCH_3, 5-OCH_3	$-nC_3H_7$	$2\text{-}C_3H_7$	$2\text{-}C_3H_7$	4	H
P50	3-OCH_3, 5-OCH_3	$-nC_3H_7$	$-nC_4H_9$	$-nC_4H_9$	4	H
P51	3-CH_3	$-nC_3H_7$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P52	3-CH_3	$-nC_3H_7$	$-nC_3H_7$	$-nC_3H_7$	4	H
P53	3-CH_3	$-nC_3H_7$	$2\text{-}C_3H_7$	$2\text{-}C_3H_7$	4	H
P54	3-CH_3	$-nC_3H_7$	$-nC_4H_9$	$-nC_4H_9$	4	H
P55	4-CH_3	$-nC_3H_7$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P56	4-CH_3	$-nC_3H_7$	$-nC_3H_7$	$-nC_3H_7$	4	H
P57	4-CH_3	$-nC_3H_7$	$2\text{-}C_3H_7$	$2\text{-}C_3H_7$	4	H
P58	4-CH_3	$-nC_3H_7$	$-nC_4H_9$	$-nC_4H_9$	4	H
P59	2-CH_3, 3-CH_3	$-nC_3H_7$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P60	2-CH_3, 3-CH_3	$-nC_3H_7$	$-nC_3H_7$	$-nC_3H_7$	4	H

P61	2-CH_3, 3-CH_3	-nC_3H_7	2-C_3H_7	2-C_3H_7	4	H
P62	2-CH_3, 3-CH_3	-nC_3H_7	-nC_4H_9	-nC_4H_9	4	H
P63	3-OCF_3	-nC_3H_7	-CH_2CH_3	-CH_2CH_3	4	H
P64	3-OCF_3	-nC_3H_7	-nC_3H_7	-nC_3H_7	4	H
P65	3-OCF_3	-nC_3H_7	2-C_3H_7	2-C_3H_7	4	H
P66	3-OCF_3	-nC_3H_7	-nC_4H_9	-nC_4H_9	4	H
P67	3-SCH_3	-nC_3H_7	-CH_2CH_3	-CH_2CH_3	4	H
P68	3-SCH_3	-nC_3H_7	-nC_3H_7	-nC_3H_7	4	H
P69	3-SCH_3	-nC_3H_7	2-C_3H_7	2-C_3H_7	4	H
P70	3-SCH_3	-nC_3H_7	-nC_4H_9	-nC_4H_9	4	H
P71	none	-CH_2Ph	-CH_2CH_3	-CH_2CH_3	4	ci-Me
P72	none	-H	-CH_2CH_3	-CH_2CH_3	4	ci-Me
P73	none	-$CH_2CH{=}CH_2$	-CH_2CH_3	-CH_2CH_3	4	ci-Me
P74	none	-nC_3H_7	-CH_2CH_3	-CH_2CH_3	4	ci-Me
P75	3-OCH_3	-CH_2Ph	-CH_2CH_3	-CH_2CH_3	4	ci-Me
P76	3-OCH_3	-H	-CH_2CH_3	-CH_2CH_3	4	ci-Me
P77	3-OCH_3	-$CH_2CH{=}CH_2$	-CH_2CH_3	-CH_2CH_3	4	ci-Me
P78	3-OCH_3	-nC_3H_7	-CH_2CH_3	-CH_2CH_3	4	ci-Me
P79	none	-CH_2Ph	-CH_2CH_3	-CH_2CH_3	4	tr-Me
P80	none	-H	-CH_2CH_3	-CH_2CH_3	4	tr-Me
P81	none	-$CH_2CH{=}CH_2$	-CH_2CH_3	-CH_2CH_3	4	tr-Me
P82	none	-nC_3H_7	-CH_2CH_3	-CH_2CH_3	4	tr-Me
P83	none	-nC_3H_7	-CH_2CH_3	-CH_2CH_3	4	H
P84	none	-nC_3H_7	-nC_3H_7	-nC_3H_7	3	H
P85	none	-nC_3H_7	-CH_2Ph	-CH_2CH_3	3	H
P86	none	-nC_3H_7	-$(CH_2)_5$-		3	H
P87	* 2,3-CH=CHCH=CH-	-nC_3H_7	-CH_2CH_3	-CH_2CH_3	3	H
P88	* 2,3-CH=CHCH=CH-	-nC_3H_7	-nC_3H_7	-nC_3H_7	4	H
P89	3,4-$(CH_2)_4$-	-nC_3H_7	-CH_2CH_3	-CH_2CH_3	4	H
P90	3,4-$(CH_2)_4$-	-nC_3H_7	-nC_3H_7	-nC_3H_7	4	H

P91	3,4-$CH_2CH_2CH_2$-	-nC_3H_7	-CH_2CH_3	-CH_2CH_3	4	H
P92	3,4-$CH_2CH_2CH_2$-	-nC_3H_7	-nC_3H_7	-nC_3H_7	4	H
P93	none		-CH_2CH_3	-CH_2CH_3	4	H
P94	m-F		-CH_2CH_3	-CH_2CH_3	4	H
P95	m-sCH_3		-CH_3	-CH_2CH_3	4	ci-Me
P96	none		-CH_2CH_3	-CH_2CH_3	4	H
P97	m-oCH_3		-nC_3H_7	-nC_3H_7	4	H
P98	m-OH		-CH_3	-CH_2CH_3	4	tr-Me
P99	none		-CH_2CH_3	-CH_2CH_3	4	H
P100	o-F		-nC_3H_7	-nC_3H_7	4	H
P101	o-CH_3		-CH_3	-CH_2CH_3	4	ci-Me
P102	none		-CH_2CH_3	-CH_2CH_3	4	H
P103	p-OH		-CH_2CH_3	-nC_3H_7	4	H
P104	p-F		-nC_3H_7	-nC_3H_7	4	tr-Me
P105	none		-CH_2CH_3	-CH_2CH_3	4	H
P106	m-sCH_3		-nC_3H_7	-nC_3H_7	4	H
P107	m-oCF_3		-CH_3	-nC_3H_7	4	ci-Me

P108	none		$-CH_2CH_3$	$-CH_2CH_3$	4	H
P109	m-CH_3		$-CH_3$	$-CH_2CH_3$	4	H
P110	2, 3-oCH_3		$-CH_3$	$-nC_3H_7$	4	H

* Ar = naphthyl is depicted as R^7 for convenience

The compounds of the present invention may be used to treat mild to moderately severe pain in warm-blooded animals, such as, humans by administration of an analgesically effective dose. The dosage range would be from about 1 to 3000 mg, in particular about 10 to 1000 mg or about 25 to 500 mg, of active ingredient 1 to 4 times per day for an average (70 kg) human although it is apparent that activity of individual compounds of the invention will vary as will the pain being treated. In regards to the use of these compounds as immunosuppressants, antiinflammatory agents, agents for the treatment of mental illness, medicaments for drug and alcohol abuse, agents for treating gastritis and diarrhea, cardiovascular agents, and agents for the treatment of respiratory diseases, a therapeutically effective dose can be determined by persons skilled in the art by use of established animal models. Such dosage would likely fall in the range of from about 1 to 3000 mg of active ingredient 1 to 4 times per day for an average (70 kg) human. Pharmaceutical compositions of the invention comprise the formula (I) compounds as defined above, particularly in admixture with a pharmaceutically-acceptable carrier.

To prepare the pharmaceutical compositions of this invention, one or more compounds of the invention or salt thereof as the active ingredient, is intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending of the form of preparation desired for administration, e.g., oral or parenteral such as intramuscular. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as for example, suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations

such as, for example, powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. For parenterals, the carrier will usually comprise sterile water, through other ingredients, for example, for purposes such as aiding solubility or for preservation, may be included. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed. The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful and the like, an amount of the active ingredient necessary to deliver an effective dose as described above.

The pharmaceutically acceptable salts referred to above generally take a form in which the nitrogen of the piperidinyl ring is protonated with an inorganic or organic acid. Representative organic or inorganic acids include hydrochloric, hydrobromic, hydroiodic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic, succinic, maleic, fumaric, malic, tartaric, citric, benzoic, mandelic, methanesulfonic, hydroxyethanesulfonic, benezenesulfonic, oxalic, pamoic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, salicylic or saccharic.

The following examples are offered by way of illustration and not by way of limitation.

EXAMPLES

Procedure A

N-(3-Methoxyphenyl)-1-propyl-4-piperidinamine, I1. A solution of 4.5 mL (30 mmol) of N-propyl-4-piperidone, 3.4 mL (30 mmol) of *m*-anisidine, and 1.7 mL (30mmol) of glacial acetic acid was stirred in 120 mL of 1,2-dichloroethane (DCE) and 9.49 g (45 mmol) of sodium triacetoxyborohydride was added. The solution was stirred at 25°C for 3h. The solution was washed with $NaHCO_3$ solution and brine. It was dried and the solvent was evaporated. The *m*-anisidine excess was distilled off in a Kugelrohr

at 100°C /0.05 Torr. There was obtained 3.5 g (47% yield) of N-(3-methoxyphenyl)-1-propyl-4-piperidinamine as a solid. MS *m/z* = 249 (M^+ + H). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.1 (t, 1H); 6.15-6.35 (m, 3H); 3.75 (s, 3H); 3.25 (m, 1H); 2.9 (m, 2H); 2.3 (m, 2H); 2.15 (m, 4H); 1.5 (m, 4H); 0.9 (t, 3H). Anal calcd. for $C_{15}H_{24}N_2O$: C, 72.54; H, 9.74; N, 11.28. Found: C, 72.55; H, 9.51; N, 11.21.

Example 1

N,N-Diethyl-4-[3-methoxyphenyl(1-propylpiperidin-4-yl)amino]benzamide Fumarate [1:1], C1. A solution of 3.5 g (14.1 mmol) of N-(3-methoxyphenyl)-1-propyl-4-piperidinamine, 3.61 g (14.1 mmol) of N,N-diethyl-4-bromobenzamide, 129 mg (0.141 mmol) tris(dibenzylideneacetone)-dipalladium(0) (Pd_2dba_3), 263 mg (0.423 mmol) of (R)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binapthyl (+ BINAP) and 1.89 g (19.7 mmol) of sodium *t*-butoxide in 25 mL of dry toluene was heated at 110°C under Ar in a pressure vessel for 16 h. The mixture was cooled and partitioned between CH_2Cl_2 and H_2O. The organic layer was washed with brine, dried (K_2CO_3) and the solvent was evaporated. The residue was chromatographed on a Biotage Flash 75 unit using CH_2Cl_2:MeOH:NH_4OH, 92:8:0.8 as eluent. There was obtained 3.2 g (53% yield) of N,N-diethyl-4-[3-methoxyphenyl(1-propylpiperidin-4-yl)amino]benzamide as a solid. A fumarate salt was prepared out of 2-PrOH: mp 168-169°C. MS *m/z* = 424 (M^+ + H). 300 MHz ^{1}H NMR (DMSO-d_6) δ 7.3 (t, 1H); 7.2 (d, 2H); 6.8 (d, 1H); 6.6 (m, 4H); 6.5 (s, 2H); 4.0 (m, 1H); 3.75 (s, 3H); 3.3 (q, 4H); 3.1 (d, 2H); 2.4 (m, 4H); 1.9 (d, 2H); 1.4 (m, 4H); 1.1 (t, 6H); 0.8 (t, 3H). Anal calcd. for $C_{26}H_{37}N_3O_2 \cdot C_4H_4O_4$: C, 66.77; H, 7.65; N, 7.78. Found: C, 66.69; H, 7.76; N, 7.68.

Example 2

N,N-Diethyl-4-[3-hydroxyphenyl(1-propylpiperidin-4-yl)amino]benzamide Oxalate Hydrate [1.0:0.5:0.25], C2. A solution of 1.24 g (2.93 mmol) of N,N-diethyl-4-[3-methoxyphenyl(1-propylpiperidin-4-yl)amino]benzamide, C1, in 5 mL of CH_2Cl_2 was cooled to -60°C under Ar and a solution of 17.58 mL (17.58 mmol) of 1.0

M BBr_3 in CH_2Cl_2 was added dropwise. The temperature was allowed to rise to 25°C and the mixture was stirred for 18 h. It was partitioned between $NaHCO_3$ solution and 25% EtOH in CH_2Cl_2. The organic layer was dried (Na_2SO_4) and the solvent evaporated. The residue was was heated under reflux in 100 mL of saturated $NaHCO_3$ solution. The solution was cooled and extracted with CH_2Cl_2. The solution was dried (Na_2SO_4) and concentrated to give 1.1 g (92% yield) of N,N-diethyl-4-[3-hydroxyphenyl(1-propylpiperidin-4-yl)amino]benzamide as a gum. An oxalate salt was prepared in CH_3CN, mp 196-197°C. MS *m/z* = 410 (M^+ + H). 300 MHz ^{1}H NMR (DMSO-d_6) δ 7.2(m, 3H); 6.6 (m, 3H); 6.5(d, 1H); 6.4(s, 1H); 4.1(m, 1H); 3.3(q, 4H); 3.2 (m, 2H); .2.6 (m, 4H); 2.1 (d, 2H); 1.5 (m, 4H); 1.1 (t, 6H); 0.8 (t, 3H). Anal calcd. for $C_{25}H_{33}N_3O_2$•0.5 $C_2H_2O_4$•0.25 H_2O: C, 68.03; H, 8.01; N, 9.15; H_2O, 0.98. Found: C, 67.73; H, 7.73; N, 9.11; H_2O, 0.46.

Example 3

N,N-Diethyl-4-[phenyl(1-propylpiperidin-4-yl)amino]benzamide Fumarate[1:1].

C3. Following the protocol of Procedure A and employing aniline in place of *m*-anisidine, N-phenyl-1-propyl-4-piperidinamine was obtained as a solid: mp 71-72°C. MS *m/z* = 217 (M^+ + H). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.1 (t, 2H); 6.65-6.5 (m, 3H); 3.5 (s, 1H); 3.25 (m, 1H); 3.3 (m, 1H) 2.9 (m, 2H); 2.3 (m, 2H); 2.15 (m, 4H); 1.5 (m, 4H); 0.9 (t, 3H).

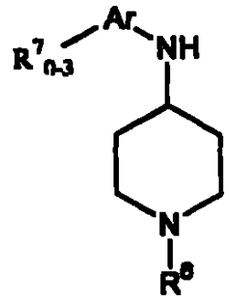
Then, following the procedure of Example 1 and employing N-phenyl-1-propyl-4-piperidinamine in place of N-(3-methoxyphenyl)-1-propyl-4-piperidinamine, N,N-diethyl-4-[phenyl(1-propylpiperidin-4-yl)amino]benzamide fumarate was obtained as the product: mp 152-154°C. MS *m/z* = 394 (M^+ + H). 300 MHz ^{1}H NMR (DMSO-d_6) δ 7.45 (t, 2H); 7.3(t, 1H); 7.2 (d, 2H); 7.05 (d, 2H); 6.55 (d, 2H); 6.5 (s, 2H); 4.0 (m, 1H); 3.3 (q, 4H); 3.1 (d, 2H); 2.4 (m, 4H); 1.9 (d, 2H); 1.4 (m, 4H); 1.1 (t, 6H); 0.8 (t, 3H).

Example 4

N-Methyl-N-phenyl-3-[phenyl(1-propylpiperidin-4-yl)amino]benzamide Fumarate[1:1.4], C4. Following the procedure of Example 1 and employing N-phenyl-1-propyl-4-piperidinamine in place of N-(3-methoxyphenyl)-1-propyl-4-piperidinamine and 3-bromo-N-methylbenzanilide in place of N,N-diethyl-4-bromobenzamide, N,N-diethyl-4-[phenyl(1-propylpiperidin-4-yl)amino]benzamide fumarate [1:1.5] was obtained as the product: mp 190-191°C. MS *m/z* = 428 (M^+ + H). 300 MHz ^{1}H NMR (DMSO-d_6) δ 7.35 (t, 4H); 7.2-6.9 (m, 4H) 6.55 (t, 2H); 6.5 (s, 2H); 3.85 (m, 1H); 3.3 (s, 3H); 2.9 (d, 2H); 2.4 (t, 2H); 2.2 (d, 2H); 1.6 (d, 2H); 1.4 (m, 2H); 1.1 (m, 2H); 0.8 (t, 3H).

Procedure B

Following the protocol of Procedure A and employing the appropriate aryl amine in place of *m*-anisidine and the requisite N-substituted piperidine in place of N-propylpiperidine, the following N-aryl-1-substituted-4-piperidinamines, I2 - I10, were prepared:



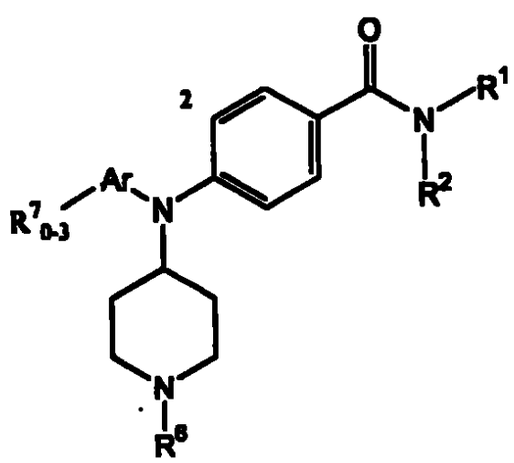
where R^6 and R^7 are dependently selected from the groups consisting of:

Cpd#	R^7-Ar	R^6	MS *m/z* (M^+ + H)
I1	3-CH_3O-Ph	1-Propyl	249

I2	3-Cl-Ph	1-Propyl	253
I3	2-CH_3O-Ph	1-Propyl	249
I4	1-Naphthyl	1-Propyl	269
I5	Ph	Methyl	191
I6	3-CH_3O-Ph	Methyl	221
I7	3-F-Ph	Methyl	209
I8	Ph	Ethyl	205
I9	3-F-Ph	Ethyl	223
I10	Ph	Benzyl	267

Example 5

Following the procedure of Example 1 and employing the appropriate N-aryl-4-piperidinamine in place of N-(3-methoxyphenyl)-1-propyl-4-piperidinamine and the requisite 4-bromobenzamide in place of N,N-diethyl-4-bromobenzamide, the following compounds C5 - C45 were obtained:



where R^1, R^2, R^6 and R^7-Ar are dependently selected from the groups consisting of:

Cpd#	R^7-Ar	R^6	R^1	R^2	MS	Isol'n
C5	3-Cl-Ph	1-Propyl	Ethyl	Ethyl	428	A

C6	3-Cl-Ph	1-Propyl	-$(CH_2)_4$-		426	A
C7	2-CH_3O-Ph	1-Propyl	Ethyl	Ethyl	424	A
C8	1-Naphthyl	1-Propyl	Ethyl	Ethyl	416	A
C9	1-Naphthyl	1-Propyl	-$(CH_2)_4$-		456	A
C10	Ph	Methyl	Ethyl	Ethyl	366	B
C11	Ph	Methyl	1-Propyl	1-Propyl	394	B
C12	Ph	Methyl	Methyl	Ethyl	352	B
C13	Ph	Methyl	2-Propyl	2-Propyl	394	B
C14	Ph	Methyl	-$(CH_2)_2$-O-$(CH_2)_2$-		380	B
C15	Ph	Methyl	-$(CH_2)_5$-		378	B
C16	Ph	Methyl	-$(CH_2)_4$-		364	B
C17	3-CH_3O-Ph	Methyl	Ethyl	Ethyl	396	B
C18	3-CH_3O-Ph	Methyl	1-Propyl	1-Propyl	424	B
C19	3-CH_3O-Ph	Methyl	Methyl	Ethyl	382	B
C20	3-CH_3O-Ph	Methyl	2-Propyl	2-Propyl	424	B
C21	3-CH_3O-Ph	Methyl	-$(CH_2)_2$-O-$(CH_2)_2$-		410	B
C22	3-CH_3O-Ph	Methyl	-$(CH_2)_5$-		408	B
C23	3-CH_3O-Ph	Methyl	-$(CH_2)_4$-		394	B
C24	3-F-Ph	Methyl	Ethyl	Ethyl	384	B
C25	3-F-Ph	Methyl	1-Propyl	1-Propyl	412	B
C26	3-F-Ph	Methyl	Methyl	Ethyl	370	B
C27	3-F-Ph	Methyl	2-Propyl	2-Propyl	412	B
C28	3-F-Ph	Methyl	-$(CH_2)_2$-O-$(CH_2)_2$-		398	B
C29	3-F-Ph	Methyl	-$(CH_2)_5$-		396	B
C30	3-F-Ph	Methyl	-$(CH_2)_4$-		382	B
C31	Ph	Ethyl	Ethyl	Ethyl	380	B
C32	Ph	Ethyl	1-Propyl	1-Propyl	408	B
C33	Ph	Ethyl	Methyl	Ethyl	366	B
C34	Ph	Ethyl	2-Propyl	2-Propyl	408	B
C35	Ph	Ethyl	-$(CH_2)_2$-O-$(CH_2)_2$-		394	B
C36	Ph	Ethyl	-$(CH_2)_5$-		392	B
C37	Ph	Ethyl	-$(CH_2)_4$-		378	B

C38	3-F-Ph	Ethyl	Ethyl	Ethyl	398	B
C39	3-F-Ph	Ethyl	1-Propyl	1-Propyl	426	B
C40	3-F-Ph	Ethyl	Methyl	Ethyl	384	B
C41	3-F-Ph	Ethyl	2-Propyl	2-Propyl	426	B
C42	3-F-Ph	Ethyl	$-(CH_2)_2-O-(CH_2)_2-$		412	B
C43	3-F-Ph	Ethyl	$-(CH_2)_5-$		410	B
C44	3-F-Ph	Ethyl	$-(CH_2)_6-$		396	B
C45	Ph	Benzyl	Ethyl	Ethyl	442	A

Isolation, Method A: chromatography on SiO_2 with CH_2Cl_2 \ MeOH \ NH_4OH; 95 \ 5 \ 0.5.

Method B: Reverse phase HPLC on YMC J' sphere H80 (20/80 MeCN/0.1% aq. TFA to 90/10 MeCN/0.1% aq. TFA)

Example 6

N,N-Diethyl-4-[3-acetoxyphenyl(1-propylpiperidin-4-yl)amino]benzamide Hydrochloride[1:1], C46. A solution of 0.96 g (2.3 mmol) of N,N-diethyl-4-[3-hydroxyphenyl(1-propylpiperidin-4-yl)amino]benzamide was stirred in 20 mL of CH_2Cl_2 and 0.17 mL of acetyl chloride was added. The mixture was stirred for 2 h. The solvent was evaporated and the residue recrystallized from 2-PrOH to give 0.7g (62% yield) of the title compound as a white crystalline solid: mp 218-219°C. MS *m/z* = 452 (M^+ + H). 300MHz ^{1}H NMR (DMSO-d_6) δ 7.3 (d 2H); 7.2 (m, 1H);6.9 (d, 2H);6.7 (m, 2H);4.1 (t, 3H); 3.6 (d, 2H); 3.4 (m, 4H); 2.8 (m, 4H); 2.4(m, 2H); 2.2(s, 3H) 2.1 (d, 2H); 1.9 (m, 2H); 1.2 (t, 6H), 1.0 (t, 3H). Anal calcd. for $C_{27}H_{37}N_3O_3 \cdot HCl$: C, 66.45; H, 7.45; N, 8.61. Found: C, 66.07; H, 7.83; N, 8.32.

Biological Testing

Delta- and mu-opioid receptor binding of the above compounds was determined according to the following procedures and the following results were obtained.

1) High Throughput Screening Assay for Delta-Opioid Receptor Binding

Materials: This is a receptor based screen to detect the competitive binding of test compounds at the opioid delta receptor against the radioligand, [^{3}H]bremazocine (S.A.=25.5 Ci/mmol, Dupont/NEN, Cambridge, Massachusetts). The receptor is a cloned human cDNA expressed in mammalian CHO cells. Membranes prepared from these cells are purchased from Receptor Biology, Baltimore, MD. The reaction buffer is composed as follows: HEPES (50 mM final), $MgCl_2 \cdot 6H_2O$ (5 mM final), o-phenanthroline (20 mg/l), aprotinin (10 mg/l), Pefabloc SC (250 mg/l), leupeptin (0.5 mg/l), pepstatin A (0.7 mg/l), trypsin inhibitor (25 mg/l), chymostatin (10 mg/l), pH = 7.2. Naloxone, 10 uM, is used to define non-specific binding. The assay employs filtration to capture receptor and bound ligand.

Procedure: The receptor (membrane) preparation (28 ug protein) is allowed to incubate with the opioid receptor radioligand ([^{3}H]bremazocine, 2.4 nM) in 96-well plates until equilibrium is reached (>2 hr). Following incubation with the radioligand at 23°C, the well contents are filtered onto 96-well Whatman GF/C filter plates using a Packard cell harvester. Radioligand bound to the receptor also remains on the filter. The filters are rinsed three times with 0.5 mL of physiological saline (0.9% NaCl) to remove any unbound radioligand from the filters. Filters are dried and scintillation fluid is then added to the filters which emits light in proportion to the amount of radioactivity on the filter which is determined using an Packard Topcount scintillation counter.

Principle: Unknown drugs included in the incubation which bind to the same receptor as the radioligand will compete for the receptor and reduce the amount of radioligand which binds to the receptor. This is detected as a decreased scintillation signal from that particular incubation. The better an unknown competes for the receptor, the larger the observed decrease in radioligand bound to the receptor; thus the assay is in the format of an inhibition study. Data are reported as percent inhibition of control binding.

Results: The following compounds were tested with the following results.

Cpd#	%I @ 25 μM	Cpd#	%I @ 25 μM
C1	97	C11	101
C3	94	C12	95

C4	41	C13	100
C5	102	C14	93
C6	101	C15	68
C7	100	C16	81
C8	69	C17	98
C9	103	C18	100
C10	100	C19	95
C20	98	C34	100
C21	70	C35	64
C22	89	C36	92
C23	91	C37	88
C24	97	C38	98
C25	100	C39	101
C26	96	C40	97
C27	97	C41	88
C28	77	C42	64
C29	85	C43	89
C30	85	C44	87
C31	100	C45	99
C32	100	C46	100
C33	98		

2) Manual Tissue Screening Assay for Delta- and Mu-Opioid Receptor Binding

A) Rat Brain δ-Opioid Receptor Binding Assay

Procedure: Male, Wistar rats (150-250 g, VAF, Charles River, Kingston, NY) are killed by cervical dislocation, and their brains removed and placed immediately in ice cold Tris HCl buffer (50 mM, pH 7.4). The forebrains are separated from the remainder of the brain by a coronal transection, beginning dorsally at the colliculi and passing ventrally through the midbrain-pontine junction. After dissection, the forebrains are homogenized in Tris buffer in a Teflon®-glass homogenizer. The homogenate is diluted to a concentration of 1 g of forebrain tissue per 100 mL Tris

buffer and centrifuged at 39,000 X G for 10 min. The pellet is resuspended in the same volume of Tris buffer with several brief pulses from a Polytron homogenizer. This particulate preparation is used for the δ-opioid binding assays. Following incubation with the δ-selective peptide ligand [^{3}H]DPDPE at 25°C, the tube contents filtered through Whatman GF/B filter sheets on a Brandel cell harvester. The tubes and filters are rinsed three times with 4 mL of 10 mM HEPES (pH7.4), and the radioactivity associated with the filter circles determined using Formula 989 scintillation fluid (New England Nuclear, Boston, MA) in a scintillation counter.

Analysis: The data are used to calculate either the % inhibition compared to control binding (when only a single concentration of test compound is evaluated) or a K_i value (when a range of concentrations is tested).

% inhibition is calculated as: 1-(test compound dpm-nonspecific dpm)/(total dpm-nonspecific dpm)*100

K_i values are calculated using the LIGAND (Munson, P.J. and Rodbard, D., Anal. Biochem. 107: 220-239, 1980) data analysis program.

B) Rat Brain μ-Opioid Receptor Binding Assay

Procedure: Male, Wistar rats (150-250 g, VAF, Charles River, Kingston, NY) are killed by cervical dislocation, and their brains removed and placed immediately in ice cold Tris HCl buffer (50 mM, pH 7.4). The forebrains are separated from the remainder of the brain by a coronal transection, beginning dorsally at the colliculi and passing ventrally through the midbrain-pontine junction. After dissection, the forebrains are homogenized in Tris buffer in a Teflon®-glass homogenizer. The homogenate is diluted to a concentration of 1 g of forebrain tissue per 100 mL Tris buffer and centrifuged at 39,000 X G for 10 min. The pellet is resuspended in the same volume of Tris buffer with several brief pulses from a Polytron homogenizer. This particulate preparation is used for the μ-opioid binding assays. Following incubation with the m- selective peptide ligand [^{3}H]DAMGO at 25°C, the tube contents are filtered through Whatman GF/B filter sheets on a Brandel cell harvester. The tubes and filters are rinsed three times with 4 mL of 10 mM HEPES (pH7.4), and the radioactivity associated with the filter circles determined using Formula 989 scintillation fluid (New England Nuclear, Boston, MA) in a scintillation counter.

Analysis: The data are used to calculate either the % inhibition compared to control binding (when only a single concentration of test compound is evaluated) or a K_i value (when a range of concentrations is tested).

% inhibition is calculated as: 1-(test compound dpm-nonspecific dpm)/(total dpm-nonspecific dpm)*100

K_i values are calculated using the LIGAND (Munson, P.J. and Rodbard, D., Anal. Biochem. 107: 220-239, 1980) data analysis program.

Results: N,N-Diethyl-4-[phenyl(1-propylpiperidin-4-yl)amino]benzamide fumarate, C4, exhibited a K_i of 25 nM in binding to the δ-opioid receptor and a K_i of 153 nM in binding to the μ-opioid receptor. N,N-Diethyl-4-[3-hydroxyphenyl(1-propylpiperidin-4-yl)amino]benzamide fumarate, C2, exhibited a K_i of 0.83 nM in binding to the δ-opioid receptor and a K_i of 2,762 nM in binding to the μ-opioid receptor.

The activity of compounds of the invention as analgesics may be demonstrated by the mouse acetylcholine-bromide induced constriction assay as described below:

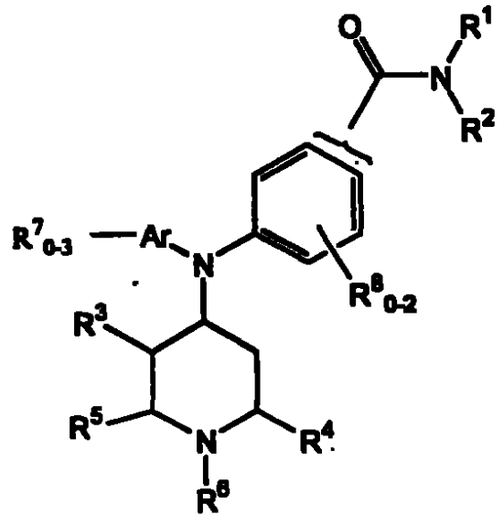
C) Mouse Acetylcholine Bromide-Induced Abdominal Constriction Assay

Procedure: The mouse acetylcholine-induced abdominal constiction assay, as described by Collier et al. in *Brit. J. Pharmacol. Chem. Ther.*, 32: 295-310, 1968, with minor modifications was used to assess analgesic potency of the compounds of formula (I). The test drugs or appropriate vehicles were administered orally (p.o.) and 30 minutes later the animal received an intraperitoneal (i.p.) injection of 5.5 mg/kg acetylcholine bromide (Matheson, Coleman and Bell, East Rutherford, NJ). The mice were then placed in groups of three into glass bell jars and observed for a ten minute observation period for the occurrence of an abdominal constriction response (defined as a wave of constriction and elongation passing caudally along the abdominal wall, accompanied by a twisting of the trunk and followed by extension of the hind limbs). The percent inhibition of this response to a nociceptive stimulus (equated to % analgesia) was calculated as follows: The % inhibition of response, i.e., % analgesia is equal to the difference between the No. of control animal responses and the No. of drug-treated animal responses times 100 divided by the No. of control animals responding.

Results: N,N-Diethyl-4-[phenyl(1-propylpiperidin-4-yl)amino]benzamide fumarate, C4, exhibited an ED_{50} of 4.2 μmol/kg in this assay.

WHAT IS CLAIMED IS:

1. A compound which binds to the delta-opioid receptor of the general formula:



I

where

Ar is phenyl, 1-naphthyl or 2-naphthyl, each optionally substituted with 1 to 3 R^7;

R^1 and R^2 are independently selected from the group consisting of hydrogen, C_{1-6}alkyl; phenyl, optionally mono-, di-, or tri-substituted with halo, C_{1-6}alkyl, C_{1-6}alkoxy or trifluoromethyl; or benzyl, optionally mono-, di-, or tri-substituted with halo, C_{1-6}alkyl, C_{1-6}alkoxy or trifluoromethyl, or alternatively, R^1 and R^2 are taken together with their N of attachment to form a ring which is selected from the group consisting of pyrrolidinyl, morpholinyl, piperidinyl and hexamethyleneiminyl, each said ring optionally substituted with 1 to 4 methyl groups;

R^3, R^4 and R^5 are independently selected from hydrogen and C_{1-4}alkyl;

R^6 is selected from the group consisting of hydrogen; C_{1-4}alkyl; C_{3-6}cycloalkylC_{1-3}alkyl, C_{3-6}alkenyl; C_{1-6}alkoxyC_{1-3}alkyl; 4-C_{1-4}alkyl-4,5-dihydro-5-oxo-1H-tretrazol-1-ylC_{1-4}alkyl; thien-2-ylC_{1-4}alkyl; thien-3-ylC_{1-4}alkyl; furan-2-ylC_{1-4}alkyl; furan-3-ylC_{1-4}alkyl; pyrrol-2-ylC_{1-4}alkyl; pyrrol-3-ylC_{1-4}alkyl; pyridin-2-ylC_{1-4}alkyl; pyridin-3-ylC_{1-4}alkyl; pyridin-4-ylC_{1-4}alkyl; pyrazinylC_{1-4}alkyl; pyrimidin-2-ylC_{1-4}alkyl; pyrimidin-4-ylC_{1-4}alkyl; pyrimidin-5-ylC_{1-4}alkyl; thiazol-2-ylC_{1-4}alkyl; thiazol-4-ylC_{1-4}alkyl; thiazol-5-ylC_{1-4}alkyl; oxazol-2-ylC_{1-4}alkyl oxazol-4-ylC_{1-4}alkyl; oxazol-5-ylC_{1-4}alkyl and phenylC_{1-4}alkyl, where the foregoing thienyl, furanyl, pyrrolyl, thiazolyl and oxazolyl are optionlly mono-, di-, or tri-substituted with a non-fused R^7 and the

foregoing pyridinyl, pyrazinyl, pyrimidinyl and phenyl is optionally mono-, di-, or tri-substituted with R^7;

R^7 is independently selected from the group consisting of hydroxy, halo, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}acyl, C_{1-3}acyloxy, cyano, amino, C_{1-3}acylamino, C_{1-3}alkylamino, di(C_{1-3}alkyl)amino, C_{1-3}alkylthio, C_{1-3}alkylsulfonyl, trifluoromethyl and trifluoromethoxy, and two R^7 can together form a single moiety selected from the group consisting of -$(CH_2)_{3-5}$- and -$O(CH_2)_{1-3}O$- attached to adjacent carbon atoms of Ar; and

R^8 is independently selected from the group consisting of halo, C_{1-4}alkyl, C_{1-4}alkoxy and trifluoromethyl..

2.. The compound of claim 1 wherein Ar is phenyl.

3. The compound of claim 1 wherein R^1 and R^2 are independently selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, i-butyl, phenyl, p-chlorophenyl, p-fluorophenyl, p-methylphenyl, p-trifluoromethylphenyl, benzyl, p-chlorobenzyl, p-fluorobenzyl, p-methylbenzyl and p-trifluoromethylbenzyl, or alternatively, R^1 and R^2 are taken together with their N of attachment to form a ring which is selected from the group consisting of pyrrolidinyl and piperidinyl.

4. The compound of claim 1 wherein R^3, R^4 and R^5 are independently selected from hydrogen, methyl, ethyl, n-propyl, i-propyl and t-butyl.

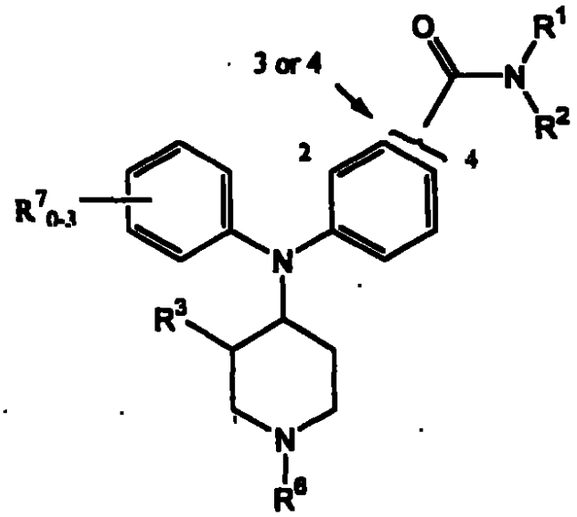
5. The compound of claim 1 wherein R^6 are selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, cyclopropylmethyl, ethenyl, allyl, methoxymethyl, benzyl, p-chlorobenzyl, p-fluorobenzyl, p-methylbenzyl, p-trifluoromethylbenzyl, p-aminobenzyl, thien-2-ylCH_2CH_2-, thien-3-ylCH_2CH_2-, pyridin-3-ylCH_2CH_2-, pyridin-4-ylCH_2CH_2-, thiazol-2-ylCH_2CH_2- and phenylCH_2CH_2-.

6. The compound of claim 1 wherein R^7 are independently selected from the

group consisting of hydroxy, chloro, bromo, fluoro, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, methoxy, ethoxy, formyl, acyl, acetoxy, cyano, amino, methylamido, methylamino, N,N-dimethylamino, methylthio, methylsulfonyl, trifluoromethoxy and trifluoromethyl, and preferred moieties where two R^7 together form a single moiety are selected from the group consisting of propylene, butylene and $-OCH_2O-$.

7. The compound of claim 1 wherein R^8 are independently selected from the group consisting of chloro, bromo, fluoro, methyl, ethyl, n-propyl, i-propyl, t-butyl, methoxy, ethoxy and trifluoromethyl.

8. The compound of claim 1 having the general structure:

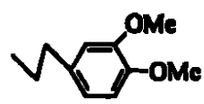
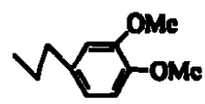


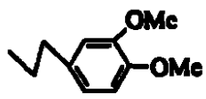
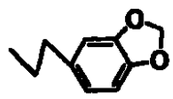
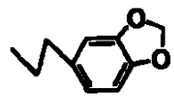
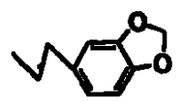
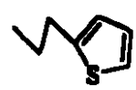
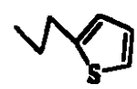
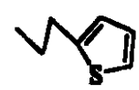
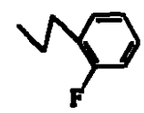
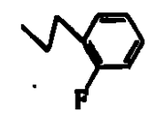
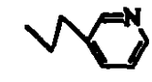
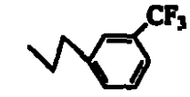
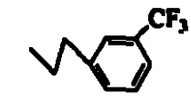
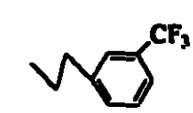
where R^1, R^2, R^3, R^6 and R^7 are dependently selected from the groups consisting of:

Cpd#	R^7	R^6	R^1	R^2	amide subst.	R^3
P1	none	$-CH_2CH=CH_2$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P2	none	$-CH_2$-cyclopropyl	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P3	3-OH	$-CH_2CH=CH_2$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P4	3-OH	$-CH_2$-cyclopropyl	$-CH_2CH_3$	$-CH_2CH_3$	4	H

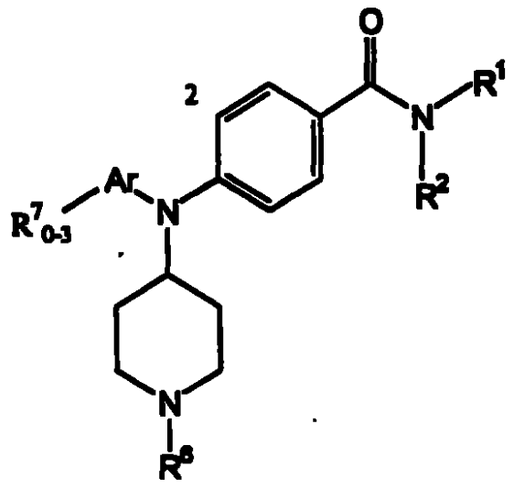
P5	3-OH	$-CH_3$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P6	3-OH	$-CH_2CH_3$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P7	3-OH	$-CH_2CH_2Ph$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P8	3-OH	$-CH_3$	$-nC_3H_7$	$-nC_3H_7$	4	H
P9	3-OH	$-CH_2CH_3$	$-nC_3H_7$	$-nC_3H_7$	4	H
P10	3-OH	$-CH_2CH_2Ph$	$-nC_3H_7$	$-nC_3H_7$	4	H
P11	3-OH	$-CH_3$	$-nC_4H_9$	$-nC_4H_9$	4	H
P12	3-OH	$-CH_2CH_3$	$-nC_4H_9$	$-nC_4H_9$	4	H
P13	3-OH	$-CH_2CH_2Ph$	$-nC_4H_9$	$-nC_4H_9$	4	H
P14	none	$-CH_3$	$-nC_4H_9$	$-nC_4H_9$	4	H
P15	none	$-CH_2CH_3$	$-nC_4H_9$	$-nC_4H_9$	4	H
P16	none	$-CH_2CH_2Ph$	$-nC_4H_9$	$-nC_4H_9$	4	H
P17	3-F	$-CH_3$	$-nC_4H_9$	$-nC_4H_9$	4	H
P18	3-F	$-CH_2CH_3$	$-nC_4H_9$	$-nC_4H_9$	4	H
P19	3-F	$-CH_2CH_2Ph$	$-nC_4H_9$	$-nC_4H_9$	4	H
P20	$3-OCH_3$	$-CH_3$	$-nC_4H_9$	$-nC_4H_9$	4	H
P21	$3-OCH_3$	$-CH_2CH_3$	$-nC_4H_9$	$-nC_4H_9$	4	H
P22	$3-OCH_3$	$-nC_4H_9$	$-nC_4H_9$	$-nC_4H_9$	4	H
P23	$3,4-OCH_2O-$	$-nC_3H_7$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P24	$3,4-OCH_2O-$	$-nC_3H_7$	$-nC_3H_7$	$-nC_3H_7$	4	H
P25	$3,4-OCH_2O-$	$-nC_3H_7$	$2-C_3H_7$	$2-C_3H_7$	4	H
P26	$3,4-OCH_2O-$	$-nC_3H_7$	$-nC_4H_9$	$-nC_4H_9$	4	H
P27	$3-N(CH_3)_2$	$-nC_3H_7$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P28	$3-N(CH_3)_2$	$-nC_3H_7$	$-nC_3H_7$	$-nC_3H_7$	4	H
P29	$3-N(CH_3)_2$	$-nC_3H_7$	$2-C_3H_7$	$2-C_3H_7$	4	H
P30	$3-N(CH_3)_2$	$-nC_3H_7$	$-nC_4H_9$	$-nC_4H_9$	4	H
P31	4-F	$-nC_3H_7$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P32	4-F	$-nC_3H_7$	$-nC_3H_7$	$-nC_3H_7$	4	H
P33	4-F	$-nC_3H_7$	$2-C_3H_7$	$2-C_3H_7$	4	H
P34	4-F	$-nC_3H_7$	$-nC_4H_9$	$-nC_4H_9$	4	H
P35	2-F	$-nC_3H_7$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P36	2-F	$-nC_3H_7$	$-nC_3H_7$	$-nC_3H_7$	4	H

P37	2-F	-nC_3H_7	2-C_3H_7	2-C_3H_7	4	H
P38	2-F	-nC_3H_7	-nC_4H_9	-nC_4H_9	4	H
P39	3-Cl, 4-OCH_3	-nC_3H_7	-CH_2CH_3	-CH_2CH_3	4	H
P40	3-Cl, 4-OCH_3	-nC_3H_7	-nC_3H_7	-nC_3H_7	4	H
P41	3-Cl, 4-OCH_3	-nC_3H_7	2-C_3H_7	2-C_3H_7	4	H
P42	3-Cl, 4-OCH_3	-nC_3H_7	-nC_4H_9	-nC_4H_9	4	H
P43	3-CF_3	-nC_3H_7	-CH_2CH_3	-CH_2CH_3	4	H
P44	3-CF_3	-nC_3H_7	-nC_3H_7	-nC_3H_7	4	H
P45	3-CF_3	-nC_3H_7	2-C_3H_7	2-C_3H_7	4	H
P46	3-CF_3	-nC_3H_7	-nC_4H_9	-nC_4H_9	4	H
P47	3-OCH_3, 5-OCH_3	-nC_3H_7	-CH_2CH_3	-CH_2CH_3	4	H
P48	3-OCH_3, 5-OCH_3	-nC_3H_7	-nC_3H_7	-nC_3H_7	4	H
P49	3-OCH_3, 5-OCH_3	-nC_3H_7	2-C_3H_7	2-C_3H_7	4	H
P50	3-OCH_3, 5-OCH_3	-nC_3H_7	-nC_4H_9	-nC_4H_9	4	H
P51	3-CH_3	-nC_3H_7	-CH_2CH_3	-CH_2CH_3	4	H
P52	3-CH_3	-nC_3H_7	-nC_3H_7	-nC_3H_7	4	H
P53	3-CH_3	-nC_3H_7	2-C_3H_7	2-C_3H_7	4	H
P54	3-CH_3	-nC_3H_7	-nC_4H_9	-nC_4H_9	4	H
P55	4-CH_3	-nC_3H_7	-CH_2CH_3	-CH_2CH_3	4	H
P56	4-CH_3	-nC_3H_7	-nC_3H_7	-nC_3H_7	4	H
P57	4-CH_3	-nC_3H_7	2-C_3H_7	2-C_3H_7	4	H
P58	4-CH_3	-nC_3H_7	-nC_4H_9	-nC_4H_9	4	H
P59	2-CH_3, 3-CH_3	-nC_3H_7	-CH_2CH_3	-CH_2CH_3	4	H
P60	2-CH_3, 3-CH_3	-nC_3H_7	-nC_3H_7	-nC_3H_7	4	H
P61	2-CH_3, 3-CH_3	-nC_3H_7	2-C_3H_7	2-C_3H_7	4	H
P62	2-CH_3, 3-CH_3	-nC_3H_7	-nC_4H_9	-nC_4H_9	4	H
P63	3-OCF_3	-nC_3H_7	-CH_2CH_3	-CH_2CH_3	4	H
P64	3-OCF_3	-nC_3H_7	-nC_3H_7	-nC_3H_7	4	H
P65	3-OCF_3	-nC_3H_7	2-C_3H_7	2-C_3H_7	4	H
P66	3-OCF_3	-nC_3H_7	-nC_4H_9	-nC_4H_9	4	H
P67	3-SCH_3	-nC_3H_7	-CH_2CH_3	-CH_2CH_3	4	H
P68	3-SCH_3	-nC_3H_7	-nC_3H_7	-nC_3H_7	4	H

