TORIO

Industria y Comercio
SUPERINTENDENCIA

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SUPERINDUSTRIA Y COMERCIO
Radicacion : 02088280
Fecha (MM) 2002-10-01 16 21:12 Folios 240
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 Suecia

Lugar de Constitución Södertälje Suecia

Teléfono 3264270 Fax 6069701

E-mail jllcco@lloredacamacho com

IDENTIFICACION

C C ☐ NIT ☐

C E ☐ Otro ☐

Cual _____

Número _____

③ REPRESENTANTE 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 William Brown y Christopher Walpole

Dirección AstraZeneca R & D Montreal 7171 Frederick Banting St Laurent Quebec H4S 1Z9 (CA) y AstraZeneca R & D Montreal 7171 Frederick Banting St Laurent Quebec H4S 1Z9 (CA)

Nacionalidad o Domicilio Quebec Canadá

⑤ PCT (86)

Solicitud Internacional No PCT/SE01/00707 Fecha 30/03/01

Publicación Internacional No WO 01/74804 A1 Fecha 11/10/01

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

⑦ Clasificación Internacional (51) C07D 401/06 405/06,409/06 211/60, A61K 31/4523, A61P 25/04 25/00

⑧ Prioridad SI ☒ NO ☐

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SE	04-04-00	0001207-0

⑨ Comprobante de Pago No 02-60 230 **Fecha** Septiembre 10/02

(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 y documentos citados en el Reporte de Búsqueda, y publicación con su traducción

(11) FIGURA CARACTERISTICA.

(12) Solicito la concesión de la patente

NOMBRE JOSE ANTONIO LLORADA

FIRMA _____

C C 17 159 681 Bta T P 10.784

2

Industria y Comercio

SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Radicacion : 02004288 00000000 Folios 240
Fecha (AMD) 2002 10-01 16:21:12
Tramite 011 PCT-PATENT 379 FASE NAC1 411 PRESENTAC
Dependencia 2020 DIVISION DE NUEVAS CREACIONES

NIT 800176089 2

RECIBO OFICIAL DE CAJA 02 - 60,230
FECHA : SEPTIEMBRE 10 DE 2002

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No PAGO	FECHA PGO	Vr PAGO
LLOREDA Y CIA S A	CONSIGNACION	BANCO POPULAR	050 00110-6	3036788	10/09/2002	15,000 00
LLOREDA Y CIA S A	CONSIGNACION	BANCO POPULAR	050-00110-6	3036789	10/09/2002	2,351,000 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 N 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 Publico

ANNA SALAMANCA DE ABREU
TRADUCTORA OFI
RES [illegible]

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

4

5

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL N RTE

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

CONSULADO DE COLOMBIA EN LONDRES
CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
03 SET 2002
PABLO MENDEZ BARAJAS
NOTARIO (E)

JAIME SALAMANCA DE ABREU
TRADUCTORA
REG. MINJUSTICIA 282

6

CERTIFICACION EN ESPAÑOL DEL CONSULADO GENERAL DE COLOMBIA EN LONDRES

Firmado **JAIME LOZADA PERDOMO**

Cónsul General

MINISTERIO DE RELACIONES EXTERIORES

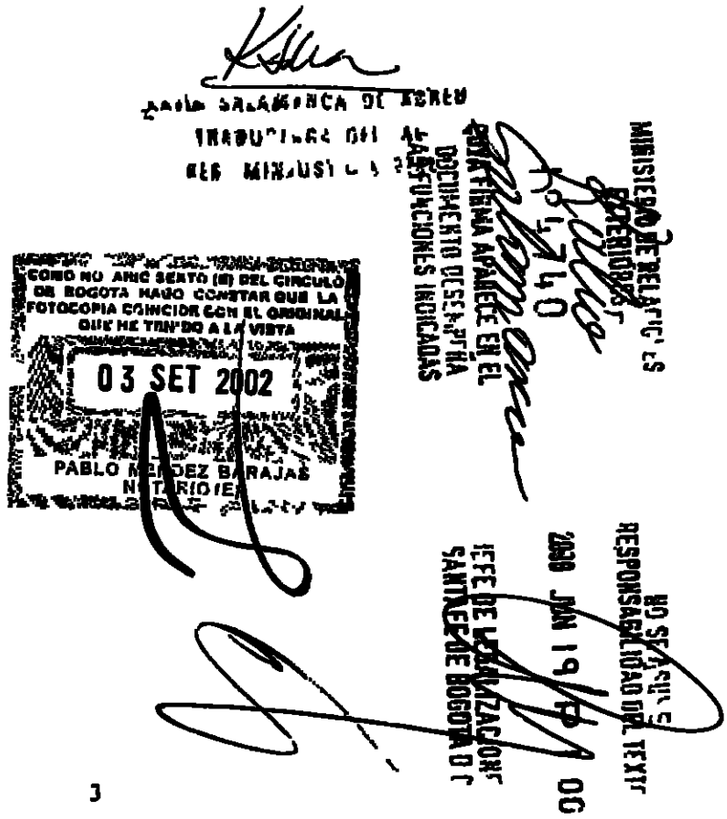
SANTA FE DE BOGOTA

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 16-19 GREAT TITCHFIELD STREET LONDON W1P 7FB
TELEPHONE 020-7637 9893 TELEFAX 020-7637 5604
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 Publico 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 organizada y existente en Sodertalje Suecia, y que cumple con su objeto social de acuerdo con las leyes de ese pais

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

CONSULADO GENERAL DE COLOMBIA LONDRES

MINISTERIO DE RELACIONES EXTERIORES
LA FIRMA APARECE
DOCUMENTO DES
LAS FUNCIONES INDICADAS
03 SET 2002
PABLO MENDEZ BARAJAS
NOTARIO
LEGALIZACION
BOGOTA D.C.

8

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 those measures which they may deem fit for the protection of our interests and in case of opposition, where the 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 arrangements 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 our representatives and/or the agents by any one of them appointed shall lawfully 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 23 Day of MARCH 2000

SUSAN MARGARET EVANS

NOTARY SHOULD EXECUTE OTHER SIDE

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)

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

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 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)

EN BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA CONCUERDA CON EL ORIGINAL QUE ME FUE PRESENTADO A LA VISTA
03 SEP 2002

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

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 del Estado de Suecia domiciliada en la ciudad de Sodertalje, Condado de Suecia, Estado de 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 legalación 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 (CORPORATION)

United States of America
State of {ss
County of
On this 23 day of March of 2000 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, domiciled at the City of Sodertalje, Sweden, and legally constituted for a period of tenure not yet expired that the deponent is authorized by said Company to confer this power of atto. y that the seal affixed hereunto by the deponent in the name and on behalf of said Corporation is the corporate seal ther f 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 under date of and hereby certifies that under the laws of said State the foregoing acknowledgment is sufficient proof that the facts therein contained are true, which he attests

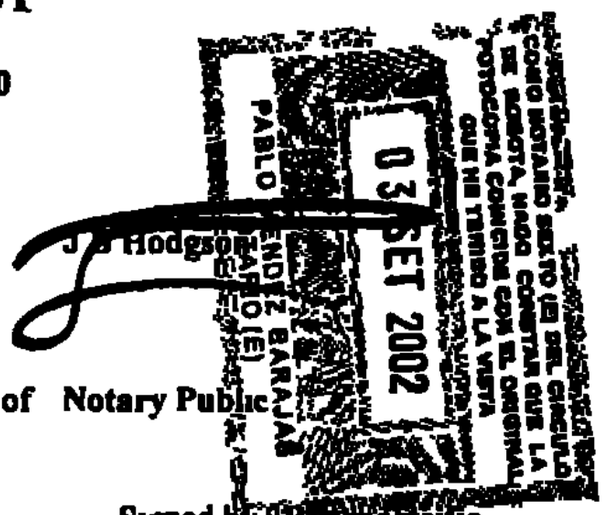
9.

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

No **D617801**

Date **15 May, 2000**

This document bears
the signature / seal of J. S. Hodgson



Acting in the capacity of **Notary Public**

Signed by D. Amarteifio



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

10

FORMATO DE DIGITALIZACION
RELACION DE ANEXOS

Royal Technologies S.A

Item	Expediente No	02088280	No de Folio
		No de Unidades	√
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 Arte final

xe exhaen tduo
10,11,12, extract ythingetc

13

TRATADO DE COOPERACION DE PATENTES
PCT
REPORTE DE BUSQUEDA INTERNACIONAL

11

(PCT Articulo 18 y Reglas 43 y 44)

Registro de referencia del solicitante o agente 100001 1 WO	**PARA FUTURAS ACCIONES** ver Notificación o Transmisión del Reporte de Búsqueda Internacional (Forma PCT/ISA/220) así como, donde aplique, el Item 5 a continuación	
Solicitud internacional No. PCT/SE 01/00707	Fecha de registro internacional *(dia/mes/año)* 30/03/01	Fecha de Prioridad (Primera) *(dia/mes/año)* 04/04/00
Solicitante **AstraZeneca AB**		

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 subsiguentemente 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 Recuadro I).

3 ☐ **Falta unidad de invención** (ver Recuadro 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.

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REPORTE DE BUSQUEDA INTERNACIONAL

Solicitud Internacional No.
PCT/SE01/00707

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

Este informe 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 hoja siguiente

2 ☐ Reivindicaciones Nos

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 busqueda internacional cubre unicamente aquellas reivindicaciones para las cuales se pagaron derechos específicamente las reivindicaciones Nos

4 ☐ El solicitante no pago 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

15

13

REPORTE DE BUSQUEDA INTERNACIONAL

Solicitud Internacional No
PCT/SE01/00707

Casilla III TEXTO DEL RESUMEN (Continuación del ítem 5 de la primera hoja)

Las reivindicaciones 15 17 se relaciona con métodos de tratamiento del cuerpo humano o animal mediante cirugía o terapia/métodos de diagnóstico practicados sobre el cuerpo humano o animal/Regla 39 1 (iv) No obstante se realizo una búsqueda para estas reivindicaciones La búsqueda se ha basado en los efectos alegados de los compuestos/composiciones

REPORTE DE BUSQUEDA INTERNACIONAL

Solicitud Internacional No.

PCT/SE 01/00707

A CLASIFICACION DE MATERIA

IPC7 C07D 401/06 C07D 403/06 C07D 409/06, 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 anteriormente

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 AKTIEBOLAG), 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	

☒ 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

'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
30 de Julio de 2001	31/07/2001
Nombre y dirección de correo de ISA Swedish Patent Office Box 5055 S-102 42 STOCKHOLM Fax +46 8 666 02 86	**Funcionario autorizado** Solveig Gustavsson/BS Tel +46 8 782 25 00

REPORTE DE BUSQUEDA INTERNACIONAL

Solicitud Internacional No
PCT/SE 01/00707

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., 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 Página 5455 – página 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 Página 3895 – página 3905 página 3897 compuesto 8 y esquema 3	7 18

18

16

REPORTE DE BUSQUEDAINTERNACIONAL

Solicitud Internacional No
PCT/SE 01/00707

Documentos de patente citados en el informe 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	00/00/00
		JP 2000502679 T	07/03/00
		NO 982807 A	19/08/98
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		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

Forma PCT/ISA/210 (anexo familia de patentes) (Julio 1992)

17 19
CH

PATENT C OPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To

Global Intellectual Property
AstraZeneca AB
151 85 Södertälje

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	CODE	DATE	NTD
100001-1 WO			

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.		International filing date (day/month/year)
PCT/SE01/00707	ANKOI 02 AUG 2001 IPS	30-03-2001

Applicant	DATA ENTERED
AstraZeneca AB et al	FINAL CHECK

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.

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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/	Authorized officer
Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No 08-667 72 88 Telex 17878 PATOREG-S	Eric Vilval Telephone No 08-782 25 00

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

20

18

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 100001-1 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 01/00707	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/SE01/00707

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.

Claims 15-17 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on 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

21 23

INTERNATIONAL SEARCH REPORT

International application No
PCT/SE 01/00707

A CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 401/06, C07D 405/06, C07D 409/06, 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 AKTIEBOLAG), 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
- L earlier application or patent but published on or after the international filing date
- I 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
- I 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)

22 24

INTERNATIONAL SEARCH REPORT

International application No
PCT/SE 01/00707

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 esquema -- --------	7,18 ✓

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/07/01

International application No
PCT/SE 01/00707

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
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		BR 9612204 A	13/07/99
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		CZ 9801768 A	16/09/98
		EP 0915855 A	19/05/99
		HU 9901304 A	30/08/99
		IL 124996 D	00/00/00
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		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

D1 24 25

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).

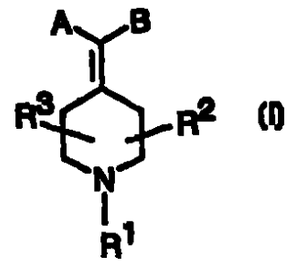
(72) Inventors; and
(75) Inventors/Applicants (*for US only*): DELORME, Daniel [CA/CA]; 793 Charbonneau, St. Lazare, Quebec J7T 2B2 (CA). ROBERTS, Edward [GB/CA]; 2541 Chestnut Circle, St. Lazare de Vaudreuil Quebec J7T 2A1 (CA). WEI Zhongyong [CA/CA]; 17750 Antoine-Faucon, Pierrefonds, Quebec H9J 3N2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

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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

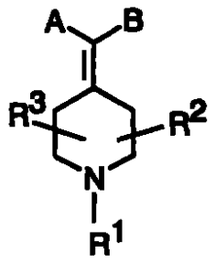
Thus, the problem underlying the present invention was to find new compounds having improved analgesic effects but also with an improved side-effect profile over current μ agonists and potential oral efficacy

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)

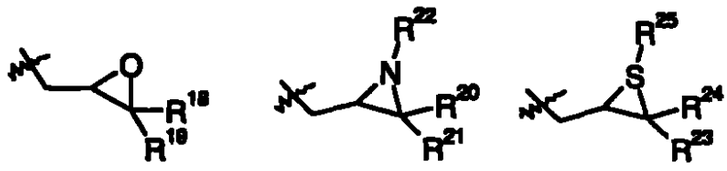
wherein

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,

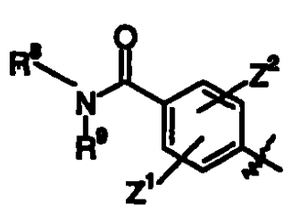
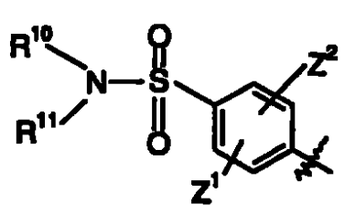
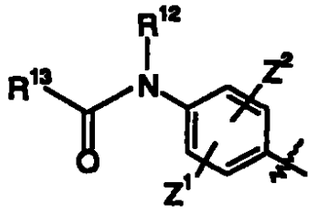
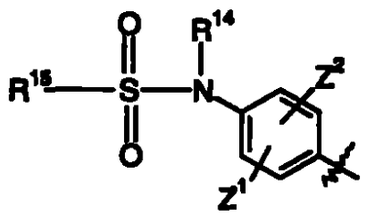
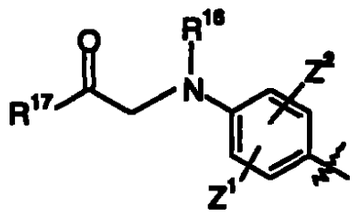
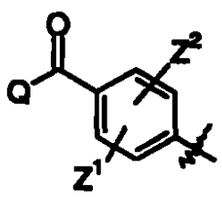
(C_1-C_2 alkyl)-(C_6-C_{10} aryl) or (C_1-C_2 alkyl)heteroaryl the heteroaryl moieties having from 5 to 10 atoms selected from any of C, S N and O, and where the aryl or heteroaryl may optionally and independently be substituted by 1 or 2 substituents independently selected from any of hydrogen CH_3 $-(CH_2)_qCF_3$ 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,

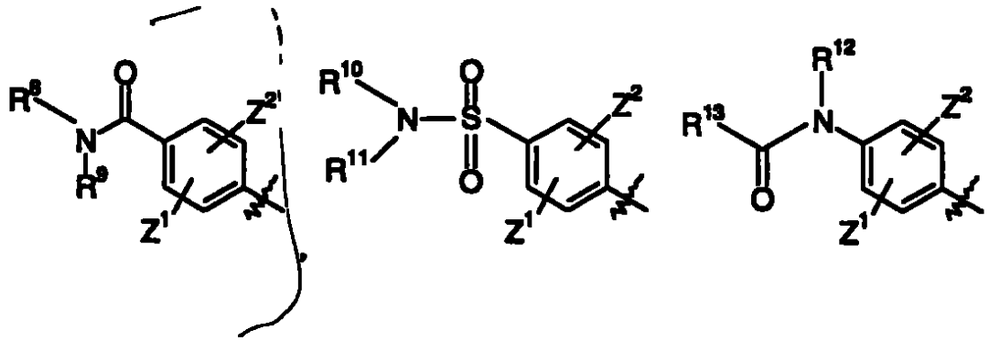
B is a substituted or unsubstituted aromatic, heteroaromatic, hydroaromatic or heterohydroaromatic moiety having from 5 to 10 atoms selected from any of C S N and O optionally and independently substituted by 1 or 2 substituents independently selected from hydrogen, CH_3 $—(CH_2)_tCF_3$ halogen $—(CH_2)_tCONR^5R^4$ $—(CH_2)_tNR^5R^4$, $—(CH_2)_tCOR^5$, $—(CH_2)_tCOOR^5$, $—OR^5$ $—(CH_2)_tSOR^5$ $—(CH_2)_tSO_2R^5$ 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

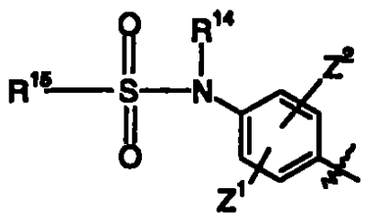
R^4 and R^5 is each and independently as defined for R^1 above.

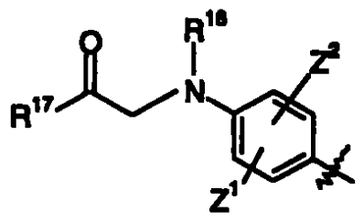
Within the scope of the invention are also pharmaceutically acceptable salts of the compounds of the formula (I) as well as isomers hydrates isoforms and prodrugs thereof

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

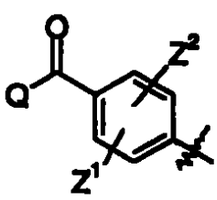
A is selected from







, 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

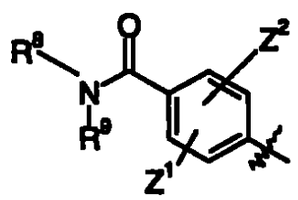
$-(CH_2)_pSO_2NR^5$ wherein R^4 and R^5 is each and independently as defined for R^1 above and p is 0 1 or 2

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.

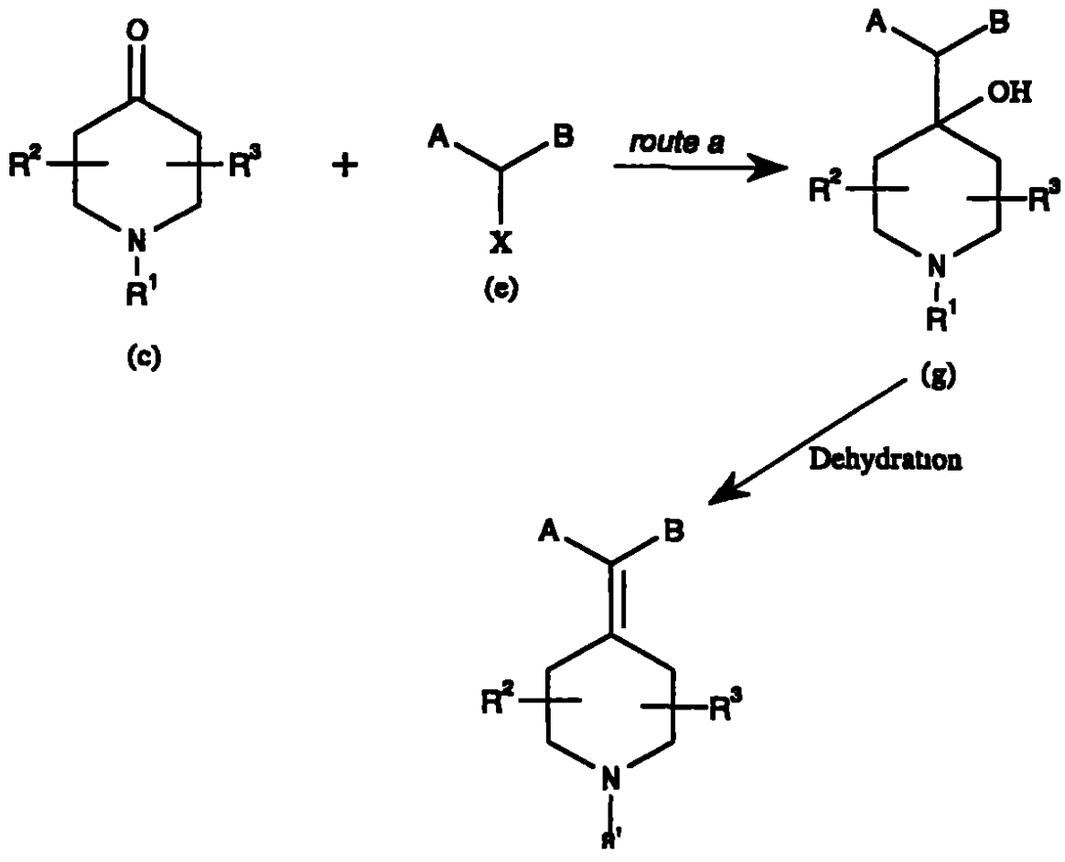
Also within the scope of the invention is the use of any of the compounds according to the formula (I) above, for the manufacture of a medicament for the treatment of any of the conditions discussed above.

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.

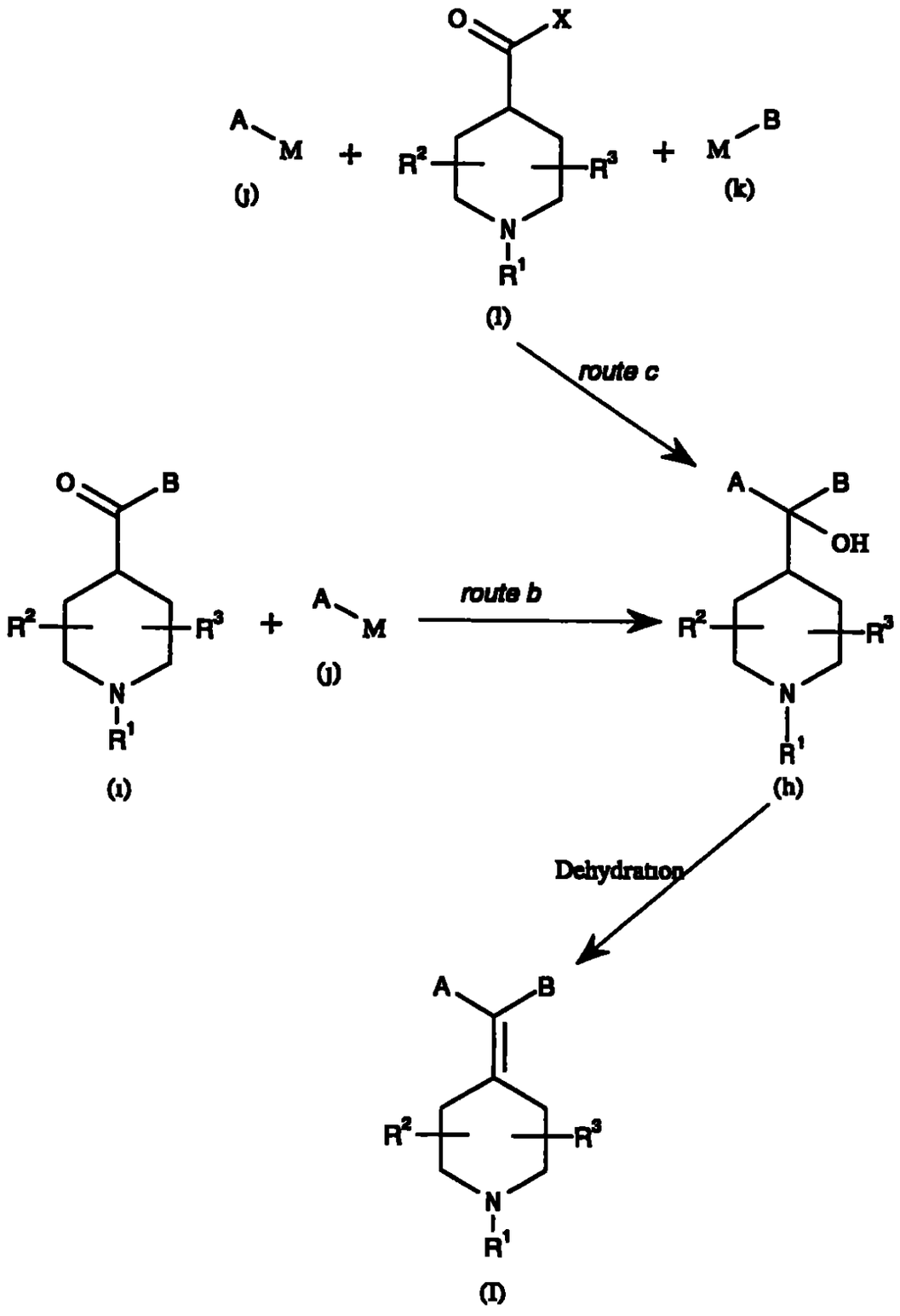
Methods of preparation

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

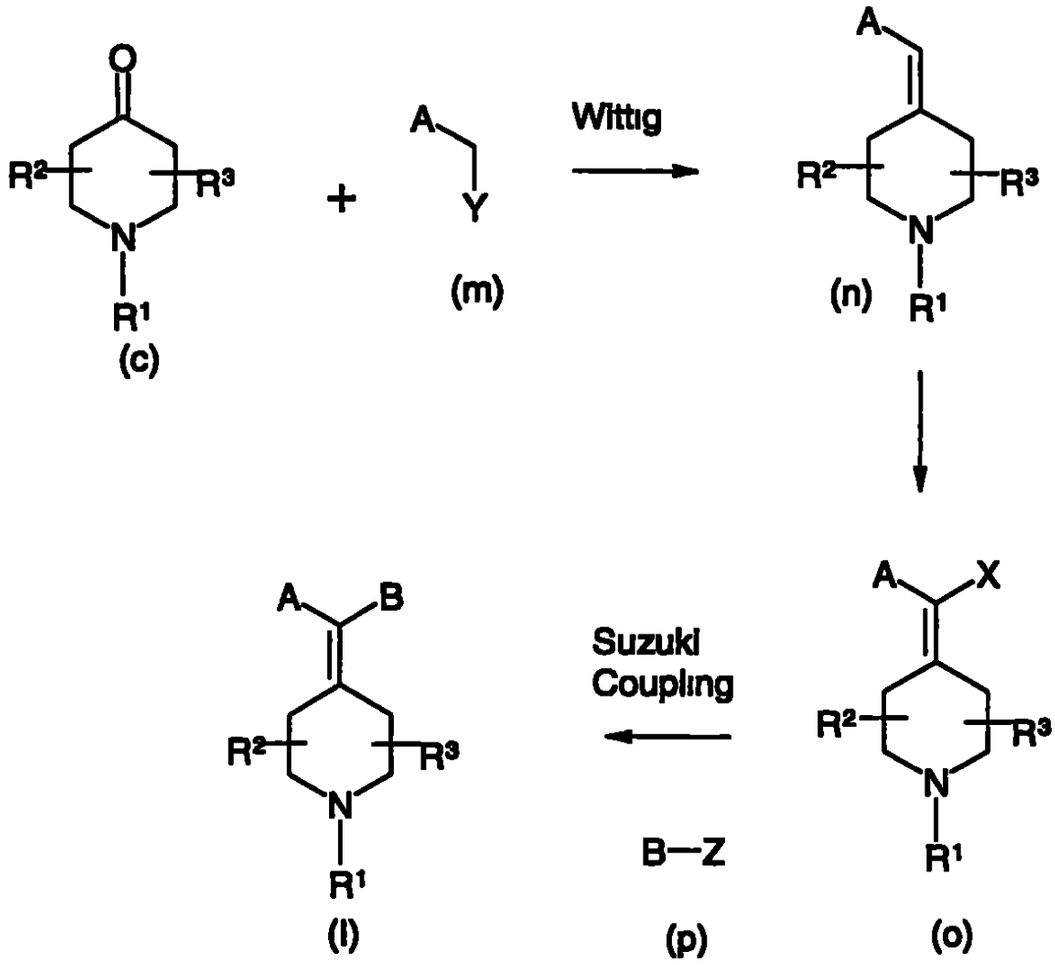
SCHEME I



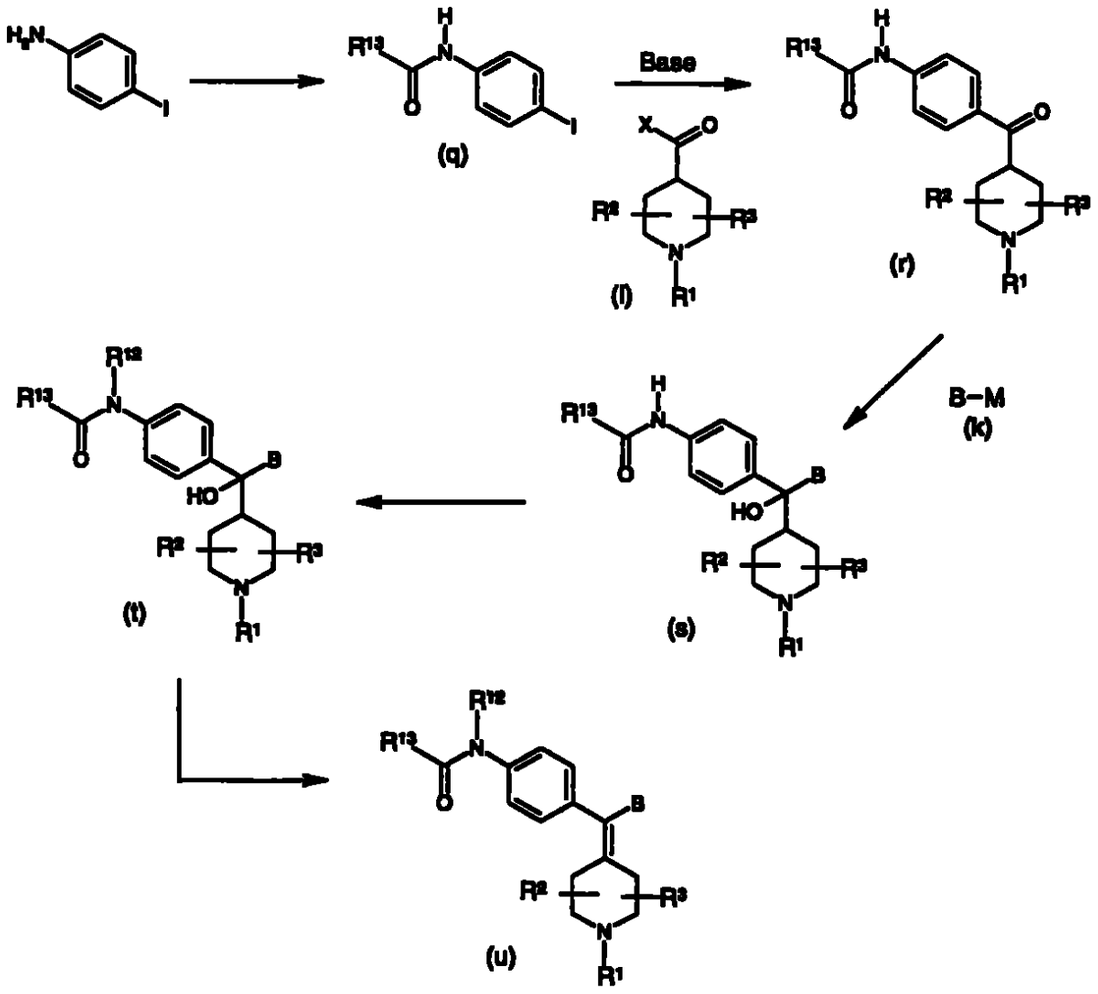
SCHEME II


O
X
A
M
(j)
+
R2
R3
N
R1
(I)
+
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 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 (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 elumination 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 elumination 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)

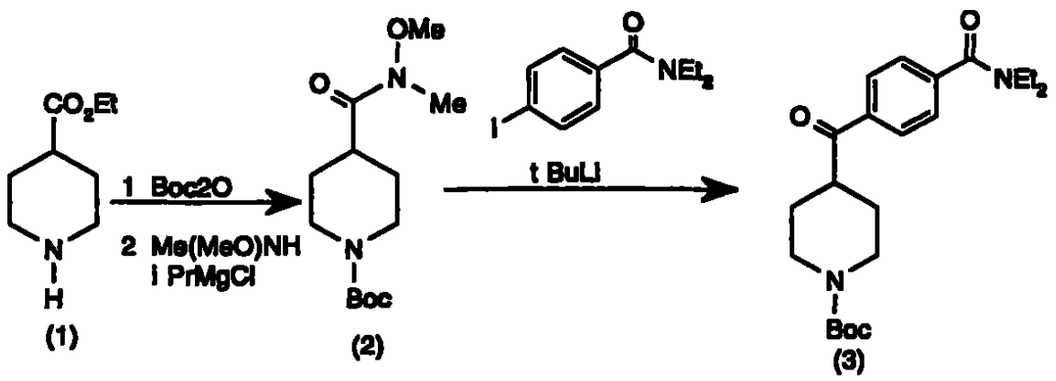
As shown in SCHEME IV compounds of formula (q) may be obtained by acylation of 4-iodoaniline using either acylanhydride or acylchloride in an organic solvent such as dichloromethane The substituent R^{13} of compound (q) is as defined above

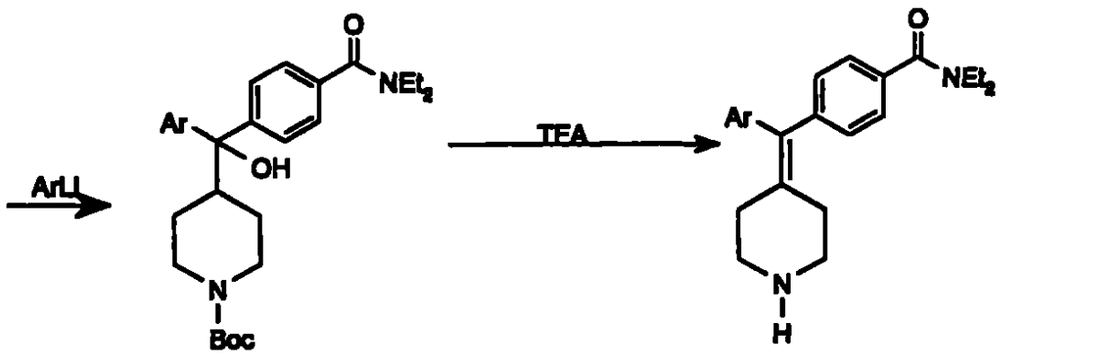
The invention will now be described in more detail by way of the following Examples which are not to be construed as limiting the invention in any way

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

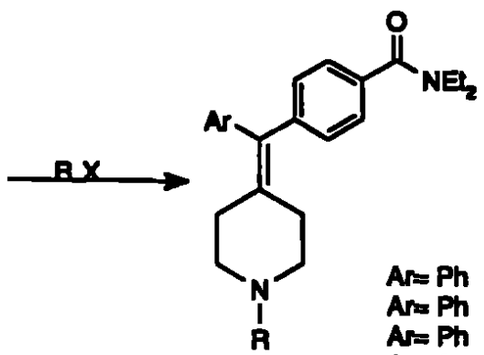
Scheme 1





Ar= 1-naphthyl (4)
Ar= 2 6-dimethylphenyl (5)

Ar= Phenyl (6) Example 1
Ar= 1-naphthyl, (7) Example 2
Ar=2 6-dimethylphenyl (8) Example 3



Ar= Ph R= PhCH2 (10) Example 5
Ar= Ph R= cyclopropylmethyl (12) Example 7
Ar= Ph R= 2,3-epoxylpropyl (11) Example 6
Ar= 1 naphthyl R=allyl (9) Example 4

(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 compund 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,

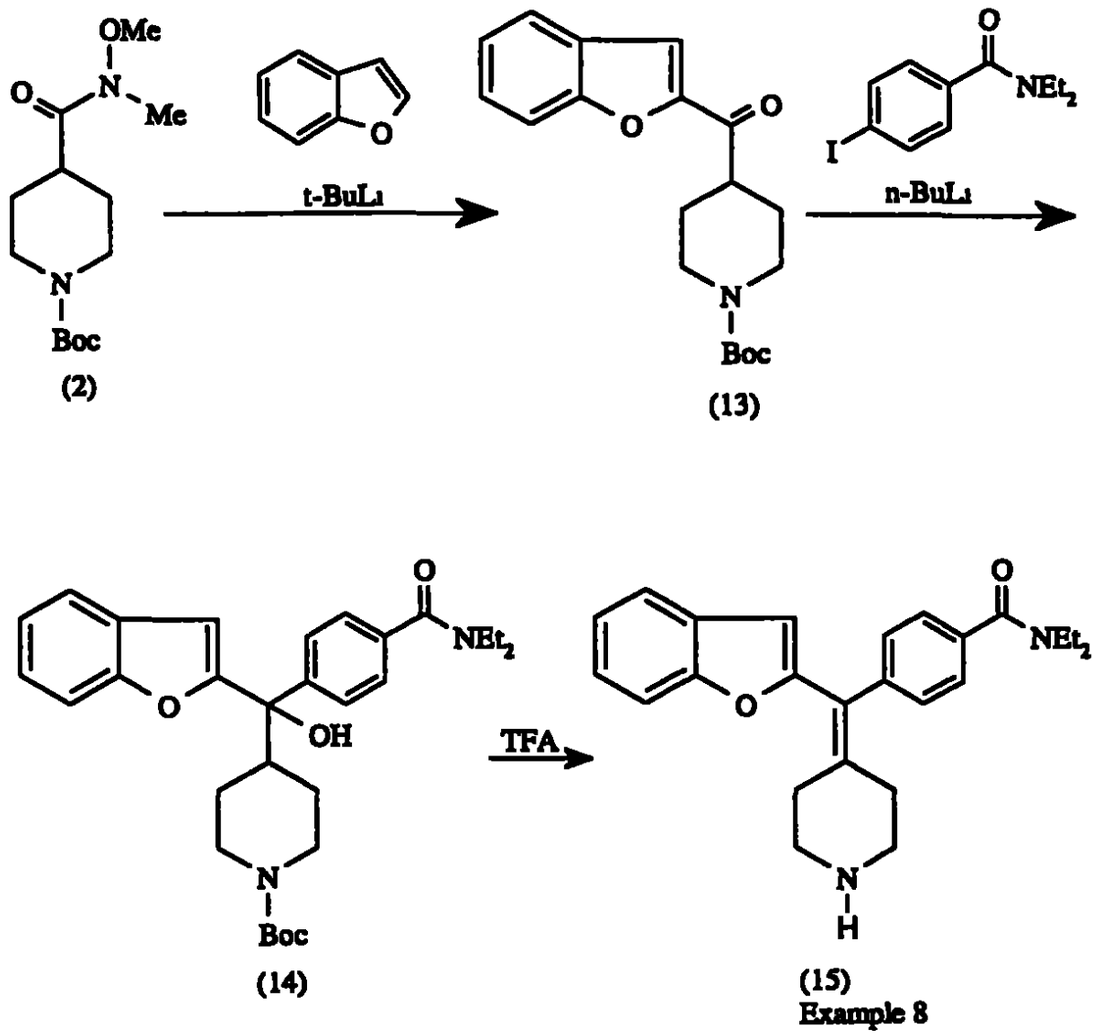
Anal Calcd.for $C_{27}H_{34}N_2O$ 1 0 HCl 0 50CH_2Cl_2 0 75H_2O· C 66 73, H, 7 64 N 5 66

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

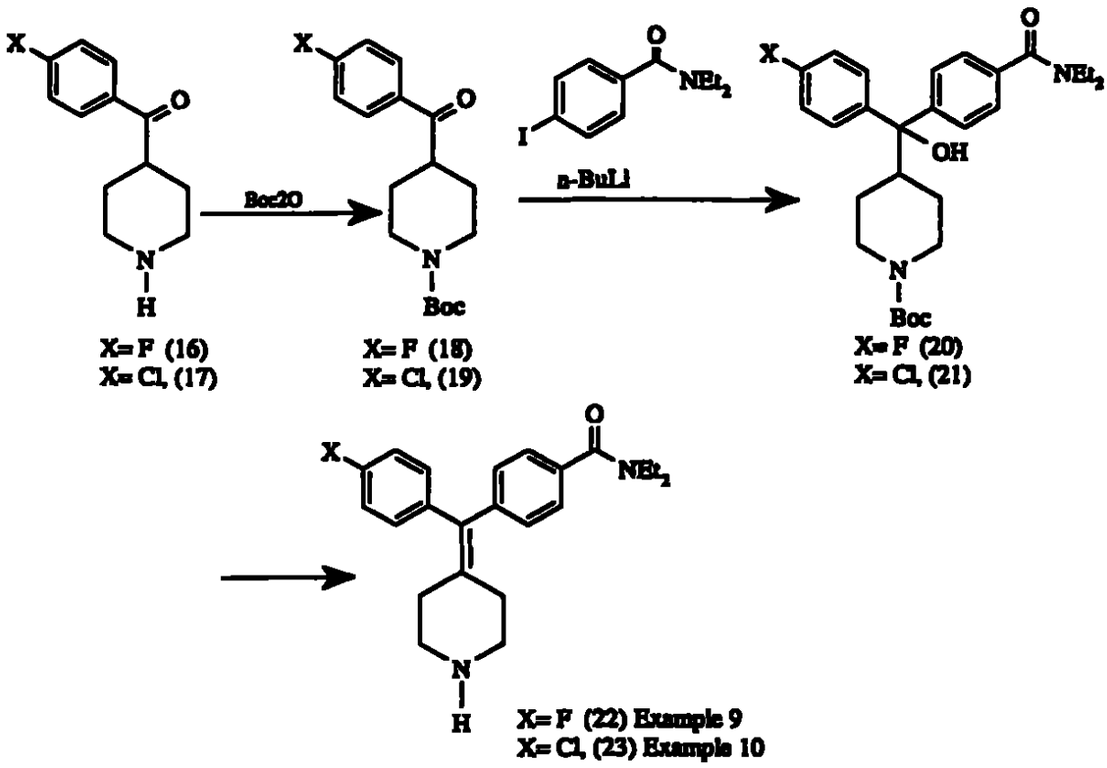
Its HCl salt: Dec ≥ 120 ^{0}C(AcOEt-Ether-CH_2Cl_2),

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-yliden-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)

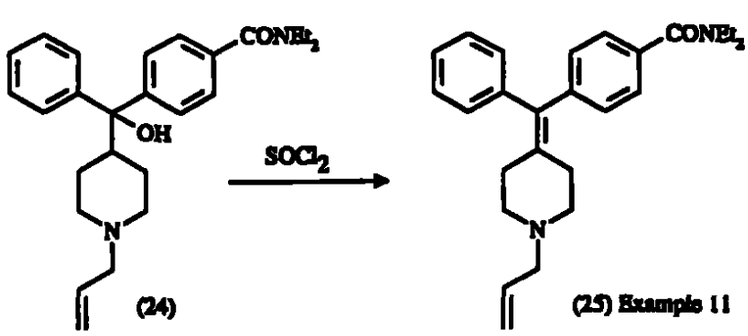
Method as described for Example 1 (compound 6) using compound 21

^{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)

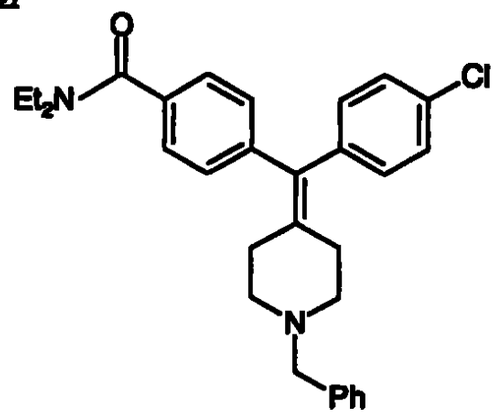
4-(α-hydroxy-α-(4-N-allylpiperidinyl)-benzyl)-N,N-diethylbenzamide (compound 24) (81mg) was dissolved in CH_2Cl_2 (10 ml) and was treated with thionyl chloride (2 ml) at r t. The reaction mixture was refluxed for 2 hrs and then condensed. The residue was dissolved in ethyl acetate (50 mL) and the resulting 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)

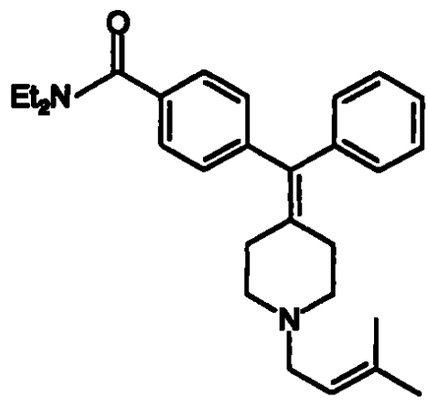
Method as described for Example 4, using compound 23 (96 mg) and benzyl bromide (43 mg) provided N,N-diethyl-4-(4-chlorophenyl-N-benzyl-piperidin-4-ylidene-methyl)-benzamide (110 mg, 93%)

^{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 °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.

