Señor
SUPERINTENDENTE DE INDUSTRIA Y COMER
DIVISION DE NUEVAS CREACIONES
E. S D.

Re: P1.- **MERCK & CO., INC**.- Solicitud de Patente de Invención para **"MODULADORES N-CICLOPENTIL DE LA ACTIVIDAD RECEPTORA DE LA QUIMIOQUINA".-** Clase A61 .-Expediente número **00-042.774**.-

1. Me refiero a mi solicitud de 8 de Junio de 2000.

2. Anexos me permito presentar a usted:

(1) Copias autenticas (2) de las primeras solicitudes de patente presentadas para el invento arriba nombrado **respecto de la cual reclamo prioridad,** a saber:

(a) Copia autentica debidamente certificada de la solicitud estadinense número 60/138.886 de 11 de Junio de 1999, junto con la traducción oficial, correspondiente a las legalizaciones y reivindicaciones de dicho documento;

(b) Copia autentica debidamente certificada de la solicitud estadinense número 09/330.810 de 11 de Junio de 1999, junto con la traducción oficial, correspondiente a las legalizaciones y reivindicaciones de dicho documento;

(2) Copia debidamente autenticada por el Notario Sexto del Circulo de Bogotá, de los documentos que acreditan la calidad de Traductor Oficial del señor Eduardo calado Noguera quien elaboró la traducción de las solicitudes estadinenses número 60/138.886 y 09/330.810, respecto de las cuales se reivindica prioridad en el presente caso.

REPUBLICA DE COLOMBIA
MINISTERIO DE RELACIONES EXTERIORES

EL SUSCRITO JEFE DEL AREA DE LEGALIZACIONES DEL MINISTERIO DE RELACIONES EXTERIORES

COMO NOTARIO SEXTO ENCARGADO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA.
SANTAFE DE BOGOTA 25 AGO. 1999
PABLO MENDEZ BARAJAS

CERTIFICA

Que revisados los registros que se llevan el al oficina de Legalizaciones aparece la firma del señor **EDUARDO CALADO NOGUERA,** como traductor e Intérprete oficial para los idiomas INGLES- ESPAÑOL, ESPAÑOL- INGLES, según resolución 541 del 27 de febrero de 1976.

La anterior certificación se expide a solicitud del interesado quien se identificó con cédula de ciudadanía 17.177.588 expedida en Bogotá.

Dada en Santa Fe de Bogotá, D.C., a los seis (6) de noviembre de 1997.

Blanca García

BLANCA ACOSTA DE GARCIA
Jefe Area de Legalizaciones (e)

COMO NOTARIO SEXTO ENCARGADO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA.
SANTAFE DE BOGOTA 25 ABR. 2000
PABLO MENDEZ BARAJAS

COMO NOTARIO SEXTO ENCARGADO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA.
SANTAFE DE BOGOTA 22 MAR. 2000
PABLO MENDEZ BARAJAS

COMO NOTARIO SEXTO ENCARGADO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA.
SANTAFE DE BOGOTA 19 JUN. 2000
PABLO MENDEZ BARAJAS

República de Colombia

Ministerio de Justicia y del Derecho

EL SECRETARIO GENERAL (E) DEL MINISTERIO DE JUSTICIA Y DEL DERECHO

CERTIFICA:

EL SUSCRITO NOTARIO SEXTO ENCARGADO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA.
SANTAFE DE BOGOTA 25 AGO. 1999
PABLO MENDEZ BARAJAS

Que por Resolución 541 del 27 de febrero de 1976, le fue expedida licencia para ejercer funciones de Traductor e Intérprete Oficial en los idiomas INGLES y ESPAÑOL al señor EDUARDO CALADO NOGUERA, identificado con la cédula de ciudadanía No. 17.177.588 expedida en Bogotá.

Que dicha Resolución se encuentra vigente en la fecha.

Se expide la presente certificación a solicitud del interesado.

Dada en Santa Fe de Bogotá, D.C., a 14 OCT. 1997

ALVARO NAMEN VARGAS

ICM/mmc

EL SUSCRITO NOTARIO SEXTO ENCARGADO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA.
SANTAFE DE BOGOTA 26 NOV. 1997

EL SUSCRITO NOTARIO SEXTO ENCARGADO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA.
SANTAFE DE BOGOTA 25 ABR. 2000
PABLO MENDEZ BARAJAS

EL SUSCRITO NOTARIO SEXTO ENCARGADO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA.
SANTAFE DE BOGOTA 22 MAR. 2000

EL SUSCRITO NOTARIO SEXTO ENCARGADO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA.
SANTAFE DE BOGOTA 13 JUN 2000
PABLO MENDEZ BARAJAS

Mayo 30, 2000
Traducción Oficial No. 0263
REF:MERCK & CO;INC
Patente No.: 60/138,886

Merck & Co; Inc
Caso -20461Y

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS
OFICINA DE MARCAS Y PATENTES

Mayo 11, 2000

Por medio del presente documento se certifica que adjunto se encuentra una fiel copia de los registros de la Oficina de Marcas y Patentes de los Estados Unidos, correspondientes a los documentos para la solicitud tal como se presentaron, con el fin de asignarle una fecha de registro bajo la norma del código 35 USC 111.

Número de Solicitud:60/138,886
Fecha de Registro:Junio 11,1999

Autorizado por:
COMISIONADO DE MARCAS Y PATENTES
Firma: T. LAWRENCE
Funcionario Encargado de Certificaciones
Hay sello de la Oficina de Marcas y Patentes realzado de color dorado.

Eduardo Calado

HOJA DE SOLICITUD PROVISIONAL

Esta es una petición para registrar una SOLICITUD PROVISIONAL bajo el código 37 CFR 1.53(C)

Número de Caso: 20461 PV

INVENTORES / SOLICITANTES

Nombre	Apellidos	Domicilio(ciudad y Estado o país extranjero)
PAUL E.	FINKE	MILLTOWN, NEW JERSEY 08850
KEVIN T.	CHAPMAN	SCOTCH PLAINS, NEW JERSEY 07076
KERRY A.	HILFIKER	WESTFIELD,NEW JERSEY 07076
JENNIFER L.	LOEBACH	WESTFIELD,NEW JERSEY 07076
MALCOLM	MACCOSS	FREEHOLD, NEW JERSEY 07728
SANDER G.	MILLS	SCOTCH PLAINS, NEW JERSEY 07076
BRYAN	OATES	WAYNE, NEW JERSEY 07470

[ ] Los inventores adicionales seran mencionados en páginas adjuntas a la presente

---

TITULO DE LA INVENCIÓN (280 Caracteres máximo)

MODULADORES DE N-CICLOPENTILO DE RECEPTORES DE ACTIVIDAD CHEMOQUINA

Eduardo Calvo L.

DIRECCIÓN PARA LA CORRESPONDENCIA

Merck & Co., Inc
Patent Department - RY60-30
P.O. Box 2000
Rahway

Estado: Nueva Jersey Código Postal: 07065 País: Estados Unidos

PARTES DE LA SOLICITUD INCLUIDAS (Verificar de que todas apliquen)

[x] ESPECIFICACIONES [214] Número de Páginas

[ ] GRÁFICA (S) [ ] Número de Páginas

[ ] Declaración de pequeña Empresa

[ ] Otros (especificar)

FORMA DE PAGO DE HONORARIOS PARA LA SOLICITUD PROVISIONAL DE ESTA PATENTE (Señalar uno)

[ ] Se adjunta un cheque o giro postal para gastos de honorarios de registro de la mencionada patente.

[x] El comisionado por la presente se encuentra autorizado a cobrar honorarios de registro y crédito al número de Cuenta Bancaria 13-2755.

Eduardo Caldo

[x] Honorarios provisionales para registro = $150.00

La invención fue realizada por una agencia del Gobierno de los Estados Unidos o bajo contrato con una agencia del Gobierno de los Estados Unidos.

[x] NO

[ ] Si, el nombre de la Agencia del Gobierno de los Estados Unidos y número de contrato son los siguientes:

Atentamente,

FIRMA:J Eric Thies

Fecha:6/11/99

No. de REGISTRO -35, 382

Teléfono: (732) 594-3809

CERTIFICADO DE ENVIÓ POSTAL

Fecha de envío:Junio 11, 1999

Correo Inmediato Certificado No: EM358364299 US

Yo, por medio del presente documento certifico que ha sido enviado por Correo Certificado como Correo Postal al Destinatario y al Comisionado Asistente para Patentes, Box Patent Application, Washington, DC., 20231.

Firma: Enviado por: Irene Samulewski Eduardo Quiñones M.

en el cual Y es seleccionado de:

un enlace único, -O-, SO2-, -NR10-, -NR10-SO2-, -SO2-NR10-, -S-, y -SO-,

en el cual R10 es seleccionado independientemente de: hidrógeno, C1-6-alquilo, bencilo, fenilo y C1-6 alquilo-C3-6 cicloalquilo,

el cual es substituido o no substituido con 1-3 substitutos donde los substitutos son seleccionados independientemente de: halo, C1-3 alquilo, C1-3 alcoxi y trifluorometilo;

R1 es seleccionado de;

(1) -CO2H,

(2) -NO2,

(3) tetrazolil,

(4) -hidroxiisoxazol,

(5) -SO2NH-(C0-3 alquilo)-R9 es seleccionado independientemente de:

hidrógeno, C1-6 alquilo, C5-6 cicloalquilo, bencilo o fenilo, el cual es substituido o no substituido con 1-3 substitutos en el

Eduardo Caludo

cual los substitutos son seleccionados independientemente de:

halo, C1-3 alquilo, C1-3 alcoxi y trifluorometilo, y

(6) -P(O)(OH)2;

R3 es seleccionado de un grupo que consiste de:

fenilo y heterociclo,

el cual es substituido o no substituido con 1-7 substitutos en el cual los substitutos son seleccionados independientemente de:

(a) halo,

(b) trifluorometilo,

(c) hidroxi,

(d) C1-3 alquilo,

(e) -O-C1-3alquilo,

(f) -CO2R9,

(g) -NR9R10, y

(h) -CONR9R10;

R4, R5 y R6 son seleccionados independientemente de:

hidrógeno, C1-10 alquilo, C3-8 cicloalquilo, C2-10 alquenilo, C2-10 alquinilo, fenilo, -(C1-6 alquilo)-C3-8 cicloalquilo,

Eduardo Calabrese

naftilo, bifenilo y heterociclo, el cual es substituido o no substituido con 1-7 o R11 son independientemente seleccionados de:

(a) halo,

(b) trifluorometilo,

(c) hidroxi,

(d) C1-3 alquilo,

(e) -O-C1-3alquilo,

(f) -CO2R9,

(g) -NR9R10, y

(h) -CONR9R10;

o donde R4 y R5 pueden ser unidos para formar un anillo saturado de 3-8 miembros el cual puede ser substituido o no substituido con 1-7 o R11,

o donde R5 y R6 pueden ser unidos para formar un anillo saturado de 3-8 miembros el cual puede ser substituido o no substituido con 1-7 o R11;

Eduardo Calvo A.

R7 es seleccionado de:

(1) hidrógeno,

(2) C1-6 alquilo, el cual es substituido o no substituido con 1-4 substitutos en el cual los substitutos son seleccionados independientemente de: hidróxi, ciano y halo,

(3) hidróxi, y

(4) halo;

R8 es seleccionado de:

hidrogeno, C1-8 cicloaqluilo, fenilo, naftilo, bifenilo y heterociclo, el cual es substituido o no substituido con 1-7 de R12 donde R12 es seleccionado independientemente de:

(a) halo,

(b) ciano,

(c) hidroxi,

(d) C1-6alquilo, el cual es substituido o no substituido con 1-5 de R13 donde R13 es seleccionado independientemente de: halo, ciano,hidroxi, C1-6 alcoxi, -CO2H, -CO2(C1-6alquilo), trifluorometilo y -NR9R10,

(e) -O-C1-6alquilo, el cual es substituido o no substituido con 1-5 de R13,

Eduardo Calado V.

(f) -CF3,

(g) -CHF2,

(h) -CH2F,

(i) -NO2,

(j) C0-6alquilo-fenilo o C0-6 alquilo-heterociclo, el cual es substituido o no substituido con 1-7 substitutos los cuales son seleccionados independientemente de:

(i) halo,

(ii) hidroxi,

(iii) C1-6 alquilo,

(iv) -O-C1-6alquilo,

(v) -CF3,

(vi) -OCF3,

(vii) -NO2,

(viii) -CN,

(ix) -SO2-C1-6alquilo,

(x) -CO2R9,

(xi) -NR9R10,

(xii) -CONR9R10,

(xiii) -SO2-NR9R10, y

(xiv) -NR9-SO2-R10;

Eduardo Calado A.

(k) -CO2R9,

(l) tetrazolil,

(m) -NR9R10,

(n) -NR9-COR10,

(o) -NR9 CO2R10

(p) -CO-NR9R10,

(q) -OCO-NR9R10,

(r) -NR9CO-NR9R10,

(s) -S(O)m-R9, en el cual m es un número entero seleccionado de 0, 1 y 2,

(t) -S(O)2-NR9R10,

(u) -NR9S(O)2-R10, y

(v) -NR9S(O)2-NR9R10;

n es un número entero seleccionado de 1,2,3 y 4;

x es un número entero seleccionado de 0, 1 y 2, e

y es un número entero seleccionado de 0, 1 y 2, siempre y cuando que la suma de x e y sea 2;

y sales farmacéuticamente aceptables del mismo e diastereomeros del mismo.

Edwardo Calado A.

2. El compuesto de acuerdo a la reivindicación 1 en la cual R1 es seleccionado de:

(1) -CO2H, y

(2) -tetrazolil.

3. El compuesto de acuerdo a la reivindicación 1 en la cual R1 es -CO2H.

4. El compuesto de acuerdo a la reivindicación 1 en la cual R3 es seleccionado de un grupo que consiste de:

fenilo e tienilo,

el cual puede ser substituido o no substituido con 1-5 substitutos en el cual los substitutos son independientemente seleccionados de:

(a) halo,

(b) trifluorometilo,

(c) hidroxi,

(d) C1-3alquilo, y

Eduardo Collado A.

(e) -O-C1-3alquilo.

5. El compuesto de acuerdo a la reivindicación 1 en el cual R3 es seleccionado de un grupo que consiste de:

fenilo e tienilo,

el cual puede ser substituido o no substituido con 1-5 substitutos en el cual los substitutos son seleccionados independientemente de:

(a) flúor,

(b) cloro,

(c) trifluorometilo,

(d) hidroxi, y

(e) C1-3alquilo.

6. El compuesto de acuerdo a la reivindicación 1 en la cual R3 es seleccionado de un grupo que consiste de:

fenilo, el cual puede ser substituido o no substituido con 1-5 substitutos en el cual los substitutos son seleccionados independientemente de:

(a) flúor, y

Eduardo Calvo A.

(b) cloro; y

tienilo no substituido.

7. El compuesto de acuerdo a la reivindicación 1 en la cual R3 es fenilo no substituido, (3-flúor) fenilo o 3-tienilo.

8. El compuesto de acuerdo a la Reivindicación 1 en la cual R4 es hidrógeno.

9. El compuesto de acuerdo a la Reivindicación 1 en el cual R5 es seleccionado de: hidrógeno, C1-6 alquilo, C3-8 cicloalquilo, C1-6 alquilo-C3-8 cicloalquilo y fenilo.

10. El compuesto de acuerdo a la reivindicación 1 en la cual R5 es seleccionado de: hidrógeno, metilo, n-propilo, isopropilo, n-butilo, t-butilo, isobutilo, sec-butilo, ciclohexilo, -CH2-ciclopropilo, -CH2-ciclobutilo y fenilo.

11. El compuesto de acuerdo a la Reivindicación 1 en el cual R5 es seleccionado de: isopropilo, isobutilo, sec-butilo y ciclohexilo.

Eduardo Calado A.

12. El compuesto de acuerdo a la reivindicación 1 en el cual R6 es seleccionado de: hidrógeno, C1-6 alquilo, C3-8 cicloalquilo, C1-6 alquilo-C3-8 cicloalquilo y fenilo.

13. El compuesto de acuerdo a la reivindicación 1 en el cual R6 es seleccionado de: hidrógeno, metilo, n-butilo, t-butilo, isobutilo, sec-butilo, -CH2-ciclopropilo, -CH2-ciclopropilo, -CH2-ciclobutilo e ciclohexilo.

14. El compuesto de acuerdo a la reivindicación 1 en el cual R6 es seleccionado de: hidrógeno, metilo, -CH2-ciclopropilo, -CH2-ciclobutilo y ciclohexilo.

15. El compuesto de acuerdo a la Reivindicación 1 en el cual R7 es hidrógeno, flúor, hidróxi o C1-6 alquilo.

16. El compuesto de acuerdo a la Reivindicación 1 en el cual R7 es hidrógeno.

17. El compuesto de acuerdo a la reivindicación 1 en el cual X es:

Eduardo Calvado A.

-(C0-4alquilo)-Y-(C0-4alquilo),

en el cual el alquilo es substituido o no substituido con 1-4 substitutos donde los substitutos son seleccionados independientemente de:

(a) halo,

(b) hidroxi,

(c) -O-C1-3alquilo, y

(d) trifluorometilo,

en el cual Y es seleccionado de:

un enlace único, -O-, SO2-, -NR10-, -NR10-SO2-, -SO2-NR10-, -S-, y -SO-,

en el cual R10 es seleccionado independientemente de:

hidrógeno, C1-6-alquilo, bencilo, fenilo y C1-6 alquilo-C3-6 cicloalquilo,

el cual es substituido o no substituido con 1-3 substitutos donde los substitutos son seleccionados independientemente de: halo, C1-3 alquilo, C1-3 alcoxi y trifluorometilo;

Eduardo Calado M

18. El compuesto de acuerdo a la reivindicación 1 en la cual X es:

-(C0-4alquilo)-Y-(C0-4alquilo),

en el cual el alquilo es substituido o no substituido con 1-4 substitutos donde los substitutos son seleccionados independientemente de:

(a) halo,

(b) hidroxi,

(c) -O-C1-3alquilo, y

(d) trifluorometilo,

en el cual Y es seleccionado de:

un enlace único, -O-, SO2-, -NR10-, -NR10-SO2-, -SO2-NR10-, -S-, y -SO-,

en el cual R10 es seleccionado independientemente de:

hidrógeno, C1-6-alquilo, bencilo, fenilo y C1-6 alquilo-C3-6 cicloalquilo,

el cual es substituido o no substituido con 1-3 substitutos donde los substitutos son seleccionados independientemente de: halo, C1-3 alquilo, C1-3 alcoxi y trifluorometilo;

Eduardo Calado

19. El compuesto de acuerdo a la Reivindicación 1 en la cual X es seleccionado de:

-(C0-4alquilo)-Y-(C0-4alquilo),

en el cual el alquilo es substituido o no substituido con flúor,

y en el cual Y es seleccionado de:

un único enlace, -SO2-, -SO-, y -NR10-,

donde R10 es seleccionado independientemente de: hidrógeno, C1-3 alquilo, C2-3 alquenilo y c2-3 alquinilo.

20. El compuesto de acuerdo a la reivindicación 1 en el cual X es seleccionado de:

(1) un enlace único,

(2) -CH2CH2-,

(3) -CH2CH2CH2-,

(4) -CH2CH2-CF2-,

(5) - CH2CH2-SO2-, y

(6) -CH2CH2-SO-

21. El compuesto de acuerdo a la reivindicación 1 en al cual R8 es seleccionado de: fenilo, naftilo, ciclohexilo, benzoimidazolil.

Eduardo Calaza

benzofurazanil, imidazopiridilo, imidazolil, isoxazolil, oxazolil, pirazinilo, piridazinilo, piridilo, pirimidilo, tiazolil y tetrazolopiridilo,

el cual es substituido o no substituido con 1-7 substitutos en el cual los substitutos son independientemente seleccionados de:

(a) halo,

(b) ciano,

(c) hidróxi,

(d) C1-6alquilo, el cual es substituido o no substituido con 1-5 de R13 donde R13 es seleccionado independientemente de: halo, ciano,hidroxi, C1-6 alcoxi, -CO2H, -CO2(C1-6alquilo), trifluorometilo y -NR9R10, en el cual R9 y R10 son seleccionados independientemente de: hidrógeno, C1-6 alquilo, C5-6 cicloalquilo, bencilo, o fenilo, el cual es substituido o no substituido con 1-3 substitutos, en el cual el substituto es seleccionado independientemente de; halo, C1-3 alquilo, C1-3 alcoxi y trifluorometilo;

Eduardo Calvado A.