P69	3-SCH_3	-nC_3H_7	2-C_3H_7	2-C_3H_7	4	H
P70	3-SCH_3	-nC_3H_7	-nC_4H_9	-nC_4H_9	4	H
P71	none	-CH_2Ph	-CH_2CH_3	-CH_2CH_3	4	ci-Me
P72	none	-H	-CH_2CH_3	-CH_2CH_3	4	ci-Me
P73	none	-$CH_2CH{=}CH_2$	-CH_2CH_3	-CH_2CH_3	4	ci-Me
P74	none	-nC_3H_7	-CH_2CH_3	-CH_2CH_3	4	ci-Me
P75	3-OCH_3	-CH_2Ph	-CH_2CH_3	-CH_2CH_3	4	ci-Me
P76	3-OCH_3	-H	-CH_2CH_3	-CH_2CH_3	4	ci-Me
P77	3-OCH_3	-$CH_2CH{=}CH_2$	-CH_2CH_3	-CH_2CH_3	4	ci-Me
P78	3-OCH_3	-nC_3H_7	-CH_2CH_3	-CH_2CH_3	4	ci-Me
P79	none	-CH_2Ph	-CH_2CH_3	-CH_2CH_3	4	tr-Me
P80	none	-H	-CH_2CH_3	-CH_2CH_3	4	tr-Me
P81	none	-$CH_2CH{=}CH_2$	-CH_2CH_3	-CH_2CH_3	4	tr-Me
P82	none	-nC_3H_7	-CH_2CH_3	-CH_2CH_3	4	tr-Me
P83	none	-nC_3H_7	-CH_2CH_3	-CH_2CH_3	4	H
P84	none	-nC_3H_7	-nC_3H_7	-nC_3H_7	3	H
P85	none	-nC_3H_7	-CH_2Ph	-CH_2CH_3	3	H
P86	none	-nC_3H_7	-$(CH_2)_5$-		3	H
P87	* 2,3-CH=CHCH=CH-	-nC_3H_7	-CH_2CH_3	-CH_2CH_3	3	H
P88	* 2,3-CH=CHCH=CH-	-nC_3H_7	-nC_3H_7	-nC_3H_7	4	H
P89	3,4-$(CH_2)_4$-	-nC_3H_7	-CH_2CH_3	-CH_2CH_3	4	H
P90	3,4-$(CH_2)_4$-	-nC_3H_7	-nC_3H_7	-nC_3H_7	4	H
P91	3,4-$CH_2CH_2CH_2$-	-nC_3H_7	-CH_2CH_3	-CH_2CH_3	4	H
P92	3,4-$CH_2CH_2CH_2$-	-nC_3H_7	-nC_3H_7	-nC_3H_7	4	H
P93	none		-CH_2CH_3	-CH_2CH_3	4	H
P94	m-F		-CH_2CH_3	-CH_2CH_3	4	H

P95	m-sCH$_3$		-CH$_3$	-CH$_2$CH$_3$	4	ci-Me
P96	none		-CH$_2$CH$_3$	-CH$_2$CH$_3$	4	H
P97	m-oCH$_3$		-nC$_3$H$_7$	-nC$_3$H$_7$	4	H
P98	m-OH		-CH$_3$	-CH$_2$CH$_3$	4	tr-Me
P99	none		-CH$_2$CH$_3$	-CH$_2$CH$_3$	4	H
P100	o-F		-nC$_3$H$_7$	-nC$_3$H$_7$	4	H
P101	o-CH$_3$		-CH$_3$	-CH$_2$CH$_3$	4	ci-Me
P102	none		-CH$_2$CH$_3$	-CH$_2$CH$_3$	4	H
P103	p-OH		-CH$_2$CH$_3$	-nC$_3$H$_7$	4	H
P104	p-F		-nC$_3$H$_7$	-nC$_3$H$_7$	4	tr-Me
P105	None		-CH$_2$CH$_3$	-CH$_2$CH$_3$	4	H
P106	m-sCH$_3$		-nC$_3$H$_7$	-nC$_3$H$_7$	4	H
P107	m-oCF$_3$		-CH$_3$	-nC$_3$H$_7$	4	ci-Me
P108	none		-CH$_2$CH$_3$	-CH$_2$CH$_3$	4	H
P109	m-CH$_3$		-CH$_3$	-CH$_2$CH$_3$	4	H
P110	2, 3-oCH$_3$		-CH$_3$	-nC$_3$H$_7$	4	H

8. The compound of claim 1 having the general structure:



where R^1, R^2, R^6 and R^7-Ar are dependently selected from the groups consisting of:

Cpd#	R^7-Ar	R^6	R^1	R^2
C1	3-CH_3O-Ph	1-Propyl	Ethyl	Ethyl
C2	3-HO-Ph	1-Propyl	Ethyl	Ethyl
C3	Ph	1-Propyl	Ethyl	Ethyl
C4	Ph	1-Propyl	Methyl	Ph
C5	3-Cl-Ph	1-Propyl	Ethyl	Ethyl
C6	3-Cl-Ph	1-Propyl	-$(CH_2)_4$-	
C7	2-CH_3O-Ph	1-Propyl	Ethyl	Ethyl
C8	1-Naphthyl	1-Propyl	Ethyl	Ethyl
C9	1-Naphthyl	1-Propyl	-$(CH_2)_4$-	
C10	Ph	Methyl	Ethyl	Ethyl
C11	Ph	Methyl	1-Propyl	1-Propyl
C12	Ph	Methyl	Methyl	Ethyl
C13	Ph	Methyl	2-Propyl	2-Propyl
C14	Ph	Methyl	-$(CH_2)_2$-O-$(CH_2)_2$-	
C15	Ph	Methyl	-$(CH_2)_3$-	
C16	Ph	Methyl	-$(CH_2)_4$-	

C17	3-CH_3O-Ph	Methyl	Ethyl	Ethyl
C18	3-CH_3O-Ph	Methyl	1-Propyl	1-Propyl
C19	3-CH_3O-Ph	Methyl	Methyl	Ethyl
C20	3-CH_3O-Ph	Methyl	2-Propyl	2-Propyl
C21	3-CH_3O-Ph	Methyl	-$(CH_2)_2$-O-$(CH_2)_2$-	
C22	3-CH_3O-Ph	Methyl	-$(CH_2)_3$-	
C23	3-CH_3O-Ph	Methyl	-$(CH_2)_4$-	
C24	3-F-Ph	Methyl	Ethyl	Ethyl
C25	3-F-Ph	Methyl	1-Propyl	1-Propyl
C26	3-F-Ph	Methyl	Methyl	Ethyl
C27	3-F-Ph	Methyl	2-Propyl	2-Propyl
C28	3-F-Ph	Methyl	-$(CH_2)_2$-O-$(CH_2)_2$-	
C29	3-F-Ph	Methyl	-$(CH_2)_3$-	
C30	3-F-Ph	Methyl	-$(CH_2)_4$-	
C31	Ph	Ethyl	Ethyl	Ethyl
C32	Ph	Ethyl	1-Propyl	1-Propyl
C33	Ph	Ethyl	Methyl	Ethyl
C34	Ph	Ethyl	2-Propyl	2-Propyl
C35	Ph	Ethyl	-$(CH_2)_2$-O-$(CH_2)_2$-	
C36	Ph	Ethyl	-$(CH_2)_3$-	
C37	Ph	Ethyl	-$(CH_2)_4$-	
C38	3-F-Ph	Ethyl	Ethyl	Ethyl
C39	3-F-Ph	Ethyl	1-Propyl	1-Propyl
C40	3-F-Ph	Ethyl	Methyl	Ethyl
C41	3-F-Ph	Ethyl	2-Propyl	2-Propyl
C42	3-F-Ph	Ethyl	-$(CH_2)_2$-O-$(CH_2)_2$-	
C43	3-F-Ph	Ethyl	-$(CH_2)_3$-	
C44	3-F-Ph	Ethyl	-$(CH_2)_4$-	
C45	Ph	Benzyl	Ethyl	Ethyl
C46	3-$CH_3C(O)O$-	n-Propyl	Ethyl	Ethyl

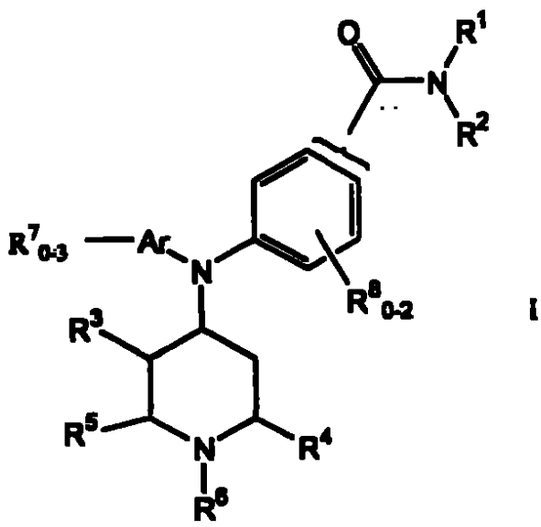
11. The compounds of claim 1 which are effective analgesics.

12. The compounds of claim 1 which are effective immunosuppressants, antiinflammatory agents, agents for the treatment of mental illness, medicaments for drug and alcohol abuse, agents for treating gastritis and diarrhea, cardiovascular agents, and agents for the treatment of respiratory diseases.

13. A method for the treatment of pain in mammals comprising administering an effective amount of a compound of claim 1.

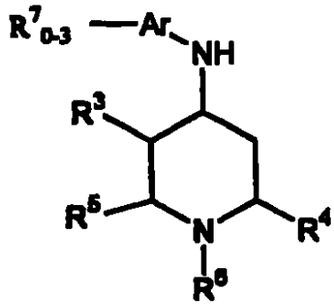
14. A method of the therapeutic treatment of a mammal comprising administering a compound of claim 1 which is effective as an immunosuppressant, antiinflammatory agent, agent for the treatment of mental illness, medicament for drug and alcohol abuse, agent for treating gastritis and diarrhea, cardiovascular agent, or agent for the treatment of respiratory diseases, in an effective amount to such mammal in need of the same.

15. A method to make a compound of the formula:

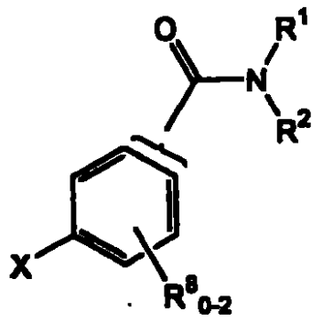


I

comprising the step of arylating a compound of the formula:



in the presence of a palladium catalyst, a phosphine ligand and a base with a compound of the forumla:



X = Br, I, OSO_2CF_3

where

Ar is phenyl, 1-naphthyl or 2-naphthyl, each optionally substituted with 1 to 3 R^7;

R^1 and R^2 are independently selected from the group consisting of hydrogen, C_{1-8}alkyl; phenyl, optionally mono-, di-, or tri-substituted with halo, C_{1-6}alkyl, C_{1-6}alkoxy or trifluoromethyl; or benzyl, optionally mono-, di-, or tri-substituted with halo, C_{1-6}alkyl, C_{1-6}alkoxy or trifluoromethyl, or alternatively, R^1 and R^2 are taken together with their N of attachment to form a ring which is selected from the group consisting of pyrrolidinyl, morpholinyl, piperidinyl and hexamethyleneiminyl, each said ring optionally substituted with 1 to 4 methyl groups;

R^3, R^4 and R^5 are independently selected from hydrogen and C_{1-4}alkyl;

R^6 is selected from the group consisting of hydrogen; C_{1-8}alkyl; C_{3-6}cycloalkylC_{1-3}alkyl, C_{1-6}alkenyl; C_{1-6}alkoxyC_{1-3}alkyl; 4-C_{1-4}alkyl-4,5-dihydro-5-oxo-1H-tretrazol-1-

ylC$_{1-4}$alkyl; thien-2-ylC$_{1-4}$alkyl; thien-3-ylC$_{1-4}$alkyl; furan-2-ylC$_{1-4}$alkyl; furan-3-ylC$_{1-4}$alkyl; pyrrol-2-ylC$_{1-4}$alkyl; pyrrol-3-ylC$_{1-4}$alkyl; pyridin-2-ylC$_{1-4}$alkyl; pyridin-3-ylC$_{1-4}$alkyl; pyridin-4-ylC$_{1-4}$alkyl; pyrazinylC$_{1-4}$alkyl; pyrimidin-2-ylC$_{1-4}$alkyl; pyrimidin-4-ylC$_{1-4}$alkyl; pyrimidin-5-ylC$_{1-4}$alkyl; thiazol-2-ylC$_{1-4}$alkyl; thiazol-4-ylC$_{1-4}$alkyl; thiazol-5-ylC$_{1-4}$alkyl; oxazol-2-ylC$_{1-4}$alkyl oxazol-4-ylC$_{1-4}$alkyl; oxazol-5-ylC$_{1-4}$alkyl and phenylC$_{1-4}$alkyl, where the foregoing thienyl, furanyl, pyrrolyl, thiazolyl and oxazolyl are optionlly mono-, di-, or tri-substituted with a non-fused R^7 and the foregoing pyridinyl, pyrazinyl, pyrimidinyl and phenyl is optionally mono-, di-, or tri-substituted with R^7;

R^7 is independently selected from the group consisting of hydroxy, halo, C$_{1-3}$alkyl, C$_{1-3}$alkoxy, C$_{1-3}$acyl, C$_{1-3}$acyloxy, cyano, amino, C$_{1-3}$acylamino, C$_{1-3}$alkylamino, di(C$_{1-3}$alkyl)amino, C$_{1-3}$alkylthio, C$_{1-3}$alkylsulfonyl, trifluoromethyl and trifluoromethoxy, and two R^7 can together form a single moiety selected from the group consisting of -(CH$_2$)$_{3-5}$- and -O(CH$_2$)$_{1-3}$O- attached to adjacent carbon atoms of Ar; and

R^8 is independently selected from the group consisting of halo, C$_{1-6}$alkyl, C$_{1-6}$alkoxy and trifluoromethyl..

INTERNATIONAL SEARCH REPORT

Int. ational Application No
PCT/US 98/27350

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D211/58 A61K31/445 C07D405/12 C07D405/06 C07D409/06
C07D401/06 A61K31/535

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 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 98 28270 A (ROBERTS EDWARD ;ASTRA PHARMA INC (CA); ASTRA AB (SE); PELCMAN BENJ) 2 July 1998 Compounds 14,15,17,18 see page 8, line 27 - line 30; claim 1; examples 1-10	1-15
A	WO 97 23466 A (PLOBECK NIKLAS ;ROBERTS EDWARD (CA); ASTRA PHARMA INC (CA); WAHLES) 3 July 1997 cited in the application see page 12, line 9 - line 12; claim 1	1-15
A	WO 97 10230 A (SMITHKLINE BEECHAM SPA ;DONDIO GIULIO (IT); RONZONI SILVANO (IT)) 20 March 1997 cited in the application see claim 1	1-15

-/—

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 April 1999	20.04.99

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gettins, M

2

INTERNATIONAL SEARCH REPORT

Int. ..ational Application No
PCT/US 98/27350

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 36620 A (SMITHKLINE BEECHAM SPA ;DONDIO GIULIO (IT); RONZONI SILVANO (IT)) 21 November 1996 cited in the application	1-15
A	WO 93 15062 A (WELLCOME FOUND) 5 August 1993 cited in the application see page 1, line 8; claim 1; example 6	1-15
A	EP 0 383 579 A (GLAXO INC) 22 August 1990 see page 16, line 24; claim 1	1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/27350

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 14 and 14 are related to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/27350

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9828270	A	02-07-1998	AU	5351398 A	17-07-1998
WO 9723466	A	03-07-1997	AU	1216297 A	17-07-1997
			CZ	9801768 A	16-09-1998
			NO	982807 A	19-08-1998
			PL	327403 A	07-12-1998
WO 9710230	A	20-03-1997	IT	MI951930 A	17-03-1997
			AU	7084796 A	01-04-1997
			CA	2232161 A	20-03-1997
			CN	1202164 A	16-12-1998
			CZ	9800785 A	12-08-1998
			EP	0873330 A	28-10-1998
			NO	981131 A	16-03-1998
			NZ	318774 A	26-08-1998
			PL	325552 A	03-08-1998
WO 9636620	A	21-11-1996	IT	MI951020 A	19-11-1996
			AU	5899896 A	29-11-1996
			BR	9608458 A	05-01-1999
			CA	2221380 A	21-11-1996
			CN	1190393 A	12-08-1998
			CZ	9703652 A	17-06-1998
			EP	0825991 A	04-03-1998
			NO	975294 A	18-11-1997
			PL	323385 A	30-03-1998
WO 9315062	A	05-08-1993	AU	675928 B	27-02-1997
			AU	3457393 A	01-09-1993
			CA	2129046 A	05-08-1993
			EP	0649414 A	26-04-1995
			IL	104582 A	30-10-1998
			JP	7503247 T	06-04-1995
			NZ	246916 A	27-08-1996
			US	5658908 A	19-08-1997
			US	5681830 A	28-10-1997
			US	5574159 A	12-11-1996
			US	5854249 A	29-12-1998
			ZA	9300717 A	02-08-1994
EP 0383579	A	22-08-1990	US	5019583 A	28-05-1991
			AT	140451 T	15-08-1996
			AU	636330 B	29-04-1993
			AU	4973190 A	23-08-1990
			CA	2010011 A,C	15-08-1990
			CY	2002 A	05-12-1997
			DE	69027794 D	22-08-1996
			DE	69027794 T	02-01-1997
			DK	383579 T	14-10-1996
			ES	2088961 T	01-10-1996
			GR	3020719 T	30-11-1996
			HK	78297 A	20-06-1997
			IE	77156 B	03-12-1997
			JP	2300167 A	12-12-1990
			LU	90011 A	11-03-1997
			MX	9203024 A	01-07-1992
			PT	93137 A,B	31-08-1990
			SG	47967 A	17-04-1991

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte..ational Application No
PCT/US 98/27350

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0383579 A		LV 5741 A	20-10-1996

136

DZ

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 241/04, 295/04, A61K 31/495, 51/04 — A1

(11) International Publication Number: WO 97/23466

(43) International Publication Date: 3 July 1997 (03.07.97)

(21) International Application Number: PCT/SE96/01635

(22) International Filing Date: 11 December 1996 (11.12.96)

(30) Priority Data:
9504661-1 22 December 1995 (22.12.95) SE

(71) Applicant (*for all designated States except MG US*): ASTRA PHARMA INC. [CA/CA]; 1004 Middlegate Road, Mississauga, Ontario L4Y 1M4 (CA).

(71) Applicant (*for MG only*): ASTRA AKTIEBOLAG (publ) [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): ROBERTS, Edward [GB/CA]; 2541 Chestnut Circle, St. Lazare de Vaudreuil, Quebec J7T 2A1 (CA). PLOBECK, Niklas [SE/CA]; Apartment 412, 4655 Boulevard Henri-Bourassa West, Ville St. Laurent, Quebec H4L 5H6 (CA). WAHLESTEDT, Claes [SE/CA]; 6 Chelsea Place, Montreal, Quebec H3G 2J9 (CA).

(74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).

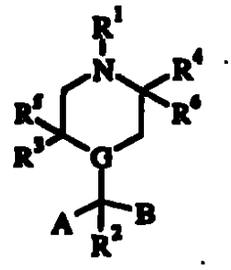
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: NOVEL COMPOUNDS WITH ANALGESIC EFFECT

(57) Abstract

Compounds of formula (I) as well as their pharmaceutically acceptable salts, and pharmaceutical compositions comprising the novel compounds. The novel compounds of formula (I) are useful in the management of pain.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic			SE	Sweden
CG	Congo	KR	Republic of Korea	SG	Singapore
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LR	Liberia	SZ	Swaziland
CS	Czechoslovakia	LT	Lithuania	TD	Chad
CZ	Czech Republic	LU	Luxembourg	TG	Togo
DE	Germany	LV	Latvia	TJ	Tajikistan
DK	Denmark	MC	Monaco	TT	Trinidad and Tobago
EE	Estonia	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	UG	Uganda
FI	Finland	ML	Mali	US	United States of America
FR	France	MN	Mongolia	UZ	Uzbekistan
GA	Gabon	MR	Mauritania	VN	Viet Nam

NOVEL COMPOUNDS WITH ANALGESIC EFFECT

Field of the invention

The present invention is related to novel compounds, to a process for their preparation, their use and pharmaceutical compositions comprising the novel compounds. The novel compounds are used in therapy, and in particular for the treatment of pain.

Background and prior art

The δ receptor has been identified as having a role in many bodily functions such as circulatory and pain systems. Ligands for the δ receptor may therefore find potential use as analgesics, and/or as antihypertensive agents. Ligands for the δ receptor have also been shown to posess immunomodulatory activities.

The identification of at least three different populations of opioid receptors (μ, δ and κ) is now well established and all three are apparent in both central and peripheral nervous systems of many species including man. Analgesia has been observed in various animal models when one or more of these receptors has been activated.

With few exceptions, currently available selective opioid δ ligands are peptidic in nature and are unsuitable for administration by systemic routes. Some non-peptidic δ antagonists have been available for some time (see Takemori and Portoghese, 1992, Ann. Rev. Pharmacol. Tox., 32: 239-269. for review). These compounds, *e.g.* naltrindole, suffer from rather poor (*i.e.*, < 10-fold) selectivity for the δ receptor vs μ receptor binding and exhibit no analgesic activity, a fact which underscores the need for the development of highly selective non-peptidic δ agonists..

Recently, a non-peptidic δ agonist, BW 373U86, was described by Chang *et al.*, 1993, J. Pharmacol. Exp. Ther., 267: 852-857., as the first δ-selective non-peptide with analgesic activity, however, it shows significant affinity for the μ receptor.

Thus, the problem underlying the present invention was to find new analgesics having excellent analgesic effects, but also with an improved side-effect profile over current μ agonists and potential oral efficacy.

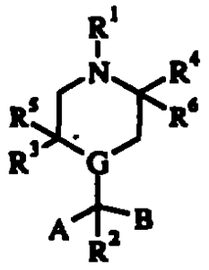
Analgesics that have been identified and are existing in the prior art have many disadvantages in that they suffer from poor pharmacokinetics and are not analgesic when administered by systemic routes. Also, it has been documented that preferred compounds, described within the prior art, show significant convulsive effects when administered systemically.

In WO 93/15062 and WO 95/045051, some diarylmethylpiperazine and diarylmethyl-piperidine compounds, including BW 373U86, are disclosed, but these prior art compounds are structurally distinct from the compounds acccording to the present invention.

The problem mentioned above has been solved by developing novel piperazine and piperidine compounds, as will be described below.

Outline of the invention

The novel compounds according to the present invention are defined by the formula (I)



(I)

wherein

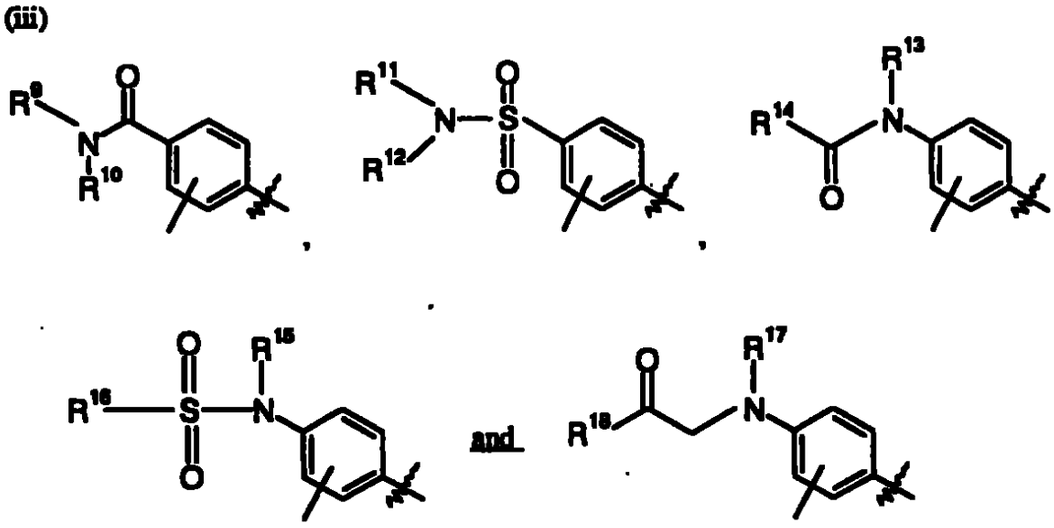
G is a carbon atom or a nitrogen atom;

A is selected from

(i) phenyl substituted by any of -COOH, - $CONH_2$, $COOCH_3$, -CN, NH_2 or -$COCH_3$;

(ii) naphtyl, benzofuranyl, and quinolinyl; and

(iii)



and

wherein the phenyl ring of each A substituent may be optionally and independently substituted by 1 or 2 substituents selected from hydrogen, CH_3, $(CH_2)_oCF_3$, halogen, $CONR^7R^8$, CO_2R^7, COR^7, $(CH_2)_oNR^7R^8$, $(CH_2)_oCH_3(CH_2)_oSOR^7$, $(CH_2)_oSO_2R^7$ and $(CH_2)_oSO_2NR^7R^8$ wherein o is 0, 1, or 2, and R^7 and R^8 are as defined below;

R^1 is selected from hydrogen; a branched or straight C_1-C_6 alkyl, C_1-C_6 alkenyl, -CO(C_1-C_6 alkyl); (C_1-C_6 alkyl)-B wherein B is as defined below; C_3-C_8 cycloalkyl, C_4-C_8 (alkyl-cycloalkyl) wherein alkyl is C_1-C_2 alkyl and cycloalkyl is C_3-C_6 cycloalkyl; C_6-C_{10} aryl; and heteroaryl having from 5 - 10 atoms selected from any of C, S, N and O; and whereby the C_6-C_{10} aryl and the heteroaryl may optionally be substituted by 1 or 2 substituents selected from hydrogen, CH_3, $(CH_2)_oCF_3$, halogen, $CONR^7R^8$, CO_2R^7, COR^7, $(CH_2)_oNR^7R^8$, $(CH_2)_oCH_3(CH_2)_oSOR^7$, $(CH_2)_oSO_2R^7$ and $(CH_2)_oSO_2NR^7R^8$, wherein o is 0, 1, or 2, and R^7 and R^8 are as defined below;

R^7 and R^8 is each and independently as defined for R^1 above;

R^2 is selected from hydrogen, CH_3, OR^1, CO_2R^1, and $CH_2CO_2R^1$ wherein R^1 is as defined above;

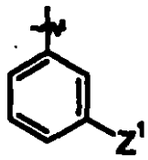
R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18}, is each and independently as defined for R^1 above;

B is a substituted or unsubstituted aromatic; an optionally substituted C_5-C_{10} hydroaromatic; a heteroaromatic or a heterohydroaromatic moiety, each having from 5 to 10 atoms selected from any of C, S, N and O, and each being optionally and independently substituted by 1 or 2 substituents independently selected from hydrogen, CH_3, CF_3, halogen, $(CH_2)_pCONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pCOR^7$, $(CH_2)_pCO_2R^7$, OR^7, $(CH_2)_pSOR^7$, $(CH_2)_pSO_2R^7$, and $(CH_2)_pSO_2NR^7R^8$;

wherein p is 0, 1, 2 or 3 and wherein R^7 and R^8 are as defined above;

R^3, R^4, R^5 and R^6 is each and independently selected from R^7, $(CH_2)_pCONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pCONR^7R^8$, $(CH_2)_pCO_2R^7$, $(CH_2)_pPh$, $(CH_2)_p$(p-OH Ph), $(CH_2)_p$-3-indolyl, $(CH_2)_pSR^7$, and $(CH_2)_pOR^7$;
wherein p is 0, 1, 2, 3, or 4, and R^7 and R^8 are as defined above;

with the proviso that when A is a phenyl ring substituted by a -CN group or by a $-NH_2$ group, B may not be



wherein
Z^1 is hydroxy, and esters thereof;
hydroxymethyl, and esters thereof; or
amino, and carboxamides and sulfonamides.

Within the scope of the invention are also pharmaceutically acceptable salts of the compounds of the formula (I), as well as isomers, hydrates, isoforms and prodrugs thereof.

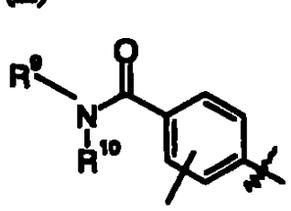
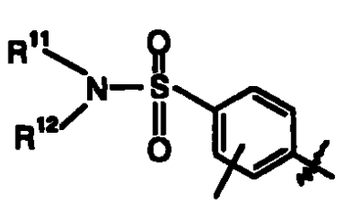
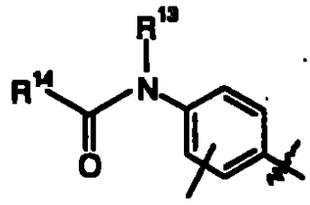
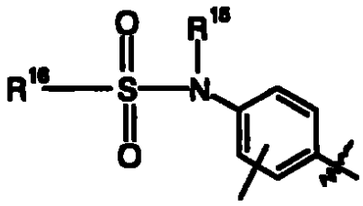
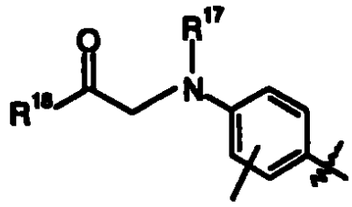
Preferred compounds according to the invention are compounds of the formula (I) wherein

G is a carbon atom or a nitrogen atom;
A is selected from

(i) phenyl substituted by any of -COOH, - $CONH_2$, $COOCH_3$, -CN, NH_2 or $-COCH_3$;

(ii) naphtyl, benzofuranyl, and quinolinyl; and

(iii)





and


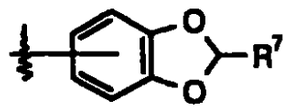
wherein the phenyl ring of each A substituent may be optionally and independently substituted by 1 or 2 substituents selected from hydrogen, CH_3, $(CH_2)_oCF_3$, halogen, $CONR^7R^8$, CO_2R^7, COR^7, $(CH_2)_oNR^7R^8$, $(CH_2)_oCH_3(CH_2)_oSOR^7$, $(CH_2)_oSO_2R^7$ and $(CH_2)_oSO_2NR^7R^8$, wherein o is 0, 1, or 2, and R^7 and R^8 are as defined below;

R^1, R^7 and R^8 is each and independently selected from hydrogen; a branched or straight C_1-C_4 alkyl, allyl, -CO-(C_1-C_6 alkyl); (C_1-C_6 alkyl)-B wherein B is as defined below; C_3-C_5 cycloalkyl, C_4-C_8 (alkyl-cycloalkyl) wherein alkyl is C_1-C_2 alkyl and cycloalkyl is C_3-C_6 cycloalkyl; and phenyl;

R^2 is hydrogen, methyl, or OR^1 wherein R^1 is as defined above;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18}, is each and independently as defined for R^1 above;

B is selected from phenyl, naphthyl, indolyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl, pyrryl, furanyl, quinolinyl, isoquinolinyl, cyclohexyl, cyclohexenyl, cyclopentyl, cyclopentenyl, indanyl, indenyl, tetrahydronaphthyl, tetrahydroquinyl, tetrahydroisoquinolinyl, tetrahydrofuranyl, pyrrolidinyl, indazolinyl, and

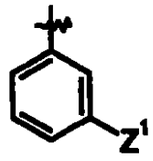


;

each B group being optionally substituted by 1-2 substituents independently selected from hydrogen, CH_3, CF_3, halogen, $(CH_2)_pCONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pCOR^7$, $(CH_2)_pCO_2R^7$, and OR^7;
wherein p is 0 or 1, and wherein R^7 and R^8 are as defined above; and

R^3, R^4, R^5 and R^6 is each and independently selected from hydrogen, CH_3, $CH(Me)_2$, $CH_2CH(Me)_2$, $CH(Me)CH_2CH_3$ $(CH_2)_pCONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pCONR^7R^8$, $(CH_2)_pCO_2R^7$, $(CH_2)_pPh$, $(CH_2)_p$(p-OH Ph), $(CH_2)_p$-3-indolyl, $(CH_2)_pSR^7$, and $(CH_2)_pOR^7$, wherein p is 0, 1, 2, or 3, and wherein R^7 and R^8 are as defined above;

with the proviso that when A is a phenyl ring substituted by a -CN group or by a $-NH_2$ group, B may not be



wherein

Z^1 is hydroxy, and esters thereof;

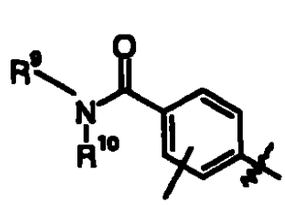
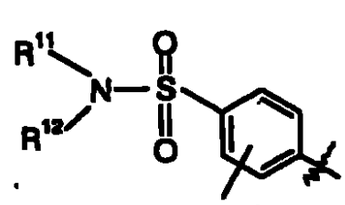
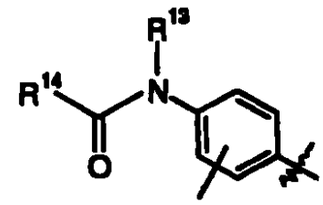
hydroxymethyl, and esters thereof; or

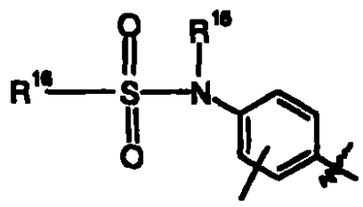
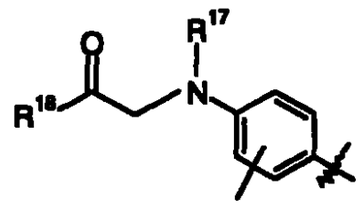
amino, and carboxamides and sulfonamides.

Especially preferred compounds according to the invention are compounds of the formula (I) wherein

G is a nitrogen atom;

A is selected from


and


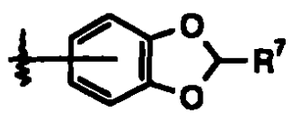
wherein

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18} is each an ethyl group;

R^1 is selected from hydrogen, methyl, ethyl, allyl, or CH_2-cyclopropyl;

R^2 is H, methyl, or OR^1, wherein R1 is as defined above;

B is selected from phenyl, naphthyl, indolyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl, furanyl, quinolinyl, isoquinolinyl, cyclohexyl, cyclohexenyl, cyclopentyl, cyclopentenyl, indanyl, indenyl, tetrahydronaphthyl, tetrahydroquinyl, tetrahydroisoquinolinyl, tetrahydrofuranyl, indazolinyl, and



;

each B group being optionally substituted by 1-2 substituents independently selected from hydrogen, methyl, CF_3, halogen, $(CH_2)_pCONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pCOR^7$, $(CH_2)_pCO_2R^7$, and OR^7,

wherein p is 0, 1, or 2, and wherein R^7 and R^8 are as defined for R^1 above;

R^3, R^4, R^5 and R^6 is each and independently selected from H, CH_3, $CH(Me)_2$, $CH_2CH(Me)_2$, $CH(Me)CH_2CH_3$ $(CH_2)_pCONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pCONR^7R^8$, $(CH_2)_pCO_2R^7$, $(CH_2)_pPh$, $(CH_2)_p$(p-OH Ph), $(CH_2)_p$-3-indolyl, $(CH_2)_pSR^7$, and $(CH_2)_pOR^7$

wherein p is 0, 1 or 2, and wherein R^7 and R^8 are as defined above;

The substituents A and B respectively, may optionally be substituted at any position of the ring.

By "halogen" we mean chloro, fluoro, bromo and iodo.

By "aryl" we mean an aromatic ring having from 6 - 10 carbon atoms, such as phenyl and naphtyl.

By "heteroaryl" we mean an aromatic ring in which one or more of the 5 -10 atoms in the ring are elements other than carbon, such as N, S and O.

By "hydroaromatic" we mean a partly or fully saturated aromatic ring structure having 5-10 carbon atoms in the ring.

By "heterohydroaromatic" we mean a partly or fully saturated aromatic ring structure in which one or more of the 5-10 atoms in the ring are elements other than carbon, such as N, S and O.

By "isomers" we mean compounds of the formula (I), which differ by the position of their functional group and/or orientation. By "orientation" we mean stereoisomers, diastereoisomers, regioisomers and enantiomers.

By "isoforms" we mean compounds of the formula (I) which differ by their crystal lattice, such as crystalline compound and amorphous compounds.

By "prodrug" we mean pharmacologically acceptable derivatives, e.g. esters and amides, such the resulting biotransformation product of the derivative is the active drug. The reference by Goodman and Gilmans, The Pharmacological basis of Therapeutics, 8th ed., McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs, p. 13-15, describing prodrugs generally, is hereby incorporated.

The novel compounds of the present invention are useful in therapy, especially for the treatment of pain.

The compounds are also useful for modulating the analgesic effects acting at the μ opioid receptor subtype, the modulation of side effects seen with agents acting at the μ opioid

receptor subtype such as morphine, especially respiratory depression, gut motility and abuse liability.

Compounds of the invention are also useful as immunomodulators, especially for autoimmune diseases, such as arthritis, for skin grafts, organ transplants and similar surgical needs, for collagen diseases, various allergies, for use as anti tumour agents and anti viral agents.

Compounds of the invention are useful in disease states where degeneration or dysfunction of opioid receptors is present or implicated in that paradigm. This may involve the use of isotopically labeled versions of the compounds of the invention in diagnostic techniques and imaging applications such as positron emission tomography (PET).

Compounds of the invention are useful for the treatment of diarrhea, depression, urinary incontinence, various mental illnesses, cough, lung oedema, various gastro-intestinal disorders, spinal injury and drug addiction, including the treatment of alcohol, nicotine, opioid and other drug abuse and for disorders of the sympathetic nervous system for example hypertension.

The best mode of performing the present invention known at present, is to use the compounds according to Example 21 (compound 33), Example 22 (compound 34), Example 23 (compound 37), Example 24 (compound 38), Example 25 (compound 41), Example 26 (compound 42), Example 27 (compound 45), Example 29 (compound 51), Example 30 (compound 54), Example 35 (compound 64), Example 36 (compound 65), Example 50, and Example 51. The numbering of the compounds is in accordance with the Examples below, as well as in accordance with the numbering in the Schemes presented in the following.

Methods of preparation

Generalized Method A

An aldehyde or ketone is treated with a nucleophile such as a Grignard or organolithium species to produce the corresponding alcohol. This alcohol may then be converted into a suitable leaving group (X) such as an ester, sulphonate or halide which may in turn be displaced with a nucleophilic species such as a substituted or unsubstituted piperazine. N-(4)-unsubstituted piperazine derivatives may then be suitably substituted with a variety of groups via their organo halide or equivalent species, or acylated with a number of different acylating compounds. This sequence of events will give rise to compounds according to general formula I.

Generalized Method B

An N-protected amino acid, as its activated ester, may be reacted with a second amino acid ester. On treatment with an acid this species may then cyclize to form a piperazinedione. This dione may be reduced via a number of standard methods to the corresponding piperazine (*e.g.* a reducing agent such as lithium aluminium hydride, by conversion to the thioamide and subsequent desulphurization, hydrogenation in the presence of $POCl_3$ etc.) This piperazine may then be alkylated or acylated on one or more of the nitrogens and/or may be used subsequently in generalized method A.

Deprotection of functional groups or further modifications may then be necessary, these are described for each individual case. Specific examples for the above transformations are given in the experimental.

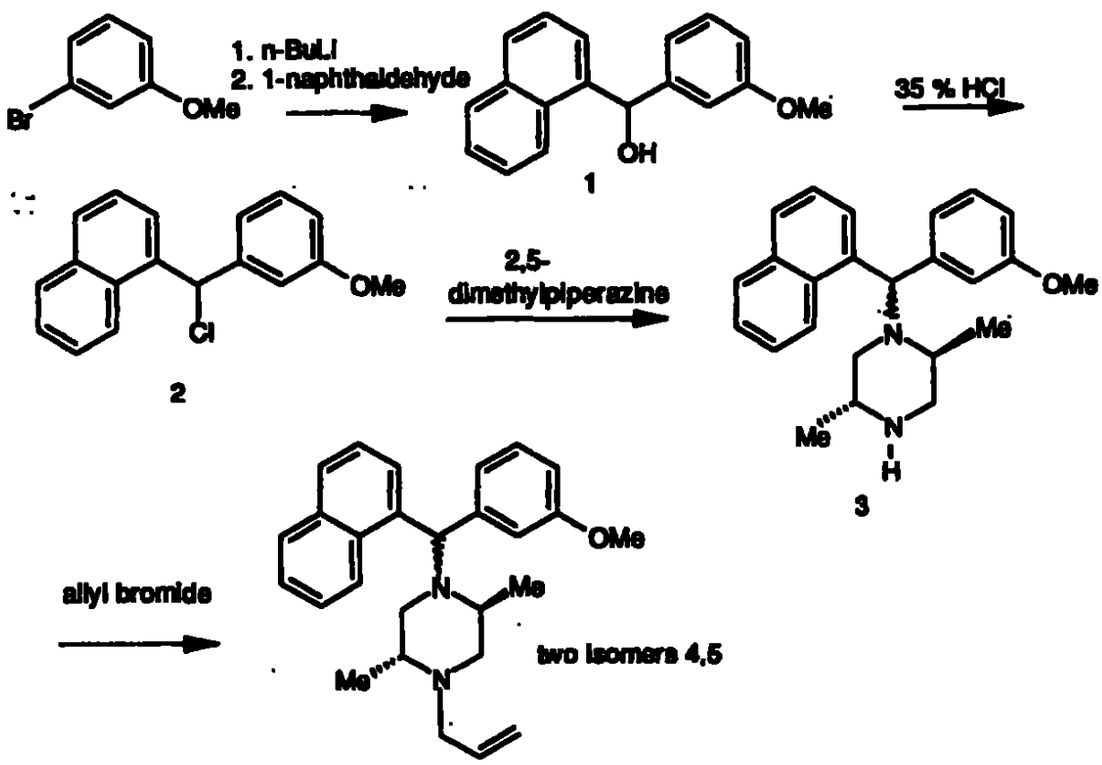
All transformations contemplated use reagents (including salts) and solvents known to the art of chemistry and to biotransformations carried out in a suitable biological medium to bring about these transformations and includes all reaction enhancing agents (*e.g.* HMPA), and chiral resolutions using chiral salt formation and chiral biological resolutions.

Detailed description of the invention

The invention will now be described in more detail by the following examples, which are not to be construed as limiting the invention.

Scheme 1

(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-1-naphthyl)anisole (4 & 5).



EXAMPLES

The compounds according to Examples 1-3 were synthesized as shown in Scheme 1 above.

A.

I. Preparation of 3-methoxy-α-(1-naphthyl)benzyl alcohol (compound 1)

To a solution of 3-bromoanisole (5.61 g, 30.0 mmol) in dry THF (80 mL) was dropwise added n-butyl lithium-hexane solution (1.6 M, 37.5 mL, 60 mmol) under nitrogen at -78°C. The reaction mixture was allowed to warm to r.t. in 2h and cooled down again to -78°C prior to addition of 1-naphthaldehyde (4.69 g, 30.0 mmol, in 10 mL THF). The mixture was warmed to r.t. in 3h, and then quenched with aqueous NH_4Cl solution, extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$. Removal of solvents *in vacuo* provided 3-methoxy-α-(1-naphthyl)benzyl alcohol (4.25 g, 54%). GC-MS (R_t = 10.41 min) 264 (M^+), 245, 231, 215, 202, 155, 135, 128, 109.

II. Preparation of 3-methoxy-α-(1-naphthyl)benzyl chloride (compound 2)

To a solution of 3-methoxy-α-(1-naphthyl)benzyl alcohol (2.5 g, 9.5 mmol) in diethyl ether (5 mL) was added 35% hydrochloric acid (10 mL) at 0°C. The reaction mixture was warmed to r.t. in 1h, and then extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with aqueous NH_4Cl solution and brine, dried over $MgSO_4$. Evaporation of solvents gave 3-methoxy-α-(1-naphthyl)benzyl chloride (1.94 g, 72%). GC-MS (R_t = 10.30 min) 282 (M^+), 247, 232, 215, 202, 189, 163, 151, 139, 123, 101.

Example 1

Preparation of (±)-trans-1-(3-methoxy-α-(1-naphthyl)benzyl)-2,5-dimethylpiperazine (compound 3)

A mixture of *trans*-2,5-dimethylpiperazine (456 mg, 4.0 mmol), 3-methoxy-α-(1-naphthyl)benzyl chloride (430 mg, 1.5 mmol) and triethylamine (2 mL) in dry DMF (10 mL) was refluxed for 2h under nitrogen. after cooling down to r.t., the reaction mixture was quenched with 1 N aqueous NH_4OH solution, and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with 0.5 N aqueous NaOH solution, saturated aqueous NH_4Cl and brine, dried over $MgSO_4$. Removal of solvents gave (±)-trans-1-(3-methoxy-α-(1'-naphthyl)benzyl)-2,5-dimethylpiperazine, which was used directly in the next step: GC-MS (two isomers: R_t = 12.98 & 13.10 min) 360 (M^+), 301, 276, 247, 232, 215, 189, 165, 131, 113.

Example 2 and 3

Preparation of (±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-1-naphthyl)anisole (compounds 4 & 5)

A mixture of above (±)-trans-1-(3-methoxy-α-(1-naphthyl)benzyl)-2,5-dimethylpiperazine, K_2CO_3 (276 mg, 2.0 mmol) and allyl bromide (242 mg, 2.0 mmol) in DMF (5 mL)/THF (10 mL) was stirred for 3h at r.t. The reaction mixture was quenched with 1 N NH_4OH and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with saturated aqueous NH_4Cl and brine, dried over $MgSO_4$. Evaporation of solvents provided crude (±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-1-naphthyl)anisole, which were purified by silica gel column eluting with AcOEt-Hexane(2 : 98 → 100 : 0) to yield the two isomers (totally 267 mg, 45% from 2):

The first isomer, compound 4: GC-MS (R_t = 14.84 min) 401.15 (M^++1, 0.3%), 400.15 (M^+, 0.9), 359.15 (0.6), 330.15 (0.4), 302.15 (3.2), 274.15 (8.0), 247.05 (23.0), 215.10 (12.7), 202.05 (7:8),153.15 (100), 126.15 (10.1); δ_H (400 MHz, $CDCl_3$) 1.02 (d, J=6.4 Hz,

6H), 2.15 (dd, J=11.2, 6.4 Hz, 1H), 2.31 (dd, J=11.2, 6.4 Hz, 1H), 2.60 (m, 1H), 2.74 (dd, J=11.2, 3.2 Hz, 1H), 2.80 (dd, J=11.2, 3.2 Hz, 1H), 2.94 (dd, J=13.6, 7.2 Hz, 1H), 3.03 (dt, J=6.4, 3.2 Hz, 1H), 3.20 (dd, J=13.6, 5.6 Hz, 1H), 3.73 (s, 3H), 5.12 (m, 2H), 5.73 (brs, 1H), 5.83 (m, 1H), 6.68 (dd, J=8.0, 2.4 Hz, 1H), 7.00 (d, J=8.0 Hz, 1H), 7.12 (m, 2H), 7.42 (m, 3H), 7.62 (d, J=7.2 Hz, 1H), 7.71 (d, J=8.0 Hz, 1H), 7.80 (d, J=8.0 Hz, 1H), 8.28 (brs, 1H); δ_{C-13} (100 MHz, $CDCl_3$) 13.2, 14.2, 35.6, 52.1, 53.0, 55.1, 55.2, 57.2, 63.8, 111.6, 114.4, 117.2, 121.1, 123.8, 125.2, 125.7, 125.8, 127.2, 127.5, 127.8, 128.9, 132.1, 134.0, 135.5, 137.4, 145.5, 159.5

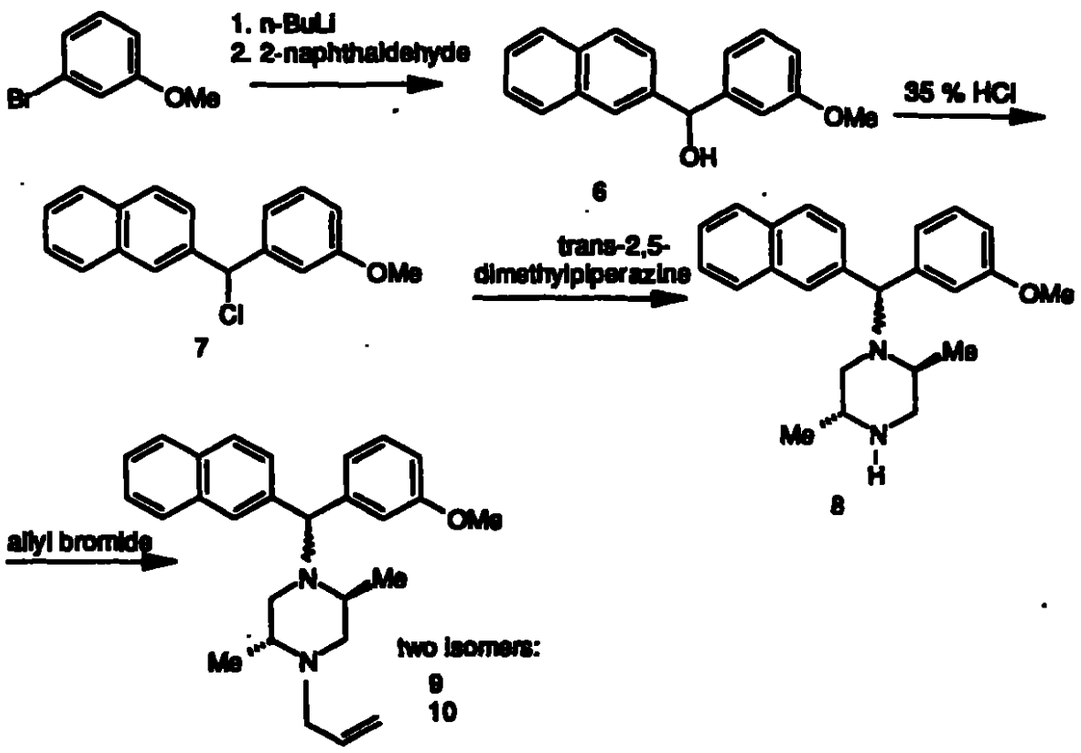
Its HCl salt: m.p. 124-135°C (Ether); ν_{max} (KBr) cm^{-1} 3483, 1601, 1264; *Anal.*Calcd.for $C_{27}H_{32}N_2O.2HCl.1.0H_2O$: C, 65.98; H, 7.38; N, 5.70. Found: C, 66.12; H, 7.25; N, 5.42.