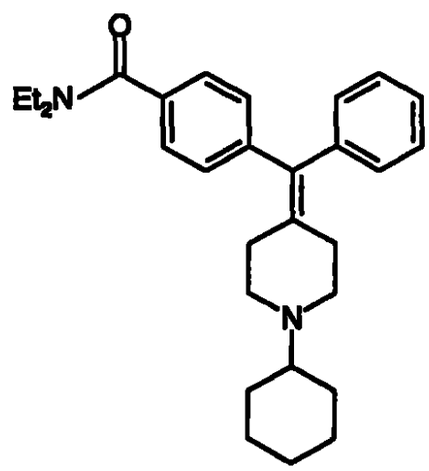
IR (NaCl Film) HCl salt ν =3432, 2976 1623 1434 cm^{-1}

^{1}H NMR. (Base) ($CDCl_3$ TMS) δ 1 10~1.30 (6H, br $OCNCH_2\underline{CH_3}$) 1 64 (3H, s, $=CC\underline{H_3}$) 1 73 (3H, s $=CC\underline{H_3}$), 2.40 (4H, m, $NC\underline{H_2}CH_2$) 2 52 (4H, m, $=CC\underline{H_2}$) 3 0 (2H, d, J=7 6Hz, $NC\underline{H_2}CH=C$), 3 20~3 60 (4H, br, $OCNC\underline{H_2}CH_3$) 5 28 (1H, m, $NCH_2C\underline{H}=C$), 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-yl)-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

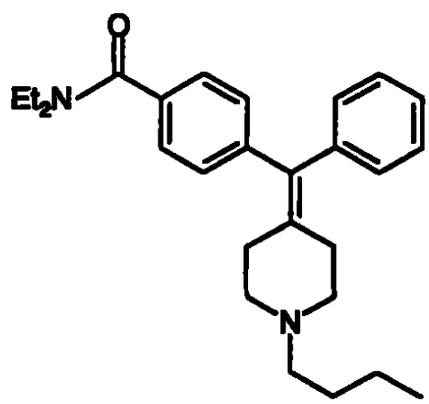
(1H, m, CH(CH)C=C) 2 30 (3H m, NCH2 and NCH) 2.60 (2H, m, NCH2) 3 20 (2H, bs NCH2CH3), 3 50 (2H, bs, NCH2CH3), 7 00-7 30 (9H, m, Ar)

^{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.

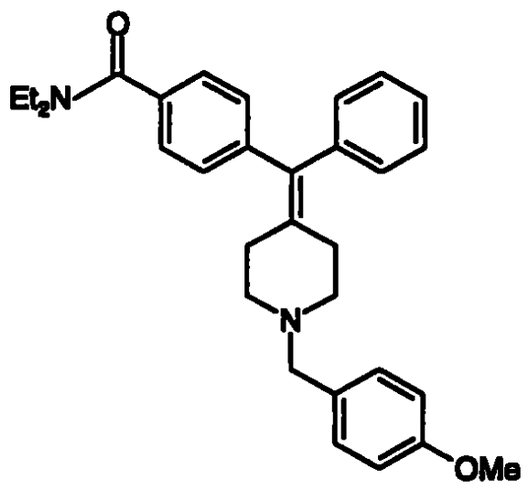
IR (NaCl Film) (HCl salt) ν =3430 2967 2499, 1622, 1433cm^{-1}

^{1}H NMR. ($CDCl_3$ TMS) δ 0 92 (3H, t, *J*=7 2Hz CH_2CH_3) 1 10–1 26 (6H br OCNCH2CH3) 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 OCNCH2CH3) 7 10–7 31 (9H m,

Ar)ppm. ANALYSIS (%) *Anal.*Calcd.for $C_{27}H_{36}N_2O \cdot HCl \cdot 0.4CH_2Cl_2 \cdot 0.4H_2O$ 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)

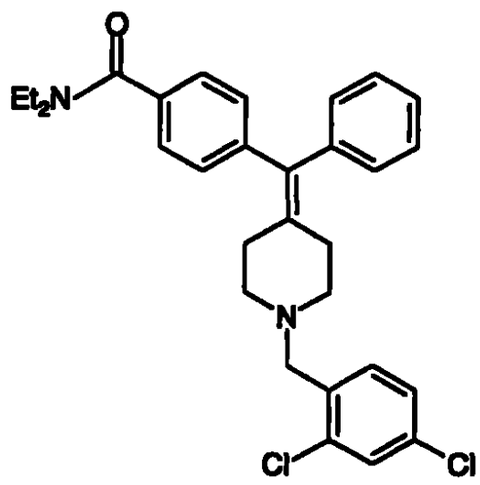
IR (KBr) 3425 2974, 1618 1515 1434 1255 cm^{-1},

Anal.Calcd.for $C_{31}H_{36}N_2O_2 \cdot 1.0HCl \cdot 0.35CH_2Cl_2$ 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)

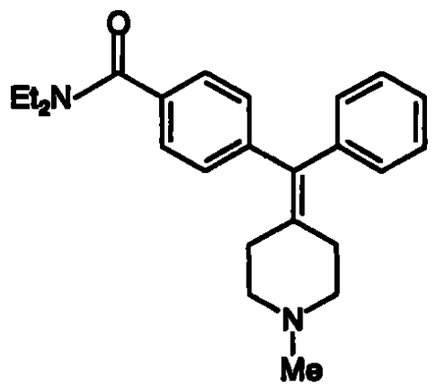
IR (KBr) 3408 2976 1620 1472, 1436 1288 1101 cm^{-1},

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 dissolved 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

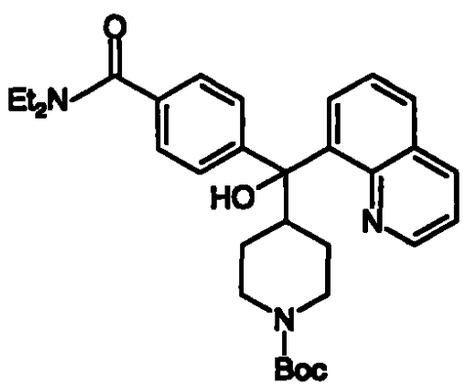
MS(free amine) 362 318, 219 189 165 144.

^{1}H 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 %

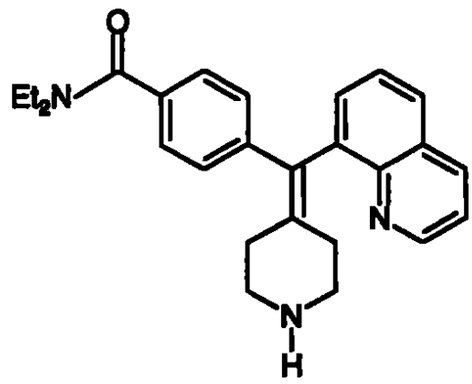
Found. C, 71 50 % H 7 75 %, ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1 07 (3 H br, CH_3CH_2N-) 1 19 (3 H, br CH_3CH_2N-) 1 24 (1 H, m, piperidine CH-) 1 43 (9 H s, CH_3C) 1 65 (1 H, m, piperidine CH-) 1 89 (2 H, m, piperidine CH-) 2 52 (1 H m, piperidine CH-) 2 64 (1 H br piperidine CH-) 2.78

(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 trifluoromethanesulfonic 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 ^{0}C (Dec)

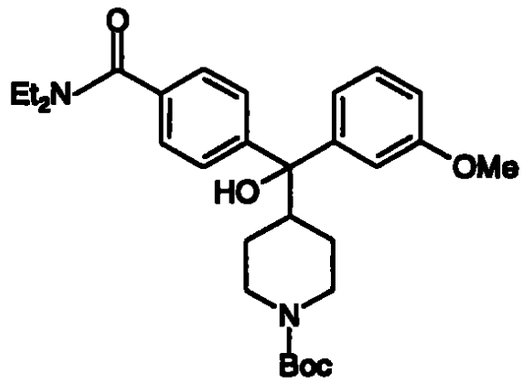
IR (KBr) 3410, 2973 1614 1551 1436 1284 cm^{-1}

Anal.Calcd.for $C_{28}H_{39}N_3O$ 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-methyll-benzamide (compound 35)



(35)

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

m.p 95-103 ^{0}C,

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

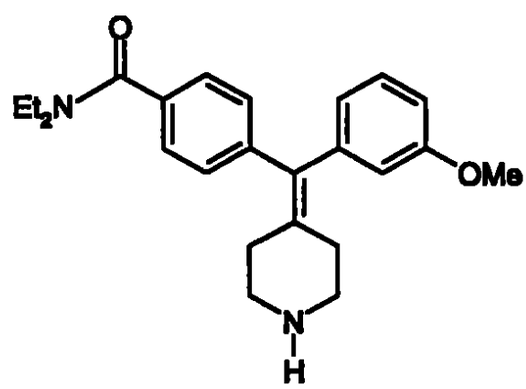
Anal.Calcd.for $C_{29}H_{40}N_2O_5$ 0 60H_2O C 68 64 % H, 8 18 % N 5 52 %

Found. C 68 66 % H, 7 98 % N 5 64 % ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1 07 (3 H, br $C\underline{H}_3CH_2N$-) 1 19 (3 H, br, $C\underline{H}_3CH_2N$-) 1 31 (4 H, m, piperidine C$\underline{H}$-) 1 41 (9 H s $C\underline{H}_3C$) 2 46 (1 H, m, piperidine C$\underline{H}$-), 2 64 (2 H, br piperidine C$\underline{H}$-) 3.22 (2 H, br $CH_3C\underline{H}_2N$-) 3 49 (2 H br $CH_3C\underline{H}_2N$-) 3 65 (1H s O$\underline{H}$), 3 72 (3H s O$C\underline{H}_3$) 4 06 (2 H, br piperidine C$\underline{H}$-) 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)

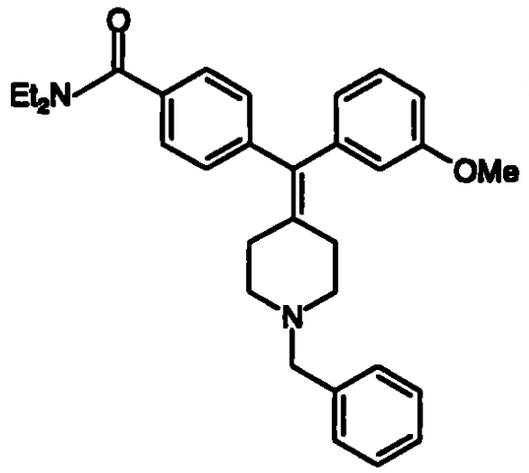
Its HCl salt. m.p > 90 °C (Dec) IR (NaCl) 2970 1621, 1430 1287 cm^{-1},

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)

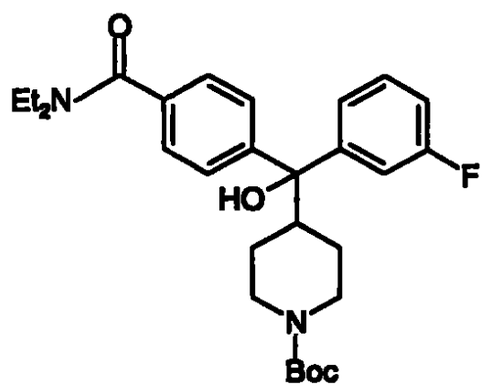
Method as for Example 4 using the compound of Example 22 (38 mg) provided N,N-diethyl-4-[(N-benzyl)-3-methoxyphenyl-piperidin-4-ylidene-methyl]-benzamide (46 mg 98 %)

^{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 48 (4 H, br, piperidine CH-) 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 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 °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)



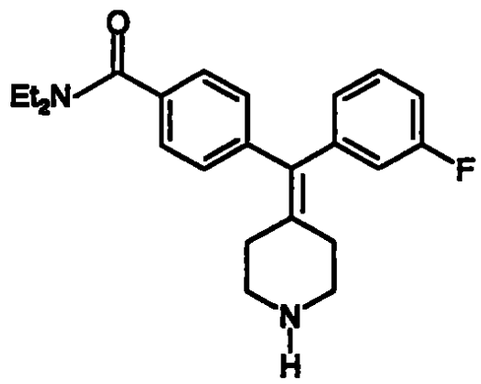
(38)

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, $C\underline{H}_3CH_2N$-) 1 19 (3 H, br $C\underline{H}_3CH_2N$-), 2.09 (1H, s, N$\underline{H}$), 2.25 (4 H, m, piperidine C$\underline{H}$-) 2 84 (4 H, br, piperidine C$\underline{H}$-) 3 23 (2 H br $CH_3C\underline{H}_2N$-), 3 47 (2 H, br $CH_3C\underline{H}_2N$-) 6 74 (1 H m, Ar$\underline{H}$) 6 86 (2H, m, Ar$\underline{H}$) 7 06 (2 H, d J = 8 0 Hz, Ar$\underline{H}$) 7 18 (1H m Ar$\underline{H}$) 7 24 (2 H, d, J = 8 0 Hz, Ar$\underline{H}$)

Its HCl salt. m.p > 70 °C (Dec)

IR (NaCl) 2978 1605, 1478 1432, 1290 cm^{-1}

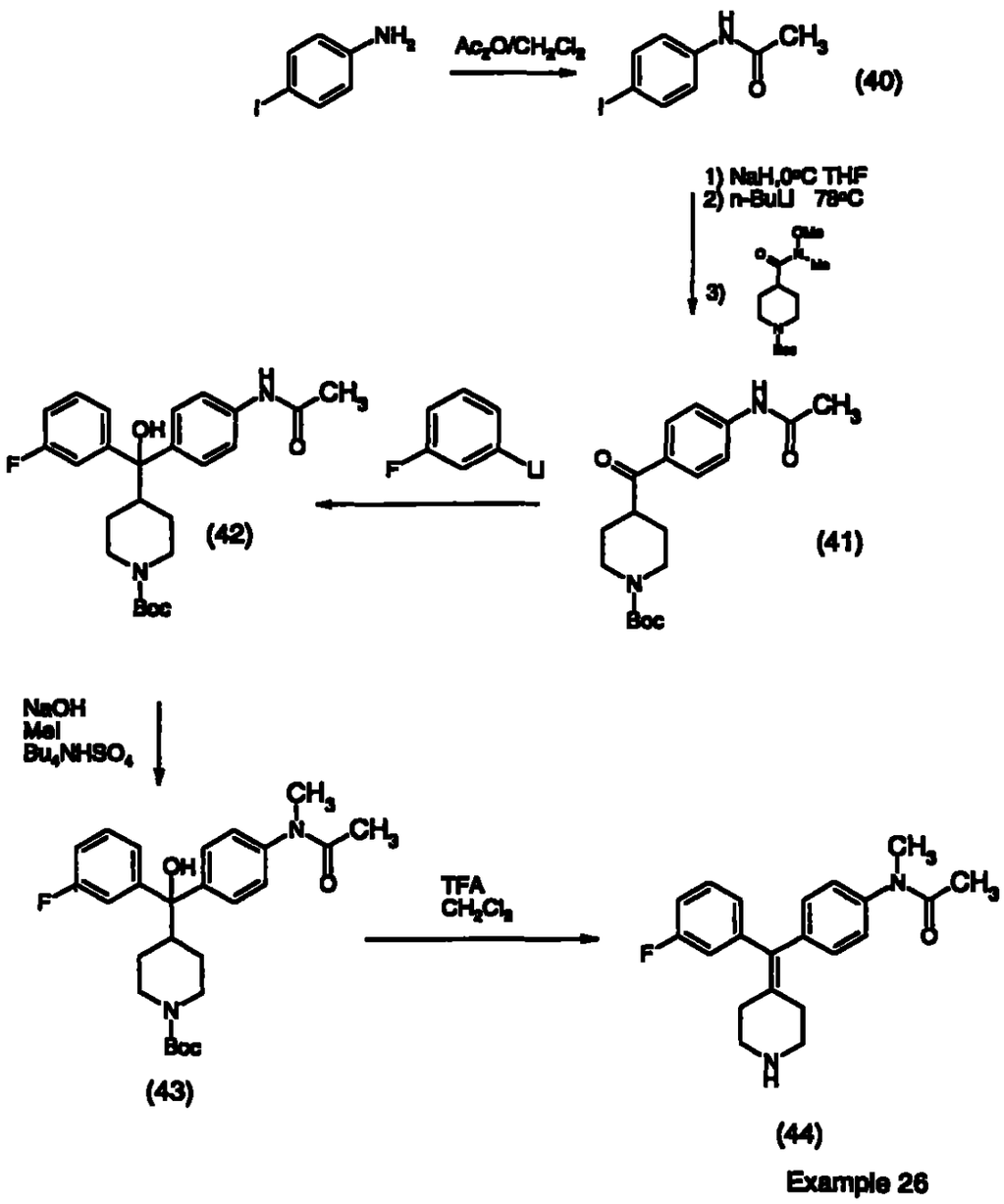
Anal.Calcd.for $C_{23}H_{27}N_2OF.HCl.0\,25\ CH_2Cl_2\ 1\,50\ H_2O$· C 61 89 % H, 7 04 % N 6 21 %

Found. C, 61 97 % H, 6 95 % N 6 22 %

E) 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-yldenemethyl)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

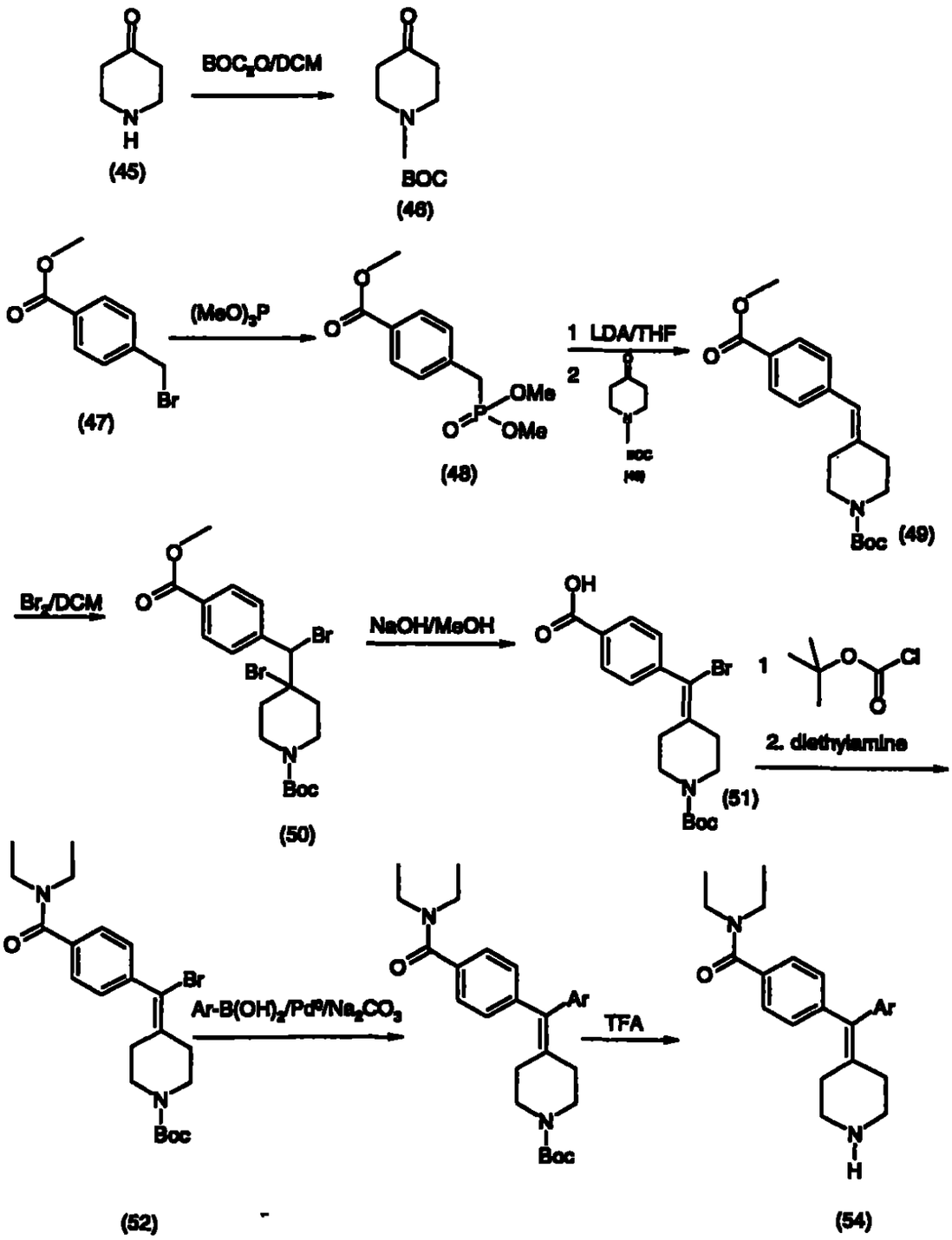
ANALYSIS (%)

*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


BOC2O/DCM
(45)
BOC
(46)
(MeO)3P
(47)
Br
(48)
OMe
OMe
1 LDA/THF
2
Boc
(49)
Br2/DCM
(50)
NaOH/MeOH
(51)
1
2. diethylamine
Ar-B(OH)2/Pd0/Na2CO3
(52)
(53)
TFA
(54)
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)-methyl]-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 HCl (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 HC1 The desired product (7) (3 8 g 87%) was isolated as a white powder by filtration

δ_H (400 MHz, $CDC1_3$) 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 $CDC1_3$) 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

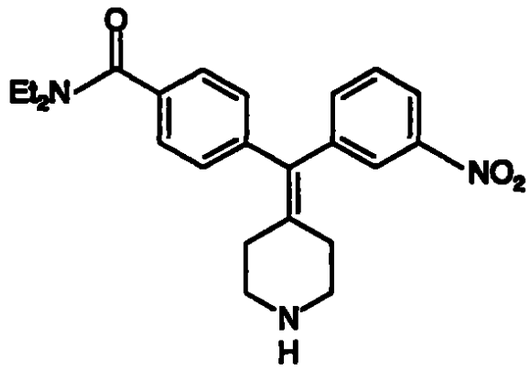
EXAMPLES 28-52

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.



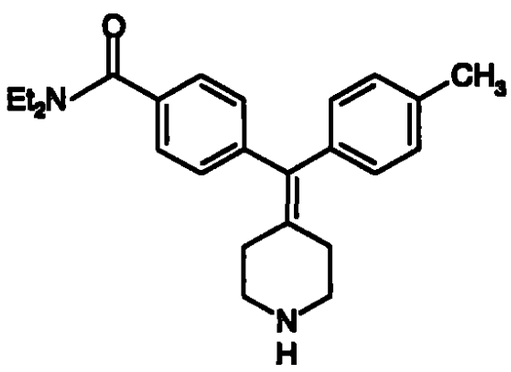
(55)

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-yldene-methyl)-benzamide (compound 56)

p-toluylboronic acid was used



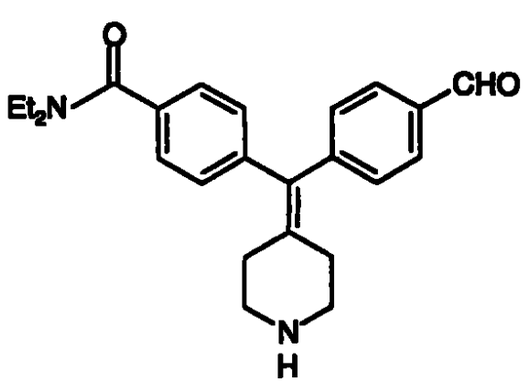
(56)

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-yldene-methyl)-benzamide (compound 57)

4-formylphenylboronic acid was used.



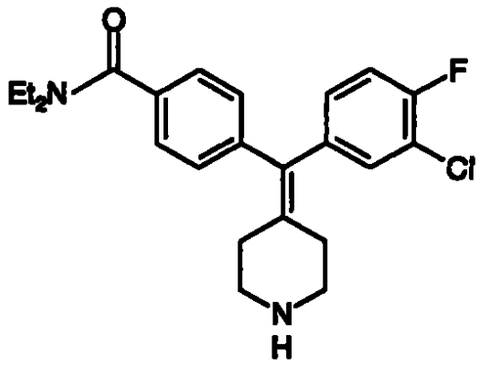
(57)

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-yldene-methyl)-benzamide (compound 58)

3-chloro-4-fluorophenylboronic acid was used.



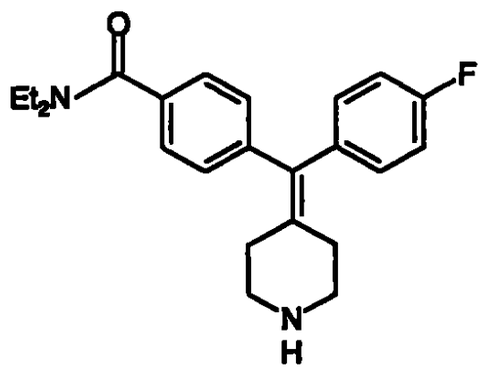
(58)

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



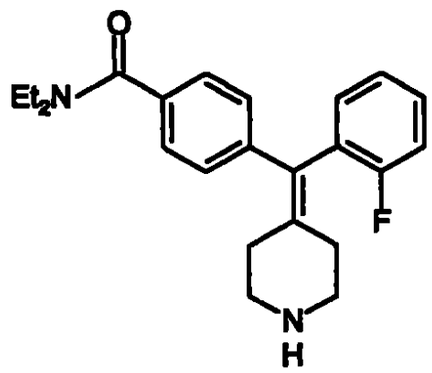
(59)

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



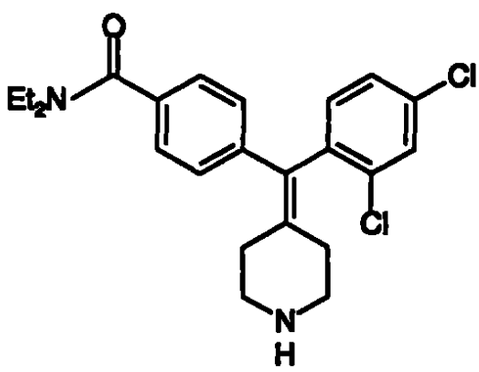
(60)

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.



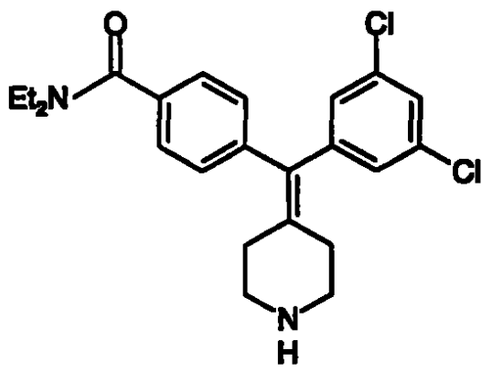
(61)

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.



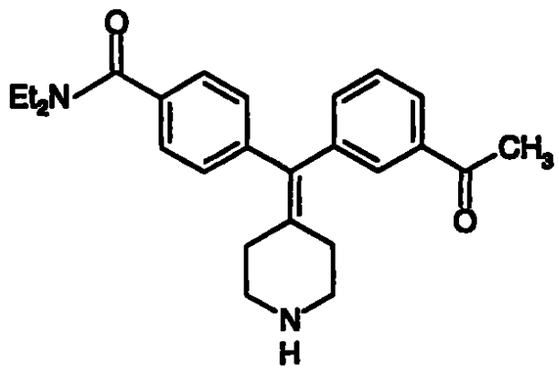
(62)

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-yldene-methyl)-benzamide (compound 63)

3-acetylphenylboronic acid was used.



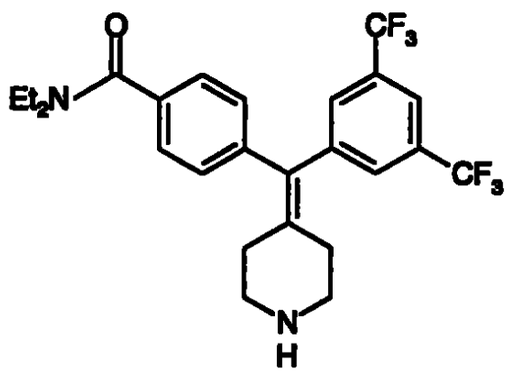
(63)

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.



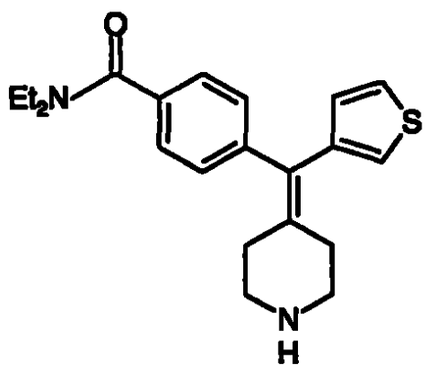
(64)

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-yldene-methyl)-benzamide (compound 65)

3-thiophenylboronic acid was used.



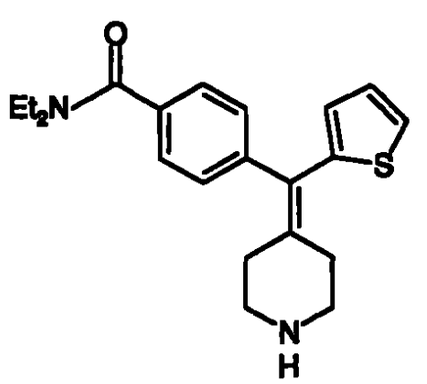
(65)

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-yldene-methyl)-benzamide (compound 66)

2-thiophenylboronic acid was used.



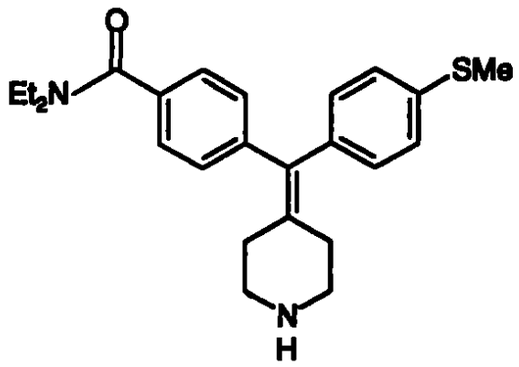
(66)

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



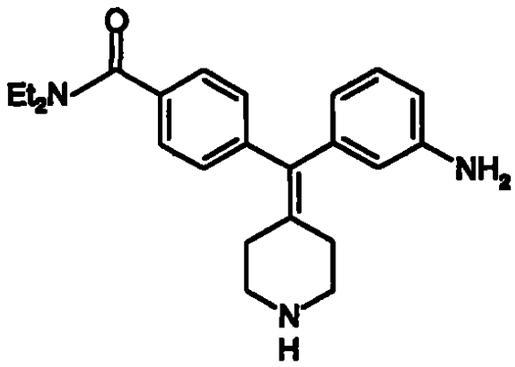
(67)

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.



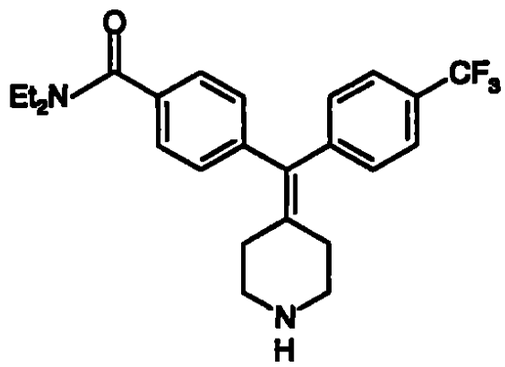
(68)

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



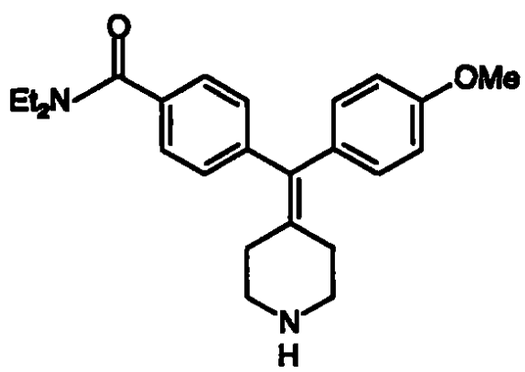
(69)

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



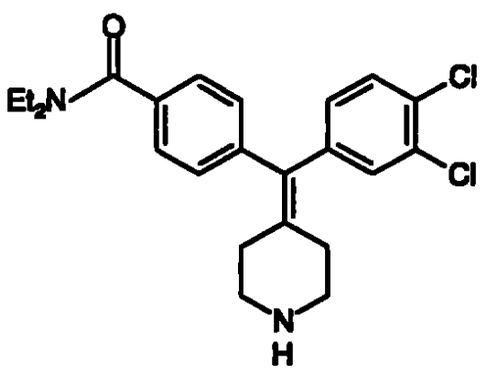
(70)

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.



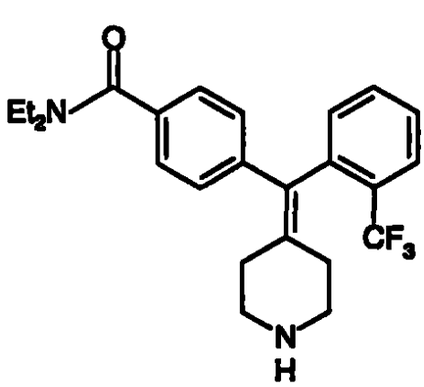
(71)

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)

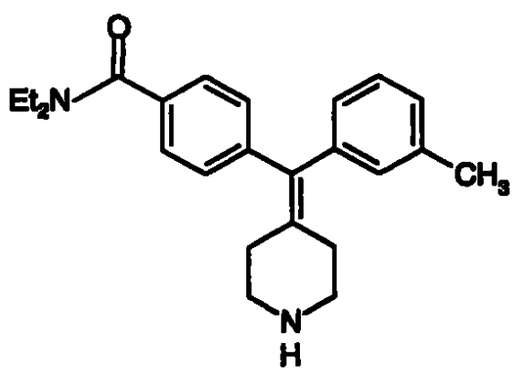
1H NMR (CDCl3) (base) δ 1.05 (br, 3H) 1 16 (br, 3H), 1 95 (m, 2H), 2 35-2.41 (m, 2H), 2 7-2 9 (m, 4H), 3 20 (br, 2H) 3 48 (br 2H), 7 2-7 6 (m, 8H)

EXAMPLE 46

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

(compound 73)

m-tolylboronic acid was used.



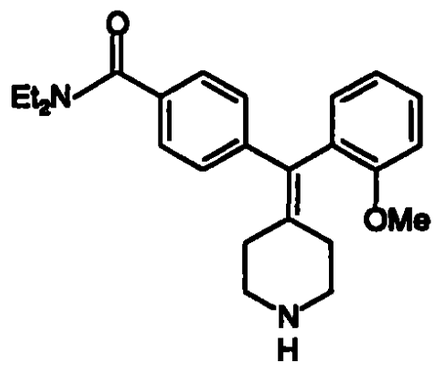
(73)

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.



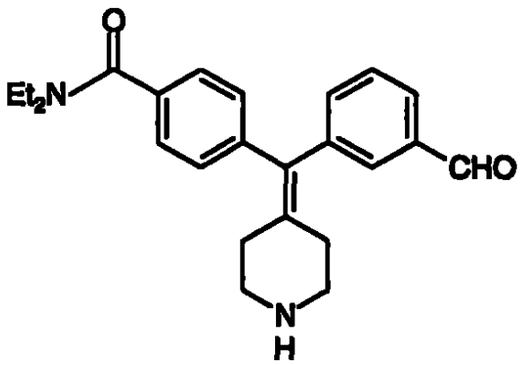
(74)

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.



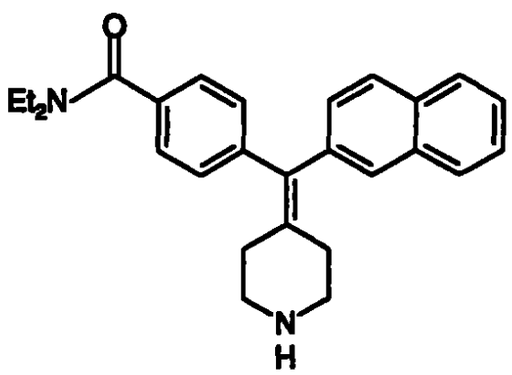
(75)

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.



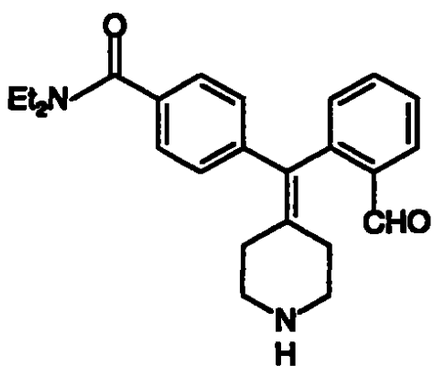
(76)

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.



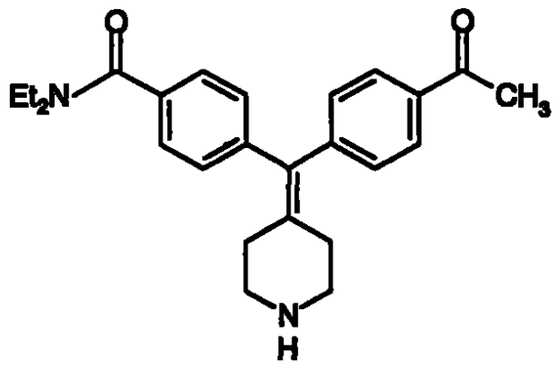
(77)

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.



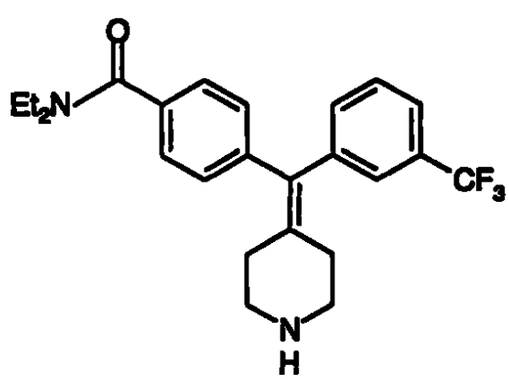
(78)

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.

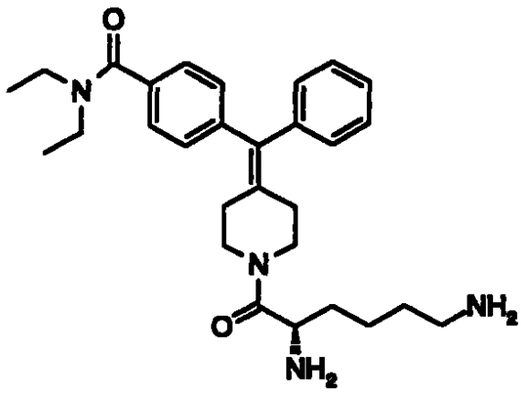


(79)

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

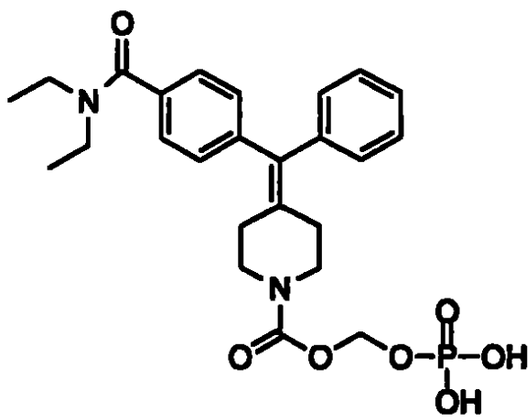
The product (0 40g, 0 56mmol) was dissolved in methylene chloride (10mL) and treated with trifluoroacetic acid (3mL) for 30min, then the volatiles were evaporated. The residue was dissolved in acetic acid (25mL) and subjected to hydrogenolysis 1 5h with hydrogen (1atm) over palladium on carbon (10% 0 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.