(e) -O-C1-6alquilo, el cual es substituido o no substituido con 1-5 de R13,

(f) -CF3,

(g) -CHF2,

(h) -CH2F,

(i) -NO2,

(j) C0-6alquilo-fenilo o C0-6 alquilo-heterociclo, el cual es substituido o no substituido con 1-7 substitutos los cuales son seleccionados independientemente de:

(i) halo,

(ii) hidroxi,

(iii) C1-6 alquilo,

(iv) -O-C1-6alquilo,

(v) -CF3,

(vi) -OCF3,

(vii) -NO2,

(viii) -CN,

(ix) -SO2-C1-6alquilo,

(x) -CO2R9,

(xi) -NR9R10,

Eduardo Calvo

(xii) -CONR9R10,

(xiii) -SO2-NR9R10, y

(xiv) -NR9-SO2-R10;

(k) -CO2R9,

(l) tetrazolil,

(m) -NR9R10,

(n) -NR9-COR10,

(o) -NR9 CO2R10

(p) -CO-NR9R10,

(q) -OCO-NR9R10,

(r) -NR9CO-NR9R10,

(s) -S(O)m-R9, en el cual m es un número entero seleccionado de 0, 1 y 2,

(t) -S(O)2-NR9R10,

(u) -NR9S(O)2-R10, y

(v) -NR9S(O)2-NR9R10;

22. El compuesto de acuerdo a la reivindicación 1 en el cual R8 es seleccionado de: fenilo, imidazopirridilo, imidazolil, oxazolil, pirazolil, pirridilo y tiazolil.

el cual es substituido o no substituido con 1-5 substitutos en el cual los substitutos son independientemente seleccionados de.

Eduardo Cabrera L.

(a) halo,

(b) ciano,

(c) -NO2,

(d) -CF3,

(e) -CHF2,

(f) -CH2F,

(h) C1-6alquilo

(i) C1-3 alquilo-fenilo o C1-3alquilo-pirridilo el cual es substituido o no substituido con 1-4 substitutos en el cual dichos substitutos son seleccionados independientemente de:

(i) halo;

(ii) C1-6 alquilo,

(iii) -O-C1 alquilo,

(iv) -CF3,

(vi) -OCF3,

(vii) -CN, y

(j) -O-C1-6 alquilo.

23. El compuesto de acuerdo a la reivindicación 1 en el

Eduardo Calvador R.

cual R8 es seleccionado de: imidazolil, oxazolil, pirazolil y tiazolil;

el cual es substituido o no substituido con 1-3 substitutos y dichos substitutos son seleccionados independientemente de:

(a) flúor,

(b) ciano,

(c) C1-3 alquilo,

(d) -CH2 fenilo, el cual es substituido o no substituido con 1-4 substitutos en el cual dichos substitutos son independientemente seleccionados de:

(i) flúor,

(ii) cloro,

(iii) -0-CH3,

(iv) -CF3,

(v) -CN, y

(e) -CF3.

24. El compuesto de acuerdo a la reivindicación 1 en el cual R8 es seleccionado de: 5-(3-bencilo)pirazolil, 5-(1-metilo-3-bencilo)pirazolil, 5--(1-etilo-3-bencilo)pirazolil, 5-(2-

Eduardo Valdés

bencilo)tiazolil, 5-(2-benilo-4-metilo)tiazolil, y 5-(2-benilo-4-etilo)tiazolil).

25. El compuesto de acuerdo a la Reivindicación 1 en el cual n es un número entero el cual es 1.

26. El compuesto de acuerdo a la Reivindicación 1 en el cual x es un número entero el cual es 1 e y es un número entero el cual es 1.

27. Una composición farmacéutica la cual consiste de un portador inerte y un compuesto de acuerdo a la reivindicación 1.

28. Un método para la modulación de actividad receptora de chemoquina en un mamífero el cual consiste en el suministro de una cantidad eficaz del compuesto de acuerdo a la reivindicación 1.

29. Un método para la prevención de infecciones de HIV positivo, el cual consiste en tratar la infección de HIV que retarda el comienzo del SIDA o el tratamiento del SIDA el cual consiste en suministrar a un paciente que necesita dicha cantidad eficaz del compuesto de la reivindicación 1.

Eduardo Calvado R.

30. Un método para la prevención o tratamiento de un trastorno inflamatorio o **inmunoregulatorio** o enfermedad a un paciente que necesite dicho tratamiento el cual consiste en el suministro de una cantidad eficaz del compuesto de acuerdo a la Reivindicación 1.

31. Un método para la prevención o tratamiento para el asma, rinitis alérgica, dermatitis, conjuntivitis, artereosclerosis o artritis reumatoide, el cual consiste en el suministro de una cantidad eficaz del compuesto de acuerdo a la reivindicación 1 a un paciente que necesite dicho tratamiento.

Eduardo Alvado A.

JOSE LLOREDA CAMACHO & CO.

C-20461 V524

PA 245039

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

May 11, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: ***60/138,886***
FILING DATE: ***June 11, 1999***

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

T. Lawrence

T. LAWRENCE
Certifying Officer

Type a plus sign (+) inside this box → [+]

PTO/SB/16 (3-97)
Approved for use through 01/31/98. OMB 0651-0037
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

529

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a **PROVISIONAL APPLICATION FOR PATENT** under **37 CFR 1.53 (C)**.

CASE NUMBER	20461PV

INVENTOR(S)

Given Name (first and middle [if any])	Family Name or Surname	Residence (City and Either State or Foreign Country)
PAUL E.	FINKE	MILLTOWN, NEW JERSEY 08850
KEVIN T.	CHAPMAN	SCOTCH PLAINS, NEW JERSEY 07076
KERRY A.	HILFIKER	WESTFIELD, NEW JERSEY 07090
JENNIFER L.	LOEBACH	WESTFIELD, NEW JERSEY 07090
MALCOLM	MACCOSS	FREEHOLD, NEW JERSEY 07728
SANDER G.	MILLS	SCOTCH PLAINS, NEW JERSEY 07076
BRYAN	OATES	WAYNE, NEW JERSEY 07470

☐ Additional inventors are being named on the__ separately numbered sheets attached hereto

TITLE OF THE INVENTION (280 characters max)

N-CYCLOPENTYL MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY

CORRESPONDENCE ADDRESS

Merck & Co., Inc.
Patent Department - RY60-30
P.O. Box 2000
Rahway

STATE	New Jersey	ZIP CODE	07065	COUNTRY	U.S.A.

ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification — *Number of Pages* 214 — ☐ Small Entity Statement

☐ Drawing(s) — *Number of Sheets* — ☐ Other (specify)

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT *(check one)*

☐ A check or money order is enclosed to cover the filing fees

☒ The Commissioner is hereby authorized to charge filing fees or credit to Deposit Account Number: 13-2755

FILING FEE AMOUNT ($) $150.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE J. Eric Thies — Date 6/11/99

TYPED or PRINTED NAME J. ERIC THIES — REGISTRATION NO. *(if appropriate)* 35,382

TELEPHONE (732) 594-3904

InTriplicate

EXPRESS MAIL CERTIFICATE
DATE OF DEPOSIT JUNE 11, 1999
EXPRESS MAIL NO. EM358364299US
I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS EXPRESS MAIL "POST OFFICE TO ADDRESSEE" BEFORE 5 P.M. ON THE ABOVE DATE IN AN ENVELOPE ADDRESSED TO ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, D.C., 20231.
MAILED BY Irene Samulewski
DATE 6-11-99

Computer generated form No. P11, Merck & Co., Inc., 12/1/97

06/11/99 JC600 U.S. PTO
06/11/99 JC541 U.S. PTO 60/138086

530

TITLE OF THE INVENTION

N-CYCLOPENTYL MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY

BACKGROUND OF THE INVENTION

Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation (reviewed in Schall, Cytokine, 3, 165-183 (1991) and Murphy, Rev. Immun., 12, 593-633 (1994)). There are two classes of chemokines, C-X-C (α) and C-C (β), depending on whether the first two cysteines are separated by a single amino acid (C-X-C) or are adjacent (C-C). The α-chemokines, such as interleukin-8 (IL-8), neutrophil-activating protein-2 (NAP-2) and melanoma growth stimulatory activity protein (MGSA) are chemotactic primarily for neutrophils, whereas β-chemokines, such as RANTES, MIP-1α, MIP-1β, monocyte chemotactic protein-1 (MCP-1), MCP-2, MCP-3 and eotaxin are chemotactic for macrophages, T-cells, eosinophils and basophils (Deng, et al., Nature, 381, 661-666 (1996)).

The chemokines bind specific cell-surface receptors belonging to the family of G-protein-coupled seven-transmembrane-domain proteins (reviewed in Horuk, Trends Pharm. Sci., 15, 159-165 (1994)) which are termed "chemokine receptors." On binding their cognate ligands, chemokine receptors transduce an intracellular signal though the associated trimeric G protein, resulting in a rapid increase in intracellular calcium concentration. There are at least seven human chemokine receptors that bind or respond to β-chemokines with the following characteristic pattern: CCR-1 (or "CKR-1" or "CC-CKR-1") [MIP-1α, MIP-1β, MCP-3, RANTES] (Ben-Barruch, et al., J. Biol. Chem., 270, 22123-22128 (1995); Beote, et al, Cell, 72, 415-425 (1993)); CCR-2A and CCR-2B (or "CKR-2A"/"CKR-2A" or "CC-CKR-2A"/"CC-CKR-2A") [MCP-1, MCP-3, MCP-4]; CCR-3 (or "CKR-3" or "CC-CKR-3") [eotaxin, RANTES, MCP-3] (Combadiere, et al., J. Biol. Chem., 270, 16491-16494 (1995); CCR-4 (or "CKR-4" or "CC-CKR-4") [MIP-1α, RANTES, MCP-1] (Power, et al., J. Biol. Chem., 270, 19495-19500 (1995)); CCR-5 (or "CKR-5" or "CC-CKR-5") [MIP-1α, RANTES, MIP-1β] (Sanson, et al., Biochemistry, 35, 3362-3367 (1996)); and the Duffy blood-group antigen [RANTES, MCP-1] (Chaudhun, et al., J. Biol. Chem., 269, 7835-7838 (1994)). The β-chemokines include eotaxin, MIP ("macrophage inflammatory protein"), MCP ("monocyte chemoattractant protein") and RANTES ("regulation-upon-activation, normal T expressed and secreted").

Chemokine receptors, such as CCR-1, CCR-2, CCR-2A, CCR-2B, CCR-3, CCR-4, CCR-5, CXCR-3, CXCR-4, have been implicated as being important mediators of inflammatory and immunoregulatory disorders and diseases, including asthma, rhinitis and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. Humans who are homozygous for the 32-basepair deletion in the CCR-5 gene appear to have less susceptibility to rheumatoid arthritis (Gomez, et al., Arthritis & Rheumatism, 42, 989-992 (1999)). A review of the role of chemokines in allergic inflammation is provided by Kita, H., et al., J. Exp. Med. 183, 2421-2426 (1996). Accordingly, agents which modulate chemokine receptors would be useful in such disorders and diseases. Compounds which modulate chemokine receptors would be especially useful in the treatment and prevention of atopic conditions including allergic rhinitis, dermatitis, conjunctivitis, and particularly bronchial asthma.

A retrovirus designated human immunodeficiency virus (HIV-1) is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous system. This virus was previously known as LAV, HTLV-III, or ARV.

Certain compounds have been demonstrated to inhibit the replication of HIV, including soluble CD4 protein and synthetic derivatives (Smith, et al., Science, 238, 1704-1707 (1987)), dextran sulfate, the dyes Direct Yellow 50, Evans Blue, and certain azo dyes (U.S. Patent No. 5,468,469). Some of these antiviral agents have been shown to act by blocking the binding of gp120, the coat protein of HIV, to its target, the CD4 glycoprotein of the cell.

Entry of HIV-1 into a target cell requires cell-surface CD4 and additional host cell cofactors. Fusin has been identified as a cofactor required for infection with virus adapted for growth in transformed T-cells, however, fusin does not promote entry of macrophagetropic viruses which are believed to be the key pathogenic strains of HIV in vivo. It has recently been recognized that for efficient entry into target cells, human immunodeficiency viruses require a chemokine receptors, most probably CCR-5 or CXCR-4, as well as the primary receptor CD4 (Levy, N. Engl. J. Med., 335(20), 1528-1530 (Nov. 14 1996). The principal cofactor for entry mediated by the envelope glycoproteins of primary macrophage-trophic strains of HIV-1 is CCR5, a receptor for the β-chemokines RANTES, MIP-1α and MIP-1β (Deng, et al., Nature, 381, 661-666 (1996)). HIV attaches to the CD4

molecule on cells through a region of its envelope protein, gp120. It is believed that the CD-4 binding site on the gp120 of HIV interacts with the CD4 molecule on the cell surface, and undergoes conformational changes which allow it to bind to another cell-surface receptor, such as CCR5 and/or CXCR-4. This brings the viral envelope closer to the cell surface and allows interaction between gp41 on the viral envelope and a fusion domain on the cell surface, fusion with the cell membrane, and entry of the viral core into the cell. It has been shown that β-chemokine ligands prevent HIV-1 from fusing with the cell (Dragic, et al., Nature, 381, 667-673 (1996)). It has further been demonstrated that a complex of gp120 and soluble CD4 interacts specifically with CCR-5 and inhibits the binding of the natural CCR-5 ligands MIP-1α and MIP-1β (Wu, et al., Nature, 384, 179-183 (1996); Trkola, et al., Nature, 384, 184-187 (1996)).

Humans who are homozygous for mutant CCR-5 receptors which do not serve as co-receptors for HIV-1 in vitro appear to be unusually resistant to HIV-1 infection and are not immuno-compromised by the presence of this genetic variant (Nature, 382, 722-725 (1996)). Absence of CCR-5 appears to confer substantial protection from HIV-1 infection (Nature, 382, 668-669 (1996)). Other chemokine receptors may be used by some strains of HIV-1 or may be favored by non-sexual routes of transmission. Although most HIV-1 isolates studied to date utilize CCR-5 or fusin, some can use both as well as the related CCR-2B and CCR-3 as co-receptors (Nature Medicine, 2(11), 1240-1243 (1996)). Nevertheless, drugs targeting chemokine receptors may not be unduly compromised by the genetic diversity of HIV-1 (Zhang, et al., Nature, 383, 768 (1996)). Accordingly, an agent which could block chemokine receptors in humans who possess normal chemokine receptors should prevent infection in healthy individuals and slow or halt viral progression in infected patients. By focusing on the host's cellular immune response to HIV infection, better therapies towards all subtypes of HIV may be provided. These results indicate that inhibition of chemokine receptors presents a viable method for the prevention or treatment of infection by HIV and the prevention or treatment of AIDS.

The peptides eotaxin, RANTES, MIP-1α, MIP-1β, MCP-1, and MCP-3 are known to bind to chemokine receptors. A compound from Takeda, TAK-779, reportedly is a nonpeptidal CCR5 antagonist with anti-HIV-1 activity (Baba, et al., Proc. Nat'l Acad. Sci., USA, 96, 5698-5703 (1999)). As noted above, the inhibitors of HIV-1 replication present in supernatants of CD8+ T cells have been characterized as the β-chemokines RANTES, MIP-1α and MIP-1β.

SUMMARY OF THE INVENTION

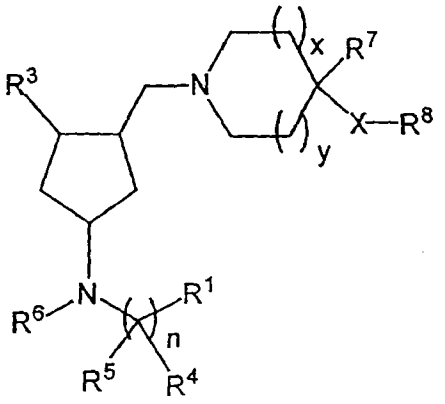
The present invention is directed to compounds which inhibit the entry of human immunodeficiency virus (HIV) into target cells and are of value in the prevention of infection by HIV, the treatment of infection by HIV and the prevention and/or treatment of the resulting acquired immune deficiency syndrome (AIDS). The present invention also relates to pharmaceutical compositions containing the compounds and to a method of use of the present compounds and other agents for the prevention and treatment of AIDS and viral infection by HIV.

The present invention is further directed to compounds which are modulators of chemokine receptor activity and are useful in the prevention or treatment of certain inflammatory and immunoregulatory disorders and diseases, allergic diseases, atopic conditions including allergic rhinitis, dermatitis, conjunctivitis, and asthma, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which chemokine receptors are involved.

SUBSTITUTE SHEET (RULE 26)

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds of formula I:



I

wherein:

X is selected from: -(C_{0-6}alkyl)-Y-(C_{0-6}alkyl)-,
-(C_{0-6}alkyl)-C_{3-8} cycloalkyl-(C_{0-6}alkyl)-,
C_{2-10} alkenyl, and C_{2-10} alkynyl,
where the alkyl is unsubstituted or substituted with 1-7 substituents where the substituents are independently selected from:
(a) halo,
(b) hydroxy,
(c) -O-C_{1-3}alkyl, and
(d) trifluoromethyl,

and where Y is selected from:
a single bond, -O-, -SO_2-, -NR^{10}-, -NR^{10}-SO_2-, -SO_2-NR^{10}-, -S-, and -SO-,

and where R^{10} is independently selected from: hydrogen, C_{1-6} alkyl, benzyl, phenyl, and C_{1-6} alkyl-C_{3-6} cycloalkyl,
which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl;

R^1 is selected from:

(1) $-CO_2H$,
(2) $-NO_2$,
(3) -tetrazolyl,
(4) -hydroxyisoxazole,
(5) $-SO_2NH-(C_{0-3}$ alkyl)$-R^9$, wherein R^9 is independently selected from: hydrogen, C_{1-6} alkyl, C_{5-6} cycloalkyl, benzyl or phenyl, which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl, and
(6) $-P(O)(OH)_2$;

R^3 is selected from the group consisting of:
phenyl and heterocycle,
which is unsubstituted or substituted with 1-7 substituents where the substituents are independently selected from:
(a) halo,
(b) trifluoromethyl,
(c) hydroxy,
(d) C_{1-3}alkyl,
(e) $-O-C_{1-3}$alkyl,
(f) $-CO_2R^9$,
(g) $-NR^9R^{10}$, and
(h) $-CONR^9R^{10}$;

R^4, R^5 and R^6 are independently selected from:
hydrogen, C_{1-10} alkyl, C_{3-8} cycloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, phenyl, $-(C_{1-6}$ alkyl)-phenyl, $-(C_{1-6}$ alkyl)$-C_{3-8}$ cycloalkyl, naphthyl, biphenyl, and heterocycle,
which is unsubstituted or substituted with 1-7 of R^{11} where R^{11} is independently selected from:
(a) halo,
(b) trifluoromethyl,
(c) hydroxy,
(d) C_{1-3}alkyl,
(e) $-O-C_{1-3}$alkyl,

(f) $-CO_2R^9$,

(g) $-NR^9R^{10}$, and

(h) $-CONR^9R^{10}$,

or where R^4 and R^5 may be joined together to form a 3-8 membered saturated ring which may be unsubstituted or substituted with 1-7 of R^{11},

or where R^5 and R^6 may be joined together to form a 3-8 membered saturated ring which may be unsubstituted or substituted with 1-7 of R^{11};

R^7 is selected from:

(1) hydrogen,

(2) C_{1-6}alkyl, which is unsubstituted or substituted with 1-4 substituents where the substituents are independently selected from: hydroxy, cyano, and halo,

(3) hydroxy, and

(4) halo;

R^8 is selected from:

hydrogen, C_{3-8} cycloalkyl, phenyl, naphthyl, biphenyl, and heterocycle, which is unsubstituted or substituted with 1-7 of R^{12} where R^{12} is independently selected from:

(a) halo,

(b) cyano,

(c) hydroxy,

(d) C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 of R^{13} where R^{13} is independently selected from: halo, cyano, hydroxy, C_{1-6}alkoxy, $-CO_2H$, $-CO_2(C_{1-6}$ alkyl), trifluoromethyl, and $-NR^9R^{10}$,

(e) $-O-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-5 of R^{13},

(f) $-CF_3$,

(g) $-CHF_2$,

(h) $-CH_2F$,

(i) $-NO_2$,

(j) C_{0-6}alkyl-phenyl or C_{0-6}alkyl-heterocycle, which is unsubstituted or substituted with 1-7 substituents where the substituents are independently selected from:

(i) halo,
(ii) hydroxy,
(iii) C_{1-6}alkyl,
(iv) -O-C_{1-6}alkyl,
(v) $-CF_3$,
(vi) $-OCF_3$,
(vii) $-NO_2$,
(viii) -CN,
(ix) $-SO_2$-C_{1-6}alkyl,
(x) $-CO_2R^9$,
(xi) $-NR^9R^{10}$,
(xii) $-CONR^9R^{10}$,
(xiii) $-SO_2-NR^9R^{10}$, and
(xiv) $-NR^9-SO_2-R^{10}$;

(k) $-CO_2R^9$,

(l) tetrazolyl,

(m) $-NR^9R^{10}$,

(n) $-NR^9-COR^{10}$,

(o) $-NR^9-CO_2R^{10}$,

(p) $-CO-NR^9R^{10}$,

(q) $-OCO-NR^9R^{10}$,

(r) $-NR^9CO-NR^9R^{10}$,

(s) $-S(O)_m-R^9$, wherein m is an integer selected from 0, 1 and 2,

(t) $-S(O)_2-NR^9R^{10}$,

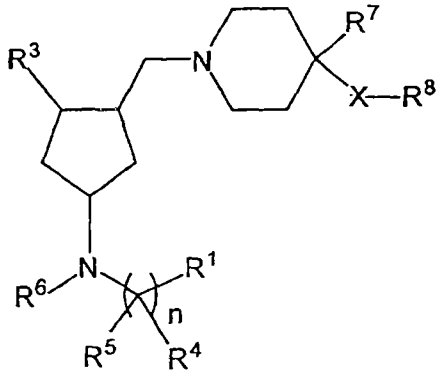
(u) $-NR^9S(O)_2-R^{10}$, and

(v) $-NR^9S(O)_2-NR^9R^{10}$;

n is an integer selected from 1, 2, 3 and 4;
x is an integer selected from 0, 1 and 2, and y is an integer selected from 0, 1 and 2, with the proviso that the sum of x and y is 2;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

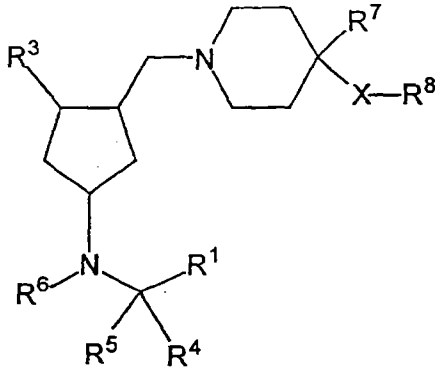
Preferred compounds of the present invention include those of formula Ia:



Ia

wherein R^1, R^3, R^4, R^5, R^6, R^7, R^8, X and n are defined herein;
and pharmaceutically acceptable salts and individual diastereomers thereof.