The second isomer, compound 5: GC-MS (R_t = 14.65 min) 401.25 (M^++1, 0.2%), 400.25 (M^+, 0.8), 359.15 (0.4), 330.15 (0.4), 302.15 (3.1), 274.15 (8.0), 247.05 (21.7), 215.10 (13.0), 202.05 (7.0),153.15 (100), 126.15 (9.7); δ_H (400 MHz, $CDCl_3$) 0.93 (d, J=6.4 Hz, 3H), 1.15 (d, J=6.4 Hz, 3H), 2.14 (m, 2H), 2.37 (m, 1H), 2.60 (dd, J=11.6, 2.8 Hz, 1H), 2.84 (m, 2H), 2.96 (m, 1H), 3.35 (dd, J=13.2, 5.2 Hz, 1H), 5.13 (m, 2H), 5.81 (s, 1H), 5.86 (m, 1H), 6.73 (dd, J=8.0, 2.8 Hz, 1H), 6.81 (s, 1H), 6.84 (d, J=8.0 Hz, 1H), 7.16 (m, 1H), 7.40 (m, 3H), 7.70 (m, 2H), 7.80 (d, J=8.0 Hz, 1H), 8.15 (d, J=8.0 Hz, 1H); δ_{C-13} (100 MHz, $CDCl_3$15.7, 16.3, 38.8, 53.6, 55.0, 55.6, 56.8, 59.3, 63.6, 111.5, 115.6, 117.4, 121.9, 124.6, 125.0, 125.1, 125.4, 126.2, 127.4, 128.5, 128.9, 131.6, 133.9, 135.0, 138.3, 142.2, 159.4.

Its HCl salt: m.p. 150.5-153°C (Ether); ν_{max} (KBr) cm^{-1} 3483, 1600, 1262; *Anal.*Calcd.for $C_{27}H_{32}N_2O.2HCl.0.75H_2O$: C, 66.59; H, 7.35; N, 5.75. Found: C, 66.41; H, 7.03; N, 5.48.

Scheme 2

(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-2-naphthyl)anisole (9 & 10).



The compounds according to Examples 4-6 were synthesized as shown in Scheme 2 above.

B.

I. Preparation of 3-methoxy-α-(2-naphthyl)benzyl alcohol (compound 6)

The compound 6 was prepared by following the synthesis procedure as described for compound 1, but substituting 1-naphtaldehyde for 2-naphtaldehyde.

GC-MS (R_t = 10.68 min) 264 (M^+), 247, 231, 215, 202, 155, 135, 128, 109; δ_H (400 MHz, $CDCl_3$) 3.15 (brs, 1H), 3.59 (s, 3H), 5.71 (s, 1H), 6.69 (dd, J=8.4, 2.8 Hz, 1H), 6.87 (m, 2H), 7.11 (t, J=8.0 Hz, 1H), 7.29 (dd, J=8.4, 1.2 Hz, 1H), 7.35 (m, 2H), 7.63 (d, J=8.4 Hz, 1H), 7.70 (m, 3H); δ_{C-13} (100 MHz, $CDCl_3$) 55.0, 75.9, 112.1, 112.8, 118.9, 124.6, 124.9, 125.7, 125.9, 127.5, 127.9, 128.1, 129.3, 132.7, 133.1, 141.0, 145.2, 159.5.

II. Preparation of 3-methoxy-α-(2-naphthyl)benzyl chloride (compound 7)

The compound 7 was prepared by following the synthesis procedure as described for compound 2, but substituting compound 1 for compound 6.

GC-MS (R_t = 10.58 min) 282 (M^+), 247, 231, 215, 202, 189, 151, 123, 101.

Example 4

Preparation of (±)-trans-1-(3-methoxy-α-(2-naphthyl)benzyl)-2,5-dimethylpiperazine (compound 8)

The compound 8 was prepared by following the synthesis procedure as described for compound 3, but substituting compound 2 for compound 7.

Used directly in the next step: GC-MS (R_t = 14.03 min) 360 (M^+), 331, 301, 276, 247, 219, 169, 131, 113.

Example 5 and 6

Preparation of (±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-2-naphthyl)anisole (compounds 9 & 10)

The compounds of these Examples were prepared by following the synthesis procedure as described for Examples 2 and 3, but substituting compound 3 for compound 8.

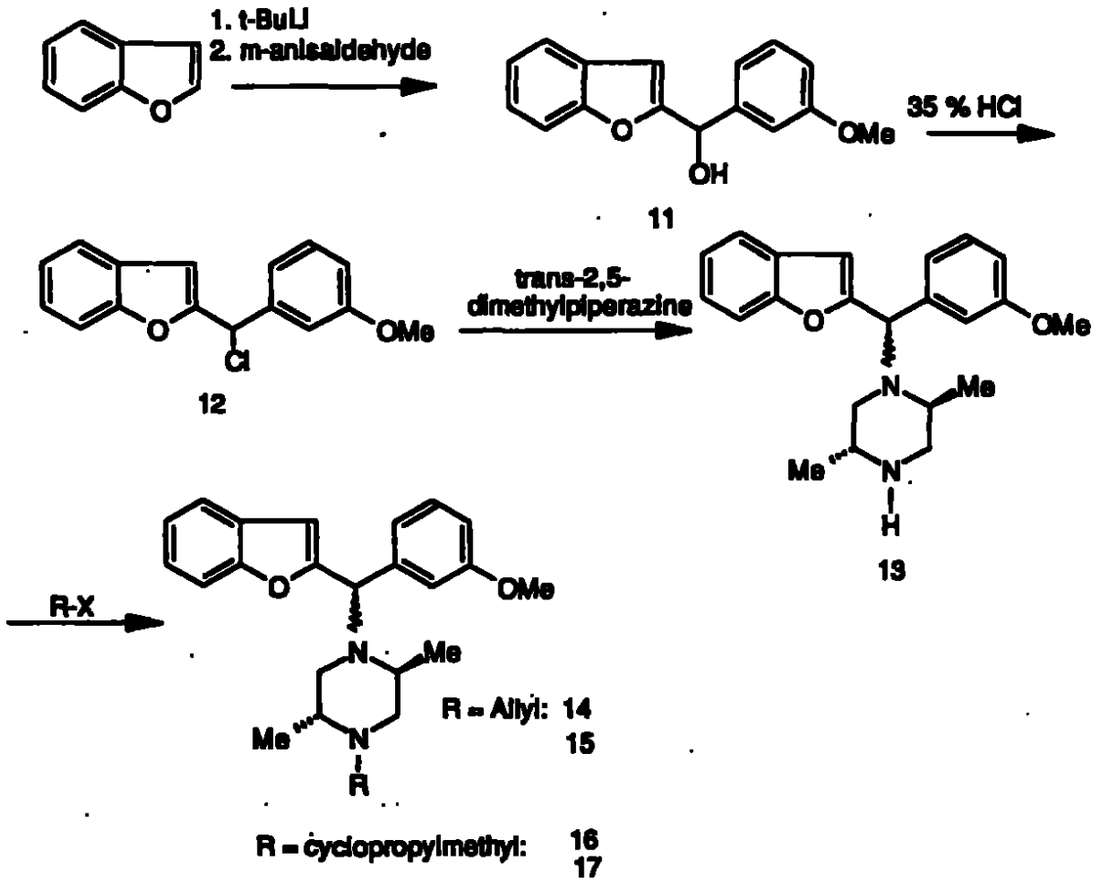
Compound 9 (one pure isomer): GC-MS (R_t = 16.05 min) 401.25 (0.2%), 400.25 (0.8), 359.15 (0.4), 330.15 (0.4), 302.15 (3.1), 274.15 (8.0), 247.05 (21.7), 215.10 (13.0), 202.05 (7.0),153.15 (100), 126.15 (9.7); δ_H (400 MHz, $CDCl_3$) 1.36 (d, J=6.4 Hz, 3H), 1.41 (d, J=6.4 Hz, 3H), 3.16 (dd, J=13.2, 2.4 Hz, 1H), 3.26 (d, J=13.2 Hz, 1H), 3.46 (m, 1H), 3.86 (s, 3H), 3.94 (dd, J=11.2, 2.8 Hz, 1H), 4.10 (m, 2H), 4.46 (m, 2H), 5.58 (m, 2H), 5.78 (s, 1H), 6.05 (m, 1H), 6.96 (dd, J=8.0, 2.0 Hz, 1H), 7.18 (s, 1H), 7.33 (m, 1H), 7.44 (m, 1H), 7.50 (m, 2H), 7.83 (m, 3H), 8.04 (d, J=8.0 Hz, 1H), 8.13 (s, 1H), 13.6 (brs, 2H).

Its HCl salt: m.p. 129-138°C (Ether); ν_{max} (KBr) cm^{-1} 3426, 1600, 1262; *Anal.*Calcd.for $C_{27}H_{32}N_2O.2HCl.\ 0.75H_2O$: C, 66.59; H, 7.35; N, 5.75. Found: C, 66.80; H, 7.11; N, 5.42.

Compound 10 (a mixture of two isomers) Its HCl salt: m.p. 160-162.5°C (Ether); ν_{max} (KBr) cm^{-1} 3380, 1600, 1261; *Anal.*Calcd.for $C_{27}H_{32}N_2O.2HCl.\ 0.50H_2O$: C, 67.21; H, 7.31; N, 5.81. Found: C, 67.13; H, 6.97; N, 5.47.

Scheme 3

(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Alkyl-2,5-dimethyl-1-piperazinyl)-2-benzofuranyl)anisole (14, 15, 16 & 17).



The compounds according to Examples 7-11 were synthesized as shown in Scheme 3 above.

C.

I. Preparation of 3-methoxy-α-(2-benzofuranyl)benzyl alcohol (compound 11)

The compound of this Example was prepared by following the synthesis procedure as described for Example 1.

GC-MS (R_t = 9.54 min) 254.15 (M^+, 100%), 237.10 (73.8), 221.05 (19.6), 194.10 (17.8), 165.10 (30.3), 147.05 (76.7), 135.10 (69.2), 118.10 (35.4), 108.10 (26.5), 91.10 (47.1); δ_H (400 MHz, $CDCl_3$) 3.21 (brs, 1H), 3.72 (s, 3H), 5.82 (s, 1H), 6.47 (s, 1H), 6.80-7.50 (m, 8H).

II. Preparation of 3-methoxy-α-(2-benzofuranyl)benzyl chloride (compound 12)

The compound 12 was prepared by following the synthesis procedure as described for compound 2, but substituting compound 1 for compound 11..

GC-MS (R_t = 9.08 min) 272.05 (M^+, 4.1%), 237.10 (100), 221.05 (4.5), 194.10 (14.7), 165.10 (23.1); δ_H (400 MHz, $CDCl_3$) 3.78 (s, 3H), 6.11 (s, 1H), 6.56 (s, 1H), 6.85-7.50 (m, 8H).

Example 7

Preparation of (±)-trans-1-(3-methoxy-α-(2'-benzofuranyl)benzyl)-2,5-dimethylpiperazine (compound 13)

The compound 13 was prepared by following the synthesis procedure as described for compound 3, but substituting compound 2 for compound 12.

GC-MS (R_t = 11.87 min & R_t = 12.09 min) 351.15 (M^++1, 2.2%), 350.15 (M^+, 8.6), 321.20 (0.4), 308.15 (0.2), 294.20 (18.3), 266.10 (58.6), 237.10 (100), 221.05 (3.0),

194.10 (10.0), 178.05 (4.1), 165.10 (13.0), 131.05 (2.9), 113.10 (43.8); δ_H (400 MHz, $CDCl_3$) (isomer at R_t = 11.87 min) 0.92 (d, J=6.4 Hz, 3H), 1.20 (d, J=6.4 Hz, 3H), 1.92 (dd, J=11.2, 10.8 Hz, 1H), 2.44 (m, 1H), 2.69 (dd, J=11.2, 10.8 Hz, 1H), 2.83 (m, 2H), 2.90 (m, 1H), 3.78 (s, 3H), 5.56 (s, 1H), 6.61 (s, 1H), 6.80 (d, J=8.0 Hz, 1H), 7.00 (d, J=8.0 Hz, 1H), 7.10 (s, 1H), 7.24 (m, 3H), 7.46 (d, J=8.0 Hz, 1H), 7.56 (d, J=8.0 Hz, 1H); (isomer at R_t = 12.09 min) 0.96 (d, J=6.4 Hz, 3H), 1.22 (d, J=6.4 Hz, 3H), 1.83 (dd, J=11.2, 10.8 Hz, 1H), 2.40 (m, 1H), 2.65 (m, 1H), 2.90 (m, 3H), 3.80 (s, 3H), 5.47 (s, 1H), 6.63 (s, 1H), 6.84 (m, 2H), 7.21 (m, 2H), 7.24 (m, 2H), 7.46 (d, J=8.0 Hz, 1H), 7.51 (d, J=8.0 Hz, 1H).

Its HCl salt: m.p. 115-125°C (Ether); ν_{max} (KBr) cm^{-1} 3373, 1595, 1257; *Anal.*Calcd.for $C_{22}H_{26}N_2O_2$.1.70HCl.0.20H_2O: C, 63.51; H, 6.81; N, 6.73. Found: C, 63.60; H, 6.80; N, 6.70.

Example 8 and 9

Preparation of (±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-2-benzofuranyl)anisole (compounds 14 & 15)

The compounds of these Examples were prepared by following the synthesis procedure as described for Examples 2 and 3, but substituting compound 3 for compound 13..

The first isomer, compound 14: GC-MS (R_t = 13.03 min) 390.20 (M^+, 1.5%), 349.15 (0.4), 320.10 (0.3), 292.10 (1.7), 264.10 (4.2), 237.10 (25.1), 221.05 (1.4), 194.10 (5.2), 165.10 (5.5), 153.15 (100), 126.15 (4.8), 98.05 (8.7), 84.10 (17.8); δ_H (400 MHz, $CDCl_3$) 0.97 (d, J=6.4 Hz, 3H), 1.21 (d, J=6.4 Hz, 3H), 2.12 (m, 2H), 2.35 (m, 1H), 2.65 (m, 1H), 2.75 (dd, J=11.6, 2.4 Hz, 1H), 2.81 (m, 3H), 3.42 (dd, J=13.6, 5.2 Hz, 1H), 3.78 (s, 3H), 5.14 (m, 2H), 5.51 (s, 1H), 5.85 (m, 1H), 6.61 (s, 1H), 6.81 (dd, J=8.0, 2.4 Hz, 1H), 7.01 (d, J=8.0 Hz, 1H), 7.11 (s, 1H), 7.24 (m, 3H), 7.44 (d, J=8.0 Hz, 1H), 7.54 (d, J=8.0 Hz, 1H); ^{a}C-13 (100 MHz, $CDCl_3$) 17.2, 17.5, 53.1, 54.4, 55.2, 56.0, 56.6, 59.2, 60.4, 106.8,

111.3, 112.1, 114.2, 117.8, 120.6, 120.7, 122.6, 123.8, 128.1, 129.0, 134.8, 141.4, 154.9, 155.2, 159.6.

Its HCl salt: m.p. 122-128°C (Ether); ν_{max} (KBr) cm^{-1} 3490, 1602, 1253; *Anal.*Calcd.for $C_{25}H_{30}N_2O_2.2HCl.\ 0.25H_2O$: C, 64.17; H, 7.00; N, 5.99. Found: C, 64.27; H, 6.92; N, 5.92.

The second isomer, compound 15: GC-MS (R_t = 13.23 min) 390.20 (M^+, 3.1%), 349.15 (0.5), 292.10 (2.2), 264.10 (5.5), 237.10 (33.2), 221.05 (1.8), 194.10 (7.1), 165.10 (7.7), 153.15 (100), 126.15 (7.1), 98.15 (18.4), 84.10 (25.0); δ_H (400 MHz, $CDCl_3$) 1.00 (d, J=6.4 Hz, 3H), 1.21 (d, J=6.4 Hz, 3H), 2.12 (m, 2H), 2.48 (m, 1H), 2.61 (m, 1H), 2.78 (dd, J=11.6, 2.4 Hz, 1H), 2.83 (m, 3H), 3.42 (dd, J=13.6, 5.6 Hz, 1H), 3.79 (s, 3H), 5.15 (m, 2H), 5.40 (s, 1H), 5.85 (m, 1H), 6.64 (s, 1H), 6.86(m, 3H), 7.20 (m, 3H), 7.44 (d, J=8.0 Hz, 1H), 7.50 (d, J=8.0 Hz, 1H).

Its HCl salt: m.p. 97-104°C (Ether); ν_{max} (KBr) cm^{-1} 3438, 1601 (s), 1260; *Anal.*Calcd.for $C_{25}H_{30}N_2O_2.2HCl.\ 0.50H_2O$: C, 63.56; H, 7.04; N, 5.93. Found: C, 63.70; H, 6.68; N, 5.83.

Example 10 and 11

Preparation of (±)-3-((αR*/S*)-α-((2S*,5R*)-4-Cyclopropylmethyl-2,5-dimethyl-1-piperazinyl)-2-benzofuranyl)anisole (compounds 16 & 17)

The compounds of these Examples were prepared by following the synthesis procedure as described for Examples 2 and 3, except using cyclopropyl methyl iodide and substituting compound 3 for compound 13.

The first isomer, compound 16: GC-MS (R_t = 14.87 min) 405.25 (M^++1, 2.3%), 404.25 (M^+, 8.2), 362.20 (0.5), 349.15 (0.4), 320.20 (0.8), 292.20 (4.1), 291.10 (3.4), 265.10 (16.5), 237.10 (65.9), 194.10 (11.5), 167.20 (100), 140.20 (3.9), 124.15 (4.6), 98.15

(44.0); δ_H (400 MHz, $CDCl_3$) 0.05 (m, 2H), 0.46 (m, 2H), 0.80 (m, 1H), 0.92 (d, J=6.0 Hz, 3H), 1.21 (d, J=6.0 Hz, 3H), 2.01 (dd, J=12.8, 7.2 Hz, 1H), 2.17 (m, 2H), 2.35 (m, 1H), 2.64 (dd, J=13.2, 6.4 Hz, 1H), 2.66 (m, 1H), 2.72 (dd, J=12.0, 2.4 Hz, 1H), 3.04 (dd, J=11.2, 3.2 Hz, 1H), 3.75 (s, 3H), 5.50 (s, 1H), 6.58 (s, 1H), 6.79 (dd, J=8.0, 2.4 Hz, 1H), 7.01 (d, J=8.0 Hz, 1H), 7.09 (s, 1H), 7.20 (m, 3H), 7.41 (d, J=8.0 Hz, 1H), 7.51 (m, 1H); δ_{C-13} (100 MHz, $CDCl_3$) 3.2, 4.7, 7.4, 17.4, 17.7, 53.1, 54.5, 55.2, 56.0, 58.3, 59.2, 60.8, 106.8, 111.3, 112.0, 114.2, 120.6, 120.7, 122.6, 123.7, 128.0, 129.0, 141.4, 154.8, 155.2, 159.6.

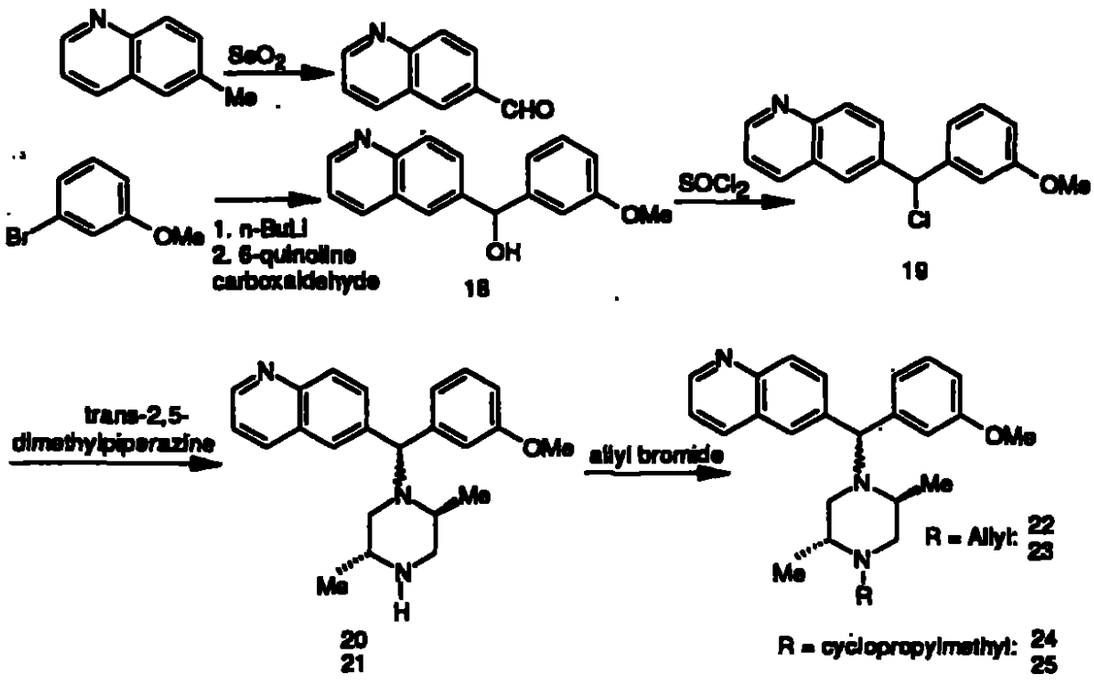
Its HCl salt: m.p. 162-164°C (Ether); ν_{max} (KBr) cm^{-1} 3414, 1599, 1255; *Anal.*Calcd.for $C_{26}H_{32}N_2O_2.2HCl.\ 0.5H_2O$: C, 64.19; H, 7.25; N, 5.76. Found: C, 64.43; H, 7.30; N, 5.78.

The second isomer, compound 17: GC-MS (R_t = 15.17 min) 405.25 (M^++1, 2.2%), 404.25 (M^+, 8.9), 362.10 (0.6), 349.15 (0.4), 320.10 (0.8), 292.10 (5.0), 291.10 (3.9), 265.10 (19.4), 237.10 (72.2), 194.10 (12.8), 167.20 (100), 140.10 (3.9), 124.15 (4.8), 98.15 (45.5); δ_H (400 MHz, $CDCl_3$) 0.08 (m, 2H), 0.48 (m, 2H), 0.82 (m, 1H), 0.97 (d, J=6.4 Hz, 3H), 1.25 (d, J=6.4 Hz, 3H), 2.10 (m, 2H), 2.28 (dd, J=11.2, 10.0 Hz, 1H), 2.49 (m, 1H), 2.62 (dd, J=13.2, 6.0 Hz, 1H), 2.63 (m, 1H), 2.83 (dd, J=11.2, 2.8 Hz, 1H), 3.02 (dd, J=11.2, 3.2 Hz, 1H), 3.78 (s, 3H), 5.43 (s, 1H), 6.64 (s, 1H), 6.87 (m, 3H), 7.21 (m, 3H), 7.45 (dd, J=7.6, 1.2 Hz, 1H), 7.50 (m, 1H); δ_{C-13} (100 MHz, $CDCl_3$) 3.3, 4.6, 7.4, 17.0, 17.6, 52.6, 55.2, 55.4, 55.6, 58.3, 60.3, 61.6, 105.7, 111.3, 112.5, 115.9, 120.5, 122.1, 112.5, 123.5, 128.4, 128.9, 137.3, 155.0, 158.3, 159.3.

Its HCl salt: m.p. 92-105°C (Ether); ν_{max} (KBr) cm^{-1} 3398, 1599, 1257; *Anal.*Calcd.for $C_{26}H_{32}N_2O_2.2HCl.\ 0.5H_2O$: C, 64.19; H, 7.25; N, 5.76. Found: C, 64.38; H, 7.14; N, 5.73.

Scheme 4

(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Alkyl-2,5-dimethyl-1-piperazinyl)-6-quinolinyl)anisole (22, 23, 24 & 25).



D.

I. Preparation of 6-Quinolinecarboxaldehyde

A mixture of 6-methylquinoline (5.72 g, 40.0 mmol) and selenium oxide (4.44 g, 40.0 mmol) was heated to 220°C for 1h. After cooling down the residue was dissolved in ethyl acetate (100 mL). The organic solution was washed with brine, dried over $MgSO_4$. Evaporation of solvents provided a solid, which was recrystalized from ether-hexane (1 : 1) mixture to give 6-quinolinecarboxaldehyde (3.45 g, 55%).

GC-MS (R_t = 5.29 min) 157.15 (M^+, 100%), 156.15 (92.2), 128.15 (62.9), 101.15 (16.0); δ_H (400 MHz, $CDCl_3$) 7.53 (m, 1H), 8.21 (m, 2H), 8.33 (m, 2H), 9.06 (m, 1H), 10.21 (s, 1H); δ_{C-13} (100 MHz, $CDCl_3$) 122.1, 126.6, 127.6, 130.7, 133.5, 134.2, 137.3, 150.8, 153.0, 191.3.

The compounds according to Examples 12-17 were synthesized as shown in Scheme 4 above.

II. Preparation of 3-methoxy-α-(6-quinolinyl)benzyl alcohol (compound 18)

The compound 18 was prepared by following the synthesis procedure as described for compound 1, but substituting 1-naphtaldehyde for 6-quinolinecarboxaldehyde.

GC-MS (R_t = 11.13 min) 265.10 (M^+, 49.0%), 248.05 (2.3), 204.05 (9.7), 156.05 (37.6), 135.00 (100), 109.00 (43.5); δ_H (400 MHz, $CDCl_3$) 3.73 (s, 3H), 5.94 (s, 1H), 6.78 (d, J=8.4 Hz, 1H), 6.95 (m, 2H), 7.22 (m, 1H), 7.31 (m, 1H), 7.61 (d, J=8.4 Hz, 1H), 7.83 (s, 1H), 7.95 (d, J=8.4 Hz, 1H), 8.07 (d, J=8.0 Hz, 1H), 8.73 (m, 1H); δ_{C-13} (100 MHz, $CDCl_3$) 55.2, 75.7, 112.3, 113.1, 119.1, 121.2, 124.6, 128.5, 129.4, 129.6, 136.3, 142.1, 145.2, 147.6, 150.1, 159.8.

III. Preparation of 3-methoxy-α-(6-quinolinyl)benzyl chloride (compound 19)

The compound 19 was prepared by following the synthesis procedure as described for compound 2, but substituting compound 1 for compound 18.

Used directly in the next step: δ_H (400 MHz, $CDCl_3$) 3.73 (s, 3H), 5.98 (s, 1H), 6.8-8.2 (m, 9H), 8.80 (s, 1H).

Example 12 and 13

Preparation of (±)-trans-1-(3-methoxy-α-(6'-quinolinyl)benzyl)-2,5-dimethylpiperazine (compounds 20 & 21)

The compounds of these Examples were prepared by following the synthesis procedure as described for compound 3, but substituting compound 2 for compound 19.

GC-MS (R_t = 14.91 min) 361.20 (M^+, 0.8%), 332.15 (0.3), 306.15 (0.6), 302.15 (14.4), 277.15 (52.5), 248.05 (100), 233.00 (10.6), 204.05 (17.1), 176.05 (2.7), 151.05 (1.4), 142.10 (1.8), 113.10 (19.9).

The first isomer, compound 20: δ_H (400 MHz, $CDCl_3$) 1.06 (d, J=6.4 Hz, 3H), 1.24 (d, J=6.4 Hz, 3H), 1.84 (dd, J=11.6, 9.2 Hz, 1H), 2.60 (m, 2H), 2.77 (m, 2H), 3.06 (m, 2H), 3.80 (s, 3H), 5.44 (s, 1H), 6.77 (s, 1H), 6.83 (d, J=8.0 Hz, 1H), 6.88 (dd, J=8.0, 2.4 Hz, 1H), 7.31 (m, 1H), 7.37 (m, 1H), 7.82 (s, 1H), 7.84 (m, 1H), 8.03 (d, J=8.8 Hz, 1H), 8.09 (d, J=8.8 Hz, 1H), 8.87 (m, 1H).

Compound 21 (a mixture of two isomers, ~25% compound 20): δ_H (400 MHz, $CDCl_3$) 1.20 (m, 6H), 2.05 (m, 1H), 2.73 (m, 2H), 2.87 (m, 1H), 3.13 (m, 2H), 3.73 & 3.76 (s, 3H), 5.38 (s, 1H), 6.38 (brs, NH), 6.70-8.15 (m, 9H), 8.84 (m, 1H).

Example 14

Preparation of (±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-6-quinolinyl)anisole (compound 22)

The compound of this Example was prepared by following the synthesis procedure as described for Examples 2 and 3, but substituting compound 3 for compound 20.

GC-MS (R_t = 17.22 min) 401.25 (M^+, 0.3%), 360.20 (0.3), 331.10 (0.2), 303.20 (1.7), 276.10 (4.5), 248.10 (17.2), 233.10 (4.5), 204.10 (8.0), 176.10 (1.3), 153.20 (100), 126.20 (5.4); δ_H (400 MHz, $CDCl_3$) 1.0 (d, J=6.4 Hz, 3H), 1.21 (d, J=6.4 Hz, 3H), 1.99 (m, 1H), 2.20 (m, 1H), 2.56 (m, 1H), 2.66 (m, 1H), 2.71 (m, 1H), 2.85 (m, 1H), 2.90 (m, 1H), 3.37 (dd, J=13.2, 4.0 Hz, 1H), 3.78 (s, 3H), 5.17 (m, 2H), 5.35 (s, 1H), 5.87 (m, 1H). 6.82 (m, 3H), 7.26 (t, J=7.6 Hz, 1H), 7.36 (m, 1H), 7.81 (s, 1H), 7.88 (d, J=8.8 Hz, 1H), 8.03 (d, J=8.8 Hz, 1H), 8.09 (d, J=7.6 Hz, 1H), 8.87 (m, 1H); δ_{C-13} (100 MHz, $CDCl_3$) 15.7, 16.4, 52.0, 53.7, 55.2, 55.5, 56.8, 58.9, 65.9, 112.1, 116.3, 117.8, 120.9, 122.5, 126.5, 127.9, 128.9, 129.0, 130.2, 134.8, 136.0, 139.2, 141.1, 147.6, 150.0, 159.5.

Its HCl salt: m.p. 128-140°C (Ether); ν_{max} (KBr) cm^{-1} 3376, 1596, 1263; *Anal.*Calcd.for $C_{26}H_{31}N_3O.2.30HCl.\ 0.1H_2O$: C, 64.10; H, 6.93; N, 8.62. Found: C, 64.08; H, 6.92; N, 8.35.

Example 15

Preparation of (±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-6-quinolinyl)anisole (compound 23)

The compound of this Example was prepared by following the synthesis procedure as described for Examples 2 and 3, but substituting compound 3 for compound 21.

GC-MS (R_t = 17.21 min) 401.35 (M^+, 0.4%), 360.30 (0.2), 331.20 (0.2), 303.20 (1.6), 276.10 (4.8), 248.10 (17.3), 233.10 (4.4), 204.10 (8.1), 176.10 (1.3), 153.20 (100), 126.20 (5.6); δ_H (400 MHz, $CDCl_3$) 1.01 (d, J=6.0 Hz. 3H), 1.21 (d, J=6.0 Hz, 3H), 1.95 (m, 1H), 2.16 (m, 1H), 2.56 (m, 1H), 2.66 (m, 1H), 2.74 (m, 1H), 2.80 (m, 1H), 2.87 (m, 1H), 3.30 (dd, J=13.6, 5.6 Hz, 1H), 3.77 (s, 3H), 5.13 (m, 2H), 5.34 (s, 1H), 5.82 (m, 1H), 6.77 (dd, J=8.0, 2.4 Hz, 1H), 6.99 (d, J=7.6 Hz, 1H), 7.11 (s. 1H), 7.21 (d, J=8.0 Hz, 1H), 7.38 (dd, J=8.4, 4.0 Hz, 1H), 7.59 (d, J=8.4 Hz, 1H), 7.66 (s, 1H), 8.03 (d, J=8.8 Hz, 1H), 8.11 (d, J=8.4 Hz, 1H), 8.88 (m, 1H); δ_{C-13} (100 MHz, $CDCl_3$) 15.3, 16.2, 51.9, 53.4, 55.2, 55.3, 56.8, 58.5, 66.1, 111.8, 114.0, 117.6, 120.6. 121.1. 127.9, 128.3, 128.9, 129.1, 131.4, 134.9, 136.0, 137.1, 144.1, 147.7, 150.2, 159.6.

Its HCl salt: m.p. 177-182°C (Ether); ν_{max} (KBr) cm^{-1} 3405, 1597, 1260; *Anal.*Calcd.for $C_{26}H_{31}N_3O.2.80HCl$: C, 62.01; H, 6.76; N, 8.34. Found: C, 61.98; H, 6.77; N, 8.03.

Example 16 and 17

Preparation of (±)-3-((αR*/S*)-α-((2S*,5R*)-4-Cyclopropylmethyl-2,5-dimethyl-1-piperazinyl)-6-quinolinyl)anisole (compounds 24 & 25)

The compounds of these Examples were prepared by following the synthesis procedure as described for Examples 2 and 3, but substituting allylbromide for cyclopropylmethylioidide..

The first isomer, compound 24: GC-MS (R_t = 20.77 min) 415.25 (M^+, 3.8%), 344.15 (2.4), 302.10 (9.5); 276.10 (58.8), 248.15 (79.1), 233.10 (17.2), 204.10 (29.4), 176.10

(4.2), 167.15 (100), 138.15 (14.2), 112.15 (47.0); δ_H (400 MHz, $CDCl_3$) 0.10 (m, 2H), 0.51 (m, 2H), 0.86 (m, 1H), 0.97 (d, J=6.4 Hz, 3H), 1.25 (d, J=6.4 Hz, 3H), 1.98 (dd, J=11.2, 8.8 Hz, 1H), 2.14 (dd, J=13.2, 6.4 Hz, 1H), 2.32 (dd, J=10.8, 5.6 Hz, 1H), 2.58 (m, 2H), 2.66 (dd, J=11.6, 2.8 Hz, 1H), 2.73 (m, 1H), 3.07 (dd, J=11.2, 3.2 Hz, 1H), 3.78 (s, 3H), 5.39 (s, 1H), 6.79 (s, 1H), 6.84 (m, 2H), 7.26 (t, J=8.0 Hz, 1H), 7.35 (dd, J=8.4, 4.0 Hz, 1H), 7.83 (s, 1H), 7.89 (d, J=8.8 Hz, 1H), 8.03 (d, J=9.2 Hz, 1H), 8.09 (d, J=8.0 Hz, 1H), 8.86 (dd, J=4.0, 2.0 Hz, 1H); δ_{C-13} (100 MHz, $CDCl_3$) 3.4, 4.4, 7.6, 16.2, 16.9, 52.1, 53.8, 55.2, 55.6, 58.5, 59.7, 65.6, 112.0, 116.3, 120.9, 122.6, 126.5, 127.9, 128.8, 129.0, 130.2, 136.0, 139.1, 141.1, 147.6, 149.9, 159.4.

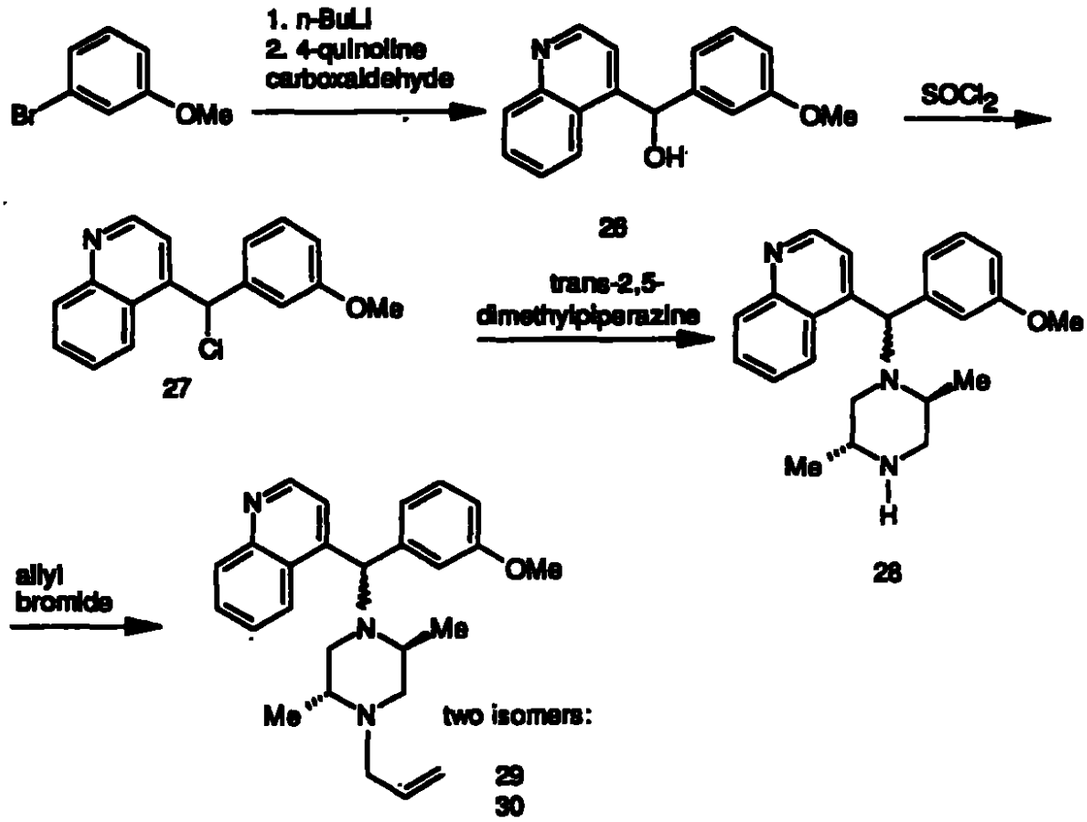
Its HCl salt: m.p. 127-157°C (Ether); ν_{max} (KBr) cm^{-1} 3402, 1596, 1262; *Anal.*Calcd.for $C_{27}H_{33}N_3O.3HCl.\ 0.75H_2O$: C, 60.23; H, 7.02; N, 7.80. Found: C, 60.49; H, 7.00; N, 7.73.

The second isomer, compound 25: GC-MS (R_t = 20.73 min) 415.25 (M^+, 3.2%), 344.05 (2.3), 302.10 (7.7), 276.10 (48.5), 248.15 (69.6), 233.10 (15.7), 204.10 (25.8), 176.10 (3.7), 167.15 (100), 138.15 (12.2), 112.15 (46.8); δ_H (400 MHz, $CDCl_3$) 0.17 (m, 2H), 0.56 (m, 2H), 0.97 (m, 1H), 1.11 (brs, 3H), 1.27 (brs, 3H), 2.24 (m, 1H), 2.38 (m, 1H), 2.51 (m, 1H), 2.61 (m, 1H), 2.87 (m, 3H), 3.13 (m, 1H), 3.77 (s, 3H), 5.34 (s, 1H), 6.78 (d, J=8.0 Hz, 1H), 6.98 (d, J=8.0 Hz, 1H), 7.08 (s, 1H), 7.22 (t, J=8.0 Hz, 1H), 7.39 (dd, J=8.4, 4.4 Hz, 1H), 7.60 (d, J=8.4 Hz, 1H), 7.73 (s, 1H), 8.04 (d, J=8.8 Hz, 1H), 8.16 (d, J=8.4 Hz, 1H), 8.89 (d, J=4.0 Hz, 1H); δ_{C-13} (100 MHz, $CDCl_3$) 4.07, 4.37, 6.9, 14.8, 15.1, 51.4, 55.2, 56.2, 58.2, 60.3, 66.4, 111.8, 114.2, 120.6, 121.2, 128.0, 128.1, 129.2, 131.0, 136.0, 137.0, 143.8, 147.7, 150.3, 159.6.

Its HCl salt: m.p. 92-105°C (Ether); ν_{max} (KBr) cm^{-1} 3345, 1596, 1259.

Scheme 5

(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Alkyl-2,5-dimethyl-1-piperazinyl)-4-quinolinyl)anisole (29 & 30)



The compounds according to Examples 18-20 were synthesized as shown in Scheme 5 above.

E.

I. Preparation of 3-methoxy-α-(4-quinolinyl)benzyl alcohol (compound 26)

The compound 26 was prepared by following the synthesis procedure as described for compound 1, but substituting 1-naphtaldehyde for 4-quinolinecarboxaldehyde..

GC-MS (R_t = 10.81 min) 266.10 (M^++1, 11.8%), 265.10 (M^+, 61.0), 248.05 (6.1), 232.00 (6.2), 216.05 (4.7), 204.00 (10.5), 191.05 (2.0), 176.00 (3.8), 156.00 (13.9), 135.10 (100), 129.10 (86.6), 109.10 (68.2), 102.10 (25.5); δ_H (400 MHz, $CDCl_3$) 3.67 (s, 3H), 5.30 (brs, 1H), 6.41 (s, 1H), 6.76 (d, J=7.2 Hz, 1H), 6.90 (m, 2H), 7.18 (t, J=7.6 Hz, 1H), 7.38 (m, 1H), 7.56 (t, J=7.6 Hz, 1H), 7.62 (m, 1H), 7.92 (d, J=8.4 Hz, 1H), 8.00 (d, J=8.4 Hz, 1H), 8.64 (dd, J=4.4, 1.2 Hz, 1H); δ_{C-13} (100 MHz, $CDCl_3$) 55.1, 72.1, 113.0, 113.2, 118.5, 119.5, 123.9. 125.7, 126.5, 129.0, 129.5, 129.7, 143.8, 147.8, 149.1, 149.9, 159.7.

II. Preparation of 3-methoxy-α-(4-quinolinyl)benzyl chloride (compound 27)

The compound 27 was prepared by following the synthesis procedure as described for compound 2, but substituting compound 1 for compound 26.

Used directly in the next step: GC-MS (R_t = 10.54 min) 285.10 (M^++2, 11.5%), 283.10 (M^+, 33.10), 268.05 (0.2), 248.15 (100), 233.10 (37.0), 217.05 (27.2), 204.10 (45.5), 178.10 (5.9), 176.10 (11.5), 151.10 (5.7), 139.05 (2.1), 108.60 (11.0), 102.10 (17.4).

Example 18

Preparation of (±)-trans-1-(3-methoxy-α-(4-quinolinyl)benzyl)-2,5-dimethyl-piperazine (compound 28)

The compound of this Example was prepared by following the synthesis procedure as described for compound 3, but substituting compound 2 for compound 27.

GC-MS (R_t = 13.96 min) 362.20 (M^++1, 1.4%), 361.20 (M^+, 6.6), 306.10 (2.0), 302.15 (18.3), 277.15 (59.6), 248.15 (100), 233.10 (15.8), 204.10 (20.9), 176.10 (3.8), 151.00 (1:8), 143.15 (1.4), 113.15 (15.8); δ_H (400 MHz, $CDCl_3$) 0.92 (d, J=6.4 Hz, 3H), 1.12 (d, J=6.4 Hz, 3H), 1.82 (dd, J=11.6, 10.0 Hz, 1H), 2.52 (brs, 1H), 2.62 (dd, J=11.6, 2.8 Hz, 1H), 2.72 (m, 1H), 2.77 (m, 1H), 2.88 (m, 1H), 2.98 (dd, J=11.6, 2.0 Hz, 1H), 3.72 (s, 3H), 5.86 (s, 1H), 6.69 (s, 1H), 6.72 (d, J=8.0, 1H), 6.78 (dd, J=8.0, 2.4 Hz, 1H), 7.20 (t, J=8.0 Hz, 1H), 7.37 (t, J=8.0 Hz, 1H), 7.60 (t, J=8.0 Hz, 1H), 7.65 (d, J=4.4 Hz, 1H), 7.99 (d, J=8.8 Hz, 1H), 8.09 (d, J=8.0 Hz, 1H), 8.89 (d, J=4.4 Hz, 1H).

Example 19 and 20

Preparation of (±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-4-quinolinyl)anisole (compounds 29 & 30)

The compounds of these Examples were prepared by following the synthesis procedure as described for Examples 2 and 3, but substituting compound 3 for compound 28.

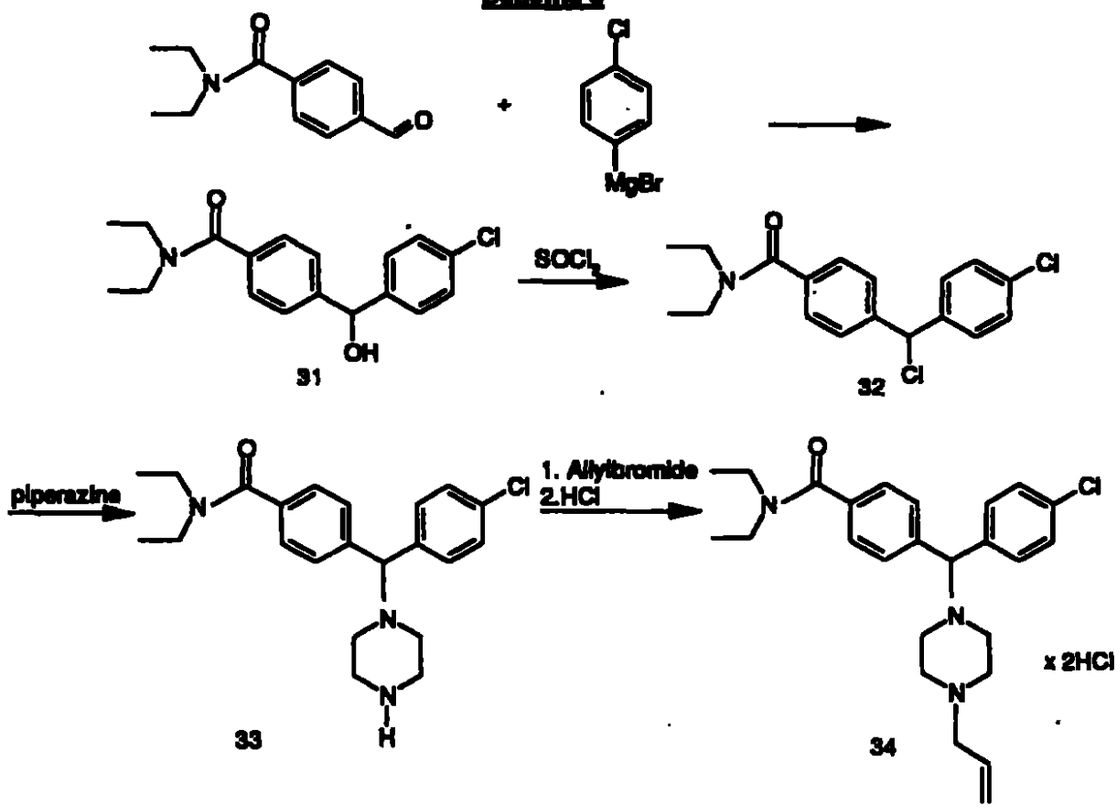
The first isomer, compound 29: GC-MS (R_t = 15.97 min) 401.15 (M^+, 0.8%), 360.20 (0.8), 303.15 (3.3), 27615 (5.7), 248.05 (15.3), 217.05 (6.3), 204.10 (10.4), 176.00 (2.2), 153.20 (100), 126.10 (5.3), 98.10 (13.8); δ_H (400 MHz, $CDCl_3$) 0.96 (d, J=6.0 Hz, 3H), 1.14 (d, J=6.0 Hz, 3H), 2.01 (m, 1H), 2.16 (t, J=10.0 Hz, 1H), 2.47 (m, 1H), 2.59 (d, J=11.2 Hz, 1H), 2.86 (m, 2H), 2.95 (t, J=6.0 Hz, 1H), 3.36 (dd, J=13.6, 4.4 Hz, 1H), 3.72 (s, 3H), 5.15 (m, 2H), 5.77 (s, 1H), 5.85 (m, 1H), 6.74 (m, 3H), 7.17 (t, J=7.6 Hz, 1H), 7.38 (t, J=8.0 Hz, 1H), 7.60 (dd, J=7.2, 0.8 Hz, 1H), 7.73 (d, J=4.4 Hz, 1H), 8.00 (d, J=8.4 Hz, 1H), 8.08 (d, J=8.8 Hz, 1H), 8.90 (d, J=3.6 Hz, 1H); δ_{C-13} (100 MHz, $CDCl_3$) 15.9, 16.6, 53.8, 55.1, 55.5, 56.7, 59.4, 63.2, 112.0, 115.7, 117.7, 120.6, 121.9, 124.4, 126.0, 126.8, 128.6, 129.3, 130.1, 134.8, 140.3, 148.5, 148.6, 150.2, 159.5.