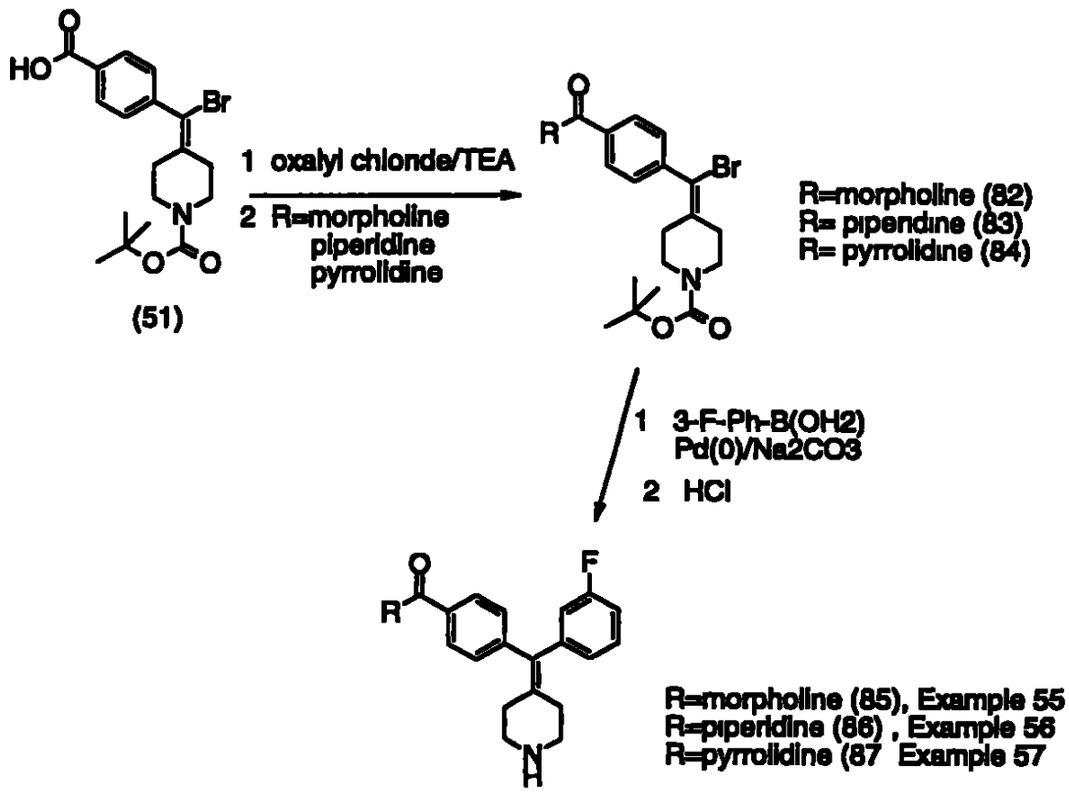
^{1}H NMR. (D_2O) δ = 1 03, 1 20 (2m, 6H, amide-Me) 2 34 (m, 4H piperidine-H), 3 19-3 61 (m, 8H, amide-CH_2, piperidine-H) 5 44 (d, *J*=13Hz, 2H, OCH_2O), 7 18-7.36 (m, 9H Ar-H)

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



(1) 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)

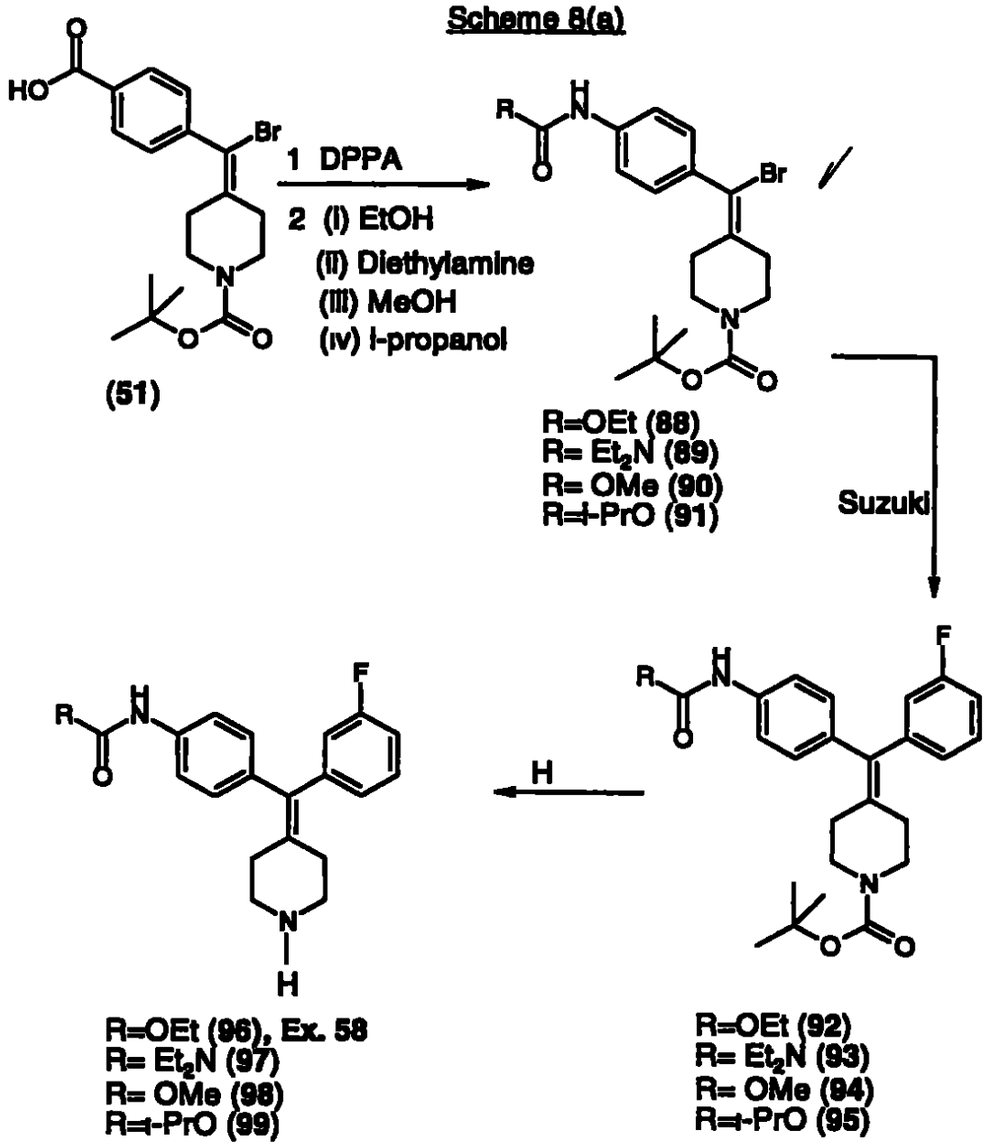
Same procedure as for the preparation of compound 85, but using compound 84 as starting material

^{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)

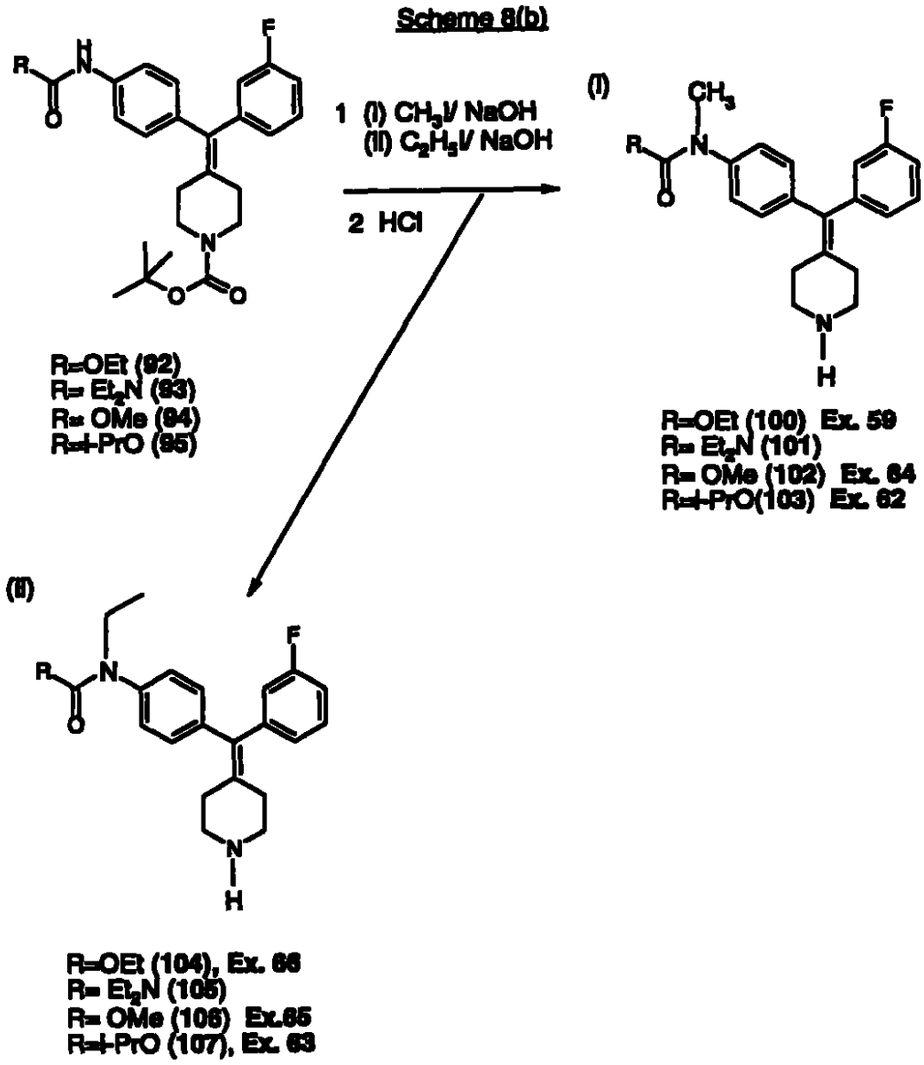
H) Synthetic scheme for the preparation of the compounds of Examples 58-68

The compounds of Examples 58-68 were prepared by following the procedure of Scheme 8 (a) -(c) below

Scheme 8(a)


HO
Br
1 DPPA
2 (i) EtOH
(ii) Diethylamine
(iii) MeOH
(iv) i-propanol
(51)
R
N
H
O
Br
N
O
O
R=OEt (88)
R= Et2N (89)
R= OMe (90)
R=i-PrO (91)
Suzuki
F
R=OEt (92)
R= Et2N (93)
R= OMe (94)
R=i-PrO (95)
H
R=OEt (96), Ex. 58
R= Et2N (97)
R= OMe (98)
R=i-PrO (99)

Scheme 8(b)

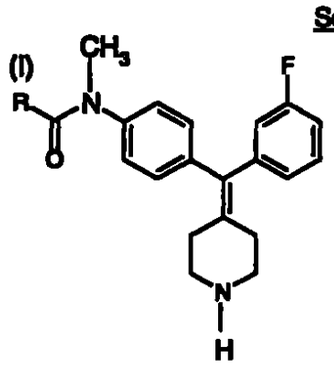


R=OEt (92)
R= Et_2N (93)
R= OMe (94)
R=i-PrO (95)

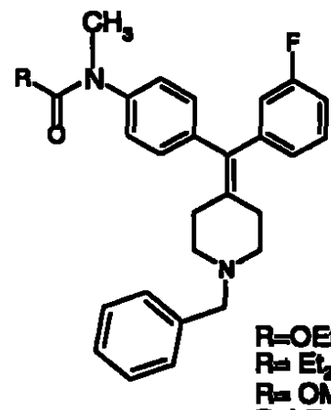
R=OEt (100) Ex. 59
R= Et_2N (101)
R= OMe (102) Ex. 64
R=i-PrO(103) Ex. 62

R=OEt (104), Ex. 66
R= Et_2N (105)
R= OMe (106) Ex.65
R=i-PrO (107), Ex. 63

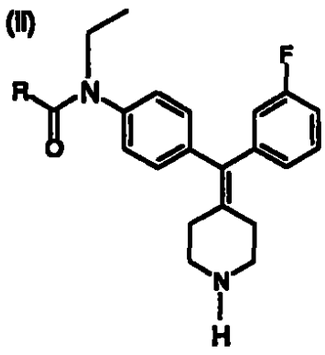
Scheme 8(c)



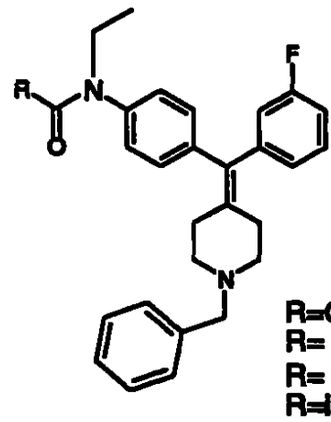
R=OEt (100) Ex. 59
R= Et_2N (101)
R= OMe (102)
R=i-PrO (103)



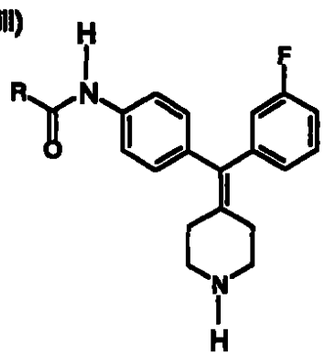
R=OEt (108), Ex. 61
R= Et_2N (109)
R= OMe (110)
R=i-PrO (111)



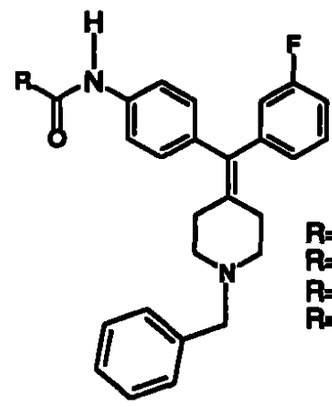
R=OEt (104), Ex. 66
R= Et_2N (105)
R= OMe (106), Ex. 65
R=i-PrO (107)



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



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-methyl]-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-methyl]-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

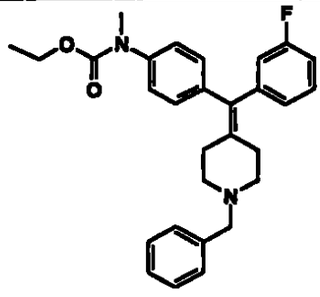
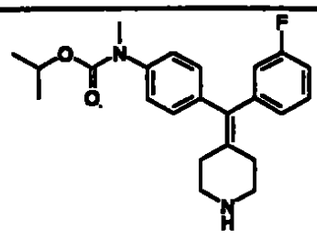
Example	*Compound*	*Chemical structure*	*Characterization data [^{1}H NMR 400 MHz ($CDCl_3$)]*	*Scheme*
61	108		δ 1 17 (t, J=7 6 Hz, 3H) 2 28-2 35 (m, 4H) 2 40-2.45 (m, 4H) 3.21 (s 3H) 3.50 (s, 2H) 4 10 (q J=7 2 Hz, 2H) 6 73 (d, J=8 7 Hz, 1H) 6 85 (m, 2H) 7 01 (d, J=8 8 Hz 2H) 7 2-7 3 (m, 8H)	8 (c)
62	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)

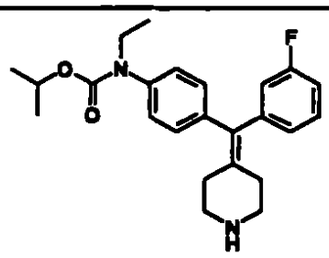
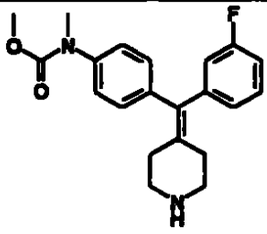
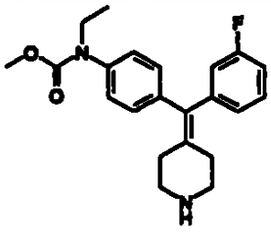
Example	*Compound*	*Chemical structure*	*Characterization data [^{1}H NMR 400 MHz ($CDCl_3$)]*	*Scheme*
63	107		δ 1 14 (t, J=7 2 Hz, 3H) 1 20 (d J=6 4 Hz, 6H) 2.92 (t, J=5 2 Hz 2H), 2 33 (t, J=5 2 Hz, 2H) 2 90 (t, J=5 2 Hz 4H) 3 66 (q J=7 6 Hz, 2H) 4 93 (quin J=6 0 Hz 1H) 6 79 (d, 1H) 6 88 (d, 2H) 7 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)

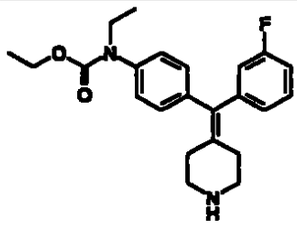
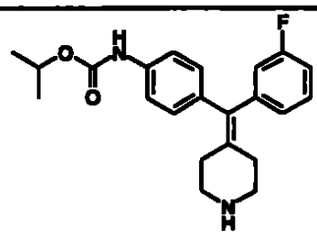
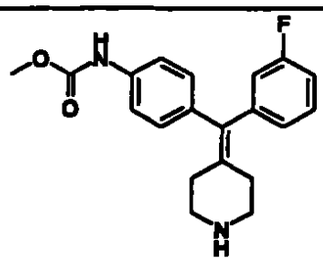
Example	*Compound*	*Chemical structure*	*Characterization data [^{1}H NMR 400 MHz ($CDCl_3$)]*	*Scheme*
66	104		δ 1 13 (t, J=6 8 Hz 3H) 1 21 (t, J=7 2 Hz, 3H) 2 30-2 36 (m, 4H) 2 91-2 93 (m, 4H) 3 67 (q J=6 8 Hz, 2H) 4 13 (q J=6 8 Hz, 2H) 6 79 (d 10 Hz, 1H) 6 88-6 90 (m, 2H) 7 06 (d, J=8 4 Hz, 2H) 7 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_d 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_d (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_d 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

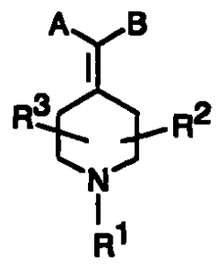
TFA = trifluoroacetic acid

THF = tetrahydrofuran

TMEDA = N,N,N ,N -tetramethylethylenediamine

CLAIMS

1 A compound of the general formula (I)



(I)

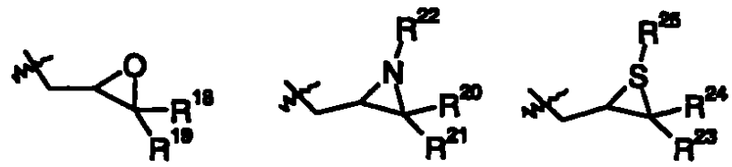
R^1 is selected from

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 $-CONR^5R^4$ $-COOR^5$ $-COR^5$ $-(CH_2)_qNR^5R^4$ $-(CH_2)_qCH_3(CH_2)_qSOR^5R^4$ $-(CH_2)_qSO_2R^5$

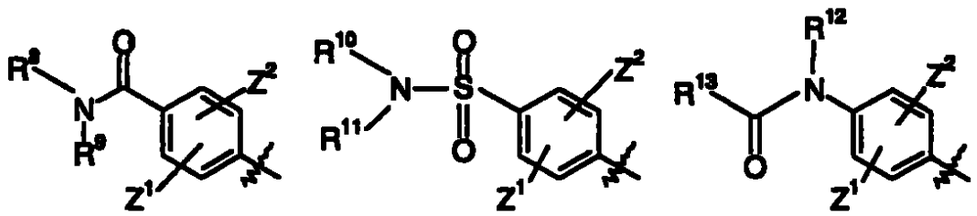
—$(CH_2)_qSO_2NR^5$ and —$(CH_2)_pOR^5$ wherein R^4 and R^5 is each and independently as defined for R^1 above and q is 0 1 or 2 and

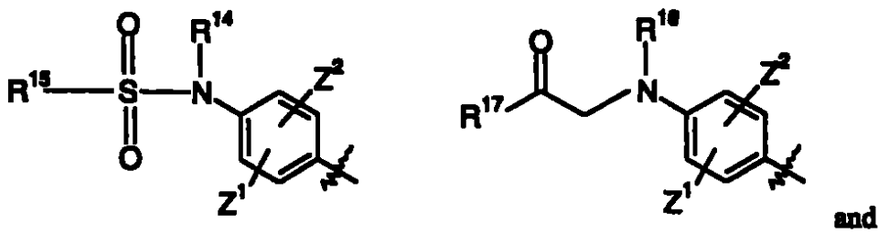


wherein R^{18} R^{19} R^{20} R^{21} R^{22} R^{23} R^{24} and R^{25} is each and independently hydrogen, C_1-C_6 alkyl or C_1-C_6 alkenyl,

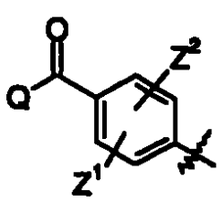
R^2 and R^3 is each and independently hydrogen or C_1-C_6 alkyl,

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

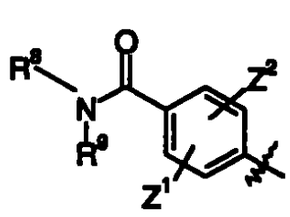
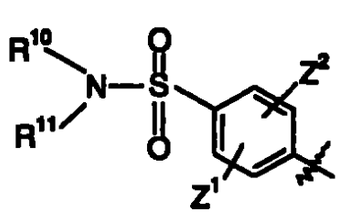
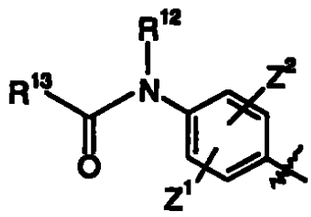
a substituted or unsubstituted aromatic heteroaromatic hydroaromatic or heterohydroaromatic moiety having from 5 to 10 atoms selected from any of C, S N and O optionally and independently substituted by 1 or 2 substituents independently selected from hydrogen CH_3 $—(CH_2)_tCF_3$ halogen, $—(CH_2)_tCONR^5R^4$ $—(CH_2)_tNR^5R^4$ $—(CH_2)_tCOR^5$ $—(CH_2)_tCOOR^5$, $—OR^5$ $—(CH_2)_tSOR^5$, $—(CH_2)_tSO_2R^5$ 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,

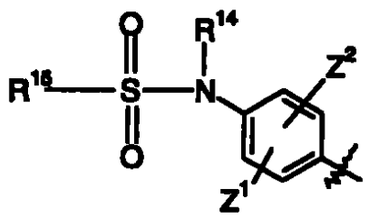
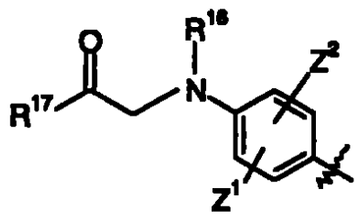
as well as pharmaceutically acceptable salts of the compounds of the formula (I) and isomers hydrates isoforms and prodrugs thereof

2 A compound of the formula (I) according to claim 1 wherein

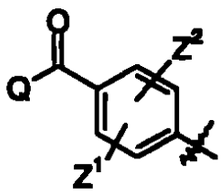
A is selected from

,

, 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

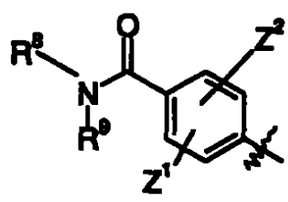
R^1 R^4 and R^5 is each and independently selected from hydrogen, a branched or straight C_1-C_4 alkyl C_3-C_5 cycloalkyl C_4-C_8 (alkyl-cycloalkyl) wherein alkyl is C_1-C_2 alkyl and cycloalkyl is C_3-C_6 cycloalkyl C_6-C_{10} aryl and heteroaryl having from 5 to 6 atoms selected from any of C, S, N 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



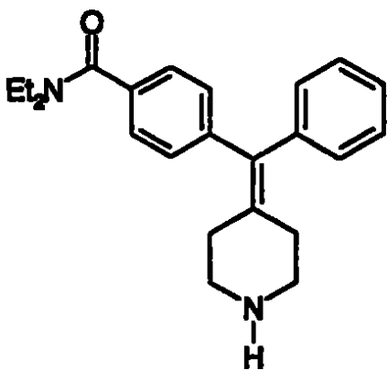
wherein R^8 and R^9 are both ethyl, and where the phenyl ring optionally and independently may be substituted at any position of the phenyl ring by 1 or 2 substituents Z^1 and Z^2 which are each and independently selected from hydrogen CH_3 —$(CH_2)_qCF_3$ halogen, —$CONR^6R^7$ —$COOR^6$, —COR^6 —$(CH_2)_rNR^6R^7$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

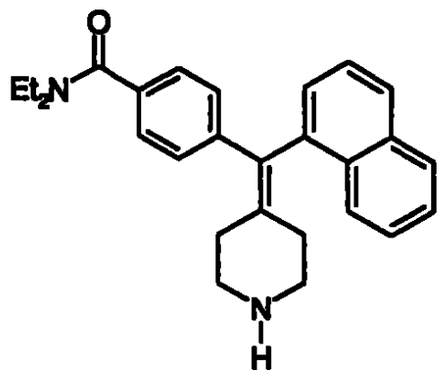
B is selected from phenyl naphthyl, indolyl benzofuranyl dihydrobenzofuranyl benzothiophenyl, furanyl quinolinyl, isoquinolinyl cyclohexyl, cyclohexenyl, cyclopentyl cyclopentenyl indanyl indenyl tetrahydronaphthyl tetrahydroquinyl tetrahydroisoquinolinyl, tetrahydrofuranyl, and indazolinyl each optionally 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

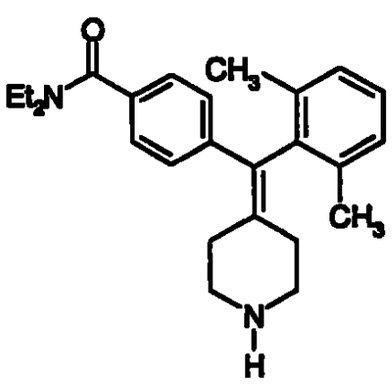
4 A compound of the formula (I) according to claim 1 which compound is any of



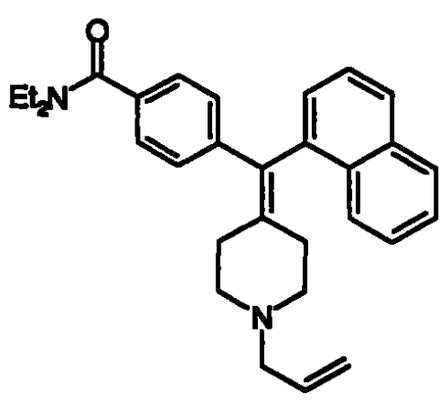
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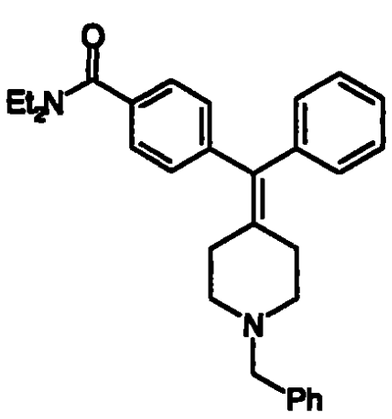
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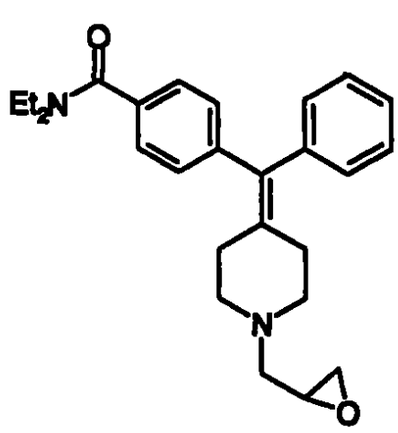
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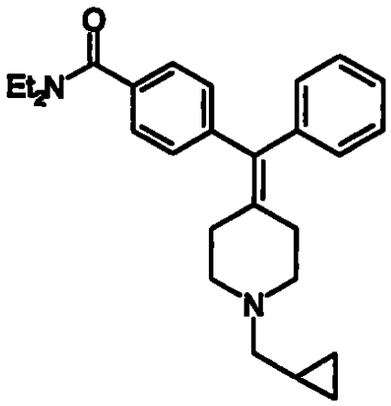
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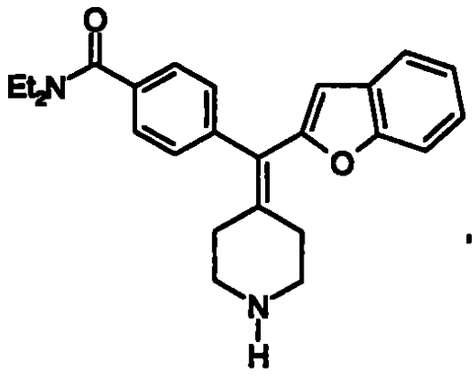
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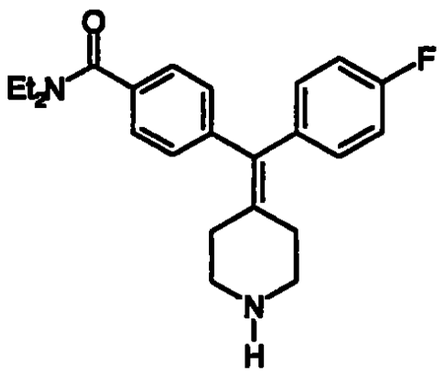
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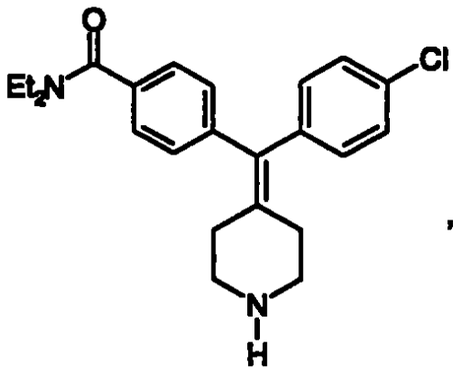


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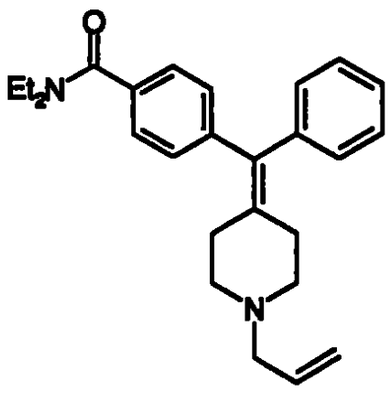


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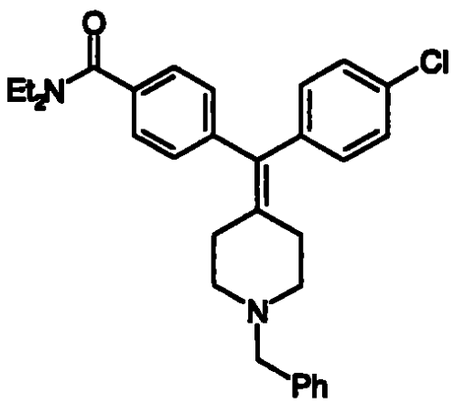




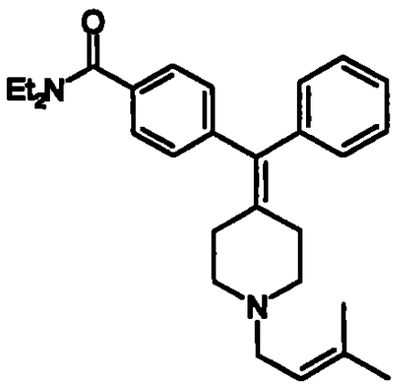
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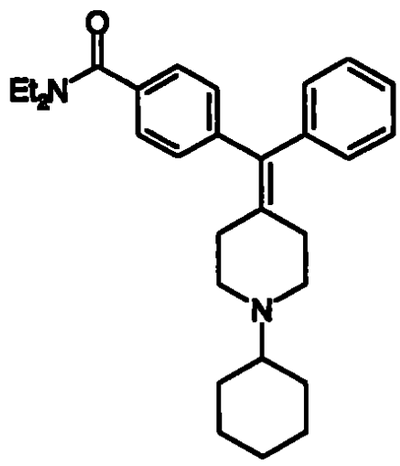


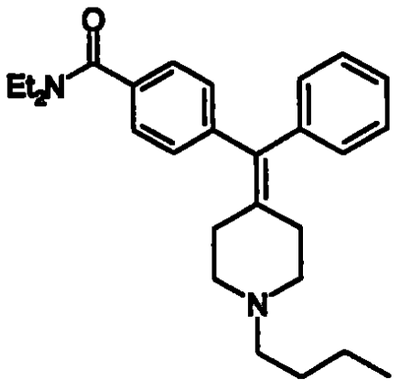
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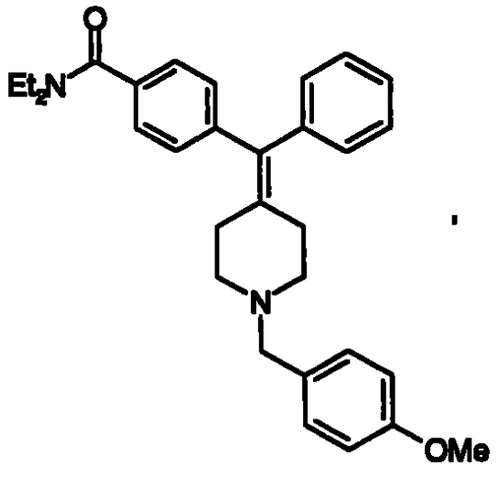


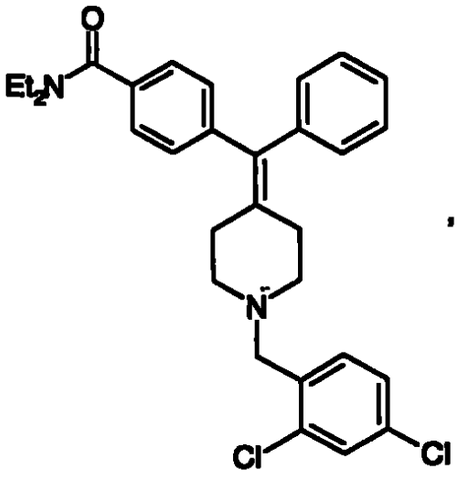
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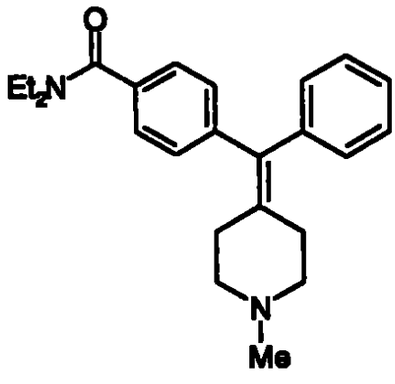


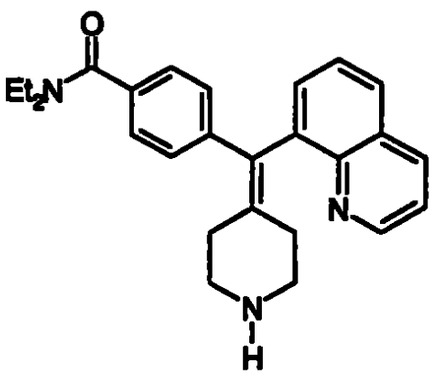


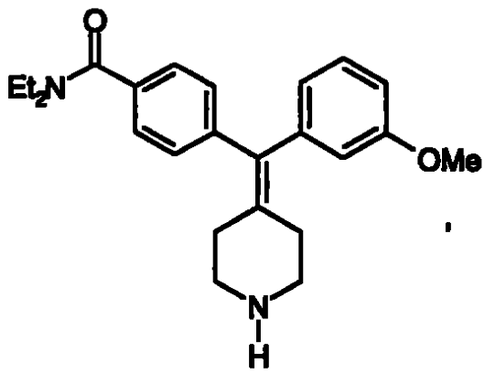


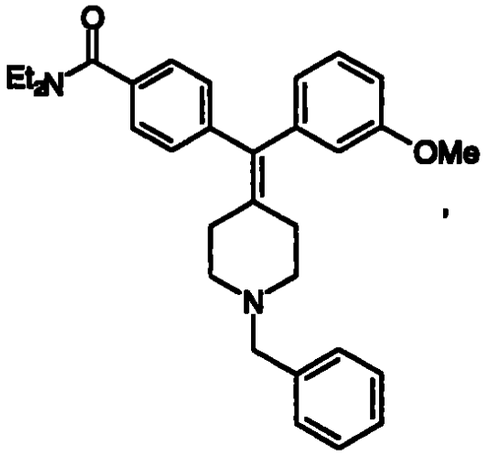


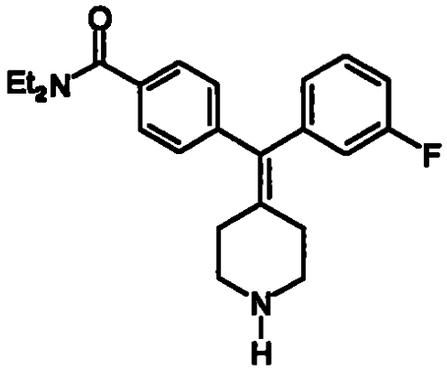


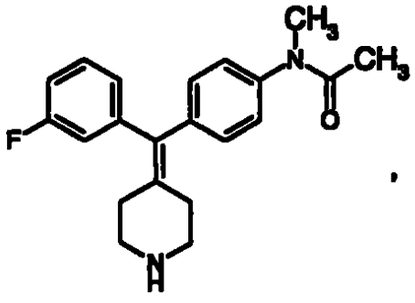


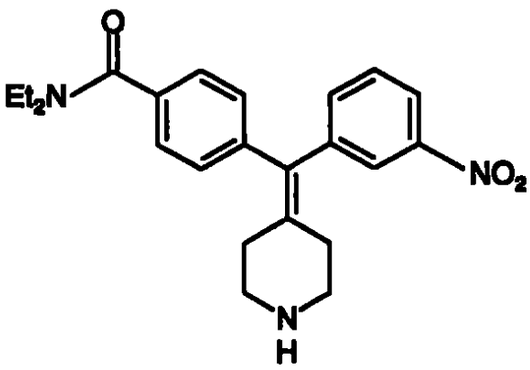


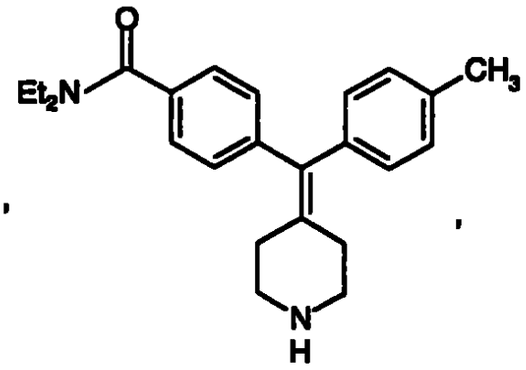


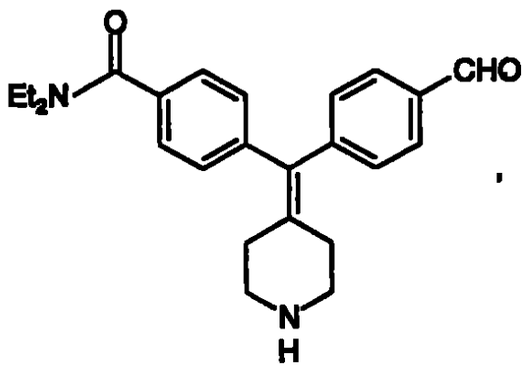


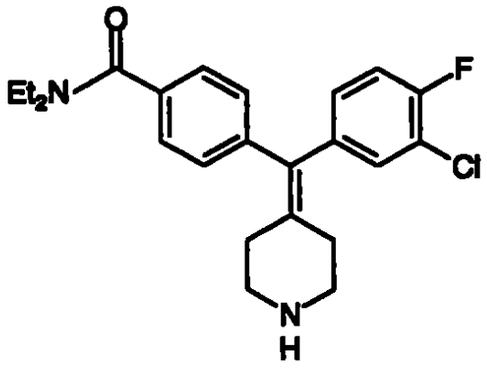


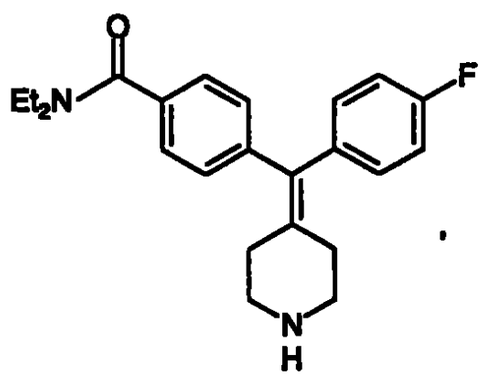


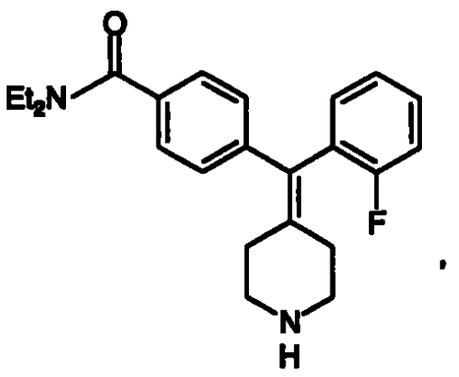


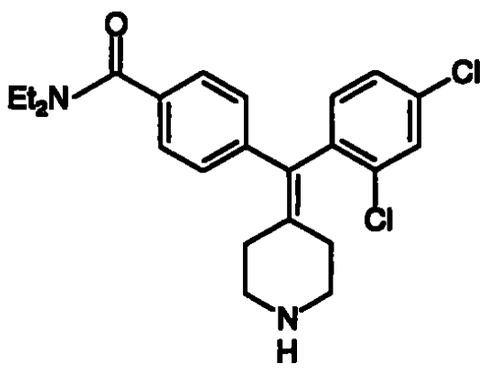


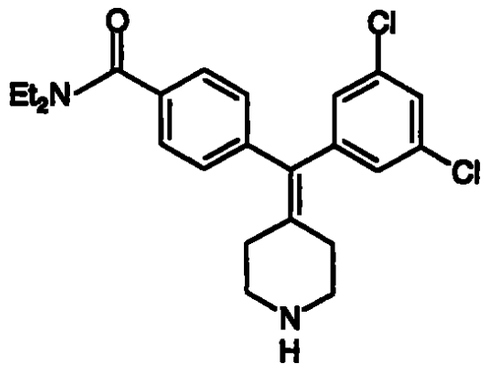


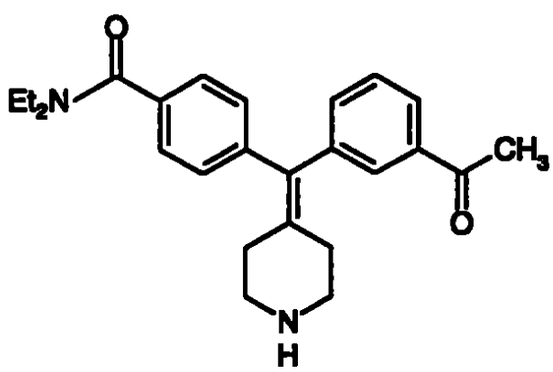


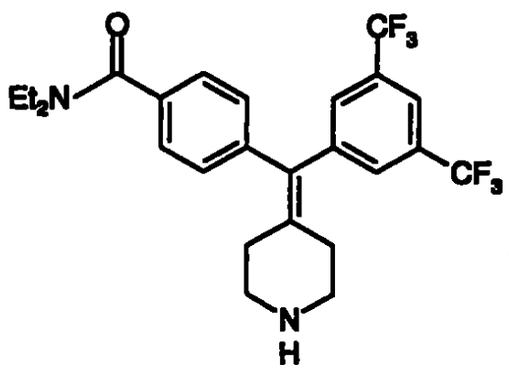


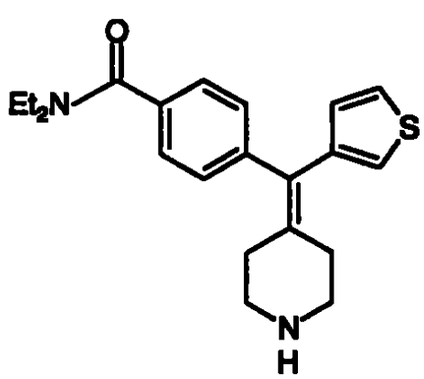


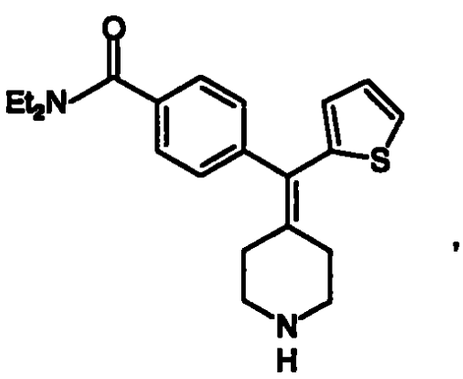


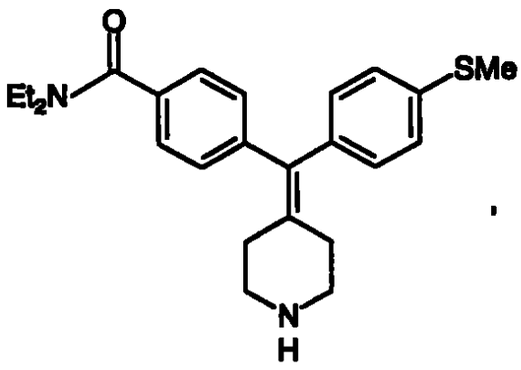




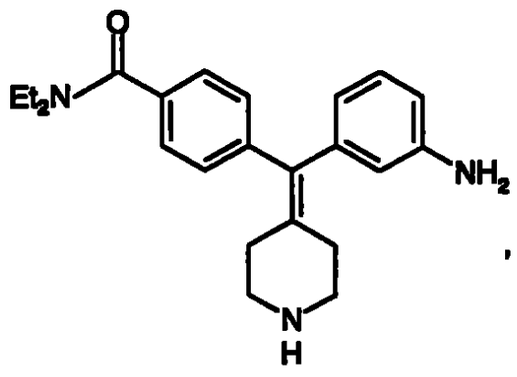




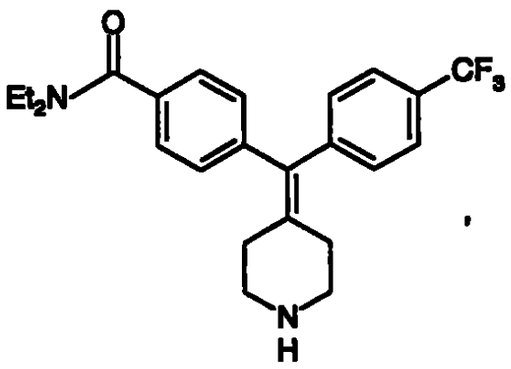




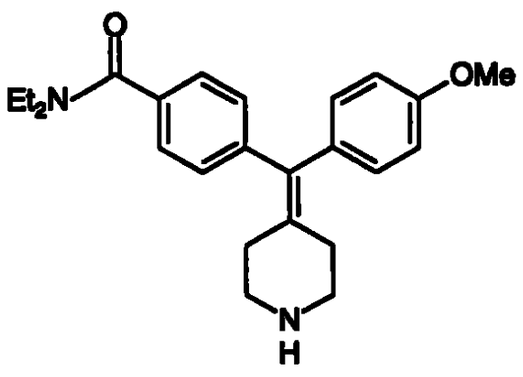
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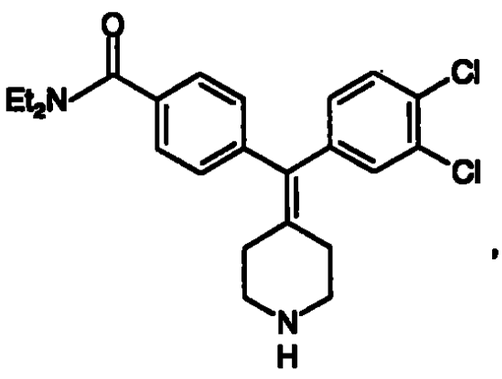
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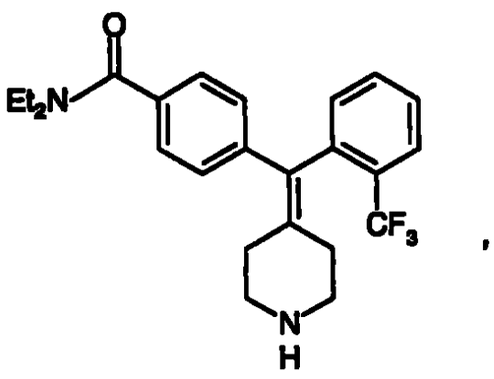
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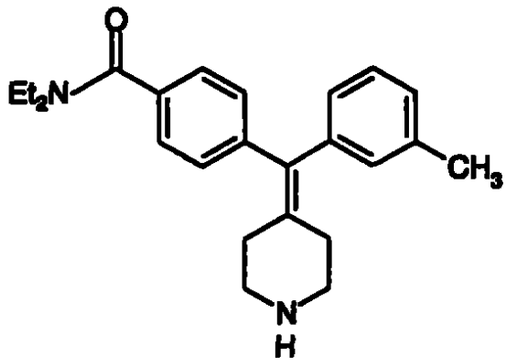
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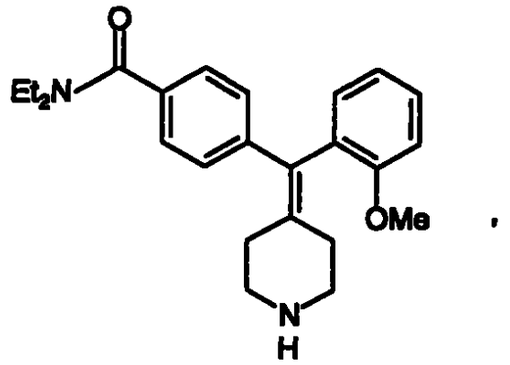
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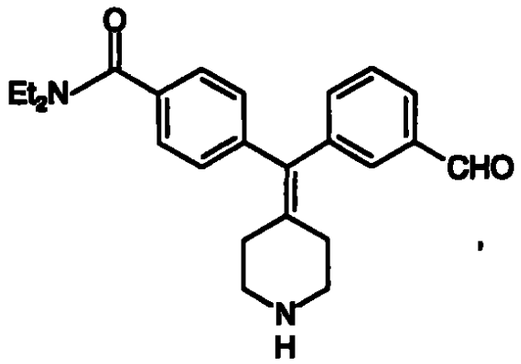
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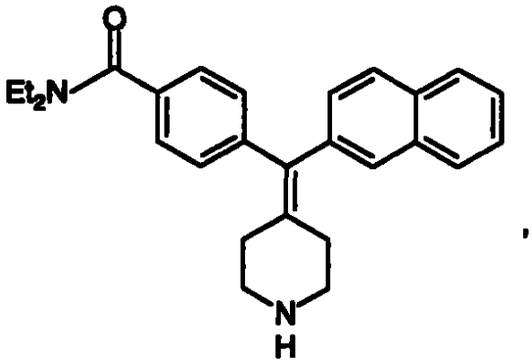
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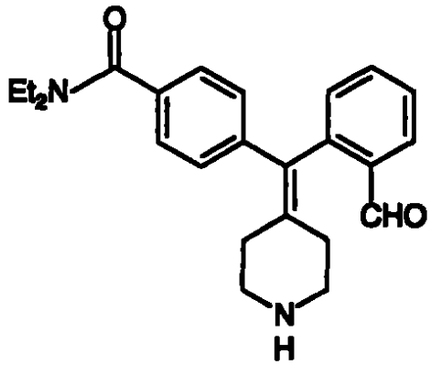
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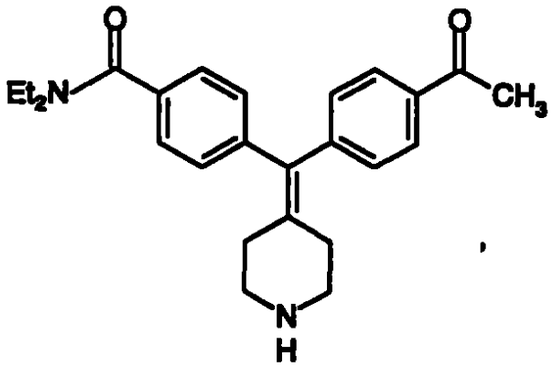
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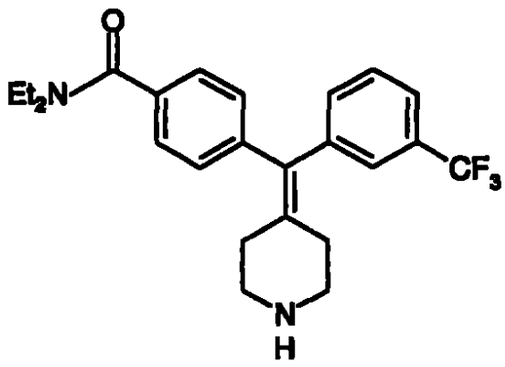