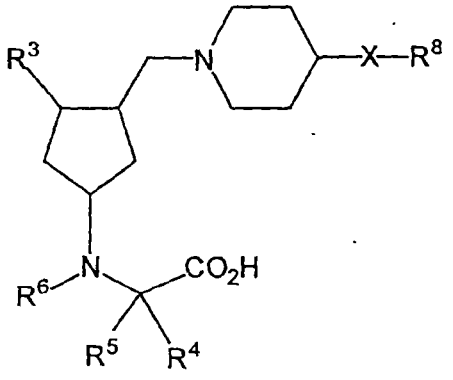
More preferred compounds of the present invention include those of formula Ic:



Ic

wherein R^1, R^3, R^4, R^5, R^6, R^7, R^8 and X are defined herein;
and pharmaceutically acceptable salts and individual diastereomers thereof.

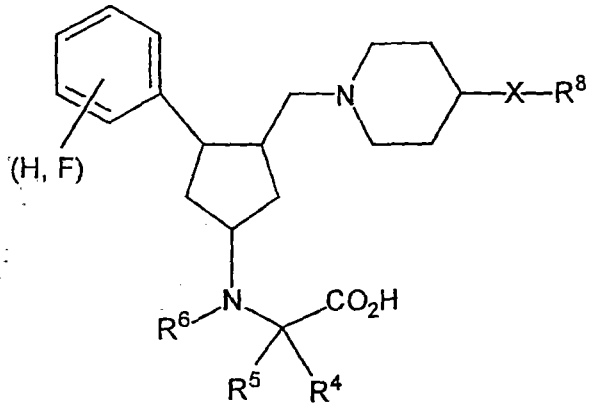
Highly preferred compounds of the present invention include those of formula Id:



Id

wherein R^3, R^4, R^5, R^6, R^8 and X are defined herein;
and pharmaceutically acceptable salts and individual diastereomers thereof.

More highly preferred compounds of the present invention include those of formula Ie:



Ie

wherein R^4, R^5, R^6, R^8 and X are defined herein;
and pharmaceutically acceptable salts and individual diastereomers thereof.

In the present invention it is preferred that R^1 is selected from:

(1) $-CO_2H$,

(2) $-P(O)(OH)_2$, and

(3) -tetrazolyl.

In the present invention it is more preferred that R^1 is selected from:

(1) $-CO_2H$, and

(2) -tetrazolyl.

In the present invention it is even more preferred that R^1 is $-CO_2H$.

In the present invention it is preferred that R^3 is selected from the group consisting of:

phenyl and thienyl,

which may be unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from:

(a) halo,

(b) trifluoromethyl,

(c) hydroxy,

(d) C_{1-3}alkyl, and

(e) $-O-C_{1-3}$alkyl.

In the present invention it is more preferred that R^3 is selected from the group consisting of:

phenyl and thienyl,

which may be unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from:

(a) fluoro,

(b) chloro,

(c) trifluoromethyl,

(d) hydroxy, and

(e) C_{1-3}alkyl.

In the present invention it is even more preferred that R^3 is selected from the group consisting of:

phenyl, which may be unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from:

(a) fluoro, and

(b) chloro; and

unsubstituted thienyl.

In the present invention it is still more preferred that R^3 is unsubstituted phenyl, (3-fluoro)phenyl or 3-thienyl.

In the present invention it is preferred that R^4 is hydrogen or C_{1-6} alkyl.

In the present invention it is more preferred that R^4 is hydrogen.

In the present invention it is preferred that R^5 is selected from: hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkyl-C_{3-8} cycloalkyl, and phenyl.

In the present invention it is more preferred that R^5 is selected from: hydrogen, methyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, -CH_2-cyclopropyl, -CH_2-cyclobutyl, and phenyl.

In the present invention it is still more preferred that R^5 is selected from: isopropyl, isobutyl, sec-butyl, and cyclohexyl.

In the present invention it is preferred that R^6 is selected from: hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkyl-C_{3-8} cycloalkyl, and phenyl.

In the present invention it is more preferred that R^6 is selected from: hydrogen, methyl, n-butyl, t-butyl, isobutyl, sec-butyl, -CH_2-cyclopropyl, -CH_2-cyclobutyl, and cyclohexyl.

In the present invention it is still more preferred that R^6 is selected from: hydrogen, methyl, -CH_2-cyclopropyl, -CH_2-cyclobutyl, and cyclohexyl.

In an alternate embodiment of the present invention it is preferred that R^5 and R^6 are joined together to form a C_{3-8} cycloalkyl ring.

In an alternate embodiment of the present invention it is more preferred that R^5 and R^6 are joined together to form a pyrrolidine ring.

542

In the present invention it is preferred that R^7 is hydrogen, fluoro, hydroxy or C_{1-6} alkyl.

In the present invention it is more preferred that R^7 is hydrogen or fluoro.

In the present invention it is even more preferred that R^7 is hydrogen.

In the present invention it is preferred that X is:
$-(C_{0-4}alkyl)-Y-(C_{0-4}alkyl)-$,

where the alkyl is unsubstituted or substituted with 1-4 substituents where the substituents are independently selected from:

(a) halo,
(b) hydroxy,
(c) $-O-C_{1-3}alkyl$, and
(d) trifluoromethyl,

and where Y is selected from:

a single bond, -O-, $-SO_2-$, $-NR^{10}-$, -S-, and -SO-,

and where R^{10} is independently selected from: hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, benzyl, phenyl, and C_{1-6} alkyl-C_{3-6} cycloalkyl, which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl.

In the present invention it is more preferred that X is:
$-(C_{0-2}alkyl)-Y-(C_{0-2}alkyl)-$,

where the alkyl is unsubstituted or substituted with 1-4 substituents where the substituents are independently selected from:

(a) halo,
(b) hydroxy,
(c) $-O-C_{1-3}alkyl$, and
(d) trifluoromethyl,

and where Y is selected from:

a single bond, -O-, $-SO_2-$, $-NR^{10}-$, -S-, and -SO-,

543

where R^{10} is independently selected from: hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, benzyl, phenyl, and C_{1-6} alkyl-C_{3-6} cycloalkyl,

which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl.

In the present invention it is even more preferred that X is selected from:

-(C_{0-2}alkyl)-Y-(C_{0-2}alkyl)-, where the alkyl is unsubstituted or substituted with fluoro,

and where Y is selected from:

a single bond, $-SO_2-$, -SO-, and $-NR^{10}-$,

where R^{10} is independently selected from: hydrogen, C_{1-3} alkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl.

In the present invention it is still more preferred that X is selected from:

(1) a single bond,
(2) $-CH_2CH_2-$,
(3) $-CH_2CH_2CH_2-$,
(4) $-CH_2CH_2-CF_2-$,
(5) $-CH_2CH_2-SO_2-$, and
(6) $-CH_2CH_2-SO-$.

In the present invention it is preferred that R^8 is selected from: phenyl, naphthyl, cyclohexyl, benzoimidazolyl, benzofurazanyl, imidazopyridyl, imidazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidyl, thiazolyl and tetrazolopyridyl,

which is unsubstituted or substituted with 1-7 substituents where the substituents are independently selected from:

(a) halo,
(b) cyano,
(c) hydroxy,

(d) C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 of R^{13} where R^{13} is independently selected from: halo, cyano, hydroxy, C_{1-6}alkoxy, $-CO_2H$, $-CO_2(C_{1-6}$ alkyl), trifluoromethyl, and $-NR^9R^{10}$, wherein R^9 and R^{10} are independently selected from: hydrogen, C_{1-6} alkyl, C_{5-6} cycloalkyl, benzyl or phenyl, which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl;

(e) $-O-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-5 of R^{13},

(f) $-CF_3$,

(g) $-CHF_2$,

(h) $-CH_2F$,

(i) $-NO_2$,

(j) C_{0-6}alkyl-phenyl or C_{0-6}alkyl-heterocycle, which is unsubstituted or substituted with 1-7 substituents where the substituents are independently selected from:

(i) halo,
(ii) hydroxy,
(iii) C_{1-6}alkyl,
(iv) $-O-C_{1-6}$alkyl,
(v) $-CF_3$,
(vi) $-OCF_3$,
(vii) $-NO_2$,
(viii) -CN,
(ix) $-SO_2-C_{1-6}$alkyl,
(x) $-CO_2R^9$,
(xi) $-NR^9R^{10}$,
(xii) $-CONR^9R^{10}$,
(xiii) $-SO_2-NR^9R^{10}$, and
(xiv) $-NR^9-SO_2-R^{10}$;

(k) $-CO_2R^9$,

(l) tetrazolyl,

(m) $-NR^9R^{10}$,

545

(n) $-NR^9-COR^{10}$,
(o) $-NR^9-CO_2R^{10}$,
(p) $-CO-NR^9R^{10}$,
(q) $-OCO-NR^9R^{10}$,
(r) $-NR^9CO-NR^9R^{10}$,
(s) $-S(O)_m-R^9$, wherein m is an integer selected from 0, 1 and 2,
(t) $-S(O)_2-NR^9R^{10}$,
(u) $-NR^9S(O)_2-R^{10}$, and
(v) $-NR^9S(O)_2-NR^9R^{10}$.

In the present invention it is more preferred that R^8 is selected from: phenyl, imidazopyridyl, imidazolyl, oxazolyl, pyrazolyl, pyridyl, and thiazolyl;

which is unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from:

(a) halo,
(b) cyano,
(c) $-NO_2$,
(d) $-CF_3$,
(e) $-CHF_2$,
(f) $-CH_2F$,
(h) C_{1-6}alkyl,
(i) C_{1-3}alkyl-phenyl or C_{1-3}alkyl-pyridyl, which is unsubstituted or substituted with 1-4 substituents where the substituents are independently selected from:
  (i) halo,
  (ii) C_{1-6}alkyl,
  (iii) $-O-C_{1-6}$alkyl,
  (iv) $-CF_3$,
  (vi) $-OCF_3$,
  (vii) -CN, and
(j) $-O-C_{1-6}$alkyl.

In the present invention it is even more preferred that R^8 is selected from: imidazolyl, oxazolyl, pyrazolyl, and thiazolyl;

which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from:

(a) fluoro,
(b) cyano,
(c) C_{1-3}alkyl,
(d) $-CH_2$-phenyl, which is unsubstituted or substituted with 1-4 substituents where the substituents are independently selected from:
  (i) fluoro,
  (ii) chloro,
  (iii) $-O-CH_3$,
  (iv) $-CF_3$,
  (v) -CN, and
(e) $-CF_3$.

In the present invention it is still more preferred that R^8 is selected from: 5-(3-benzyl)pyrazolyl, 5-(1-methyl-3-benzyl)pyrazolyl, 5-(1-ethyl-3-benzyl)pyrazolyl, 5-(2-benyl)thiazolyl, 5-(2-benyl-4-methyl)thiazolyl, and 5-(2-benyl-4-ethyl)thiazolyl).

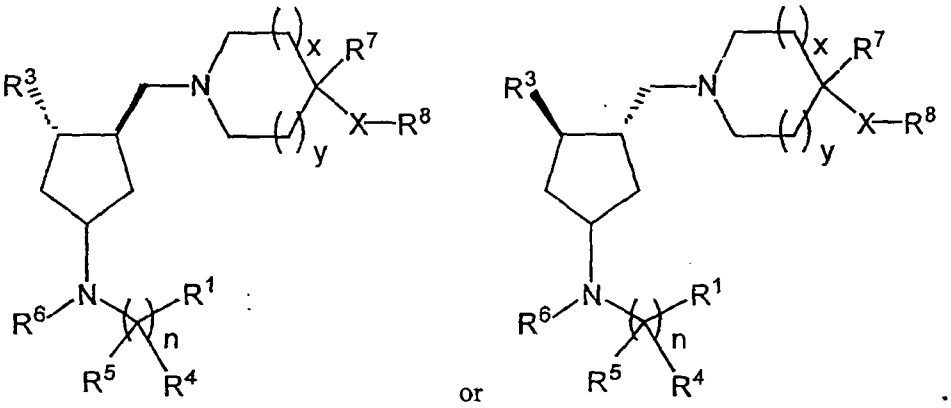
In the present invention it is preferred that n is an integer selected from 1, 2 and 3.

In the present invention it is more preferred that n is an integer which is 1.

In the present invention it is preferred that x is an integer which is 1 and y is an integer which is 1.

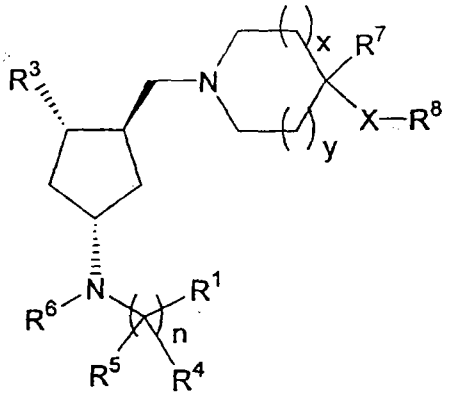
The compounds of the instant invention have at least two asymmetric centers at the ring junction of the substitutents bearing the piperidine and R^3. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified

compounds are included within the ambit of this invention. The relative configurations of the more preferred compounds of this invention are of the trans orientation, i.e. as depicted:

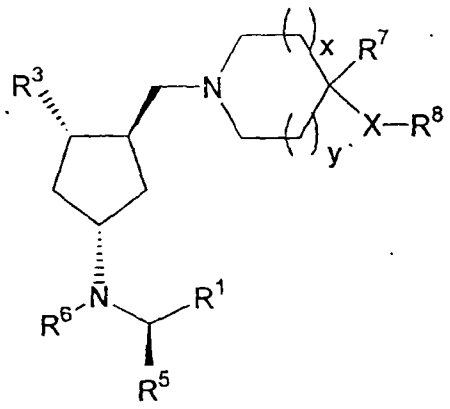


or

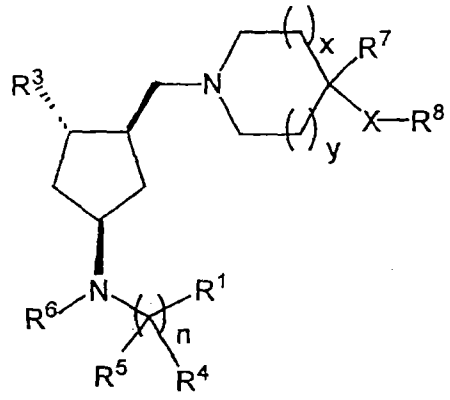
The relative configurations of the even more preferred compounds of this invention wherein R^6 is hydrogen, methyl or wherein R^5 and R^6 form a pyrrolidine ring with respect to the configuration of the nitrogen substituent on the cyclopentane ring is cis to the orientation of R^3 as depicted:



The relative configurations of the most preferred compounds of this invention wherein R^6 is hydrogen or methyl with respect to the configuration of the nitrogen substituent on the cyclopentane ring is is cis to the orientation of R^3 and with the (R)-stereochemistry of the nitrogen side chain of the orientation as depicted:



The relative configurations of the even more preferred compounds of this invention wherein R^6 is other than hydrogen or methyl with respect to the configuration of the nitrogen substituent on the cyclopentane ring is 1,3-cis of the orientation as depicted:

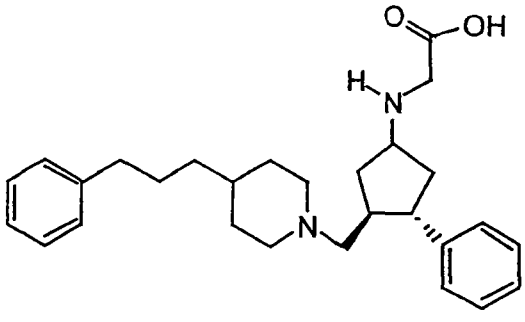


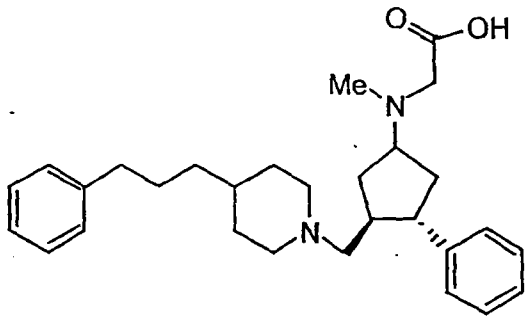
The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

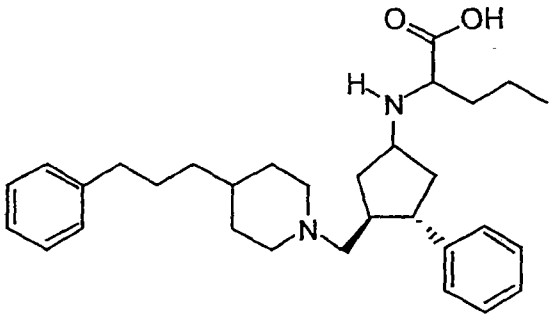
As appreciated by those of skill in the art, halo or halogen as used herein are intended to include chloro, fluoro, bromo and iodo. Similarly, C_{1-8}, as in C_{1-8}alkyl is defined to identify the group as having 1, 2, 3, 4, 5, 6, 7 or 8 carbons in a

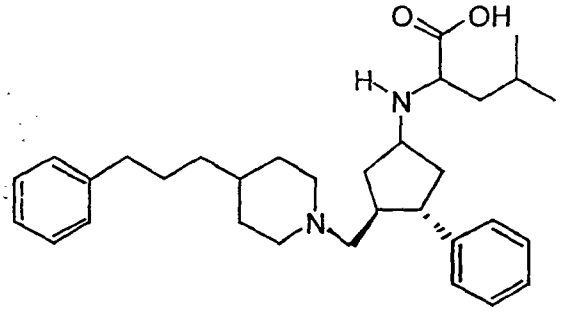
linear or branched arrangement, such that C_{1-8}alkyl specifically includes methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl and octyl. Likewise, C_0, as in C_0alkyl is defined to identify the presence of a direct covalent bond. The term "heterocycle" as used herein is intended to include the following groups: benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof. Exemplifying the invention is the use of the compounds disclosed in the Examples and herein.