Its HCl salt: m.p. 158-166°C (AcOEt-Ether); ν_{max} (KBr) cm^{-1} 3400, 1596, 1263; *Anal.*Calcd.for $C_{26}H_{31}N_3O$ .3.0HCl.0.9H_2O: C, 59.24; H, 6.85; N, 7.97. Found: C, 59.31; H, 6.94; N, 7.80.

The second isomer, compound 30: GC-MS (R_t = 16.19 min) 401.25 (M^+, 0.5%), 386.20 (0.2), 360.20 (0.7), 331.10 (0.3), 303.15 (3.3), 276.15 (4.7), 248.15 (13.7), 233.10 (5.8), 217.05 (4.9), 204.10 (9.8), 176.10 (1.8), 153.20 (100), 126.20 (5.2), 98.10 (13.9); δ_H (400 MHz, $CDCl_3$); δ_{C-13} (100 MHz, $CDCl_3$).

Its HCl salt: m.p. 155-165°C (AcOEt-Ether).

Scheme 6



The compounds according to Examples 21-22 were synthesized as shown in Scheme 6 above.

E.

I. Preparation of (±) 4-((α-Hydroxy)-4-chlorobenzyl)-N,N-diethylbenzamide (compound 31)

4-Formyl-N,N-diethylbenzamide (2.088 g, 10.1 mmol) was dissolved in 45 ml of anhydrous THF. The solution was cooled down to -78 °C, followed by a dropwise addition of 10.1 ml

(10.1 mmol) of a 1.0 M solution of 4-Chloro-phenylmagnesium bromide in ether. The mixture was warmed up to room temperature within 3 hours. Then 50 ml of a saturated NH_4Cl-solution was added and the mixture was extracted with ethyl acetate (3x30 ml). The combined organic layers were washed with water (2 x 30 ml) and brine (1 x 30 ml), dried (Na_2SO_4), filtered and the solvent was removed in *vacuo*. The residue was chromatographed on silica gel eluting with methanol:dichloromethane (1:125 - 3:125) to yiled the title compound as a colorless oil.

ν_{max} (KBr)/cm^{-1} 3329, 2977, 1595, 1461, 1289, 1094, 1051, 830; δ_H (400 MHz, $CDCl_3$) 1.09 (3H, br s), 1.21 (3H, br s), 3.22 (2H, br s), 3.33 (1H, d, J 3), 3.50 (2H, br s), 5.74 (1H, d, J 3), 7.22-7.34 (m, 8H);

II. Preparation of (±) 4-((α-Chloro)-4-chlorobenzyl)-N,N-diethylbenzamide (compound 32)

The compound 32 was prepared by following the synthesis procedure as described for compound 2, but substituting compound 1 for compound 31.

Used for the next step without further purification.

Example 21

Preparation of (±) 4-((α-(1-Piperazinyl))-4-chlorobenzyl)-N,N-diethylbenzamide (compound 33)

The compound of this Example was prepared by following the synthesis procedure as described for compound 3, but substituting compound 2 for compound 32.

m.p. 112-113°C (from acetonitrile), ν_{max} (KBr)/cm^{-1} 3347, 2947, 2809, 1615, 1451, 1318, 1284, 1094, 836; δ_H (400 MHz, $CDCl_3$) 1.10 (3H, br s), 1.21 (3H, br s), 1.69 (1H, br s), 2.33 (4H, br s), 2.86-2.89 (4H, m), 3.24 (2H, br s), 3.51 (2H, br s), 4.22 (1H, s), 7.23-7.41 (8H, m); $C_{22}H_{28}N_3OCl \cdot 0.3\ H_2O$ requires:
C: 67.52 H: 7.37 N: 10.74 Found: C: 67.68 H: 7.37 N: 10.73.

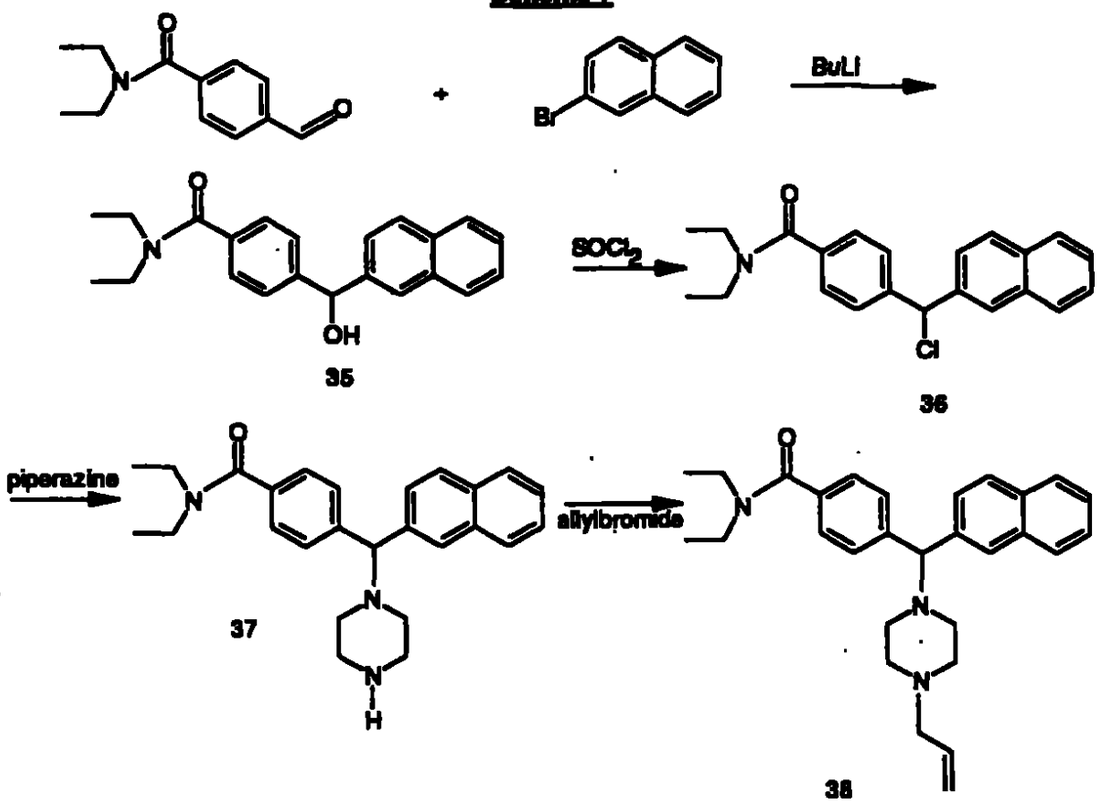
Example 22

Preparation of (±) 4-((α-((4-Allyl)-1-piperazinyl))-4-chlorobenzyl)-N,N-diethylbenzamide • 2HCl (compound 34)

The compound of this Example was prepared by following the synthesis procedure as described for Examples 2 and 3, but substituting compound 3 for compound 33.

m.p. 147-163°C (from ether), ν_{max} (KBr)/cm^{-1} 3418, 2974, 2355, 1626, 1435, 1286, 1092, 945, 812; δ_H (400 MHz, $CDCl_3$) 1.06 (3H, br s), 1.19 (3H, br s). 3.0-3.7 (14H, m), 5.4-5.6 (2H, m), 6.0-6.2 (1H, br m), 7.2-7.8 (9H, m); $C_{25}H_{34}N_3OCl_3$ requires:
C: 60.18 H: 6.87 N: 8.42 Found: C: 60.48 H: 6.89 N: 8.31.

Scheme 7



The compounds according to Examples 23-24 were synthesized as shown in Scheme 7 above.

G.

I. Preparation of (±) 4-((α-Hydroxy)-2-naphtylmethyl)-N,N-diethylbenzamide (compound 35)

The compound 35 was prepared by following the synthesis procedure as described for compound 1, but substituting 3-bromoanisole for 2-bromoanisole, and 1-naphtaldehyde for N,N-diethyl-4-carboxybenzamide..

ν_{max} (KBr)/cm^{-1} 3302, 2976, 1607, 1430, 1290, 1098, 813; δ_H (400 MHz, $CDCl_3$) 1.09 (3H, br s), 1.22 (3H, br s), 2.60 (1H, d, J 3), 3.24 (2H, br s), 3.52 (2H, br s), 6.00 (1H, d, J 3), 7.30-7.50 (7H, m), 7.76-7.88 (4H, m);

II. Preparation of (±) 4-((α-Chloro)-2-naphtyl-methyl)-N,N-diethylbenzamide (compound 36)

The compound 36 was prepared by following the synthesis procedure as described for compound 2, but substituting compound 1 for compound 35.

Used for the next step without further purification.

Example 23

Preparation of (±) 4-((α-(1-Piperazinyl))-2-naphtylmethyl)-N,N-diethylbenzamide (compound 37)

The compound of this Example was prepared by following the synthesis procedure as described for Example 1, but substituting compound 2 for compound 36.

m.p. 106-108°C (from acetonitrile), ν_{max} (KBr)/cm^{-1} 3324, 3052, 2964, 2810, 2774, 1613, 1465, 1287, 1130, 1098; δ_H (400 MHz, $CDCl_3$) 1.07 (3H, br s), 1.19 (3H, br s), 1.89 (1H, br s), 2.40 (4H, br s), 2.89-2.92 (4H, m), 3.21 (2H, br s), 3.50 (2H, br s), 4.41 (1H, s), 7.24-7.84 (11H, 3m); $C_{26}H_{31}N_3O \cdot 0.9\ H_2O$ requires:
C: 74.75 H: 7.91 N: 10.06 Found: C: 74.68 H: 7.56 N: 10.38.

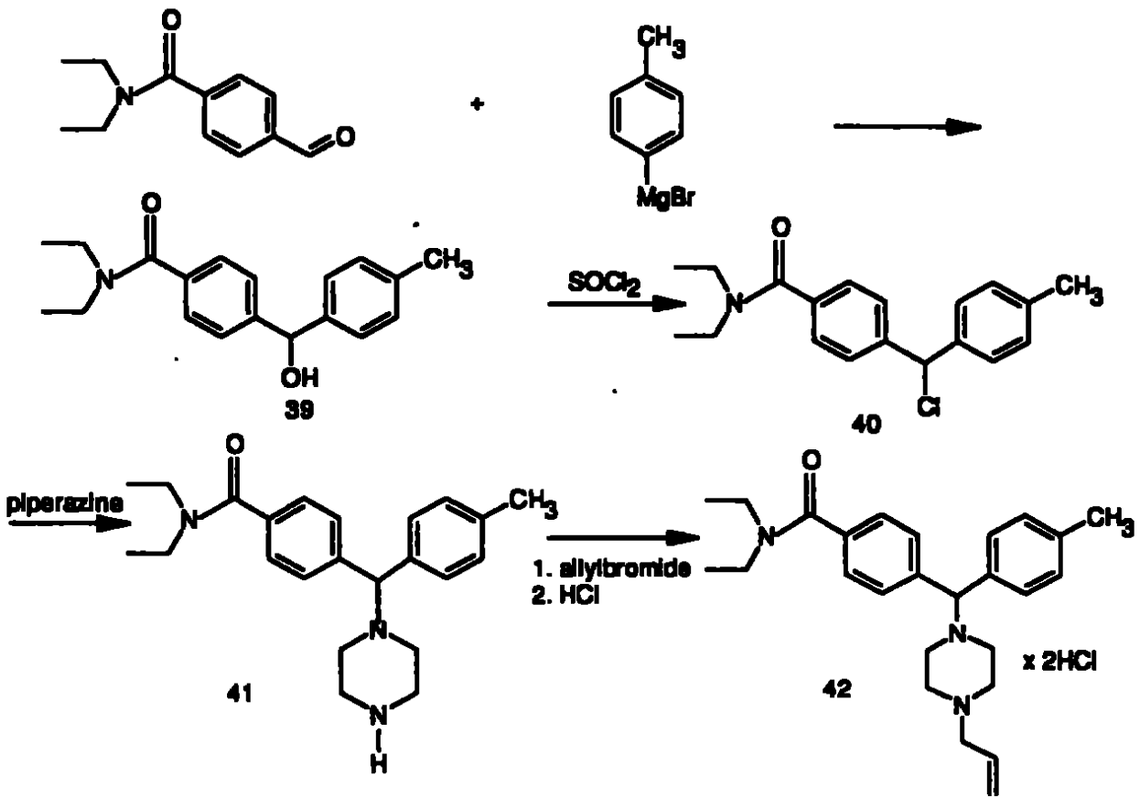
Example 24

Preparation of (±) 4-((α-((4-Allyl)-1-piperazinyl))-2-naphtylmethyl)-N,N-diethylbenzamide (compound 38)

The compound of this Example was prepared by following the synthesis procedure as described for Examples 2 and 3, but substituting compound 3 for compound 37.

ν_{max} (KBr)/cm^{-1} 3053, 2968, 2805, 1629, 1426, 1288, 1141, 1095, 921, 817; δ_H (400 MHz, $CDCl_3$) 1.06 (3H, br s), 1.19 (3H, br s), 2.49 (6H, br s), 3.00 (2H, m), 3.20 (2H, br s), 3.49 (2H, br s), 4.41 (1H, s), 5.08-5.22 (2H, m), 5.78-5.92 (1H, m), 7.26-7.84 (11H, m); $C_{25}H_{34}N_3OCl_3 \cdot 0.6\ H_2O$ requires:
C: 76.99 H: 8.07 N: 9.29 Found: C: 77.06 H: 8.09 N: 9.32 %.

Scheme 8



The compounds according to Examples 25-26 were synthesized as shown in Scheme 8 above.

H.

I. Preparation of (±) 4-((α-Hydroxy)-4-xylyl)-N,N-diethylbenzamide (compound 39)

The compound 39 was prepared by following the synthesis procedure as described for compound 31, but substituting 4-chlorophenylmagnesiumbromide for 4-toluylmagnesiumbromide.

ν_{max} (KBr)/cm^{-1} 3364, 2970, 1602, 1455, 1381, 1291, 1101, 1054, 802; δ_H (400 MHz, $CDCl_3$) 1.09 (3H, br s), 1.22 (3H, br s), 2.33 (3H, s), 2.55 (1H, br s), 3.24 (2H, br s), 3.52 (2H, br s), 5.78 (1H, d, J 3), 7.11-7.41 (8H, m);

II. Preparation of (±) 4-((α-Chloro)-4-xylyl)-N,N-diethylbenzamide (compound 40)

The compound 40 was prepared by following the synthesis procedure as described for compound 2.

Used for the next step without further purification.

Example 25

Preparation of (±) 4-((α-(1-Piperazinyl))-4-xylyl)-N,N-diethylbenzamide (compound 41)

The compound of this Example was prepared by following the synthesis procedure as described for compound 3.

m.p. 129-132°C (from acetonitrile), ν_{max} (KBr)/cm^{-1} 3320, 2957, 2811, 1610, 1437, 1285, 1128, 1010, 838; δ_H (400 MHz, $CDCl_3$) 1.10 (3H, br s), 1.20 (3H, br s), 1.83 (1H, br s), 2.30 (3H, s), 2.34 (4H, br s), 2.86-2.89 (4H, m), 3.24 (2H, br s), 3.51 (2H, br s), 4.20 (1H, s), 7.06-7.46 (8H, 3m); $C_{23}H_{31}N_3O$ requires:
C: 75.58 H: 8.55 N: 11.50 Found: C: 75.30 H: 8.54 N: 11.56.

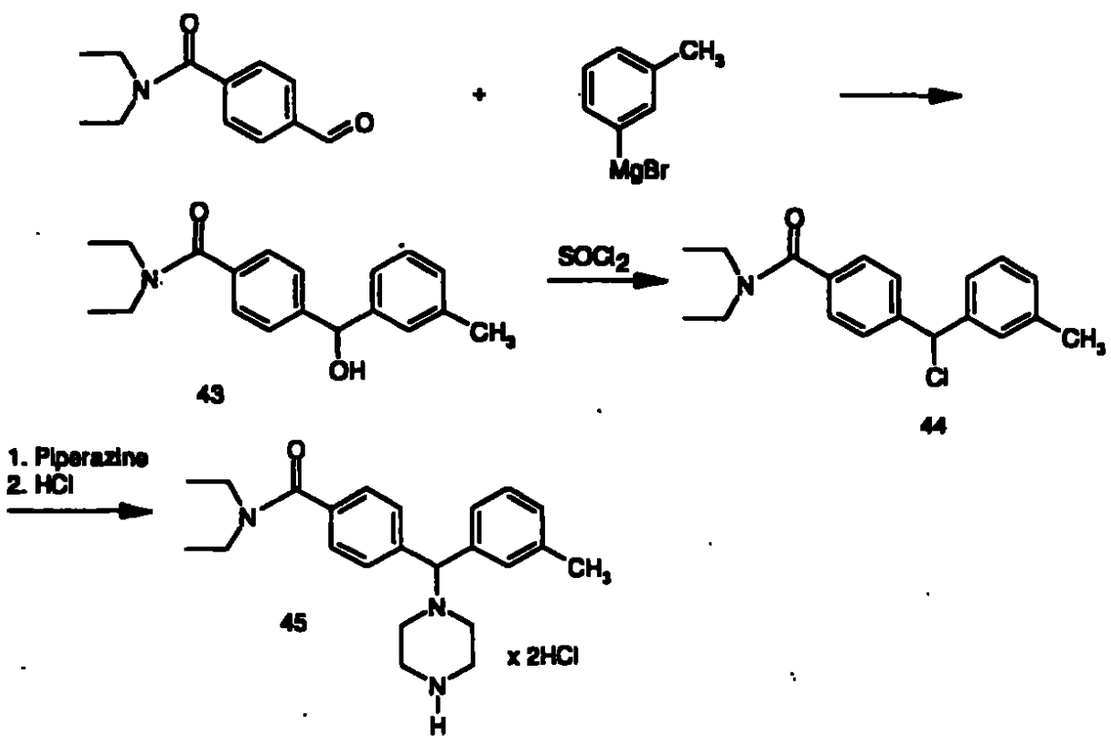
Example 26

Preparation of (±) 4-((α-((4-Allyl)-1-piperazinyl))-4-xylyl)-N,N-diethylbenzamide • 2HCl (compound 42)

The compound of this Example was prepared by following the synthesis procedure as described for Examples 2 and 3.

m.p. >160°C dec. (from ether): ν_{max} (KBr)/cm^{-1} 3437, 2973, 2402, 1625, 1433, 1289, 1097, 944, 809; δ_H (400 MHz, $CDCl_3$, free base) 1.10 (3H, br s), 1.20 (3H, br s), 2.29 (3H, s), 2.35-2.60 (6H, m), 3.03 (2H, m), 3.24 (2H, br s), 3.52 (2H, br s), 4.22 (1H, s), 5.12-5.23 (2H, m), 5.81-5.93 (1H, m), 7.05-7.45 (8H, 3m);

Scheme 9



The compounds according to Examples 27 were synthesized as shown in Scheme 9 above.

I.

I. Preparation of (±) 4-((α-Hydroxy)-3-xylyl)-N,N-diethylbenzamide (compound 43)

The compound 43 was prepared by following the synthesis procedure as described for compound 31, but substituting 4-chlorophenylmagnesiumbromide for m-toluylmagnesiumbromide.

ν_{max} (KBr)/cm^{-1} 3406, 2972, 1613, 1429, 1360, 1287, 1097, 1053, 789; δ_H (400 MHz, $CDCl_3$) 1.10 (3H, br s), 1.22 (3H, br s), 2.34 (3H, s), 2.55 (1H, d, J 3.5), 3.25 (2H, br s), 3.52 (2H, br s), 5.80 (1H, d, J 3), 7.12-7.42 (8H, m);

II. Preparation of (±) 4-((α-Chloro)-3-xylyl)-N,N-diethylbenzamide (compound 44)

The compound 44 was prepared by following the synthesis procedure as described for compound 2.

Used for the next step without further purification.

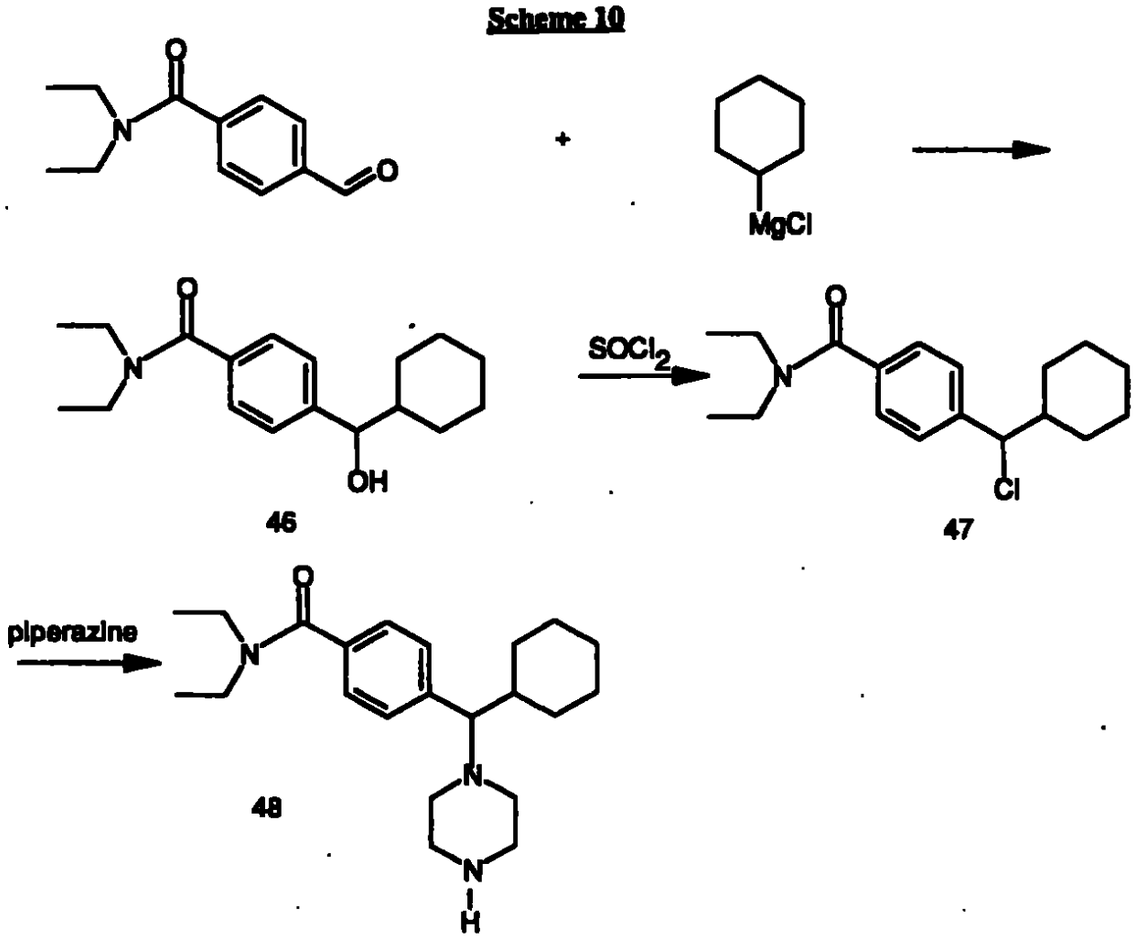
Example 27

Preparation of (±) 4-((α-(1-Piperazinyl))-4-xylyl)-N,N-diethylbenzamide • 2HCl (compound 45)

The compound of this Example was prepared by following the synthesis procedure as described for compound 3.

m.p. >130°C dec. (from ether), ν_{max} (Kbr)/cm^{-1} 2971, 2805, 2715, 1624, 1434, 1289, 1096, 783; δ_H (400 MHz, $CDCl_3$, free base) 1.10 (3H, br s), 1.20 (3H, br s), 2.31 (3H, s), 2.35-2.45 (5H, m), 2.89-2.92 (4H, m), 3.25 (2H, br s), 3.51 (2H, br s), 4.19 (1H, s), 6.98-7.46 (8H, 4m);

Scheme 10



The compounds according to Example 28 were synthesized as shown in Scheme 10 above.

I.

I. Preparation of (±) 4-((α-Hydroxy)-cyclohexylmethyl)-N,N-diethylbenzamide (compound 46)

The compound 46 was prepared by following the synthesis procedure as described for compound 31.

δ_H (400 MHz, $CDCl_3$) 0.85-2.0 (18H, m), 3.26 (2H, br s), 3.53 (2H, br s), 4.35-4.43 (1H, m), 7.28-7.36 (4H, m);

II. Preparation of (±) 4-((α-Chloro)-cyclohexylmethyl)-N,N-diethylbenzamide (compound 47)

The compound 47 was prepared by following the synthesis procedure as described for compound 2.

Used for the next step without further purification.

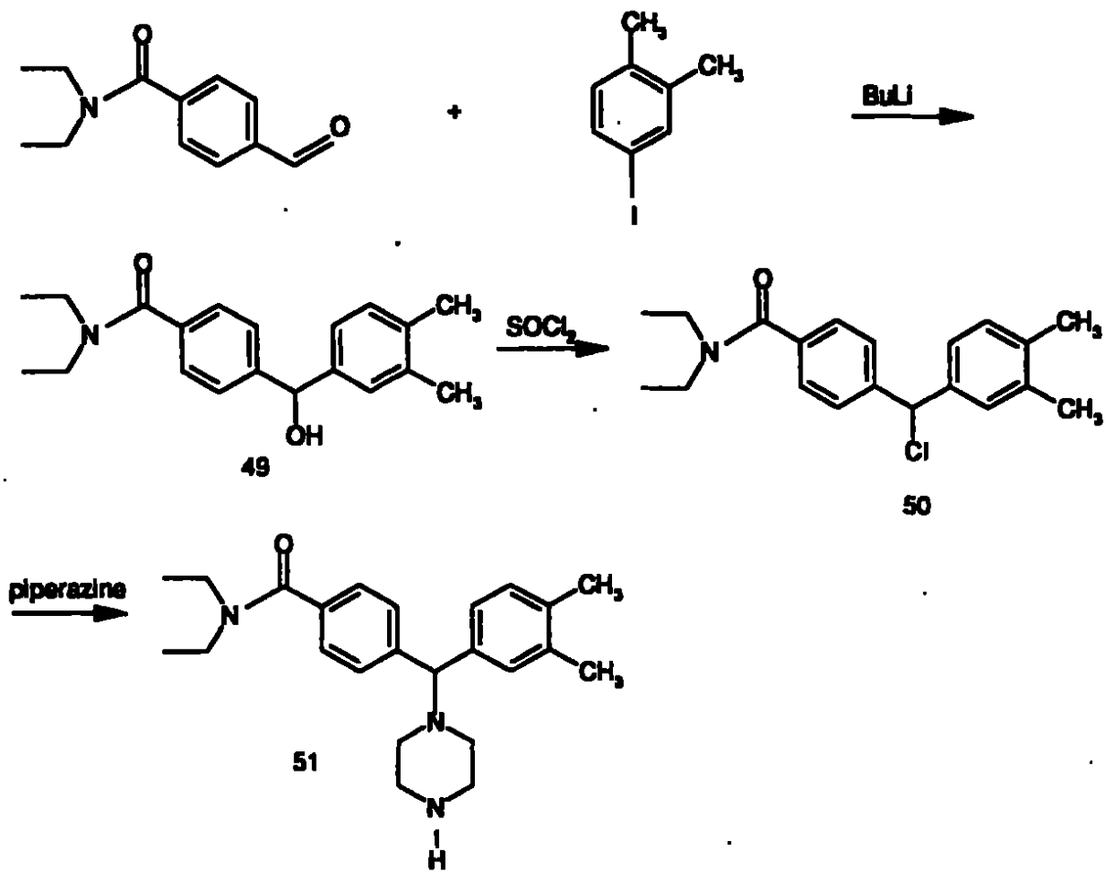
Example 28

Preparation of (±) 4-((α-(1-Piperazinyl))-cyclohexylmethyl)-N,N-diethylbenzamide (compound 48)

The compound of this Example was prepared by following the synthesis procedure as described for compound 3.

m.p. 113-116°C (from acetonitrile), ν_{max} (KBr)/cm^{-1} 3330, 2936, 2845, 1623, 1431, 1286, 1096, 823; δ_H (400 MHz, $CDCl_3$) 0.64-2.02 (18H, m), 2.18-2.40 (4H, m), 2.75-2.87 (4H, m), 3.06 (1H, d, J 8.8), 3.27 (2H, br s), 3.52 (2H, br s), 7.11 (2H, d, J 8.4), 7.29 (2H, d, J 8.4);

Scheme 11



The compounds according to Examples 29 were synthesized as shown in Scheme 11 above.

K.

I. Preparation of (±) 4-((α-Hydroxy)-3,4-dimethylbenzyl)-N,N-diethylbenzamide (compound 49)

The compound 49 was prepared by following the synthesis procedure as described for compound 1.

δ_H (400 MHz, $CDCl_3$) 1.09 (3H, br s), 2.23 (6H, s), 2.85 (1H, d, J 3), 3.24 (2H, br s), 3.51 (2H, br s), 5.73 (1H, d, J 2), 7.03-7.12 (m, 3H), 7.26-7.39 (m, 4H);

II. Preparation of (±) 4-((α-Chloro)-3,4-dimethylbenzyl)-N,N-diethylbenzamide (compound 50)

The compound 50 was prepared by following the synthesis procedure as described for compound 2.

Used for the next step without further purification.

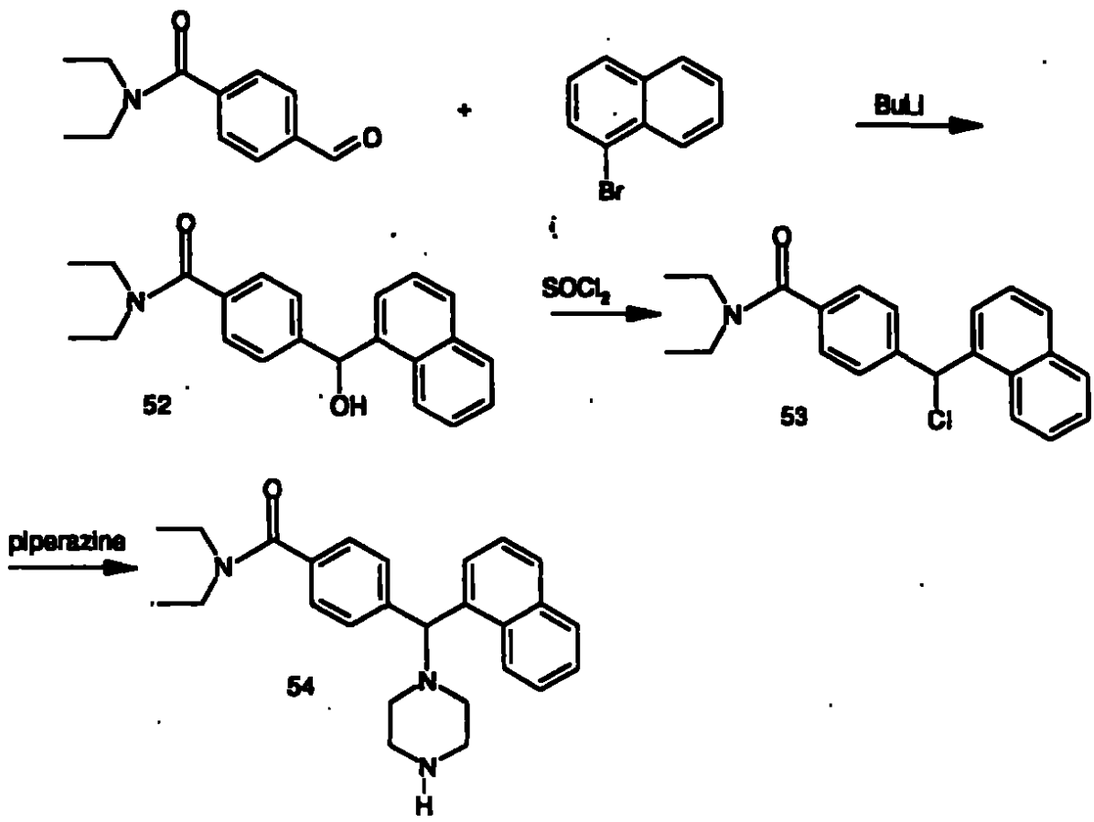
Example 29

Preparation of (±) 4-((α-(1-Piperazinyl))-3,4-dimethylbenzyl)-N,N-diethylbenzamide (compound 51)

The compound of this Example was prepared by following the synthesis procedure as described for compound 3.

ν_{max} (KBr)/cm^{-1} 3304, 2939, 2810, 1626, 1429, 1286, 1096, 846; δ_H (400 MHz, $CDCl_3$) 1.11 (3H, br s), 1.20 (3H, br s), 1.87 (1H, br s), 2.20 (3H, s), 2.22 (3H, s), 2.34 (4H, br s), 2.86-2.89 (4H, m), 3.25 (2H, br s), 3.51 (2H, br s), 4.15 (1H, s), 7.02-7.15 (3H, m), 7.26-7.30 (2H, m), 7.42-7.46 (2H, m);

Scheme 12



The compounds according to Examples 30 were synthesized as shown in Scheme 12 above.

I.

I. Preparation of (±) 4-((α-Hydroxy)-1-naphtylmethyl)-N,N-diethylbenzamide (compound 52)

The compound 52 was prepared by following the synthesis procedure as described for compound 1.

δ_H (400 MHz, $CDCl_3$) 1.06 (3H, br s), 1.20 (3H, br s), 3.01 (1H, d, J 4), 3.21 (2H, br s), 3.49 (2H, br s), 6.47 (1H, d, J 4), 7.24-7.48 (7H, m), 7.55-7.58 (1H, m), 7.78-7.87 (2H, m), 7.98-8.01 (1H, m);

II. Preparation of (±) 4-((α-Chloro)-1-naphtylmethyl)-N,N-diethylbenzamide (compound 53)

The compound 53 was prepared by following the synthesis procedure as described for compound 2.

Used for the next step without further purification.

Example 30

Preparation of (±) 4-((α-(1-Piperazinyl))-1-naphtylmethyl)-N,N-diethylbenzamide (compound 54)

The compound of this Example was prepared by following the synthesis procedure as described for compound 3.

ν_{max} (KBr)/cm^{-1} 3307, 3050, 2966, 2814, 1625, 1431, 1287, 1098, 843, 797; δ_H (400 MHz, $CDCl_3$) 1.04 (3H, br s), 1.17 (3H, br s), 2.14 (1H, br s), 2.40 (2H, br s), 2.46 (2H, br s), 2.83-2.95 (4H, m), 3.17 (2H, br s), 3.48 (2H, br s), 5.05 (1H, s), 7.22-7.28 (2H, m), 7.40-7.54 (5H, m), 7.70-7.94 (3H, m), 8.40-8.43 (1H, m);

Piperazine ring modifications: General Experimental and Examples

The compounds according to Examples 31-42 were synthesized as shown in Scheme 13 below.

M.

I. Preparation of 2-Dimethyl-5-methyl-piperazine-3,5-dione (compound 55)

N-*t*-Butoxycarbonyl-2-aminoisobutyric acid (5.0g, 25mmol) and D,L-alanine methylester hydrochloride (3.5g, 25mmol) was dissolved in dry dichloromethane (50mL) and cooled to 0°C. Triethylamine (3.5mL, 25mmol) and then 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (4.8g, 25mmol) was added and the mixture was stirred at 0°C until lumps dissolved. The reaction mixture was then left in the freezer 4d at -20°C. The organic solution was washed with water, 1M citric acid (aq.), water, dried (Na_2SO_4) and evaporated *in vacuo* to give 6.0g (83%) of coupling product. Most of the coupling product (5g) was dissolved in formic acid (50mL) and stirred 12h at 25°C. The acid was removed *in vacuo* and the residue dissolved in 2-butanol and heated at reflux for 4h. The solution was cooled to 0°C and the crystals filtered off and dried *in vacuo* at 100°C. Yield 2.6g of pure compound 55 (82%) which could be recrystallized from methanol , mp: >300°C. IR (Kbr) (cm-1): 3000 (br), 1680 (s) (C=O). ^{1}H NMR (D_2O): δ = 4.75 (s, 2H, NH), 4.21 (q, 1H, CHMe), 1.50-1.42 (m, 9H, 3Me). $C_7H_{12}N_2O_2$ requires C: 53.83, H: 7.74, N: 17.94. Found C: 53.89, H: 7.90, N: 17.79.

II. Preparation of 2-Dimethyl-5-methyl-piperazine dihydrochloride (compound 56)

Compound 55 (2.2g, 14mmol) was dissolved on dry THF (120mL). Lithium aluminum hydride (42mL, 1M in THF) was added in small portions. When addition complete, the solution was heated at reflux over night. The solution was allowed to cool, then excess hydride was destroyed by dropwise addition of water (1.6mL), NaOH (1.6mL, 15% solution) and water (4.8mL). The granular precipitate was filtered off and solvent evaporated *in vacuo*. The residue was dissolved in dichloromethane, dried (K_2CO_3) and

evaporation of solvent in vacuo gave 1.5g (84%). Treatment with excess HCl in ether gave the dihydrochloride compound 56 which could be recrystallized from methanol/ether mp: >300°C. IR (cm-1) ,KBr: 2760, 1570 (R_2NH_2+). MS (amine):128, 113, 84, 71, 58. ^{1}H NMR (D_2O+DSS): δ = 2.70-2.50 (m, 5H, CH_2-N, CH-N), 1.14 (s, 3H, 1 Me), 1.00-0.94 (s+d, 6H, 2 Me). $C_7H_{16}N_2$x2HCl requires C: 41.80, H: 9.02, N: 13.93. Found C:42.03, H:9.24, N: 14.00.

Example 31

Preparation of 4-(4-(2-Dimethyl-5-methyl-piperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide dihydrochloride (compound 57)

4-(Chloro-(3-methoxyphenyl)methyl)-N,N-diethylbenzamide (0.61g, 2.0mmol) and compound 56 (0.50g, 3.9mmol) was dissolved in dry acetonitrile (5mL). Potassium carbonate (0.26g, 2.0mmol) was added and the mixture heated at reflux for 2d. The solvent was removed *in vacuo* and the residue purified by flash chromatography on silica (CH_2Cl_2/MeOH/NH_3(aq.)), 98:1:1 to 95:5:1 to yield 0.65g (79%). Treatment with excess of HCl in ether, filtering and drying crystals *in vacuo* over KOH gave the dihydrochloride compound 57, mp: 134-36°C. IR (HCl salt, KBr) (cm-1): 3400 (br, OH), 2900 (br, R_2NH_2+), 1600 (s, C=O or R_2NH_2+), 1283, 1038 (C-O). MS (amine) 3 peaks: 423, 353, 325, 296, 127. ^{1}H NMR: (amine, $CDCl_3$): δ = 7.40-6.60 (m, 8H, Ar-H), 5.26, 5.25, 4.61 (3s, 1H, $CHAr_2$), 3.70 (s, 3H, MeO), 3.4, 3.2 (2 br. s, 4H, $MeCH_2$), 3.1-2.0 (m, 5H, piperazine-H), 1.3-0.9 (m, 15H, 5Me). $C_{26}H_{37}N_3O_2$ x2HCl requires C: 62.89, H: 7.92, N: 8.46. Found C: 63.41, H: 8.38, N: 8.56.

Example 32

Preparation of 4-(4-(1-Allyl-2-dimethyl-5-methyl-piperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide dihydrochloride (compound 58)

Compound 57 (0.39g,0.92mmol) was dissolved in dry acetonitrile (5mL). Potassium carbonate (0.13g, 0.92mmol) and allyl bromide (90μL, 1.02mmol) was added. After 3h at

25°C the solvent was evaporated and the residue purified by flash chromatography on silica (CH_2Cl_2/MeOH), 98:2 to 95:5 to give a total of 0.39g (92%). Treatment with excess of HCl in ether, filtering and drying crystals in vacuo over KOH gave the dihydrochloride, compound 58, mp: 105-21°C. IR (HCl salt, Kbr) (cm-1): 3400 (br, OH), 2500 (br, R_2NH_2+), 16200 (s) (C=O or R_2NH_2+), 1285, 1043 (C-O). ^{1}H NMR: (amine, $CDCl_3$): δ = 7.50-6.60 (m, 8H, Ar-H), 5.70 (m, 1H, allyl-H), 5.00 (m, 2H, allyl-H), 4.70 (s, 1H, *CH*Ar_2), 3.70 (s, 3H, MeO), 3.5 +3.3 (2 br. s, 4H, $MeCH_2$), 3.0-1.9 (m, 7H, piperazine-H), 1.2-0.8 (m, 15H, 5Me). $C_{29}H_{41}N_3O_2$ x2HCl requires C: 64.91, H: 8.08, N: 7.83. Found C: 65.70, H: 8.60, N: 8.29.

N.

I. Preparation of 4-Allyl-2-dimethyl-5-methyl-piperazine (compound 59)

Compound 56 (0.14g,0.91mmol) was dissolved in acetonitrile and allyl bromide (80µL, 0.91mmol) was added at 0°C. After 1h another portion of allyl bromide was added. After 2h the solvent was evaporated and the residue purified by flash chromatography on silica (CH_2Cl_2/MeOH), 95:5 to 80:20 to give the monoallyl compound 59, 116mg (69%).

Example 33

Preparation of 4-(1-(4-Allyl-2-dimethyl-5-methyl-piperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide dihydrochloride (compound 60)

The compound of this Example was prepared by following the synthesis procedure as described for Example 3.

Mp: 125-30°C. IR (2HCl, KBr) (cm-1): 3430(br), 2978, 2480(br.), 1607, 1436, 1285. MS(free amine):366 , 296, 167. ^{1}H NMR: (D_2O +DSS): δ = 7.60-6.90 (m, 9H, Ar-H), 6.0-5.5 (m, 4H, allyl-H + Ar_2CH), 3.80 (2s, 3H, MeO), 4.0-3.7 (m, 11H, allyl-H , piperazine-H,

amide-CH_2), 1.3-1.0 (m, 15H, piperazine-Me, amide-Me). Anal. calc. for $C_{29}H_{41}N_3O_2$ x 2HCl x 2.9 H_2O: C:59.15, H:8.35, N:7.14. Found: C: 59.05, H:8.00, N: 7.22.

Example 34

Preparation of 4-(1-(2-dimethyl-5-methyl-piperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide dihydrochloride (compound 61)

56 (42mg,0.33mmol) and potassium carbonate (46mg, 0.33mmol) was dissolved in water (2mL) and di-*t*-butyl dicarbonate (79mg, 0.36mmol) was added. After stirring 1h the solvent was evaporated *in vacuo* and the residue purified by chromatography on silica (CH_2Cl_2/MeOH), 90:10 to give 43 mg of the mono-N-Boc protected 55 which was dissolved in dry acetonitrile together with potassium carbonate (26mg, 0.19mmol) and 4-(Chloro-(3-methoxyphenyl)methyl)-N,N-diethylbenzamide (63mg, 0.19mmol). After heating 4 days at reflux, the solvent was removed *in vacuo* and residue purified by chromatography on silica (CH_2Cl_2/MeOH). 100:0, 95:5. Treatment with formic acid (5mL) for 3h, evaporation of solvent *in vacuo* and extraction of the residue with CH_2Cl_2/1M NaOH, drying of the organic phase (K_2CO_3) and evaporation of solvent *in vacuo* gave 27mg (33%) of the free amine. Treatment with excess HCl in ether gave the dihydrochloride which was dissolved in water and freezedried., mp:145-50°C. IR (2HCl, KBr) (cm-1): 3500-3400(br), 1601, 1442, 1285. MS(free amine): 423, 296, 325, 127. ^{1}H NMR: ($CDCl_3$): δ = 7.4-6.6 (m, 8H, Ar-H), 5.39, 5.36 (2s, 1H, Ar_2CH), 3.75 (s, 3H, MeO), 3.5, 3.25 (2 br. s, 4H, amide-Me), 2.80, 2.50, 2.05 (3m, 5H, piperazine-H), 1.5 (br.s, 1H, N-H), 1.25-1.0 (br. m, 6 H, amide-Me), 1.15 (s, 3H, Me), 0.90 (d, 3H, Me), 0.85 (s, 3H, Me). Calc. for $C_{26}H_{37}N_3O_2$ x2HCl x 7.4 H_2O: C:49.58, H:8.61, N:6.67. Found: C: 49.61, H:7.73, N: 6.56.

O.

I. Preparation of 4-(Phenyl-hydroxymethyl)-N,N-diethylbenzamide (compound 62)

The compound 62 was prepared by following the synthesis procedure as described for compound 1.

MS: 282, 211, 165, 105. ^{1}H NMR: ($CDCl_3$): δ = 7.38-7.20 (m, 9H), 5.80 (d, J=3.5Hz, 1 H), 3.5, 3.2 (2br.s, 4H), 1.2, 1.05 (2br. s, 6H).

II. Preparation of 4-(Chloro-phenyl-methyl)-N,N-diethylbenzamide (compound 63)

The compound 63 was prepared by following the synthesis procedure as described for compound 2.

GC-MS (2 peaks):296, 225, 165, 121. and 300, 266, 229, 195, 165. ^{1}H NMR: ($CDCl_3$): δ = 7.45-7.20 (m, 9H), 6.09 (s, 1H), 3.4 (br. m, 4H), 1.1 (br. m, 6H).

Example 35

Preparation of 4-((1-piperazinyl)-benzyl)- N,N-diethylbenzamide dihydrochloride (compound 64)

The compound of this Example was prepared by following the synthesis procedure as described for compound 3.

Mp: 157-69°C. IR (amine, $CDCl_3$ in KBr cell) (cm-1): 3690, 3630, 1613, 1435, 1265. MS (free amine): 351, 306, 295, 266, 194, 165. ^1H NMR: (free amine, $CDCl_3$): δ= 7.46-7.16 (m, 9H, Ar-H), 4.24 (s, 1H, $CHAr_2$), 3.5 + 3.2 (2 br. s, 4H, $MeCH_2$), 2.89 (m, 4H, piperazine-H), 2.36 (br. s, 4H, piperazine-H), 1.94 (br s, 1H, NH), 1.2 +1.1 (2 br. s, 6H, 2Me). Anal. calc. for $C_{22}H_{29}N_3O$ x 2HCl x1.90 H_2O, C: 57.61, H: 7.65, N: 9.16. Found C: 57.59, H: 7.66, N: 8.92.

Example 36

Preparation of 4-((4-Allyl-1-piperazinyl)-benzyl)-N,N-diethylbenzamide dihydrochloride (compound 65)

The compound of this Example was prepared by following the synthesis procedure as described for Examples 2 and 3.

Mp: 175-205°C. IR (amine, $CDCl_3$ in KBr cell) (cm-1): 3689, 1613, 1455, 1434, 1290, 1143. MS (free amine): 391, 165, 125. ^1H NMR: (free amine, $CDCl_3$): δ = 7.42-7.12 (m, 9H, Ar-H), 5.81 (m, 1H, allyl-H), 5.10 (m, 2H, allyl-H), 4.23 (s, 1H, $CHAr_2$), 3.5 + 3.2 (2 br. s, 4H, $MeCH_2$), 3.00 (m, 2H, allyl-H), 2.6-2.4 (br. s, 8H, piperazine-H), 1.1 (2 br. s, 6H, 2Me). Anal. calc. for $C_{25}H_{35}N_3O$ x2HCl x1.0 H_2O, C: 62.23, H: 7.73, N: 8.71. Found C: 62.22, H: 7.49, N: 8.42.