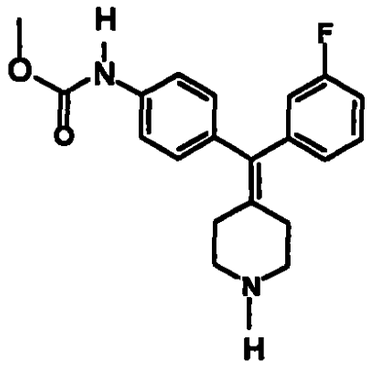
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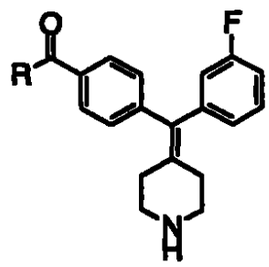


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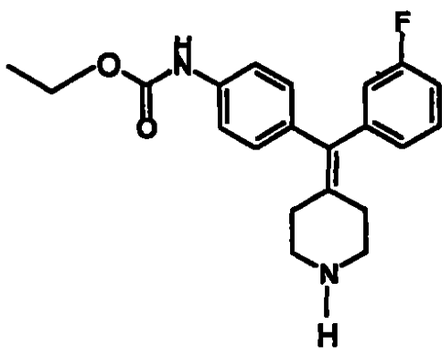
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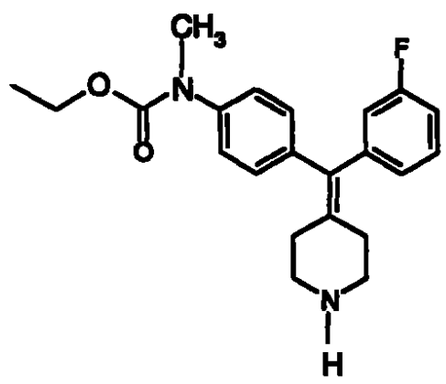


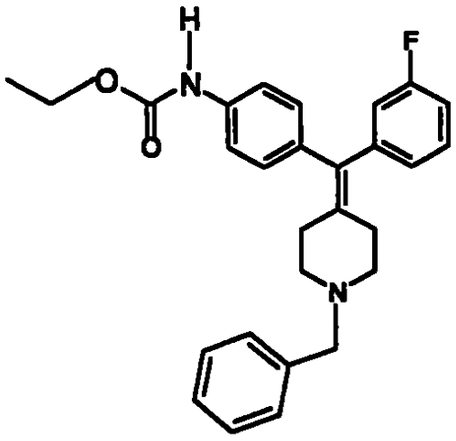


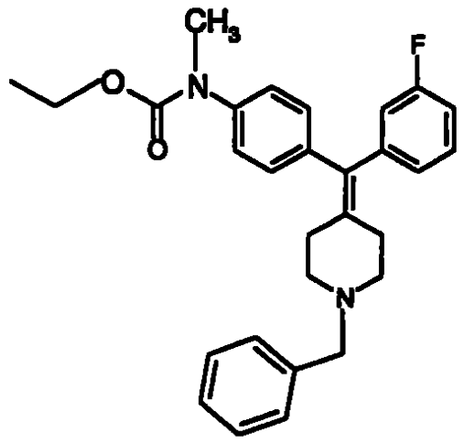


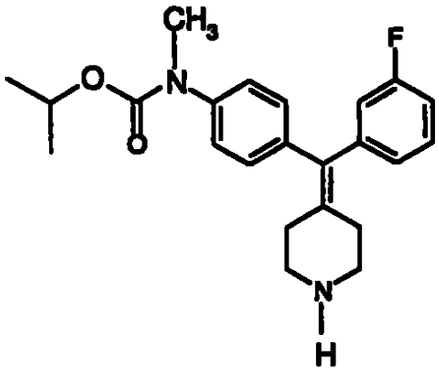
wherein R is morpholine,piperidine or pyrrolidine,

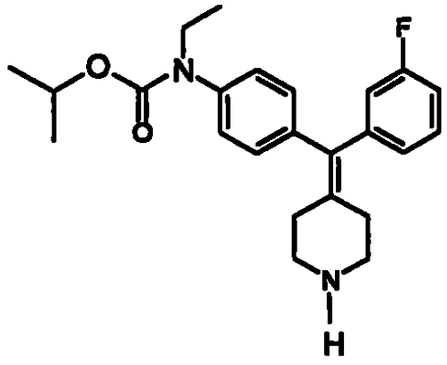


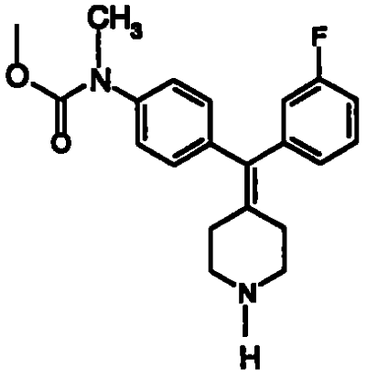


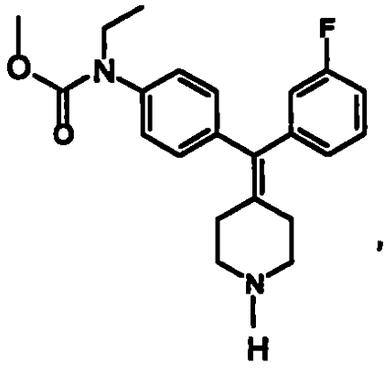

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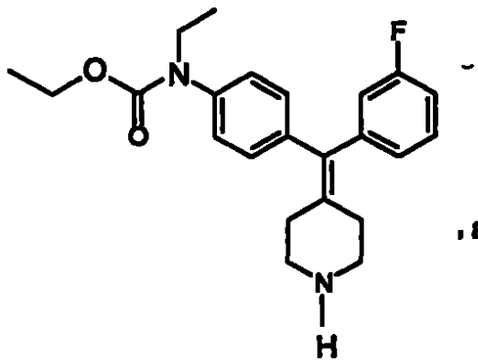

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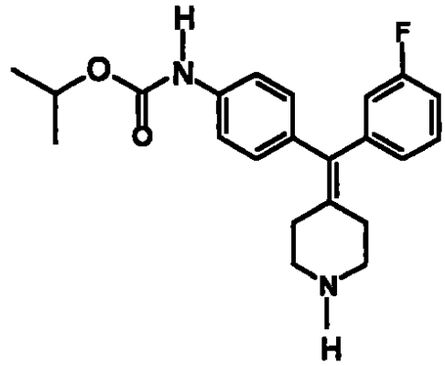

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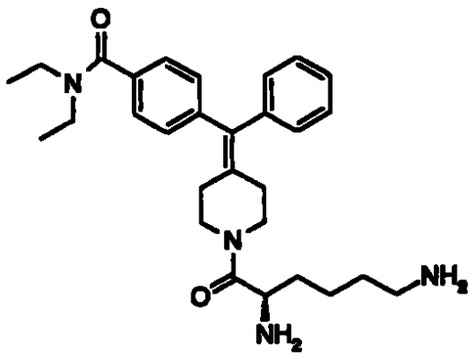
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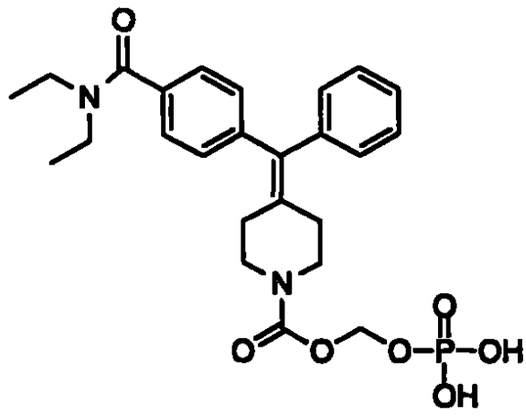
, and



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.

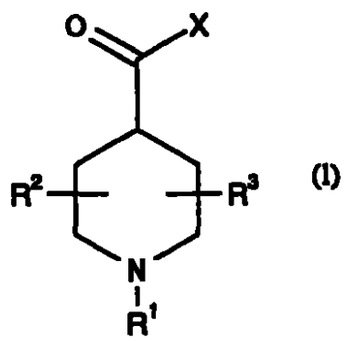
17 An isotopically labelled compound of the formula (I) of claim 1

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)



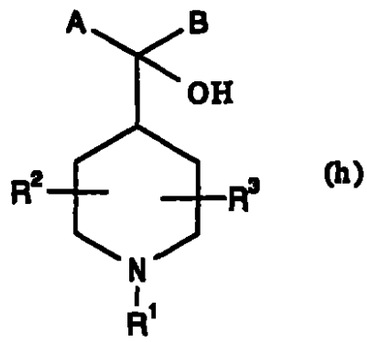
(l)

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)

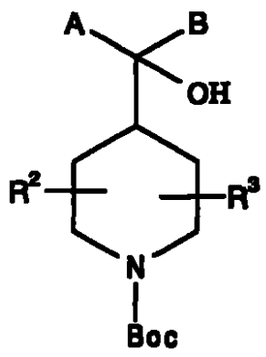


(h)

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

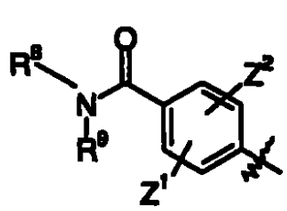


(h)

wherein A, B, R^2 and R^3 are as defined in formula (I) of claim 1

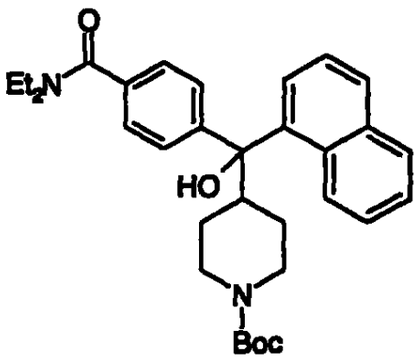
22 A compound of the formula (h) according to step a) of claim 20 wherein

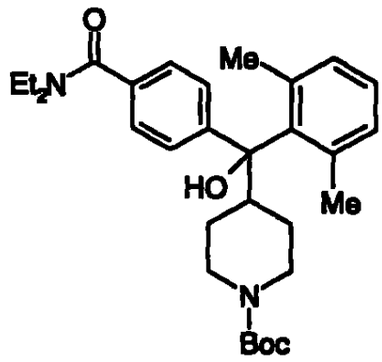
A is

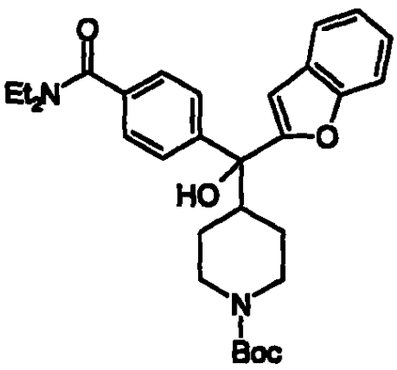


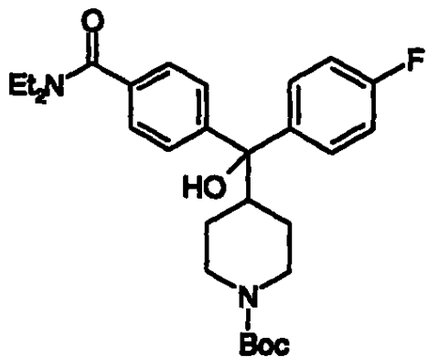
wherein R^8 and R^9 are both an ethyl group and Z^1 andd Z^2 are as defined in claim 1

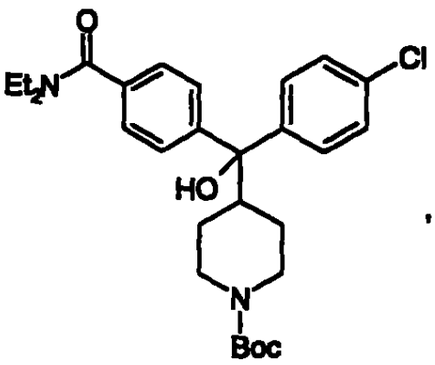
23 A compound according to claim 22 which compound is any of

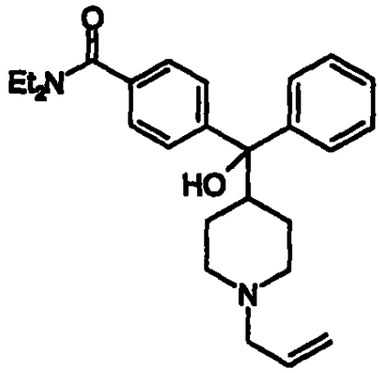


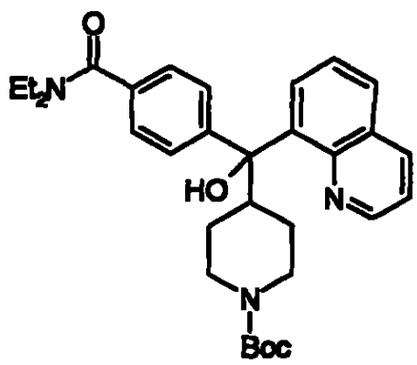




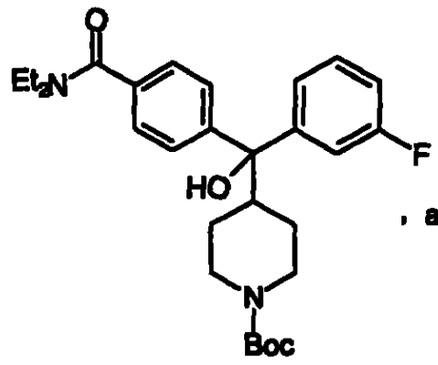




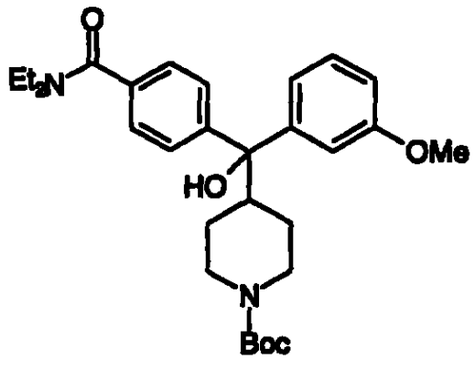




,



, 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" erlier 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 dependant 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 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)

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9504661-1 22 December 1995 (22.12.95) SE

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

(72) Inventors; and

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

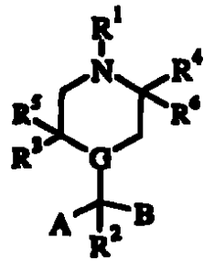
(81) Designated States: AL, AM, AT AU AZ, BA, BB BG BR BY CA, CH, CN CU CZ, DE, DK, EE, ES FI, GB GE, HU IL, IS, JP KE, KG KP KR KZ, LC LK LR, LS LT LU LV MD MG MK, MN MW MX, NO NZ, PL, PT RO, RU SD, SE, SG SI SK, TJ TM TR TT UA UG US, UZ, VN ARIPO patent (KE, LS MW SD, SZ, UG), Eurasian patent (AM, 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
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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

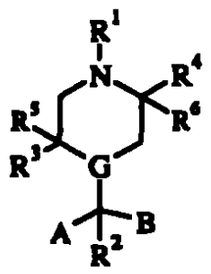
Analgesics that have been identified and are existing in the prior art have many disadvantages in that they suffer from poor pharmacokinetics and are not analgesic when administered by systemic routes Also, it has been documented that preferred compounds, described within the prior art, show significant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

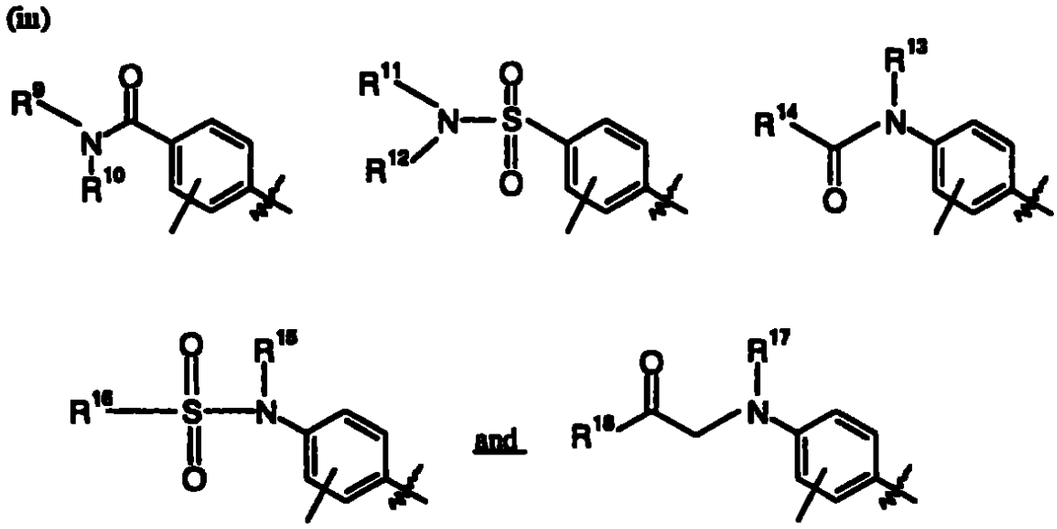
G is a carbon atom or a nitrogen atom,

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;

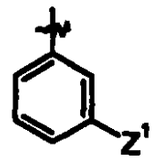
R^9 R^{10} R^{11} R^{12}, R^{13}, R^{14} R^{15} R^{16} R^{17} and R^{18} is each and independently as defined for R^1 above,

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

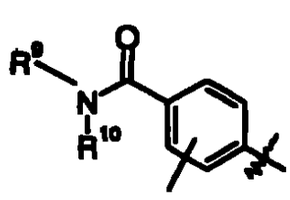
G is a carbon atom or a nitrogen atom,

A is selected from

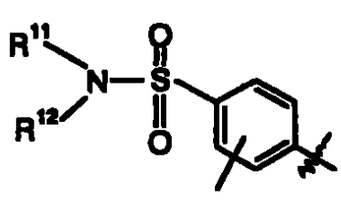
(i) phenyl substituted by any of -COOH, - $CONH_2$ $COOCH_3$, -CN, NH_2 or $-COCH_3$

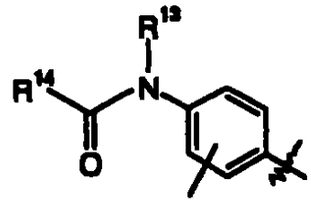
(ii) naphtyl, benzofuranyl, and quinolinyl, and

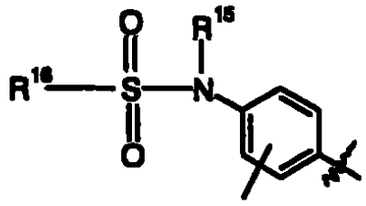
(iii)



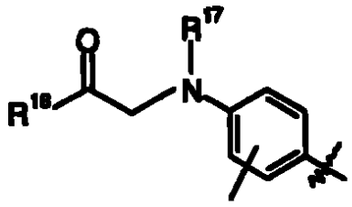
,







and



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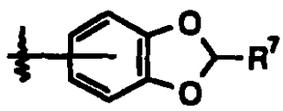
wherein the phenyl ring of each A substituent may be optionally and independently substituted by 1 or 2 substituents selected from hydrogen, CH_3, $(CH_2)_oCF_3$, halogen, $CONR^7R^8$, CO_2R^7, COR^7, $(CH_2)_oNR^7R^8$ $(CH_2)_oCH_3(CH_2)_oSOR^7$, $(CH_2)_oSO_2R^7$ and $(CH_2)_oSO_2NR^7R^8$, wherein 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,

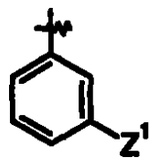
B is selected from phenyl naphthyl, indolyl benzofuranyl, dihydrobenzofuranyl, benzothiophenyl, pyrryl, furanyl, quinolinyl isoquinolinyl, cyclohexyl, cyclohexenyl, cyclopentyl, cyclopentenyl indanyl indenyl, tetrahydronaphthyl tetrahydroquinyl, tetrahydroisoquinolinyl tetrahydrofuranyl, pyrrolidinyl, 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

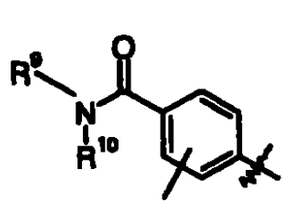
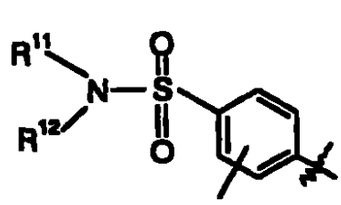
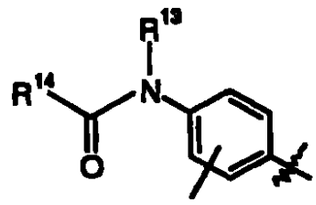
hydroxymethyl and esters thereof; or

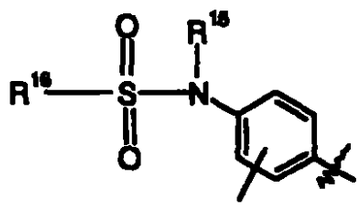
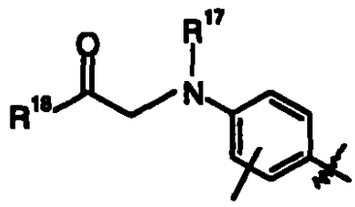
amino, and carboxamides and sulfonamides

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

G is a nitrogen atom

A is selected from


and


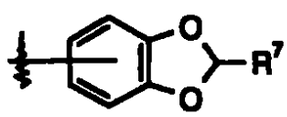
wherein

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.

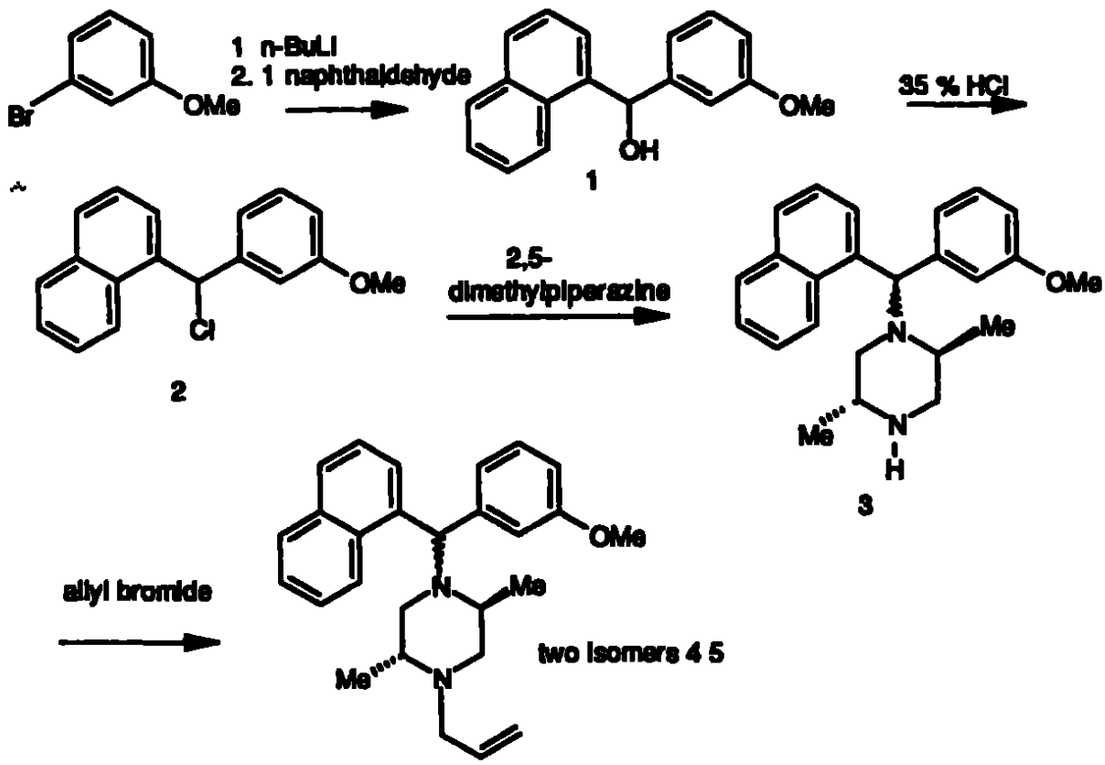
All transformations contemplated use reagents (including salts) and solvents known to the art of chemistry and to biotransformations carried out in a suitable biological medium to bring about these transformations and includes all reaction enhancing agents (*e.g.* HMPA), and chiral resolutions using 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)

Å 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

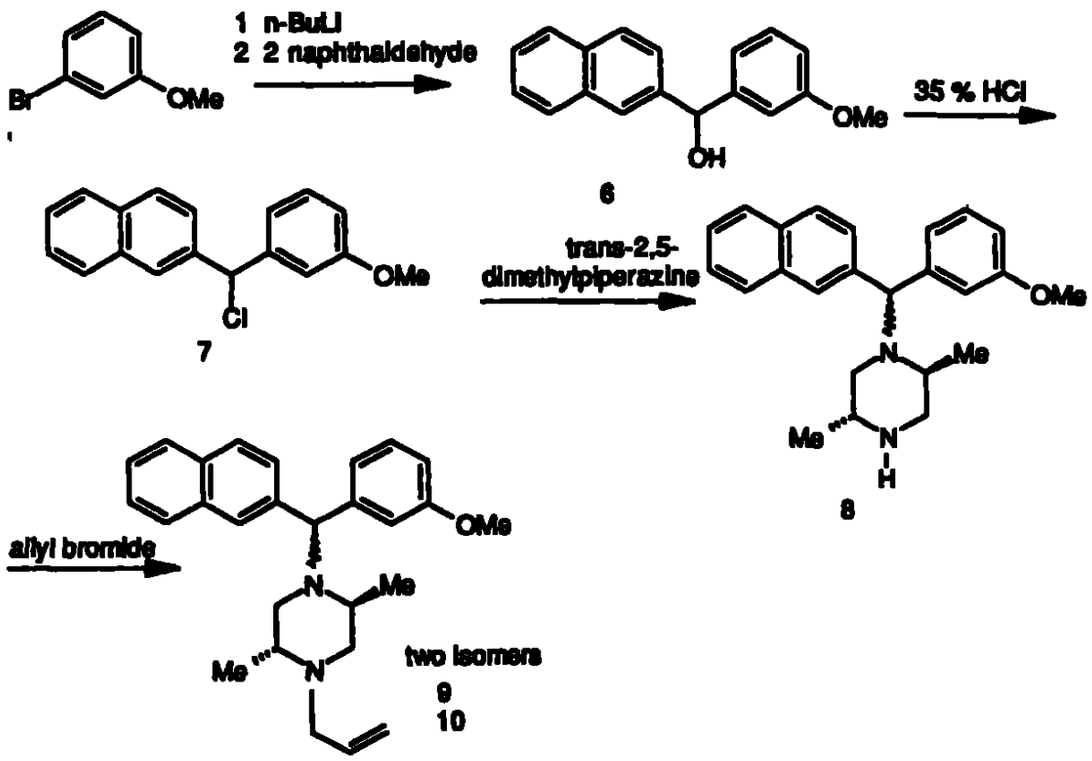
Its HCl salt. m.p 124-135°C (Ether) ν_{max} (KBr) cm^{-1} 3483 1601, 1264, *Anal* Calcd.for $C_{27}H_{32}N_2O$ 2HCl 1 $0H_2O$· C, 65 98 H 7 38 N 5 70 Found C, 66 12 H, 7 25 N 5 42

The second isomer compound 5 GC-MS (R_t = 14.65 mm) 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

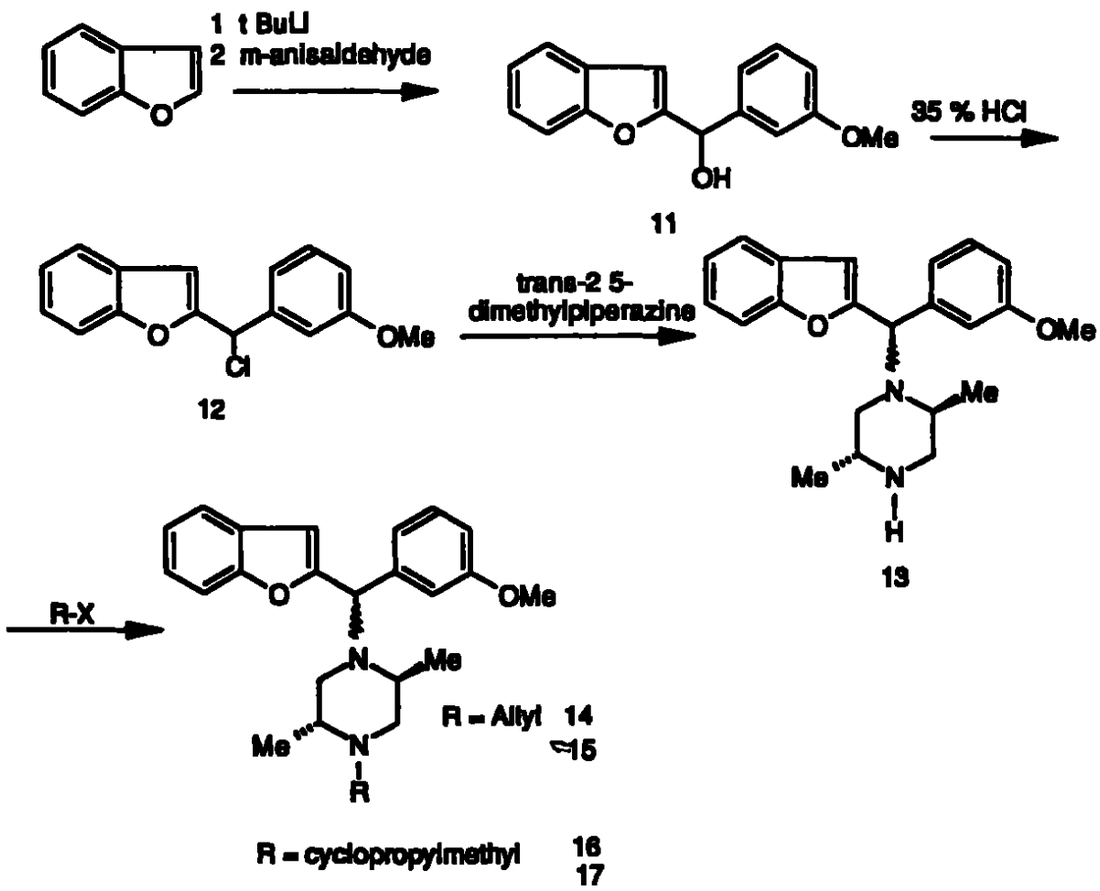
Compound 9 (one pure isomer) GC-MS (R_t = 16.05 min) 401.25 (0.2%) 400.25 (0 8), 359 15 (0.4), 330 15 (0 4), 302.15 (3 1) 274 15 (8.0), 247 05 (21 7) 215 10 (13 0) 202.05 (7.0),153 15 (100), 126 15 (9 7), δ_H (400 MHz, $CDCl_3$) 1 36 (d, J=6.4 Hz, 3H) 1 41 (d J=6 4 Hz, 3H) 3 16 (dd J=13 2 2.4 Hz, 1H) 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 mun) 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 mun) 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 mn) 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); $^{\delta}C$-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

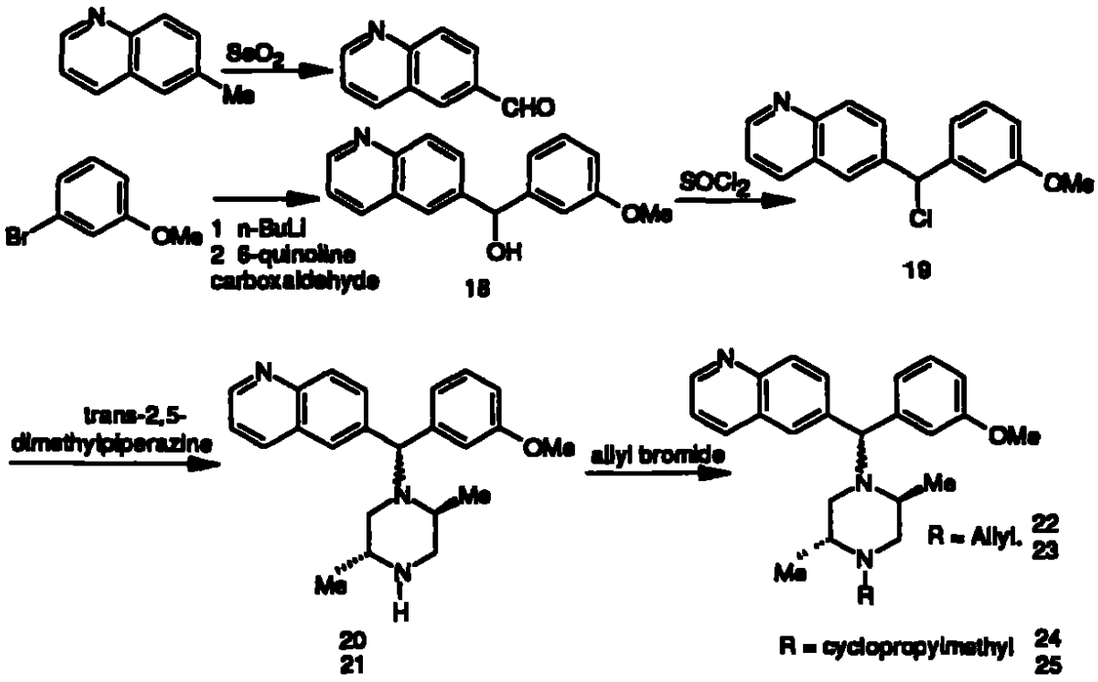
Its HCl salt: m p 162 164°C (Ether) ν_{max} (KBr) cm^{-1} 3414 1599, 1255 *Anal* Calcd for $C_{26}H_{32}N_2O_2.2HCl.0.5H_2O$ C, 64 19 H 7.25 N 5 76. Found C, 64 43 H, 7 30 N 5 78

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) $\delta_{C\ 13}$ (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 cyclopropylmethylbromide.

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

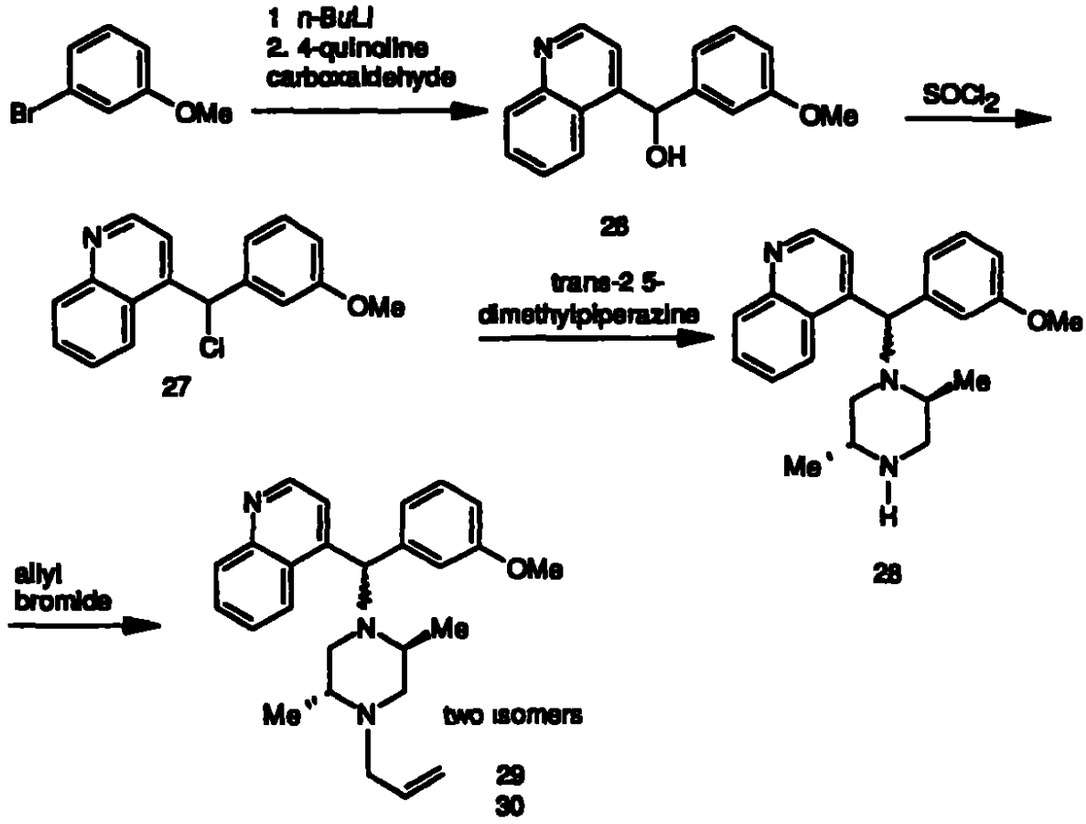
Its HCl salt. m p. 127 157°C (Ether), ν_{max} (KBr) cm^{-1} 3402 1596 1262, *Anal* Calcd for $C_{27}H_{33}N_3O$ 3HCl 0 75H_2O· C, 60 23 H 7 02 N 7 80 Found C 60 49 H 7 00 N 7 73

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.

1. 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

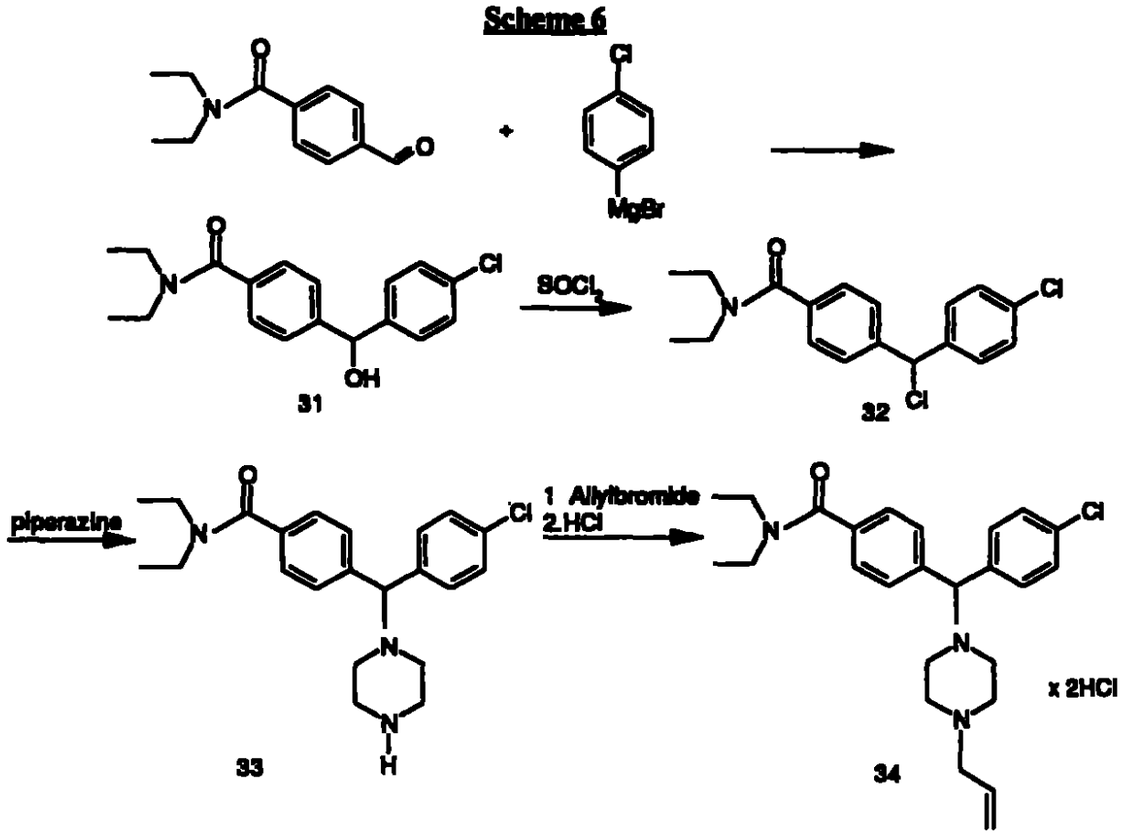
The first isomer compound 29: GC-MS (R_t = 15 97 min) 401 15 (M^+ 0 8%) 360 20 (0 8) 303 15 (3 3) 27615 (5 7) 248 05 (15 3) 217 05 (6.3) 204 10 (10 4) 176 00 (2.2) 153 20 (100) 126 10 (5 3), 98 10 (13 8) δ_H (400 MHz, $CDCl_3$) 0 96 (d, J=6 0 Hz, 3H) 1 14 (d J=6 0 Hz 3H) 2 01 (m, 1H) 2 16 (t, J=10 0 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), $\delta_{C\ 13}$ (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.