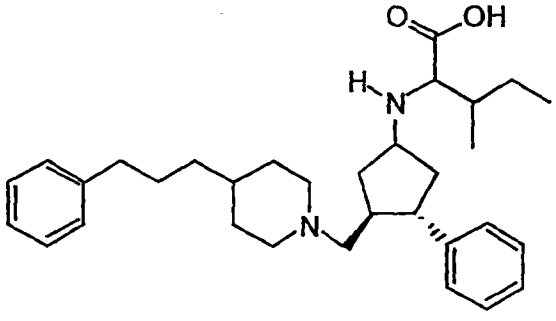
Specific compounds within the present invention include a compound which selected from the group consisting of:





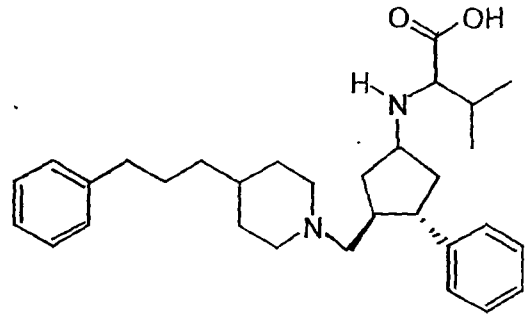


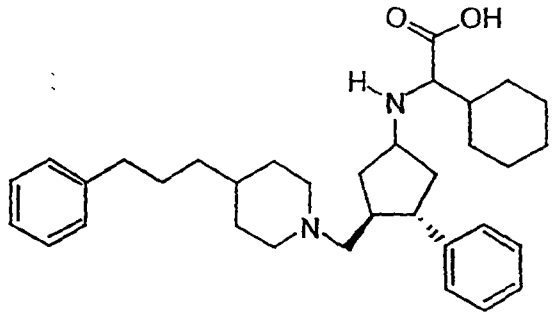


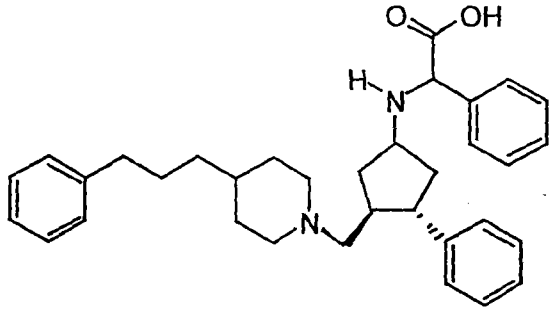


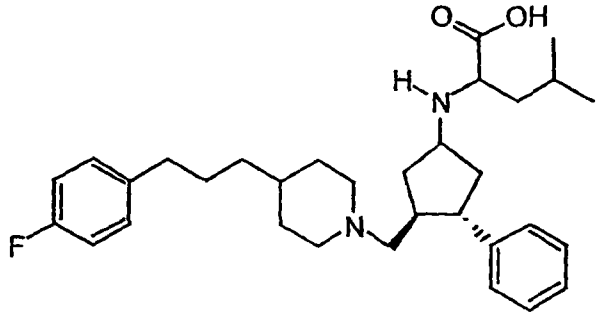
EP 1 430 005 B1

551





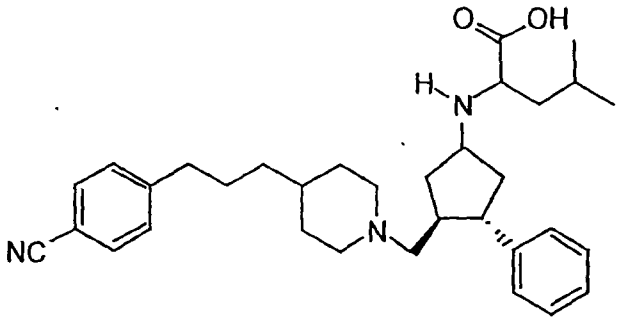


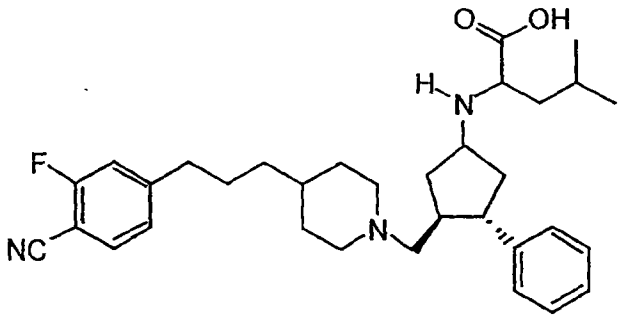


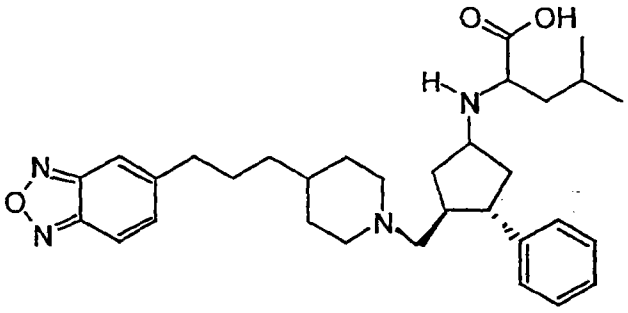
504090805 - 05410

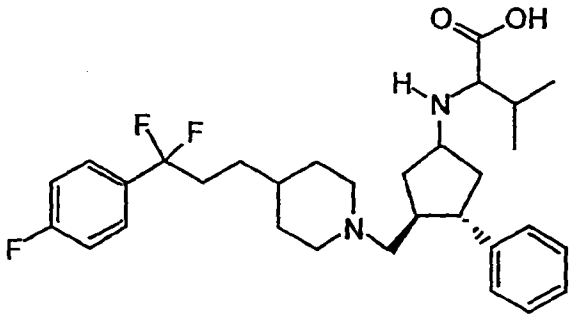
5

552



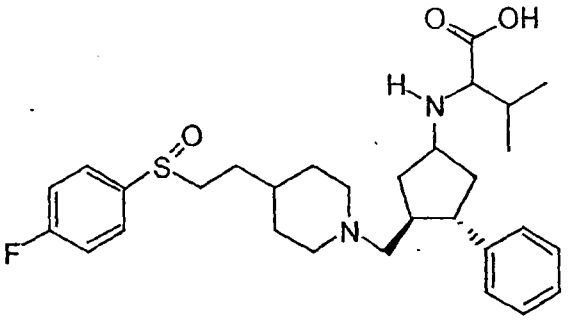


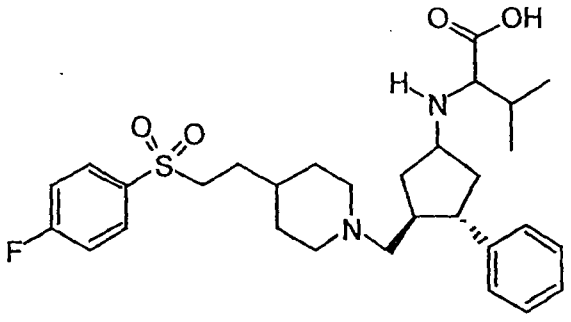


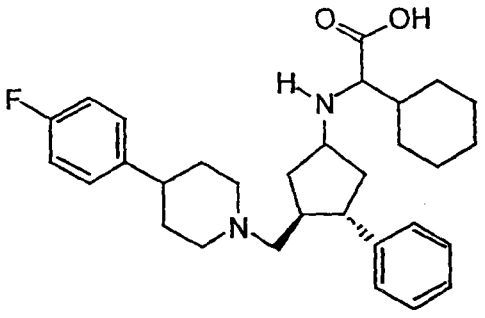


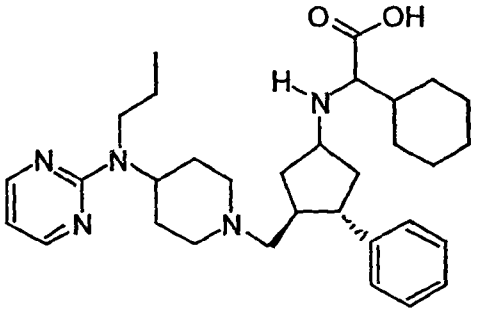
5

553

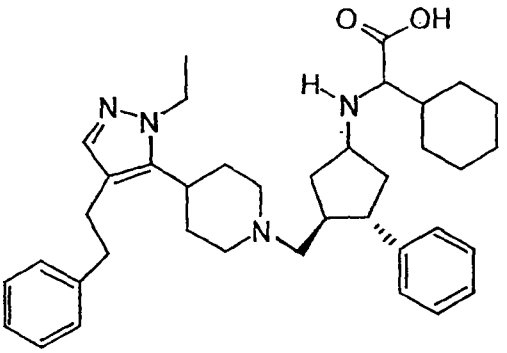


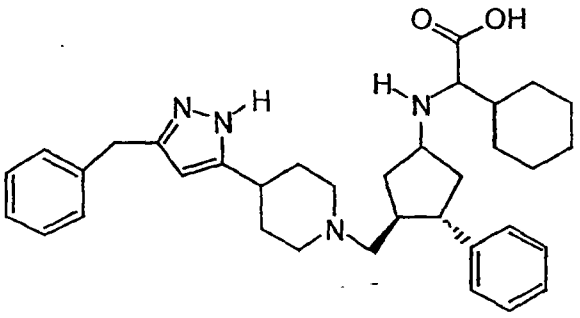


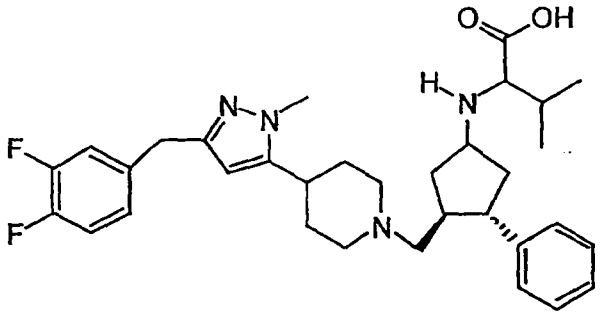


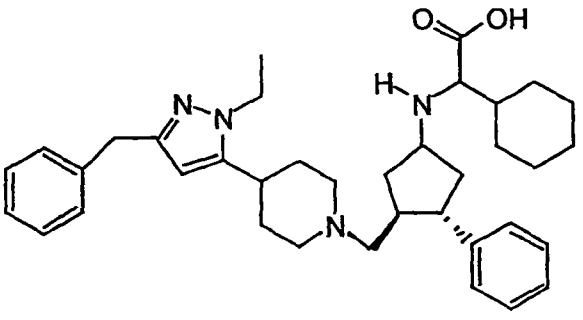


EP1809609B1



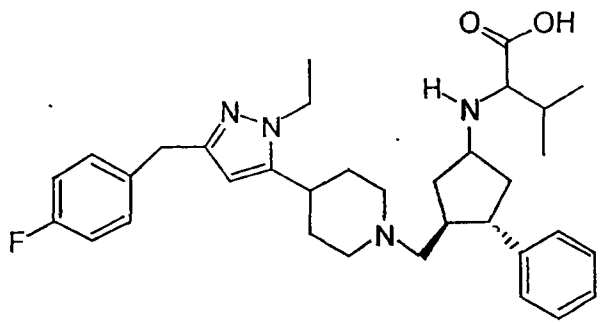


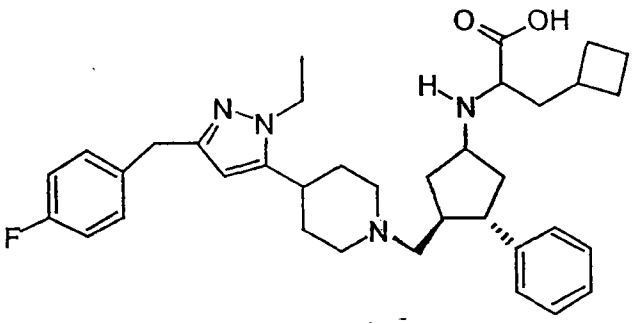


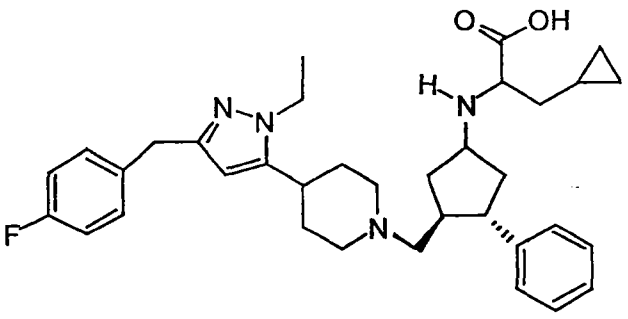


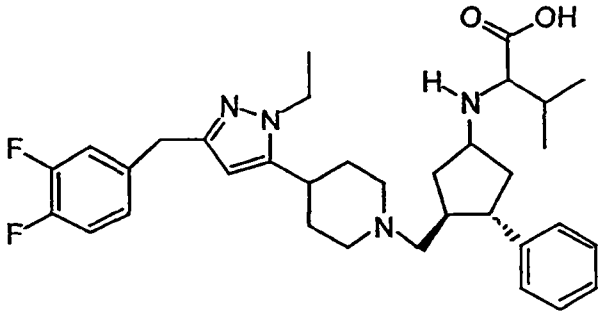
EP 2 050 744 A1

5



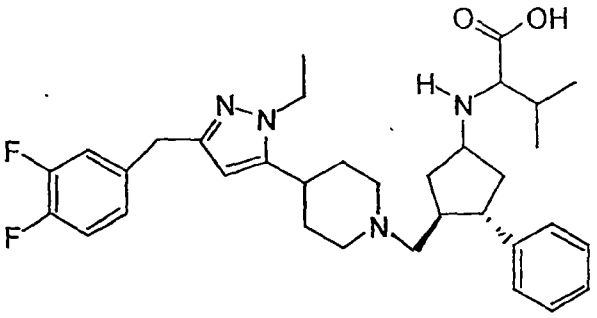


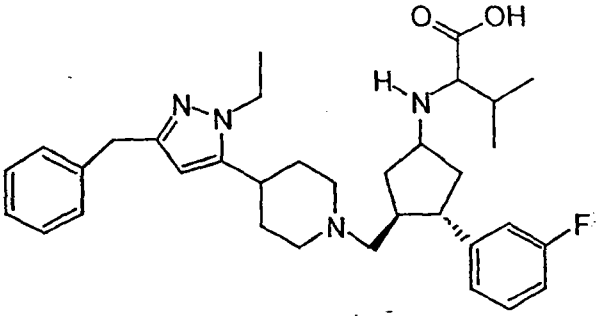


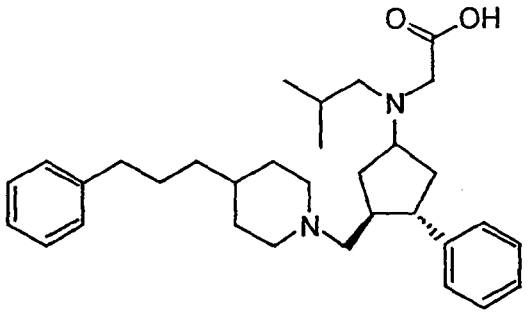


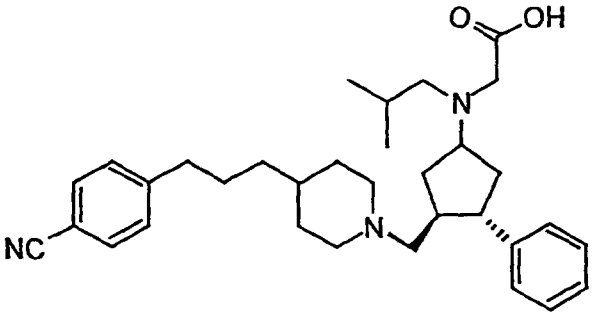
CH-PS-20461PV

556





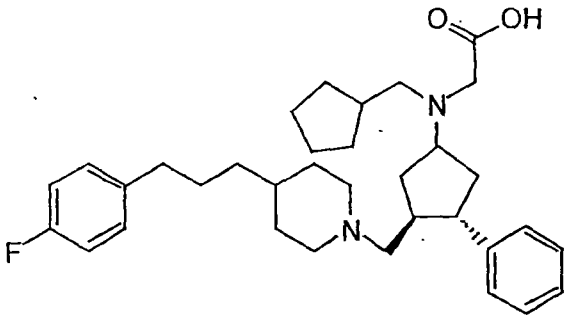


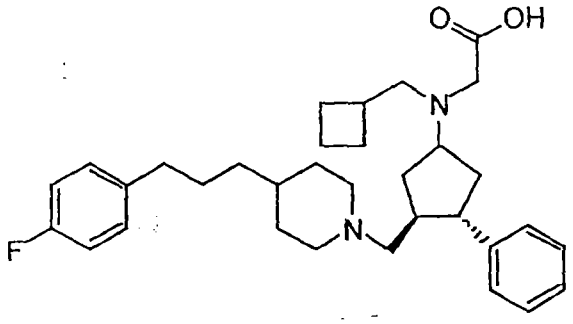


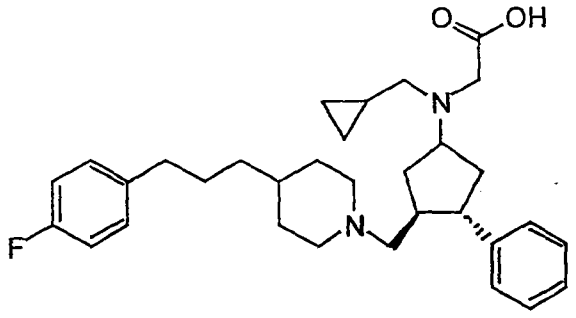
WO 2005/051890 PCT/US2004/039450

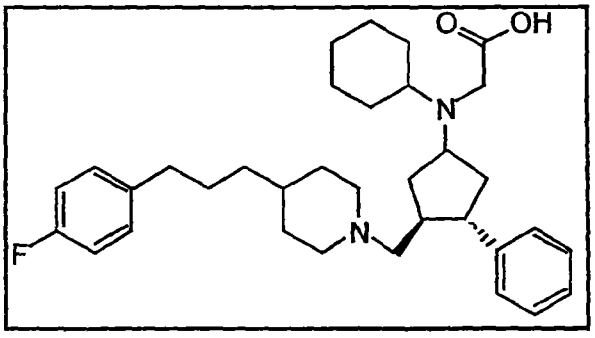
5

557

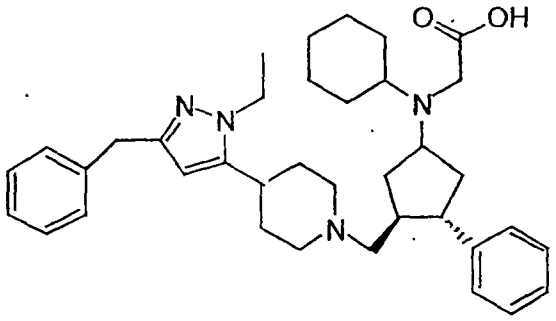


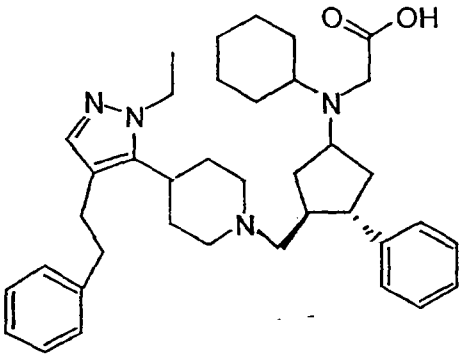


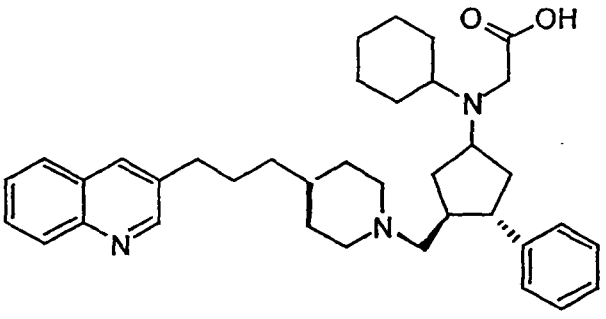


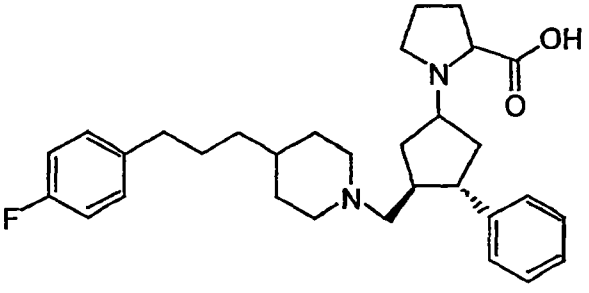


558

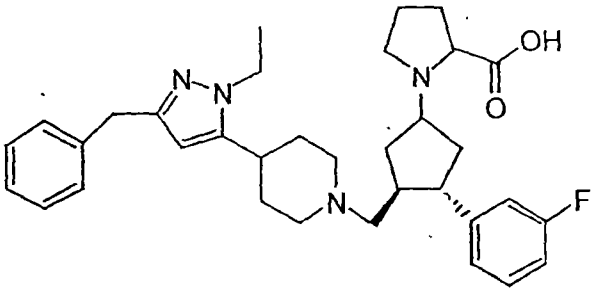


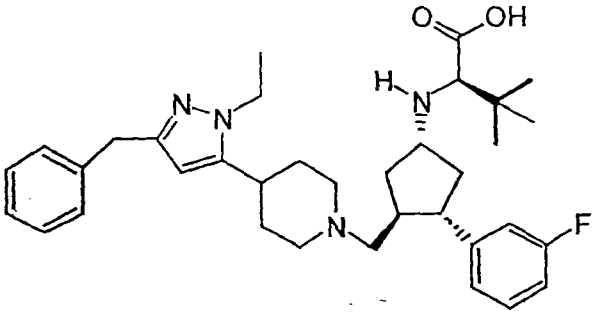


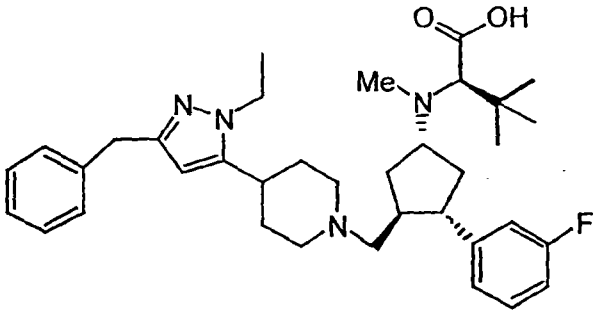


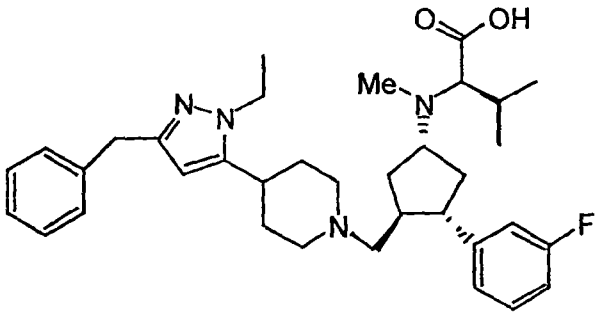


604360605 - 05.12.05

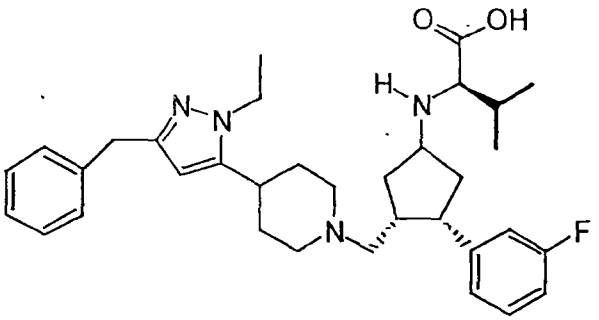


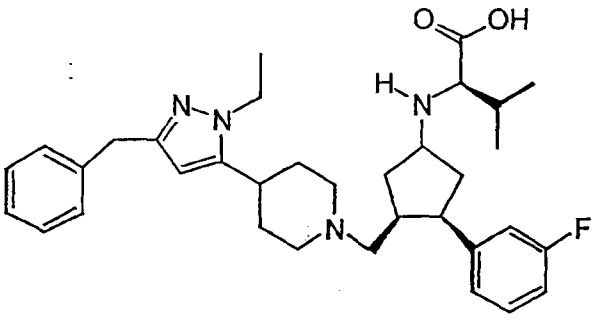


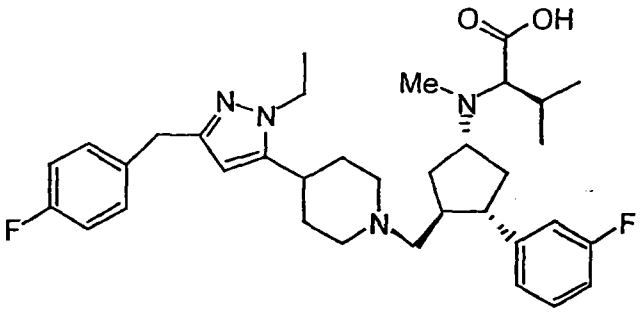


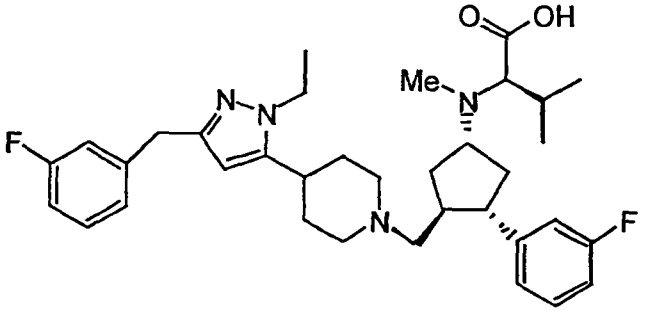


560



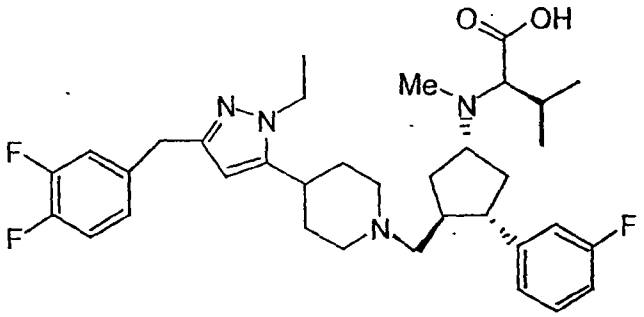


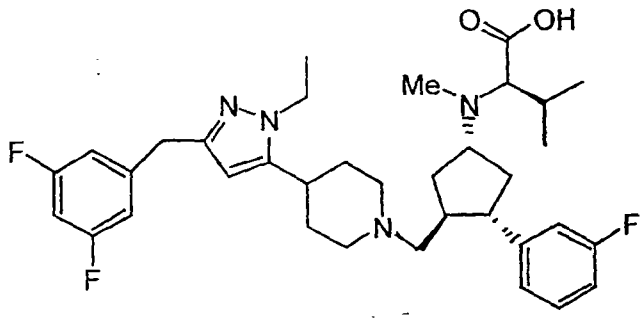


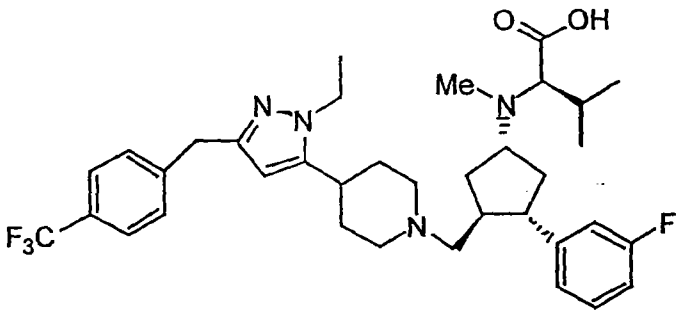


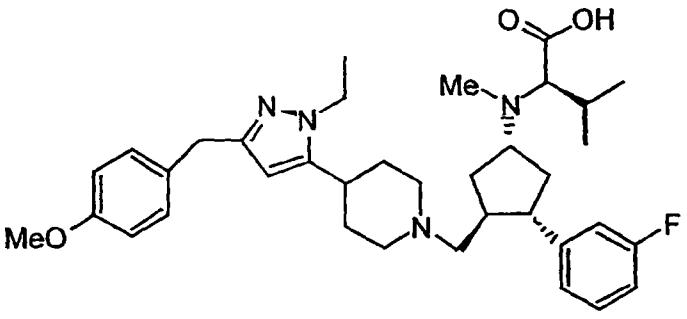
EP 1 554 259 B1

303
561



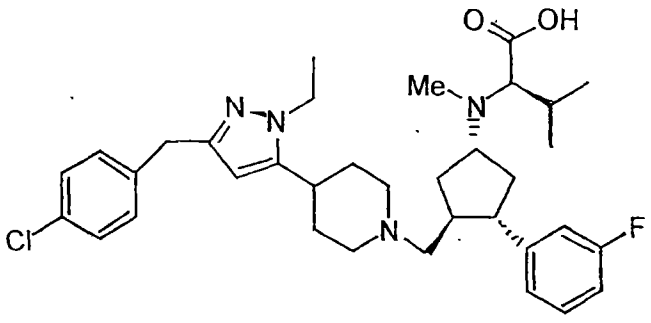


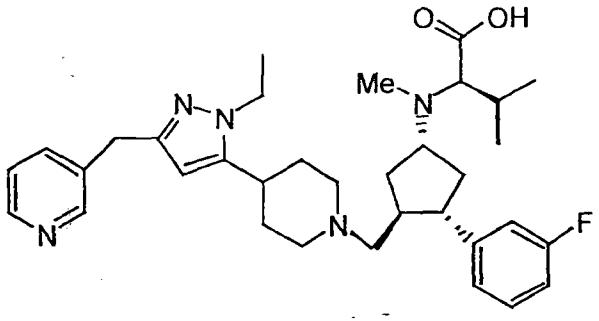


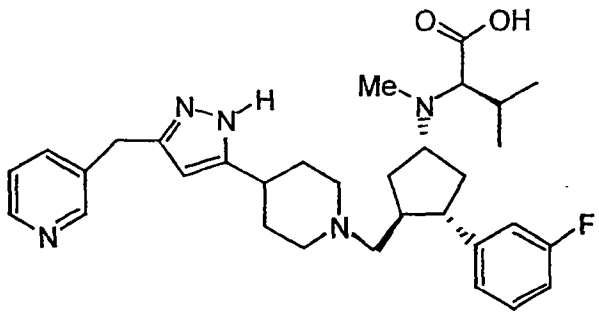


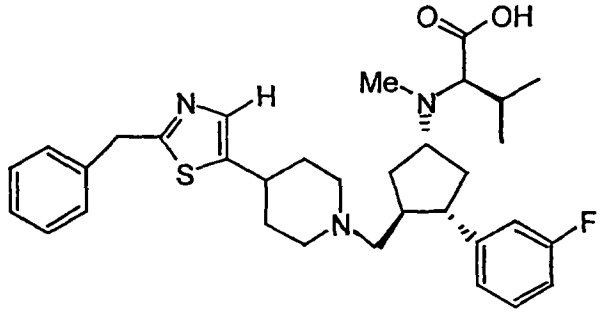
EP 1 604 980 A1

562



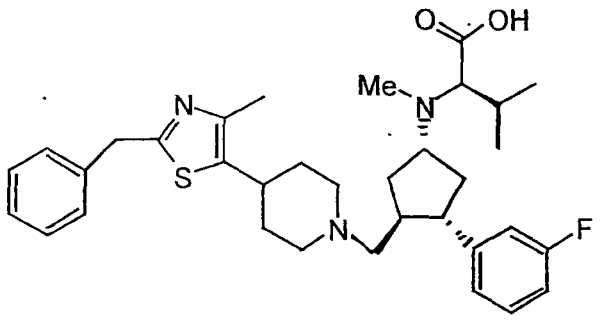


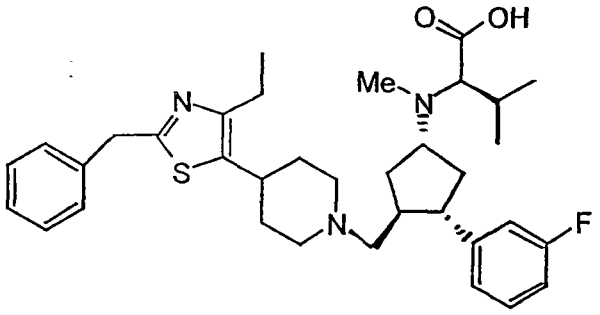


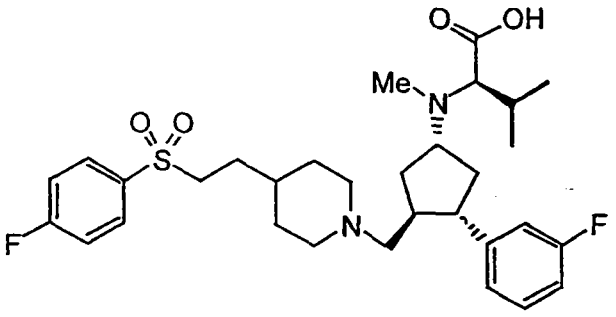


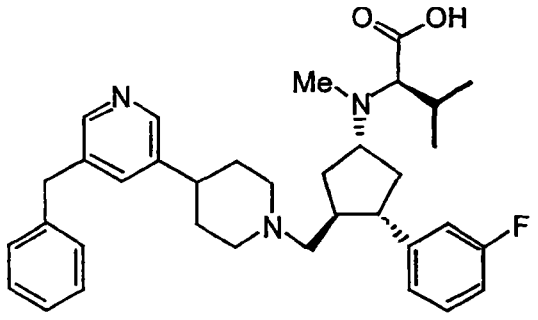
05-30-2006 05:54:30

563

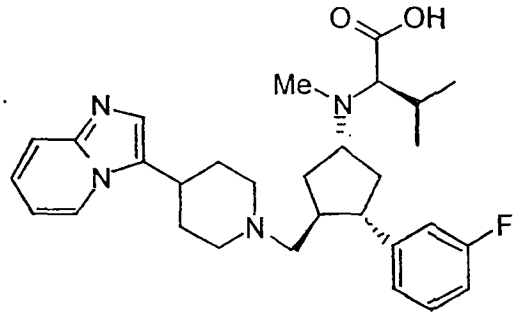








09475005.050605



and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

The subject compounds are useful in a method of modulating chemokine receptor activity in a patient in need of such modulation comprising the administration of an effective amount of the compound.

The present invention is directed to the use of the foregoing compounds as modulators of chemokine receptor activity. In particular, these compounds are useful as modulators of the chemokine receptors, including CCR-5 and/or CCR-3.

The utility of the compounds in accordance with the present invention as modulators of chemokine receptor activity may be demonstrated by methodology known in the art, such as the assay for chemokine binding as disclosed by Van Riper, et al., J. Exp. Med., 177, 851-856 (1993) which may be readily adapted for measurement of CCR-5 binding, and the assay for CCR-3 binding as disclosed by Daugherty, et al., J. Exp. Med., 183, 2349-2354 (1996). Cell lines for expressing the receptor of interest include those naturally expressing the receptor, such as EOL-3 or THP-1, or a cell engineered to express a recombinant receptor, such as CHO, RBL-2H3, HEK-293. For example, a CCR3 transfected AML14.3D10 cell line has been placed on restricted deposit with American Type Culture Collection in Rockville, Maryland as ATCC No. CRL-12079, on April 5, 1996. The utility of the compounds in accordance with the present invention as inhibitors of the spread of HIV infection in cells may be demonstrated by methodology known in the art, such as the HIV quantitation assay disclosed by Nunberg, et al., J. Virology, 65 (9), 4887-4892 (1991).