P

I. Preparation of 2-Hydroxymethyl-5-methyl-piperazine-3,5-dione (compound 66)

(D,L)-N-*t*-Butoxycarbonyl-alanine (5.0g, 26mmol) was dissolved in methylene chloride (50mL) with triethyl amine (8.1mL), dried with 4A molecular sieves and transfered to dry flask under nitrogen. *t*-Butyl chloroformate (3.8mL, 29mmol) was added at -10°C. The Solution was stirred 15min , then D,L-serine methylester hydrochloride (4.1g, 26mmol) was added and the solution was allowed to reach 25°C and stirred 12h. Washing the solution

with brine, drying ($MgSO_4$) and evaporating solvent *in vacuo* gave a solid which was treated with formic acid for 1h. The acid was removed *in vacuo* and the residue dissolved in anhydrous 2-butanol (5mL) and heated at reflux 2 days. The solvent was removed and the residue crystallized when treated with acetone to give 1g of compound 66 (24%).

II. Preparation of 2-Hydroxymethyl-5-methyl-piperazine (compound 67)

The compound 67 was prepared by following the synthesis procedure as described for compound 55.

II. Preparation of 2-(*t*-Butyldiphenylsilyloxy)methyl-5-methyl-piperazine (compound 68)

Compound 67 (0.41g, 3.1mmol) was dissolved in dry DMF (5mL). Chloro-*t*-butyldiphenylsilane (0.95g, 3.4mmol) and immidazole (0.47g, 6.9mmol) was added and stirring was continued 12h. The product was extracted by adding ethyl acetate, brine and 1M NaOH and shaking. The organic phase was dried and evaporated *in vacuo*. Chromatography of the residue on silica (CH_2Cl_2/MeOH, 100:0, 95:5, 90:10 and 80:20) gave 0.39g (34%) pure compound 68.

Example 37

Preparation of 4-(4-(2-Hydroxymethyl-5-methyl)piperazinyl-benzyl)-N,N-diethyl-benzamide dihydrochloride (compound 69)

The compound of this Example was prepared by following the synthesis procedure as described for compound 3.

Mp:145-50°C. IR (2HCl ,KBr) (cm-1): 3300(br), 2700(br), 1612, 1446, 1382, 1296, 1080. MS(free amine):381, 218, 181, 91. ^{1}H NMR: (free amine, $CDCl_3$): δ = 7.44-7.18 (m, 9H,

Ar-H), 5.17, 5.14 (2s, 1H,$ArCH_2$), 3.75-2.60 (m, 12H, piperazine-H, amide-CH_2), 2.02 (m, 1H, piperazine-H), 1.30-1.05 (m, 9H, piperazine-Me + amide-Me). Anal. calc. for $C_{24}H_{33}N_3O_2$ x2HCl x 1.8 H_2O: C: 57.55, H: 7.77, N: 8.39. Found: C: 57.05, H: 7.67, N: 8.19.

Example 38

Preparation of 4-((4-(2-Hydroxymethyl-5-methyl)piperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide dihydrochloride (compound 70)

The compound of this Example was prepared by following the synthesis procedure as described for compound 3.

Mp:185-90°C. IR (2HCl, KBr) (cm-1): 3500-2500(br), 1596, 1440, 1045. ^{1}H NMR: (free amine, $CDCl_3$): δ = 7.40-6.60 (m, 8H, Ar-H), 5.05, 5.10 (2s, 1H, Ar_2CH), 3.70 (s, 3H, MeO), 3.8-2.5 (m, 12H, piperazine, amide CH_2) 1.2-1.0 (br. s, 9H, amide-Me, piperazine-Me).

Example 39

Preparation of 4-((4-(1-Allyl-2-hydroxymethyl-5-methyl)piperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide dihydrochloride (compound 71)

The compound of this Example was prepared by following the synthesis procedure as described for Examples 2 and 3.

Mp: 125-30°C. IR (2HCl, KBr) (cm-1): 3400(br), 1603, 1445, 1285. MS(free amine): two peaks: 310, 239, 135 and 312, 241, 135. ^{1}H NMR: (free amine, $CDCl_3$): δ = 7.50-6.70 (m, 8H, Ar-H), 5.80, 5.20, 5.00 (3m, 3H, allyl-H), 4.0-2.3 (m, 14H, piperazine-H,allyl-H, amide-CH_2) 3.80 (s, 3H, MeO), 1.2 (br. s, 6H, amide-Me). Anal.calc. for $C_{25}H_{35}N_3O_3$ x2HCl x3.7 H_2O: C:55.57, H:8.06, N:6.94. Found: C: 55.53, H:7.82, N: 7.16.

Q.

I. Preparation of Methyl 3-(hydroxy-(2-naphtyl)methyl)phenyl ether (compound 72)

The compound 72 was prepared by following the synthesis procedure as described for compound 1.

MS: 264, 155, 135, 128, 109, 101. ^{1}H NMR: ($CDCl_3$): δ = 7.90-6.78 (m, 11H, Ar-H), 5.98 (d, J = 3.5Hz, 1H, Ar_2H), 3.78 (s, 3H, MeO), 2.32 (d, J = 3.5Hz, 1H, OH).

II. Preparation of Methyl 3-(chloro-(2-naphtyl)methyl)phenyl ether (compound 73)

The compound 73 was prepared by following the synthesis procedure as described for compound 2.

GC-MS (2 peaks): 278, 247, 215, 171, 155, 135 and 282, 248, 247, 231, 215. ^{1}H NMR: ($CDCl_3$): δ = 7.86-6.81 (m, 11H, Ar-H), 6.25 (s, 1H, Ar_2H), 3.76 (s, 3H, MeO).

III. Preparation of 4-Allyl-2-methylpiperazine (compound 74)

2-Methylpiperazine (0.4g, 4mmol) was dissolved in acetonitrile (5mL) and allyl bromide (86µL, 1mmol) was added at 0°C. Stirring was continued at 0°C for 1h , then at 25°C for 6h. Evaporation of solvent *in vacuo* and chromatography on silica (CH_2Cl_2/MeOH, 80:20) gave 80mg (57%) pure compound 74.

Example 40

Preparation of Methyl 3-((2-naphtyl)-(3-methyl-piperazinyl)methyl)phenyl ether dihydrochloride (compound 75)

The compound of this Example was prepared by following the synthesis procedure as described for compound 3.

Mp: 170-74°C. IR (KBr) (cm-1): 3461, 2458, 1600, 1439, 1263, 1043. MS (amine): 386, 247, 215, 139, 112. ^{1}H NMR: (amine, $CDCl_3$): δ = 7.84-6.66 (m, 11H, Ar-H), 4.33 (s, 1H, $CHAr_2$), 3.74, 3.73 (2s, 3H, MeO), 3.00-2.70 (m, 6H, piperazine-H). 1.95, 1.65 (2m, 2H, piperazine-H), 0.98-0.92 (2d, J = 6.4 Hz, 3H, piperazine-Me). Anal. calc. for $C_{23}H_{26}N_2O$ x2HCl x1.8 H_2O, C: 61.14, H: 7.05, N: 6.20. Found, C: 61.05, H: 6.48, N: 6.07.

Example 41

Preparation of Methyl 3-((2-naphtyl)-(4-allyl-2-methyl-piperazinyl)methyl)phenyl ether dihydrochloride (compound 76)

The compound of this Example was prepared by following the synthesis procedure as described for Example 3.

Mp: 173-82°C. IR (KBr) (cm-1): 3430, 2500, 2355, 1601, 1436, 1265, 1047. MS (amine): 386, 274, 247, 215, 139, 125. ^{1}H NMR: (amine, CDCl3): δ = 7.86-6.66 (m, 11H, Ar-H), 5.82 (m, 1H, allyl-H), 5.12 (m, 2H, allyl-H), 4.95 (br. s, 1H, $CHAr_2$), 3.76, 3.75 (2s, 3H, MeO), 3.04-2.32 (m, 9H, piperazine-H), 1.15-1.11 (2d, 3H, Me). Anal. calc. for $C_{26}H_{32}N_2O$ x2HCl x0.4 H_2O, C: 66.92, H: 7.08, N: 6.00. Found C: 67.03, H: 7.09, N: 5.88.

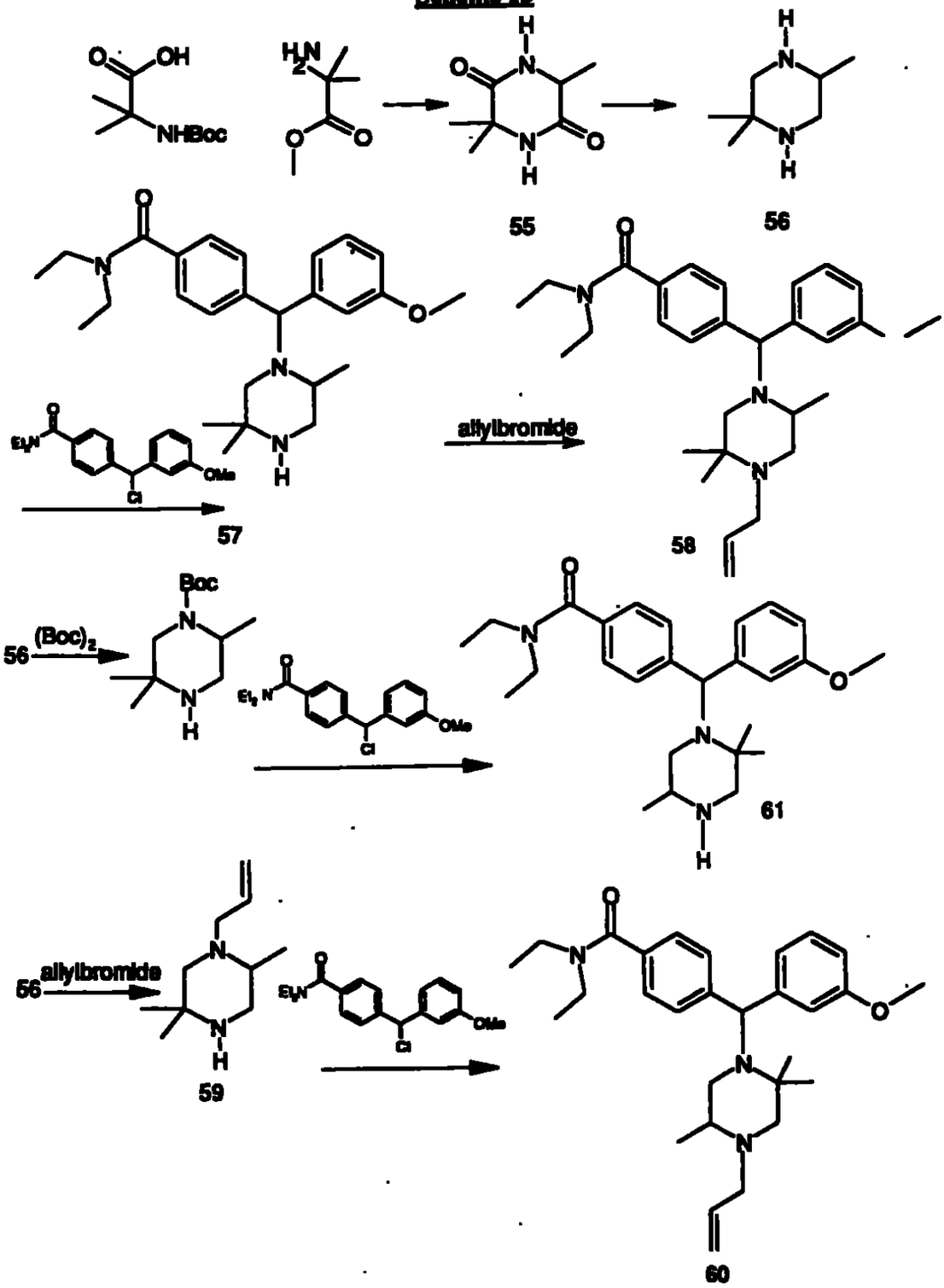
Example 42

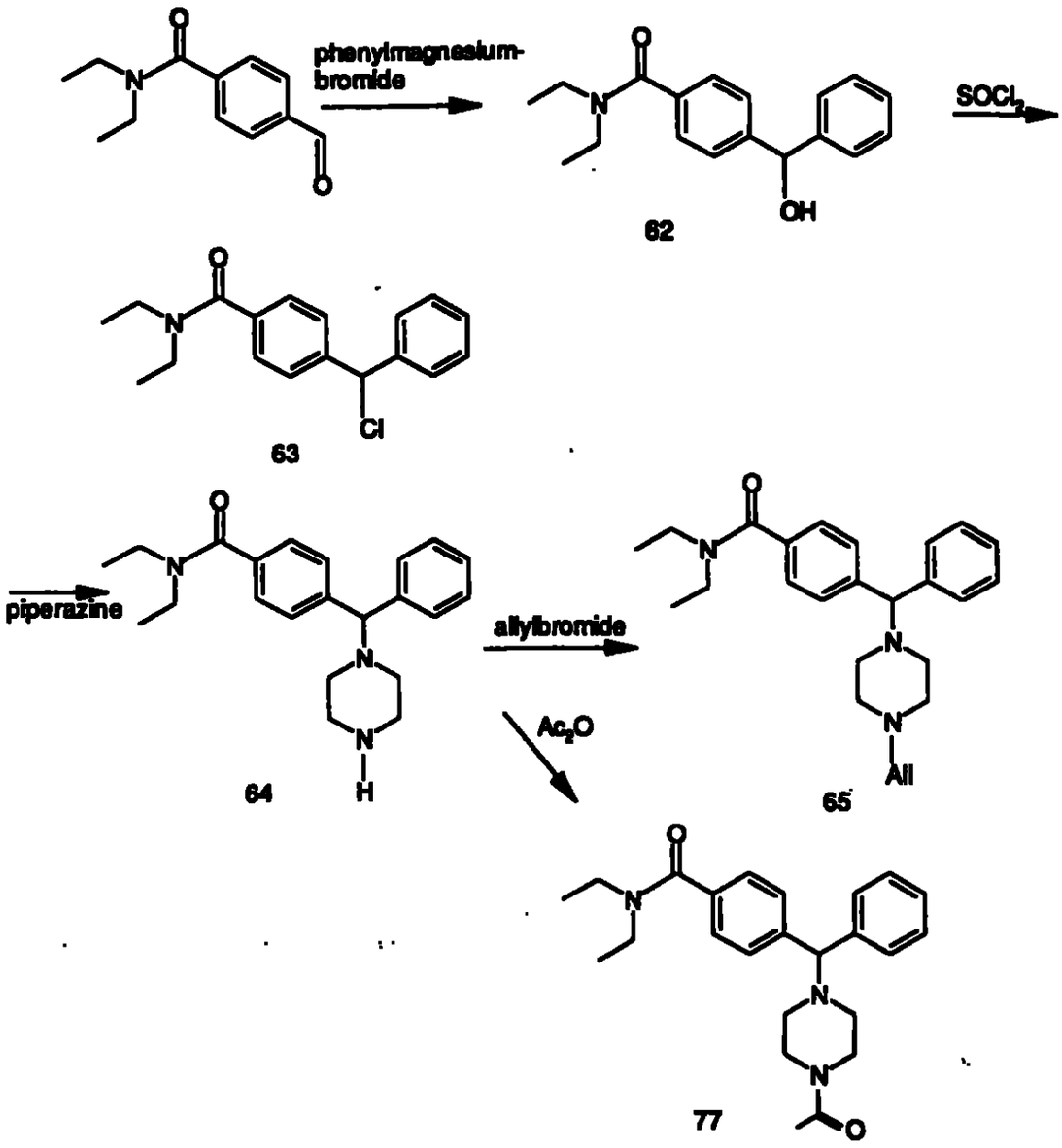
Preparation of 4-((4-Acetyl-1-piperazinyl)-benzyl)- N,N-diethylbenzamide hydrochloride (compound 77)

The free amine of compound 64 (100 mg, 0.28 mmol) was dissolved in methylene chloride (5 ml), cooled to 0°C. Triethyl amine (43 µl, 0.31 mmol) was added and then acetyl chloride (22 µl, 0.31 mmol) was added dropwise. After 10 min, the solution was washed with potassium carbonate (10 %), dried (K_2CO_3) and evaporated *in vacuo*. The residue was purified by chromatography on silica (CH_2Cl_2/MeOH/NH_3, 95:5:0.5) to give 116 mg of compound 77 (~ 100 %).

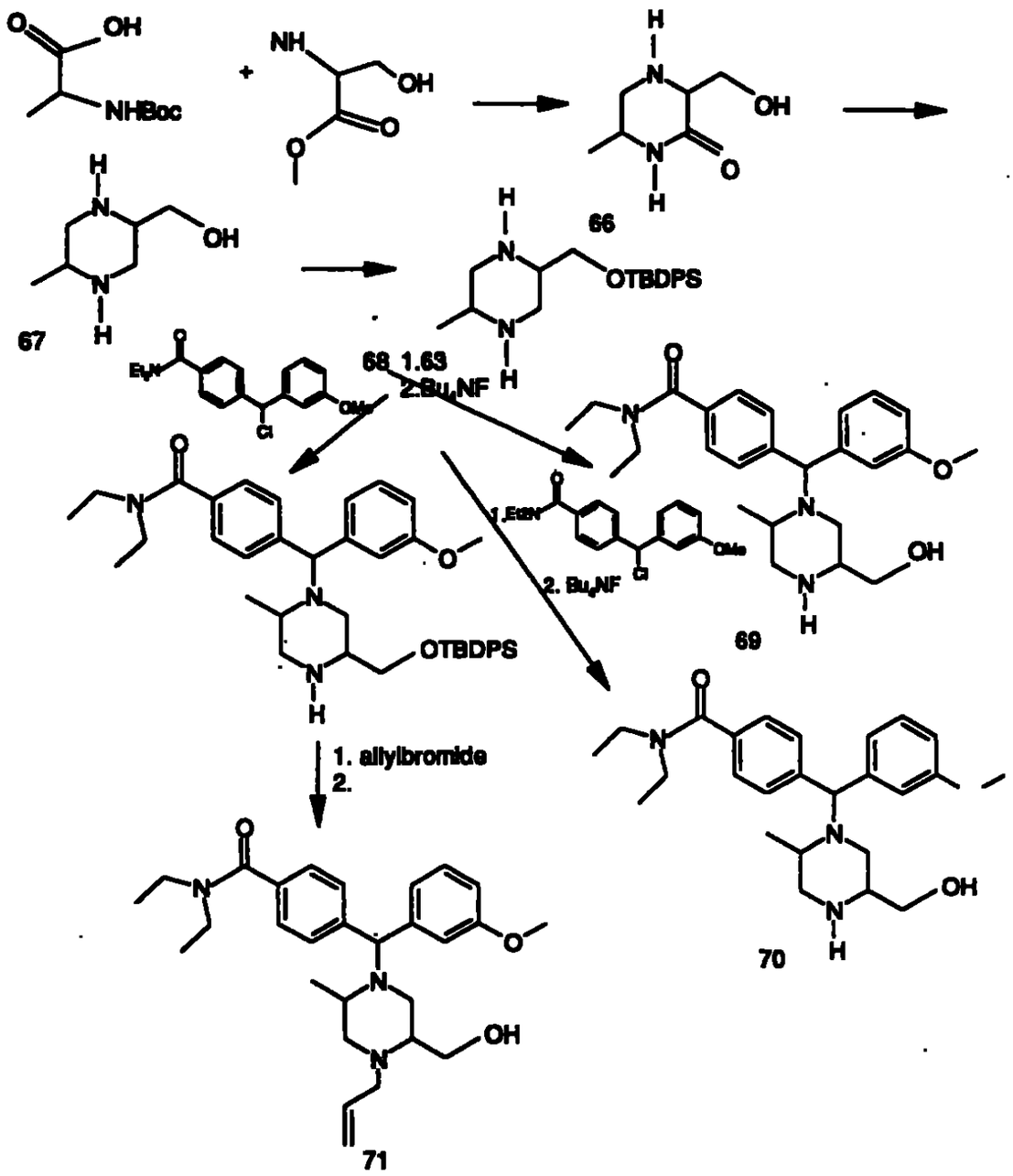
Mp: 140-50°C. IR (KBr) (cm-1): 3480(br), 2987, 2500(br), 1623, 1429, 1285,1245. MS (free amine): 393, 267, 165, 127. ^{1}H NMR: (free amine, $CDCl_3$): δ = 7.46-7.18 (m, 9H, Ar-H), 4.25 (s, 1H, $CHAr_2$), 3.70- 3.15 (m, 8H, amide-CH_2, piperazine-H), 2.36 (m, 4H, piperazine-H), 2.05 (s, 3H, MeCO), 1.15 (br. m, 6H, amide-Me). Anal. calc. for $C_{24}H_{31}N_3O_2$ x1HCl x0.80 H_2O, C: 64.87, H: 7.62. N: 9.46. Found C: 65.01, H:7.76, N: 9.42.

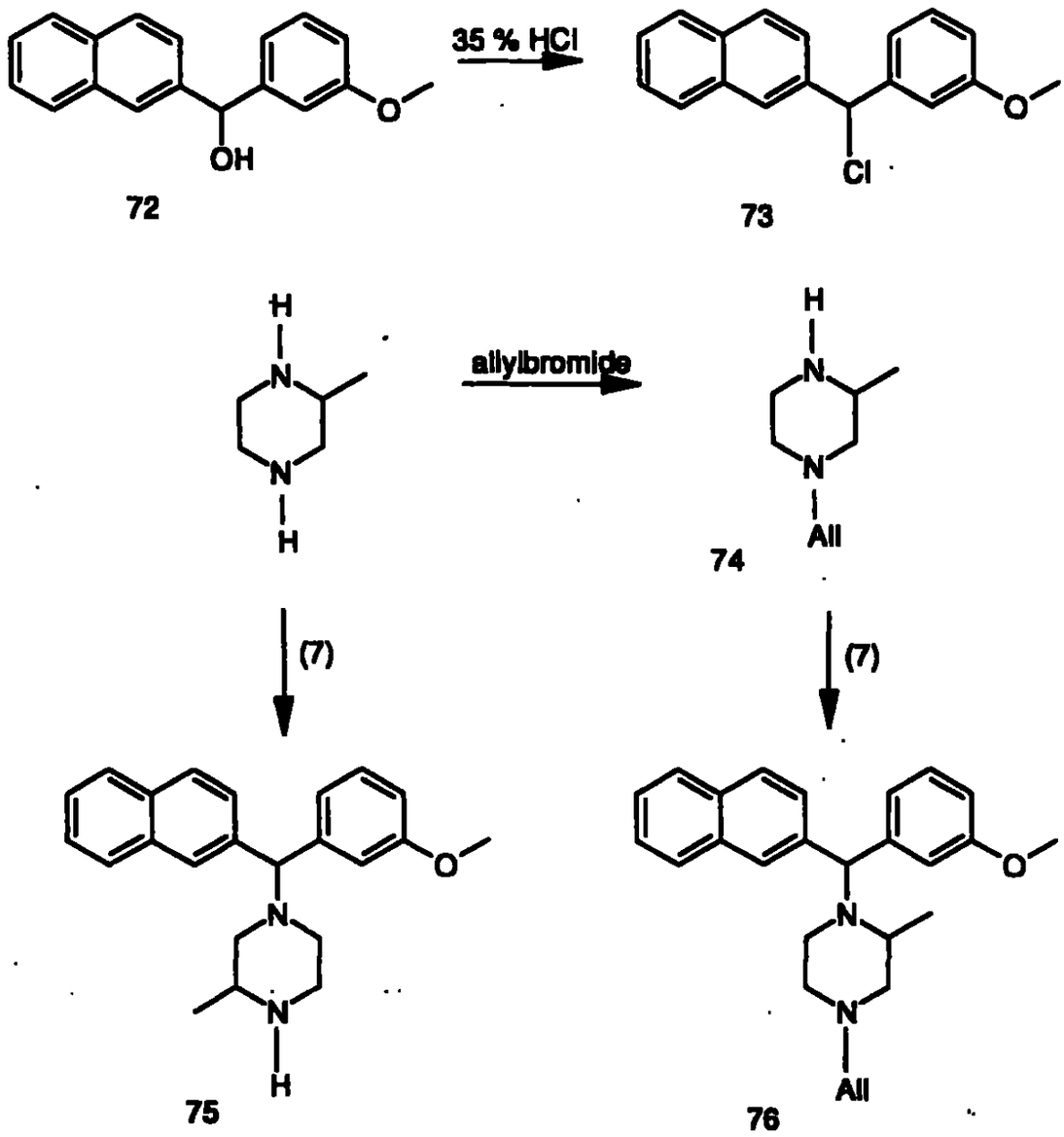
Scheme 13




phenylmagnesium-
bromide
SOCl2
OH
62
Cl
63
piperazine
64
H
allylbromide
Ac2O
All
65
77
O

66


NHBoc
OH
NH
OH
O
H
N
OH
O
H
N
H
66
OTBDPS
67
68
1.63
2.Bu4NF
Et2N
Cl
OMe
1.Et2N
2. Bu4NF
69
OTBDPS
1. allylbromide
2.
70
71



5

Diethylbenzamide replacements etc.

The compounds according to Examples 43-48 were prepared as shown in Scheme 14 below.

R.

I. Preparation of 4-((4-t-Butoxycarbonyl-1-piperazinyl)-benzyl)-benzoic acid (compound 78)

Compound 64 (6.0g, 17mmol) was dissolved in 6N hydrochloric acid and heated at 120°C for 3 days. The solution was then neutralized with aquous NaOH (~12g). The solution was concentrated to 100mL, mixed with THF (100mL) and di-*t*-butyl dicarbonate (3.7g, 17mmol) added dissolved in THF (50mL). After stirring 1h at 25°C, the aquous phase was acidified with 1M citric acid and extracted two times with ethyl acetate. The organic phase was dried (K_2CO_3) and evaporated, and the residue purified by chromatography on silica (EtOAc/ heptane/ AcOH, 10:90:0 to 66:33:1) to give a total of 3.85g (57%) of compound 78.

Example 43

Preparation of 4-((1-piperazinyl)-benzyl)-benzoic acid dihydrochloride (compound 79)

Compound 78 (150mg, 0.38mmol) was treated with excess HCl in acetic acid 1h. Acid removed *in vacuo* and residue dissolved in methanol and precipitated by addition of ether. The precipitate was dried in vacuum at 100°C. Mp: 172-80°C. IR (KBr) (cm-1): 3000(br),1700, 1606, 1454. ^{1}H NMR: (DMSO-d6): δ = 12.85 (s, 1H, CO_2H), 8.95 (s, 2H, NH), 7.92 -7.20 (m, 9H, Ar-H), 4.56 (s, 1H, Ar_2CH), 3.33 (s, 8H, piperazine-H). Anal. calc. for $C_{18}H_{20}N_2O_2$x2HCl, C:58.54, H:6.00, N:7.59. Found: C:59.9, H:6.47, N:7.88.

Example 44 and 45

Preparation of Methyl 4-((4-t-butoxycarbonyl-1-piperazinyl)-benzyl)benzoate (compound 80) and Methyl 4-((1-piperazinyl)-benzyl)benzoate dihydrochloride (compound 81)

Compound 78 (0.15g, 0.38mmol) and cesium carbonate (0.25g, 0.76mmol) was mixed in DMF (2mL) and methyl iodide (72µL, 1.1mmol) was added. After 2h at 25°C, potassium carbonate (10% ,aq.) and the solution was extracted with ethyl acetate. After evaporation of solvent *in vacuo*, the residue was purified by chromatography on silica (EtOAc/ heptane, 30:70) to yield 0.13g (87%) of the methyl ester, compound 80. Boc-deprotection was acheived by treatment with excess HCl in methanol at 50°C. The solvent was removed and the residue was purified again on silica. The dihydrochloride, compound 81 (35mg), was prepared according to previous methodology. Mp: 185-95°C. IR (KBr) (cm-1): 3400(br), 2700(br), 1720, 1612, 1430, 1285, 1190, 1112. MS (EI, free amine): 310, 265, 225, 206, 165. ^{1}H NMR: (D_2O/CD_3OD + DSS): δ = 8.20-7.34 (m, 9H, Ar-H), 5.03 (s, 1H, $CHAr_2$), 3.89 (s, 3H, MeO), 3.42 (m, 4H, piperazine-H), 3.08 (m, 4H, piperazine-H). Anal. calc. for $C_{19}H_{22}N_2O_2$ x2HCl x $1H_2O$, C:56.86, H:6.53, N:6.98. Found C:56.82, H:6.54, N:7.00.

S.

I. Preparation of 4-((1-piperazinyl)-benzyl)-benzamide dihydrochloride (compound 82)

Compound 78 (0.11g, 0.28mmol) was dissolved in dry methylene chloride/ THF, 1:1 (5mL) and cooled to -20°C. Triethylamine (78µL, 0.56mmol) was added and then i-butyl chloroformate (37µL, 028mmol). After 10 min, ammonia in methylene chloride (0.51mL, 1.1M, 0.56mmol) was added and the temperature was allowed to rise slowly to 25°C. After 3h, the solvent was removed *in vacuo* and the residue was purified by chromatograpy on silica (CH_2Cl_2/ MeOH/ NH_3, 95:5:1 and 90:10:1) to give 70mg (62%). Treatment with HCl in methanol 3h at 50°C, removal of solvent *in vacuo* and chromatograpy on silica (CH_2Cl_2/ MeOH/ NH_3, 90:10:1 and 80:20:1) gave the free amine which was converted to the dihydrochloride salt 82. Mp: 192-200°C. IR (KBr) (cm-1): 3939(br), 3184(br), 2700(br), 1665, 1610, 1565, 1426. MS (amine): 295, 250, 210, 165, 152. ^{1}H NMR: (amine, CD_3OD): δ = 7.96 -7.22 (m, 9H, Ar-H), 4.93 (s, 2H, NH), 4.40 (s, 1H, Ar_2CH), 2.94 + 2.46 (2m, 8H, piperazine-H). Anal. calc. for $C_{18}H_{21}N_3O$ x2HCl x1.1H_2O, C:55.70, H:6.54, N:10.83. Found C:55.83, H:6.76, N:10.75.

Example 46

Preparation of 4-((1-piperazinyl)-benzyl)-N-ethylbenzamide hydrochloride (compound 83)

The compound of this Example was prepared by following the synthesis procedure as described for compound 82, but substituting ammonia for ethylamine.

Mp: 180-85°C. IR (KBr) (cm-1): 3331(br), 2700(br), 1640, 1545, 1440, 1308. MS: (EI, amine) 323, 278, 267, 238, 195, 165. ^{1}H NMR: (amine, CD_3OD): δ = 7.84 -7.14 (m, 9H, Ar-H), 4.9 (br. s, NH), 4.45 (s, 1H, Ar_2CH), 3.40 (m, 2H, ethyl-CH_2), 3.25, 2.65 (2m, 8H, piperazine-H), 1.20 (m, 3H, ethyl-Me).

Example 47

Preparation of 4-(1-piperazinyl-benzyl)-benzonitril dihydrochloride (compound 84)

Compound 82 (45mg, 0.11mol) was dissolved in dry THF (2mL) and cooled to 0°C. Pyridine (36µL, 0.44mg) and trifluoroacetic anhydride (31µL, 0.22mmol) was added and stirring was continued for 1h at 25°C. Water was added and the solution was extracted with ethyl acetate. The organic phase was washed with dilute $NaHCO_3$ (aq), dried (K_2CO_3) and evaporated *in vacuo*. The residue was treated with HCl in methanol 3h at 50°C. Removal of solvent *in vacuo* and chromatograpy on silica (CH_2Cl_2/ MeOH/ NH_3, 90:10:1) of residue gave 15mg (49%). Treatment with excess HCl in ether/ methanol gave the dihydrochloride compound 84 which was precipitated, dissolved in water and freezedried. Mp: 141-45°C. IR (KBr) (cm-1): 3400(br), 2700(br), 2230, 1434. MS (free amine): 277, 232, 192, 165. ^{1}H NMR: (free amine, $CDCl_3$): δ = 7.58-7.18 (m, 9H, Ar-H), 4.27 (s, 1H, $CHAr_2$) 2.89, 2.35 (2m, 8H, piperazine-H), 1.70 (s, NH). Anal. calc. for $C_{18}H_{19}N_3x2HCl$ x$1H_2O$, C:58.70, H: 6.29, N: 11.41. Found C: 58.88, H: 6.46, N: 11.24.

Example 48

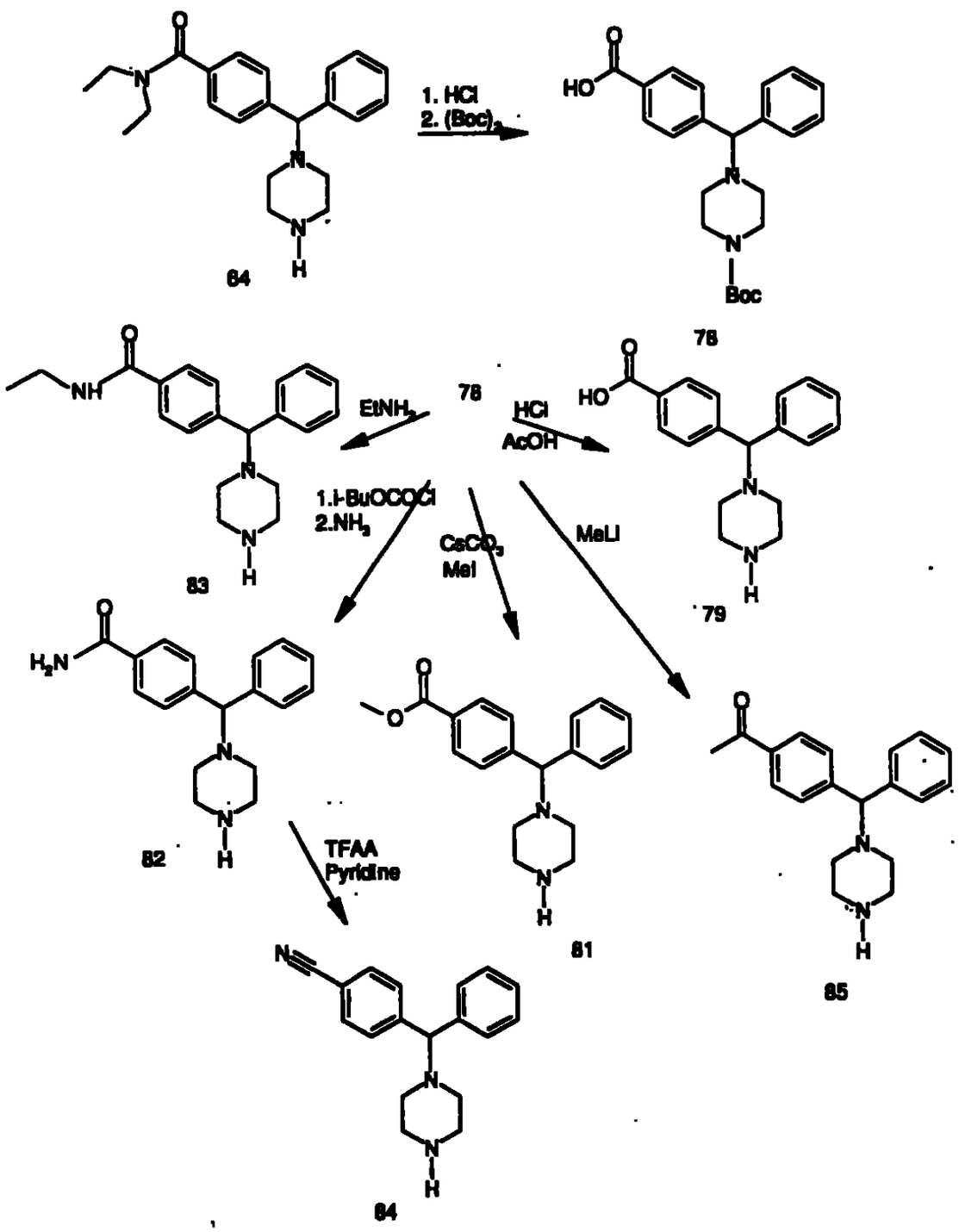
Preparation of 4-(1-piperazinyl-benzyl)-acetophenone dihydrochloride (compound 85)

Compound 78 (0.20g, 0.50mmol) was dissolved in dry THF (5mL) and cooled to 0°C under nitrogen. Methyl lithium (3.1mL, 0.8M in ether, 2.5mmol) was added during 1 min and stirring was continued for 2h. Chlorotrimethylsilane (0.63mL, 5.0mmol) was added and the temperature was allowed to reach 25°C, then ammonium chloride (aq) was added. The organic phase was decanted off, evaporated and the residue purified by chromatography on silica (CH_2Cl_2/ MeOH/ NH_3, 95:5:1) to give 0.11g (75%) of ketone without Boc-group. The dihydrochloride salt, compound 85 was prepared by treatment with excess HCl in ether. Mp: 175-85°C. IR (KBr) (cm-1): 3400(br), 2700(br), 1680, 1607, 1424, 1269. MS (EI, free amine): 294, 249, 209, 165. ^{1}H NMR: (free amine, $CDCl_3$): δ = 7.77-7.04 (m, 9H,

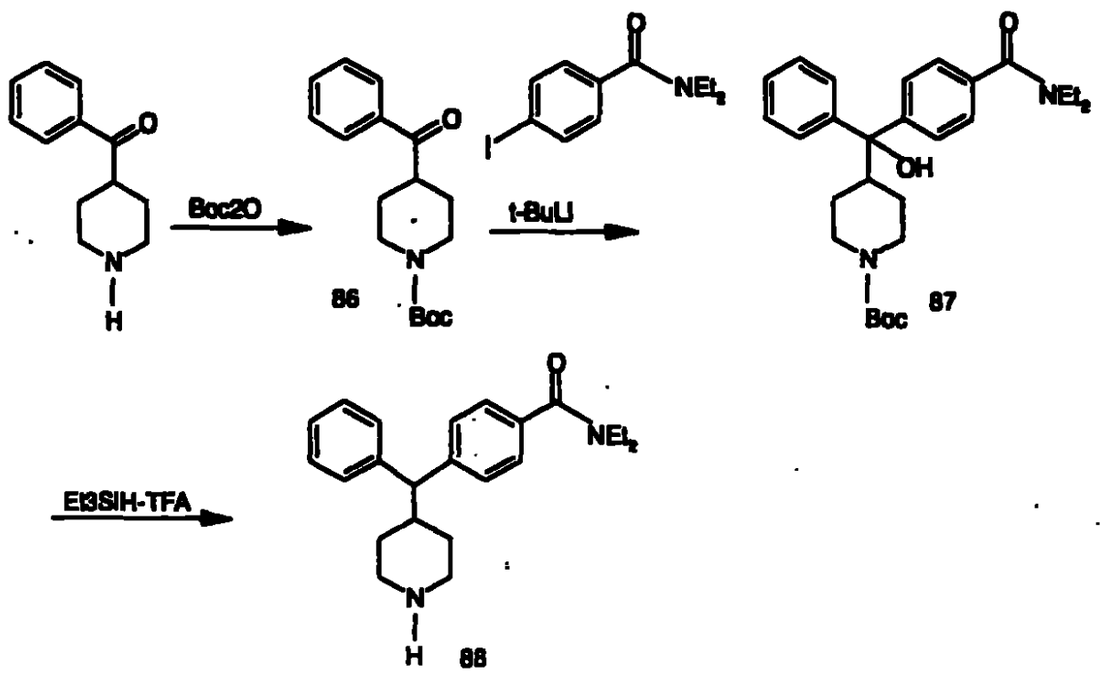
Ar-H), 4.22 (s, 1H, $CHAr_2$), 2.92 (m, 4H, piperazine-H), 2.43 (s, 3H, MeCO), 2.40 (m, 4H, piperazine-H).

Anal. calc. for $C_{19}H_{22}N_2O$ x2HCl x1.6 H_2O, C: 57.61, H: 6.92, N: 7.07. Found C: 57.54, H: 6.75, N: 6.91.

Scheme 14


1. HCl
2. (Boc)2O
64
78
Boc
EtNH2
78
HCl
AcOH
1.i-BuOCOCl
2.NH3
CsCO3
MeI
MeLi
83
79
82
81
85
TFAA
Pyridine
84

Scheme 15



The compounds according to Example 49 were synthesized as shown in Scheme 15 above.

I.

I. Preparation of 4-benzoyl-N-t-butoxylcarbonylpiperidine (compound 86)

A mixture of 4-benzoylpiperidine hydrochloride (6.77 g, 30.0 mmol), di-tert-butyldicarbonate (7.2 g, 33.0 mmol) and $KHCO_3$ (6.0 g, 60 mmol) in H_2O-THF (50/20 mL) was refluxed for 1h. The reaction mixture was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$. Removal of solvents gave 4-benzoyl-N-t-butoxylcarbonyl-piperidine (8.54 g, 98 %); δ_H (400 MHz, $CDCl_3$) 1.47 (s, 9H), 1.70 (m, 2H), 1.83 (m, 2H), 2.91 (m, 2H), 3.42 (m, 2H), 4.18 (brs, 2H), 7.46 (m, 2H), 7.56 (m, 1H), 7.93 (m, 2H).

II. Preparation 4-(α-Hydroxy-α-(4-N-t-butoxycarbonylpiperidinyl)-benzyl)-N,N-diethylbenzamide (compound 87)

To a solution of 4-iodo-N,N-diethylbenzamide (3.03 g, 10.0 mmol) and TMEDA (1.28 g, 11.0 mmol) in dry THF (30 mL) was added t-butyllithium (10.0 mL, 1.7 M, 17.0 mmol) at -78°C. After 10 min, 4-benzoyl-N-t-butoxylcarbonylpiperidine (2.89 g, 10.0 mmol) in THF (5 mL) was dropwise added. The reaction mixture was warmed to r.t. and then quenched with aqueous NH_4Cl solution and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$. Removal of solvents gave a crude product, which was purified by silica gel column eluting with MeOH-CH_2Cl_2 (0 : 100 → 2 : 98) to provide 4-(α-hydroxy-α-(4-N-t-butoxylcarbonylpiperidinyl)-benzyl)-N,N-diethylbenzamide (MTL 0327, 2.60 g, 56%): m.p.: 100-103°C (CH_2Cl_2): ν_{max} (KBr) cm^{-1} 3426, 2973, 1687, 1618, 1428, 1289, 1168; δ_H (400 MHz, $CDCl_3$) 1.08 (brs, 3H), 1.20 (brs, 3H), 1.30 (m, 4H), 1.41 (s, 9H), 2.50 (t, J=11.2 Hz, 1H). 2.66 (m, 2H), 2.86 (s, OH), 3.22 (brs, 2H), 3.50 (brs, 2H), 4.09 (brs, 2H), 7.18 (m, 1H), 7.26 (m, 4H), 7.45 (m, 4H); δ_{C-13} (100 MHz, $CDCl_3$) 12.8, 14.1, 26.2, 28.3, 39.1, 43.2, 44.3, 53.3, 79.2, 79.4, 125.75, 125.79, 126.2, 126.6, 128.1, 135.1, 145.3, 146.8, 154.6, 171.0.

Example 49

Preparation 4-((α-4-piperidinyl)-benzyl)-N,N-diethylbenzamide (compound 88)

To a solution of 4-(α-hydroxy-α-(4-N-t-butoxylcarbonylpiperidinyl)-benzyl)-N,N-diethylbenzamide (466 mg, 1.0 mmol) and triethylsilane (232 mg, 2.0 mmol) in dry dichloromethane (10 mL) was added trifluoroacetic acid (10.0 mL) at r.t. After 30 min at r.t., more triethylsilane (232 mg, 2.0 mmol) was added. The reaction mixture was stirred for 14 h at r.t., and then condensed. The residue was dissolved in AcOEt (100 ml). The resulting solution was washed with 1 N NaOH solution, aqueous NH_4Cl solution and brine, dried over $MgSO_4$. Removal of solvents gave a crude product, which was purified by silica gel column eluting with NH_4OH (1 N)-MeOH-CH_2Cl_2 (2.5 : 15 : 82.5) to provide 4-((α-4-

piperidinyl)-benzyl)-N,N-diethylbenzamide (245 mg, 70%): m.p.: 160-162°C (CH_2Cl_2); ν_{max} (KBr) cm^{-1} 3325, 2937, 1613, 1461, 1283, 1095; δ_H (400 MHz, $CDCl_3$) 1.05 (brs, 3H), 1.07 (m, 2H), 1.19 (brs, 3H), 1.53 (m, 2H), 2.04 (brs, NH), 2.20 (m, 1H), 2.55 (t, J=11.6 Hz, 2H) , 3.01 (m, 2H), 3.23 (brs, 2H), 3.51 (d, J=10.4 Hz, 1H), 3.52 (brs, 2H), 7.15 (m, 1H), 7.27 (m, 8H); δ_{C-13} (100 MHz, $CDCl_3$) 12.8, 14.1, 32.2, 39.0, 39.9, 43.1, 46.5, 59.0, 126.1, 126.5, 127.9, 128.0, 128.3, 134.8, 143.0, 144.7, 171.0.

Example 50

Preparation of N,N-Diethyl-4-(3-methoxybenzyl-1-piperazinyl)-benzamide

Procedure as for N,N-Diethyl-4-[(2,5,5-trimethyl-1-piperazinyl)-3-methoxybenzyl]-benzamide. N,N-Diethyl-4-(chloro-3-methoxybenzyl)-benzamide (1.6g, 4.8mmol) was reacted with piperazine (1.6g, 19mmol) in acetonitrile (20mL) for 4 h at 80 °C to give a total of 1.1g product (63%) which was converted into the dihydrochloride salt. Mp: 165-82 °C. IR (amine, $CDCl_3$ in KBr cell) (cm-1): 3688. 1611. 1458, 1436, 1285. MS(free amine): 381, 336, 296, 224, 196, 165, 152, 112. ^{1}H NMR: (amine, $CDCl_3$): δ = 1.05, 1.15 (2 br. s, 6H, 2Me), 2.51, 3.02 (2br. s, 8H, piperazine-H), 3.2, 3.45 (2 br. s, 4H, $MeCH_2$) 3.72, 3.73 (2s, 3H, MeO), 4.21 (s, 1H, $CHAr_2$), 4.5 (br. s. 1H. NH), 6.60- 7.40 (m, 8H, Ar-H). $C_{23}H_{31}N_3O_2$ x2HCl x0.80 H_2O requires: C: 58.92, H: 7.44, N: 8.96. Found: C: 58.98, H: 7.76, N: 8.86.