1. 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

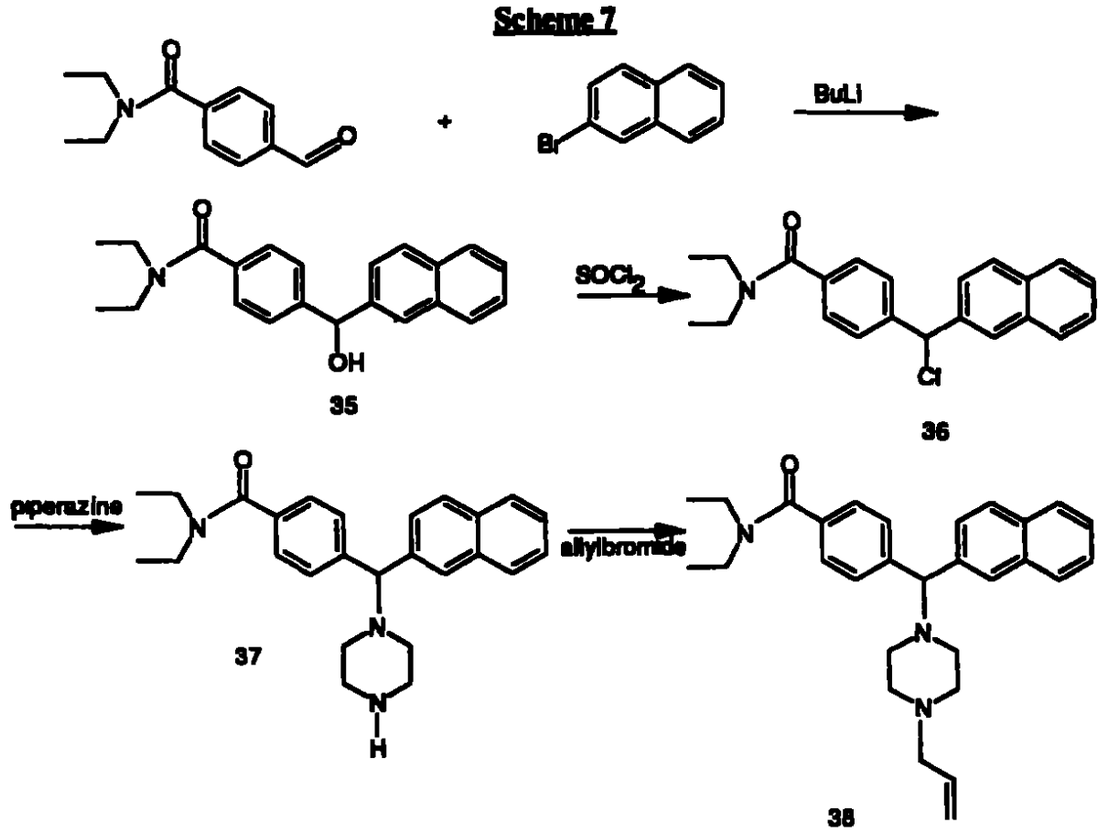
Preparation of (±) 4-((α-((4-Allyl)-1-piperazinyl))-4-chlorobenzyl)-N,N diethylbenzamide • 2HCl (compound 34)

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

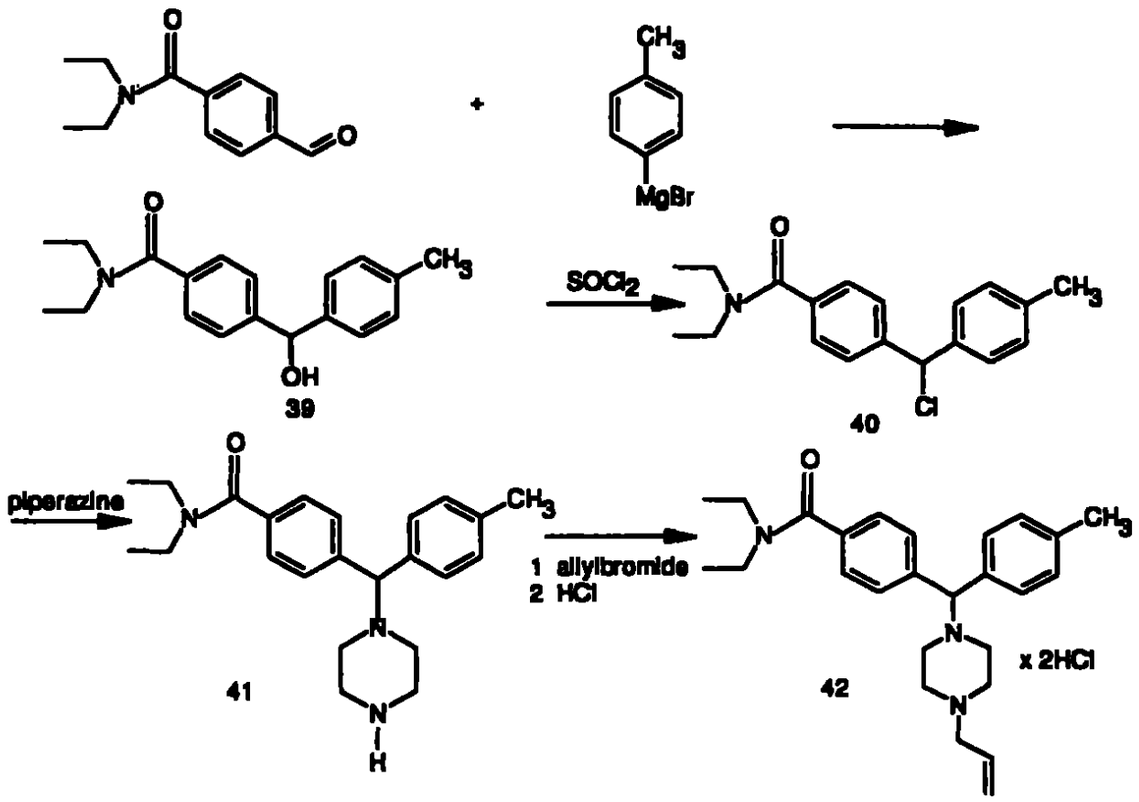
Preparation of (±) 4-((α-((4-Allyl)-1-piperazinyl))-2-naphtylmethyl)-N,N-diethylbenzamide (compound 38)

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.

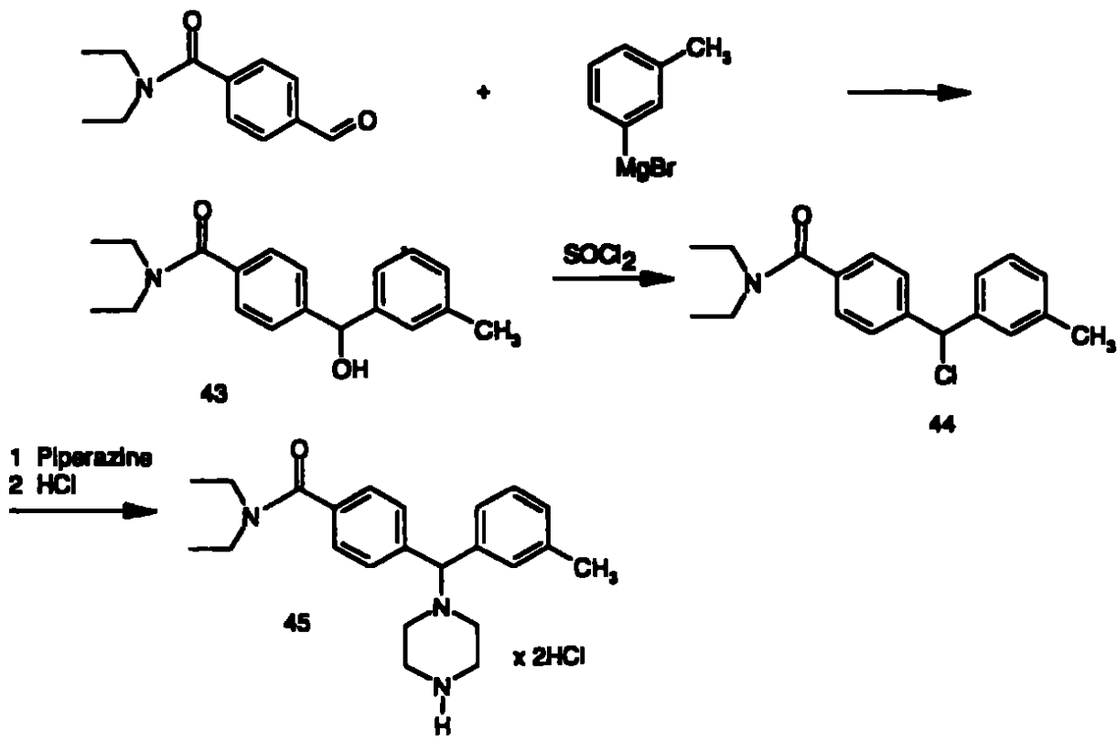
Example 26

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 2



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.

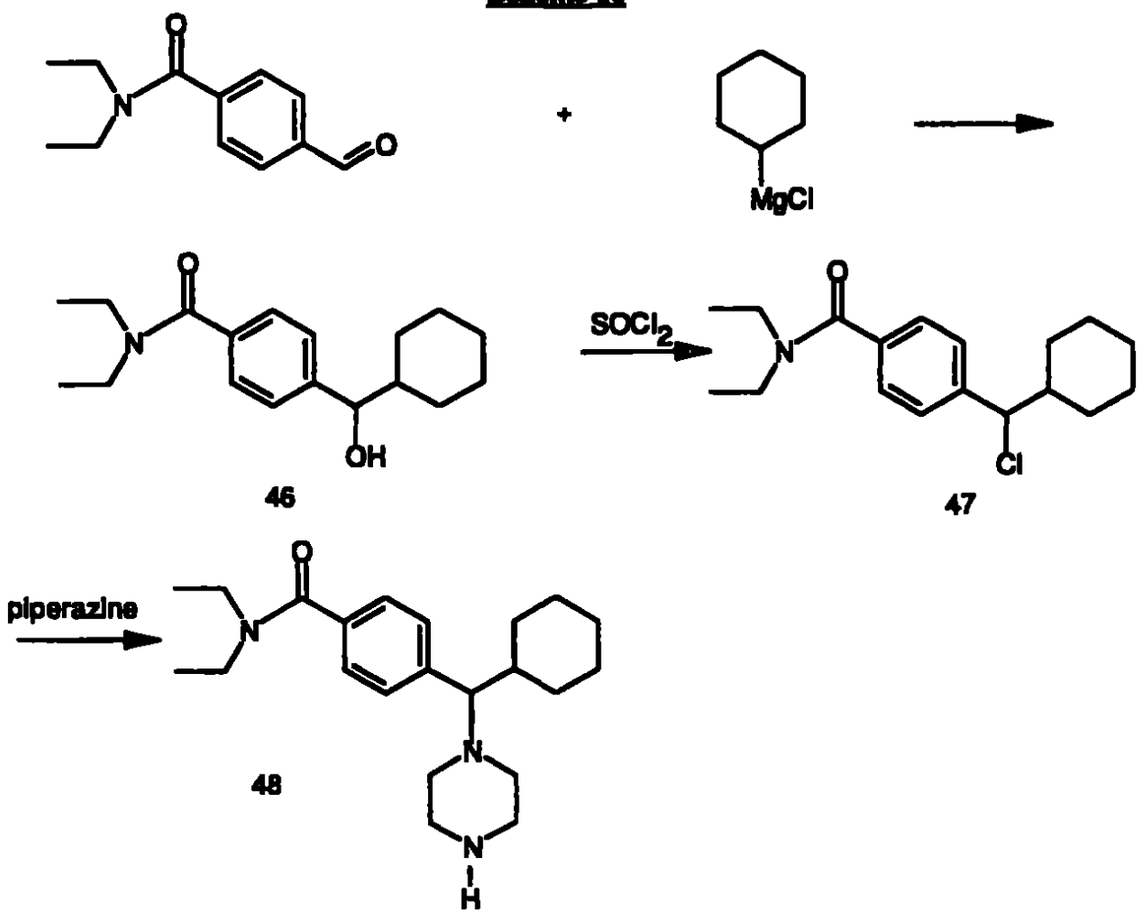
Example 27

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

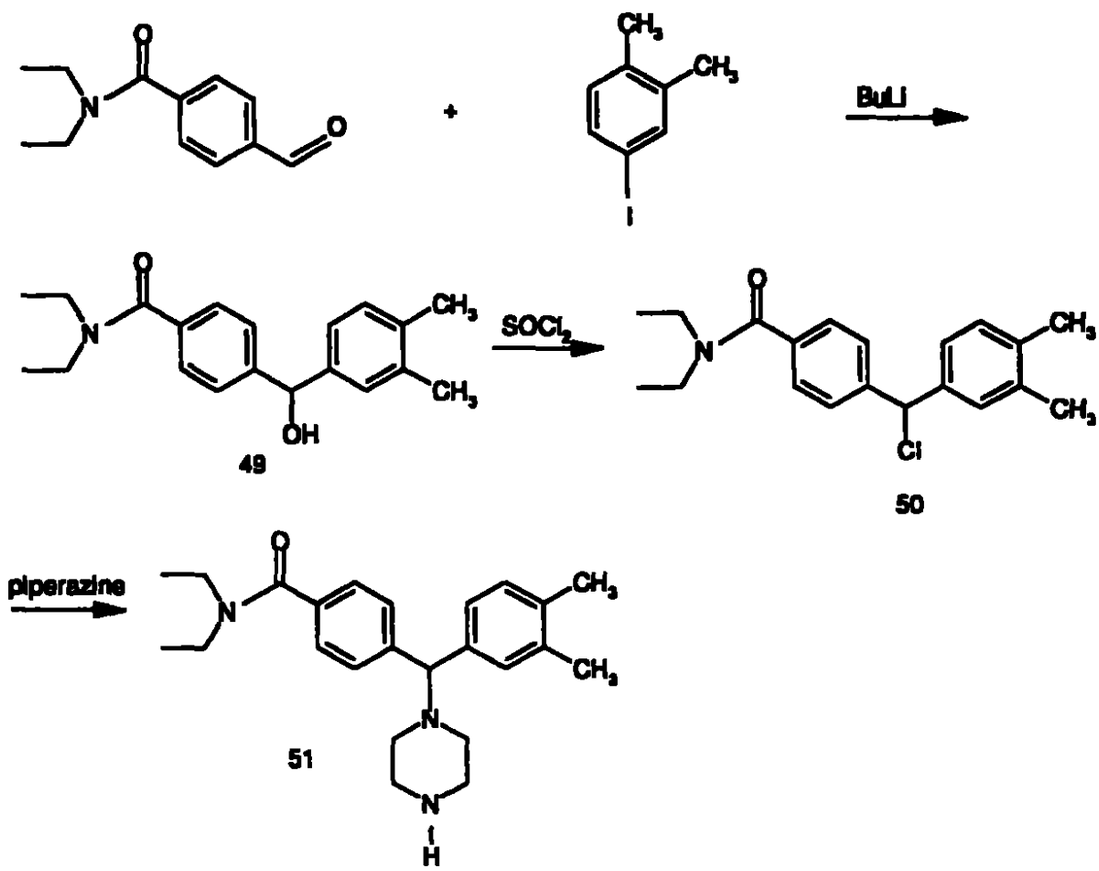
Example 28

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.

L. 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

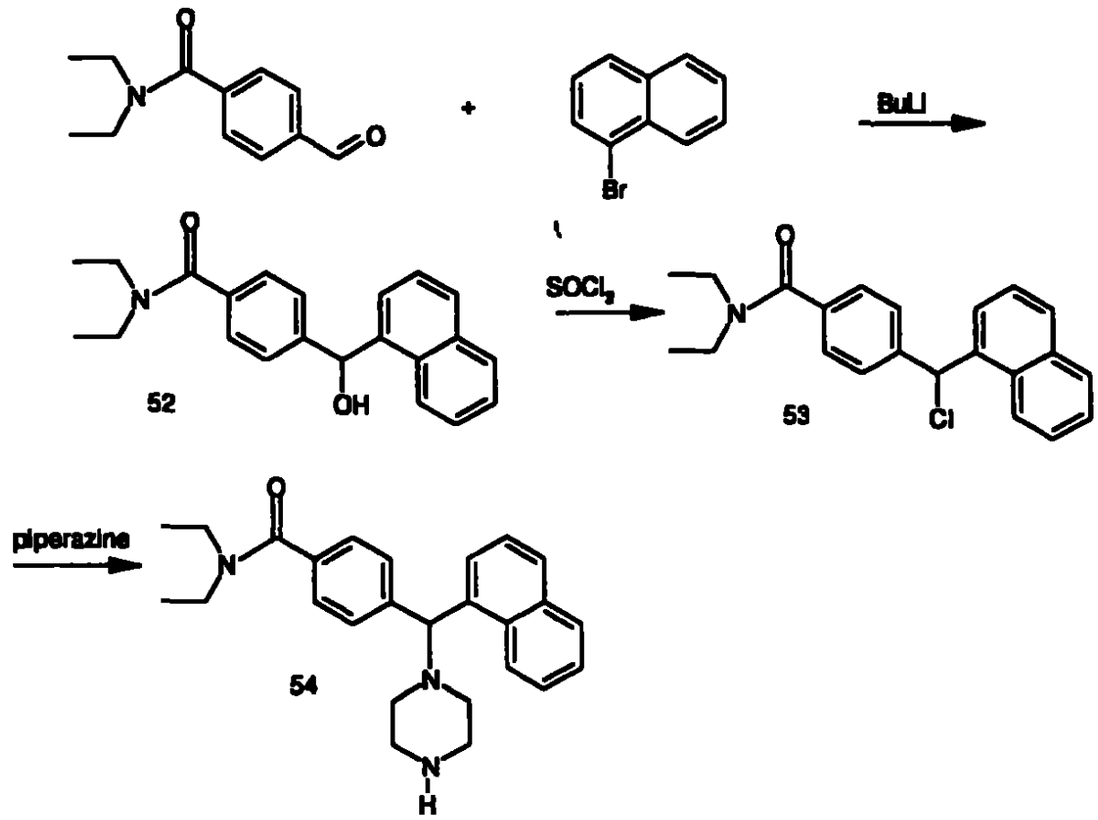
Example 29

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

Q.

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 ^{1}H 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 ^{1}H 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

L 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. *i*-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 imidazole (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

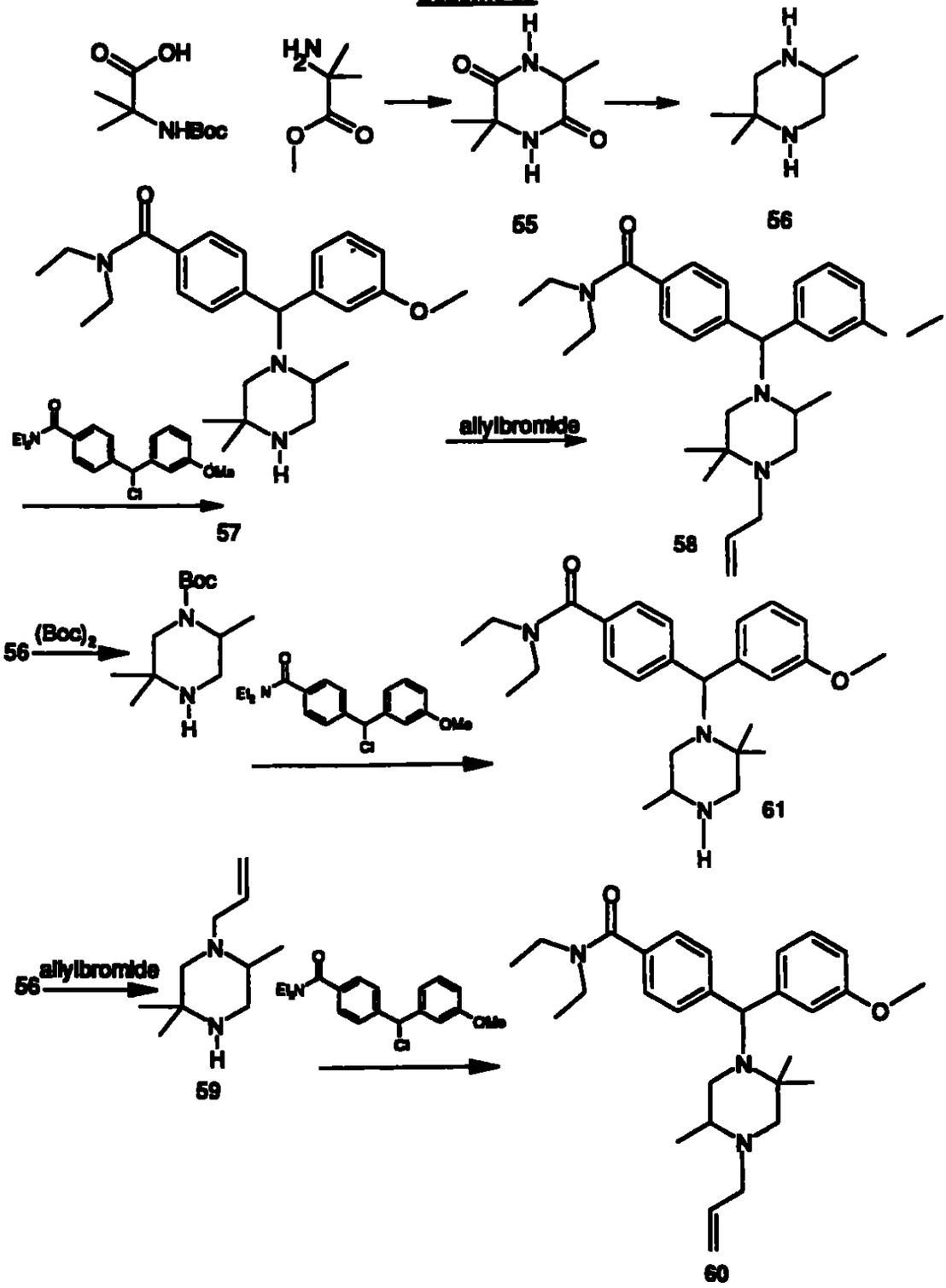
Example 42

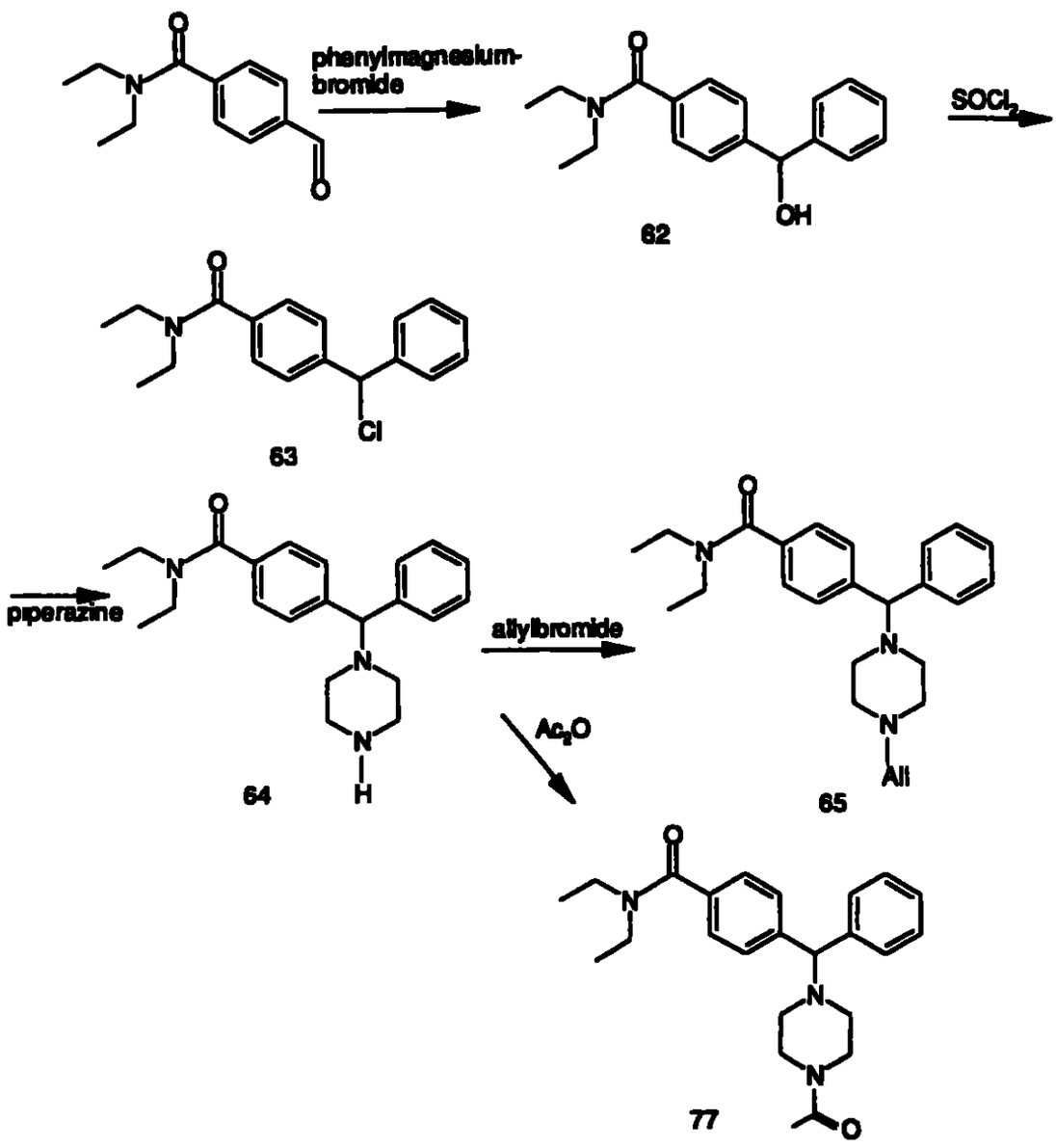
Preparation of 4-((4-Acetyl-1-piperazinyl)-benzyl)- N,N-diethylbenzamide hydrochloride (compound 77)

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 %)

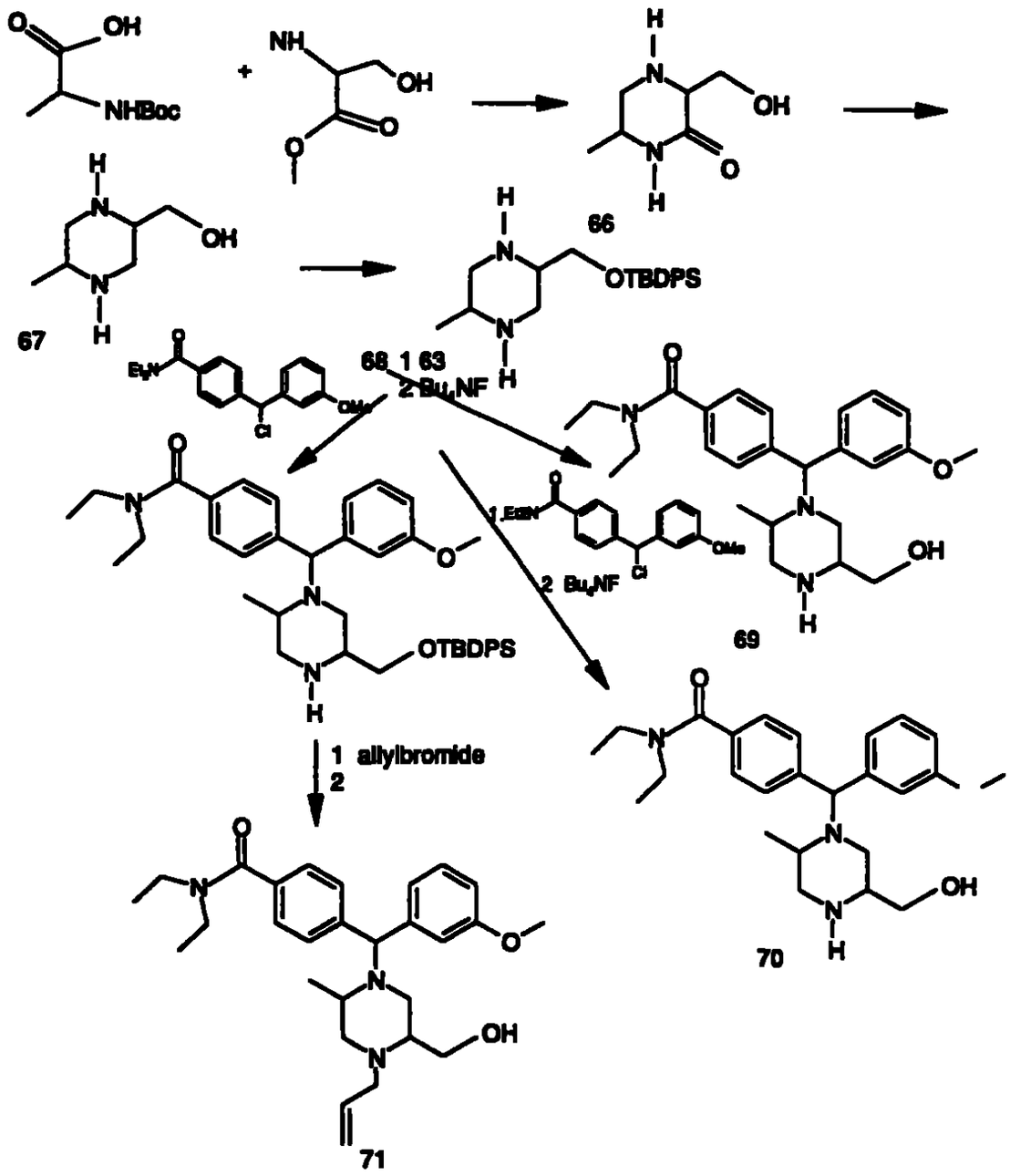
Mp 140-50°C. IR (KBr) (cm 1) 3480(br) 2987 2500(br) 1623 1429 1285,1245 MS (free amine) 393 267 165 127 ^{1}H NMR (free amine $CDCl_3$) δ = 7 46-7 18 (m 9H Ar-H) 4 25 (s 1H $CHAr_2$) 3 70- 3 15 (m 8H amide CH_2 piperazine H), 2 36 (m, 4H piperazine-H) 2 05 (s, 3H MeCO) 1 15 (br m, 6H amide-Me) Anal calc 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

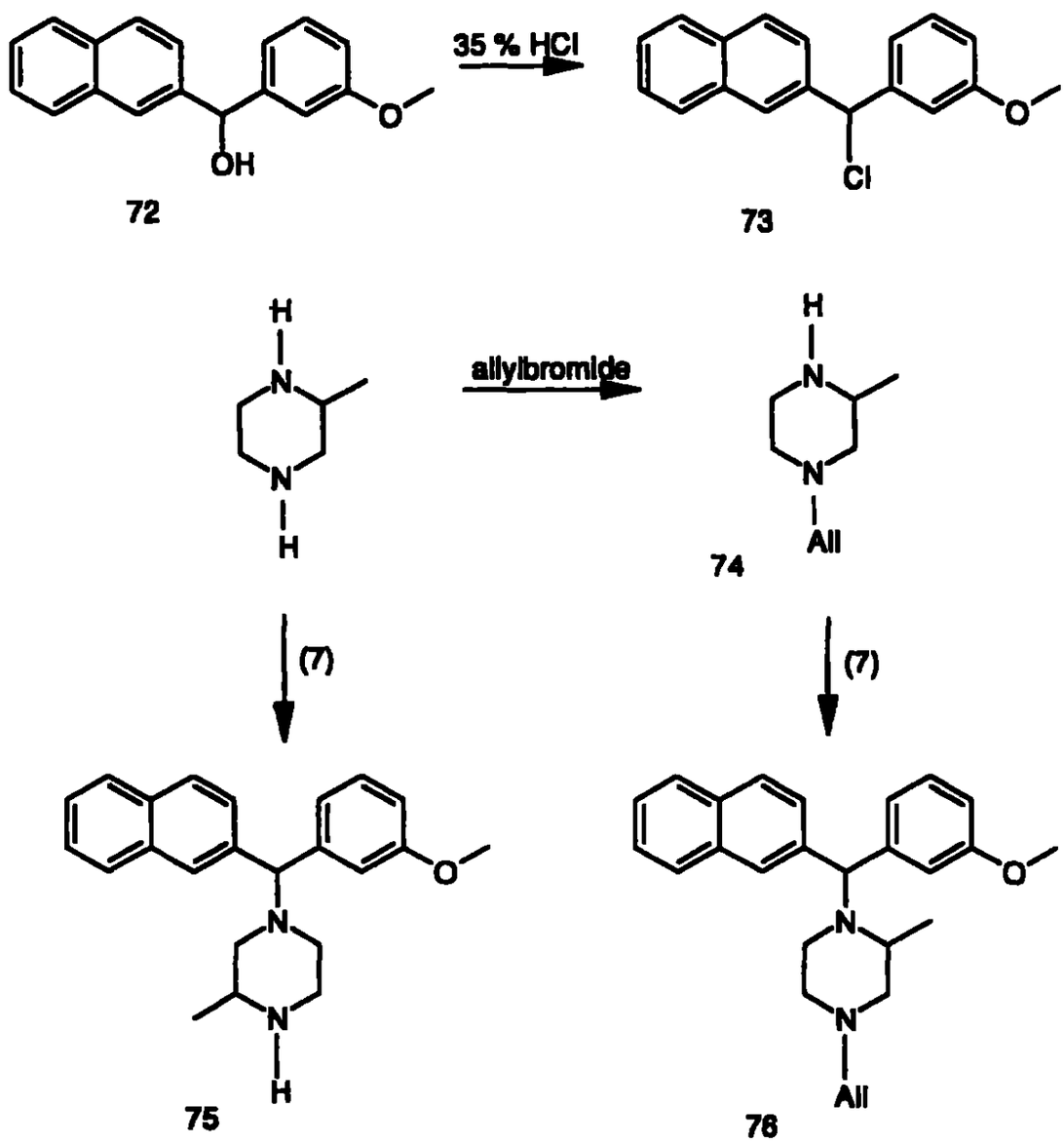
Scheme 13




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
N
H
66
OTBDPS
67
68
1 63
2 Bu4NF
Et3N
Cl
OMe
1 Et3N
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 aqueous 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 aqueous 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 $C_{18}H_{20}N_2O_2x2HCl$, 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 achieved 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 $C_{18}H_{19}N_3x2HCl\ x1H_2O$ C 58 70 H 6 29 N 11 41 Found C 58 88 H 6 46 N 11 24

Example 48

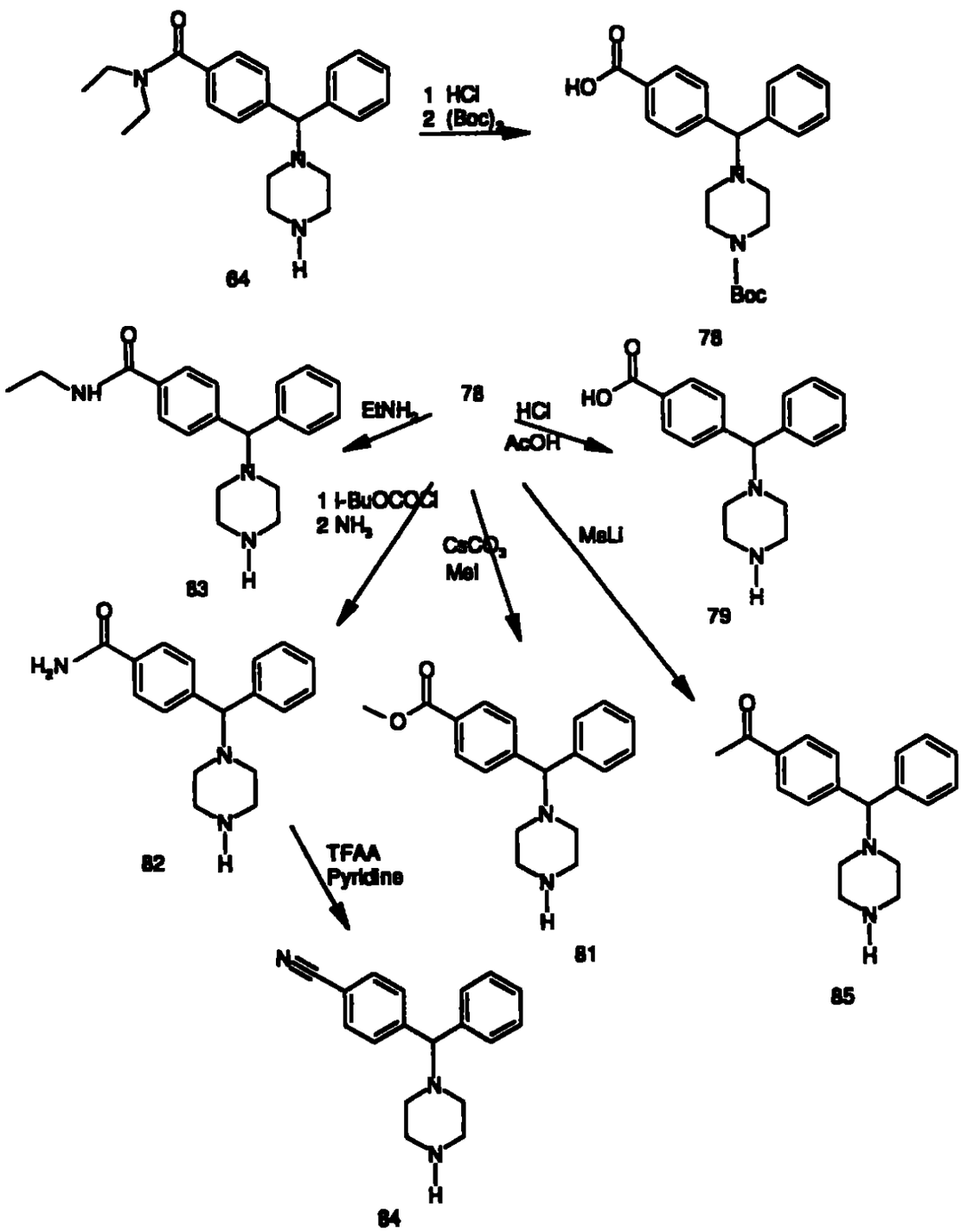
Preparation of 4-(1 piperazinyl-benzyl)-acetophenone dihydrochloride (compound 85)

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)

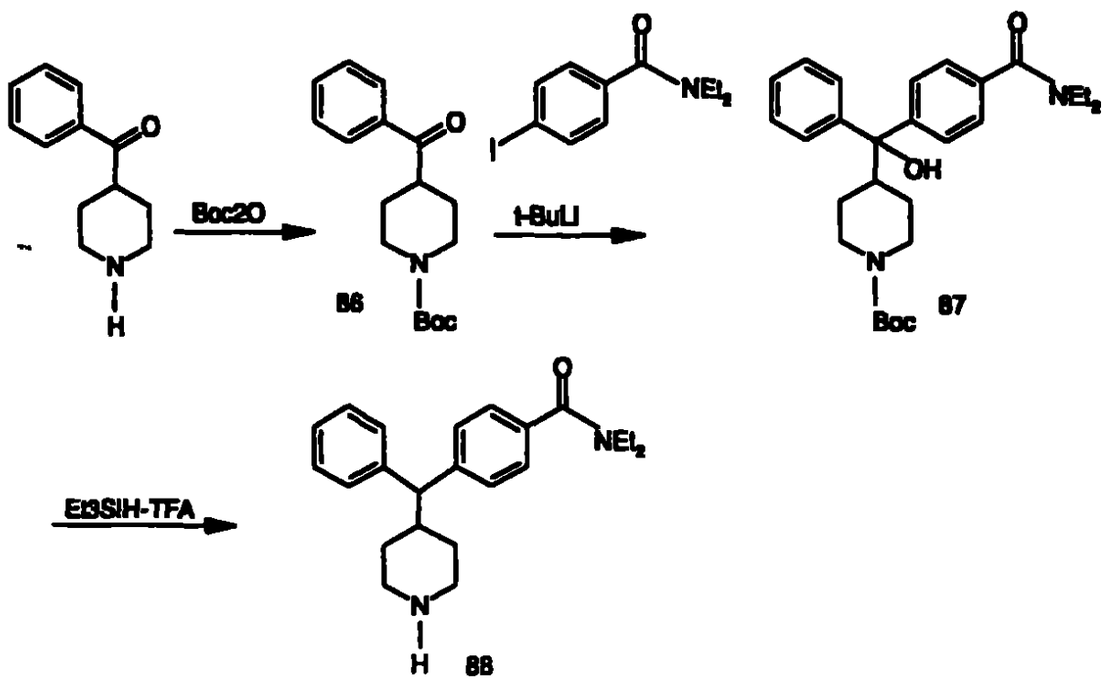
Anal calc. for $C_{19}H_{22}N_2O$ x2HCl x1 6 H_2O C 57 61 H 6.92, N 7 07 Found C: 57 54 H 6 75, N 6 91

Scheme 14


1 HCl
2 (Boc)2O
64
78
Boc
EtNH2
HCl
AcOH
1 t-BuOCOCl
2 NH3
Cs2CO3
MeI
MeLi
83
79
82
81
85
TFAA
Pyridine
84

5

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.

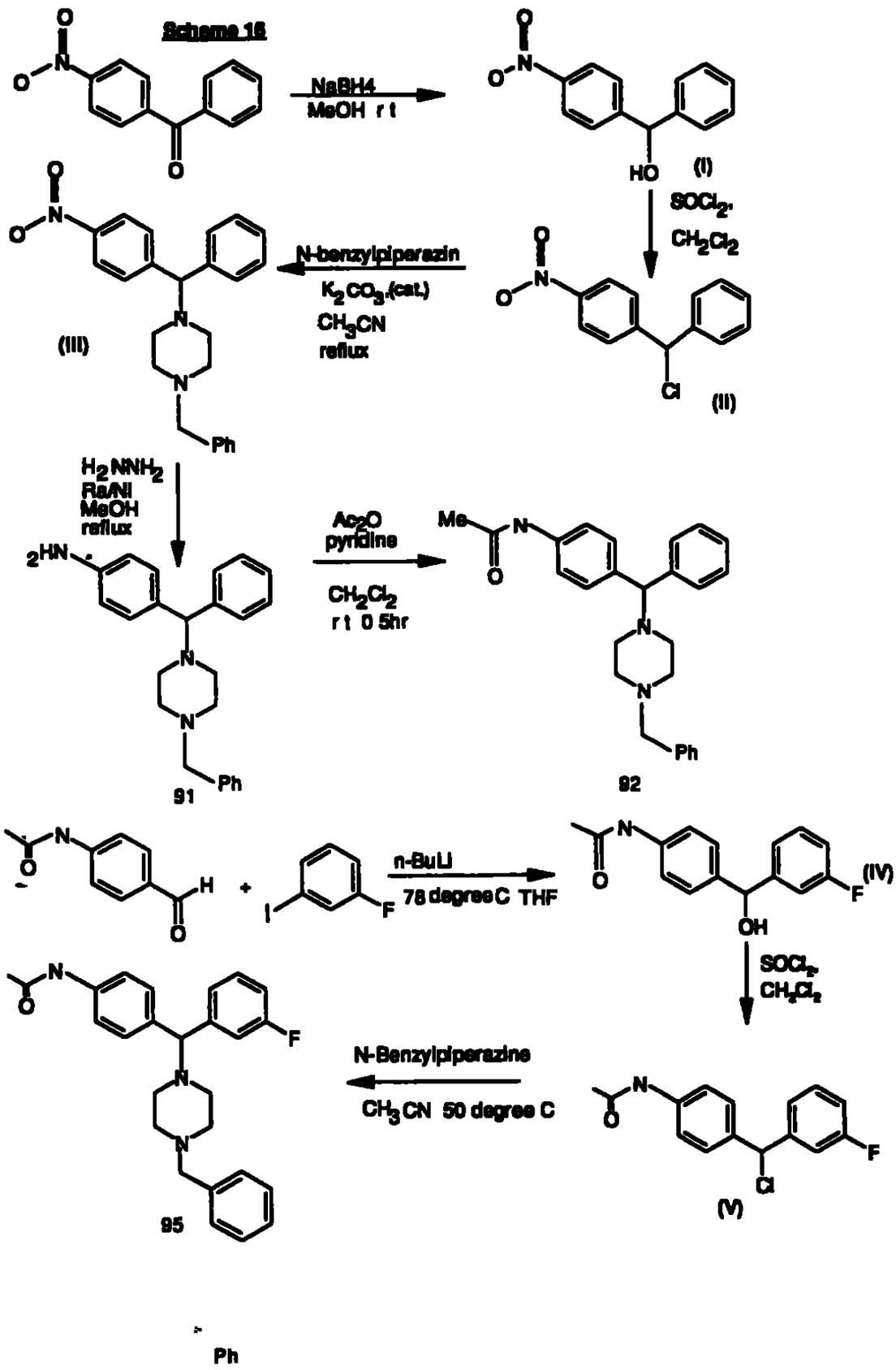
Example 51

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 acetonitrile, 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 -N<u>H</u>$_2$), 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

ν^{KBr} 3404(br) 2922(br) 1745 1610 1517, 1439 1207cm^{-1}

^1H 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 $C_{27}H_{31}N_3O_2$·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, $OCC\underline{H}_3$) 2.55 (1H, s br $O\underline{H}$), 5 76 (1H d *J*=3 2Hz, Ar-C<u>H</u>-Ar) 7 35 (1H s CON<u>H</u>) 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, $OCC\underline{H}_3$) 6 10 (1H, s, Ar-C<u>H</u>-Ar) 7 84 (1H, s, CON<u>H</u>), 6 90~7 6 (8H m, Ar) 7 84 (1H, s, CON<u>H</u>)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 $C_{26}H_{28}FN_3O \cdot 2HCl \cdot 1.6CH_2Cl_2 \cdot 2H_2O$ 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 convement 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_d 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_d (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_d 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.

$$50\%\ g\ threshold = 10^{(Xf+kd)} / 10{,}000$$

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

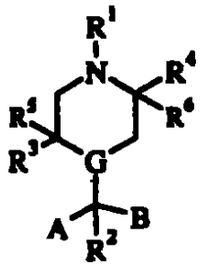
$$\% \text{ MPE} = \frac{\text{Drug treated threshold (g) - allodynia threshold (g)}}{\text{Control threshold (g) - allodynia threshold (g)}} \times 100$$

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

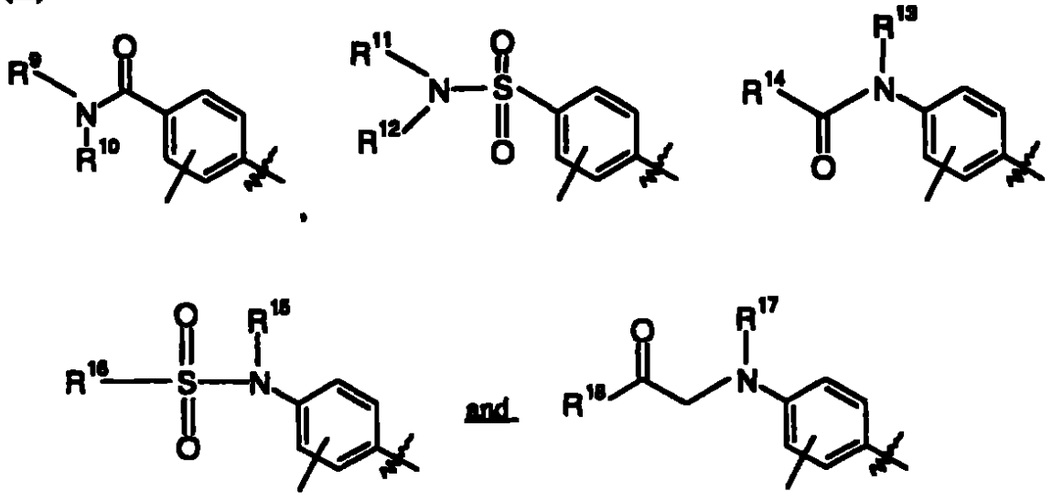
G is a carbon atom or a nitrogen atom

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,

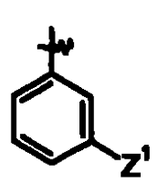
B is a substituted or unsubstituted aromatic, an optionally substituted C_5-C_{10} hydroaromatic; a heteroaromatic or a heterohydroaromatic moiety each having from 5 to 10 atoms selected from any of C, S, N and O and each being optionally substituted by 1 or 2 substituents independently selected from 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

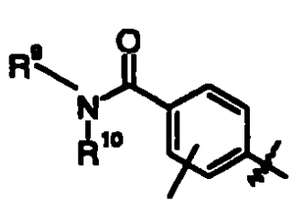
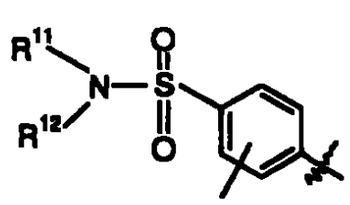
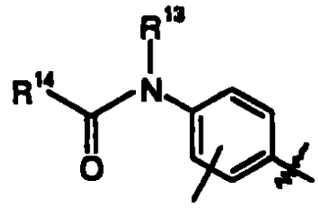
G is a carbon atom or a nitrogen atom,

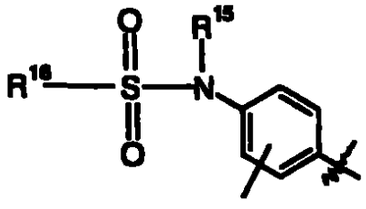
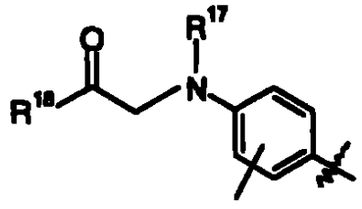
A is selected from

(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


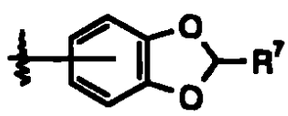
wherein the phenyl ring of each A substituent may be optionally and independently substituted by 1 or 2 substituents selected from hydrogen, CH_3, $(CH_2)_oCF_3$, halogen, $CONR^7R^8$, CO_2R^7 COR^7 $(CH_2)_oNR^7R^8$ $(CH_2)_oCH_3(CH_2)_oSOR^7$, $(CH_2)_oSO_2R^7$ and $(CH_2)_oSO_2NR^7R^8$, wherein o 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

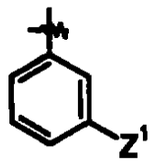
B is selected from phenyl naphthyl indolyl benzofuranyl dihydrobenzofuranyl benzothiophenyl, pyrryl, furanyl, quinolinyl isoquinolinyl cyclohexyl, cyclohexenyl, cyclopentyl, cyclopentenyl indanyl indenyl, tetrahydronaphthyl, tetrahydroquinyl, tetrahydroisoquinolinyl, tetrahydrofuranyl pyrrolidinyl, indazolinyl, 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

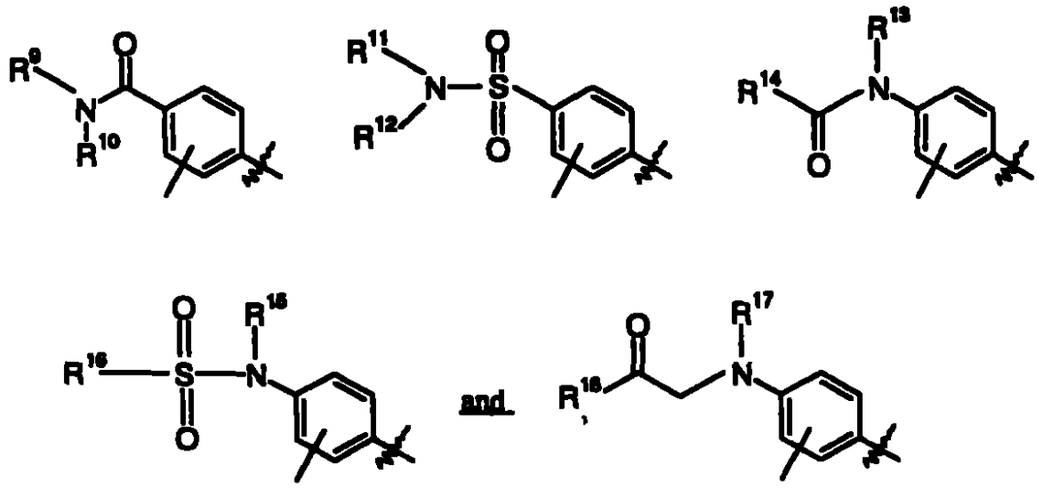
hydroxymethyl and esters thereof; or

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

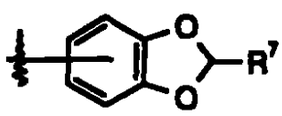
wherein

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.