In particular, the compounds of the following examples had activity in binding to the CCR-5 or the CCR-3 receptor in the aforementioned assays, generally with an IC_{50} of less than about 1 μM. Such a result is indicative of the intrinsic activity of the compounds in use as modulators of chemokine receptor activity.

Mammalian chemokine receptors provide a target for interfering with or promoting eosinophil and/or lymphocyte function in a mammal, such as a human. Compounds which inhibit or promote chemokine receptor function, are particularly useful for modulating eosinophil and/or lymphocyte function for therapeutic purposes. Accordingly, the present invention is directed to compounds which are useful in the prevention and/or treatment of a wide variety of inflammatory and immunoregulatory disorders and diseases, allergic diseases, atopic conditions including allergic rhinitis, dermatitis, conjunctivitis, and asthma, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis.

For example, an instant compound which inhibits one or more functions of a mammalian chemokine receptor (e.g., a human chemokine receptor) may be administered to inhibit (i.e., reduce or prevent) inflammation. As a result, one or more inflammatory processes, such as leukocyte emigration, chemotaxis, exocytosis (e.g., of enzymes, histamine) or inflammatory mediator release, is inhibited. For example, eosinophilic infiltration to inflammatory sites (e.g., in asthma) can be inhibited according to the present method.

Similarly, an instant compound which promotes one or more functions of a mammalian chemokine receptor (e.g., a human chemokine) is administered to stimulate (induce or enhance) an inflammatory response, such as leukocyte emigration, chemotaxis, exocytosis (e.g., of enzymes, histamine) or inflammatory mediator release, resulting in the beneficial stimulation of inflammatory processes. For example, eosinophils can be recruited to combat parasitic infections.

In addition to primates, such as humans, a variety of other mammals can be treated according to the method of the present invention. For instance, mammals including, but not limited to, cows, sheep, goats, horses, dogs, cats, guinea pigs, rats or other bovine, ovine, equine, canine, feline, rodent or murine species can be treated. However, the method can also be practiced in other species, such as avian species (e.g., chickens).

Diseases and conditions associated with inflammation and infection can be treated using the method of the present invention. In a preferred embodiment, the disease or condition is one in which the actions of eosinophils and/or lymphocytes are to be inhibited or promoted, in order to modulate the inflammatory response.

Diseases or conditions of humans or other species which can be treated with inhibitors of chemokine receptor function, include, but are not limited to: inflammatory or allergic diseases and conditions, including respiratory allergic

diseases such as asthma, particularly bronchial asthma, allergic rhinitis, hypersensitivity lung diseases, hypersensitivity pneumonitis, eosinophilic pneumonias (e.g., Loeffler's syndrome, chronic eosinophilic pneumonia), delayed-type hypersentitivity, interstitial lung diseases (ILD) (e.g., idiopathic pulmonary fibrosis, or ILD associated with rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, systemic sclerosis, Sjogren's syndrome, polymyositis or dermatomyositis); systemic anaphylaxis or hypersensitivity responses, drug allergies (e.g., to penicillin, cephalosporins), insect sting allergies; autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus, myasthenia gravis, juvenile onset diabetes; glomerulonephritis, autoimmune thyroiditis, Behcet's disease; graft rejection (e.g., in transplantation), including allograft rejection or graft-versus-host disease; inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis; spondyloarthropathies; scleroderma; psoriasis (including T-cell mediated psoriasis) and inflammatory dermatoses such an dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria; vasculitis (e.g., necrotizing, cutaneous, and hypersensitivity vasculitis); eosinphilic myositis, eosinophilic fasciitis; cancers with leukocyte infiltration of the skin or organs. Other diseases or conditions in which undesirable inflammatory responses are to be inhibited can be treated, including, but not limited to, reperfusion injury, atherosclerosis, certain hematologic malignancies, cytokine-induced toxicity (e.g., septic shock, endotoxic shock), polymyositis, dermatomyositis.