Example 51

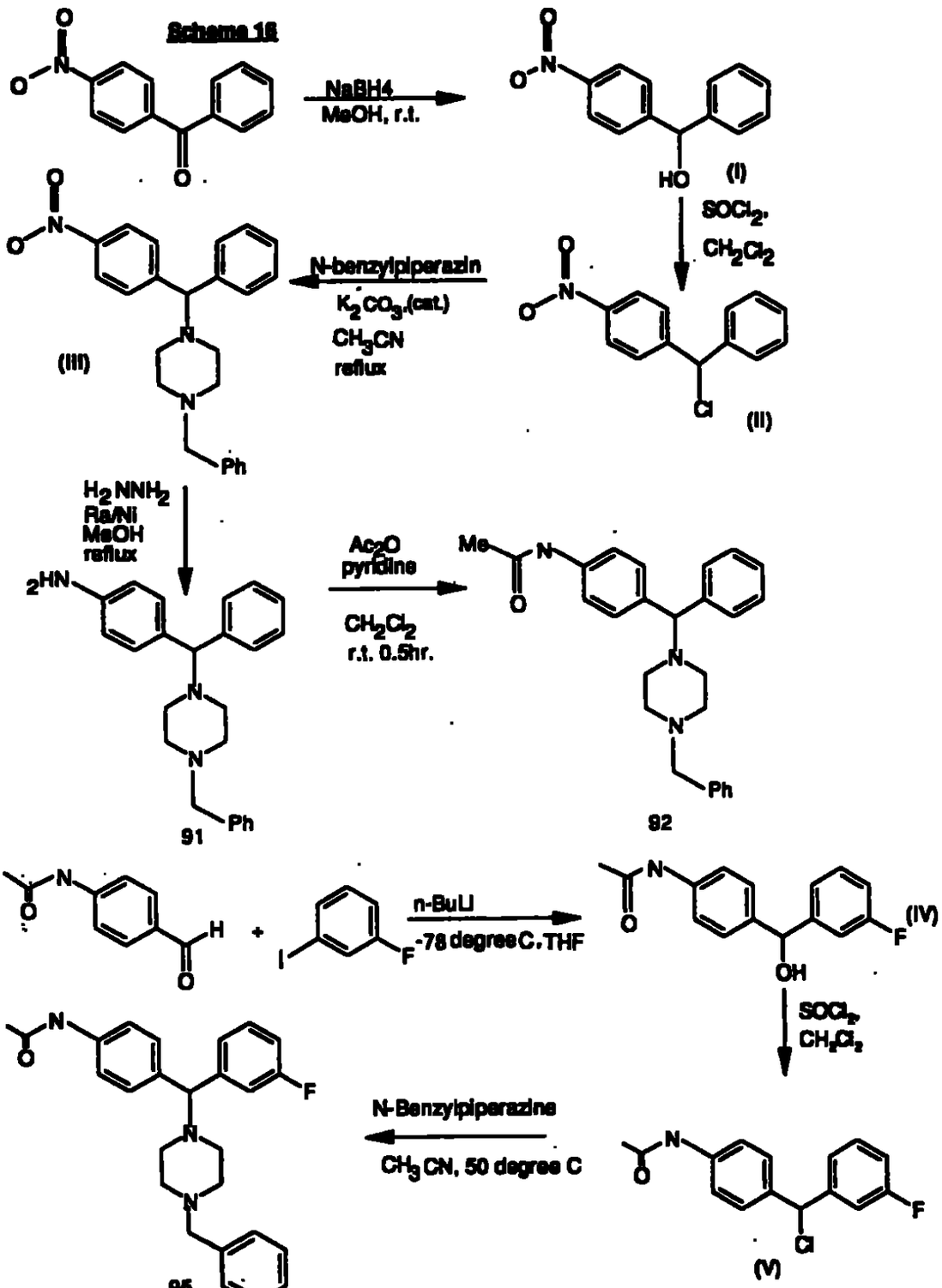
Preparation of N,N-Diethyl-4-[(4-allyl-1-piperazinyl)-3-methoxybenzyl]-benzamide

Procedure as for N,N-Diethyl-4-[(4-allyl-2,5,5-trimethyl-1-piperazinyl)-3-methoxybenzyl]-benzamide.

N,N-Diethyl-4-(3-methoxybenzyl-1-piperazinyl)-benzamide (0.16g, 0.42mmol) gave 30mg product (20%) which was converted to dihydrochloride salt. Mp: 151-76 °C. IR (amine,

$CDCl_3$ in KBr cell) (cm-1): 3688, 1611, 1457, 1435, 1288. MS(free amine): 421, 125. ^1H NMR: (amine, $CDCl_3$): δ =1.1 (2 br. s, 6H, 2Me), 2.3- 2.6 (br. s, 8H, piperazine-H), 3.00 (m, 2H, allyl-H), 3.2- 3.5 (2 br. s, 4H, $MeCH_2$), 3.78 (s, 3H, MeO), 4.20 (s, 1H, $CHAr_2$), 5.14 (m, 2H, allyl-H), 5.85 (m, 1H, allyl-H), 6.70-7.46 (m, 8H, Ar-H). $C_{26}H_{35}N_3O_2$ x2HCl x1.4 H_2O requires: C: 60.09, H: 7.72, N: 8.08. Found C: 60.12, H: 7.59, N: 7.88.

Scheme 16


NaBH4
MeOH, r.t.
(I)
SOCl2,
CH2Cl2
(II)
N-benzylpiperazin
K2CO3,(cat.)
CH3CN
reflux
(III)
H2NNH2
Ra/Ni
MeOH
reflux
Ac2O
pyridine
CH2Cl2
r.t. 0.5hr.
91
92
n-BuLi
-78 degree C, THF
(IV)
SOCl2,
CH2Cl2
N-Benzylpiperazine
CH3CN, 50 degree C
(V)
95
Ph

The compounds of Examples 52 - 55 were synthesized as shown in Scheme 16 above.

II.

Compound I: 4-(α-hydroxybenzyl)-nitrobenzene

4-nitrobenzoin (4.55g, 20.1mmol) was dissolved in 70ml of anhydrous methanol cooled down to 0°C in an ice bath, $NaBH_4$ (0.915g, 24.2mmol) was then added under N_2, the mixture was stirred at r.t., for overnight, quenched with NH_4Cl sat'd aqueous solution, MeOH was evaporated and EtOAc was added, the mixture was washed with water, the organic layer was dried over $MgSO_4$ and concentrated to give a solid as the desired product(~4.58g, ~100% yield).

^1H NMR ($CDCl_3$, TMS):δ(ppm): 2.40 (s, br, 1H, OH); 5.92 (d, *J*= 3.2Hz,1H, Ar-CH-OH); 7.30-7.40 (m, 5H, Ar); 7.58 (d, J=8.6. 2H, Ar-NO_2); 8.18 (d, *J*=8.6Hz, 2H, Ar-NO_2).

Compound II: 4-(α-chlorobenzyl)-nitrobenzene

Compound I (4.58g, 20mmol) was dissolved in anhydrous CH_2Cl_2, thionyl chloride (4.68g, 39.4mmol) was then added to the mixture under N_2, the reaction mixture was refluxed for 5 hr and was cooled down to r.t., the solvent and excess of thionyl chloride were evaporated under vacuum to give a yellowish solid as the desired product (~100%yield).

^1H NMR ($CDCl_3$, TMS):δ(ppm): 6.16 (s, 1H, -CH-Cl); 7.30-7.40 (m, 5H, Ar); 7.59 (d, *J*=8.6Hz, 2H, Ar-NO_2); 8.20 (d, *J*=8.6Hz, 2H, Ar-NO_2).

Compound III: 4-[(N-benzyl-1-piperazinyl)-benzyl]-nitrobenzene

To compound II (1.0g, 4.1mmol) and N-benzylpiperazine (1.45g, 8.2mmol) dissolved in anhydrous acetoniltrile, catalytic amount of potassium carbonate was added and the reaction mixture was then refluxed overnight. After cooling down to r.t., the mixture was washed with brine, the organic layer was concentrated under vacuum to give an oil, it was then

purified by MPLC using CH_2Cl_2/MeOH/NH_4OH=95/5/1 as the eluent to give the pure desired product (1.2g, 76% yield).

^1H NMR($CDCl_3$, TMS):δ: 2.41-2.48 (8H, br, piperazin ring), 3.51 (2H, s, Ph-CH_2), 4.34 (1H, s, Ar-C<u>H</u>-Ar), 7.20-8.12 (14H, Ar)ppm.

^{13}C NMR($CDCl_3$, TMS): δ: 51.7, 53.1, 62.9, 75.5, 123.8, 127.0, 128.1, 128.5, 128.7, 129.2, 137.9, 140.9, 146.8, 150.6ppm.

<u>Example 52</u>

<u>Preparation of 4-[(N-benzyl-1-piperazinyl)-benzyl]-aniline (compound 91)</u>

To compound III (900mg, 2.33mmol) dissolved in 10ml of MeOH, Ra-Ni (150mg) was added and the temperature was increased to 35°C, hydrazine (380mg, 11.63mmol) was then added slowly via a syringe while it was stirring, the temperature of the mixture was increased to 70°C, until the evolution of the gas seized, the reaction mixture was cooled down to r.t., filtered over celite and concentrated to give an oil, which was purified by MPLC using CH_2Cl_2/MeOH= 99/1—99/5 as the eluent to give a yellowish solid as the desired product (660mg, ~80%yield).

Elemental Analysis Calcd.for: $C_{24}H_{27}N_3.0.2H_2O$: C, 79.64; H, 7.43; N, 11.55. Found: C, 79.83; H, 7.65; N, 11.64.

IR (NaCl Film): ν =2807, 1620, 1513, 1451, 1282, 1137cm^{-1}.

^1H NMR(CDCl3, TMS):δ: 2.3-2.48 (8H, br, piperazine ring), 3.45 (2H, s, br, -NH_2), 3.48 (2H, s, Ph-CH_2), 4.10 (1H, s, Ar-C<u>H</u>-Ar), 6.51 (2H, m, Ar), 7.11-7.37 (12H, m, Ar)ppm.

<u>Example 53</u>

<u>Preparation of 4-[(N-benzyl-1-piperazinyl)-benzyl]-acetanilide (compound 92)</u>

To 4-[(N-benzyl-1-piperazinyl)-benzyl]-aniline (compound 91) (50mg, 0.14mmol) and anhydrous pyridine(excess) were dissolved in anhydrous dichloromethane, followed by the

addition of acetic anhydride (4eq.). The reaction mixture was stirred at r.t., for 30 min. and quenched by H_2O, then washed with sat'd $NaHCO_3$ aqueous solution and brine, the organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated to give an oil as the product (44mg, 80%yield).

^1H NMR: ($CDCl_3$, TMS) δ: 2.1(3H, s, -CH_3), 2.3-2.48 (8H, br, pipyrazin ring), 3.48 (2H, s, Ph-CH_2), 4.16 (1H, s, Ar-CH-Ar), 7.20-8.12 (14H, Ar)ppm.

Elemental Analysis Calcd.for: $C_{26}H_{29}N_3O$. 2.1HCl. 0.3H_2O: C, 64.83; H, 6.64; N, 8.40. Found: C, 64.86; H, 6.64; N, 8.73

Example 54

Preparation of 4-[(N-benzyl-1-piperazinyl)-benzyl]-methanesulfonamide

To 4-[(N-benzyl-1-piperazinyl)-benzyl]-aniline (compound 91) (100mg, 0.28mmol) and pyridine (excess) were dissolved in anhydrous dichloromethane (5 ml) followed by the addition of methanesufonic anhydride(97.55mg, 0.56mmol), the reaction mixture was stirred at rt. for 20 min. followed by TLC, then it was quenched by adding drop of water, 10 ml of EtOAc was added, the mixture was washed with saturated NH_4Cl aqueous solution and brine, the organic layer was dried over $MgSO_4$, concentrated and purified by MPLC using CH_2Cl_2/MeOH=99/1~95/5 as the solvent to give the pure product as a white solid (~90mg, ~70%yield).

Melting point: 195~200°C(dcp.)

^1H NMR: ($CDCl_3$, TMS) δ: 2.3-2.48 (8H, br, pipyrazin ring), 2.96 (3H, s, CH_3SO_2), 3.51 (2H, s, Ph-CH_2), 4.21 (1H, s, Ar-CH-Ar), 6.25 (1H, br, S-NH-), 7.10-7.41 (14H, m, Ar)ppm.

^{13}C NMR:($CDCl_3$) δ: 142.4, 140.2, 137.9, 135.3, 129.2, 129.1, 128.5, 128.1, 127.9, 127.0, 121.0, 75.5, 63.0, 53.2, 51.8, 39.3ppm.

Elemental analysis: Calcd.for: $C_{25}H_{29}N_3O_2S$. $0.9H_2O$: C, 66.46; H, 6.87; N, 9.30. Found: C, 66.53; H, 6.61; N, 9.23.

Example 55

Preparation of Methyl-N-4-[(N-benzyl-1-piperazinyl)-benzyl]-2-methylacetate

To 4-[(N-benzyl-1-piperazinyl)-benzyl]-aniline (compound 91) (100mg, 0.28mmol), Lithium hydride (2.5mg, 0.3mmol) and 1-bromomethylacetate (44.16mg, 0.28mmol) were mixed in anhydrous THF, the reaction mixture were refluxed for 2 hr. and cooled down to rt., then quenched with drops of water, washed with brine twice, dried over anhydrous $MgSO_4$ and concentrated to an oil, purified by MPLC using CH_2Cl_2/MeOH=98/2 as the solvent to give an oil as the product (~23mg, 20%).

IR (NaCl Film): HCl salt

$\bar{\nu}$=3404(br), 2922(br), 1745,1610, 1517, 1439, 1207cm^{-1}

^{1}H NMR: ($CDCl_3$) δ: 2.40 (8H, br, piperazine ring), 3.50 (2H, s, Ph-CH_2), 3.75 (3H, s, -O-CH_3), 3.85 (2H, d, *J*=5.2Hz, N-CH_2), 4.12 (1H, s, Ar-CH-Ar), 4.18 (1H, t, *J*=5.2Hz, Ar-NH-CH_2), 6.49 (2H, d, *J*=8.4Hz, -N-Ar), 7.14~7.38 (12H, m, Ar)ppm.

*Anal.*Calcd.for: $C_{27}H_{31}N_3O_2 \cdot 3HCl$: C, 60.17; H, 6.36; N, 7.80. Found: C, 59.97; H, 6.61; N, 7.46.

Compound IV: 4-(3-fluoro-α-hydroxybenzyl)-acetonitrile

To 1-Fluoro-3-iodo-benzene (7.53g, 33.9mmol) was dissolved in anhydrous THF and was cooled down to -78°C, n-Butyllithium (2.5M in THF, 33.9mmol) was added slowly into the reaction mixture via a syringe, the mixture was stirred for 10 min. followed by the addition of the solution of 4-Acetamidobenzaldehyde (1.84g, 11.3mmol) in 5ml of dry DME, the reaction mixture was then stirred at -78°C for 30 min. before quenched with NH_4Cl aqueous solution. The organic layer was washed with brine and dried over anhydrous $MgSO_4$, filtered and concentrated to an oil, purified by MPLC using 10% heptane in CH_2Cl_2 and 100%CH_2Cl_2 to give the pure product (1.65g, 56% yield).

^{1}H NMR: ($CDCl_3$) δ: 2.14 (3H, s, $OCCH_3$), 2.55 (1H, s, br, OH), 5.76 (1H, d, *J*=3.2Hz, Ar-CH-Ar), 7.35 (1H, s, CONH), 6.90~7.50 (8H, m, Ar)ppm.

Compound V: 4-(3-fluoro-α-chlorobenzyl)-acetonitrile

This was prepared using the same method as described for the preparation of compound (II) but using compound (IV). It was used directly for the next step reaction without purification.

^{1}H NMR: ($CDCl_3$) δ: 2.15 (3H, s, $OCCH_3$), 6.10 (1H, s, Ar-CH-Ar), 7.84 (1H, s, CONH), 6.90~7.6 (8H, m, Ar), 7.84 (1H, s, CONH)ppm.

Example 56

Preparation of 4-[(N-benzyl-1-piperazinyl)-3-fluorobenzyl]-acetanilide (compound 95)

This was prepared using the same method as described for the preparation of compound (III) but using compound (V).

^{1}H NMR: ($CDCl_3$) δ: 2.14 (3H, s, $OCCH_3$), 2.40 (8H, br, piperazine), 3.51 (2H, s, Ph-CH_2), 4.19 (1H, s, Ar-CH-Ar), 6.80–7.40 (13H, m, Ar)ppm.

ANALYSIS:

*Anal.*Calcd.for: $C_{36}H_{38}FN_3O \cdot 2HCl \cdot 1.6CH_2Cl_2 \cdot 2H_2O$: C, 56.24; H, 6.02; N, 7.13. Found: C, 56.29; H, 6.10; N, 6.88.

Pharmaceutical compositions

The novel compounds according to the present invention may be administered per orally, intramuscularly, subcutaneously, intraperitoneally, intrathoracially, intravenously, intrathecally and intracerebroventricularly.

The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level at the most appropriate for a particular patient.

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the

necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized molds and allowed to cool and solidify.

Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

Pharmaceutically acceptable salts are acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium acetate, camsylate, carbonate, chloride, cetrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, glucaptate, gluconate. glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannata, tartrate, teoclate, triethiodide, benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminium, calcium, lithium, magnesium, potassium, sodium, and zinc.

Preferred pharmaceutically acceptable salts are the hydrochlorides and citrates.

The term composition is intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid from compositions include solutions, suspensions, and emulsions. Sterile water or water-propylene glycol solutions of the active compounds may be mentioned as an example of liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Preferably the pharmaceutical compositions is in unit dosage form. In such form, the composition is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparations, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

Biological evaluation

A) *IN VITRO* MODEL

Cell culture

Human 293S cells expressing cloned human μ, δ, and κ receptors and neomycin resistance were grown in suspension at 37°C and 5% CO_2 in shaker flasks containing calcium-free DMEM10% FBS, 5% BCS, 0.1% Pluronic F-68, and 600 μg/ml geneticin.

Membrane preparation

Cells were pelleted and resuspended in lysis buffer (50 mM Tris, pH 7.0, 2.5 mM EDTA, with PMSF added just prior to use to 0.1 mM from a 0.1 M stock in ethanol), incubated on ice for 15 min, then homogenized with a polytron for 30 sec. The suspension was spun at 1000g (max) for 10 min at 4°C. The supernatant was saved on ice and the pellets resuspended and spun as before. The supernatants from both spins were combined and spun at 46,000 g(max) for 30 min. The pellets were resuspended in cold Tris buffer (50 mM Tris/Cl, pH 7.0) and spun again. The final pellets were resuspended in membrane buffer (50 mM Tris, 0.32 M sucrose, pH 7.0). Aliquots (1 ml) in polypropylene tubes were frozen in dry ice/ethanol and stored at -70°C until use. The protein concentrations were determined by a modified Lowry assay with SDS.

Binding assays

Membranes were thawed at 37°C, cooled on ice, passed 3 times through a 25-gauge needle, and diluted into binding buffer (50 mM Tris, 3 mM $MgCl_2$, 1 mg/ml BSA (Sigma A-7888), pH 7.4, which was stored at 4°C after filtration through a 0.22 m filter, and to which had been freshly added 5 μg/ml aprotinin, 10 μM bestatin, 10 μM diprotin A, no DTT). Aliquots of 100 μl (for μg protein, see Table 1) were added to iced 12x75 mm polypropylene tubes containing 100 μl of the appropriate radioligand (see Table 1) and 100

µl of test peptides at various concentrations. Total (TB) and nonspecific (NS) binding were determined in the absence and presence of 10 µM naloxone respectively. The tubes were vortexed and incubated at 25°C for 60-75 min, after which time the contents are rapidly vacuum-filtered and washed with about 12 ml/tube iced wash buffer (50 mM Tris, pH 7.0, 3 mM $MgCl_2$) through GF/B filters (Whatman) presoaked for at least 2h in 0.1% polyethyleneimine. The radioactivity (dpm) retained on the filters was measured with a beta counter after soaking the filters for at least 12h in minivials containing 6-7 ml scintillation fluid. If the assay is set up in 96-place deep well plates, the filtration is over 96-place PEI-soaked unifilters, which were washed with 3 x 1 ml wash buffer, and dried in an oven at 55°C for 2h. The filter plates were counted in a TopCount (Packard) after adding 50 µl MS-20 scintillation fluid/well.

Data analysis

The specific binding (SB) was calculated as TB-NS, and the SB in the presence of various test peptides was expressed as percentage of control SB. Values of IC_{50} and Hill coefficient (n_H) for ligands in displacing specifically bound radioligand were calculated from logit plots or curve fitting programs such as Ligand, GraphPad Prism, SigmaPlot, or ReceptorFit. Values of K_i were calculated from the Cheng-Prussoff equation. Mean ± S.E.M. values of IC_{50}, K_i and n_H were reported for ligands tested in at least three displacement curves.

Receptor saturation experiments

Radioligand K_S values were determined by performing the binding assays on cell membranes with the appropriate radioligands at concentrations ranging from 0.2 to 5 times the estimated K_S (up to 10 times if amounts of radioligand required are feasable). The specific radioligand binding was expressed as pmole/mg membrane protein. Values of K_S and B_{max} from individual experiments were obtained from nonlinear fits of specifically bound (B) vs. nM free (F) radioligand from individual according to a one-site model.

B) BIOLOGICAL MODEL (*IN VIVO* MODEL)

FREUND'S COMPLETE ADJUVANT (FCA), AND SCIATIC NERVE CUFF INDUCED MECHANO-ALLODYNIA IN RAT

Animals

Male Sprague-Dawley rats (Charles River, St-Constant, Canada) weighing 175-200g at the time of surgery were used. They were housed in groups of three in rooms thermostatically maintained at 20° C with a 12:12 hr light/dark cycle, and with free access to food and water. After arrival, the animals were allowed to acclimatize for at least 2 days before surgery. The experiments were approved by the appropriate Medical Ethical Committee for animal studies.

EXPERIMENTAL PROCEDURE

FREUND'S COMPLETE ADJUVANT

The rats were first anesthetized in a Halothane chamber after which 10µl of FCA was injected s.c. into the dorsal region of the left foot, between the second and third external digits. The animals were then allowed to recover from anesthesia under observation in their home cage.

SCIATIC NERVE CUFF

The animals were prepared according to the method described by Mosconi and Kruger (1996). Rats were anesthetized with a mixture of Ketamine / Xylazine i.p. (2ml/kg) and placed on their right side and an incision made over, and along the axis of, the lateral aspect of the left femur. The muscles of the upper quadriceps were teased apart to reveal the sciatic nerve on which a plastic cuff (PE-60 tubing, 2mm long) was placed around. The wound was then closed in two layers with 3-0 vicryl and silk sutures.

DETERMINATION OF MECHANO-ALLODYNIA USING VON FREY TESTING

Testing was performed between 08:00 and 16:00h using the method described by Chaplan et al. (1994). Rats were placed in Plexiglas cages on top of a wire mesh bottom which allowed access to the paw, and were left to habituate for 10-15 min. The area tested was the mid-plantar left hind paw, avoiding the less sensitive foot pads. The paw was touched with a series of 8 Von Frey hairs with logarithmically incremental stiffness (0.41, 0.69, 1.20, 2.04, 3.63, 5.50, 8.51, and 15.14 grams; Stoelting, Ill, USA). The von Frey hair was applied from underneath the mesh floor perpendicular to the plantar surface with sufficient force to cause a slight buckling against the paw, and held for approximately 6-8 seconds. A positive response was noted if the paw was sharply withdrawn. Flinching immediately upon removal of the hair was also considered a positive response. Ambulation was considered an ambiguous response, and in such cases the stimulus was repeated.

TESTING PROTOCOL

The animals were tested on postoperative day 1 for the FCA-treated group and on post-operative day 7 for the Sciatic Nerve Cuff group. The 50% withdrawal threshold was determined using the up-down method of Dixon (1980). Testing was started with the 2.04 g hair, in the middle of the series. Stimuli were always presented in a consecutive way, whether ascending or descending. In the absence of a paw withdrawal response to the initially selected hair, a stronger stimulus was presented; in the event of paw withdrawal, the next weaker stimulus was chosen. Optimal threshold calculation by this method requires 6 responses in the immediate vicinity of the 50% threshold, and counting of these 6 responses began when the first change in response occurred, e.g. the threshold was first crossed. In cases where thresholds fell outside the range of stimuli, values of 15.14 (normal sensitivity) or 0.41 (maximally allodynic) were respectively assigned. The resulting pattern of positive and negative responses was tabulated using the convention, X = no withdrawal; = withdrawal, and the 50% withdrawal threshold was interpolated using the formula:

$$50\%\ g\ threshold = 10^{(Xf+k\delta)} / 10{,}000$$

where Xf = value of the last von Frey hair used (log units); k = tabular value (from Chaplan et al. (1994)) for the pattern of positive / negative responses; and δ = mean difference between stimuli (log units). Here $\delta = 0.224$.

Von Frey thresholds were converted to percent of maximum possible effect (MPE), according to Chaplan et al. 1994. The following equation was used to compute % MPE:

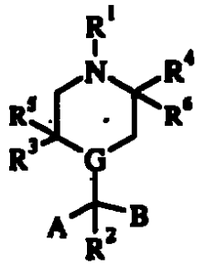
$$\% \text{ MPE} = \frac{\text{Drug treated threshold (g) - allodynia threshold (g)}}{\text{Control threshold (g) - allodynia threshold (g)}} \times 100$$

ADMINISTRATION OF TEST SUBSTANCE

Rats were injected (subcutaneously, intraperitoneally, or orally) with a test substance prior to von Frey testing, the time between administration of test compound and the von Frey test varied depending upon the nature of the test compound.

Claims

1. A compound of the general formula (I)



(I)

wherein

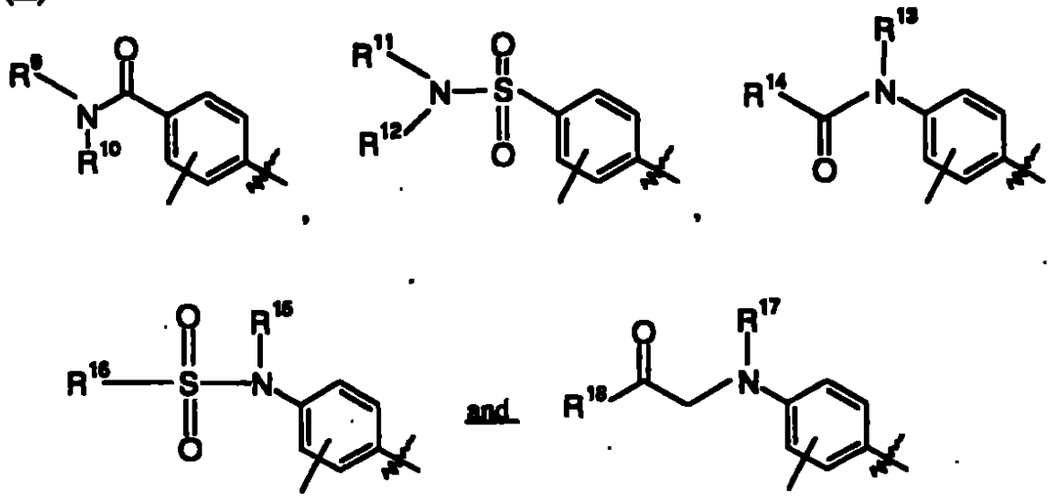
G is a carbon atom or a nitrogen atom;

A is selected from

(i) phenyl substituted by any of -COOH. - $CONH_2$, $COOCH_3$, -CN, NH_2 or $-COCH_3$;

(ii) naphtyl, benzofuranyl, and quinolinyl; and

(iii)



and

wherein the phenyl ring of each A substituent may be optionally and independently substituted by 1 or 2 substituents selected from hydrogen, CH_3, $(CH_2)_oCF_3$, halogen, $CONR^7R^8$, CO_2R^7, COR^7, $(CH_2)_oNR^7R^8$, $(CH_2)_oCH_3(CH_2)_oSOR^7$, $(CH_2)_oSO_2R^7$ and $(CH_2)_oSO_2NR^7R^8$ wherein o is 0, 1, or 2. and R^7 and R^8 are as defined below;

R^1 is selected from hydrogen; a branched or straight C_1-C_6 alkyl, C_1-C_6 alkenyl, -$CO(C_1$-C_6 alkyl); (C_1-C_6 alkyl)-B wherein B is as defined below; C_3-C_8 cycloalkyl, C_4-C_8 (alkyl-cycloalkyl) wherein alkyl is C_1-C_2 alkyl and cycloalkyl is C_3-C_6 cycloalkyl; C_6-C_{10} aryl; and heteroaryl having from 5 - 10 atoms selected from any of C, S, N and O; and whereby the C_6-C_{10} aryl and the heteroaryl may optionally be substituted by 1 or 2 substituents selected from hydrogen, CH_3, $(CH_2)_oCF_3$, halogen, $CONR^7R^8$, CO_2R^7, COR^7, $(CH_2)_oNR^7R^8$, $(CH_2)_oCH_3(CH_2)_oSOR^7$, $(CH_2)_oSO_2R^7$ and $(CH_2)_oSO_2NR^7R^8$; wherein o is 0, 1, or 2, and R^7 and R^8 are as defined below;

R^7 and R^8 is each and independently as defined for R^1 above;

R^2 is selected from hydrogen, CH_3, OR^1, CO_2R^1, and $CH_2CO_2R^1$ wherein R^1 is as defined above;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18}, is each and independently as defined for R1 above;

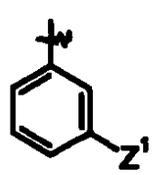
B is a substituted or unsubstituted aromatic; an optionally substituted C_5-C_{10} hydroaromatic; a heteroaromatic or a heterohydroaromatic moiety, each having from 5 to 10 atoms selected from any of C, S, N and O, and each being optionally substituted by 1 or 2 substituents independently selected from hydrogen, CH_3, CF_3, halogen, $(CH_2)_pCONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pCOR^7$, $(CH_2)_pCO_2R^7$, OR^7, $(CH_2)_pSOR^7$, $(CH_2)_pSO_2R^7$, and $(CH_2)_pSO_2NR^7R^8$;

wherein p is 0, 1, 2 or 3 and wherein R^7 and R^8 are as defined above;

R^3, R^4, R^5 and R^6 is each and independently selected from R^7, $(CH_2)_pCONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pCONR^7R^8$, $(CH_2)_pCO_2R^7$, $(CH_2)_pPh$, $(CH_2)_p$(p-OH Ph), $(CH_2)_p$-3-indolyl, $(CH_2)_pSR^7$, and $(CH_2)_pOR^7$;
wherein p is 0, 1, 2, 3, or 4, and R^7 and R^8 are as defined above;

as well as pharmaceutically acceptable salts of the compounds of the formula (I), isomers, hydrates, isoforms and prodrugs thereof;

with the proviso that when A is a phenyl ring substituted by a -CN group or by a $-NH_2$ group, B may not be



wherein

Z^1 is hydroxy, and esters thereof;

hydroxymethyl, and esters thereof; or

amino, and carboxamides and sulfonamides..

2. A compound of the formula I according to claim 1, wherein

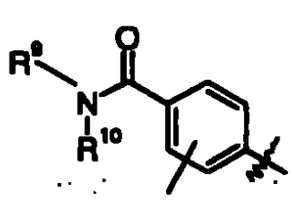
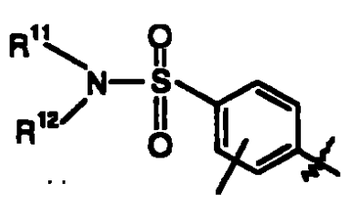
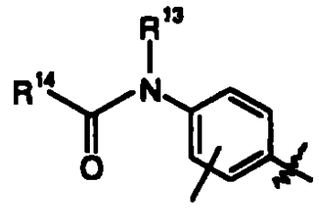
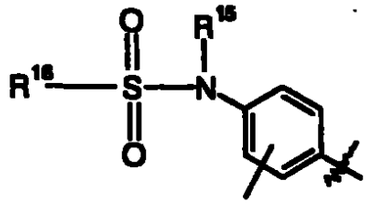
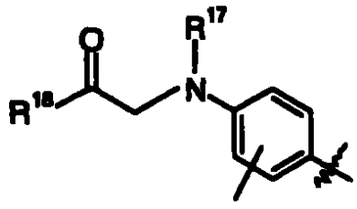
G is a carbon atom or a nitrogen atom;

A is selected from

(i) phenyl substituted by any of -COOH, - $CONH_2$, $COOCH_3$, -CN, NH_2 or -$COCH_3$;

(ii) naphtyl, benzofuranyl, and quinolinyl; and

(iii)





and


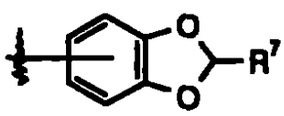
wherein the phenyl ring of each A substituent may be optionally and independently substituted by 1 or 2 substituents selected from hydrogen, CH_3, $(CH_2)_oCF_3$, halogen, $CONR^7R^8$, CO_2R^7, COR^7, $(CH_2)_oNR^7R^8$, $(CH_2)_oCH_3(CH_2)_oSOR^7$, $(CH_2)_oSO_2R^7$ and $(CH_2)_oSO_2NR^7R^8$, wherein o is 0, 1, or 2, and R^7 and R^8 are as defined below;

R^1, R^7 and R^8 is each and independently selected from hydrogen; a branched or straight C_1-C_4 alkyl, allyl, -CO-(C_1-C_6 alkyl); (C_1-C_6 alkyl)-B wherein B is as defined below; C_3-C_5 cycloalkyl, C_4-C_8 (alkyl-cycloalkyl) wherein alkyl is C_1-C_2 alkyl and cycloalkyl is C_3-C_6 cycloalkyl; and phenyl;

R^2 is hydrogen, methyl, or OR^1 wherein R^1 is as defined above;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18}, is each and independently as defined for R^1 above;

B is selected from phenyl, naphthyl, indolyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl, pyrryl, furanyl, quinolinyl, isoquinolinyl, cyclohexyl, cyclohexenyl, cyclopentyl, cyclopentenyl, indanyl, indenyl, tetrahydronaphthyl, tetrahydroquinyl, tetrahydroisoquinolinyl, tetrahydrofuranyl, pyrrolidinyl, indazolinyl, and

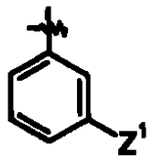


;

each B group being optionally substituted by 1-2 substituents independently selected from hydrogen, CH_3, CF_3, halogen, $(CH_2)_pCONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pCOR^7$, $(CH_2)_pCO_2R^7$, and OR^7,
wherein p is 0 or 1, and wherein R^7 and R^8 are as defined above; and

R^3, R^4, R^5 and R^6 is each and independently selected from hydrogen, CH_3, $CH(Me)_2$, $CH_2CH(Me)_2$, $CH(Me)CH_2CH_3$ $(CH_2)_pCONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pCONR^7R^8$, $(CH_2)_pCO_2R^7$, $(CH_2)_pPh$, $(CH_2)_p$(p-OH Ph), $(CH_2)_p$-3-indolyl, $(CH_2)_pSR^7$, and $(CH_2)_pOR^7$, wherein p is 0, 1, 2, or 3, and wherein R^7 and R^8 are as defined above;

with the proviso that when A is a phenyl ring substituted by a -CN group or by a $-NH_2$ group, B may not be



wherein

Z^1 is hydroxy, and esters thereof;

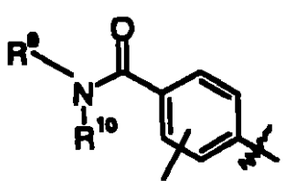
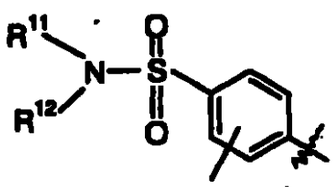
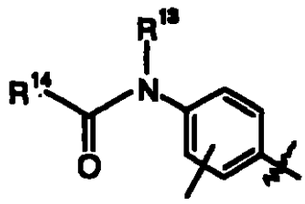
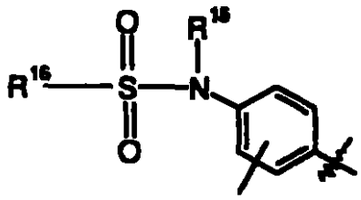
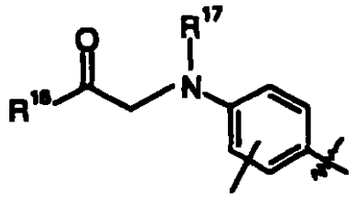
hydroxymethyl, and esters thereof; or

amino, and carboxamides and sulfonamides.

3. A compound of the formula I according to claim 1, wherein

G is a nitrogen atom;

A is selected from





and


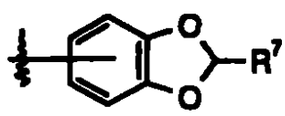
wherein

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18} is each an ethyl group;

R^1 is selected from hydrogen, methyl, ethyl, allyl, or CH_2-cyclopropyl;

R^2 is H, methyl, or OR^1;

B is selected from phenyl, naphthyl, indolyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl, furanyl, quinolinyl, isoquinolinyl, cyclohexyl, cyclohexenyl, cyclopentyl, cyclopentenyl, indanyl, indenyl, tetrahydronaphthyl, tetrahydroquinyl, tetrahydroisoquinolinyl, tetrahydrofuranyl, indazolinyl, and



each B group being optionally substituted by 1-2 substituents independently selected from hydrogen, methyl, CF_3, halogen, $(CH_2)_pCONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pCOR^7$, $(CH_2)_pCO_2R^7$, and OR^7,

wherein p is 0, 1, or 2, and wherein R^7 and R^8 are as defined for R^1 above;

R^3, R^4, R^5 and R^6 is each and independently selected from H, CH_3, $CH(Me)_2$, $CH_2CH(Me)_2$, $CH(Me)CH_2CH_3$ $(CH_2)_pCONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pCONR^7R^8$, $(CH_2)_pCO_2R^7$, $(CH_2)_pPh$, $(CH_2)_p$(p-OH Ph), $(CH_2)_p$-3-indolyl, $(CH_2)_pSR^7$, and $(CH_2)_pOR^7$

wherein p is 0, 1 or 2, and wherein R^7 and R^8 are as defined above.

4. A compound of the formula (I) of claim 1 above, being anyone of

(±)-trans-1-(3-methoxy-α-(1-naphthyl)benzyl)-2,5-dimethylpiperazine (compound 3);
(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-1-naphthyl)anisole (compound 4 and 5);
(±)-trans-1-(3-methoxy-α-(2-naphthyl)benzyl)-2,5-dimethylpiperazine (compound 8);
(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-2-naphthyl)anisole (compound 9 and 10);
(±)-trans-1-(3-methoxy-α-(2'-benzofuranyl)benzyl)-2,5-dimethylpiperazine (compound 13);
(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-2-benzofuranyl)anisole (compound 14 and 15);
(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Cyclopropylmethyl-2,5-dimethyl-1-piperazinyl)-2-benzofuranyl)anisole (compound 16 and 17);
(±)-trans-1-(3-methoxy-α-(6'-quinolinyl)benzyl)-2,5-dimethylpiperazine (compound 20 and 21);
(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-6-quinolinyl)anisole (compound 22);
(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-6-quinolinyl)anisole (compound 23);
(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Cyclopropylmethyl-2,5-dimethyl-1-piperazinyl)-6-quinolinyl)anisole (compound 24 and 25);
(±)-trans-1-(3-methoxy-α-(4-quinolinyl)benzyl)-2,5-dimethyl-piperazine (compound 28);
(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-4-quinolinyl)anisole (compound 29 and 30);
(±) 4-((α-(1-Piperazinyl))-4-chlorobenzyl)-N,N-diethylbenzamide (compound 33);
(±) 4-((α-((4-Allyl)-1-piperazinyl))-4-chlorobenzyl)-N,N-diethylbenzamide • 2hcl (compound 34);
(±) 4-((α-(1-Piperazinyl))-2-naphtylmethyl)-N,N-diethylbenzamide (compound 37);
(±) 4-((α-((4-Allyl)-1-piperazinyl))-2-naphtylmethyl)-N,N-diethylbenzamide (compound 38);

(±) 4-((α-(1-Piperazinyl))-4-xylyl)-N,N-diethylbenzamide (compound 41);

(±) 4-((α-((4-Allyl)-1-piperazinyl))-4-xylyl)-N,N-diethylbenzamide • 2HCl (compound 42);

(±) 4-((α-(1-Piperazinyl))-3-xylyl)-N,N-diethylbenzamide • 2HCl (compound 45);

(±) 4-((α-(1-Piperazinyl))-cyclohexylmethyl)-N,N-diethylbenzamide (compound 48);

(±) 4-((α-(1-Piperazinyl))-3,4-dimethylbenzyl)-N,N-diethylbenzamide (compound 51);

(±) 4-((α-(1-Piperazinyl))-1-naphtylmethyl)-N,N-diethylbenzamide (compound 54);

4-(4-(2-Dimethyl-5-methyl-piperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide dihdrochloride (compound 57);

4-(4-(1-Allyl-2-dimethyl-5-methyl-piperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide dihydrochloride (compound 58);

4-(1-(4-Allyl-2-dimethyl-5-methyl-piperazinyl)-3-methoxybenzyl)- N,N-diethylbenzamide dihydrochloride (compound 60);

4-(1-(2-dimethyl-5-methyl-piperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide dihydrochloride (compound 61);

4-((1-piperazinyl)-benzyl)- N,N-diethylbenzamide dihydrochloride (compound 64);

4-((4-Allyl-1-piperazinyl)-benzyl)-N,N-diethylbenzamide dihydrochloride (compound 65);

4-((4-Acetyl-1-piperazinyl)-benzyl)- N,N-diethylbenzamide hydrochloride (compound 77);

4-(4-(2-Hydroxymethyl-5-methyl)piperazinyl-benzyl)-N,N-diethyl-benzamide dihydrochloride (compound 69);

4-((4-(2-Hydroxymethyl-5-methyl)piperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide dihydrochloride (compound 70);

4-((4-(1-Allyl-2-hydroxymethyl-5-methyl)piperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide dihydrochloride (compound 71);

Methyl 3-((2-naphtyl)-(3-methyl-piperazinyl)methyl)phenyl ether dihydrochloride (compound 75);

Methyl 3-((2-naphtyl)-(4-allyl-2-methyl-piperazinyl)methyl)phenyl ether dihydrochloride (compound 76);

4-((1-piperazinyl)-benzyl)-benzoic acid dihydrochloride (compound 79);

4-((1-piperazinyl)-benzyl)-N-ethylbenzamide hydrochloride (compound 83);

Methyl 4-((4-*t*-butoxycarbonyl-1-piperazinyl)-benzyl)benzoate (compound 80);

Methyl 4-((1-piperazinyl)-benzyl)benzoate dihydrochloride (compound 81);
4-(1-piperazinyl-benzyl)-benzonitril dihydrochloride (compound 84);
4-(1-piperazinyl-benzyl)-acetophenone dihydrochloride (compound 85);
4-((α-4-piperidinyl)-benzyl)-N,N-diethylbenzamide (compound 88);
N,N-Diethyl-4-(3-methoxybenzyl-1-piperazinyl)-benzamide (Example 50);
N,N-Diethyl-4-[(4-allyl-1-piperazinyl)-3-methoxybenzyl]-benzamide (Example 51);
4-[(N-benzyl-1-piperazinyl)-benzyl]-aniline (compound 91);
4-[(N-benzyl-1-piperazinyl)-benzyl]-acetanilide (compound 92);
4-[(N-benzyl-1-piperazinyl)-benzyl]-methanesulfonamide (Example 54);
Methyl-N-4-[(N-benzyl-1-piperazinyl)-benzyl]-2-methylacetate (Example 55); and
4-[(N-benzyl-1-piperazinyl)-3-fluorobenzyl]-acetanilide (compound 95).

5. A compound according to any of claims 1-4, in form of its hydrochloride salt.

6. A compound according to any of claims 1-5, for use in therapy.

7. A compound according to claim 6, wherein the therapy is pain management.

8. A compound according to claim 6, wherein the therapy is directed towards gastrointestinal disorders.

9. A compound according to claim 6, wherein the therapy is directed towards spinal injuries.

10. A compound according to claim 6, wherein the therapy is directed to disorders of the sympathetic nervous system.

11. Use of a compound according to any of claims 1-5 for the manufacture of a medicament for use in the treatment of pain.

12. Use of a compound according to any of claims 1-5 for the manufacture of a medicament for use in the treatment of gastrointestinal disorders.

13. Use of a compound according to any of claims 1-5 for the manufacture of a medicament for use in the treatment of spinal injuries.

14. A compound according to any of claims 1-5, further characterized in that it is isotopically labelled.

15. Use of a compound according to claim 14 as a diagnostic agent.

16. A pharmaceutical composition comprising a compound according to any of claims 1-5 as an active ingredient, together with a pharmaceutically acceptable carrier.

17. A process for the preparation of a compound according to any of claims 1-5, whereby

A) (i) An aldehyde or ketone is treated with a nucleophile, giving the corresponding alcohol;
(ii) the alcohol is converted into a suitable leaving group, which in turn is displaced with a nucleophile; and
(iii) a N-(4)-unsubstituted piperazine derivative is substituted via its organo halide or equivalent species, or acylated; or

B) (i) A N-protected amino acid ester is reacted with a second amino acid ester, and thereafter treated with an acid, giving a piparazinedione;
(ii) the dione is reduced to the corresponding piperazine; and
(iii) the piperazine is alkylated or acylated on one or more of the nitrogens.

18. A method for the treatment of pain, whereby an effective amount of a compound according to any of claims 1-5 is administered to a subject in need of pain management.

(12) SOLICITUD INTERNACIONAL PUBLICADA SEGÚN EL TRATADO DE COOPERACION DE PATENTES (PCT)

(19) Organización Mundial de Propiedad Intelectual
Oficina Internacional

(43) Fecha de Publicación
Octubre 11 de 2001 (11.10.2001)

PCT

(10) Número de Publicación Internacional
WO 01/74806 A1

(51) Clasificación Internacional de Patentes[7]: C07D 401/14, 405/14, 409/14, 211/68, A61K 31/4523, A61P25/04 25/00

(21) Número de Solicitud Internacional: PCT/SE01/00708

(22) Fecha de Registro Internacional: Marzo 30 de 2001 (03.30.2001)

(25) Idioma de registro: Inglés

(26) Idioma de Publicación: Inglés

(30) Información de Prioridad:

0001208-8 Abril 4 de 2000 (04.04.2000) SE

(71) Solicitante: (Para todos los Estados designados excepto (Estados Unidos de América): ASTRAZENECA AB (SE/SE); S-151 85 Södertälje (SE)

(72) Inventores; e
(75) Inventores/Solicitantes (para Estados Unidos de América solamente): BROWN, William (CA/CA); AstraZeneca R & D Montreal, 7171 Frederick-Banting, St. Laurent, Quebec H4S 1Z9 (CA). WALPOLE, Christopher (GA/CA); AstraZeneca R & D Montreal, 7171 Frederick-Banting, St. Laurent, Quebec H4S 1Z9 (CA).

(74) Agentes: ASTRAZENECA AB; Global Intellectual Property, S-151 85 Södertälje (SE).

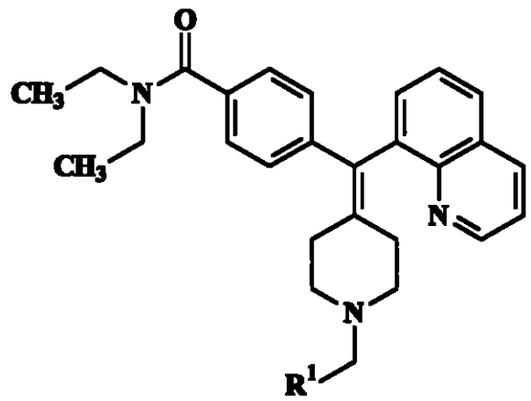
(81) Estados Designados (nacionales): AE, AG, AL, AM, AT,AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO,RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Estados Designados (regionales): Patente ARIPO (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), patente Euroasiatica (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM) Patente Europea (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Publicada:
- *con reporte de búsqueda internacional*
- *antes de la expiración del límite de tiempo para modificar las reivindicaciones y ser publicada de nuevo en el caso de recibo de modificaciones*

Para los códigos de dos letras y otras abreviaturas, refiérase a "Las Notas Guías sobre Códigos y Abreviaturas" que aparecen al comienzo de cada emisión regular de la Gaceta PCT.

(54) Título: "DERIVADOS DE QUINOLINIL-PIPERIDIN-4-ILIDEN-METIL-BENZAMIDA PARA EL TRATAMIENTO DEL DOLOR"



(I)

Se revelan y reivindican en la presente solicitud compuestos de fórmula general (I), en donde R^1 se selecciona de cualquiera de fenil, piridinil, tienil, furanil, imidazolil y triazolil; en donde cada anillo fenilo R^1 y cada anillo heteroaromático R^1 puede estar además substituido opcional e independientemente con 1, 2 o 3 substituyentes seleccionados de alquilo C_1-C_6 de cadena recta y ramificada, NO_2, CF_3, alcoxi C_1-C_6, cloro, flúor, bromo y yodo, en donde las substituciones sobre el anillo fenilo y el anillo heteroaromático pueden tener lugar en cualquier posición sobre dichos sistemas de anillo, como también sus sales farmacéuticamente aceptables y composiciones farmacéuticas que comprenden los novedosos compuestos y su uso en terapia, en particular en el manejo del dolor.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 October 2001 (11.10.2001)

PCT

(10) International Publication Number
WO 01/74806 A1

(51) International Patent Classification[7]: C07D 401/14, 405/14, 409/14, 211/68, A61K 31/4523, A61P 25/04, 25/00

(21) International Application Number: PCT/SE01/00708

(22) International Filing Date: 30 March 2001 (30.03.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0001208-8 4 April 2000 (04.04.2000) SE

(71) Applicant *(for all designated States except US)*: ASTRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BROWN, William [CA/CA]; AstraZeneca R & D Montreal, 7171 Frederick-Banting, St. Laurent, Quebec H4S 1Z9 (CA). WALPOLE, Christopher [GA/CA]; AstraZeneca R & D Montreal, 7171 Frederick-Banting, St. Laurent, Quebec H4S 1Z9 (CA).