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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
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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
"B" 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

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
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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
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INTERNATIONAL SEARCH REPORT

Information on patent family members

04/03/97

International application No
PCT/SE 96/01635

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1347

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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

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(30) Priority Data
60/068 794 24 December 1997 (24.12.97) US

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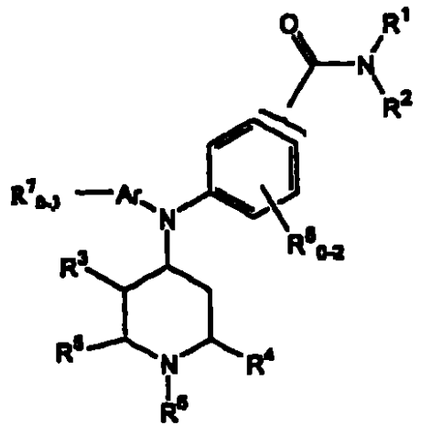
(72) Inventors; and
(75) Inventors/Applicants (*for US only*): CARSON John, R [–/US]; 551 Rittenhouse Boulevard, Norristown, PA 19403 (US). CARMOSIN Richard, J [–/US]; 122 Woodview Drive, Quakertown, PA 18851 (US). FITZPATRICK, Louis, J [–/US]; 204 Heatherfield Drive, Souderton, PA 18964 (US). REITZ, 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]

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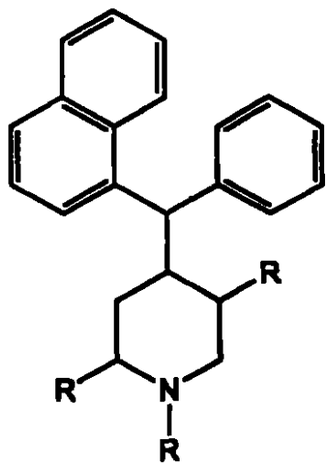
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4-[ARYL(PIPERIDIN-4-YL)] AMINOBENZAMIDES WHICH BIND TO THE DELTA-OPIOID RECEPTOR

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

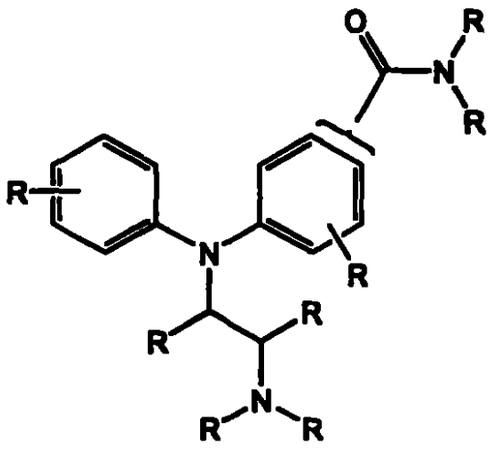
BACKGROUND OF THE INVENTION

WO9723466 to Plobeck N et al discloses compounds (approximately) of the formula



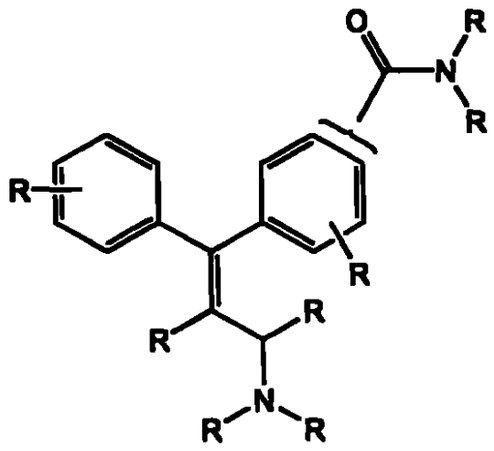
which are mu-opioid antagonists

WO9636620 to Dondio G discloses compounds (most relevantly) of the formula



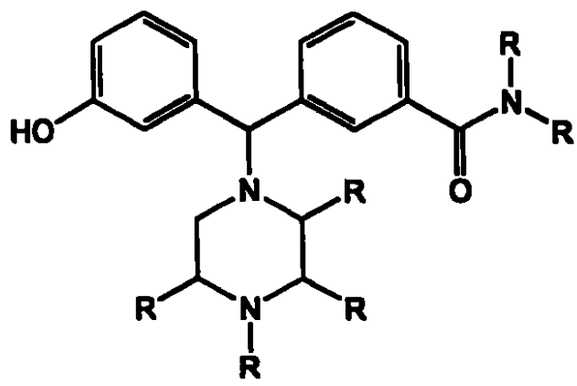
which are delta-opioid agonists/antagonists

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

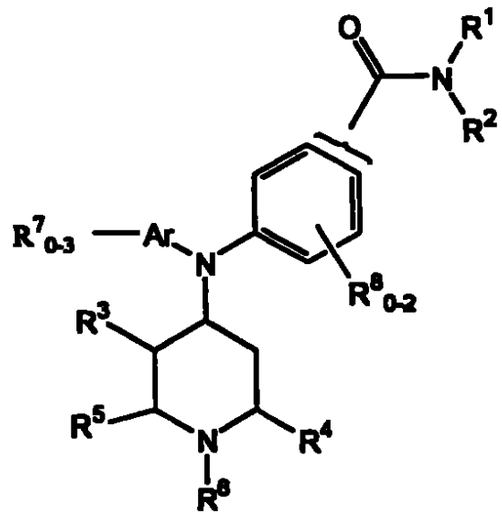
It is another object of the present invention to provide delta-opioid receptor selective agonists as analgesics having reduced side-effects

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_{1-5}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 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

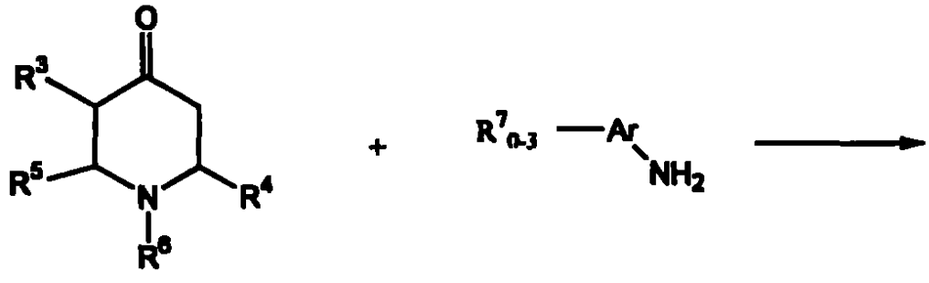
As delta-opioid receptor agonists, such compounds are useful as analgesics Depending on their agonist/antagonist effect, such compounds may also be useful immunosuppressants, antiinflammantory agents, agents for treatment of mental illness, medicaments for drug and alcohol abuse, agents for treating gastritis and diarrhea, cardiovascular agents, and agents for the treatment of respiratory diseases

DETAILED DESCRIPTION OF THE INVENTION

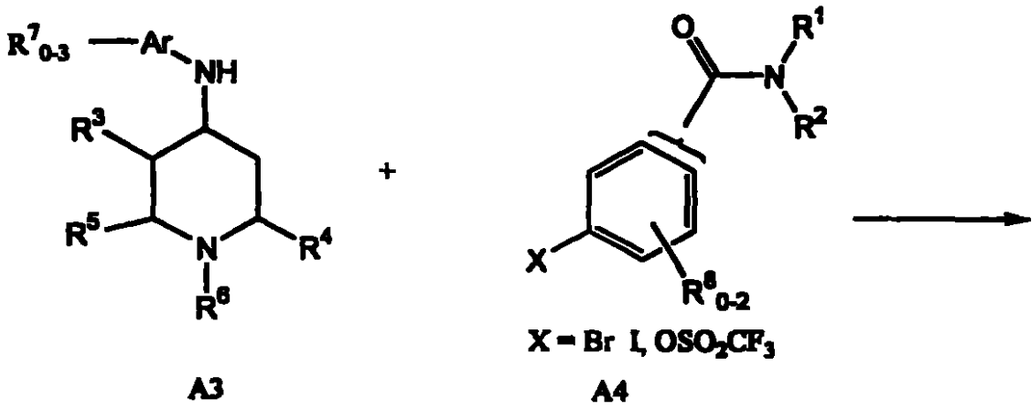
The core structure of the compounds of the present invention can be made in a two step process. This process must be modified as required by the strategy employed to obtain the various substituents In a first strategy the starting materials are substituted as desired with the final substituents and, 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

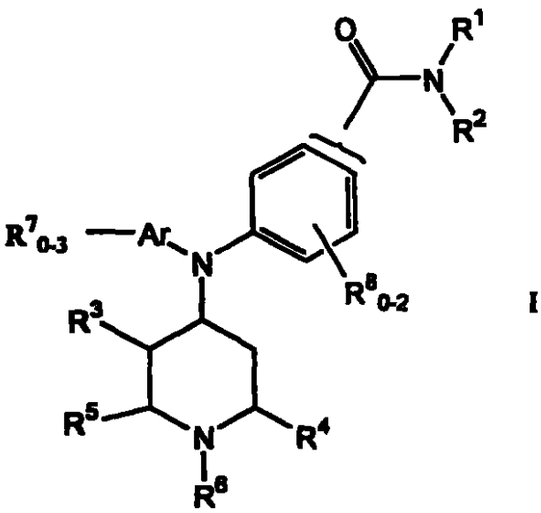
SCHEME A



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

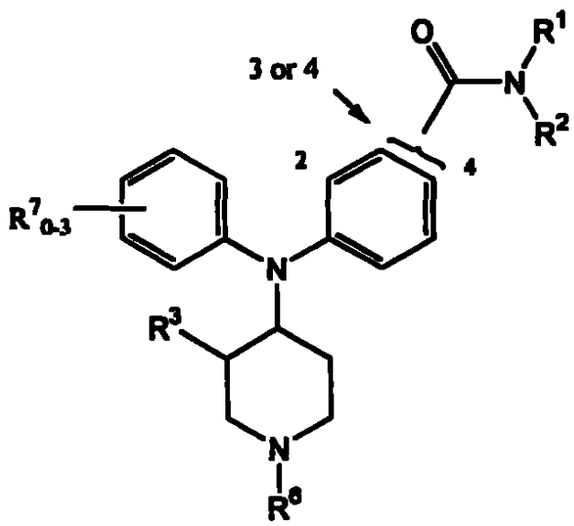
Preferred R^6 are selected from the group consisting of hydrogen, methyl ethyl n-propyl i-propyl n-butyl i-butyl t-butyl cyclopropylmethyl ethenyl allyl methoxymethyl, benzyl p-chlorobenzyl p-fluorobenzyl, p-methylbenzyl

p-trifluoromethylbenzyl p-aminobenzyl thien-2-ylCH_2CH_2- thien-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

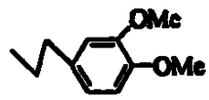
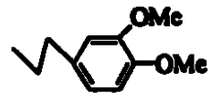
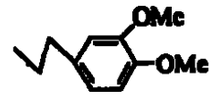
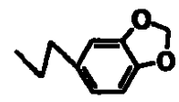
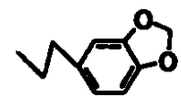
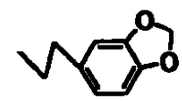
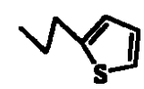
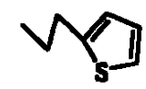
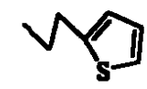
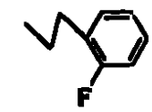
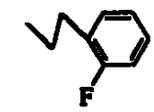


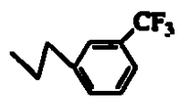
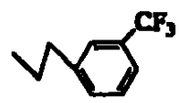
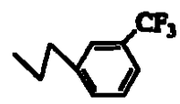
where R^1 R^2 R^3 R^6 and R^7 are dependently selected from the groups consisting of

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	$-CH_2$—◁	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P3	3-OH	$-CH_2CH=CH_2$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P4	3-OH	$-CH_2$—◁	$-CH_2CH_3$	$-CH_2CH_3$	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-$N(CH_3)_2$	$-nC_3H_7$	$2\text{-}C_3H_7$	$2\text{-}C_3H_7$	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
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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	cı-Me
P72	none	-H	-CH_2CH_3	-CH_2CH_3	4	cı-Me
P73	none	-$CH_2CH{=}CH_2$	-CH_2CH_3	-CH_2CH_3	4	cı-Me
P74	none	-nC_3H_7	-CH_2CH_3	-CH_2CH_3	4	cı-Me
P75	3-OCH_3	-CH_2Ph	-CH_2CH_3	-CH_2CH_3	4	cı-Me
P76	3-OCH_3	-H	-CH_2CH_3	-CH_2CH_3	4	cı-Me
P77	3-OCH_3	-$CH_2CH{=}CH_2$	-CH_2CH_3	-CH_2CH_3	4	cı-Me
P78	3-OCH_3	-nC_3H_7	-CH_2CH_3	-CH_2CH_3	4	cı-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	α-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	α-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	α-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 $C_{23}H_{33}N_3O_2$•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)

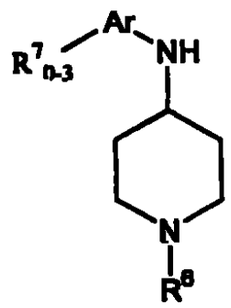
Then, following the procedure of Example 1 and employing N-phenyl-1-propyl-4-piperidinamine in place of N-(3-methoxyphenyl)-1-propyl-4-piperidinamine, N N-diethyl-4-[phenyl(1-propylpiperidin-4-yl)amino]benzamide fumarate was obtained as the product mp 152-154°C MS *m/z* = 394 (M^+ + H) 300 MHz ^{1}H 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



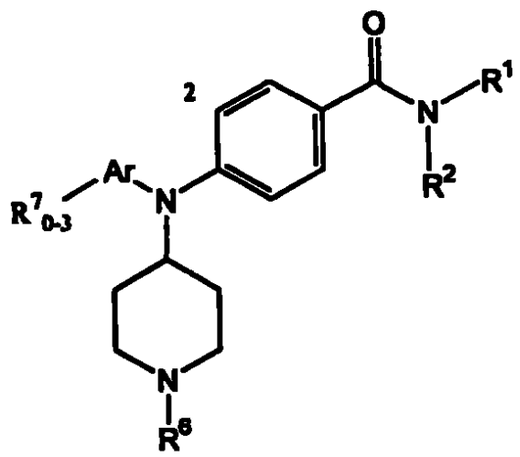
where R^6 and R^7 are dependently selected from the groups consisting of

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	$-(CH_2)_3-$		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	$-(CH_2)_3-$		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	$-(CH_2)_3-$		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	$-(CH_2)_3-$		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	-$(CH_2)_4$-		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 $C_{27}H_{37}N_3O_3$•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 $6H_2O$ (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

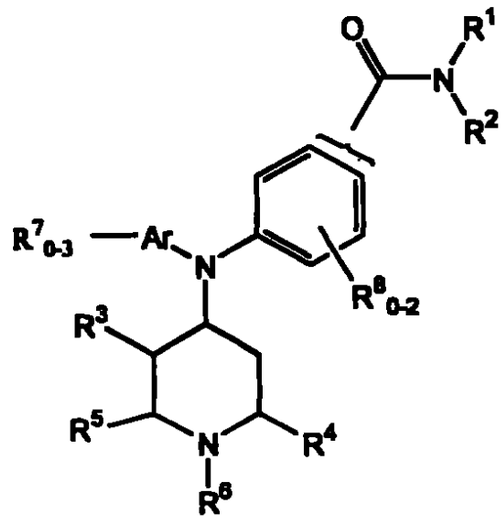
C) Mouse Acetylcholine Bromide-Induced Abdominal Constriction Assay

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_{1-8}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 -$(CH_2)_{2-5}$- 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

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

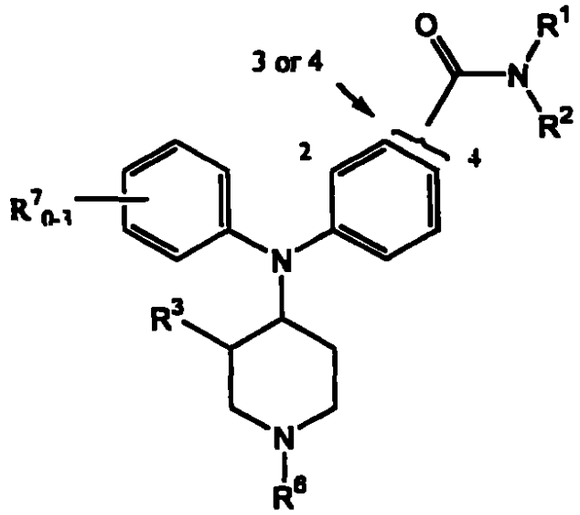
5 The compound of claim 1 wherein R^6 are selected from the group consisting of hydrogen, methyl ethyl n-propyl i-propyl n-butyl i-butyl, t-butyl cyclopropylmethyl ethenyl allyl methoxymethyl, benzyl p-chlorobenzyl p-fluorobenzyl p-methylbenzyl p-trifluoromethylbenzyl p-aminobenzyl thien-2-ylCH_2CH_2- 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^6 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

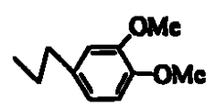
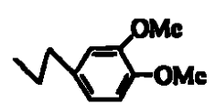


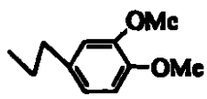
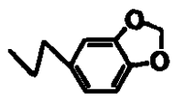
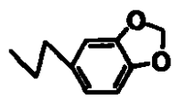
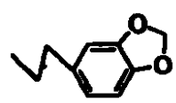
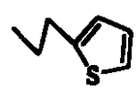
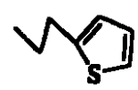
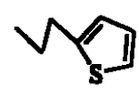
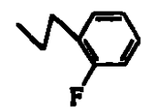
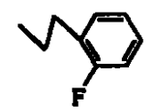
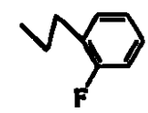
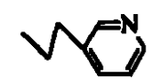
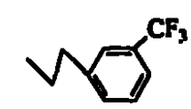
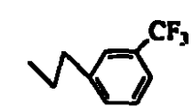
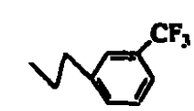
where R^1 R^2 R^3 R^6 and R^7 are dependently selected from the groups consisting of

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	$-CH_2-\triangleleft$	$-CH_2CH_3$	$-CH_2CH_3$	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

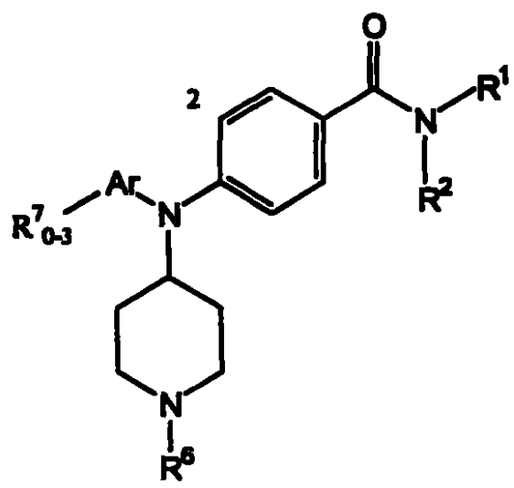
P5	3-OH	$-CH_3$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P6	3-OH	$-CH_2CH_3$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P7	3-OH	$-CH_2CH_2Ph$	$-CH_2CH_3$	$-CH_2CH_3$	4	H
P8	3-OH	$-CH_3$	$-nC_3H_7$	$-nC_3H_7$	4	H
P9	3-OH	$-CH_2CH_3$	$-nC_3H_7$	$-nC_3H_7$	4	H
P10	3-OH	$-CH_2CH_2Ph$	$-nC_3H_7$	$-nC_3H_7$	4	H
P11	3-OH	$-CH_3$	$-nC_4H_9$	$-nC_4H_9$	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-	$-nC_3H_7$	$2-C_3H_7$	$2-C_3H_7$	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	$2\text{-}C_3H_7$	$2\text{-}C_3H_7$	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	$-nC_3H_7$	$2\text{-}C_3H_7$	$2\text{-}C_3H_7$	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	$-nC_3H_7$	$2\text{-}C_3H_7$	$2\text{-}C_3H_7$	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	cs-Me
P72	none	-H	-CH_2CH_3	-CH_2CH_3	4	cs-Me
P73	none	-$CH_2CH{=}CH_2$	-CH_2CH_3	-CH_2CH_3	4	cs-Me
P74	none	-nC_3H_7	-CH_2CH_3	-CH_2CH_3	4	cs-Me
P75	3-OCH_3	-CH_2Ph	-CH_2CH_3	-CH_2CH_3	4	cs-Me
P76	3-OCH_3	-H	-CH_2CH_3	-CH_2CH_3	4	cs-Me
P77	3-OCH_3	-$CH_2CH{=}CH_2$	-CH_2CH_3	-CH_2CH_3	4	cs-Me
P78	3-OCH_3	-nC_3H_7	-CH_2CH_3	-CH_2CH_3	4	cs-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	-$(CH_2)_5$-	
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	-$(CH_2)_5$-	
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	-$(CH_2)_5$-	
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	-$(CH_2)_5$-	
C44	3-F-Ph	Ethyl	-$(CH_2)_4$-	
C45	Ph	Benzyl	Ethyl	Ethyl
C46	3-$CH_3C(O)O$-	n Propyl	Ethyl	Ethyl

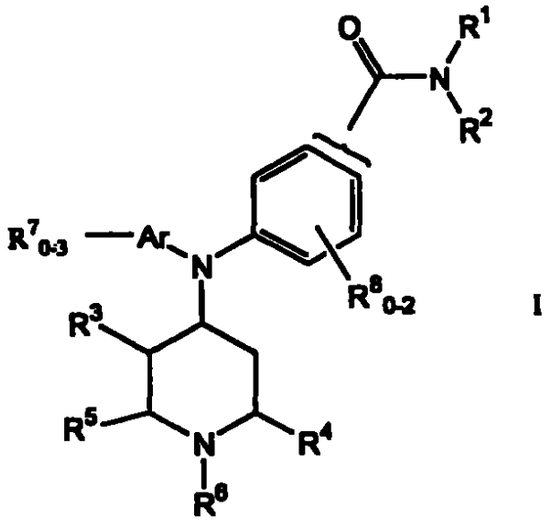
11 The compounds of claim 1 which are effective analgesics

12 The compounds of claim 1 which are effective immunosuppreasants, 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

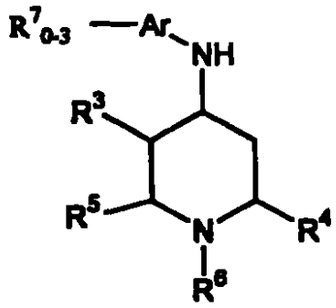
14 A method of the therapeutic treatment of a mammal comprising administering a compound of claim 1 which is effective as an immunosuppressant, antiinflammatory agent, agent for the treatment of mental illness, medicament for drug and alcohol abuse, agent for treating gastritis and diarrhea, cardiovascular 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

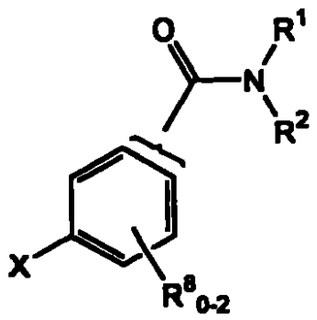


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comprising the step of arylating a compound of the formula



in the presence of a palladium catalyst, a phosphine ligand and a base with a compound of the formula



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_{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$_{1-6}$alkyl C$_{1-6}$alkoxy and trifluoromethyl

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INTERNATIONAL SEARCH REPORT

Int. ..ional 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

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[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

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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 98/27358

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
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Intl. ational Application No
PCT/US 98/27350

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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D4 169 167

J Med Chem. 1999 *42,* 5455–5463

Probes for Narcotic Receptor Mediated Phenomena 28 [1–3] Synthesis and Biological Evaluation of Diarylmethylpiperazines and Diarylmethylpiperidines as Novel Nonpeptidic δ Opioid Receptor Ligands

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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.

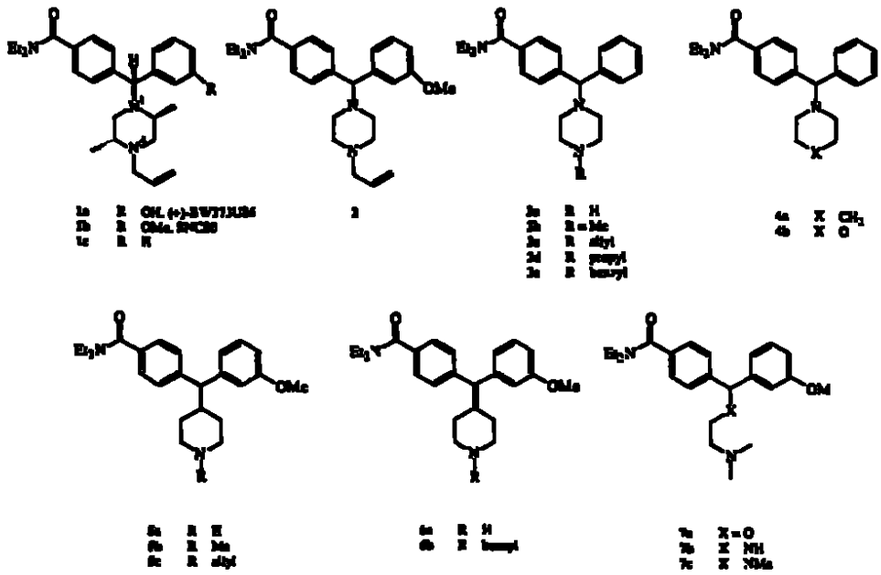
Classification of opioid receptors into mu (μ), delta (δ), and kappa (κ) is widely accepted and they have been identified by molecular cloning and pharmacological means.[4−6] Recent advances in the understanding of the physiological functions of the δ opioid receptors have highlighted the important role 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

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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]

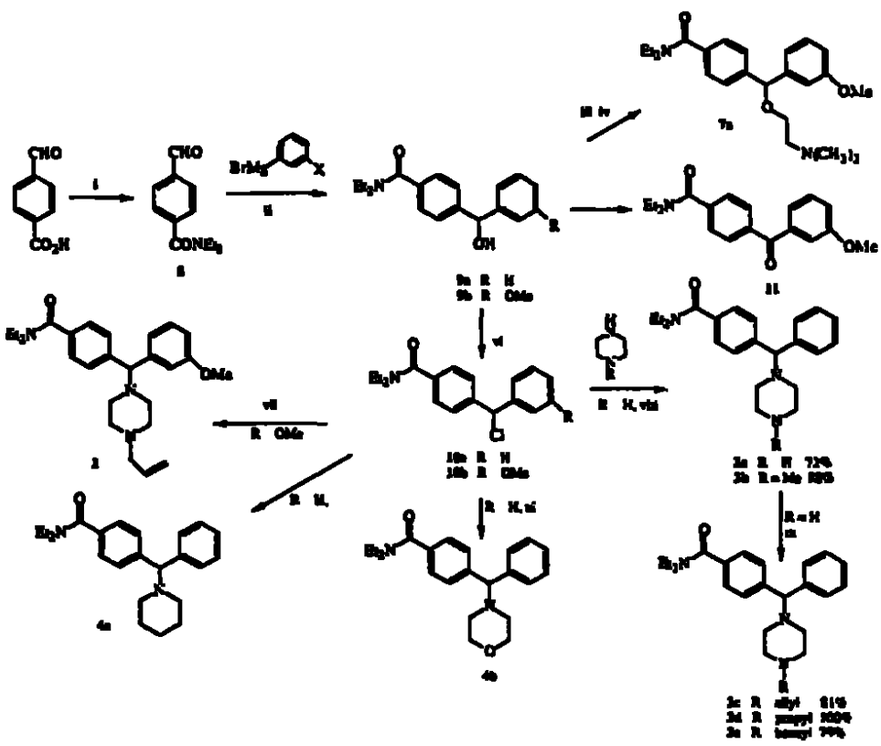
Chemistry

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-ethyl carbodiimide (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 8a 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 dimethyl amine.

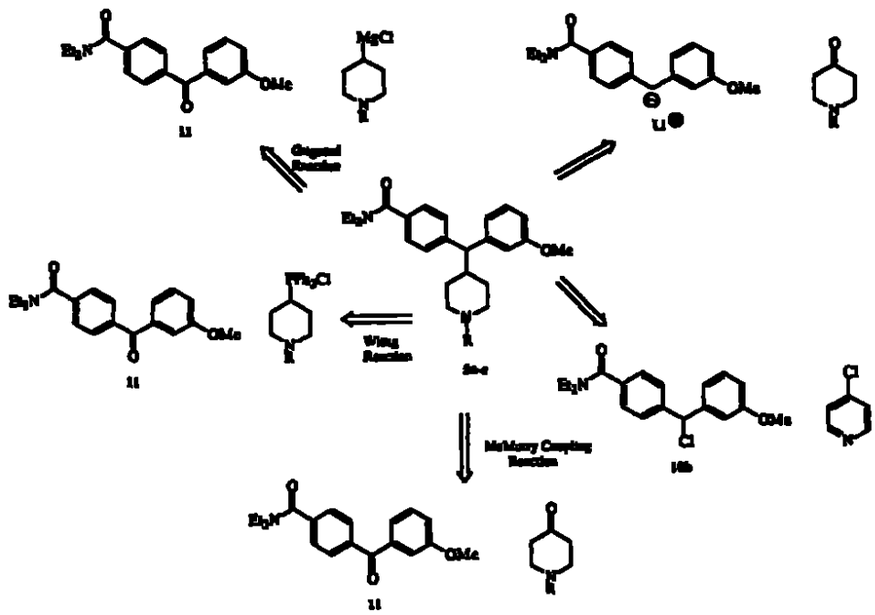
Several approaches different from that of Delorme et al [24] were examined to construct the diarylmethylpiperidines 5[29,30] (Scheme 2) and only the McMurry coupling reaction[31] of 11[2,23] with *N*-benzyl 1 piperidone gave the desired intermediate 6b[24] in reasonable yield (Scheme 3) Hydrogenation of 6b with a catalytic

Scheme 1[a]



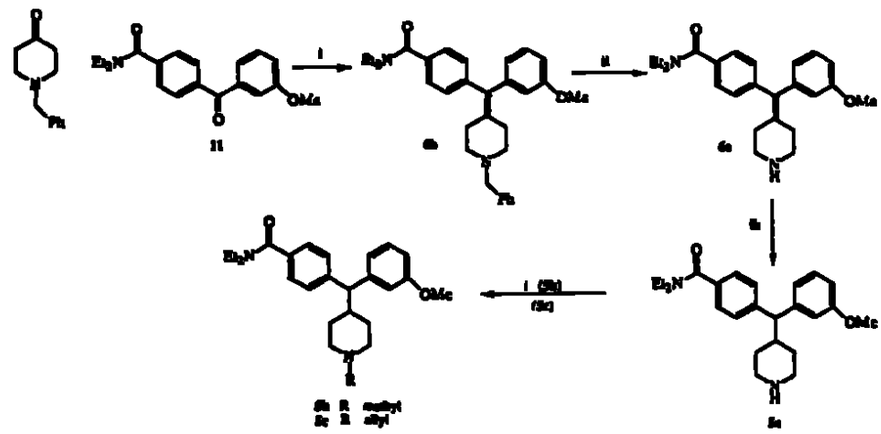
Conditions: (i) EDCI, Et_2NH, CH_2Cl_2, rt 97%; (ii) THF rt, 91%; (iii) H^+ 2-chloroethanol, $PhCH_3$, reflux, (iv) $HNMe_2$ K_2CO_3, KI THF 60–65 °C sealed 72%; (v) MnO_2, CH_2Cl_2, 100%; (vi) HCl (conc) $CHCl_3$, 100%; (vii) *N*-allylpiperazine, K_2CO_3, CH_3CN 68%, (viii) K_2CO_3, CH_3CN (ix) alkyl halide K_2CO_3, CH_3CN (x) piperidine, K_2CO_3, CH_3CN 38%; (xi) morpholine, K_2CO_3, CH_3CN 78%.

Scheme 2



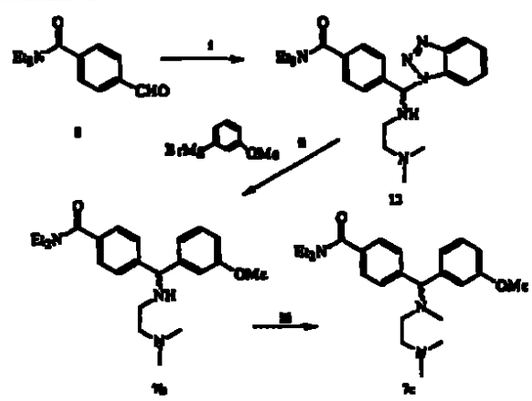
amount of Pd/C (10%) in acetic acid yielded a partially reduced intermediate **6a** [24] which was further reduced with an equal amount of Pd/C (30%) to give diaryl methylpiperidines **5a**. Eschweiler–Clarke reaction of **5a** afforded *N*-methyl analogue **5b** while alkylation of **5a** with allyl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

Scheme 3[a]



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]



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

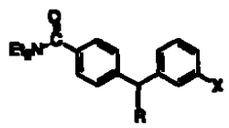
All compounds were tested for inhibition of specific binding of [^{3}H]DAMGO (Tyr-D-Ala-Gly (Me) Phe-Gly ol)[34] to μ receptors and [^{3}H]DADLE (Tyr-D-Ala-Gly Phe-D-Leu)[35] to δ receptors at rat brain membranes as previously reported.[1-3] The affinity of these derivatives for κ receptors was determined 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 diide methylpiperazine 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, benzyloxymorphindole.[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

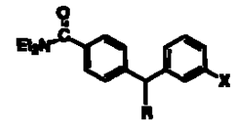
Table 1 Binding Affinities of Diarylmethylpiperazines and Diarylmethylpiperidines for μ δ, and κ Receptors



compd	R	X	mp (°C)	formula[a]	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	$C_{25}H_{32}N_2O_2 \cdot C_2H_2O_4$	10000 (6300)[h]	27 ± 2	10000 (8000)[h]	>230
3a	*N*-piperazinyl	H	168–169	$C_{23}H_{28}N_2O$	10000 (6800)[h]	4.85 ± 0.51	ND	>1400
3b	*N*-methyl-1-piperazinyl	H	182[a]	$C_{24}H_{30}N_2O \cdot HCl \cdot 2H_2O$	10000 (5600)[h]	43.2 ± 3	10000 (7000)[h]	>130
3c	*N*-allyl-1-piperazinyl	H	150[a]	$C_{26}H_{32}N_2O \cdot HCl \cdot 2.5H_2O$	10000 (6800)[h]	10.5 ± 0.8	ND	>600
3d	*N*-propyl-1-piperazinyl	H	170–172	$C_{26}H_{34}N_2O \cdot C_2H_2O_4$	10000 (6800)[h]	44.2 ± 3.9	10000 (7000)[h]	>150
3e	*N*-benzyl 1-piperazinyl	H	153–155	$C_{30}H_{32}N_2O \cdot C_2H_2O_4 \cdot 0.25H_2O$	10000 (6800)[h]	1.48 ± 0.8	2000 (1400)[h]	>4500
4a	*N*-1-piperidinyl	H	125–127	$C_{24}H_{29}NO \cdot 0.5H_2O$	10000 (6800)[h]	3000 (1700)[h]	10000 (7000)[h]	>4
4b	*N*-morpholinyl	H	98–100	$C_{23}H_{27}NO_2$	10000 (6800)[h]	3000 (1700)[h]	10000 (7000)[h]	>4
5a	4-piperidinyl	OCH_3	98	$C_{24}H_{31}NO_2 \cdot HCl \cdot H_2O$	10000 (6300)[h]	20 ± 2	10000 (8000)[h]	>300
5b	*N*-methyl-4-piperidinyl	OCH_3	59[a]	$C_{25}H_{33}NO_2 \cdot HCl \cdot 1.75H_2O$	10000 (6300)[h]	328 ± 21	10000 (8000)[h]	>15
5c	*N*-allyl-4-piperidinyl	OCH_3	75[a]	$C_{27}H_{33}NO_2 \cdot HCl \cdot 0.5H_2O$	10000 (6300)[h]	27 ± 2	10000 (8000)[h]	>200
6a	4-piperidinylidene	OCH_3	83–85	$C_{24}H_{29}NO_2 \cdot HCl \cdot 0.5H_2O$	10000 (6300)[h]	5 ± 0.3	10000 (8000)[h]	>1200
6b	*N*-benzyl-4-piperidinylidene	OCH_3	82–85	$C_{31}H_{33}NO_2 \cdot HCl \cdot 0.5H_2O$	10000 (6300)[h]	12 ± 1	7650 ± 429	>500
7a	2-(*N*,*N*-dimethylamino)ethoxy	OCH_3	81	$C_{22}H_{31}NO_2 \cdot C_2H_2O_4$	10000 (6300)[h]	258 ± 30	10000 (8000)[h]	>20
7b	2-(*N*,*N*-dimethylamino)ethamino	OCH_3	92–94	$C_{21}H_{31}N_2O_{10}$	10000 (6300)[h]	622 ± 42	10000 (8000)[h]	>10
7c	2-(*N*,*N*-dimethylamino)-*N*-methylethylamino	OCH_3	95–97	$C_{24}H_{36}N_2O_2 \cdot 2HCl \cdot 1.5H_2O$	10000 (6300)[h]	248 ± 26	10000 (8000)[h]	>20

Amorphous powder [a]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



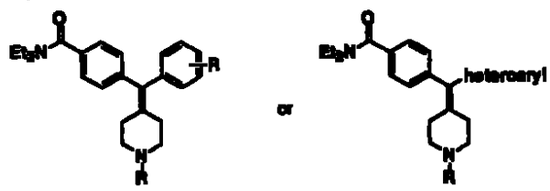
compd	R	X	IC_{50} (nM ± SEM) GPI (μ)	MVD (δ)	μ/δ ratio
1b	*trans*-2,5,5/*R*-dimethyl-*N*-allyl-1-piperazinyl	OCH_3	5450 ± 2050	2.73 ± 0.48	2000
1c[a]	*trans*-2,5,5/*R*-dimethyl-*N*-allyl-1-piperazinyl	H	8580 ± 1300	10.5 ± 0.4	813
2	*N*-allyl-1-piperazinyl	OCH_3	20300 ± 1300	33.1 ± 3.0	610
3e	*N*-benzyl-1-piperazinyl	H	9850 ± 1050	25.7 ± 6.5	382
6a	4-piperidinylidene	OCH_3	27700 ± 900	125 ± 28	220

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 consistent 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 8a−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 8a−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)[24] 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), 7.93 (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)[2,25] 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), 7.29−7.42 (m, 5H).