Diseases or conditions of humans or other species which can be treated with promoters of chemokine receptor function, include, but are not limited to: immunosuppression, such as that in individuals with immunodeficiency syndromes such as AIDS, individuals undergoing radiation therapy, chemotherapy, therapy for autoimmune disease or other drug therapy (e.g., corticosteroid therapy), which causes immunosuppression; immunosuppression due congenital deficiency in receptor function or other causes; and infectious diseases, such as parasitic diseases, including, but not limited to helminth infections, such as nematodes (round worms); (Trichuriasis, Enterobiasis, Ascariasis, Hookworm, Strongyloidiasis, Trichinosis, filariasis); trematodes (flukes) (Schistosomiasis, Clonorchiasis), cestodes (tape worms) (Echinococcosis, Taeniasis saginata, Cysticercosis); visceral worms, visceral larva migrans (e.g., Toxocara), eosinophilic gastroenteritis (e.g., Anisaki spp., *Phocanema ssp.)*, cutaneous larva migrans (*Ancylostona braziliense, Ancylostoma caninum*).

The compounds of the present invention are accordingly useful in the prevention and treatment of a wide variety of inflammatory and immunoregulatory disorders and diseases, allergic conditions, atopic conditions, as well as autoimmune pathologies.

In another aspect, the instant invention may be used to evaluate putative specific agonists or antagonists of chemokine receptors, including CCR-5 and/or CCR-3. Accordingly, the present invention is directed to the use of these compounds in the preparation and execution of screening assays for compounds which modulate the activity of chemokine receptors. For example, the compounds of this invention are useful for isolating receptor mutants, which are excellent screening tools for more potent compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other compounds to chemokine receptors, e.g., by competitive inhibition. The compounds of the instant invention are also useful for the evaluation of putative specific modulators of the chemokine receptors, including CCR-5 and/or CCR-3. As appreciated in the art, thorough evaluation of specific agonists and antagonists of the above chemokine receptors has been hampered by the lack of availability of non-peptidyl (metabolically resistant) compounds with high binding affinity for these receptors. Thus the compounds of this invention are commercial products to be sold for these purposes.

The present invention is further directed to a method for the manufacture of a medicament for modulating chemokine receptor activity in humans and animals comprising combining a compound of the present invention with a pharmaceutical carrier or diluent.

The present invention is further directed to the use of these compounds in the prevention or treatment of infection by a retrovirus, in particular, the human immunodeficiency virus (HIV) and the treatment of, and delaying of the onset of consequent pathological conditions such as AIDS. Treating AIDS or preventing or treating infection by HIV is defined as including, but not limited to, treating a wide range of states of HIV infection: AIDS, ARC (AIDS related complex), both symptomatic and asymptomatic, and actual or potential exposure to HIV. For example, the compounds of this invention are useful in treating infection by HIV after suspected past exposure to HIV by, e.g., blood transfusion, organ transplant, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

In a preferred aspect of the present invention, a subject compound may be used in a method of inhibiting the binding of a chemokine to a chemokine receptor, such as CCR-5 or CCR-3, of a target cell, which comprises contacting the target cell with an amount of the compound which is effective at inhibiting the binding of the chemokine to the chemokine receptor.

The subject treated in the methods above is a mammal, preferably a human being, male or female, in whom modulation of chemokine receptor activity is desired. "Modulation" as used herein is intended to encompass antagonism, agonism, partial antagonism, inverse agonism and/or partial agonism. In a preferred aspect of the present invention, modulation refers to antagonism of chemokine receptor activity. The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention to the individual in need of treatment.

Combined therapy to modulate chemokine receptor activity and thereby prevent and treat inflammatory and immunoregulatory disorders and diseases, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis, and those pathologies noted above is illustrated by the combination of the compounds of this invention and other compounds which are known for such utilities.

For example, in the treatment or prevention of inflammation, the present compounds may be used in conjunction with an antiinflammatory or analgesic agent such as an opiate agonist, a lipoxygenase inhibitor, such as an inhibitor of 5-lipoxygenase, a cyclooxygenase inhibitor, such as a cyclooxygenase-2 inhibitor, an interleukin inhibitor, such as an interleukin-1 inhibitor, an NMDA antagonist, an inhibitor of nitric oxide or an inhibitor of the synthesis of nitric oxide, a non-steroidal

antiinflammatory agent, or a cytokine-suppressing antiinflammatory agent, for example with a compound such as acetaminophen, asprin, codiene, fentanyl, ibuprofen, indomethacin, ketorolac, morphine, naproxen, phenacetin, piroxicam, a steroidal analgesic, sufentanyl, sunlindac, tenidap, and the like. Similarly, the instant compounds may be administered with a pain reliever; a potentiator such as caffeine, an H2-antagonist, simethicone, aluminum or magnesium hydroxide; a decongestant such as phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxy-ephedrine; an antiitussive such as codeine, hydrocodone, caramiphen, carbetapentane, or dextramethorphan; a diuretic; and a sedating or non-sedating antihistamine. Likewise, compounds of the present invention may be used in combination with other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which compounds of the pressent invention are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention. Examples of other active ingredients that may be combined with a compound of the present invention, either administered separately or in the same pharmaceutical compositions, include, but are not limited to: (a) VLA-4 antagonists such as those described in US 5,510,332, WO95/15973, WO96/01644, WO96/06108, WO96/20216, WO96/22966, WO96/31206, WO96/40781, WO97/03094, WO97/02289, WO 98/42656, WO98/53814, WO98/53817, WO98/53818, WO98/54207, and WO98/58902; (b) steroids such as beclomethasone, methylprednisolone, betamethasone, prednisone, dexamethasone, and hydrocortisone; (c) immunosuppressants such as cyclosporin, tacrolimus, rapamycin and other FK-506 type immunosuppressants; (d) antihistamines (H1-histamine antagonists) such as bromopheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripelennamine, hydroxyzine, methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, antazoline, pheniramine pyrilamine, astemizole, terfenadine, loratadine, cetirizine, fexofenadine, descarboethoxyloratadine, and the like; (e) non-steroidal anti-asthmatics such as β2-

570

agonists (terbutaline, metaproterenol, fenoterol, isoetharine, albuterol, bitolterol, and pirbuterol), theophylline, cromolyn sodium, atropine, ipratropium bromide, leukotriene antagonists (zafirlukast, montelukast, pranlukast, iralukast, pobilukast, SKB-106,203), leukotriene biosynthesis inhibitors (zileuton, BAY-1005); (f) non-steroidal antiinflammatory agents (NSAIDs) such as propionic acid derivatives (alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, pirprofen, pranoprofen, suprofen, tiaprofenic acid, and tioxaprofen), acetic acid derivatives (indomethacin, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin, and zomepirac), fenamic acid derivatives (flufenamic acid, meclofenamic acid, mefenamic acid, niflumic acid and tolfenamic acid), biphenylcarboxylic acid derivatives (diflunisal and flufenisal), oxicams (isoxicam, piroxicam, sudoxicam and tenoxican), salicylates (acetyl salicylic acid, sulfasalazine) and the pyrazolones (apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone, phenylbutazone); (g) cyclooxygenase-2 (COX-2) inhibitors; (h) inhibitors of phosphodiesterase type IV (PDE-IV); (i) other antagonists of the chemokine receptors, especially CCR-1, CCR-2, CCR-3 and CCR-5; (j) cholesterol lowering agents such as HMG-CoA reductase inhibitors (lovastatin, simvastatin and pravastatin, fluvastatin, atorvastatin, and other statins), sequestrants (cholestyramine and colestipol), nicotinic acid, fenofibric acid derivatives (gemfibrozil, clofibrat, fenofibrate and benzafibrate), and probucol; (k) anti-diabetic agents such as insulin, sulfonylureas, biguanides (metformin), α-glucosidase inhibitors (acarbose) and glitazones (troglitazone and pioglitazone); (l) preparations of interferon beta (interferon beta-1α, interferon beta-1β); (m) other compounds such as 5-aminosalicylic acid and prodrugs thereof, antimetabolites such as azathioprine and 6-mercaptopurine, and cytotoxic cancer chemotherapeutic agents. The weight ratio of the compound of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with an NSAID the weight ratio of the compound of the present invention to the NSAID will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be

within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

The present invention is further directed to combinations of the present compounds with one or more agents useful in the prevention or treatment of AIDS. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of the AIDS antivirals, immunomodulators, anti-infectives, or vaccines known to those of ordinary skill in the art.

ANTIVIRALS

Drug Name	Manufacturer	Indication
097	Hoechst/Bayer	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
141 W94	Glaxo Wellcome	HIV infection, AIDS, ARC (protease inhibitor)
1592U89	Glaxo Wellcome	HIV infection, AIDS, ARC
Acemannan	Carrington Labs (Irving, TX)	ARC
Acyclovir	Burroughs Wellcome	HIV infection, AIDS, ARC, in combination with AZT
AD-439	Tanox Biosystems	HIV infection, AIDS, ARC
AD-519	Tanox Biosystems	HIV infection, AIDS, ARC
Adefovir dipivoxil	Gilead Sciences	HIV infection

AL-721	Ethigen (Los Angeles, CA)	ARC, PGL HIV positive, AIDS
Alpha Interferon	Glaxo Wellcome	Kaposi's sarcoma, HIV in combination w/Retrovir
Ansamycin LM 427	Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT)	ARC
Antibody which neutralizes pH labile alpha aberrant Interferon	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC
AR177	Aronex Pharm	HIV infection, AIDS, ARC
beta-fluoro-ddA	Nat'l Cancer Institute	AIDS-associated diseases
(-) 6-Chloro-4(S)-cyclopropylethynyl-4(S)-trifluoro-methyl-1,4-dihydro-2H-3,1-benzoxazin-2-one	Merck	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
CI-1012	Warner-Lambert	HIV-1 infection
Cidofovir	Gilead Science	CMV retinitis, herpes, papillomavirus
Curdlan sulfate	AJI Pharma USA	HIV infection
Cytomegalovirus immune globin	MedImmune	CMV retinitis
Cytovene Ganciclovir	Syntex	sight threatening CMV peripheral CMV retinitis
Delaviridine	Pharmacia-Upjohn	HIV infection, AIDS, ARC (protease inhibitor)

Dextran Sulfate	Ueno Fine Chem. Ind. Ltd. (Osaka, Japan)	AIDS, ARC, HIV positive asymptomatic
ddC Dideoxycytidine	Hoffman-La Roche	HIV infection, AIDS, ARC
ddI Dideoxyinosine	Bristol-Myers Squibb	HIV infection, AIDS, ARC; combination with AZT/d4T
DMP-450	AVID (Camden, NJ)	HIV infection, AIDS, ARC (protease inhibitor)
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
Efavirenz, DMP-266	DuPont-Merck Pharmaceuticals	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
Famciclovir	Smith Kline	herpes zoster, herpes simplex
FTC	Emory University	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
GS 840	Gilead	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
GW 141	Glaxo Welcome	HIV infection, AIDS, ARC (protease inhibitor)
GW 1592	Glaxo Welcome	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)

0043666 - 051409

HBY097	Hoechst Marion Roussel	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
Hypericin	VIMRx Pharm.	HIV infection, AIDS, ARC
Recombinant Human Interferon Beta	Triton Biosciences (Almeda, CA)	AIDS, Kaposi's sarcoma, ARC
Interferon alfa-n3	Interferon Sciences	ARC, AIDS
Indinavir	Merck	HIV infection, AIDS, ARC, asymptomatic HIV positive, also in combination with AZT/ddI/ddC
ISIS 2922	ISIS Pharmaceuticals	CMV retinitis
KNI-272	Nat'l Cancer Institute	HIV-assoc. diseases
Lamivudine, 3TC	Glaxo Wellcome	HIV infection, AIDS, ARC (reverse transcriptase inhibitor); also with AZT
Lobucavir	Bristol-Myers Squibb	CMV infection
Nelfinavir	Agouron Pharmaceuticals	HIV infection, AIDS, ARC (protease inhibitor)
Nevirapine	Boeheringer Ingleheim	HIV infection, AIDS, ARC (protease inhibitor)
Novapren	Novaferon Labs, Inc. (Akron, OH)	HIV inhibitor
Peptide T Octapeptide Sequence	Peninsula Labs (Belmont, CA)	AIDS

575

Trisodium Phosphonoformate	Astra Pharm. Products, Inc	CMV retinitis, HIV infection, other CMV infections
PNU-140690	Pharmacia Upjohn	HIV infection, AIDS, ARC (protease inhibitor)
Probucol	Vyrex	HIV infection, AIDS
RBC-CD4	Sheffield Med. Tech (Houston TX)	HIV infection, AIDS, ARC
Ritonavir	Abbott	HIV infection, AIDS, ARC (protease inhibitor)
Saquinavir	Hoffmann-LaRoche	HIV infection, AIDS, ARC (protease inhibitor)
Stavudine; d4T Didehydrodeoxy-thymidine	Bristol-Myers Squibb	HIV infection, AIDS, ARC
T-20	Trimeris	HIV infection, AIDS, ARC
Valaciclovir	Glaxo Wellcome	genital HSV & CMV infections
Virazole Ribavirin	Viratek/ICN (Costa Mesa, CA)	asymptomatic HIV positive, LAS, ARC
Amprenivir VX-478	Vertex	HIV infection, AIDS, ARC
Zalcitabine	Hoffmann-La Roche	HIV infection, AIDS, ARC, with AZT
Zidovudine; AZT	Glaxo Wellcome	HIV infection, AIDS, ARC, Kaposi's sarcoma, in combination with other therapies

IMMUNO-MODULATORS

Drug Name	Manufacturer	Indication
AS-101	Wyeth-Ayerst	AIDS
Bropirimine	Pharmacia Upjohn	advanced AIDS
Acemannan	Carrington Labs, Inc. (Irving, TX)	AIDS, ARC
CL246,738	American Cyanamid Lederle Labs	AIDS, Kaposi's sarcoma
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
Gamma Interferon	Genentech	ARC, in combination w/TNF (tumor necrosis factor)
Granulocyte Macrophage Colony Stimulating Factor	Genetics Institute Sandoz	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Hoeschst-Roussel Immunex	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Schering-Plough	AIDS, combination w/AZT
HIV Core Particle Immunostimulant	Rorer	seropositive HIV
IL-2 Interleukin-2	Cetus	AIDS, in combination w/AZT
IL-2 Interleukin-2	Hoffman-La Roche Immunex	AIDS, ARC, HIV, in combination w/AZT
IL-2 Interleukin-2 (aldeslukin)	Chiron	AIDS, increase in CD4 cell counts

Immune Globulin Intravenous (human)	Cutter Biological (Berkeley, CA)	pediatric AIDS, in combination w/AZT
IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
Imuthiol Diethyl Dithio Carbamate	Merieux Institute	AIDS, ARC
Alpha-2 Interferon	Schering Plough	Kaposi's sarcoma w/AZT, AIDS
Methionine-Enkephalin	TNI Pharmaceutical (Chicago, IL)	AIDS, ARC
MTP-PE Muramyl-Tripeptide	Ciba-Geigy Corp.	Kaposi's sarcoma
Granulocyte Colony Stimulating Factor	Amgen	AIDS, in combination w/AZT
Remune	Immune Response Corp.	immunotherapeutic
rCD4 Recombinant Soluble Human CD4	Genentech	AIDS, ARC
rCD4-IgG hybrids		AIDS, ARC
Recombinant Soluble Human CD4	Biogen	AIDS, ARC
Interferon Alfa 2a	Hoffman-La Roche	Kaposi's sarcoma AIDS, ARC, in combination w/AZT
SK&F106528 Soluble T4	Smith Kline	HIV infection
TAK-779	Takeda	HIV infection
Thymopentin	Immunobiology Research Institute	HIV infection

SEC 578

Tumor Necrosis Factor; TNF	Genentech	ARC, in combination w/gamma Interferon

ANTI-INFECTIVES

Drug Name	Manufacturer	Indication
Clindamycin with Primaquine	Pharmacia Upjohn	PCP
Fluconazole	Pfizer	cryptococcal meningitis, candidiasis
Pastille Nystatin Pastille	Squibb Corp.	prevention of oral candidiasis
Ornidyl Eflornithine	Merrell Dow	PCP
Pentamidine Isethionate (IM & IV)	LyphoMed (Rosemont, IL)	PCP treatment
Trimethoprim		antibacterial
Trimethoprim/sulfa		antibacterial
Piritrexim	Burroughs Wellcome	PCP treatment
Pentamidine isethionate for inhalation	Fisons Corporation	PCP prophylaxis
Spiramycin	Rhone-Poulenc	cryptosporidial diarrhea
Intraconazole-R51211	Janssen Pharm.	histoplasmosis; cryptococcal meningitis
Trimetrexate	Warner-Lambert	PCP

OTHER

Drug Name	Manufacturer	Indication
Daunorubicin	NeXstar, Sequus	Karposi's sarcoma

Recombinant Human Erythropoietin	Ortho Pharm. Corp.	severe anemia assoc. with AZT therapy
Recombinant Human Growth Hormone	Serono	AIDS-related wasting, cachexia
Leukotriene B4 Receptor Antagonist	-	HIV infection
Megestrol Acetate	Bristol-Myers Squibb	treatment of anorexia assoc. w/AIDS
Soluble CD4 Protein and Derivatives	-	HIV infection
Testosterone	Alza, Smith Kline	AIDS-related wasting
Total Enteral Nutrition	Norwich Eaton Pharmaceuticals	diarrhea and malabsorption related to AIDS

It will be understood that the scope of combinations of the compounds of this invention with AIDS antivirals, immunomodulators, anti-infectives or vaccines is not limited to the list in the above Table, but includes in principle any combination with any pharmaceutical composition useful for the treatment of AIDS.

Preferred combinations are simultaneous or alternating treatments with a compound of the present invention and an inhibitor of HIV protease and/or a non-nucleoside inhibitor of HIV reverse transcriptase. An optional fourth component in the combination is a nucleoside inhibitor of HIV reverse transcriptase, such as AZT, 3TC, ddC or ddI. Preferred agents for combination therapy include: Zidovudine, Lamivudine, Stavudine, Efavirenz, Ritonavir, Nelfinavir, Abacavir, Indinavir, 141-W94 (4-amino-N-((2 syn,3S)-2-hydroxy-4-phenyl-3-((S)-tetrahydrofuran-3-yloxycarbonylamino)-butyl)-N-isobutyl-benzenesulfonamide), N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(2-benzo[b]furanylmethyl)-2(S)-N'(t-butylcarbox-amido)-piperazinyl))-pentaneamide, and Delavirdine. A preferred inhibitor of HIV protease is indinavir, which is the sulfate salt of N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(3-pyridyl-methyl)-2(S)-N'-(t-butylcarbo-xamido)-piperazinyl))-pentane-amide ethanolate, and is synthesized according to U.S. 5,413,999. Indinavir is generally administered at a dosage of 800

mg three times a day. Other preferred inhibitors of HIV protease include nelfinavir and ritonavir. Preferred non-nucleoside inhibitors of HIV reverse transcriptase include (-) 6-chloro-4(S)-cyclopropylethynyl-4(S)-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one, which may be prepared by methods disclosed in EP 0,582,455. The preparation of ddC, ddI and AZT are also described in EPO 0,484,071. These combinations may have unexpected effects on limiting the spread and degree of infection of HIV. Preferred combinations with the compounds of the present invention include the following: (1) Zidovudine and Lamivudine; (2) Stavudine and Lamivudine; (3) Efavirenz; (4) Ritoavir; (5) Nelfinavir; (6) Abacavir; (7) Indinavir; (8) 141-W94; and (9) Delavirdine. Preferred combinations with the compounds of the present invention further include the following (1) indinavir, with efavirenz or (-) 6-chloro-4(S)-cyclopropylethynyl-4(S)-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one, and, optionally, AZT and/or 3TC and/or ddI and/or ddC; (2) indinavir, and any of AZT and/or ddI and/or ddC.

In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

The compounds of the present invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, monkeys, etc., the compounds of the invention are effective for use in humans.

The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In

the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Patents 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy- propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum

tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally- occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the present invention are employed. (For purposes of this application, topical application shall include mouthwashes and gargles.)

The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions.

In the treatment or prevention of conditions which require chemokine receptor modulation an appropriate dosage level will generally be about 0.01 to 500 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.1 to about 250 mg/kg per day; more preferably about 0.5 to about 100 mg/kg per day. A suitable dosage level may be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage may be 0.05 to 0.5, 0.5 to 5 or 5 to 50 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active

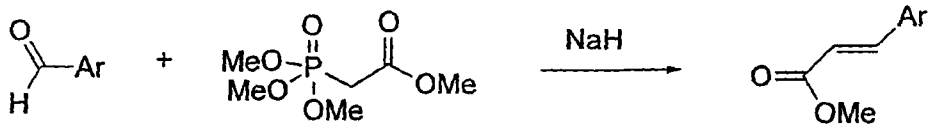
ingredient, particularly 1.0, 5.0, 10.0, 15.0. 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples. Starting materials are made from known procedures or as illustrated.