(74) Agent: ASTRAZENECA AB; Global Intellectual Property, S-151 85 Södertälje (SE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

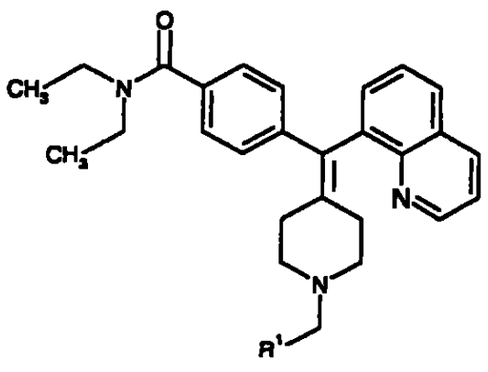
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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

WO 01/74806 A1

(54) Title: QUINOLINYL-PIPERIDIN-4-YLIDENE-METHYL-BENZAMIDE DERIVATIVES FOR THE TREATMENT OF PAIN



(I)

(57) Abstract: Compounds of general formula (I), where R^1 is selected from any one of phenyl, pyridinyl, thienyl, furanyl, imidazolyl, and triazolyl; where each R^1 phenyl ring and R^1 heteroaromatic ring may optionally and independently be further substituted by 1, 2 or 3 substituents selected from straight and branched C_1-C_6 alkyl, NO_2, CF_3, C_1-C_6 alkoxy, chloro, fluoro, bromo, and iodo. The substitutions on the phenyl ring and on the heteroaromatic ring may take place in any position on said ring systems; are disclosed and claimed in the present application, as well as their pharmaceutically acceptable salts and pharmaceutical compositions comprising the novel compounds and their use in therapy, in particular in the management of pain.

191 ~~191~~

TRATADO DE COOPERACION DE PATENTES
PCT
REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL

(PCT Articulo 36 y Regla 70)

Registro de referencia del solicitante o agente 100002-1 WO	**PARA FUTURAS ACCIONES** Ver Notificación o Tranamisión del Reporte de Examen Preliminar Internacional (Formato PCT/IPEA/416)	
Solicitud Internacional No. PCT/SE01/00708	Fecha de registro internacional (día/mes/año) 30.03.2001	Fecha de prioridad (día/mes/año) 04.04.2000
Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC 7 C07D 401/14, C07D 405/14, C07D 409/14, C07D 211/68, A61K 31/4523, A61P 25/04, A61P 25/00		
Solicitante **AstraZeneca AB et al**		

1. Este informe de examen preliminar internacional ha sido preparado por esta Autoridad Examinadora Preliminar Internacional y se transmite al solicitante de conformidad con el Articulo 36.

2. Este REPORTE consta de un total de 4 páginas, incluyendo la carátula.

   ☒ Este reporte también está acompañado de ANEXOS, es decir, páginas de descripción, reivindicaciones y/o dibujos que han sido modificados y son la base de este informe y/o páginas que contienen rectificaciones hechas ante esta Autoridad (ver Regla 70.16 y la Sección 607 de las Instrucciones Administrativas de conformidad con el PCT).
   Estos anexos constan de un total de _____ páginas.

3. Este informe contiene indicaciones relacionadas con los siguientes ítems:

   - I ☒ Bases del Reporte
   - II ☐ Prioridad
   - III ☒ No establecimiento de opinión respecto a novedad, nivel inventivo y aplicabilidad Industrial.
   - IV ☐ Falta de unidad de invención
   - V ☒ Afirmación razonada de conformidad con el Artículo 35(2) con respecto a novedad, nivel inventivo o aplicabilidad industrial; citaciones y explicaciones que sustentan dicha afirmación.
   - VI ☐ Ciertos documentos citados
   - VII ☐ Ciertos defectos en la solicitud internacional
   - VIII ☐ Ciertas observaciones sobre la solicitud internacional

Fecha de presentación de la demanda 12.10.2001	Fecha de terminación de este reporte 09.07.2002
Nombre y dirección de la autoridad internacional de examen preliminar: Patent-och registreringsverket Telex Box 5055 17978 S-102 42 STOCKHOLM PATOREG-S Facsimile No. 08-667 72 88	Funcionario autorizado Solveig Gustavsson/BS Teléfono No.08-782 25 00

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL | Solicitud internacional No. **PCT/SE01/00708** 142

I. Bases del reporte

1. Respecto a los elementos de la solicitud internacional:*

☒ la solicitud internacional según se presentó originalmente

☐ la descripción:

Páginas , según se presentaron originalmente

Páginas , presentadas con la demanda

Páginas , registradas con la carta de

☐ las reivindicaciones:

Páginas , según se presentaron originalmente

Páginas , según se enmendaron (junto con cualquier declaración) de conformidad con el artículo 19

Páginas , presentadas con la demanda

Páginas , presentadas con la carta de

☐ los dibujos:

Páginas , según se presentaron originalmente

Páginas , presentadas con la demanda

Páginas , presentadas con la carta de

☐ la secuencia que enumera parte de la especificación:

Páginas , según se presentaron originalmente

Páginas , presentadas con la demanda

Páginas , registradas con la carta de

2. Respecto al idioma, todos los elementos marcados anteriormente estuvieron disponibles o fueron suministrados a esta Autoridad en el idioma en el cual la solicitud internacional fue presentada, a menos que se indique lo contrario bajo este ítem.

Estos elementos estuvieron disponibles o fueron suministrados a esta Autoridad en el idioma, el cual es:

☐ el idioma de una traducción suministrada para una búsqueda internacional (según la Regla 23.1 (b)).

☐ el idioma de una publicación de la solicitud internacional (según la Regla 48.3 (b)).

☐ el idioma de la traducción suministrada para el examen preliminar internacional (según las Reglas 55.2 y/o 55.3).

3. Respecto al **nucleótido y/o secuencia amino ácida** revelado en la solicitud internacional, se llevó a cabo el examen preliminar internacional según el listado de secuencia:

☐ contenido en la solicitud internacional en forma escrita.

☐ registrado junto con la solicitud internacional en forma legible por computador.

☐ proporcionado subsiguientemente a esta Autoridad en forma escrita.

☐ proporcionado subsiguientemente a esta Autoridad en forma legible por computador.

☐ Se ha proporcionado la afirmación respecto a la cual el listado de secuencia escrito proporcionado subsiguientemente no va más allá de la revelación en la solicitud internacional según se presentó.

☐ Se ha proporcionado la afirmación respecto a la cual la información presentada en forma legible por computador es idéntica al listado de secuencia escrita.

4. ☐ Las modificaciones han resultado en la cancelación de:

☐ la descripción, páginas

☐ las reivindicaciones, Nos.

☐ los dibujos, páginas

5. ☐ Este reporte ha sido establecido como si (algunas) de las modificaciones no se hubiesen hecho, ya que se ha considerado que van más allá de la revelación según se presentó, como se indicó en Casilla Suplementaria (Regla 70.2 (c)):

* *Las páginas de remplazo que se han proporcionado a la Oficina que recibe en respuesta a una invitación según el Artículo 14 a las que se hace referencia en este informe como "registradas originalmente" y se anexan a este informe ya que no contienen enmiendas (Norma 70.16 y 70.17).*

** Cualquier página de remplazo que contenga dichas enmiendas debe hacerse referencia bajo el ítem I y anexarse a este informe.

REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL	Solicitud internacional No. PCT/SE01/00708

III. No establecimiento de opinión respecto a la novedad, nivel inventivo y aplicabilidad industrial

1. Las preguntas como quiera que la invención reivindicada parezca ser novedosa, para comprender un nivel inventivo (para no ser obvio), o para ser aplicable industrialmente no se han examinado en relación con:

☐ toda la solicitud internacional.

☒ las reivindicación Nos. 15-17

Porque:

☒ dicha solicitud internacional, o dichas reivindicación Nos. 15-17
Se relaciona con el siguiente asunto/materia que no requiere examen preliminar Internacional (especificar):

Ver Regla PCT 67.1. (iv).: Métodos para el tratamiento del cuerpo humano o animal por cirugía o terapia, como también métodos de diagnóstico.

☐ la descripción, reivindicaciones o dibujos (indican elementos particulares a continuación) o dichas reivindicaciones Nos. Son tan imprecisas que no pudo formarse una opinión significativa (especifique):

☐ las reivindicaciones o dichas reivindicaciones Nos. están sustentadas tan inadecuadamente por la descripción que no pudo formarse una opinión significativa.

☐ no se ha establecido un informe de búsqueda internacional para dichas reivindicaciones Nos.

2. Un examen internacional significativo no puede llevarse a cabo debido a la falla del nucleótido y/o listado de secuencia amino ácida para cumplir con el estándar preparado en el Anexo C de las Instrucciones Administrativas:

☐ el formulario escrito no ha sido proporcionado o no cumple con el estándar.

☐ la forma legible por computador no ha sido proporcionado o no cumple con el estándar.

REPORTE DE EXAMEN PRELIMINAR INTERNACI NAL	Solicitud internacional No.PCT/US01/00708

V. Afirmación razonada bajo el Articulo 35(2) respecto a novedad, nivel inventivo o aplicabilidad industrial; citaciones y explicaciones que sustentan dicha afirmación

1. Afirmación

Novedad (N)	Reivindicaciones	1-6, 8-14	SI
	Reivindicaciones	7, 18	NO
Nivel inventivo (IS)	Reivindicaciones	1-6, 8-14	SI
	Reivindicaciones	7, 18	NO
Aplicabilidad industrial (IA)	Reivindicaciones	1-14, 18	SI
	Reivindicaciones		NO

2. Citaciones y explicaciones (Regla 70.7)

Los siguientes documentos son citados en el reporte de búsqueda:
D1) WO 9828275 A1
D2) WO 9723466 A1
D3) WO 9933806 A1
D4) J. Med. Chem., Vol. 42, 1999, p 5455-5463.
D5) J. Med. Chem., Vol. 43, 2000, p 3895-3905.
Documento D1 es considerado como el estado de la técnica más cercano.

Las reivindicaciones 1-6 y 8-14 se relacionan con una selección de compuestos, que están incluidos en la fórmula general en las reivindicaciones 1 y 3 del documento D1. Los compuestos de los documentos citados también tienen la misma aplicación que los compuestos de la presente solicitud.

Sin embargo, no hay compuestos ejemplificados en el documento citado como los de las presentes reivindicaciones.
El solicitante ha mostrado que los compuestos de acuerdo con las presentes reivindicaciones tienen efectos ventajosos comparados con los compuestos cercanamente relacionados de D1.

Por lo tanto, se considera que las reivindicaciones 1-6 y 8-14 cumplen con los requisitos de novedad, nivel inventivo y aplicación industrial.

La reivindicación 7 se relaciona con un proceso para la preparación de los compuestos y la reivindicación 18 a un compuesto intermediario.

El proceso acorde con la reivindicación 7 es conocido a partir de D1, ver página 55, la etapa del compuesto 52 al compuesto 53.

Adicionalmente, el intermediario de acuerdo con la reivindicación 18 es conocido a partir de D1 (compuesto 52). Observar la definición de grupo protector de tipo bencilo, el cual incluye Boc, en la reivindicación 7 y en la descripción página 4 línea 14 de la presente solicitud.

Así, se considera que las reivindicaciones 7 y 18 carecen de novedad.

195

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
100002-1 WO		
International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/SE01/00708	30.03.2001	04.04.2000

International Patent Classification (IPC) or national classification and IPC

C07D 401/14, C07D 405/14, C07D 409/14, C07D 211/68, A61K 31/4523, A61P 25/04, A61P 25/00

Applicant

AstraZeneca AB et al

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12.10.2001	09.07.2002
Name and mailing address of the IPEA/SE	Authorized officer
Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667 72 88	Telex 17978 PATOREG-S Solveig Gustavsson/BS Telephone No. 08-782 25 00

Form PCT/IPEA/409 (cover sheet) (January 1998)

8
14.
196

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE01/00708

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed

☐ the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the claims:
pages _____, as originally filed
pages _____, as amended (together with any statement) under article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the drawings:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheet/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2 (c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under Item I and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. 192
PCT/SE01/00708

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 15-17

because:

☒ the said international application, or the said claims Nos. 15-17 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE01/00708

~~197~~ 198

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-6,8-14	YES
	Claims	7,18	NO
Inventive step (IS)	Claims	1-6,8-14	YES
	Claims	7,18	NO
Industrial applicability (IA)	Claims	1-14,18	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The following documents are cited in the search report:
D1) WO 9828275 A1
D2) WO 9723466 A1
D3) WO 9933806 A1
D4) J. Med. Chem., Vol.42, 1999, p 5455-5463.
D5) J. Med. Chem., Vol.43, 2000, p 3895-3905.

Document D1 is considered to be the closest related prior art.

Claims 1-6 and 8-14 relate to a selection of compounds, which compounds are included in the general formula in claims 1 and 3 of document D1. The compounds of the cited documents also have the same use as the compounds of the present application.

However, no compounds according to the present claims are exemplified in the cited document.
The applicant has shown that the compounds according to the present claims have advantageous effects compared to some of the closely related compounds D1.

Therefore, claims 1-6 and 8-14 are considered to fulfil the requirements of novelty, inventive step and industrial applicability.

Claim 7 relates to a process for the preparation of the compounds and claim 18 to an intermediate compound.
The process according to claim 7 is known from D1, see page 55 the step from compound 52 to compound 53.
Also the intermediate according to claim 18 is known from D1 (compound 52).Observe the definition of benzyl-like protecting group, which includes Boc, in claim 7 and the description page 4 line 14 of the present application.
Thus, claims 7 and 18 are considered to lack novelty.

DERIVADOS DE QUINOLINIL-PIPERIDIN-4-ILIDEN-METIL-BENZAMIDA PARA EL TRATAMIENTO DEL DOLOR

RESUMEN – OBJETO Y FINALIDAD

Se revelan y reivindican en la presente solicitud compuestos de fórmula general (I), en donde R^1 se selecciona de cualquiera de piridinil, tienil, furanil, imidazolil y triazolil; en donde cada anillo heteroaromático R^1 puede estar además substituido opcional e independientemente con 1, 2 o 3 substituyentes seleccionados de alquilo C_1-C_6 de cadena recta y ramificada, NO_2, CF_3, alcoxi C_1-C_6, cloro, flúor, bromo y yodo, en donde las substituciones sobre el anillo heteroaromático pueden tener lugar en cualquier posición sobre dichos sistema de anillo, como también los enantiomeros separados de los compuestos y las sales y composiciones farmacéuticas que comprenden los novedosos compuestos y su uso en terapia, en particular en el manejo del dolor.

Astrazeneca
1000602 IP
200

DERIVADOS QUINOLINIL-PIPERIDIN-4-ILIDEN-METIL-BENZAMIDA PARA EL TRATAMIENTO DEL DOLOR

Campo de la invención

La presente invención se refiere a compuestos novedosos, a un proceso para su preparación, a su uso y a las composiciones farmacéuticas que contienen tales compuestos novedosos. Los compuestos novedosos son útiles en la terapéutica, y en particular en el tratamiento del dolor.

Antecedentes de la Invención y Estado Anterior de la Técnica

Se ha identificado el receptor δ como un receptor que desempeña un papel en muchas funciones corporales tales como en los sistemas circulatorio y del dolor. Los ligandos del receptor δ pueden por lo tanto encontrar un uso potencial como analgésicos, y/o como agentes antihipertensores. Los ligandos del receptor δ han demostrado también poseer actividades inmunomodulatorias.

La identificación de por lo menos tres diferentes poblaciones de receptores opiáceos (μ, δ y κ) se encuentra bien establecida en la actualidad, y todos los tres están presentes en los dos sistemas nerviosos -central y periférico- de muchas especies entre las que se incluye el hombre. En diversos modelos de experimentación en animales, se ha observado analgesia cuando se activa uno ó más de dichos receptores.

Con pocas excepciones, los ligandos δ opiáceos selectivos actualmente disponibles son de naturaleza peptídica y resultan inapropiados para su administración por rutas sistémicas. Un ejemplo de un δ-agonista no peptídico es el compuesto SNC80 (*Bilsky E.J et al., Journal de Famacology and Experimental Therapeutics, 273(1), pp. 359-366 (1995)*). Existe, sin embargo, la necesidad de contar con agonistas selectivos de los receptores δ

que no solamente exhiban una mejorada selectividad, sino también un mejorado perfil de efectos secundarios.

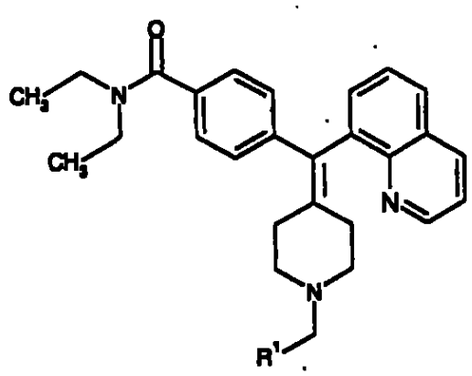
Por consiguiente, el problema fundamental que pretende resolver la presente invención es el de suministrar nuevos analgésicos con mejorados efectos analgésicos pero que a la vez exhiban un mejorado perfil de efectos secundarios frente a los μ-agonistas ya existentes, y que adicionalmente, exhiban una mejorada eficacia sistémica.

Los analgésicos existentes o identificados en el estado anterior de la técnica presentan muchas desventajas en cuanto que exhiben una pobre farmacocinética y no son analgésicos cuando se administran por rutas sistémicas. Además, se ha documentado que los compuestos δ-agonistas preferidos, descritos en el estado anterior de la técnica, exhiben significativos efectos convulsivantes cuando se administran sistémicamente.

Hemos encontrado ahora que ciertos compuestos no específicamente revelados, pero incluidos dentro del alcance de la patente mundial WO 98/28275, exhiben, de manera sorprendente, mejoradas propiedades δ-agonistas y mejorada potencia *en vivo*.

Descripción de la invención

Los novedosos compuestos acordes con la presente invención se definen por la fórmula I:



I

en donde

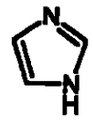
R^1 se selecciona del grupo conformado por

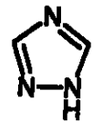
(i) fenil 

(ii) piridinil  ;

(iii) tienil  ;

(iv) furanil  ;

(v) imidazolil  ;

(vi) triazolil  ;

en donde cada anillo fenílico R^1 y cada anillo heteroaromático R^1 pueden, opcionalmente e independientemente, ir adicionalmente sustituidos con 1, 2 ó 3 sustituyentes seleccionados entre alquil C_1-C_6 de cadena recta ó ramificada, NO_2, CF_3, alcoxi C_1-C_6, cloro, fluoro, bromo, y yodo. Las sustituciones en el anillo heteroaromático pueden tener lugar en cualquier posición de dichos sistemas anulares;

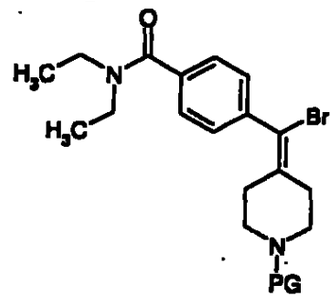
Una práctica preferida de la presente invención es un compuesto acorde con la fórmula estructural I en donde R^1 corresponde a lo previamente definido y cada anillo fenílico R^1 y cada anillo heteroaromático R^1 pueden de manera independiente ir adicionalmente sustituidos con un grupo metil.

Una práctica más preferida de la presente invención es un compuesto acorde con la fórmula estructural I en donde R^1 es piridinil, tienil ó furanil.

Caen también dentro del alcance de la presente invención, las sales y enantiómeros de los compuestos de fórmula I, incluyendo las sales de los enantiómeros.

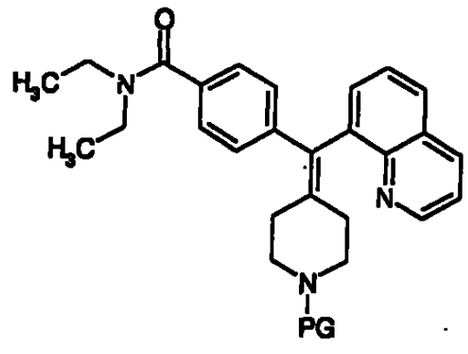
Cuando el anillo fenílico y el ó los anillos heteroaromáticos van sustituidos, los sustituyentes preferidos se seleccionan independientemente entre CF_3, metil, yodo, bromo, fluoro y cloro.

El paso de reacción g del Esquema 1, *vide infra*, se lleva a cabo por reacción de un compuesto intermediario de fórmula general II



II

en donde PG es un grupo protector del tipo de uretano ó bencil, como por ejemplo Boc, con ácido 8-quinolinilbórico, usando un catalizador a base de paladio, v.g., $Pd(PPh_3)_4$, en presencia de una base, v.g., Na_2CO_3, para obtener un compuesto de fórmula general III,



III

compuesto el cual luego se desprotege bajo condiciones estándar, y se alquila bajo condiciones reductoras con un compuesto de fórmula general R^1-CHO, para producir así compuestos de fórmula general I.

Entre los catalizadores a base de paladio apropiados se incluyen, sin hacer una lista exhaustiva de éstos, $PdCl_2$ (+ una fosfina), $Pd(OAc)_2$ (+ una fosfina), $Pd(dba)_2$, $PdCl_2(dppf)$ CH_2Cl_2, $Pd(PF_3)_4$, Pd/C.

Entre las bases apropiadas se incluyen, sin hacer una lista exhaustiva de éstas, trietilamina, carbonato de sodio ó de potasio.

Entre los agentes reductores apropiados a emplear se incluyen, sin hacer una lista exhaustiva de éstos, cianoborohidruro de sodio y triacetoxiborohidruro de sodio.

Los compuestos novedosos de la presente invención son útiles en la terapéutica, especialmente en el tratamiento de diversas estados de dolor tales como dolor crónico, dolor neuropático, dolor agudo, dolor causado por cáncer, dolor causado por artritis reumatoide, migraña, dolor visceral, etc. Esta lista no deberá considerarse exhaustiva.

Los compuestos de la presente invención son útiles como inmunomoduladores, especialmente en enfermedades autoimmunes como por ejemplo la artritis, en injertos de piel, transplantes de órganos y necesidades quirúrgicas similares, en enfermedades del colágeno, diversidad de alergias, como también como agentes anti-tumorales y agentes antivirales.

Los compuestos de la presente invención son útiles en aquellos estados patológicos en donde está presente la degeneración o disfunción de los receptores opiáceos, o en los estados implicados en dicho paradigma. Aquí se puede incluir el uso de versiones isotópicamente marcadas de los compuestos de la presente invención en técnicas de diagnóstico y aplicaciones en el campo de las imágenes diagnósticas tales como la tomografía de emisión de positrones (PET, sigla en inglés).

Los compuestos de la presente invención son útiles para el tratamiento de la diarrea, depresión, ansiedad, incontinencia urinaria, diversas enfermedades mentales, tos, edema pulmonar, diversos desórdenes gastrointestinales, lesiones de la columna vertebral y adicción a drogas, incluyendo el

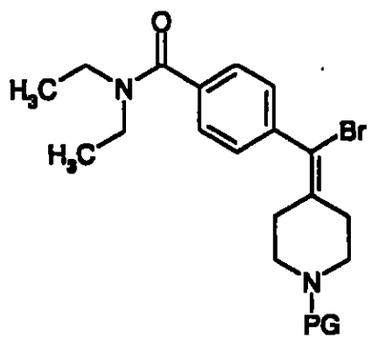
tratamiento del abuso de alcohol, nicotina, opiáceos y de otras drogas, y para el tratamiento de desórdenes del sistema nervioso simpático, por ejemplo, la hipertensión.

Los compuestos de la presente invención son útiles como agentes analgésicos de uso durante la anestesia general y los cuidados monitoreados de la anestesia. Con frecuencia se usan combinaciones de agentes con diferentes propiedades con el fin de lograr un equilibrio en los efectos requeridos para mantener el estado anestésico (v.g., amnesia, analgesia, relajación muscular y sedación). Se incluyen en tales combinaciones anestésicos inhalados, hipnóticos, ansiolíticos, bloqueadores neuromusculares y opiáceos.

Cae también dentro del alcance de la presente invención el uso de cualquiera de los compuestos acordes con la fórmula I, ya definida, en la manufactura de un medicamento para el tratamiento de cualquiera de las condiciones patológicas antes mencionadas.

Un aspecto adicional de la presente invención es un método de tratamiento de un sujeto que sufra cualquiera de las condiciones antes mencionadas, método consistente en la administración de una cantidad eficaz de un compuesto acorde con la fórmula I a un paciente en necesidad de dicho tratamiento.

Un aspecto más de la presente invención son los intermediarios de fórmula general II,



II

en donde PG es un grupo protector tipo uretano ó bencil, como por ejemplo Boc.

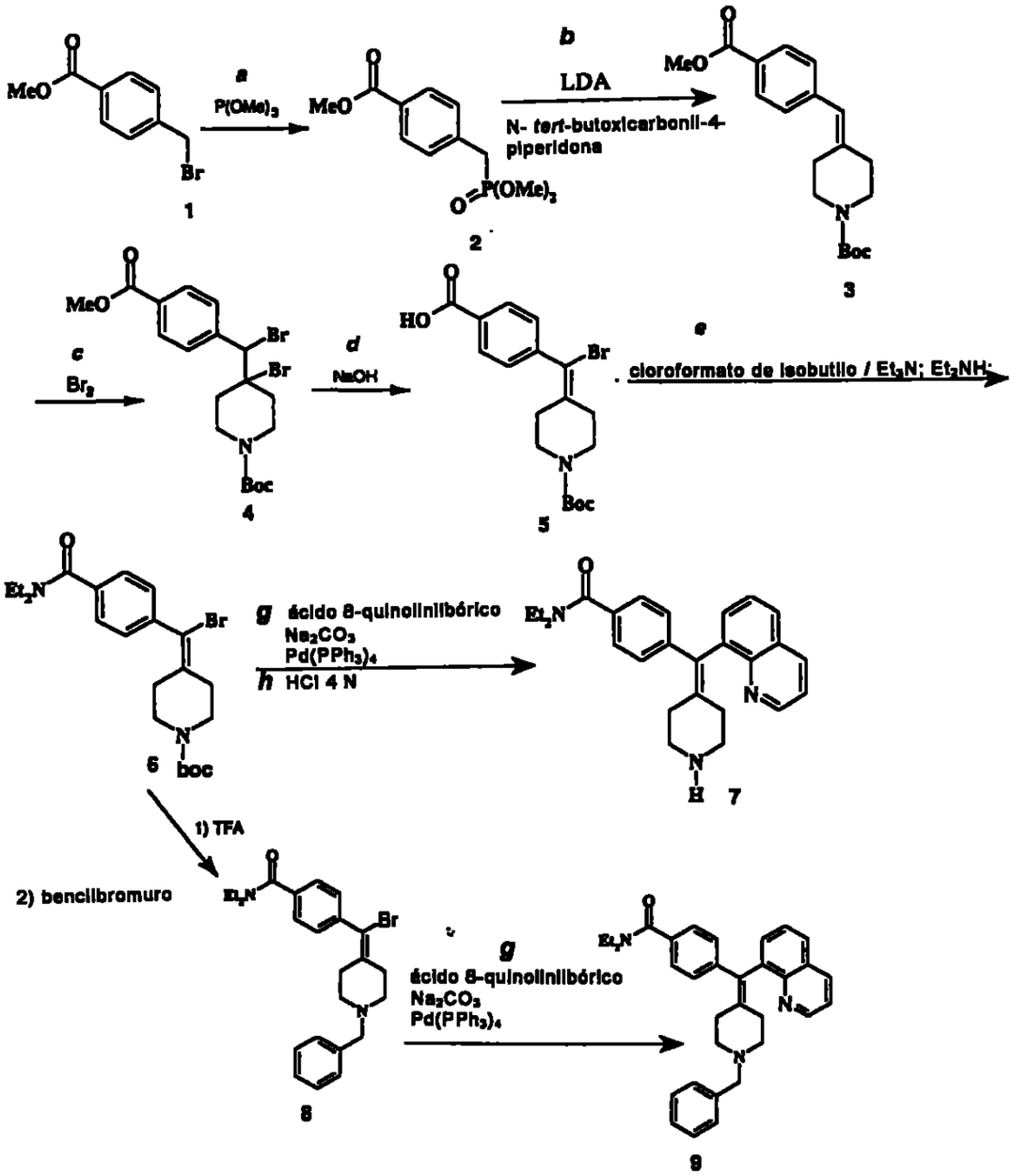
Métodos de preparación

Los compuestos acordes con la presente invención pueden prepararse mediante los siguientes procedimientos conocidos, descritos, v.g., en *"Advanced Organic Chemistry" Tercera Edición, de Jerry March, John Willey and Sons Inc.; New York (1985): Paso (a): p848; Paso (b): p848; Paso (c): p657; Paso (d): p875; Paso (e): p371-373; Paso (f): p364-366; Paso (g): N. Miyaura and A. Suzuki, Chem. Rev., 95, 2457-2483 (1995); Paso (h): "Protective Groups in Organic synthesis" p327-329, de Theodora W. Greene and Peter G.M. Wuts, Second Edición, John Wiley and Sons Inc.; New York (1991).* Obras citadas aquí con propósitos de mera referencia.

EJEMPLOS

La invención se describirá ahora con mayor detalle a través de los siguientes Ejemplos, los cuales no tienen el propósito de limitar el alcance de la presente invención.

Esquema 1


a
P(OMe)3
b
LDA
N- tert-butoxicarbonil-4-piperidona
c
Br2
d
NaOH
e
cloroformato de isobutilo / Et3N; Et2NH;
g ácido 8-quinolinilbórico
Na2CO3
Pd(PPh3)4
h HCl 4 N
1) TFA
2) bencilbromuro
g
ácido 8-quinolinilbórico
Na2CO3
Pd(PPh3)4
1
2
3
4
5
6
7
8
9

Ejemplo 1

Preparación de *N,N*-dietil-4-(8-quinolinil-piperidin-4-iliden-metil)benzamida (compuesto 7)

(I) Preparación del Acido 4-(4-metoxicarbonil-benciliden)-piperidina-1-carboxílico, *tert*-butil éster (compuesto 3)

Se sometió a reflujo una mezcla del **compuesto 1** (11,2 g, 49 mmol) y trimetil fosfito (25 mL) bajo N_2 durante 5 hr. Se removió el exceso de trimetil fosfito mediante co-destilación con tolueno para producir así el **compuesto 2** con rendimiento cuantitativo:

RMN ^{1}H (CDCl3) δ 3,20 (d, 2H, J=22 Hz), 3,68 (d, 3H, 10,8 Hz), 3,78 (d, 3H, 11,2 Hz), 3,91 (s, 3H), 7,38 (m, 2H), 8,00 (d, 2H, J=8 Hz).

(ii) A una solución del producto anterior (**compuesto 2**) en THF seco (200 mL) se agregó gota a gota diisopropilamida de litio (32,7 mL, 1,5 M en hexanos, 49 mmol) a -78 ^{0}C. La mezcla de reacción se dejó luego que calentar hasta temperatura ambiente antes de la adición de N-*tert*-butoxicarbonil-4-piperidona (9,76 g, 49 mmol en 100 mL THF seco). Después de 12 hr, la mezcla de reacción se extinguió con agua (300 mL) y se extrajo con acetato de etilo (3 x 300 mL). Las fases orgánicas combinadas se secaron sobre $MgSO_4$ y se evaporaron con lo cual se obtuvo un producto crudo, el cual se purificó por cromatografía flash para obtener así el **compuesto 3** a manera de un sólido blanco (5,64 g, 35%):

IR (NaCl) 3424, 2974, 2855, 1718, 1688, 1606, 1427, 1362, 1276 cm^{-1};

RMN ^{1}H ($CDCl_3$) δ 1,44 (s, 1H), 2,31 (t, J=5,5 Hz, 2H), 2,42 (t, J=5,5 Hz, 2H), 3,37 (t, J=5,5 Hz, 2H), 3,48 (t, J=5,5 Hz, 2H), 3,87 (s, 3H), 6,33 (s, 1H), 7,20 (d J=6,7 Hz, 2H), 7,94 (d, J=6,7 Hz, 2H);

RMN ^{13}C ($CDCl_3$) δ 28,3, 29,2, 36,19, 51,9, 123,7, 127,8, 128,7, 129,4, 140,5, 142,1, 154,6, 166,8.

(iii) Preparación de ácido 4-[bromo-4-[bromo-(4-metoxicarbonil-fenil)-metil]-piperidina-1-carboxílico, *tert*-butil éster (compuesto 4)

A una mezcla del **compuesto 3** (5,2 g, 16 mmol) y K_2CO_3 (1,0 g) en diclorometano seco (200 mL) se agregó una solución de bromo (2,9 g, 18 mmol) en 30 mL de CH_2Cl_2 a 0 ^{0}C. Luego de 1,5 hr a temperatura ambiente, la solución después de filtración del K_2CO_3 se condensó. El residuo se disolvió luego en acetato de etilo (200 mL), se lavó con agua (200 mL), HCl 0,5 M (200 mL) y salmuera (200 mL), y se secó sobre $MgSO_4$. La remoción de los solventes proporcionó un producto crudo, el cual se recristalizó a partir de metanol con lo cual se obtuvo el **compuesto 4** a manera de un sólido blanco (6,07 g, 78%):

IR (NaCl) 3425, 2969, 1725, 1669, 1426, 1365, 1279, 1243 cm^{-1};

RMN ^{1}H ($CDCl_3$) δ 1,28 (s, 9H), 1,75 (m, 2H), 1,90 (m, 2H), 2,1 (m, 4H), 3,08 (br, 4H), 3,90 (s, 3H), 4,08 (br, 4H), 5,14 (s, 1H), 7,57 (d, J=8,4 Hz, 2H) 7,98 (d, J=8,4 Hz, 2H);

RMN ^{13}C ($CDCl_3$) δ 28,3, 36,6, 38,3, 40,3, 52,1, 63,2, 72,9, 129,0, 130,3, 130,4, 141,9, 154,4, 166,3.

(iv) Preparación de ácido 4-[bromo-(4-caboxi-fenil)-metilen]-piperidina-1-carboxílico, *tert*-butil éster (compuesto 5)

Una solución del **compuesto 4** (5,4 g, 11 mmol) en metanol (300 mL) y 2,0 M NaOH (100 mL) se calentó a 40 ^{0}C durante 3 hr. El sólido se recolectó mediante filtración, y se secó durante una noche bajo vacío. La sal seca se disolvió en acetonitrilo al 40%/agua, y se ajustó a pH 2 usando HCl concentrado. El compuesto del producto deseado, **compuesto 5** (3,8 g, 87%) se aisló a manera de un polvo blanco por filtración:

RMN ^{1}H ($CDCl_3$) δ 1,45 (s, 9H), 2,22 (dd, J=5,5 Hz, 6,1 Hz, 2H), 2,64 (dd, J=5,5 Hz, 6,1 Hz, 2H), 3,34 (dd, J=5,5 Hz, 6,1 Hz 2H), 3,54 (dd, J=5,5 Hz, 6,1 Hz, 2H), 7,35 (d, J=6,7 Hz, 2H), 8,08 (d, J=6,7 Hz, 2H);

RMN ^{13}C ($CDCl_3$) δ 28,3, 31,5, 34,2, 44,0, 115,3, 128,7, 129,4, 130,2, 137,7, 145,2, 154,6, 170,3.

(v) **Preparación del ácido 4-[bromo-(4-dietilcarbamoil-fenil)-metilen]-piperidina-1-carboxílico, *tert*-butil éster (compuesto 6)**

A una solución del **compuesto 5** (1,0 g, 2,5 mmol) en diclorometano seco (10 mL) a -20 ^0C, se agregó cloroformato de isobutilo (450 mg, 3,3 mmol). Después de 20 min a -20 ^0C, se agregó dietilamina (4 mL) y la reacción se dejó que alcanzará la temperatura ambiente. 1,5 horas después, los solventes se evaporaron y el residuo se particionó entre acetato de etilo y agua. La fase orgánica se lavó con salmuera y se secó sobre $MgSO_4$. La remoción de los solventes proporcionó un producto crudo, el cual se purificó por cromatografía flash para producir así el **compuesto 6** a manera de agujas blancas (800 mg, 73%):

IR (NaCl) 3051, 2975, 1694, 1633, 1416, 1281, 1168, 1115 cm^{-1};

RMN ^1H ($CDCl_3$) δ 1,13 (br, 3H), 1,22 (br, 3H), 1,44 (s, 9H), 2,22 (t, J=5,5 Hz, 2H), 2,62 (t, J=5,5 Hz, 2H), 3,33 (m, 4H), 3,55 (m, 2H), 7,31 (d, J=8,0 Hz, 2H), 7,36 (d, J=8,0 Hz, 2H);

RMN ^{13}C ($CDCl_3$) δ 12,71 14,13, 28,3, 31,5, 34,2, 39,1, 43,2, 79,7, 115,9, 126,3, 129,3, 136,8, 137,1, 140,6, 154,6, 170.

(vi) **Preparación de *N,N*-dietil-4-(8-quinolinil-piperidin-4-iliden-metil)benzamida (compuesto 7)**

Una mezcla del **compuesto 6** (902 mg, 2,0 mmol), ácido 9-quinolinilbórico (860 mg, 5,0 mmol), Na_2CO_3 2M (2,5 mL), y tetrakis(trifenilfosfina) paladio(0) (20 mg) en tolueno (desgasificado, 5 mL) y etanol (desgasificado, 5 mL) se sometió a reflujo a 90 ^0C durante 4 hr bajo N_2. La mezcla de reacción luego se enfrío a t.a., y se extrajo con acetato de etilo (2 x 100 mL). Las fases orgánicas combinadas se secaron sobre $MgSO_4$ y se evaporaron para producir así un producto crudo.

Este producto crudo se se trató con HCl 4,0 M en dioxano a 50 ^{0}C durante 2 hr. Después de evaporación, el residuo se disolvió en HCl 1 M (100 mL) y se extrajeron las impurezas con dietil éter (3 x 100 mL). La fase acuosa se alcalinizó con NH_4OH y se extrajo con diclorometano (3 x 100 mL). Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ y se evaporaron para producir así el compuesto del título, 7 (729 mg, 91 %):

RMN ^{1}H (400 MHz, $CDCl_3$) δ 1,07 (3H, br m, C<u>H</u>$_3$CH$_2$-), 1,20 (3 H, br m, CH$_3$C<u>H</u>$_2$-), 2,00 (2 H, piperidina CH-), 2,46 (1 H, s, N<u>H</u>), 2,52 (2 H, m, piperidina C<u>H</u>-), 2,75 (1 H, m, piperidina C<u>H</u>-), 2,92 (2 H, m, piperidina C<u>H</u>-), 3,05 (1 H, m, piperidina C<u>H</u>-), 3,22 (2 H, m, C<u>H</u>$_2$N-), 3,49 (2 H, m, C<u>H</u>$_2$N-), 7,23 (2 H, m, Ar<u>H</u>), 7,32 (2 H, m, Ar<u>H</u>), 7,36 (1 H, m, Ar<u>H</u>), 7,49 (2 H, m, Ar<u>H</u>), 7,72 (1 H, dd, J = 6,4, 3,2 Hz, Ar<u>H</u>), 8,11 (1 H, dd, J = 8,4, 1,6 Hz, Ar<u>H</u>), 8,91 (1 H, dd, J=4,0, 1,6 Hz, Ar<u>H</u>); Su sal HCl: m.p. (punto de fusión > 170 ^{0}C (Desc.);

IR (NaCl) 3410, 2973, 1614, 1551, 1436, 1284 cm^{-1}.

<u>Ejemplo 2</u>

<u>Preparación de *N,N*-dietil-4-(8-quinolinil-N-bencil-piperidin-4-iliden-metil)benzamida (compuesto 9)</u>

(l) <u>Preparación de *N,N*-dietil-4-(bromo-N-bencil-piperidin-4-iliden-metil)benzamida (compuesto 8)</u>

El compuesto 6 preparado en el Ejemplo 1(v) anterior (2,26 g, 5,0 mmoL), se trató con TFA (25 mL) en diclorometano (25 mL) a temperatura ambiente. Después de 2 hr, la mezcla de reacción se condensó con lo cual se obtuvo un residuo, el cual se disolvió en acetonitrilo (20 mL), y se hizo reaccionar con bromuro de bencilo (5,0 mmol) a t.a. durante 2 hr. La mezcla de reacción se condensó. y luego se disolvió en acetato de etilo (100 mL). La solución orgánica se lavó con NH_4OH 1 N y salmuera, se secó sobre MgSO4. La remoción de los solventes proporcionó un producto crudo, el

cual se purificó por cromatografía flash para producir así el **compuesto 8** a manera de un aceite (1,0 g, 45%):

IR (NaCl) 2971, 1630, 1427, 1287, 1094 cm^{-1}

RMN ^1H ($CDCl_3$) δ 1,13 (br, 3H), 1,23 (br, 3H), 2,28 (m, 2H), 2,37 (m, 2H), 2,55 (m, 2H), 2,69 (m, 2H), 3,27 (m, 2H), 3,53 (br, 4H), 7,31 (m, 4H).

(ii) Preparación de *N,N*-dietil-4-(8-quinolinil-N-bencil-piperidin-4-ilíden-metil)benzamida (compuesto 9)

Una mezcla de **compuesto 8** preparado en el paso (i) anterior (1,32 mg, 3,0 mmol), ácido 8-quinolinilbórico (1,04 mg, 6,0 mmol), Na_2CO_3 2M (3,0 mL), y tetrakis(trifenilfosfina) paladio(0) (20 mg) en tolueno (desgasificado, 5 mL) y etanol (desgasificado 5 mL), se sometió a reflujo a 90 ^0C durante 2 hr bajo N_2. La mezcla de reacción luego se enfrió hasta t.a., y se extrajo con acetato de etilo (2 x 100 mL). Las fases orgánicas combinadas se lavaron con salmuera, y se secó sobre $MgSO_4$. La remoción de los solventes proporcionó un producto crudo, el cual se purificó por cromatografía flash para producir así el compuesto del título deseado, **9** (832 mg, 57%):

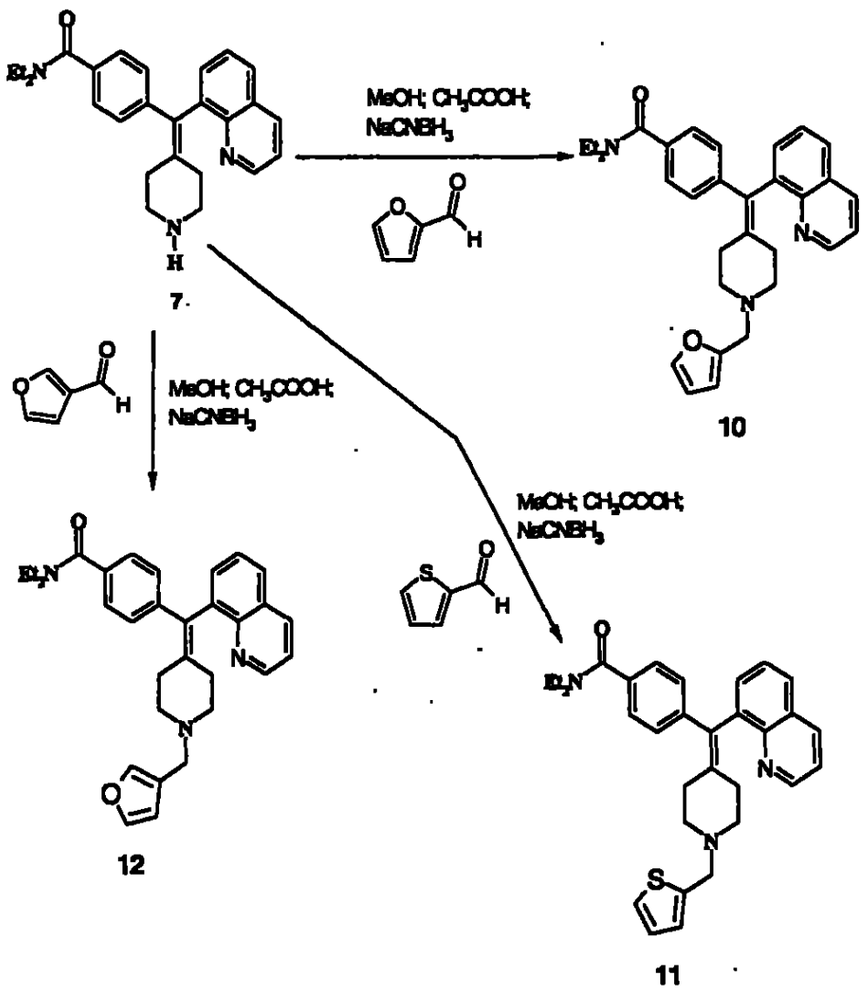
IR (NaCl) 2971, 1625, 1551, 1426, 1287 cm^{-1};

RMN ^1H (400 MHz, $CDCl_3$) δ 1,04 (3 H, br m, $C\underline{H}_3CH_2$-), 1,17 (3 H, br m, $C\underline{H}_3CH_2$-), 2,03 (2 H, m, piperidina C<u>H</u>-), 2,30 (1 H, m, piperidina C<u>H</u>), 2,51 (2H, m, piperidina C<u>H</u>), 2,59 (2 H, m, piperidina C<u>H</u>-), 2,68 (1H m piperidina C<u>H</u>-), 3,19 (2 H, m, $C\underline{H}_2N$-), 3,49 (2 H, m, $C\underline{H}_2N$-), 3,52 (2H, s, $PhC\underline{H}_2N$), 7,35(10 H, m, Ar<u>H</u>), 7,46 (2 H m Ar<u>H</u>), 7,71 (1 H, m, Ar<u>H</u>), 8,10 (1 H, m, Ar<u>H</u>), 8,90 (1 H, m, Ar<u>H</u>).

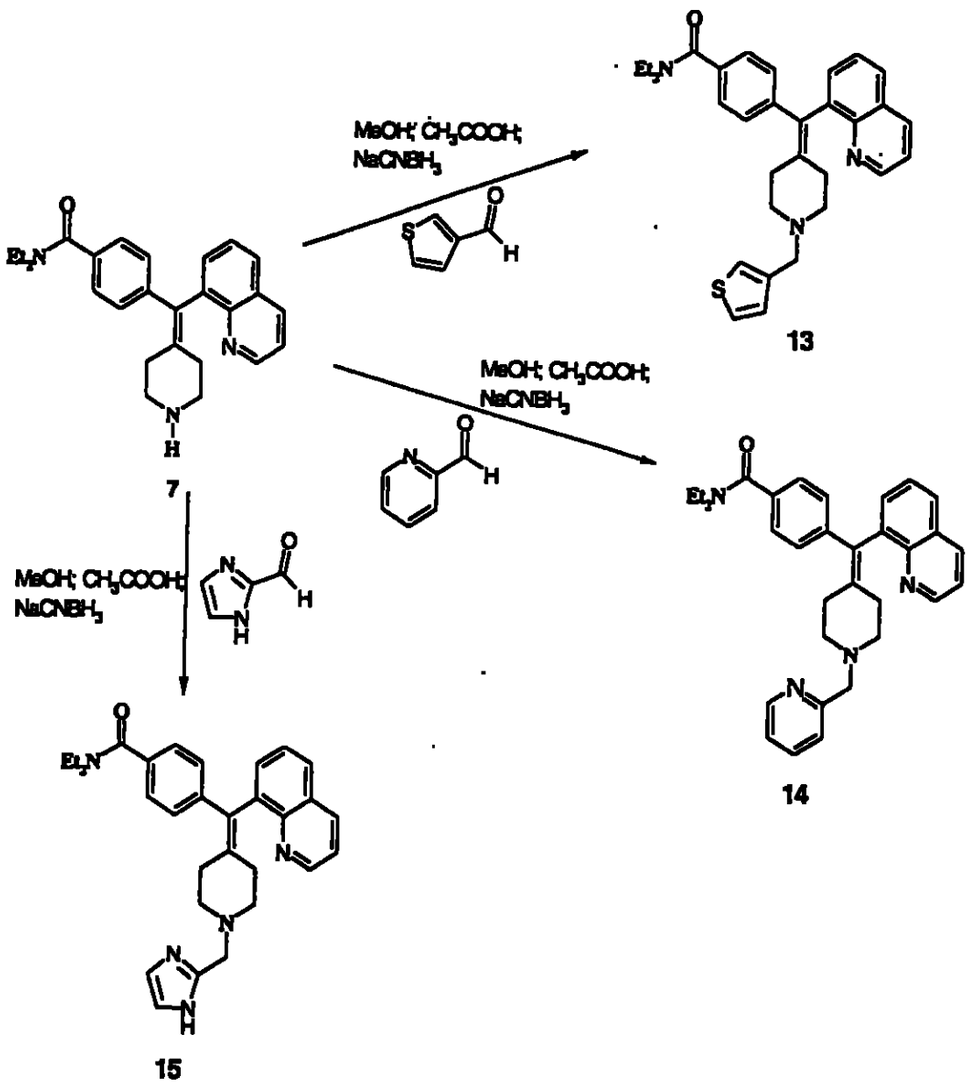
Ejemplos 3-11

Los compuestos 10-18 de los Ejemplos 3-11, se prepararon siguiendo los procedimientos de síntesis ilustrados en el Esquema 2 preseantado a continuación.