4-(3-Methoxybenzoyl)-*N,N*-diethylbenzamide (11)[2,26] To a solution of 9b (10.8 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 = 1.98, 8.48 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)[23,27] A mixture of 10b[2] (1.36 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), 2.99 (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, $C=CH_2$), 5.75−5.80 (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. ($C_{28}H_{38}N_3O_7 \cdot C_2H_2O_4$) 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] 157−159 °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), 7.16−7.32 (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, 1.68 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)[22,17] A mixture of 3a (0 21 g, 0 60 mmol) allyl bromide (0.09 g, 0 72 mmol) K_2CO_3 (0 17 g, 1 20 mmol) and anhydrous acetonitrile (6 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 97 (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 0.38 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 48–1.60 (m, 4H) 2.28–2.45 (m, 8H) 3 24 (bs, 2H) 3 51 (bs 2H) 4 24 (s, 1H CHN) 7 18–7 29 (m, 5H) 7.38–7 45 (m, 4H) MS (CI–NH_3) *m/e* 384 (MH^+) Compound 3d·oxalate· mp 170–172 °C. Anal ($C_{25}H_{33}N_3O$ $C_2H_2O_4$) C H N

4 [(4-Benzyl 1-piperazinyl)benzyl] *N,N*-diethylbenzamide (3e)[23] 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 (6 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 ($C_{30}H_{35}N_3O$ $C_2H_2O_4$·0.25H_2O) C H N

4-[(1-Piperidinyl)benzyl]-*N,N*-diethylbenzamide (4a) A mixture of 10a (0.50 g, 1 66 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 19–7 30 (m 5H) 7–7 44 (m 4H) MS (CI–NH_3) *m/e* 351 (MH^+) Anal ($C_{23}H_{30}N_2O$ 0 $5H_2O$) C H N

4-[(4-Morpholinyl)benzyl]-*N,N*-diethylbenzamide (4b) A mixture of 10a (0.50 g, 1.66 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 38–2 39 (m, 4H 2NH_2) 3 21 (bs 2H $CONCH_2$) 3.52 (bs, 2H $CO\backslash CH_2$) 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 ($C_{22}H_{28}N_2O_2$) C H N

4 [(1 Benzyl 4 piperidinylidene) 3 methoxybenzyl] *N,N*-diethylbenzamide (5b)[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 56 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 76 (s, 3H OCH_3) 6.65–6 78 (m, 3H) 7 13–7.33 (m, 5H) MS *m/e* calcd for $C_{31}H_{38}N_2O_2$ 468.2777 found 468.2763 Compound 6b HCl lyophilizate mp 92–95 C (lit.[24] 100–110 C Anal ($C_{31}H_{38}N_2O_2$·HCl·0 $5H_2O$) C H N

4 [(4 Piperidinylidene) 3-methoxybenzyl]-*N,N*-diethylbenzamide (6a)[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 6a as a glass ^{1}H NMR δ 1.21–1.33 (m, 6H 2CH_3) 2.37–2.41 (m, 4H) 2 96–3.00 (m. 4H) 3.36 (bs, 2H $CONCH_2$) 3.61 (bs, 2H $CONCH_2$) 3 95 (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 44 128 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 6a 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 6a[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 $C_{24}H_{32}N_2O_2$ 380.2464 found 380.2467 Compound 5a HCl mp 98 °C (soften) Anal ($C_{24}H_{32}N_2O_2$ 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) 1.56 (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 $C_{25}H_{34}N_2O_2$: 394 2620 found 394 2637 Compound 5b HCl lyophilizate mp 59 C (soften) Anal ($C_{25}H_{34}N_2O_2$ 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 90:9 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), 2.88 (d, J = 11.7 Hz, 2H), 2.97 (d, J = 6.9 Hz, 2H), 3.25 (bs, 2H, $CONCH_2$), 3.48–3.60 (m, 3H), 3.78 (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 $C_{21}H_{28}NO_3$: 420.2777. found 420.2772. Compound 5c HCl: mp 75 °C (soften). Anal. ($C_{21}H_{28}NO_3$ HCl·0.5H_2O) C, H, N.

4-[(2,2-Dimethylaminoethanoxy)-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. ^{1}H NMR δ 1.13–1.26 (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 20 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. ^{1}H 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.[28,29] 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 2.28 g (59%) of 7b as a glass. ^{1}H NMR δ 1.17–1.22 (bd, 6H), 1.67 (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, $CONCH_2$), 3.78 (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. ($C_{21}H_{41}N_3O_{10}$) 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. ^{1}H NMR δ 1.11–1.25 (bd, 6H), 2.16 (s, 6H, $2NCH_3$), 2.17 (s, 3H, NCH_3), 2.44–2.46 (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), 6.97–6.98 (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.[30] 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 14–80 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.[40] 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.

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

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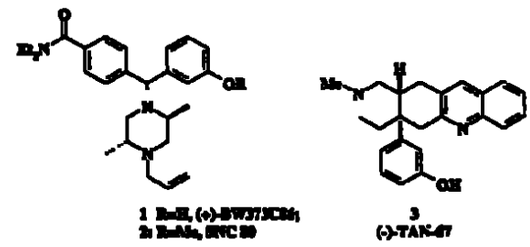
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The design synthesis, and pharmacological evaluation of a novel class of δ opioid receptor agonists *N,N*-diethyl 4-(phenylpiperidin-4 ylidenemethyl)benzamide (6a) and its analogues, are described These compounds formally derived from SNC-80 (2) by 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



1 R=H, (+)-BW373U86; 2 R=Me, SNC 80 3 (-)-TAN-67

Figure 1 Structures of compounds 1−3

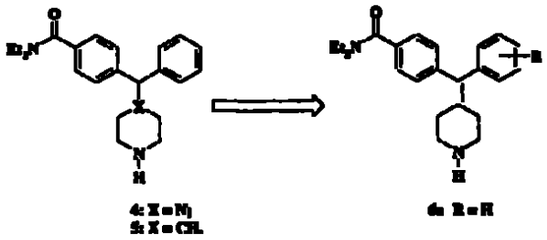
Due to the presence of three asymmetric carbon atoms, (+)-4 [(α*R*)-α-((2*S*,5*R*)-4-allyl 2 5-dimethyl 1-piperazinyl)-3-methoxybenzyl] *N,N*-diethylbenzamide (SNC-80 2) has seven possible stereoisomers which should exhibit different pharmacological profiles As described in the first paper in the series [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

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4: X = N;
5: X = CH.

6a: R = H

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)

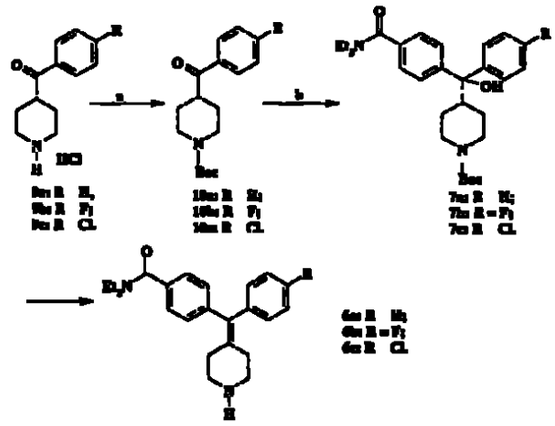
Introduction of conformational constraints in biologically active compounds is a well-established approach for enhancing receptor binding affinity and selectivity On the basis of the above assumption, incorporation of an exocyclic carbon−carbon double bond into the piperidine ring of 5 became the most 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]



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 *NN*-diethylaminocarbonyl)benzoyl piperidine 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 *NN*-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

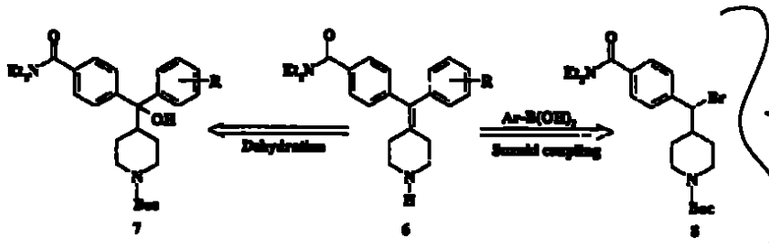
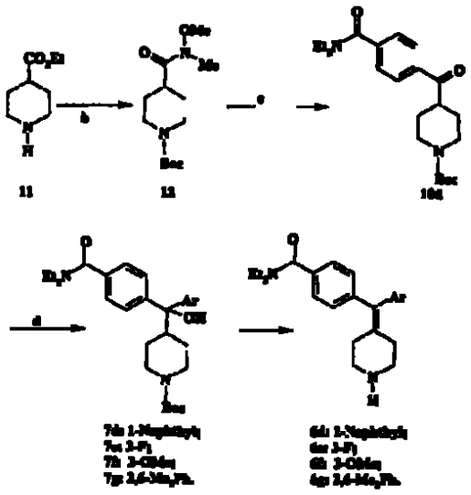


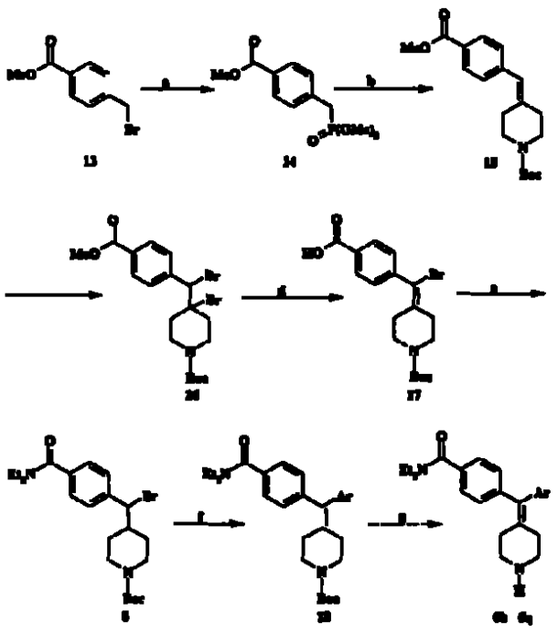
Figure 3. Reactions to prepare compound 6.

Scheme 2[a]



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]

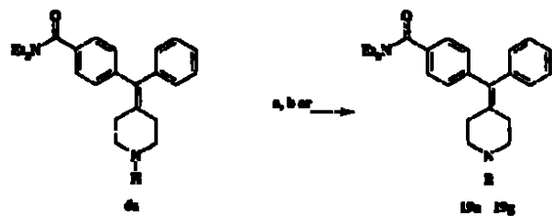


Reagents. (a) $P(OMe)_3$; (b) LDA *N*-*tert*-butoxycarbonyl-4-piperidone; (c) Br_2; (d) NaOH (e) $(COCl)_2$/Et_3N Et_2NH (f) Ar-$B(OH)_2$ $Pd(PPh_3)_4$ Na_2CO_3, (g) 4 N HCl

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]



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

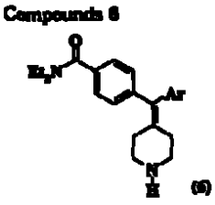
In Vitro Pharmacology The binding affinities (IC_{50}) of all compounds were determined using cloned human δ μ and κ opioid receptors and the δ agonist potency (EC_{50}) was measured with the GTP[γ ^{35}S] binding assay

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,

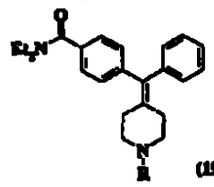
Table 1 Binding Affinities and Agonist Activities of Compounds 6



(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		187 ± 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)

compd	R	IC_{50} (nM) δ	μ	κ	selectivity ratio μ/δ	κ/δ	δ EC_{50}(nM)	δ 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]

compd	% parent remaining at 10 μM	100 μM
SNC-80	1 ± 1 (*n* = 5)	24 ± 8 (*n* = 5)
6a	77 ± 7 (*n* = 7)	95 ± 8 (*n* = 7)
6e	55 ± 14 (*n* = 3)	94 ± 6 (*n* = 3)
6f	1 (*n* = 2)	58 ± 3 (*n* = 2)
6h	75 ± 2 (*n* = 3)	85 ± 3 (*n* = 3)
6i	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

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

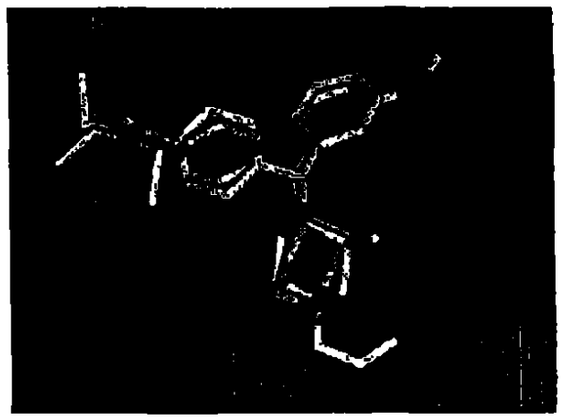


Figure 6 Superposition of the crystal structures between SNC 80 (carbon atoms in light green) and compound 6a (carbon atoms in gold)

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 (μ/δ = 4370) and κ receptors (κ/δ = 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 (8.77 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), 7.48 (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, 168.9, 200.4.

4-(4-Chlorobenzoyl)-*N*-*tert*-butoxycarbonylpiperidine (10c). Following the same method as used to prepare 10a but starting with 9c (2.80 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, 129.6, 134.1, 139.4, 154.8, 200.7.

4-(α-Hydroxy-α-(4-*N*-*tert*-butoxycarbonylpiperidinyl)-benzyl)-*N*,*N*-diethylbenzamide (7a). To a solution of 4-iodo-*N*,*N*-diethylbenzamide (6.87 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 (6.56 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), 2.88 (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, 28.2, 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 84–88 °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, 43.8, 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), 2.63 (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); ^{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, 127.8, 131.9, 134.8, 144.1, 148.8, 154.3, 170.7.

***N*,*N*-Diethyl-4-(phenylpiperidin-4-ylidenemethyl)benzamide (8a).** To a solution of 7a (832 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), 2.98 (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. ($C_{24}H_{30}N_2O$·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, 3H, CH_3CH$_2$), 1.24 (brm, 3H, CH_3CH$_2$), 2.32 (m, 4H, piperidine CH_2), 2.54 (brm, 1H, NH), 2.91 (m, 4H, piperidine CH_2), 3.27 (brm, 2H, CH_2N), 3.52 (brm, 2H, CH_2N), 7.00 (m, 2H, ArH), 7.09 (m, 2H, ArH), 7.11 (d, J = 8.0 Hz, 2H, ArH), 7.29 (d, J = 8.0 Hz, 2H, ArH); Anal. ($C_{24}H_{29}FN_2O$·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, 3H, CH_3CH$_2$), 1.22 (brm, 3H, CH_3CH$_2$), 2.02 (brm, 1H, NH), 2.30 (m, 4H, piperidine CH_2), 2.90 (m, 4H, piperidine CH_2), 3.28 (brm, 2H, CH_2N), 3.53 (brm, 2H, CH_2N), 7.04 (d, J = 8.0 Hz, 2H, ArH), 7.11 (d, J = 8.0 Hz, 2H, ArH), 7.25 (d, J = 8.0 Hz, 2H, ArH), 7.30 (d, J = 8.0 Hz, 2H, ArH); HCl salt: mp 115–120 °C (CH_2Cl_2); IR (KBr) 3337, 1618 cm^{-1}; Anal. ($C_{24}H_{27}ClN_2O$·1.6HCl) C, H, N.

***N*-*tert*-Butoxycarbonyl-*N*-methyl-*N*-methoxyisonipecotamide (11).** Method as described for 10a, but starting with ethyl isonipecotate (11.4, 71 g, 30.0 mmol) led to *N*-*tert*-butoxycarbonyl ethyl isonipecotate (7.67 g): ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 3H), 1.45 (s, 9H), 1.82 (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, 80.2, 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), 2.85 (m, 3H), 3.02 (s, 3H), 3.56 (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 (8.98 g, 80.0 mmol) in dry THF (80 mL) was added *tert*-butyllithium (35.0 mL, 1.7 M, 80.0 mmol) at −78 °C. After 30 min, 12 (8.0 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 (2.9%) 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, 39.2, 43.3, 45.4, 78.3, 80.4, 124.1, 124.9, 125.2, 125.3, 128.0, 127.3, 128.8, 129.2, 131.4, 135.0, 135.2, 139.4, 148.5, 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_2N), 1.15 (br, 3H, CH_3CH_2N), 1.19–1.29 (m, 4H, piperidine CH), 1.35 (s, 9H, CH_3C), 2.39 (m, 1H, piperidine CH), 2.59 (br, 2H, piperidine CH), 3.17 (br, 2H, CH_3CH_2N), 3.28 (s, 1H, OH), 3.45 (br, 2H, CH_3CH_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), 7.38 (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_2N), 1.19 (br, 3H, CH_3CH_2N), 1.31 (m, 4H, piperidine CH), 1.41 (s, 9H, CH_3C), 2.46 (m, 1H, piperidine CH), 2.64 (br, 2H, piperidine CH), 3.22 (br, 2H, CH_3CH_2N), 3.49 (br, 2H, CH_3CH_2N), 3.85 (s, 1H, OH), 3.72 (s, 3H, OCH_3), 4.06 (br, 2H, piperidine CH), 6.89 (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. ($C_{36}H_{46}N_2O_5$·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 12.8, 14.0, 25.0, 27.7, 28.2, 39.1, 42.9, 43.1, 44.4, 53.3, 79.1, 83.0, 125.8, 128.3, 127.2, 131.2, 135.3, 136.7, 142.9, 147.8, 154.5, 170.7. Anal. ($C_{38}H_{48}N_2O_4$·0.5H_2O) C, H, N.

***N*,*N*-Diethyl-4-(1-naphthylpiperidin-4-ylidenemethyl)benzamide (8d).** Method as described for 8a, but starting with 7d (517 mg, 1.0 mmol) led to 8d (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), 2.84 (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, 32.8, 33.5, 39.1, 43.2, 47.8, 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. Anal. ($C_{27}H_{30}N_2O$·0.4HCl) C, H, N.

***N*,*N*-Diethyl-4-(3-fluorophenylpiperidin-4-ylidenemethyl)benzamide (8e).** Method as described for 8a but starting with 7e (242 mg, 0.5 mmol) led to 8e (159 mg, 87%). ^1H NMR ($CDCl_3$) δ 1.08 (br, 3H, CH_3CH_2N), 1.19 (br, 3H, CH_3CH_2N), 2.09 (s, 1H, NH), 2.25 (m, 4H, piperidine CH), 2.84 (br, 4H, piperidine CH), 3.23 (br, 2H, CH_3CH_2N), 3.47 (br, 2H, CH_3CH_2N), 6.74 (m, 1H, ArH), 6.88 (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. ($C_{29}H_{31}FN_2O$·2.2HCl) C, H, N.

***N*,*N*-Diethyl-4-(3-methoxyphenylpiperidin-4-ylidenemethyl)benzamide (8f).** Method as described for 8a but starting with 7f (198 mg, 0.4 mmol) led to 8f[13] (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 (8g).** Method as described for 8a but starting with 7g (495 mg, 1.0 mmol) led to 8g (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 (9.76 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, 1608 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, 36.19, 51.9, 123.7, 127.8, 128.7, 129.4, 140.5, 142.1, 154.8, 166.8. 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, 18 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 6, 170.3. Anal ($C_{18}H_{28}BrNO_4$) 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) 2.82 (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, 154.6 170.5. Anal ($C_{20}H_{31}BrN_2O_3$) C H N

***N,N*-Diethyl-4 [piperidin-4-ylidene(3-trifluoromethylphenyl)methyl]benzamide (8h)** 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 8h (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 98 (s, 1 H, NH) 2.28 (m, 2 H piperidine CH-) 2.33 (m, 2 H piperidine CH-) 2 82 (m, 4 H piperidine CH-) 3.28 (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 (8i)** Method as for 8h using 8 (600 mg, 1 3 mmol) and 3 4-dichlorophenylboronic acid (500 mg, 2 6 mmol) provided 8i (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 ($C_{23}H_{26}Cl_2N_2O$ 1 5HCl) C H N

***N,N*-Diethyl-4-(3-acetylphenylpiperidin-4-ylidenemethyl)benzamide (8j)** Method as for 8h using 8 (500 mg, 1 1 mmol) and 3-acetylphenylboronic acid (500 mg 3.0 mmol) provided 8j (401 mg, 93%) ^{1}H NMR ($CDCl_3$) δ 1 11 (br 3H) 1 20 (br 3H) 2 06 (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 (8k)** Method as for 8h but using 3 nitrophenylboronic acid provided 8k 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 85−8 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 (8l)** Method as for 8h but using 2 fluorophenylboronic acid provided 8l 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 (8m)** Method as for 8h but using 2 thiophenylboronic acid provided 8m 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 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) Anal ($C_{21}H_{28}N_2OS$ 1.5HCl) C H N

***N,N*-Diethyl-4-(4-methylthiophenylpiperidin-4-ylidenemethyl)benzamide (8n)** Method as for 8h but using 4-methylthiophenylboronic acid provided 8n 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 28 (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 (8o)** Method as for 8h but using 3-aminophenylboronic acid provided 8o in quantitative yield ^{1}H NMR ($CDCl_3$) δ 1 11 (br 3H) 1.20 (br 3H) 2 27−2.33 (m, 4H) 2.88−2 90 (m, 4H) 3 27 (br 2H) 3.51 (br 2H) 3.57 (br 2H) 3.88 (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 28 (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 (8p)** Method as for 8h but using 4 methoxyphenylboronic acid provided 8p 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 26 (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 (8q)** Method as for 8h but using 2-methoxyphenylboronic acid provided 8q 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 (19a)** *N,N*-Diethyl-4 [(piperidin-4-ylidene)phenylmethyl]benzamide (8a 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 49 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 (19b)** Method as described for compound 19a, using allyl bromide as the alkylating reagent provided 19b (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 6HCl) C H N

***N,N*-Diethyl-4-[*N*-(3-methyl-2-butenyl)phenylpiperidin-4 ylidenemethyl]benzamide (19c)** Method as described for compound 19a using 1 bromo-3 methyl 2-butene as the alkylating reagent provided 19c (71%) ^{1}H NMR ($CDCl_3$) δ 1 10−1 30 (br 6 H $OCNCH_2CH_3$) 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$_2$C*H*=C) 7 18–7 45(m, 9 H
ICl salt. IR (NaCl) 1623 cm^{-1} Anal ($C_{28}H_{38}N_2O$ 1.8HCl)
N

N-Diethyl-4-(*N*-butylphenylpiperidin-4-ylidenemeth-
nzamide (19d) Method as described for compound 18a,
1-iodobutane as the alkylating reagent provided 19d
^{1}H NMR ($CDCl_3$) δ 0.92 (t, J = 7 2 Hz, 3 H CH_2CH_3)
1 28 (br 6 H OCNCH$_2$C*H*$_3$) 1.32 (m, 2 H C*H*$_2$CH$_3$) 1.53
H CH$_2$C*H*$_2$CH$_3$) 2.42 (m, 6 H NC*H*$_2$) 2 55 (m, 4 H =
) 3 20–3.60 (br 4 H OCNC*H*$_2$CH$_3$) 7 10–7.31 (m, 9 H
ICl salt: IR (NaCl) 1622 cm^{-1} Anal ($C_{32}H_{38}N_2O$ 1.8HCl)
N

N-Diethyl-4-(1-cyclopropylmethylphenylpiperidin-
ylenemethyl)benzamide (19e) Method as described for
ound 19a using compound 6 and cyclopropylmethyl
ide provided 19e (86%) ^{1}H NMR ($CDCl_3$) δ 0.20 (m 2H)
(m 2H) 1 04 (m, 1H) 1 14 (brs, 3H) 1.24 (brs, 3H) 2 48
= 6.4 Hz, 2H) 2 56 (brs, 4H) 2 80 (brs, 4H) 3.29 (brs,
3 53 (brs 2H) 7 14 (m, 4H) 7.22 (m 1H) 7.27 (m, 4H)
MR ($CDCl_3$) δ 4 18 7.3 12.8 14 1 30.3, 39.2, 43.2 54.3
128.2 128 8, 128.0 129.5 129 6 134.1 135.3, 136 3
142.9 171.0 HCl salt. dec ≥ 100 °C (CH_2Cl_2) IR (KBr)
cm^{-1} Anal ($C_{32}H_{34}N_2O$·2.3HCl) C H N

[(1 Cyclohexylpiperidin 4-ylidene)phenylmethyl]
diethylbenzamide (19f). A mixture of 6a (100 mg, 0.29
l) cyclohexanone (36 ul 0.35 mmol) and Ti(OPr-i)$_4$ (0.17
0.58 mmol) was ultrasonicated for 1 h and then stirred
on[redacted]mperature overnight under a nitrogen atmosphere
mixture was diluted with ethanol (5 mL) followed by
lon of $NaBH_4$ (33 mg, 0.87 mmol) The resulting mixture
stirred for 12 h at room temperature 2 N NH_3 H_2O was
d to quench the reaction and the mixture filtered through
e The filtrate was extracted with ethyl acetate several
s and the combined organic phases were washed with
r and brine and dried over Na_2SO_4 Concentration in
o and MPLC purification (0 100 to 100:0 EtOAc.heptane
ng on silica gel 60) gave the title compound 11f (24 mg,
^{1}H 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 80 (*m* 2H) 3.20
2H) 3.50 (bs, 2H) 7 00–7 30 (m, 9H) ^{13}C NMR ($CDCl_3$) δ
14 1 25 9 26.7 32 0, 39 1 43.2, 50 7 50.8, 63.6 126 0,
3 127 9 129.7 129 8 134.7 134 9 136.9 142 0 143 4
? mp (HCl salt) 105–109 °C. Anal. ($C_{25}H_{32}N_2O$ 2.0HCl)

[(1 Phenylpiperidin-4-ylidene)phenylmethyl]-*N*,*N*-
hylbenzamide (19g).A mixture of 6a (44 mg, 0.13 mmol)
yl bromide (20 uL 0.19 mmol) Pd(dba)$_2$ (1 mg, 0.0017
ol) BINAP (2.5 mg 0.004 mmol) and sodium *tert*-butoxide
mg, 0 20 mmol) in 2 mL toluene was heated at 80–90 °C
12 h under a nitrogen atmosphere The solvent was
oved in vacuo and the residue purified by MPLC (0 to
% of EtOAc in heptane on silica gel) to give the desired
compound 19g (30 mg, 56%) ^{1}H NMR ($CDCl_3$) δ 1 0–1 4
[redacted]45 (m 4H) 3 1–3 7 (m, 8H) 6 8–7 5 (m, 14H) ^{13}C
R ([redacted]Cl_2) δ 12.77 13.97 31.29 39 10 43.21 51.03, 116.23,
21 126 12 126 49 127.98 128 98, 129 68, 129.72 135.13
63, 135 73 141.81 143 15 151.00 171 09· IR (HCl salt)
3 cm^{-1} Anal ($C_{26}H_{28}N_2O$ 1 7HCl) C H N

Iological Assays. 1 Cell Culture and Membrane
paration. Human HEK-293S cells were subject to stable
sfection with cDNA encoding the human μ δ and κ
ptors. Clones were chosen for high receptor expression and
n in suspension culture Cells were harvested and P2
ibrane preparations were produced

Receptor Binding Assays. Membranes were combined
test compounds and approximately 0 07 nM of the
ropriate radioligand [^{125}I][D-Ala^2]deltorphin II (K_d = 0.93
at δ) [^{125}I]FK33824 (K_d = 1 14 nM at μ) and [^{125}I]-D-Pro^{10}-
orphin 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-
vity were determined at equilibrium by filtration. The
specific (NS) binding was defined in the presence of 10 μM
zocine 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 *h*DOR/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 respective y 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 proteins, 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.

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(71) Solicitante *(para todos los Estados designados excepto US)*: AstraZeneca AB [SE/SE] S-151 85 Södertälje (SE).

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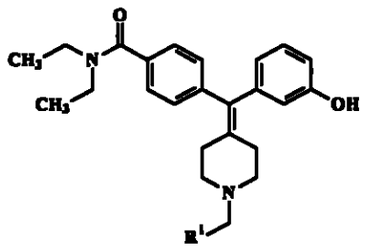
Publicado
— *con reporte de búsqueda internacional*
— *antes de la expiración del límite de tiempo para modificar las reivindicaciones y ser publicada de nuevo en el caso de recibo de modificaciones*

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 HIDROXIFENIL-PIPERIDIN-4-ILIDEN METIL-BENZAMIDA PARA EL TRATAMIENTO DEL DOLOR

(57) Resumen



(I)

Compuestos de fórmula general (I), en donde R^1 se selecciona de cualquiera de fenil pyridinil tienil furanil imidazolil triazolil y tiazolil 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 sobre el anillo heteroaromático pueden tener lugar en cualquier posición sobre dichos sistemas de anillo, como también las sales y composiciones farmacéuticas que comprenden los novedosos compuestos y su uso en terapia, en particular en el manejo del dolor

ASTRAZENECA AB 100001 IP-CO
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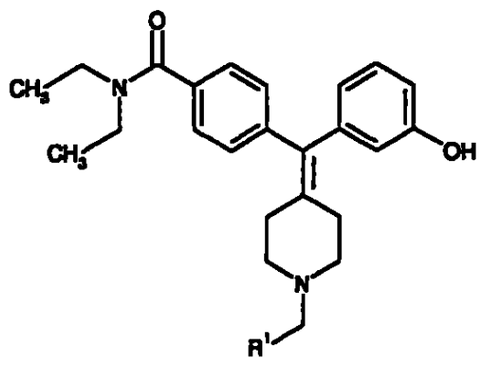
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(84) Designated States *(regional)* ARIPO patent (GH GM KE, LS MW MZ, SD SL, SZ, TZ, UG ZW), Eurasian patent (AM AZ, BY KG KZ, MD RU TJ TM) European patent (AT BE, CH CY DE, DK ES FI, FR, GB GR IE, IT LU MC, NL, PT SE, TR) OAPI patent (BF BJ CF CG CI CM GA GN GW ML, MR NE, SN TD TG).

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— *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.

(54) Title: HYDROXYPHENYL-PIPERIDIN-4-YLIDENE-METHYL-BENZAMIDE DERIVATIVES FOR THE TREATEMENT OF PAIN



(I)

(57) Abstract: Compounds of general formula (I) where R^1 is selected from any one of phenyl, pyridinyl, thienyl, furanyl imidazolyl triazolyl and thiazolyl 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 salts and pharmaceutical compositions comprising the novel compounds and their use in therapy in particular in the management of pain

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TRATADO DE COOPERACION DE PATENTES
PCT
REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL

(PCT Artículo 36 y Regla 70)

Registro de referencia del solicitante o agente 100001 1 WO	**PARA FUTURAS ACCIONES**	Ver Notificación o Transmisión del Reporte de Examen Preliminar Internacional (Formato PCT/IPEA/416)
Solicitud Internacional No PCT/SE01/00707	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 401/06** C07D 405/06 C07D 409/06 C07D 211/68 A61K 31/4523 A61P 25/04 A61P 25/00		
Solicitante **AstraZeneca AB**		

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 Artículo 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 correo de Patent och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No 08-667 72 88	Telex 17978 PATOREG-S
Funcionario autorizado Solveig Gustavsson/BS Teléfono No 08-782 25 00	

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REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL

Solicitud internacional No
PCT/SE01/00707

I Base del informe

1 Respecto a los elementos de la solicitud internacional *

☒ la solicitud internacional segun se presentó originalmente

☐ la descripción

páginas _____ como originalmente se presentaron
páginas _____ presentadas con la demanda

páginas _____, presentadas con la carta de _____

☐ las reivindicaciones

páginas _____ como originalmente se presentaron
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 _____ como originalmente se presentaron
páginas _____ presentadas con la demanda
páginas _____ presentadas con la carta de _____

☐ la secuencia que enumera parte de la descripcion

páginas _____ como originalmente se presentaron
páginas _____ presentadas con la demanda
páginas _____ presentadas 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 (segun 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 (segun 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

☐ presentada 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 segun se registró

☐ Se ha proporcionado la afirmación respecto a la cual la información registrada en forma legible por computador es idéntica al listado de secuencia escrita

4 ☐ Las enmiendas han resultado en la cancelación de

☐ la descripción, páginas _____
☐ las reivindicaciones Nos _____
☐ los dibujos, página/fig _____

5 ☐ Este informe ha sido establecido como si (algunas) las enmiendas no se hubiesen hecho, ya que se ha considerado que van más allá de la revelación según se registró, 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 segun el Artículo 14 a las que se hace referencia en este informe como presentadas originalmente y se anexan a este informe ya*
Que no contienen enmiendas (Reglas 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/SE01/00707

III No establecimiento de opinión respecto a la novedad, nivel inventivo y aplicabilidad industrial

1 Las preguntas ya sea que la invención reivindicada aparezca como novedad, para comprender un nivel inventivo (para no ser obvio) o para ser aplicable industrialmente no se han examinado respecto a

☐ toda la solicitud internacional,

☒ las reivindicaciones Nos 15 17

porque

☒ dicha solicitud internacional o dichas reivindicaciones Nos 15 17
se relacionan 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 cirugia o terapia, como también métodos de diagnóstico

☐ la descripción, reivindicaciones o dibujos (*indique 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 busqueda 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 INTERNACIONAL

Solicitud internacional No
PCT/SE01/00707

V Afirmación razonada bajo el Artículo 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

El 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 se ejemplifican compuestos acordes con las presentes reivindicaciones en el documento citado

El solicitante ha mostrado que los compuestos acorde con las presentes reivindicaciones tiene efectos ventajosos comparado con algunos de los compuestos estrechamente relacionados de D1

Por lo tanto se considera que las reivindicaciones 1-6 y 8 14 cumplen 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
Además el intermediario acorde con la reivindicación 18 es conocido a partir de D1 (compuesto 52) Observar la definición de grupo protector del tipo bencil, la 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

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant s or agent s file reference 100001-1 WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/SE01/00707	International filing date *(day/month/year)* 30 03 2001	Priority date *(day/month/year)* 04 04 2000
International Patent Classification (IPC) or national classification and IPC C07D 401/06, C07D 405/06, C07D 409/06 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 Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Telex 17978 PATOREG-S Facsimile No 08-667 72 88	Authorized officer Solveig Gustavsson/BS Telephone No 08-782 25 00

Form PCT/IPEA/409 (cover sheet) (January 1998)

ASTRAZENECA AB 100001-1P CO
1958
193

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No
PCT/SE01/00707

I Basis of the report

1 With regard to the elements of the international application *

- [x] 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
PCT/SE01/00707 194

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

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INTERNATI NAL PRELIMINARY EXAMINATION REPORT

International application No
PCT/SE01/00707

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

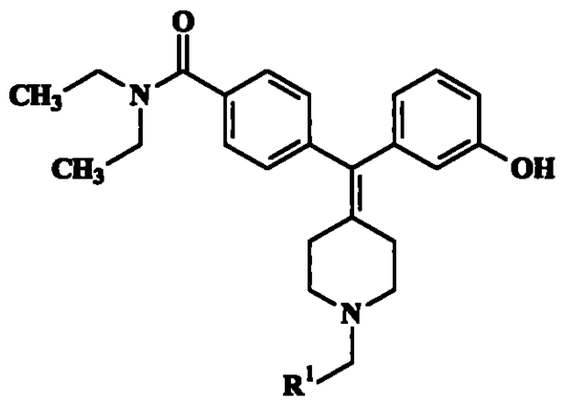
Therefore, claims 1-6 and 8-14 are considered to fulfil the requirements of novelty, inventive step and industrial applicability

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

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DERIVADOS DE HIDROXIFENIL-PIPERIDIN-4-ILIDEN-METIL-BENZAMIDA PARA EL TRATAMIENTO DEL DOLOR

RESUMEN – OBJETO Y FINALIDAD DE LA INVENCION



(I)

Compuestos de fórmula general (I), en donde R^1 se selecciona de cualquiera de fenil, piridinil, tienil, furanil, imidazolil, triazolil y tiazolil, en donde cada anillo fenilo R1 y cada anillo heteroaromático R^1 puede estar ademas 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, fluor, bromo y yodo, en donde las substituciones sobre el anillo fenilo y sobre el anillo heteroaromático pueden tener lugar en cualquier posicion sobre dichos sistemas de anillo, como tambien las sales y composiciones farmacéuticas que comprenden los novedosos compuestos y su uso en terapia, en particular en el manejo del dolor

DERIVADOS HIDROXIFENIL-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 terapeutica, 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 analgesicos, y/o como agentes antihipertensores Los ligandos del receptor δ han demostrado también poseer actividades inmunomodulatorias

La identificacion 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 periferico- de muchas especies entre las que se incluye el hombre En diversos modelos de experimentacion 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 peptidico 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

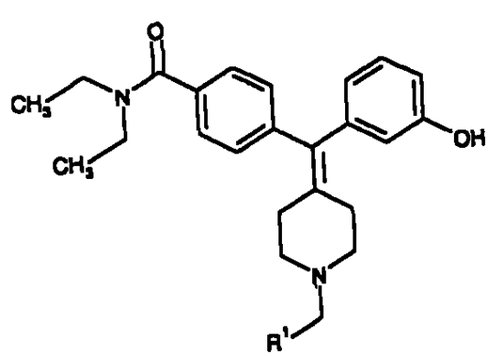
Por consiguiente, el problema fundamental que pretende resolver la presente invención es el de suministrar nuevos analgésicos con mejorados efectos analgésicos pero que a la vez exhiban un mejorado perfil de efectos secundarios frente a los μ-agonistas ya existentes, y que adicionalmente, exhiban una mejorada eficacia sistémica

Los analgesicos existentes o identificados en el estado anterior de la técnica presentan muchas desventajas en cuanto que exhiben una pobre farmacocinetica y no son analgesicos cuando se administran por rutas sistémicas Además, se ha documentado que los compuestos δ-agonistas preferidos, descritos en el estado anterior de la tecnica exhiben significativos efectos convulsivantes cuando se administran sistémicamente

Hemos encontrado ahora que ciertos compuestos no especificamente 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*

<u>Descripción de la invención</u>

Los novedosos compuestos acordes con la presente invención se definen por la fórmula I



I

en donde

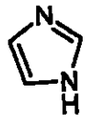
R^1 se selecciona del grupo conformado por

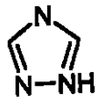
(i) fenil 

(ii) piridinil 

(iii) tienil 

(iv) furanil 

(v) imidazolil 

(vi) triazolil 

(vii) tiazolil 

en donde cada anillo fenilico 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,

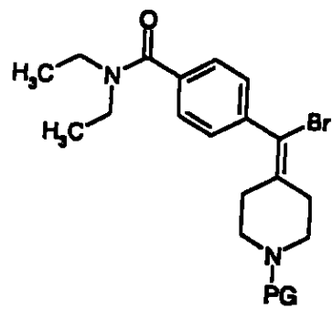
Una práctica preferida de la presente invención es un compuesto acorde con la fórmula estructural I en donde R^1 corresponde a lo previamente definido y cada anillo fenílico R^1 y cada anillo heteroaromático R^1 pueden de manera independiente ir adicionalmente sustituidos con un grupo metil

Una práctica mas 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

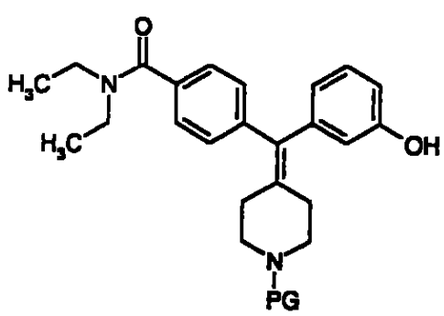
Cuando el anillo fenílico y el ó los anillos heteroaromáticos van sustituidos, los sustituyentes preferidos se seleccionan independientemente entre CF_3, metil, yodo bromo, fluoro y cloro

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 acido 3-hidroxifenil bórico, 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 estandar 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 se incluyen, sin hacer una lista exhaustiva de estos, $PdCl_2$ (+ 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 estas 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 invencion son utiles en la terapeutica, especialmente en el tratamiento de diversas estados de dolor tales como dolor cronico, dolor neuropatico dolor agudo, dolor causado por cáncer, dolor causado por artritis reumatoide migrafia, dolor visceral etc Esta lista no debera considerarse exhaustiva

Los compuestos de la presente invencion son utiles 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 colageno, diversidad de alergias, como tambien como agentes anti-tumorales y agentes antivirales

Los compuestos de la presente invención son utiles en aquellos estados patológicos en donde está presente la degeneración o disfunción de los receptores opiáceos, o en los estados implicados en dicho paradigma Aqui se puede incluir el uso de versiones isotopicamente marcadas de los compuestos de la presente invención en tecnicas de diagnostico y aplicaciones en el campo de las imágenes diagnósticas tales como la tomografía de emisión de positrones (PET, sigla en ingles)

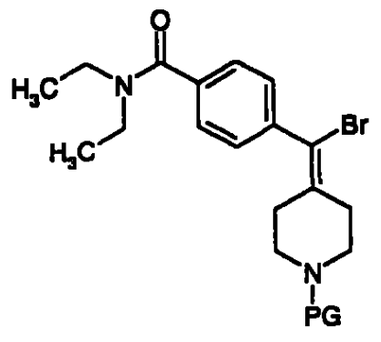
Los compuestos de la presente invención son utiles para el tratamiento de la diarrea, depresión ansiedad incontinencia urinaria, diversas enfermedades mentales, tos, edema pulmonar diversos desórdenes gastro-intestinales, lesiones de la columna vertebral y adiccion a drogas, incluyendo el tratamiento 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 utiles como agentes analgesicos 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 sedacion) 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 tipo bencil, como por ejemplo Boc

Métodos de preparacion

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 (j) p364-366 Step (g) N Miyaura and A Suzuki Chem Rev , 95, 2457-2483 (1995) paso (12) "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 (199 l) Obras citadas aquí con propósitos de mera referencia

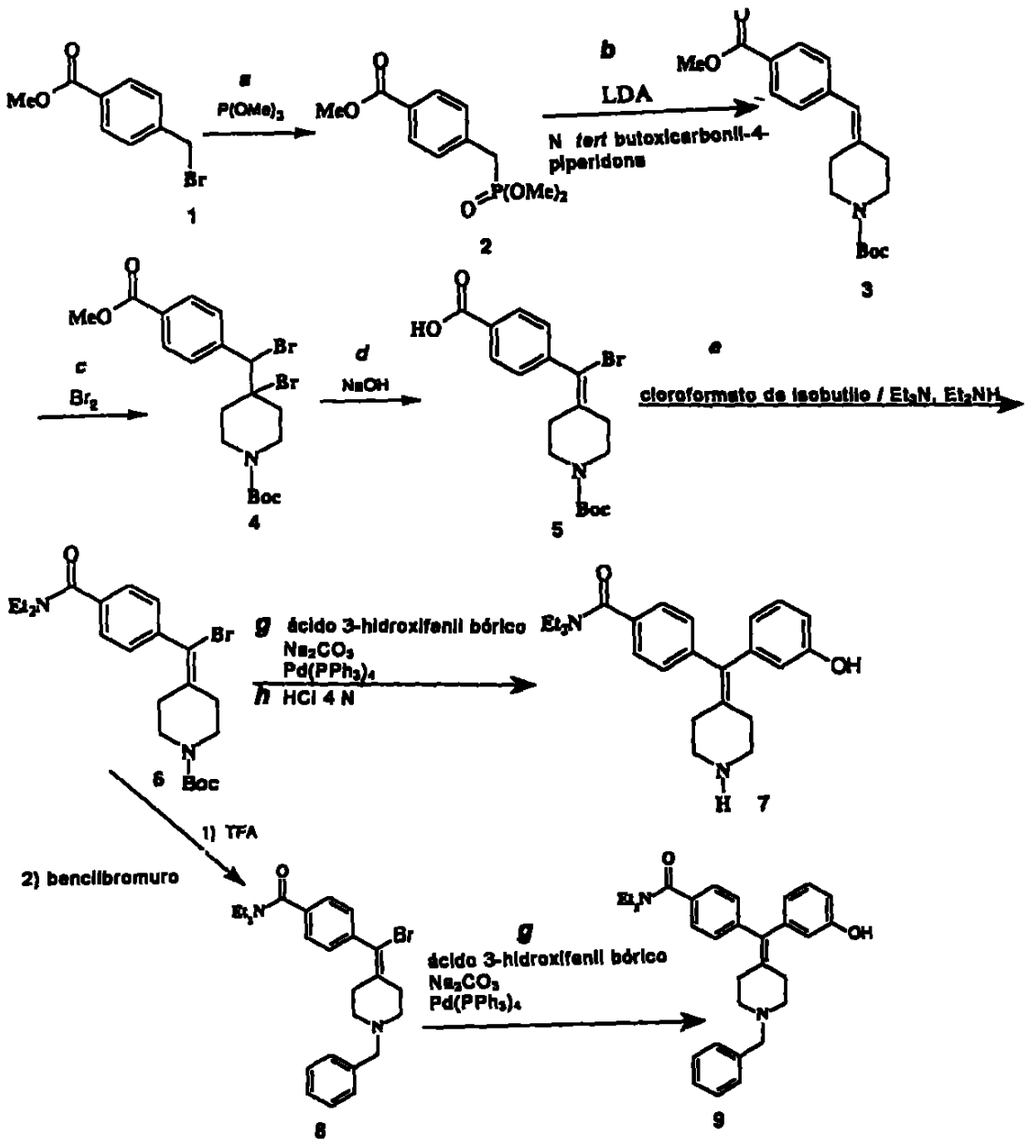
EJEMPLOS

La invención se describira ahora con mayor detalle a través de los siguientes Ejemplos, los cuales no tienen el propósito de limitar el alcance de la presente invencion

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Esquema 1



Ejemplo 1

Preparación de *N,N*-dietil-4-(3-hidroxilfenil-piperidin-4-iliden-metil)benzamida (compuesto 7)

(i) **Preparación del Acido 4-(4-metoxicarbonil-benciliden)-piperidina-1-carboxilico, *tert*-butil éster (compuesto 3)**

Se sometio a reflujo una mezcla de **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 ($CDCl_3$) 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)

(ii) A una solución del producto anterior (**compuesto 2**) en THF seco (200 mL) se agrego 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 de THF seco) Despues de 12 hr la mezcla de reacción se extinguio 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 purifico por cromatografía flash para obtener asi el **compuesto 3** a manera de un solido 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 condenso 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-carboxi-fenil)-metilen]-piperidina-1-carboxilico, *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 calento a 40 ^{0}C durante 3 hr El solido se recolecto mediante filtración, y se secó durante una noche bajo vacio 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 filtracion 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 solucion del **compuesto 5** (1,0 g, 2,5 mmol) en diclorometano seco (10 mL) a -20 ^{0}C, se agrego cloroformato de isobutilo (450 mg, 3,3 mmol) Después de 20 min a -20 ^{0}C se agrego dietilamina (4 mL) y la reacción se dejó que alcanzará la temperatura ambiente 1,5 horas despues, los solventes se evaporaron y el residuo se particionó entre acetato de etilo y agua La fase orgánica se lavo con salmuera y se seco sobre $MgSO_4$ La remoción de los solventes proporcionó un producto crudo, el cual se purificó por cromatografía flash para producir asi el **compuesto 6** a manera de agujas blancas (800 mg 73%)