5004300.0054

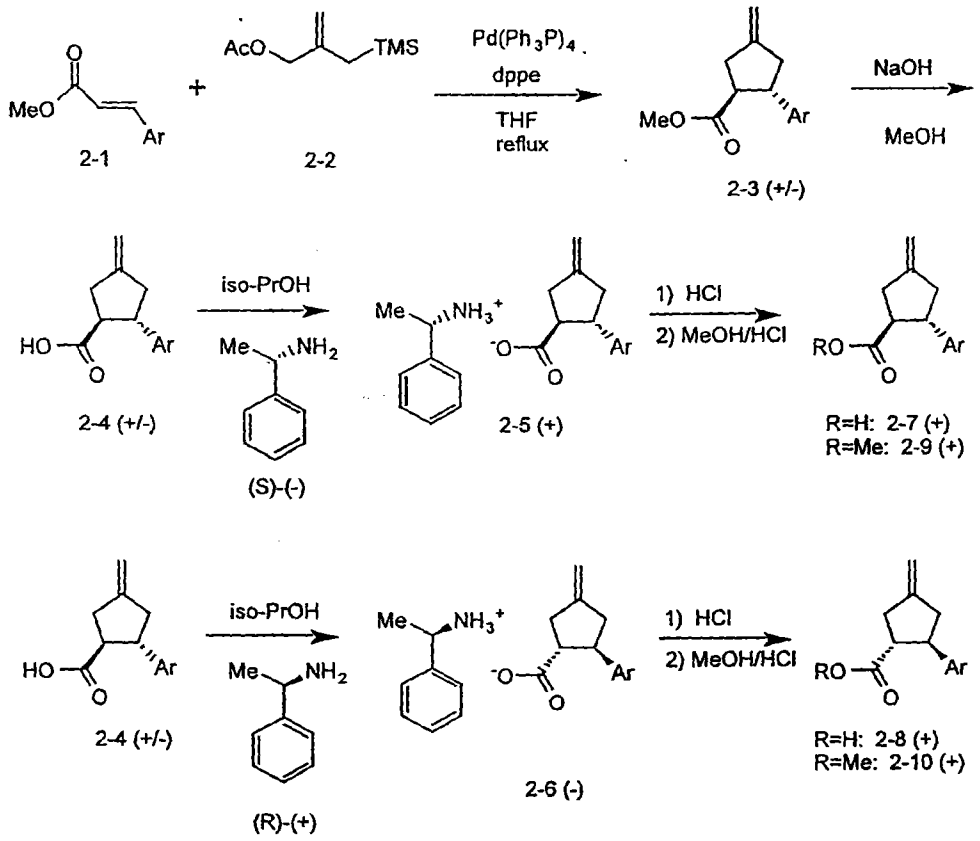
SCHEME 1



1-1 1-2 1-3

The preparation of cinnamate esters such as 1-3 as intermediates that can be used for the synthesis of compounds within the scope of the instant invention is detailed in Scheme 1. Cinnamate esters of structure 1-3 can be obtained commercially or can be synthesized by reacting a suitable aromatic aldehyde 1-1 with a phosphonoacetate such as 1-2 in the presence of sodium hydride or other bases such as sodium, lithium or potassium hexamethyldisilazide, potassium t-butoxide, and the like. The aldehyde 1-1 can be obtained commercially or can be prepared in a variety of ways from commercial materials (see March J. "Advanced Organic Chemistry", 4th ed., John Wiley & Sons, New York, pp. 1270-1271 (1992)).

SCHEME 2

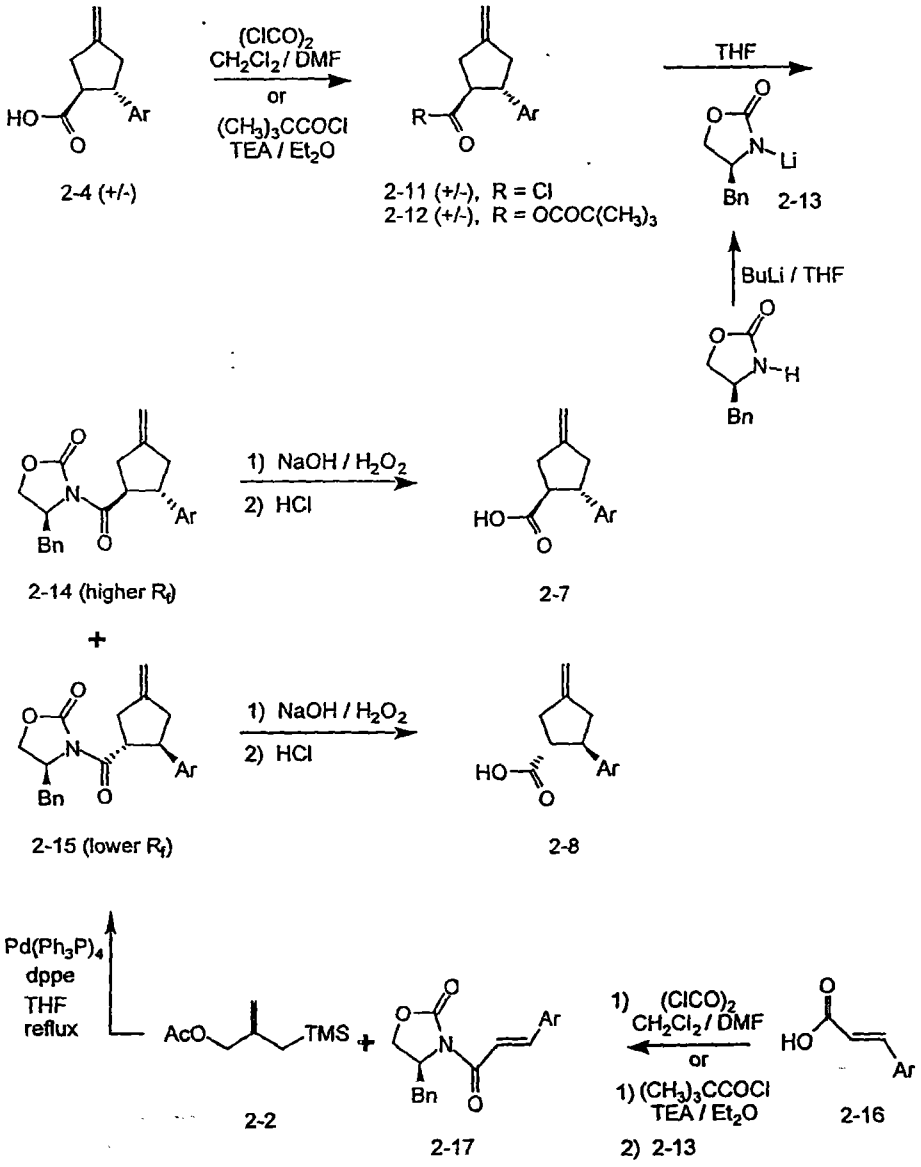


A preparation of cyclopentane intermediates having a C-4 aryl substituent within the scope of the instant invention is detailed in Scheme 2 and can be used to prepare non-racemic cyclopentane derivatives when the resolution steps are done. Treatment of a *trans*-cinnamic ester such as 2-1 (see Scheme 1) with 2-((trimethylsilyl)methyl)-2-propen-1-yl acetate (2-2) in the presence of a catalytic amount of tetrakis(triphenylphosphine) palladium (0) and 1,2-bis(diphenylphosphino)ethane in THF at reflux afforded the exo-methylene cyclopentane 2-3. Hydrolysis of the ester can be done several ways, such as with aqueous sodium or lithium hydroxide in methanol or THF, to obtain the racemic acid 2-4. Resolution of the enantiomers can be accomplished by fractional crystallization from isopropanol, or other suitable solvents, of the salts with either (R)-(+)- or (S)-(-)-α-methylbenzyl amine to give the salts 2-5 and 2-6. The non-racemic acids 2-7 and

2-8 are recovered by acidification and extraction. Reesterification to non-racemic 2-9 and 2-10 can be done in a variety of ways, such as with trimethylsilyldiazomethane or acid catalyzed esterification in methanol.

0074050 - 0074060

SCHEME 2A



2-4 (+/-)

2-11 (+/-), R = Cl
2-12 (+/-), R = OCOC(CH3)3

2-13

2-14 (higher Rf)

2-7

2-15 (lower Rf)

2-8

2-2

2-17

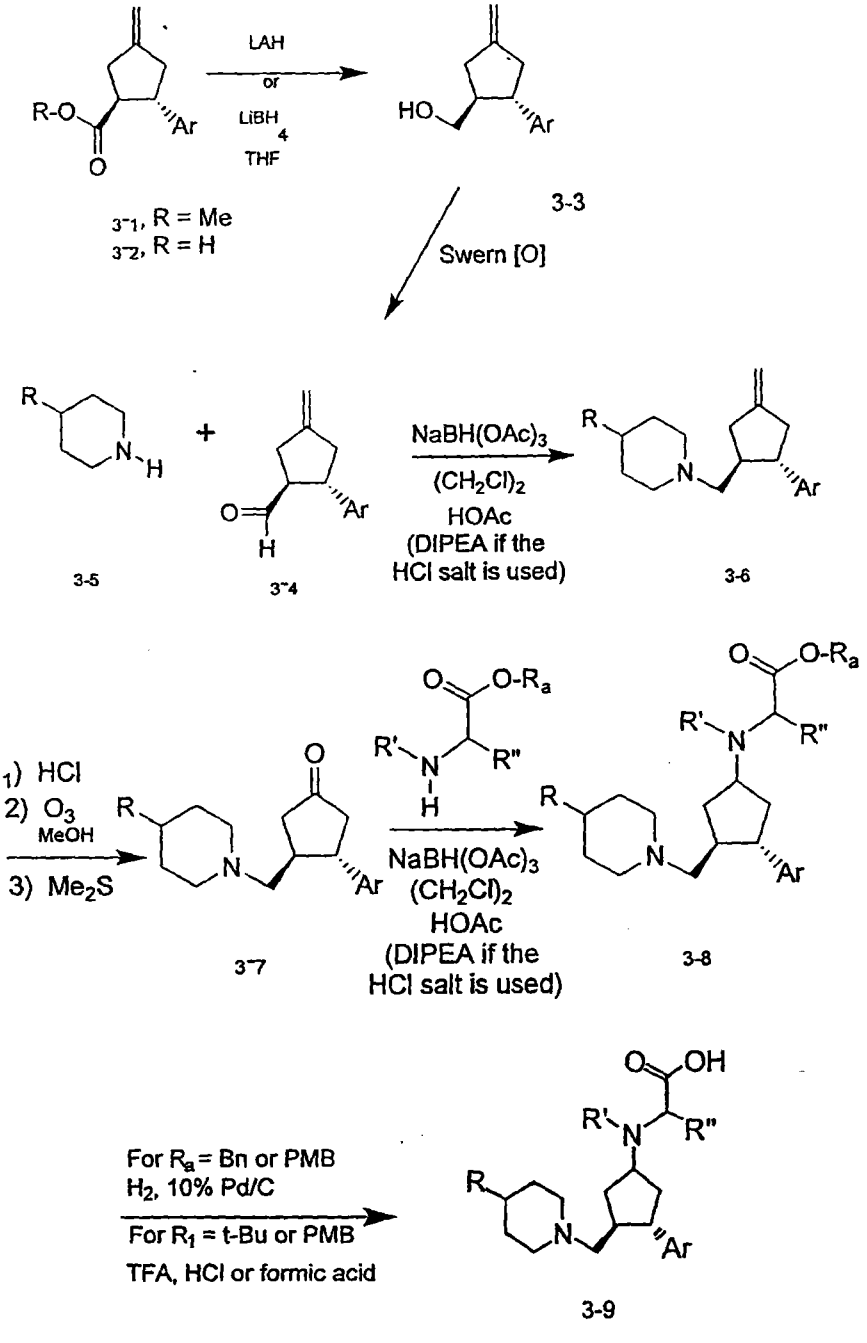
2-16

An alternative preparation of non-racemic cyclopentane intermediates having a C-4 aryl substituent within the scope of the instant invention is detailed in Scheme 2A. Conversion of the cyclopentane acid 2-4 to the acid chloride 2-11 under standard conditions, such as with oxalyl chloride in methylene chloride with a catalytic amount of DMF, or to the mixed anhydride 2-12, prepared in situ with

trimethylacetyl chloride in ether with TEA as base, followed by reaction with the preformed lithium salt of (S)-(-)-4-benzyl-2-oxazolidinone 2-13, afforded the two non-racemic diastereomeric products 2-14 and 2-15, which are then separable by chromatography. Hydrolysis of each diastereomer under standard conditions, such as with lithium hydroxide and hydrogen peroxide or trimethylamine-N-oxide, affords the two non-racemic acids 2-7 and 2-8. Alternatively, in order to obtain an enhanced amount of the desired diastereomer 2-14 before separation, similar conversion of the starting *trans* -cinnamic acid 2-16 (Scheme 1) to the chiral *trans* -cinnamate 2-17 followed by the ring formation reaction with 2-((trimethylsilyl)methyl)-2-propen-1-yl acetate (2-2) as detailed in Scheme 2 affords a 60 : 40 product mixture of 2-14 : 2-15.

SUBSTITUTE SHEET (RULE 26)

SCHEME 3

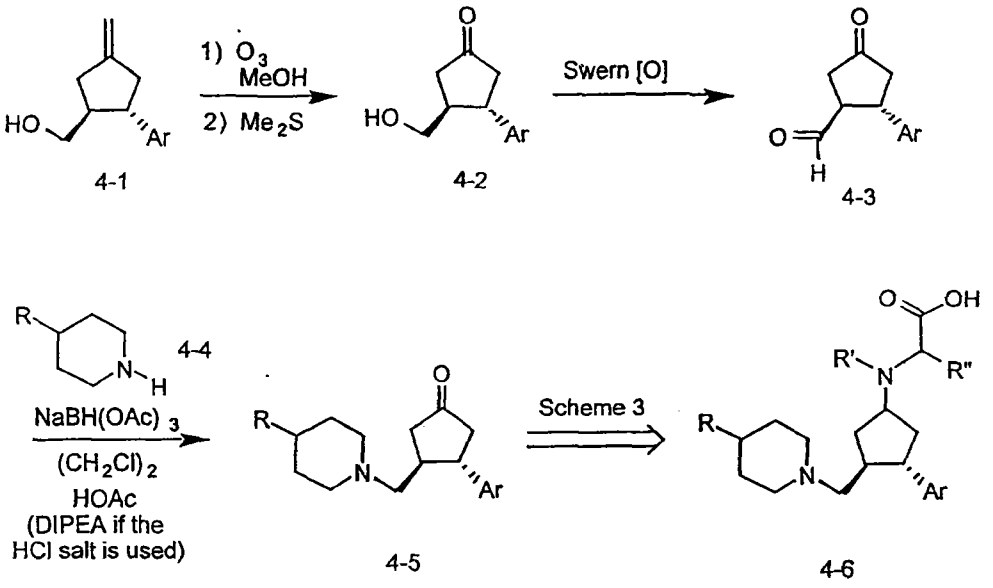

LAH
or
LiBH4
THF
R-O
Ar
O
HO
3-1, R = Me
3-2, R = H
3-3
Swern [O]
R
N
H
O
H
3-5
3-4
NaBH(OAc)3
(CH2Cl)2
HOAc
(DIPEA if the
HCl salt is used)
3-6
1) HCl
2) O3
MeOH
3) Me2S
3-7
O-Ra
R'
R"
3-8
For Ra = Bn or PMB
H2, 10% Pd/C
For R1 = t-Bu or PMB
TFA, HCl or formic acid
OH
3-9

Preparation of some 1,3,4-trisubstituted cyclopentanes within the scope of the instant invention is given in Scheme 3. Reduction of ester 3-1 (either racemic or non-racemic) (Scheme 2), for example, with lithium borohydride, diisobutylaluminum hydride, lithium aluminium hydride, or sodium bis(2-methoxyethoxy)aluminum hydride in a suitable solvent, such as ether or THF, provides the primary alcohol 3-3. Alternatively, reduction of the acid 3-2 (either racemic or non-racemic) (Scheme 2 or 2A), for example with lithium aluminium hydride in THF, will also afford the alcohol 3-3. In cases where the Ar moiety is not amenable to salt resolution as detailed in Scheme 2, an alternative resolution can often be achieved using chiral HPLC methods to separate the enantiomers of 3-3. Oxidation of 3-3 to the aldehyde 3-4 can be carried out under numerous conditions, such as with DMSO and oxalyl chloride at low temperature, followed by triethylamine (Swern oxidation), with the Dess-Martin periodinane, with *N*-methylmorpholine in the presence of a catalytic amount of TPAP, or with various chromium trioxide-based reagents (see March J. "Advanced Organic Chemistry", 4th ed., John Wiley & Sons, New York, pp. 1167-1171 (1992)). Reductive alkylation of a cyclic amine, such as piperidine 3-5 (see Schemes 12 to 29), using for example sodium triacetoxyborohydride or sodium cyanoborohydride in a suitable solvent such as methylene chloride, 1,2-dichloroethane, THF, acetonitrile or methanol, with 3-4 then provides a 3-((4-substitutedpiperidin-1-yl)methyl)cyclopentane derivative 3-6. In the cases where the R group of the piperidine is stable to ozone, ozonolysis of the exo-methylene followed by a reductive work-up with dimethyl sulfide affords the ketone 3-7. Alternatively, 3-7 can be obtained from 3-6 through a stepwise oxidation using catalytic osmium tetroxide in the presence of *N*-methylmorpholine-N-oxide followed by sodium periodate cleavage of the intermediate diol. A second reductive alkylation of a D- and/or L-amino-acid ester, such as the methyl, ethyl, t-butyl, benzyl or 4-methoxybenzyl ester of glycine (R" = H), alanine (R" = Me), valine (R" = iso-Pr), leucine (R" = iso-Bu), isoleucine (R' = sec-Bu), cyclopropylalanine (R" = CH_2cycPr), cyclobutylalanine (R" = CH_2cycBu), cyclohexylglycine (R" = cycHex) or a *N*-alkyl amino-acid, such as N-methyl glycine (R' = Me), or a cyclic amino-acid, such as proline (R'R" = -$(CH_2)_3$-), with 3-7 as described above with sodium triacetoxyborohydride or sodium cyanoborohydride affords 3-8. Final deprotection of the ester under conditions to which the R group is stable, such as HCl in ether, TFA or formic acid for t-butyl and 4-methoxybenzyl esters, hydrogenation for benzyl esters or

standard hydrolysis for alkyl or benzyl esters, affords the final product(s) 3-9 which are within the scope of the instant invention and which can be chemokine receptor modulators. The two individual C-1 isomers (four diastereomers when either the cyclopentyl scaffold or the amino-acid are racemic) can be separated by flash chromatography, Prep TLC or HPLC methods as either the penultimate esters 3-8 and/or the final compounds 3-9.