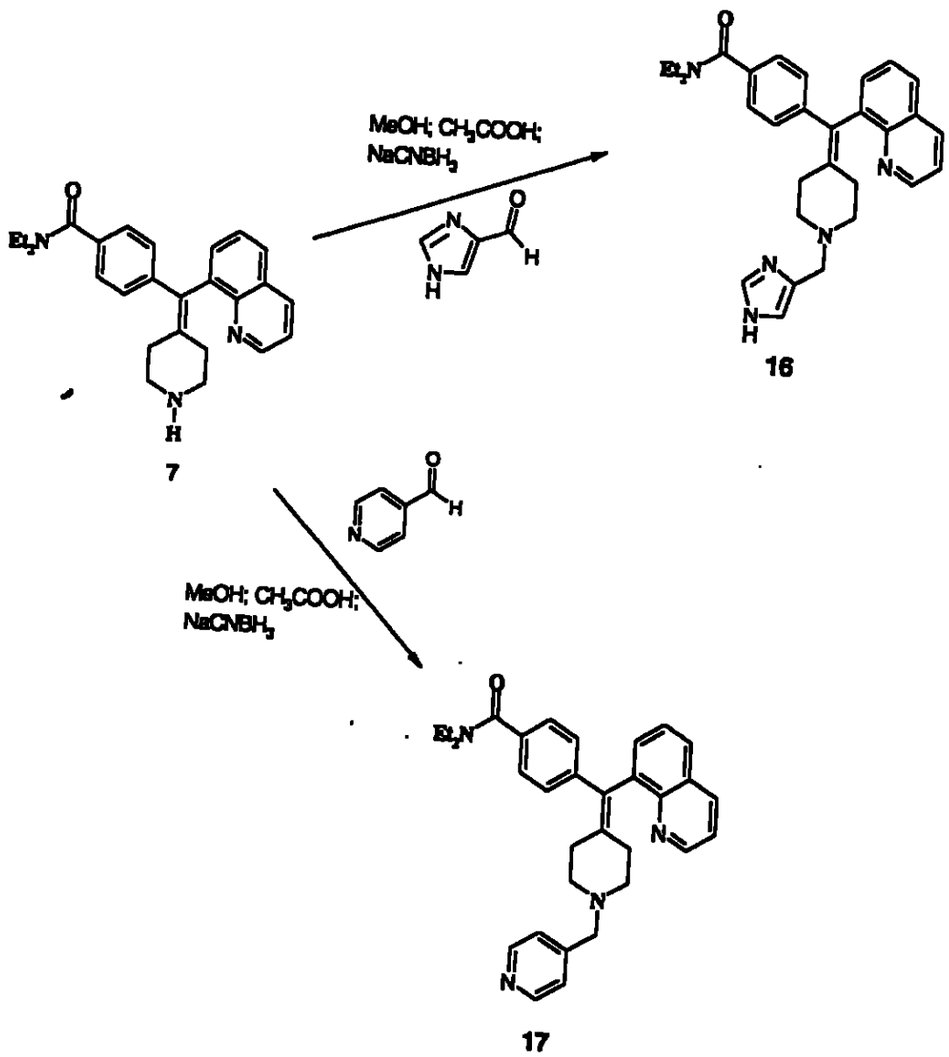
Esquema 2:1(3)



Esquema 2:2(3)


MsOH; CH3COOH;
NaCNBH3
MsOH; CH3COOH;
NaCNBH3
MsOH; CH3COOH;
NaCNBH3
Et2N
7
13
14
15

Esquema 2:3(3)



Ejemplo 3

Preparación de *N,N*-dietil-4-[[1-(2-furilmetil)-4-piperidiniliden](8-quinolino)metil]benzamida (compuesto 10)

A una solución a temperatura ambiente de amina secundaria (300 mg; 0,75 mmol) en metanol (15 mL) se agregó 2-furaldehido (261 µL; 3,15 mmol), seguido por ácido acético (0,5 mL). La mezcla se agitó durante dos horas y luego se agregó cianoborohidruro de sodio (198 mg; 3,15 mmol). La mezcla de reacción se agitó durante una noche, luego se agregó hidróxido de sodio 2 N y la mezcla se extrajo con cloruro de metileno. Los extractos cloruro de metileno combinados se secaron sobre sulfato de sodio anhidro, se filtraron y concentraron bajo condiciones de presión reducida. Purificación en fase reversa.

(M+1) calculado: 480,62, (M+1) observado: 480,16

Análisis calculado para ($C_{31}H_{33}N_3O_2$ X 2,20 $C_2HO_2F_3$ X 1,00 H_2O): C:56,81%,. H:5,01%; N:5,61%; Encontrado: C:56,84%; H:4,96%; N:5,59%.

RMN ^1H (CD_3OD): 8,86-8,90 (m, 1H), 8,38-8,50 (m, 1H), 7,86-7.96 (m, 1H), 7,48-7,66 (m, 4H), 7,31 (d, 2H, J=7,6Hz), 7,21 (d, 2H, J=7,6Hz), 6,61-6,62 (m, 1H), 6,43-6,44 (m, 1H), 4,34 (s, 2H), 2,04-3,62 (m, 12H), 1,07-1,16 (m, 3H), 0,94-1,03 (m, 3H).

Ejemplo 4

Preparación de *N,N*-dietil-4-{(8-quinolinil)[1-(2-tienilmetil)-4-piperidiniliden]metil}benzamida (compuesto 11)

A una solución a temperatura ambiente de amina secundaria (300 mg; 0,75 mmol) en metanol (8 mL) se agregó tiofeno-2-carboxaldehido (294,4 µL; 3,15 mmol), seguido por ácido acético (0,5 mL). La mezcla se agitó durante dos horas y luego se agregó cianoborohidruro de sodio (198 mg, 3,15 mmol). La mezcla de reacción se agitó durante una noche, luego se agregó

hidróxido de sodio 2 N y la mezcla se extrajo con cloruro de metileno. Los extractos cloruro de metileno combinados se secaron sobre sulfato de sodio anhidro, se filtraron y concentraron bajo condiciones de presión reducida. Purificación en fase reversa.

(M+l) calculado: 496,69, (M+1) observado: 496,09

Análisis calculado para: ($C_{31}H_{33}N_3OS$ X 2,50 $C_2HO_2F_3$ X 0,60 H_2O): C:54,63%; H:4,67%; N:5,31%; Encontrado: C:54,62%; H:4,64%; N:5,45%

RMN ^1H (CD_3OD): 8,89-8,90 (m, 1H), 8,42-8,56 (m, 1H), 7,86-7,98 (m, 1H), 7,53 (d, 1H, J=5,2 Hz), 7,50-7,70 (m, 3H), 7,30 (d, 2H, J=7,6 Hz), 7,20-7,24 (m, 1H), 7,20 (d, 2H, J=8,0 Hz), 7,02-7,06 (m, 1H), 4,50 (s, 2H), 2,04-3,66 (m, 12H), 1,06-1,16 (m, 3H), 0,94-1,02 (m, 3H).

Ejemplo 5

Preparación de *N,N*-dietil-4-[[1-(3-furilmetil)-4-piperidiniliden](8-quinolinil)metil]benzamida (compuesto 12)

A una solución a temperatura ambiente de amina secundaria (300 mg; 0,75 mmol) en metanol (8 mL) se agregó 3-furaldehido (272,4 µL; 3.15 mmol), seguido por ácido acético (0,5 mL). La mezcla se agitó durante dos horas y se agregó luego cianoborohidruro de sodio (198 mg; 3,15 mmol). La mezcla de reacción se agitó durante una noche, luego se agregó hidróxido de sodio 2N y la mezcla se extrajo con cloruro de metileno. Los extractos cloruro de metileno combinados se secaron sobre sulfato de sodio anhidro, se filtraron y concentraron bajo condiciones de presión reducida. Purificación en fase reversa.

(M+1) calculado: 480,62, (M+1) observado: 480,33

Análisis calculado para: ($C_{31}H_{33}N_3O_2$ X 1,80 $C_2HO_2F_3$ X 0,80 H_2O): C:59,43%; H:5,25%; N:6,01%; Encontrado: C:59,38%; H:5,24%; N:5,98%

RMN ^1H (CD_3OD): 8,80-8,88 (m, 1H), 8,30-8,42 (m, 1H), 7,80-7,92 (m, 1H), 7,44-7,68 (m, 4H), 7,26-7,36 (m, 2H), 7,16-7,24 (m, 3H), 6,50 (s, 1H) 4,15 (s, 2H), 2,86-3,62 (m, 9H), 2,48-2,66 (m, 1H), 2,06-2,36 (m, 2H), 1,06-1,16 (m, 3H), 0,94-1,04 (m, 3H).

Ejemplo 6

Preparación de *N,N*-dietil-4-{8-quinolinil-[1-(3-tienilmetil)-4-piperidiniliden]metil}benzamida (compuesto 13)

A una solución a temperatura ambiente de amina secundaria (300 mg; 0,75 mmol) en metanol (8 mL) se agregó tiofeno-3-carboxaldehido (276 µL; 3.15 mmol), seguido por ácido acético (0,5 mL). La mezcla se agitó durante dos horas y se agregó luego cianoborohidruro de sodio (198 mg: 3,15 mmol). La mezcla de reacción se agitó durante una noche, luego se agregó hidróxido de sodio 2N y la mezcla se extrajo con cloruro de metileno. Los extractos cloruro de metileno combinados se secaron sobre sulfato de sodio anhidro, se filtraron y concentraron bajo condiciones de presión reducida. Purificación en fase reversa.

(M+1) calculado: 496,69, (M+1) observado: 496,11

Análisis calculado para: ($C_{31}H_{33}N_3OS$ X 2,70 $C_2HO_2F_3$ X 0,70 H_2O): C:53,57%; H:4,58%; N:5,15%; Encontrado: C:53,56%; H:4,54%; N:5,40%

RMN ^1H (CD_3OD): 8,82-8,90 (m, 1H), 8,34-8,50 (m, 1H), 7,82-7,96 (m, 1H), 7,42-7,70 (m, 4H), 7,24-7,36 (m, 2H), 7,20 (d, 2H, J=7,2 Hz), 7,08-7,14 (m, 2H), 4,28 (s, 2H), 2,04-3,58 (m, 12H), 1,06-1,16 (m, 3H), 0,92-1,03 (m, 3H).

Ejemplo 7

Preparación de *N,N*-dietil-4-[[1-(2-piridinilmetil)-4-piperidiniliden](8-quinolinil)metil]benzamida (compuesto 14)

A una solución a temperatura ambiente de amina secundaria (300 mg; 0,75

mmol) en metanol (8 mL) se agregó 2-piridinocarboxaldehido (299,6 µL; 3,15 mmol), seguido por ácido acético (0,5 mL). La mezcla se agitó durante dos horas y se agregó luego cianoborohidruro de sodio (198 mg; 3.15 mmol). La mezcla de reacción se agitó durante una noche, se agregó luego hidróxido de sodio 2 N y la mezcla se extrajo con cloruro de metileno. Los extractos cloruro de metileno combinados se secaron sobre sulfato de sodio anhidro, se filtraron y concentraron bajo condiciones de presión reducida. Purificación en fase reversa.

(M+1) calculado: 491,65, (M+1) observado: 491,11

Análisis calculado para: ($C_{32}H_{34}N_4O$ X 2,40 $C_2HO_2F_3$ X 1,00 H_2O): C:56,50%; H:4,95%; N:7,16%; Encontrado: C:56,47%; H:4,97%; N:7,27%

RMN ^1H (CD_3OD): 8,91 (dd, 1H, J=4,4, 1,2 Hz), 8,57 (d, 1H, l=4,4 Hz), 8,47 (dd, 1H, J=8,0, 1,6 Hz), 7,91 (dd, 1H, J=7,2, 2,8 Hz), 7,79 (dt, 1H, J=8,0, 1,6 Hz), 7,56-7,62 (m, 3H), 7,39 (d, 1H, J=7,2 Hz), 7,32 (d, 2H, J=8,0 Hz), 7,30-7,36 (m, 1H), 7,21 (d, 2H, J=8,4 Hz), 4,41 (s, 2H), 3,08-3,56 (m, 8H), 2,72-2,88 (m, 2H), 2,18-2,36 (m, 2H), 1,06-1,16 (m, 3H), 0,92-1,02 (m, 3H).

Ejemplo 8

Preparación de *N,N*-dietil-4-[[1-(1*H*-imidazol-2-ilmetil)-4-piperidiniliden][(8-quinolinil)metil]benzamida (compuesto 15)

A una solución a temperatura ambiente de amina secundaria (300 mg; 0,75 mmol) en metanol (8 mL) se agregó 2-imidazolcarboxaldehido (302,7 mg; 3,15 mmol), seguido por ácido acético (0,5 mL). La mezcla se agitó durante dos horas luego se agregó cianoborohidruro de sodio (198 mg; 3,15 mmol). La mezcla de reacción se agitó durante una noche, luego se agregó hidróxido de sodio 2 N y la mezcla se extrajo con cloruro de metileno. Los extractos cloruro de metileno combinados se secaron sobre sulfato de sodio anhidro, se filtraron y concentraron bajo condiciones de presión reducida. Purificación en fase reversa.

(M+1) calculado: 480,63, (M+1) observado: 479,97

Análisis calculado para: ($C_{30}H_{33}N_5O$ X 2,80 $C_2HO_2F_3$ X 2,20 H_2O): C:50,99%; H:4,83%; N:8,35%; Encontrado: C:51,07%; H:4,90%; N:8,10%

RMN ^1H (CD_3OD): 8,91 (dd, 1H, J=4,4, 1,2 Hz), 8,60 (d, 1H, J=7,6 Hz), 7,96 (dd, 1H, J=6,4, 3,6 Hz), 7,62-7,68 (m, 3H), 7,39 (s, 2H), 7,30 (d, 2H, J=8,0 Hz), 7,19 (d, 2H, J=8,8 Hz), 4,09 (s, 2H), 3,34-3,46 (m, 2H), 3,02-3,22 (m, 4H), 2,78-2,88 (m, 2H), 2,60-2,70 (m, 2H), 2,04-2,18 (m, 2H), 1,06-1,16 (m, 3H), 0,92-1,02 (m, 3H).

Ejemplo 9

Preparación de *N,N*-dietil-4-[[1-(1*H*-imidazol-4-ilmetil)-4-piperidiniliden](8-quinolinil)metil]benzamida (compuesto 16)

A una solución a temperatura ambiente de amina secundaria (300 mg; 0,75 mmol) en metanol (8 mL) se agregó 4(5)-imidazolcarboxaldehido (302,7 mg; 3.15 mmol), seguido por ácido acético (0.5 mL). La mezcla se agitó durante dos horas y se agregó luego cianoborohidruro de sodio (198 mg, 3.15 mmol). La mezcla de reacción se agitó durante una noche, y luego se agregó hidróxido de sodio 2 N y la mezcla se extrajo con cloruro de metileno. Los extractos cloruro de metileno combinados se secaron sobre sulfato de sodio anhidro, se filtraron y concentraron bajo condiciones de presión reducida. Purificación en fase reversa.

(M+1) calculado: 480,63, (M+1) observado: 480,15

Análisis calculado para: ($C_{30}H_{33}N_5O$ X 3,70 $C_2HO_2F_3$ X 1,20 H_2O): C:48,66%; H:4,27%; N:7,59%; Encontrado: C:48,68%; H:4,33%; N:7,49%

RMN ^1H (CD_3OD): 8,90 (dd, 1H, J=4,4, 1,2 Hz), 8,71-8,74 (m, 1H), 8,53 (d, 1H, 1=8,0 Hz), 7,93 (dd, 1H, J=6,4, 3,6 Hz), 7,58-7,63 (m, 4H), 7,29 (d, 2H, J=8,0 Hz), 7,19 (d, 2H, J=8,8 Hz), 4,40 (s, 2H), 3,28-3,50 (m, 4H), 3,08-3,24 (m, 4H), 2,68-2,84 (m, 2H), 2,14-2,50 (m, 2H), 1,05-1,14 (m, 3H), 0,92-1,02 (m, 3H).

Ejemplo 10

Preparación de *N,N*-dietil-4-[[1-(4-piridinilmetil)-4-piperidiniliden](8-quinolinil)metil]benzamida (compuesto 17)

A una solución a temperatura ambiente de amina secundaria (300 mg; 0,75 mmol) en metanol (8 mL) se agregó 4-piridinocarboxaldehido (241 mg; 2,25 mmol), seguido por ácido acético (0,5mL). La mezcla se agitó durante 30 minutos y luego se agregó cianoborohidruro de sodio (142 mg; 2,25 mmol). La mezcla de reacción se agitó durante una noche, luego se agregó hidróxido de sodio 2 N y la mezcla se extrajo con cloruro de metileno. Los extractos cloruro de metileno combinados se secaron sobre sulfato de sodio anhidro, se filtraron y concentraron bajo condiciones de presión reducida. Purificación en fase reversa.

(M+1) calculado: 491,28, (M+1) observado: 491,09

Análisis calculado para: ($C_{32}H_{34}N_4O$ X 2,60 $C_2HO_2F_3$ X 1,50 H_2O): C:54,88%; H:4,90%; N:6,88%; Encontrado: C:54,87%; H:4,90%; N:6,75%
RMN ^1H (CD_3OD): 8,86-896 (m, 1H), 8,62-8,70 (m, 1H), 8,42-8,52 (m, 1H), 7,88-7,98 (m, 1H), 7,50-7,70 (m, 4H), 7,28-7,38 (m, 3H), 7,16-7,26 (m, 3H), 4,36 (s, 2H), 2,90-3,60 (m, 8H), 2,50-2,90 (m, 2H), 2,00-2,40 (m, 2H), 0,82-1,16 (m, 6H).

Composiciones Farmacéuticas

Los compuestos novedosos acordes con la presente invención pueden administrarse por vía oral, intramuscular, subcutánea, tópica, intranasal, intraperitoneal, intratoráxica, intravenosa, epidural, intratecal, intracerebroventricular o mediante inyección en las articulaciones.

Las rutas de administración preferidas son la oral, la intravenosa o la intramuscular.

La dosificación dependerá de la ruta de administración, la severidad de la enfermedad, edad y peso corporal del paciente y otros factores normalmente considerados por el médico tratante en el momento de determinar el régimen y nivel individual de dosificación que resulte más apropiado para un paciente en particular.

En la preparación de las composiciones farmacéuticas basadas en los compuestos de la presente invención, se pueden utilizar vehículos portadores inertes, farmacéuticamente aceptables, los cuales pueden ser sólidos ó líquidos. Entre las preparaciones en formas sólidas se incluyen los polvos, tabletas, granulados dispersibles, cápsulas, sobres, y los supositorios.

Un portador sólido puede tratarse de una o más sustancias las cuales pueden también actuar como diluentes, agentes saborizantes, solubilizantes, lubricantes, agentes suspensores, aglutinantes, ó agentes desintegrantes de tabletas. Pueden también tratarse de un material de encapsulación.

En el caso de los polvos, el vehículo portador es un sólido finamente dividido el cual se mezclará con el ingrediente activo finamente dividido. En las tabletas, el ingrediente activo se mezcla con el vehículo portador en apropiadas proporciones y con las propiedades de aglomeración necesarias para luego compactar dicha mezcla en la forma y tamaño deseadas.

Para preparar composiciones en forma de supositorios, se funde en primer lugar una cera de bajo punto de fusión tal como una mezcla de glicéridos de ácidos grasos y manteca de cacao, y luego se dispersa el ingrediente activo dentro de dicha mezcla, por ejemplo, por agitación. La mezcla fundida homogénea luego se vierte en moldes del tamaño adecuado y se deja enfriar y solidificar.

Entre los vehículos portadores apropiados se encuentran el carbonato de magnesio, el estearato de magnesio, talco, lactosa, azúcar, pectinas, dextrina, almidón, goma tragacanto, metilcelulosa, carboximetilcelulosa sódica, una cera de bajo punto de fusión, manteca de cacao, y similares.

Entre las sales farmacéuticamente aceptables se incluyen las sales acetato, bencenosulfonato, benzoato, bicarbonato, bitartrato, bromuro, acetato de calcio, camsilato, carbonato, cloruro, citrato, diclorhidrato, edetato, edisilato, estolato, esilato, fumarato, glucaptato, gluconato, glutamato, glicolilarsanilato, hexilresorcinato, hidrabamina, bromhidrato, clorhidrato, hidroxinaftoato, isetionato, lactato, lactobionato, malato, maleato, mandelato, mesilato, metilbromuro, metilnitrato, metilsulfato, mucato, napsilato, nitrato, pamoato (embonate), pantotenato, fosfato/difosfato, poligalacturonato, salicilato, estearato, subacetato, succinato, sulfato, tanato, tartrato, teoclato.

Entre los ejemplos de sales farmacéuticamente aceptables dentro del alcance de la presente invención se encuentran: yodato, perclorato, y tetrafluoroborato.

Entre las sales farmacéuticamente aceptables preferidas se incluyen las sales clorhidrato, sulfato, y bitartrato.

Particularmente preferidas son las sales sulfato y clorhidrato.

Con el término composición se pretende incluir la formulación del ingrediente activo con material de encapsulación a manera de vehículo portador con lo cual se proporciona una cápsula en la cual el ingrediente activo (con ó sin otros vehículos portadores) va rodeado por un vehículo portador el cual entra en asociación con éste. Similarmente, también se incluyen los sobres.

Las tabletas, polvos, sobres, y cápsulas pueden usarse como formas de dosificación sólidas apropiadas para administración oral.

Entre las composiciones líquidas se incluyen las soluciones, suspensiones, y las emulsiones. Las soluciones acuosas ó en agua-propilenglicol, estériles, de los compuestos activos pueden mencionarse como ejemplo de

preparaciones líquidas apropiadas para administración parenteral. Las composiciones líquidas pueden también formularse en solución en forma de soluciones acuosas de polietilenglicol.

Las soluciones acuosas para administración oral pueden prepararse mediante la disolución del ingrediente activo en agua y agregando luego los apropiados colorantes, agentes saborizantes, estabilizantes, y agentes espesantes, según sea deseado. Las suspensiones acuosas para uso oral pueden prepararse por dispersión del ingrediente activo finamente dividido en agua junto con un material viscoso tal como gomas naturales o sintéticas, resinas, metilcelulosa, carboximetilcelulosa sódica, y otros agentes suspensores conocidos en el campo de la formulación farmacéutica.

Preferiblemente, las composiciones farmacéuticas se encuentran en una forma de dosificación unitaria. En dicha forma, la composición se divide en dosis unitarias que contienen las cantidades apropiadas de ingrediente activo. La forma de dosificación unitaria puede tratarse de una preparación envasada o empacada, en donde el envase/empaque contiene cantidades discretas de las preparaciones, por ejemplo, tabletas, cápsulas y polvos envasados en viales o ampollas. La forma de dosificación unitaria puede también encontrarse en forma de cápsula, sobre, ó tableta, ó puede ir empacada de modo que haya cierto número de formas empacadas o envasadas.

EVALUACION BIOLOGICA

Modelo In Vitro

Cultivo de Células

A. Se sembraron células humanas 293S las cuales expresan los receptores humanos clonados μ, δ y κ, y la resistencia a la neomicina, en una suspensión a 37 ^{0}C y presencia de 5% de CO_2 en recipientes con agitación que contenían FBS al 10% en DMEM libre de calcio, BCS al 5%, Pluronic F-68 al 0,1%, y 600 μg/mL de geneticina.

B. Se pesaron cerebros de ratón y rata y se lavaron en PBS (que contenía EDTA 2,5 mM, pH 7,4) enfriada con hielo. Los cerebros se homogeneizaron con un polytron durante 15 seg (ratón) ó durante 30 seg (rata) en buffer para lisis enfriado en hielo (Tris 50 mM, pH 7,0, EDTA 2,5 mM, a lo cual se le agregó fluoruro de fenilmetilsulfonilo justo antes de su uso hasta una concentración de 0,5 mM partiendo de un stock 0,5 M en DMSO:etanol).

Preparación de las membranas

Las células se peletizaron y se volvieron a suspender en el buffer de lisis (Tris 50 mM, pH 7,0, EDTA 2,5 mM, a lo cual se le agregó PMSF justo antes de su uso hasta una concentración de 0,5 mM partiendo de un stock 0,1 M en etanol), se incubaron en hielo durante 15 min, y luego se homogeneizaron con un polytron durante 30 seg. La suspension se centrifugó a 100 g (máx) durante 10 min a 4 °C. El sobrenadante se recuperó sobre hielo y los pellets se volvieron a suspender y centrifugar de la forma antes descrita. Los sobrenadantes provenientes de ambas centrifugaciones se combinaron y se centrifugaron a 46 000 g (máx) durante 30 min. Los pellets obtenidos se volvieron a suspender en buffer Tris enfriado (Tris/Cl 50 mM, pH 7,0) y nuevamente se centrifugaron. Los pellets finales se volvieron a suspender en el buffer para membranas (50 mM de Tris, 0,32 M de sacarosa, pH 7,0). Se tomaron alícuotas (de 1 mL) en tubos de polipropileno y se congelaron en hielo seco/etanol y se conservaron a -70 ^{0}C hasta el momento de su uso. Las concentraciones de proteína se determinaron a través de un ensayo de Lowry modificado con dodecilsulfato de sodio.

Ensayos de ligamiento

Las membranas se descongelaron a 37 ^{0}C, se enfriaron en hielo, se pasaron 3 veces a través de una aguja de calibre 25, y se diluyeron en el buffer de ligamiento (50 mM de Tris, 3 mM de $MgCl_2$, 1 mg/mL de BSA (Sigma A-7888), pH 7,4, lo cual se conservó a 4 ^{0}C después de la filtración a través de

un filtro de 0,22 µ, y a lo cual se le había agregado recientemente 5 µg/mL de aprotinina, 10 µM de bestatina, 10 µM de diprotina A, sin DTT). Se agregaron alícuotas de 100 µL a tubos de polipropileno de 12x75 mm enfriados con hielo que contenían 100 µL del radioligando apropiado y 100 µL de compuesto de prueba a diversas concentraciones. Se determinó el Ligamiento Total (TB) y el ligamiento No Específico (NS) en ausencia y presencia de naloxona 10 µM, respectivamente. Los tubos se agitaron con vórtice y se incubaron a 25 ^{0}C durante 60-75 min, después de lo cual se filtró y lavó rápidamente al vacío con aprox. 12 mL/tubo de buffer de lavado enfriado en hielo (50 mM de Tris, pH 7,0, 3 mM de $MgCl_2$) a través de filtros GF/B (Whatman) pre-empapados durante por lo menos 2 hr en polietilenimina al 0,1%. Se midió luego la radioactividad (dpm) retenida en los filtros usando un contador de rayos beta después de empapar los filtros durante por lo menos 12 hr en miniviales que contenían 6-7 mL de fluido de centelleo. En caso de que el ensayo se monte en una placa de microvaloración de 96 orificios profundos, la filtración se realiza en unifiltros (unidades filtrantes) de 96 lugares de filtración, pre-empapados con PEI, los cuales se lavan con 3 x 1 mL de buffer de lavado, y se secan en un horno a 55 ^{0}C durante 2 h. Se realiza luego el conteo en las placas de filtración usando un TopCount (Packard) después de la adición de 50 µL de fluido de centelleo MS-20/orificio.

Ensayos Funcionales

La actividad agonista de los compuestos se midió por determinación del grado en el cual el complejo receptores - compuestos activa el ligamiento de la GTP a las proteínas G a las cuales se acoplan los receptores. En el ensayo de ligamiento de GTP, la GTP[γ]^{35}S se combina con los compuestos y membranas de ligamiento provenientes de las células HEK-2935 expresantes de receptores opiáceos clonados humanos o provenientes de los cerebros homogeneizados de rata y ratón. Los agonistas estimulan el ligamiento de la GTP[γ]^{35}S en estas membranas. La CE_{50} y valores $E_{máx}$ de los compuestos se determinan a partir de curvas dosis-respuesta. Se efectúan corrimientos a la derecha de las curva dosis-respuesta mediados por el

delta-antagonista (antagonista del receptor delta) naltrindol a fin de verificar que la actividad agonista se encuentra mediada por los receptores delta.

Análisis de los datos

El ligamiento específico (SB) se calculó como la resta de TB - NS, y el SB en presencia de diversos compuestos de prueba se expresó como porcentaje del SB del control. Se calcularon los valores de la CI_{50} y el coeficiente de Hill (n_H) para los ligandos, referido al desplazamiento del radioligando específicamente ligado, usando gráficas logit ó programas de ajuste de curvas tales como Ligand, GraphPad Prism, SigmaPlot, ó ReceptorFit. Los valores de K_i se calcularon a partir de la ecuación de Cheng-Prussoff. Se reportan los valores promedio S.E.M. (mediana del error estándar) de la CI_{50}, K_i y n_H para los ligandos sometidos a prueba en por lo menos tres curvas de desplazamiento. Los datos biológicos se encuentran tabulados en las siguientes páginas.

Tabla 1: Datos Biológicos

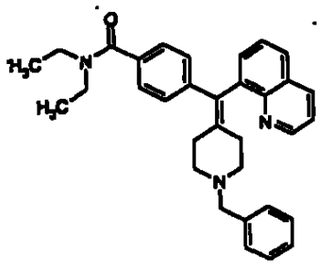
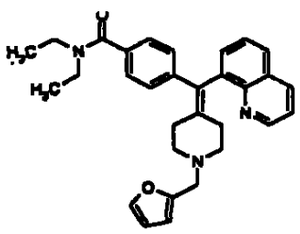
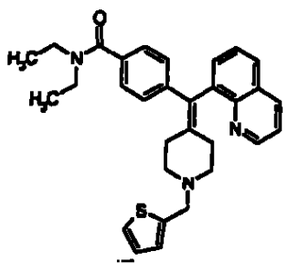
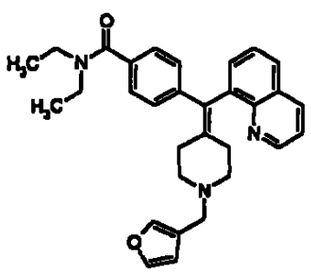
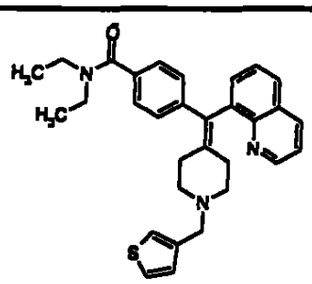
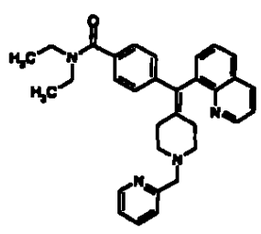
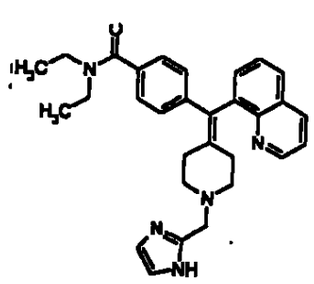
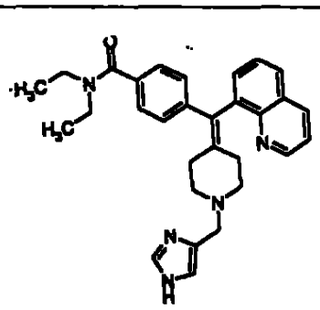
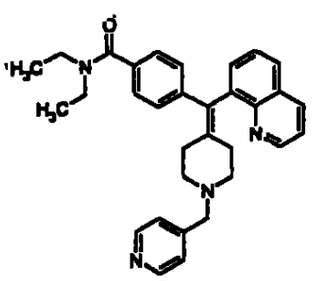
Ej #	ESTRUCTURA MOLECULAR	HDELTA	HDELTA		CEREBRO DE RATA		CEREBRO DE RATON	
			CE_{50}	% E máx	CE_{50}	% E máx	CE_{50}	% E máx
2		1,08	0,49	90,48	3,88	103,53	3,6	111,62
3		0,727	0,18	102,7	4,29	129,65	8,39	145,68
4		0,762	0,26	98,49	1,85	120,16	3,71	140,12
5		0,404	0,14	99,04	1,05	135,2	2,06	146,91

Tabla 1: Datos Biológicos (continuación)

Ej #	ESTRUCTURA MOLECULAR	HDELTA	HDELTA		CEREBRO DE RATA		CEREBRO DE RATON	
			CE_{50}	% E máx	CE_{50}	% E máx	CE_{50}	% E máx
6		0,549	0,38	122,78	3,45	134,62	4,41	140,21
7		0,583	0,25	97,6	2,32	126,28	2,88	124,31
8		0,381	0,28	110,98	3,84	148,15	4,59	138,38
9		0,808	1,9	100,25	38,34	112,17	59,61	122,69
10		0,765	0,8	118,41	33,5	108,52	37,8	110,11

Experimentos de saturación de receptores

Se determinaron los valores Kδ de radioligandos realizando ensayos de ligamiento en las membranas celulares usando los apropiados radioligandos a concentraciones que variaban de 0,2 a 5 veces la Kδ estimada (hasta 10 veces, si las cantidades de radioligando requeridas lo permiten). El ligamiento específico del radioligando se expresó en pmol/mg de proteína de membrana. Los valores de Kδ y Bmáx de los experimentos individuales se obtuvieron a partir de ajustes no lineares del radioligando específicamente ligado (B) versus nM del radioligando libre), de acuerdo a un modelo de un solo sitio.

DETERMINACION DE LA MECANO-ALODINIA USANDO LA PRUEBA DE VON FREY

La prueba se ejecutó entre las 08:00 y 16:0 horas usando el método descrito por Chaplan et al. (1994). Las ratas se colocaron en jaulas de Plexiglas encima de una malla de alambre que permitía el acceso a sus garras, y se dejaron habituar al ambiente durante 10-15 mm. El área de prueba fue la porción media plantar de las patas traseras, evitando aquellas porciones plantares menos sensibles. La garra se tocó con una serie de 8 pelos Von Frey con una dureza logarítmicamente incrementada (0,41, 0,69, 1,20, 2,04, 3,63, 5,50, 8,51, y 15,14 gramos; Stoelting, Ill, USA). El pelo de von Frey se aplicó desde abajo del piso de la malla de alambre, en forma perpendicular a la superficie plantar, con suficiente fuerza para causar un ligero combamiento de la garra, y se sostuvo durante aproximadamente 6-8 segundos. Se registraba como respuesta positiva el hecho de que la garra fuera rápidamente retirada. El estremecimiento del animal inmediatamente después de la remoción del pelo también se consideró como respuesta positiva. La deambulación se consideró como una respuesta ambigua, y en tales casos, el estímulo tenía que repetirse.

PROTOCOLO DE LA PRUEBA

Los animales se sometieron a prueba cumplido el día postoperatorio 1 en

el grupo tratado con FCA. El umbral del retiro 50% se determinó usando el método de Dixon, hacia arriba/hacia abajo (1980). La prueba comenzó con el pelo de 2,04 g, en la mitad de la serie. Los estímulos se proporcionaron de manera consecutiva, ya sea de manera ascendente o descendente. En ausencia de una respuesta de retiro de la pata ante el pelo inicialmente seleccionado, se utilizaba un estímulo más fuerte; y si había retiro de la pata, se escogía el siguiente estímulo más débil. El cálculo óptimo del umbral por este método exige 6 respuestas en la inmediata vecindad del umbral 50%, y el conteo de tales 6 respuestas comenzó cuando ocurría el primer cambio en la respuesta, v.g., el umbral que fue primeramente cruzado. En aquellos casos en donde los umbrales caían por fuera del rango de estímulos, se asignaron valores de 15,14 (sensibilidad normal) ó 0,41 (máximamente alodínico), respectivamente. El patrón resultante de respuestas positivas y negativas se tabuló usando la convención, X = no retiro; 0 = retiro, y el umbral de retiro 50% se interpoló usando la fórmula:

$$\text{Umbral 50\% g} = 10^{(Xf + k\delta)} / 10\,000$$

en donde xf = valor del último pelo von Frey usado (unidades log); k = valor tabular (tomado de Chaplan et al., (1994)) para el patrón de respuestas positivas / negativas; y δ, diferencia promedio entre los estímulos (unidades log). En el presente caso, δ = 0,224.

Los umbrales de von Frey se convirtieron a porcentaje de efecto máximo posible (% MPE, sigla en inglés), según Chaplan et al., 1994. Se usó la siguiente ecuación para calcular el % MPE:

$$\%\ \text{MPE} = \frac{\text{Umbral de tratados con la droga (g)} - \text{umbral de alodinia (g)}}{\text{Umbral de Control (g)} - \text{umbral de alodinia (g)}} \times 100$$

ADMINISTRACION DE LA SUSTANCIA DE PRUEBA

Las ratas se inyectaron (subcutánea, intraperitonea, intravenosa u

oralmente) con una sustancia de prueba antes de la prueba de von Frey, el tiempo entre la administración del compuesto de prueba y la prueba de von Frey variaba dependiendo de la naturaleza del compuesto de prueba.

PRUEBA DE WRITHING

El ácido acético causa contracciones abdominales cuando se administra intraperitonealmente en ratones. Estos estirarán sus cuerpos en un patrón típico. Al administrar drogas analgésicas, tal movimiento característico se observa con mucha menor frecuencia y la droga seleccionada que lo disminuya será una excelente candidata a ser analgésica.

Un reflejo completo y típico de Writhing se considera únicamente cuando están presentes los siguientes elementos: el animal no se encuentra en movimiento; la porción inferior de la espalda se encuentra ligeramente deprimida (bajada); el aspecto plantar de ambas garras es observable. En este ensayo, los compuestos de la presente invención demuestran una significativa inhibición de las respuestas de Writhing después de la dosificación oral de 1-100 µmol/kg.

(i) Preparación de las soluciones

Acido acético (AcOH): 120 µL de ácido acético se agregan a 19,88 mL de agua destilada para obtener un volumen final de 20 mL con una concentración final de 0,6% de AcOH. La solución luego se mezcla (en remolino) y se alista para inyección.

Compuesto (droga): Cada compuesto se prepara y disuelve en el vehículo más apropiado acorde con los procedimientos estándares.

(ii) Administración de las soluciones

El compuesto (droga) se administra por vía oral, intraperitoneal (i.p.),

subcutánea (s.c.) ó intravenosa (i.v.) a una dosis de 10 mL/kg (tomando en cuenta el peso corporal promedio de los ratones) 20, 30 ó 40 minutos (según la clase de compuesto y sus características) antes de la prueba. Si el compuesto se administra centralmente: Intraventricularmente (i.c.v.) ó intratecalmente (i.t.), debe administrarse un volumen de 5 µL.

El AcOH se administra intraperitonealmente (i.p) en dos sitios a dosis de 10 mL/kg (tomando en cuenta el peso corporal promedio de los ratones) inmediatamente antes de la prueba.

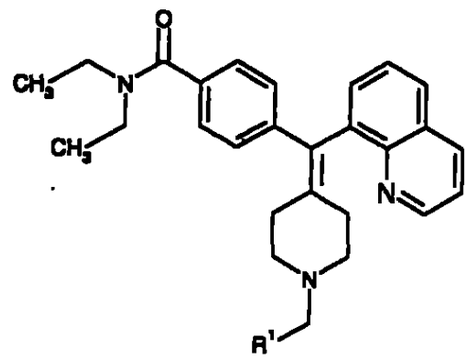
(lii) Prueba

El animal (ratón) se observa durante un período de 20 minutos y el número de eventos reflejos (reflejo de Writhing) se anota y compila al final del experimento. Los ratones se mantienen en jaulas tipo "caja de zapatos" con cama. Se observa usualmente un total de 4 ratones al mismo tiempo: uno de control y tres con dosis de la droga.

~~234~~
234

Reivindicaciones

1. Un compuesto de fórmula I



I

en donde

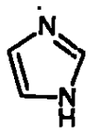
R^1 se selecciona del grupo conformado por

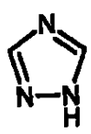
(i) fenil  ;

(ii) piridinil  ;

(iii) tienil  ;

(iv) furanil  ;

(v) imidazolil  ;

(vi) triazolil  ;

en donde cada anillo fenílico R^1 y cada anillo heteroaromático R^1 pueden, opcionalmente e independientemente, ir adicionalmente sustituidos con 1, 2 ó 3 sustituyentes seleccionados entre alquil C_1-C_6 de cadena recta ó ramificada, NO_2, CF_3, alcoxi C_1-C_6, cloro, fluoro, bromo, y yodo,

como también las sales de éste;

2. Un compuesto acorde con la Reivindicación 1, en donde cada anillo fenílico R^1 y cada anillo heteroaromático R^1 pueden de manera independiente ir adicionalmente sustituidos con 1, 2 ó 3 sustituyentes seleccionados entre metil, CF_3, cloro, fluoro, bromo, y yodo.

3. Un compuesto acorde con la Reivindicación 1, en donde cada anillo fenílico R^1 y cada anillo heteroaromático R^1 pueden de manera independiente ir adicionalmente sustituidos con un grupo metil.

4. Un compuesto acorde con la Reivindicación 1, en donde R^1 es piridinil, tienil ó furanil.

5. Un compuesto acorde con la Reivindicación 1, seleccionado del grupo conformado por:

- *N,N*-dietil-4-(8-quinolinil-N-bencil-piperidin-4-iliden-metil)-benzamida;
- *N,N*-dietil-4-[[1-(2-furilmetil)-4-piperidiniliden](8-quinolino)metil]benzamida;
- *N,N*-dietil-4-{8-quinolinil)[1-(2-tienilmetil)-4-piperidiniliden]-metil}benzamida;
- *N,N*-dietil-4-[[1-(3-furilmetil)-4-piperidiniliden](8-quinolinil)metil]-benzamida;
- *N,N*-dietil-4-{8-quinolinil[1-(3-tienilmetil)-4-piperidiniliden]metil}-benzamida;

- *N,N*-dietil-4-[[1-(2-piridinilmetil)-4-piperidiniliden](8-quinolinil)-metil]benzamida;

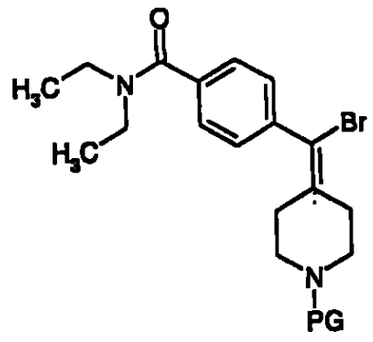
- *N,N*-dietil-4-[[1-(1*H*-imidazol-2-ilmetil)-4-piperidiniliden](8-quinolinil)[metil] benzamida;

- *N,N*-dietil-4-[[1-(1*H*-imidazol-4-ilmetil)-4-piperidiniliden](8-quinolinil)metil]benzamida; y

- *N,N*-dietil-4-[[1-(4-piridinilmetil)-4-piperidiniliden](8-quinolinil)-metil]benzamida;

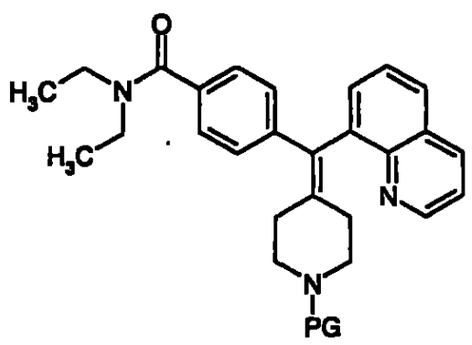
6. Un compuesto acorde con cualquiera de las Reivindicaciones precedentes, en forma de sus sales clorhidrato, diclorhidrato, sulfato, tartrato, ditrifluoroacetato ó citrato.

7. Un proceso para la preparación de un compuesto de fórmula I, proceso que comprende la reacción de un compuesto de fórmula general II



II

en donde PG es un grupo protector tipo uretano ó tipo bencil, con ácido 8-quinolinilbórico, usando un catalizador a base de paladio en presencia de una base para obtener un compuesto de fórmula general III,



III

compuesto el cual luego se desprotege bajo condiciones estándar, y se alquila bajo condiciones reductoras con un compuesto de fórmula general R^1-CHO, para producir así compuestos de fórmula general I.

8. Un compuesto acorde con la Reivindicación 1 de uso en terapia.

9. Un compuesto acorde con la Reivindicación 8, en donde la terapia es el manejo del dolor.

10. Un compuesto acorde con la Reivindicación 8, en donde la terapia se dirige a los desórdenes gastrointestinales.

11. Un compuesto acorde con la Reivindicación 8, en donde la terapia se dirige a las lesiones de la columna vertebral.

12. Un compuesto acorde con la Reivindicación 5, en donde la terapia se dirige a los desórdenes del sistema nervioso simpático.

13. El uso de un compuesto acorde con la fórmula I de la Reivindicación 1, para la manufactura de un medicamento útil en el tratamiento del dolor, desórdenes gastrointestinales o de lesiones de la columna vertebral.

14. Una composición farmacéutica que comprende un compuesto de fórmula I acorde con la Reivindicación 1 como ingrediente activo, junto con un vehículo portador farmacéuticamente aceptable.

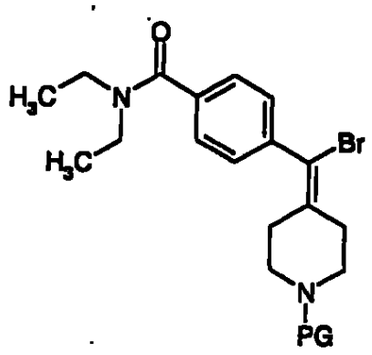
15. Un método para el tratamiento del dolor, mediante el cual una cantidad eficaz de un compuesto de fórmula I acorde con la Reivindicación 1, se administra a un sujeto en necesidad de manejo del dolor.

16. Un método de tratamiento de desórdenes gastrointestinales, mediante el cual una cantidad eficaz de un compuesto de fórmula I acorde con

la Reivindicación 1, se administra a un sujeto que sufra dicho desorden gastrointestinal.

17. Un método de tratamiento de lesiones de la columna vertebral, mediante el cual una cantidad eficaz de un compuesto de fórmula I acorde con la Reivindicación 1, se administra a un sujeto que sufra dicha lesión espinal.

18. Un compuesto de fórmula general II



II

en donde PG es un grupo protector tipo uretano ó bencil.

239

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE

PATENTE DE INVENCIÓN [X] **MODELO DE UTILIDAD [ ]**

- Indicación de que se solicita la concesión de una patente [X] 1
- Datos de identificación del solicitante o de la persona que presenta la solicitud [X] 1
- Descripción de la invención [X]
- *Dibujos de ser estos pertinentes* [ ]
- Comprobante de Pago de las tasas establecidas [X] 2

COMPLETA [X] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

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

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de trazado. [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud. [ ]
- Representación gráfica del esquema de trazado [ ]
- Comprobante de pago de las tasas establecidas. [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

SUPERINDUSTRIA Y COMERCIO
Radicacion : 02004271 00000000 Folios: 238
Fecha (AMD): 2002-10-01 16:18:04
Tramite 1 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Fecl

Carrera 13 No. 27-00 Piso 5 y 10
Conmutador: 334 12 21-2-3-4
Fax: 281 31 25 e-mail: info@sic.gov.co
Santa Fe de Bogotá D.C. - Colombia