IR (NaCl) 3051 2975 1694 1633, 1416, 1281 1168 1115 cm ^{1}

RMN ^{1}H ($CDCl_3$) 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, 170,5

(vi) **Preparación del ácido 3-hidroxilfenilbórico**

Se trató 3-bromofenol (8,65 g, 50 mmol) en THF seco (150 mL) con hidruro de sodio (al 60%, 2,4 g, 60 mmol) a t a (temperatura ambiente) Después de 1 h, se agrego sec-butillitio (1 3 M 50 mL, 65 mmoL) gota a gota a la solución de reacción a -78 ^{0}C La mezcla de reacción se dejó luego en agitación a la misma temperatura durante 30 min antes de la adicion de trimetilborato (15 mL) Después de calentar a t a durante 2 hr la mezcla de reacción se extinguió con agua (50 mL) y se extrajo con diclorometano (2 x 100 mL) Las fases organicas combinadas se secaron sobre $MgSO_4$ y se

evaporaron para producir así el compuesto del título a manera de un sólido blanco (4,0 g, 58 %), el cual se usó en las reacciones de acoplamiento de Zusuki sin purificación adicional

(vii) **Preparación de *N,N*-dietil-4-(3-hidroxilfenil-piperidin-4-iliden-metil)benzamida (compuesto 7)**

Una mezcla del **compuesto 6** (451 mg, 1,0 mmol), ácido 3-hidroxilfenilbórico (230 mg, 1,7 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 ^{0}C durante 4 hr bajo N_2 La mezcla de reacción luego se enfrio 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 trató con HCl 4 0 M en dioxano a 50 ^{0}C durante 2 hr Después de evaporacion 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 organicas combinadas se lavaron con salmuera se secaron sobre $MgSO_4$ y se evaporaron para producir así el **compuesto** del titulo, 7 (305 mg, 88 %)

RMN ^{1}H (400 MHz $CDCl_3$) δ 1 12 (3H, br m $C\underline{H}_3CH_2$-) 1 23(3 H br m $C\underline{H}_3CH_2$-), 2 33 (4 H piperidina CH-), 2,89 (4H, m, piperidina C<u>H</u>-) 3,29 (3 H, br m N<u>H</u> & $CH_3C\underline{H}_2N$-) 3,53 (2 H br m, CH_3CHN-), 4,71 (1 H s, OH), 6,57 (2 H, m Ar<u>H</u>), 6,65 (1 H, m, Ar<u>H</u>), 7 09 (1 H m Ar<u>H</u>), 7 12 (2 H, d J = 8,0 Hz, Ar<u>H</u>) 7 28 (2 H d, J = 8 0 Hz, Ar<u>H</u>), Su sal HCl m p (punto de fusión) > -130 °C (Con desc), IR (NaCl) 2975, 1598, 1442, 1293 cm ^{1}

Ejemplo 2

Preparación de *N,N*-dietil-4-(3-hidroxifenil-N-bencil-piperidin-4-iliden-metil)benzamida (compuesto 9)

(i) **Preparación de *N,N*-dietil-4-(bromo-N-bencil-piperidin-4-iliden-metil)benzamida (compuesto 8)**

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 reaccion 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 organica se lavó con NH_4OH 1 N y salmuera, se seco sobre MgSO4 La remocion de los solventes proporciono 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-(3-hidroxifenil-N-bencil-piperidin-4-iliden-metil)benzamida (compuesto 9)**

Una mezcla de **compuesto 8** preparado en el paso (i) anterior (600 mg, 1,36 mmol), acido 3-hidroxilfenil bórico (414 mg 3 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 (482 mg 78%)

IR (NaCl) 3350, 2974, 1606, 1442 1291 cm^{-1},

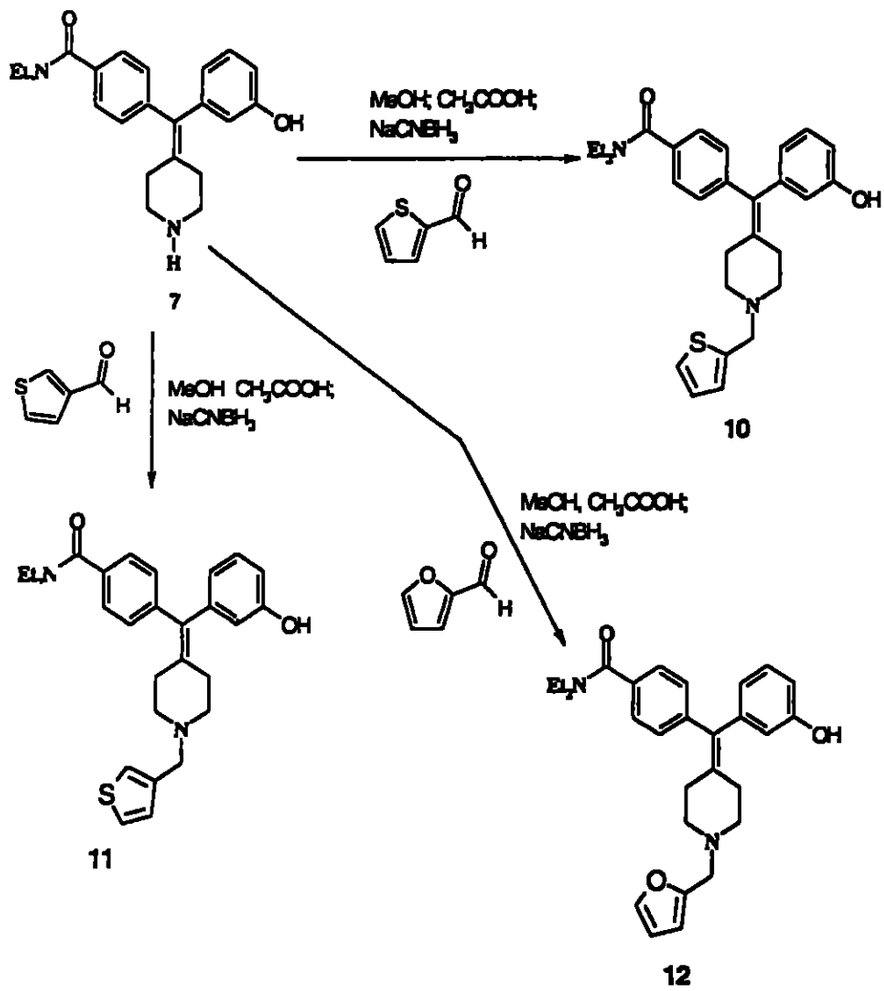
RMN ^1H (400 MHz $CDCl_3$) δ 1 11 (3 H br m, $\underline{CH_3}CH_2$-) 1 24 (3 H br m $C\underline{H_3}CH_2$-), 2,36 (4 H m, piperidina C$\underline{H}$-), 2,46 (4 H, m, piperidina C$\underline{H}$-),

3,26 (2 H, br m, $CH_3C\underline{H_2}N$-) 3 53 (4 H br m $pHC\underline{H_2}$-N & $CH_3C\underline{H_2}N$-) 6,53 (1 H, m, Ar<u>H</u>) 6 57 (1 H, m, Ar<u>H</u>), 6,63 (1 H, m, Ar<u>H</u>), 7,07 (3 H, m, Ar<u>H</u>), 7,25 (7 H m Ar<u>H</u>)

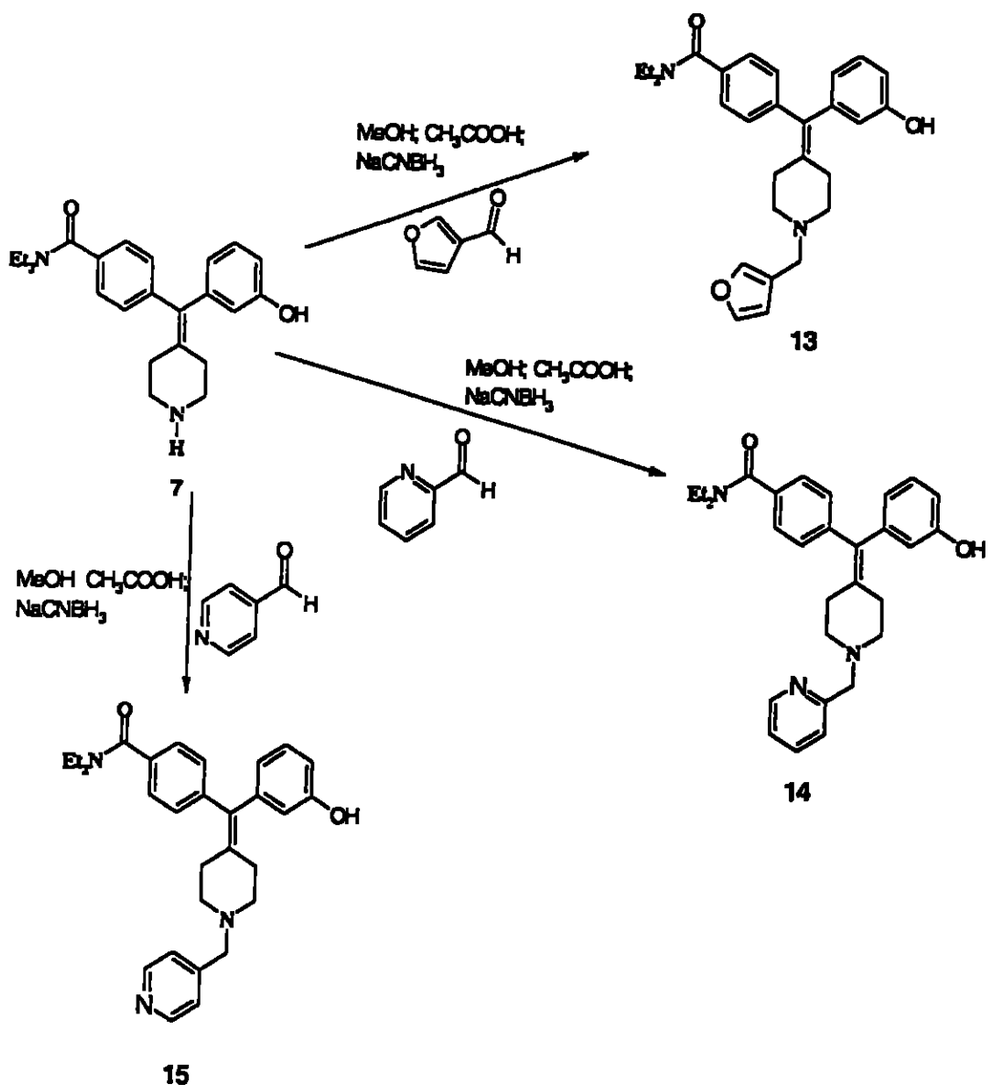
<u>Ejemplos 3-11</u>

Los compuestos 10-18 de los Ejemplos 3-11, se prepararon siguiendo los procedimientos de síntesis ilustrados en el Esquema 2 presentado a continuación

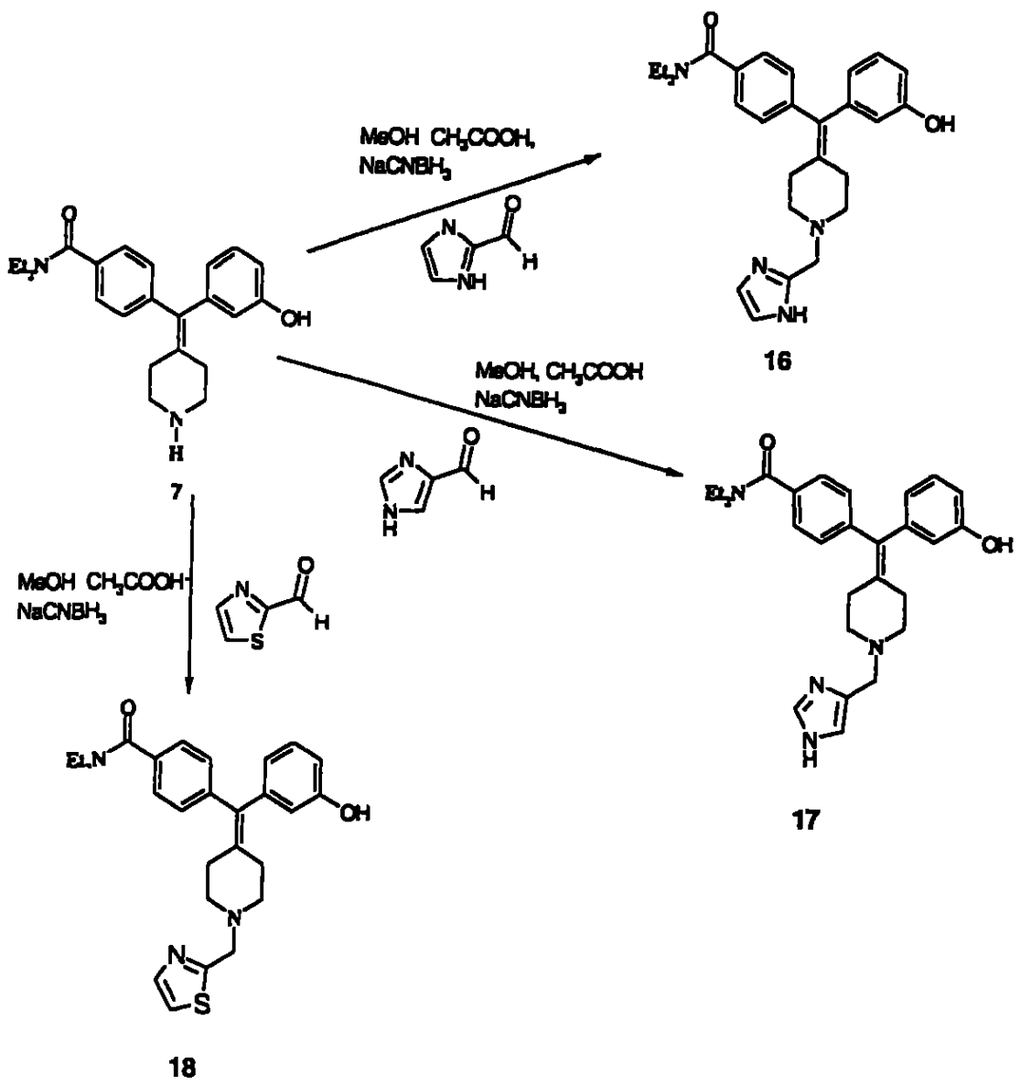
Esquema 2 1(3)


MsOH; CH3COOH;
NaCNBH3
MsOH CH3COOH;
NaCNBH3
MsOH, CH3COOH;
NaCNBH3
7
10
11
12

Esquema 2 2(3)


MeOH; CH3COOH;
NaCNBH3
MeOH; CH3COOH;
NaCNBH3
MeOH CH3COOH;
NaCNBH3
Et2N
OH
7
13
14
15

Esquema 2 3(3)



7

16

17

18

Ejemplo 3

Preparación de *N,N*-dietil-4-{(3-hidroxifenil)[1-(2-tienilmetil)-4-piperidinilliden]metil}benzamida (compuesto 10)

A una solución a temperatura ambiente de amina secundaria (600 mg, 1,65 mmol) en metanol (15 mL) se agregó tiofeno-2-carboxaldehido (153,8 µL, 1,65 mmol) seguido por ácido acético (1 ml) La mezcla se agito durante dos horas y luego se agregó cianoborohidruro de sodio (311 mg, 4,95 mmol) La mezcla de reacción se agitó durante una noche luego se agrego agua y la mezcla se extrajo con cloruro de metileno Los extractos cloruro de metileno combinados se secaron sobre sulfato de sodio anhidro se filtró y concentro bajo condiciones de presion reducida Purificacion en fase reversa

(M+l) calculado 461 64 (M+1) observado 461,06

Análisis calculado para ($C_{28}H_{32}N_2O_2S$ X 1,60 $C_2HO_2F_3$ X 0,20 H_2O)
C 57,95%, H 5,30%, N 4 33% Encontrado C 57,90% H 5 34% N 4,36%

RMN ^1H (CD_3OD) 7,54 (dd, 1H, J=5,2, 1,6 Hz), 7,25 (d, 2H, J=8 Hz), 7,23-7,24 (m 1H), 7 15 (d, 2H, J=8 Hz) 7,03-7 08 (m, 2H), 6 58-6 62 (dd, 1H, J=8 0 2 8 Hz) 6,52-6,55 (dd 1H, J=7,6 1,6 Hz)), 6,44-6,46 (dd, 1H, J=2 8 1,6 Hz), 4,50 (s 2H), 3,40-3 50 (m 4H) 3 15-3 25 (m 2H), 2,95-3,05 (m, 2H), 2,60-2,80 (m 2H), 2 35-2 45 (m, 2H), 1,10-1,15 (m, 3H), 1 00-1 05 (m 3H)

Ejemplo 4

Preparación de *N,N*-dietil-4-{(3-hidroxifenil)[1-(3-tienilmetil)-4-piperidinilliden]metil}benzamida (compuesto 11)

A una solucion a temperatura ambiente de amina secundaria (500 mg, 1,37 mmol) en metanol (13 mL) se agrego tiofeno-3-carboxaldehido (144,0 µL, 1,65 mmol), seguido por acido acético (1 mL) La mezcla se agitó durante tres horas y luego se agregó cianoborohidruro de sodio (258 mg 4 11

mmol) La mezcla de reacción se agitó durante una noche luego se agregó agua y la mezcla se extrajo con cloruro de metileno La fase acuosa se neutralizó con bicarbonato de potasio y se extrajo nuevamente con cloruro de metileno Los extractos cloruro de metileno combinados se secaron sobre sulfato de sodio anhidro, y se filtro y concentró bajo condiciones de presion reducida Purificación en fase reversa

(M+l) calculado 461 64 (M+l) observado 461,07

Análisis Calculado para ($C_{28}H_{32}N_2O_2S$ X 1,10 $C_2HO_2F_3$ X 0 50 H_2O)
C 60,96% H 5,78%, N 4,71% Encontrado C 60 97% H 5,78%, N 4 65%

RMN ^1H (CD_3OD) 7,59 (dd, 1H J=3 2, 1 6 Hz), 7 49 (dd, IH J=5 2 3 2 Hz), 7,26 (d, 2H, J=8,0 Hz) 7 16 (d 2H J=8 0 Hz) 7,15 (m, 1H) 7 07 (dd 1H J=8,0, 7,2 Hz), 6,61 (dd, 1H J=8,0, 2,0 Hz), 6,55 (d 1H J=7 2 Hz), 6 47 (dd, 1H, J=2,0, 1 6 Hz) 4 29 (s 2H) 3 40-3 50 (m 4H) 3 15-3 25 (m, 2H), 2,95-3,05 (m, 2H), 2,60-2 80 (m 2H) 2 35-2,45 (m, 2H), 1,15-1,20 (t, 3H, J=6,4 Hz) 1 00-1,05 (t, 3H, J=6,4 Hz)

Ejemplo 5

Preparación de *N,N*-dietil-4-[[1-(2-furilmetil)-4-piperidinilideno](3-hidroxifenil)metil]benzamida (compuesto 12)

A una solución a temperatura ambiente de amina secundaria (500 mg, 1,37 mmol) en metanol (13mL) se agregó 2-furaldehido (136 0 µL 1,65 mmol), seguido por acido acético (1 mL) La mezcla se agitó durante tres horas y luego se agregó cianoborohidruro de sodio (258 mg 4,1 mmol) La mezcla de reaccion se agitó durante una noche luego se agregó agua y la mezcla se extrajo con cloruro de metileno La fase acuosa se neutralizó con bicarbonato de potasio y se extrajo nuevamente 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 Purificacion en fase reversa

(M+1) calculado 445,57 (M+1) observado 445,13

Analisis calculado para ($C_{28}H_{32}N_2O_3$ X 1 30 $C_2HO_2F_3$ X 0,10 H_2O) C 61,81%, H 5 68% N 4 71%, Encontrado C 61,88%, H 5 74% N 4 73%

RMN ^1H (CD_3OD) 7 58 (d, 1H, J=1,6 Hz), 7,26 (d 2H J=8 0 Hz) 7 16 (d 2H, J=8 0 Hz) 7,07 (t, 1H, J=8,0 Hz) 6,62-6 64 (m 1H), 6,60-6,61 (m, 1H) 6,53-6,55 (m 1H) 6 46-6,47 (m, 1H), 6,43-6 45 (m 1H) 4 34 (s, 2H), 3 40-3,50 (m 4H) 3,15-3,25 (m 2H) 2 95-3 05 (m 2H), 2,55-2,80 (m, 2H), 2 35-2 50 (m, 2H), 1,15-1 20 (t 3H J=6,4 Hz), 1,00-1,05 (t 3H J=6 4 Hz)

Ejemplo 6

Preparación de *N,N*-dietil-4-[[1-(3-furilmetil)-4-piperidinilideni](3 hidroxifenil)metil]benzamida (compuesto 13)

A una solución a temperatura ambiente de amina secundaria (300 mg, 0,82 mmol) en metanol (8 mL) se agregó 3-furaldehido (214 0 µL 2,47 mmol) seguido por acido acético (0,5mL) y cianoborohidruro de sodio (155 mg 2,47 mmol) La mezcla de reacción se agitó durante una noche, se extinguió con bicarbonato de sodio y 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 presion reducida Purificacion en fase reversa

(M+1) calculado 445,57, (M+1) observado 445 15

Analisis calculado para ($C_{28}H_{32}N_2O_3$ X 0,50 $C_2HO_2F_3$ X 0,10 H_2O) C 69,20% H 6 55% N 5 56% Encontrado C 69 14% H 6,57%, N 5,28%

RMN ^1H (CD_3OD) 7,75 (s, 1H), 7,61-7,62 (m, 1H), 7,33 (d, 2H, J=8,0 Hz), 7,23 (d, 2H J=8 0 Hz), 7,13 (dd, 1H, J=8 4 8,0 Hz), 6,66-6,69 (m, 1H), 6,57-6,63 (m 2H), 6,51-6,53 (m, 1H), 4 22 (s 2H), 3,45-3,55 (m, 4H), 3 25-

3,30 (m, 2H), 2,95-3 10 (m, 2H), 2,65-2 85 (m 2H) 2 40-2 55 (m 2H), 1,15-1,25 (m, 3H), 1,05-1 15 (m, 3H)

Ejemplo 7

Preparación de *N,N*-dietil-4-{(3-hidroxifenil)[1-(2-piridinilmetil)-4-piperidinilideno]metil}benzamida (compuesto 14)

A una solución a temperatura ambiente de amina secundaria (384,3 mg, 1,05 mmol) en metanol (10 mL) se agregó 2-piridinacarboxaldehido (201,0 µL 2,11 mmol), seguido por ácido acético (1 mL) La mezcla se agito durante 30 minutos y se agregó luego cianoborohidruro de sodio (199 mg 3 16 mmol) La mezcla de reacción se agito durante una noche, luego se agregó agua y la mezcla se extrajo con cloruro de metileno La fase acuosa se neutralizó con bicarbonato de sodio y se extrajo nuevamente con cloruro de metileno Los extractos cloruro de metileno combinados se secaron sobre sulfato de sodio anhidro se filtraron y concentraron bajo condiciones de presion reducida Purificacion en fase reversa

(M+l) calculado 456 60 (M+1) observado 456,12

Análisis calculado para ($C_{29}H_{33}N_3O_2$ X 1 70 $C_2HO_2F_3$ X 0,40 H_2O) C 59 26%, H 5,45%, N 6 40% Encontrado C 59,21%, H 5,46%, N 6,35%

RMN ^1H (CD_3OD) 8,57 (d, 1H J=5 2 Hz), 7,78 (dt, 1H, J=8,0, 1,2 Hz), 7 38 (d 1H, J=8,0 Hz) 7 34 (dd 1H J=8 0, 5,2 Hz), 7,24 (d, 2H, J=8 0 Hz) 7 15 (d, 2H, J=8,0 Hz) 7 05 (t, 1H J=8,0 Hz), 6,59 (dd, 1H, J=8 0 2 4 Hz), 6,54 (d, 1H J=8 0 Hz) 6,45 (dd, 1H, J=2,4 1,2 Hz) 4 39 (s 2H), 3 40-3,46 (m 2H), 3,26-3 34 (m 4H) 3,16-3,22 (m, 2H), 2,54-2,64 (m 4H) 1,13 (t 3H, J=6,4 Hz), 1,01 (t 3H J=6 4 Hz)

Ejemplo 8

Preparación de *N,N*-dietil-4-{(3-hidroxifenil)[1-(4-piridinilmetil)-4-piperidinilideno]metil}benzamida (compuesto 15)

A una solución a temperatura ambiente de amina secundaria (300 mg 0 82 mmol) en metanol (8 mL) se agregó 4-piridinacarboxaldehido (236,1 µL 2,47 mmnol), seguido por ácido acético (0,5ml) La mezcla se agitó durante 30 minutos y luego se agregó cianoborohidruro de sodio (155 mg 2 47 mmol) La mezcla de reacción se agitó durante una noche, se extinguio con bicarbonato de sodio y 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 456,60, (M+1) observado 456 10

Análisis calculado para ($C_{29}H_{33}N_3O_2$ X 1,80 $C_2HO_2F_3$ X 0,40 H_2O) C 58 61%, H 5,37% N 6,29%, Encontrado C 58 64% H 5,32%, N 6,46%

RMN ^1H (CD_3OD) 8,64 (s, 2H), 7,61 (d, 2H, J=5,2 Hz), 7,25 (2H, J=8,0 Hz), 7,14 (d, 2H J=8,0 Hz), 7,05 (t, 1H J=8 0 Hz), 6,59 (dd, 1H, J=8,0, 1,6 Hz), 6,53 (d, 1H, J=8,0 Hz) 6 43-6 46 (m, 1H), 4,34 (s, 2H) 3 42-3,44 (m, 2H), 3,18-3 24 (m 6H), 2,54-2,57 (m 4H) 1,13 (t, 3H, J=6,4 Hz), 1 02 (t, 3H, J=6,4 Hz)

Ejemplo 9

Preparación de *N,N*-dietil-4-{(3-hidroxifenil)[1-(1*H*-imidazol-2-ilmetil)-4-piperidinilideno]metil}benzamida (compuesto 16)

A una solución a temperatura ambiente de amina secundaria (300 mg, 0,82 mmol) en metanol (8 mL) se agregó 2-imidazolcarboxaldehido (237,3 mg, 2,47 mmol), seguido por ácido acético (0 5mL) y cianoborohidruro de sodio (155 mg, 2,47 mmol) La mezcla de reaccion se agitó durante una noche, se extinguio con bicarbonato de sodio y se extrajo con cloruro de metileno Los extractos cloruro de metileno combinados se secaron sobre sulfato de sodio anhidro, se filtraron y se concentraron bajo condiciones de presión reducida Purificación en fase reversa

(M+1) calculado 445,58, (M+1) observado 445,16

Analisis calculado para ($C_{27}H_{32}N_4O_2$ X 2,10 $C_2HO_2F_3$ X 0 50 H_2O) C 54,07%, H 5,11%, N 8,08% Encontrado C 54 04% H 5 05% N 8 09% RMN ^1H (CD_3OD) 7 38 (s 2H) 7 20-7 22 (m, 2H), 7 11 (d, 2H, J=8 0 Hz) 7,0 (t, 1H J=8 0 Hz) 6 55 (dd, 1H J=8 0 3,6 Hz), 6,49-6,50 (m, 1H), 6,42-6,43 (m, 1H), 4,08 (s, 2H), 3,41-3,43 (m, 2H), 3,18-3,20 (m, 3H), 2,79-2,82 (m 4H), 2,39-2,45 (m 4H) 1 08-1 16 (m 3H) 0 96-1 16 (m 3H)

Ejemplo 10

Preparación de *N,N*-dietil-4-{(3-hidroxifenil)[1-(1*H*-imidazol-4-ilmetil)-4-piperidinilideno]metil}benzamida (compuesto 17)

A una solución a temperatura ambiente de amina secundaria (300 mg, 0 82 mmol) en metanol (10 mL) se agregó 4(5)-imidazolcarboxaldehido (94,9 mg, 0,99 mmol), seguido por ácido acético (0 5 mL) La mezcla se agitó 1 hora y luego se agrego cianoborohidruro de sodio (62,1 mg, 0,99 mmol) La mezcla de reaccion se agitó durante una noche se extinguió con bicarbonato de sodio y 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 445 58, (M+1) observado 445,16

Análisis calculado para ($C_{27}H_{32}N_4O_2$ X 2,20 $C_2HO_2F_3$) C 54 23% H 4 96% N 8,06%, Encontrado C 54,43%, H 4,99%, N 7,73%

RMN ^1H (CD_3OD) 8,54 (s, 1H), 7,57 (s, 1H), 7,23 (d, 2H, J=8,4 Hz), 7 13 (d, 2H J=8,0 Hz), 7,03 (dd, 1H J=8,0 7,6 Hz), 6,57-6,59 (m 1H) 6,51-6,53 (m, 1H), 6,43-6,44 (m, 1H), 4,35 (s, 2H), 3,41-3,43 (m, 2H), 3 18-3,23 (m, 8H), 2,53-2,56 (m, 4H) 1 08-1 16 (m 3H), 0,96-1 04 (m 3H)

Ejemplo 11

Preparación de *N,N*-dietil-4-{(3-hidroxifenil)[1-(1,3-tiazol-2-ilmetil)-4-piperidinilideno]metil}benzamida (compuesto 18)

A una solución a temperatura ambiente de amina secundaria (143 2 mg, 0,39 mmol) en metanol (4 mL) se agrego 2-tiazolcarboxaldehido (41,4 µL, 0,47 mmol), seguido por ácido acético (0,2 mL) La mezcla se agitó 1 hora y luego se agrego cianoborohidruro de sodio (129 6 mg, 1 48 mmol) La mezcla de reacción se agitó durante una noche, se extinguió con bicarbonato de sodio y 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 Punficacion en fase reversa

(M+1) calculado 462,63, (M+1) observado 462,10

Análisis calculado para ($C_{27}H_{31}N_3O_2S$ X 1,10 $C_2HO_2F_3$ X 1,10 H_2O) C 57 79%, H 5,70%, N 6,92% Encontrado C 57,75%, H 5,60% N 7,13%

RMN ^1H (CD_3OD) 7,86 (d, 1H, J=4,0 Hz), 7,68 (d, 1H, J=4,0 Hz), 7,26 (d, 2H, J=8,0 Hz), 7,16 (d, 2H, J=8,0 Hz), 7,07 (dd 1H J=8,4, 8,0 Hz), 6 60-6,62 (m, 1H), 6,54-6,56 (m 1H), 6,46-6,47 (m, 1H), 4 65 (s, 2H), 3,21-3,45 (m 8H), 2,56-2 58 (m, 4H), 1,12-1 20 (m, 3H), 1,00-1,08 (m 3H)

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 medico tratante en el momento de determinar el régimen

y nivel individual de dosificación que resulte más apropiado para un paciente en particular

En la preparacion de las composiciones farmaceuticas basadas en los compuestos de la presente invención, se pueden utilizar vehículos portadores inertes, farmaceuticamente aceptables, los cuales pueden ser solidos ó liquidos Entre las preparaciones en formas sólidas se incluyen los polvos, tabletas, granulados dispersibles cápsulas, sobres y los supositorios

Un portador solido 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 tambien tratarse de un material de encapsulacion

En el caso de los polvos, el vehiculo 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 fusion tal como una mezcla de glicerídos de acidos 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 azucar pectinas dextrina, almidon 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, tannato tartrato teoclato trietilyoduro benzatina clorprocaina, colina, dietanolamina etilendiamina meglumina, procaina las sales de aluminio calcio litio magnesio, potasio, sodio y zinc

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 encapsulacion a manera de vehículo portador con lo cual se proporciona una capsula en la cual el ingrediente activo (con ó sin otros vehículos portadores) va rodeado por un vehiculo portador el cual entra en asociación con éste Similarmente, también se incluyen los sobres

Las tabletas, polvos sobres y capsulas pueden usarse como formas de dosificación solidas apropiadas para administración oral

Entre las composiciones líquidas se incluyen las soluciones, suspensiones, y las emulsiones Las soluciones acuosas ó en agua-propilenglicol esteriles

de los compuestos activos pueden mencionarse como ejemplo de preparaciones liquidas apropiadas para administracion parenteral Las composiciones líquidas pueden también formularse en solución en forma de soluciones acuosas de polietilenglicol

Las soluciones acuosas para administracion oral pueden prepararse mediante la disolucion del ingrediente activo en agua y agregando luego los apropiados colorantes agentes saborizantes estabilizantes. y agentes espesantes segun sea deseado Las suspensiones acuosas para uso oral pueden prepararse por dispersion del ingrediente activo finamente dividido en agua junto con un material viscoso tal como gomas naturales o sintéticas, resinas metilcelulosa carboximetilcelulosa sodica y otros agentes suspensores conocidos en el campo de la formulación farmacéutica

Preferiblemente las composiciones farmacéuticas se encuentran en una forma de dosificacion unitaria En dicha forma la composicion se divide en dosis unitarias que contienen las cantidades apropiadas de ingrediente activo La forma de dosificación unitaria puede tratarse de una preparacion envasada o empacada en donde el envase/empaque contiene cantidades discretas de las preparaciones, por ejemplo tabletas, capsulas y polvos envasados en viales o ampollas La forma de dosificación unitaria puede también encontrarse en forma de capsula, sobre, o tableta, ó puede ir empacada de modo que haya cierto numero de formas empacadas o envasadas

EVALUACION BIOLOGICA

Modelo In Vitro

Cultivo de Celulas

A Se sembraron celulas 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 raton y rata y se lavaron en PBS (que contenia EDTA 2 5 mM, pH 7,4) enfriada con hielo Los cerebros se homogeneizaron con un polytron durante 15 seg (raton) 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 agrego fluoruro de fenilmetilsulfonilo justo antes de su uso hasta una concentracion de 0 5 mM partiendo de un stock 0 5 M en DMSO etanol)

Preparación de las membranas

Las celulas 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 agrego PMSF justo antes de su uso hasta una concentracion 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 centrifugo a 100 g (max) durante 10 min a 4 °C El sobrenadante se recupero 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 alicuotas (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 proteina se determinaron a través de un ensayo de Lowry modificado con dodecilsulfato de sodio (SDS)

Ensayos de ligamiento

Las membranas se descongelaron a 37 ^{0}C se enfriaron en hielo se pasaron 3 veces a traves 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 conservo a 4 ^{0}C después de la filtración a traves de

un filtro de 0,22 µ y a lo cual se le habia agregado recientemente 5 µg/mL de aprotinina, 10 µM de bestatina 10 µM de diprotina A sin DTT) Se agregaron alicuotas 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 determino el Ligamiento Total (TB) y el ligamiento No Especifico (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 lavo rapidamente al vacio 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 traves de filtros GF/B (Whatman) pre-empapados durante por lo menos 2 hr en polietilenimina al 0,1% Se midio luego la radioactividad (dpm) retenida en los filtros usando un contador de rayos beta despues de empapar los filtros durante por lo menos 12 hr en minivials que contenian 6-7 mL de fluido de centelleo En caso de que el ensayo se monte en una placa de microvaloracion de 96 orificios profundos la filtración se realiza en unifiltros (unidades filtrantes) de 96 lugares de filtracion, 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) despues de la adición de 50 µL de fluido de centelleo MS-20/orificio

Ensayos Funcionales

La actividad agonista de los compuestos se midió por determinacion 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 opiaceos 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 efectuan 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

Analisis 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 graficas 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 paginas

Tabla 1 Datos Biológicos

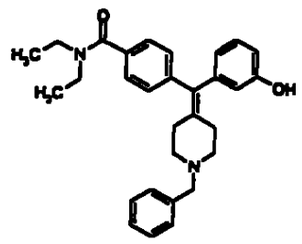
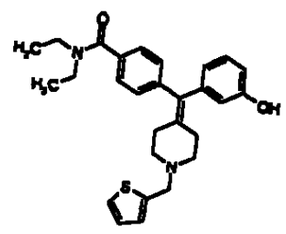
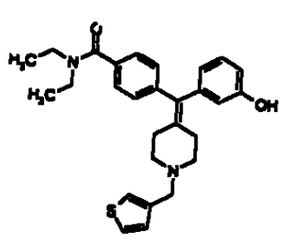
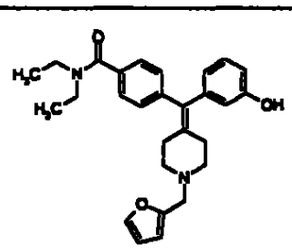
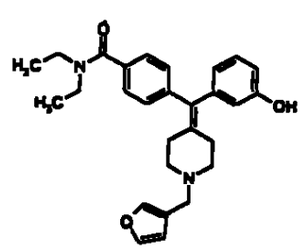
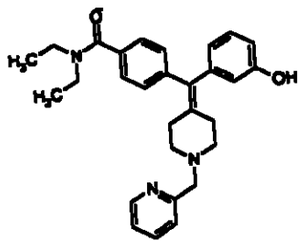
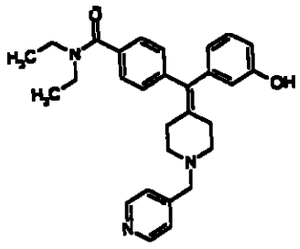
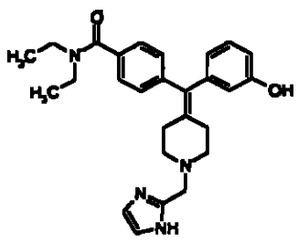
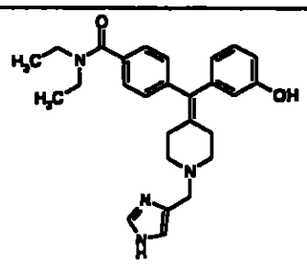
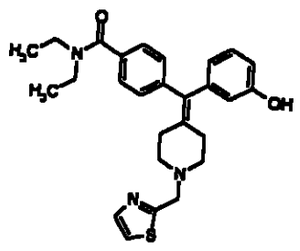
Ej #	ESTRUCTURA MOLECULAR	HDELTA	HDELTA		CEREBRO DE RATA		CEREBRO DE RATON	
			CE_{50}	% E máx	CE_{50}	% E máx	CE_{50}	% E máx
2		0 408	0 1	104 09	0 6	112 2	0 79	103 77
3		0 521	0 15	98 18	0 93	167 51	1 52	186 36
4		0 366	0,152	94 60	0 398	138 60	0 57	144 70
5		0 266	0 09	94 78	0 81	132,09	1 07	134 16
6		0 196	0 096	93 30	0 133	158 4	0 21	161 70

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
7		0 209	0 07	103 29	0 33	134 88	0 55	137,63
8		0 346	0 3	112 34	3 3	81 44	4 65	78 19
9		0 117	0 27	106 1	0 68	151 01	0 81	135 98
10		0 172	0 48	107 23	4 64	101 93	5 06	103 53
11		0 282	0 34	115 37	2 99	119 82	2 19	117 99

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 especifico del radioligando se expreso en pmol/mg de proteina 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 determino 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 escogia el siguiente estimulo más débil El cálculo óptimo del umbral por este metodo exige 6 respuestas en la inmediata vecindad del umbral 50%, y el conteo de tales 6 respuestas comenzó cuando ocurria 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 (maximamente alodinico), 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 formula

$$\text{Umbral 50\% g} = 10^{(Xf + k\delta)} / 10\,000$$

en donde xf = valor del ultimo 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 estimulos (unidades log) En el presente caso, δ = 0,224

Los umbrales de von Frey se convirtieron a porcentaje de efecto maximo posible (% MPE sigla en inglés), segun Chaplan et al 1994 Se usó la siguiente ecuación para calcular el % MPE

$$\% \text{ MPE} = \frac{\text{Umbral de tratados con la droga (g)} - \text{umbral de alodinia (g)}}{\text{Umbral de Control (g)} \quad \text{umbral de alodinia (g)}} \times 100$$

ADMINISTRACION DE LA SUSTANCIA DE PRUEBA

Las ratas se inyectaron (subcutanea, intraperitonea, intravenosa u oralmente) con una sustancia de prueba antes de la prueba de von Frey el

tiempo entre la administracion 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 estiraran sus cuerpos en un patrón típico Al administrar drogas analgesicas tal movimiento caracteristico se observa con mucha menor frecuencia y la droga seleccionada que lo disminuya sera una excelente candidata a ser analgésica

Un reflejo completo y tipico de Writhing se considera unicamente 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 invencion demuestran una significativa inhibición de las respuestas de Writhing después de la dosificacion oral de 1-100 µmol/kg

(i) Preparación de las soluciones

Acido acetico (AcOH) 120 µL de ácido acetico se agregan a 19,88 mL de agua destilada para obtener un volumen final de 20 mL con una concentracion final de 0,6% de AcOH La solucion luego se mezcla (en remolino) y se alista para inyeccion

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 via oral intraperitoneal (i p), subcutanea (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 (segun la clase de compuesto y sus caracteristicas) 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

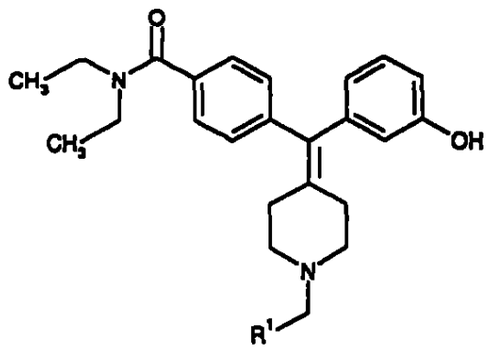
El AcOH se administra intraperitonealmente (i p) en dos sitios a dosis de 10 mL/kg (tomando en cuenta el peso corporal promedio de los ratones) inmediatamente antes de la prueba

(iii) 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

Reivindicaciones

1 Un compuesto de fórmula I



en donde

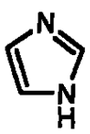
R^1 se selecciona del grupo conformado por

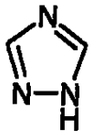
(i) fenil 

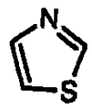
(ii) piridinil 

(iii) tienil 

(iv) furanil 

(v) imidazolil  ,

(vi) triazolil  ,

(vii) tiazolil  ,

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-(3-hidroxilfenil-N-bencil-piperidin-4-iliden-metil)-benzamida,
- *N N*-dietil-4-{(3-hidroxifenil)[1-(2-tienilmetil)-4-piperidinil]iden]metil}benzamida,
- *N N*-dietil-4-{(3-hidroxifenil)[1-(3-tienilmetil)-4-piperidinil]iden]metil}benzamida,
- *N N*-dietil-4-[[1-(2-furilmetil)-4-piperidinil]iden](3-hidroxifenil)metil]benzamida,

- *N N*-dietil-4-[[1-(3-furilmetil)-4-piperidinilíden](3-hidroxifenil)metil]benzamida,

- *N N*-dietil-4-{(3-hidroxifenil)[1-(2-piridinilmetil)-4-piperidinilíden]metil}benzamida,

- *N,N*-dietil-4-{(3-hidroxifenil)[1-(4-piridinilmetil)-4-piperidinilíden]metil}benzamida,

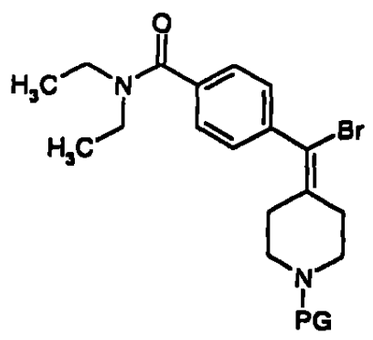
- *N N*-dietil-4-{(3-hidroxifenil)[1-(1*H*-imidazol-2-ilmetil)-4-piperidinilíden]metil}benzamida,

- *N N*-dietil-4-{(3-hidroxifenil)[1-(1*H*-imidazol-4-ilmetil)-4-piperidinilíden]metil}benzamida, y

- *N N*-dietil-4-{(3-hidroxifenil)[1-(1,3-tiazol-2-ilmetil)-4-piperidinilíden]metil}benzamida

6 Un compuesto acorde con cualquiera de las Reivindicaciones precedentes, en forma de sus sales clorhidrato, diclorhidrato, sulfato, tartrato, ditrifluoroacetato ó citrato

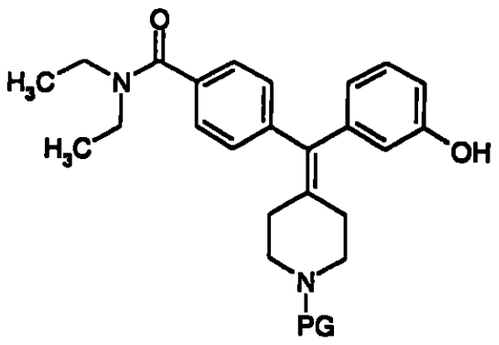
7 Un proceso para la preparación de un compuesto de fórmula I, proceso que comprende la reacción de un compuesto de fórmula general II



II

en donde PG es un grupo protector tipo uretano ó tipo bencil, como por

ejemplo Boc, con ácido 3-hidroxifenil bórico, 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 8, 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

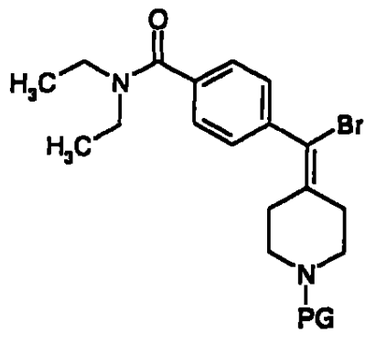
14 Una composición farmacéutica que comprende un compuesto de fórmula I acorde con la Reivindicación 1 como ingrediente activo, junto con un vehículo portador farmacéuticamente aceptable

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