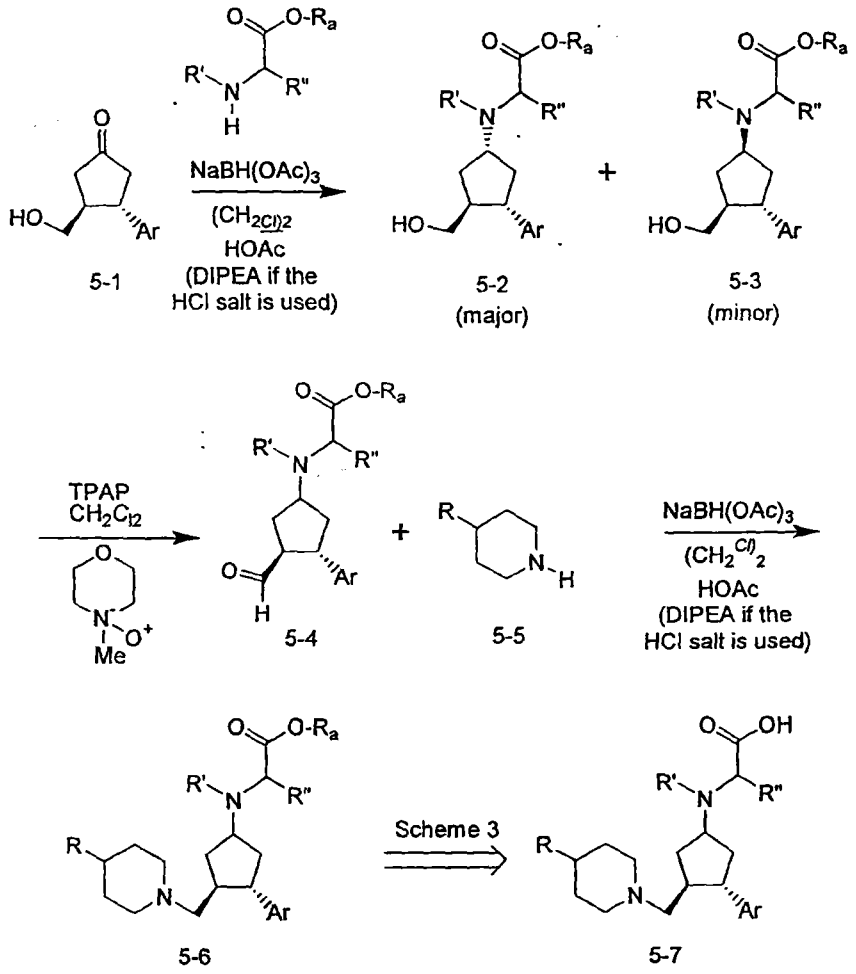
SUBSTITUTE SHEET (RULE 26)

SCHEME 4



An alternative route for the preparation of some 1,3,4-trisubstituted cyclopentanes within the scope of the instant invention is given in Scheme 4. In the cases where the R group of the piperidine in Scheme 3 is not stable to ozone or the osmium tetroxide/sodium periodate sequence, oxidation of the exo-methylene can be done prior to the reductive alkylation of the piperidine. Thus, ozonolysis of the alcohol 4-1 (Scheme 3) followed by a reductive work-up with dimethyl sulfide affords the ketone-alcohol 4-2. Oxidation to the ketone-aldehyde 4-3 can be done as described for Scheme 3 with *N*-methylmorpholine/TPAP or under Swern conditions. Selective reductive alkylation of the 4-substitutedpiperidine 4-4 (see Schemes 12 to 29) with the aldehyde of 4-3, using for example sodium triacetoxyborohydride or sodium cyanoborohydride in a suitable solvent such as methylene chloride, 1,2-dichloroethane, THF, acetonitrile or methanol, then provides the 3-((4-substitutedpiperidin-1-yl)methyl)cyclopentane derivative 4-5 (same as 3-7). This can then be converted to the final product(s) 4-6 as described in Scheme 3.

SCHEME 5

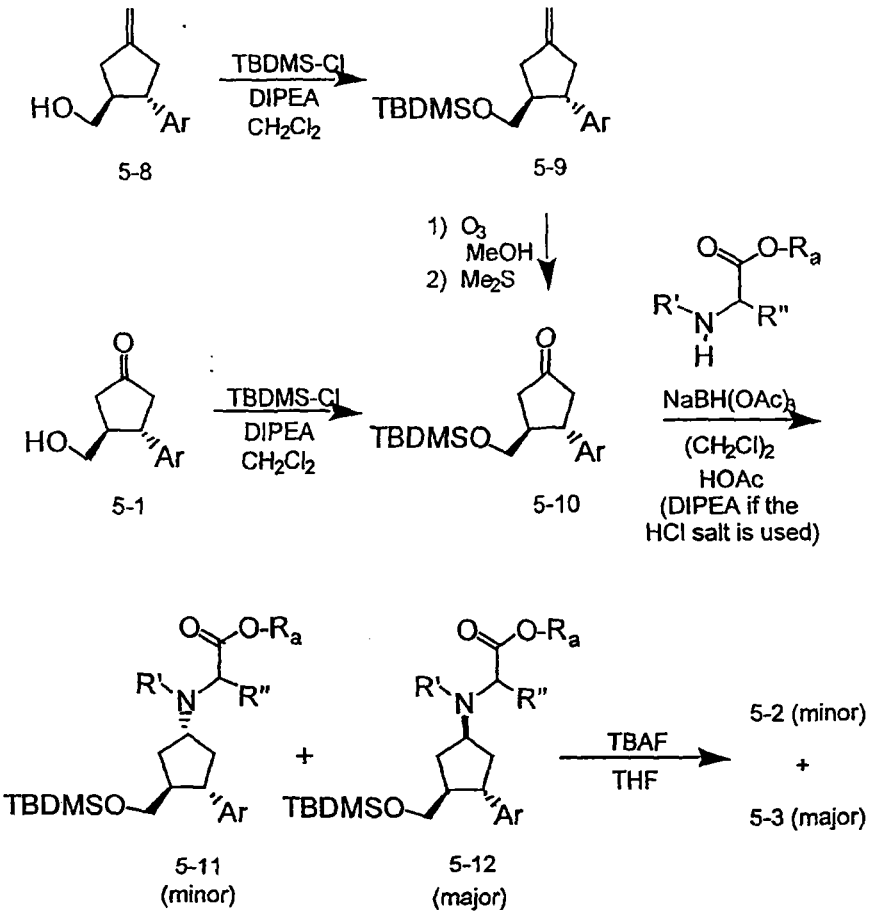


An alternative route for the preparation of some 1,3,4-trisubstituted cyclopentanes within the scope of the instant invention is given in Scheme 5. Reductive alkylation with ketone alcohol 5-1 (Scheme 4) of a variety of amino-acid esters (See Scheme 3) affords the alcohols 5-2 and 5-3, of which 5-2 is the major product (lower R_f when R" is (S), higher R_f when R" is (R)) and 5-3 is the minor product (higher R_f when R" is (S), lower R_f when R" is (R)). Separation of the individual diastereomers (2 when both reactants are non-racemic, 4 when only one is non-racemic) can be done at this intermediate or at a later step. Oxidation of 5-2 and/or 5-3 to the aldehyde(s) 5-4 can be done as described in Scheme 3, preferably

now with *N*-methylmorpholine/TPAP due to the presence of the secondary N-H. Reductive alkylation of a 4-substitutedpiperidine 5-5 (see Schemes 12 to 29) with the aldehyde of 5-4, using for example sodium triacetoxyborohydride or sodium cyanoborohydride in a suitable solvent such as methylene chloride, 1,2-dichloroethane, THF, acetonitrile or methanol, then provides the 3-((4-substitutedpiperidin-1-yl)methyl)cyclopentane derivative 5-6. The intermediate ester(s) 5-6 can then be converted to the final product(s) 5-7 as described in Scheme 3.

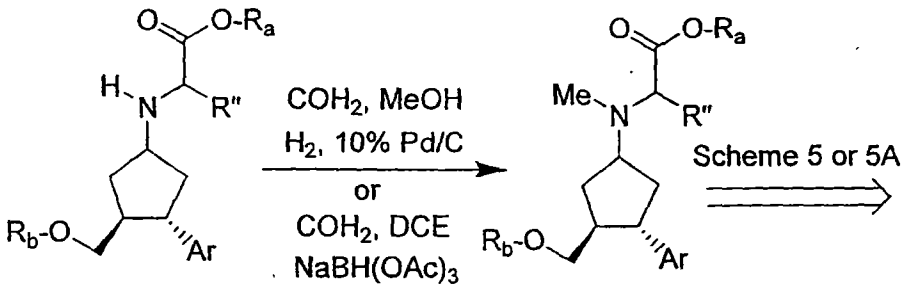
EC0003-0054-00

SCHEME 5A



An alternative preparation of the intermediates 5-2 and 5-3 in Scheme 5 which reverses the C-1 isomeric selectivity is shown in Scheme 5A. Silylation of the alcohol moiety of 5-1 (Scheme 4) gives the silyl ether 5-10. Alternatively, silylation of the alcohol 5-8 (Scheme 3) gives 5-9 which on ozonolysis can also afford the silyl ether 5-10. Reductive alkylation of the aforementioned amino-acid esters now using the silyl ether 5-10 affords the products 5-11 and 5-12 in an essentially opposite ratio as is obtained in Scheme 5 for 5-2 and 5-3. TBAF desilylation then affords primarily 5-3. Thus, the preferred C-1 orientation can be selected for depending on the requirements of the desired final compounds.

SCHEME 5B



5-13

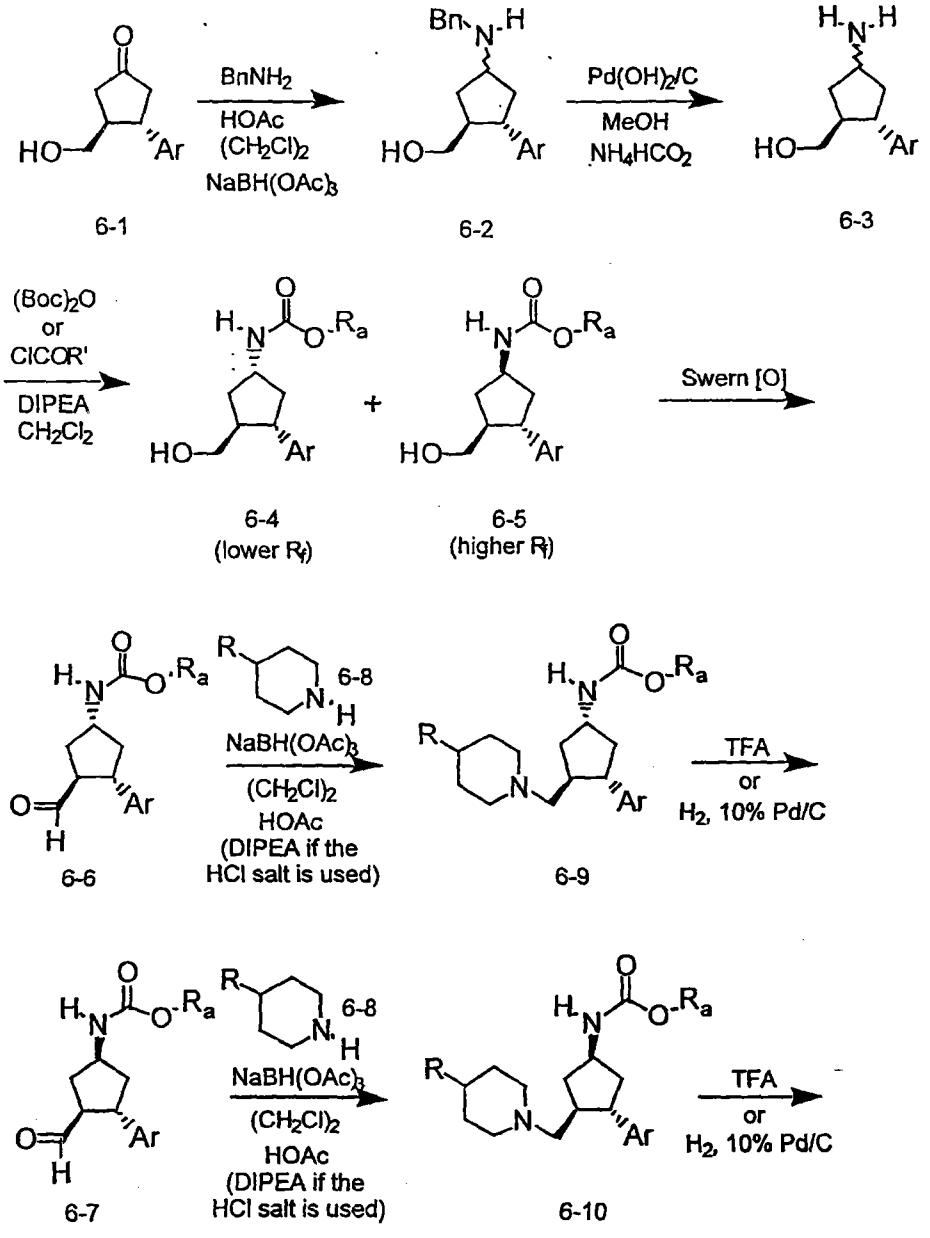
R_b = H or TBDMS

5-14

Rb = H or TBDMS

An alternative preparation of the intermediates 5-2 or 5-3 in Scheme 5 and intermediates 5-11 and 5-12 in Scheme 5A when R' is Me is shown in Scheme 5B. When 5-13 is formed in the reductive amination with ketones 5-1 (R_b = H) or 5-10 (R_b = TBDMS), a second reductive amination of 5-13 with formaldehyde, either in the presence of hydrogen and a suitable catalyst, such as 10% Pd/C or Pearlman's catalyst, in methanol or standard reaction with sodium triacetoxyborohydride in 1,2-dichloroehthane, affords the methylated intermediates 5-14. These intermediates can be further elaborated to the final products as described in Scheme 5 and/or 5A.

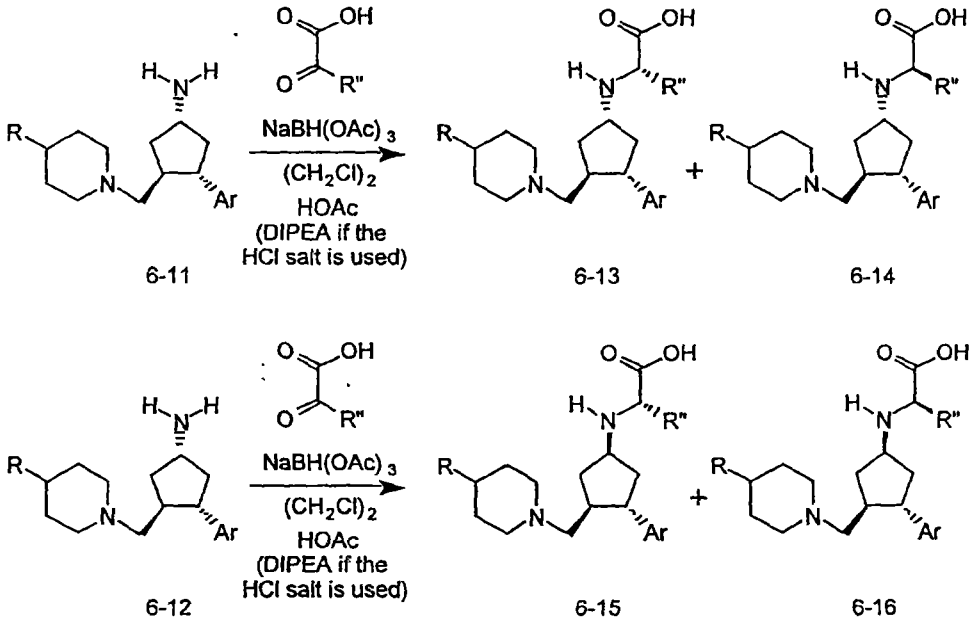
SCHEME 6


BnNH2
HOAc
(CH2Cl)2
NaBH(OAc)3
Pd(OH)2/C
MeOH
NH4HCO2
6-1
6-2
6-3
(Boc)2O
or
ClCOR'
DIPEA
CH2Cl2
Swern [O]
6-4
(lower Rf)
6-5
(higher Rf)
6-8
NaBH(OAc)3
(CH2Cl)2
HOAc
(DIPEA if the
HCl salt is used)
6-6
6-9
TFA
or
H2, 10% Pd/C
6-7
6-10

5

598

SCHEME 6 (cont'd)

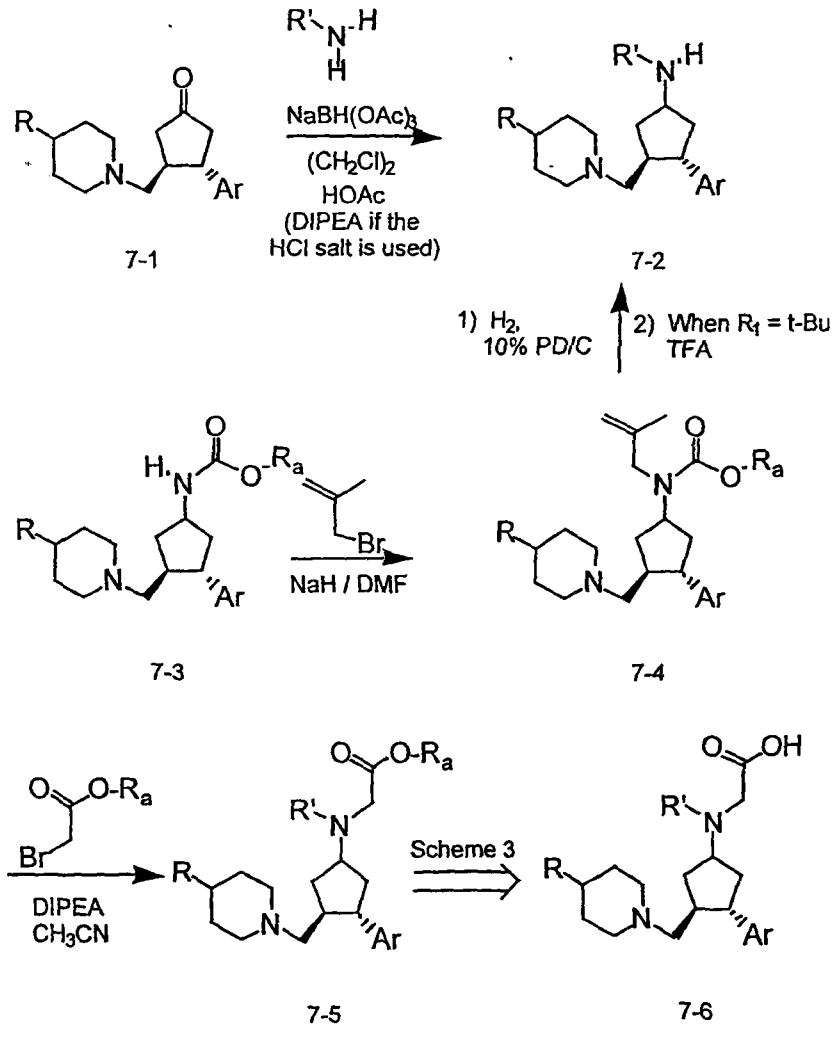


An alternative route for the preparation of some 1,3,4-trisubstituted cyclopentanes within the scope of the instant invention is given in Scheme 6. Reductive alkylation of benzylamine with ketone-alcohol 6-1 (Scheme 4, either racemic or non-racemic), using for example sodium triacetoxyborohydride or sodium cyanoborohydride, gives 6-2 which can be hydrogenated under standard conditions in methanol in the presence of a palladium catalyst, for example Pd/C or Pearlman's catalyst and using either hydrogen under pressure or ammonium formate at reflux, to afford the primary amine 6-3. Reaction of the amine with CBZ chloride or Boc anhydride gives the amine protected carbamates 6-4 and 6-5 as a mixture of C-1 isomers which can be separated. Oxidation to the aldehydes 6-6 and 6-7 is carried out under Swern conditions or with *N*-methylmorpholine/TPAP. The relative stereochemistry of the C-1 to the C-3 and C-4 substituents was determined by NMR Noe experiments on either the alcohols 6-4 and 6-5 or the aldehydes 6-6 and 6-7. Reductive alkylation of a 4-substitutedpiperidine 6-8 with the individual aldehydes 6-6 and 6-7, using for example sodium triacetoxyborohydride or sodium cyanoborohydride in a suitable solvent such as methylene chloride, 1,2-dichloroethane, THF, acetonitrile or methanol, then provides each of the C-1 amino-

protected isomeric 3-((4-substitutedpiperidin-1-yl)methyl)cyclopentane derivatives 6-9 and 6-10. Deprotection of the C-1 amino with either TFA (for R_a = t-butyl) or standard hydrogenation (for R_a = Bn) depending on the stability of the piperidine R group affords the amines 6-11 and 6-12. These amines can then be individually reductively alkylated as above with 2-oxo-acetic acids, such as 2-oxovaleric (R" = n-Pr), 4-methyl-2-oxovaleric (R" = iso-Bu), 2-oxophenylacetic (R" = Ph), to afford the final compounds 6-13 and 6-14 and 6-15 and 6-16 as mixtures of the R" isomers. In the case of R" = iso-Bu and non-racemic cyclopentyl scaffold, comparison of the HPLC of these products with those obtained in Scheme 5 allowed the stereochemical assignments of all the final products and intermediates.

SUBSTITUTE SHEET (RULE 26)

SCHEME 7



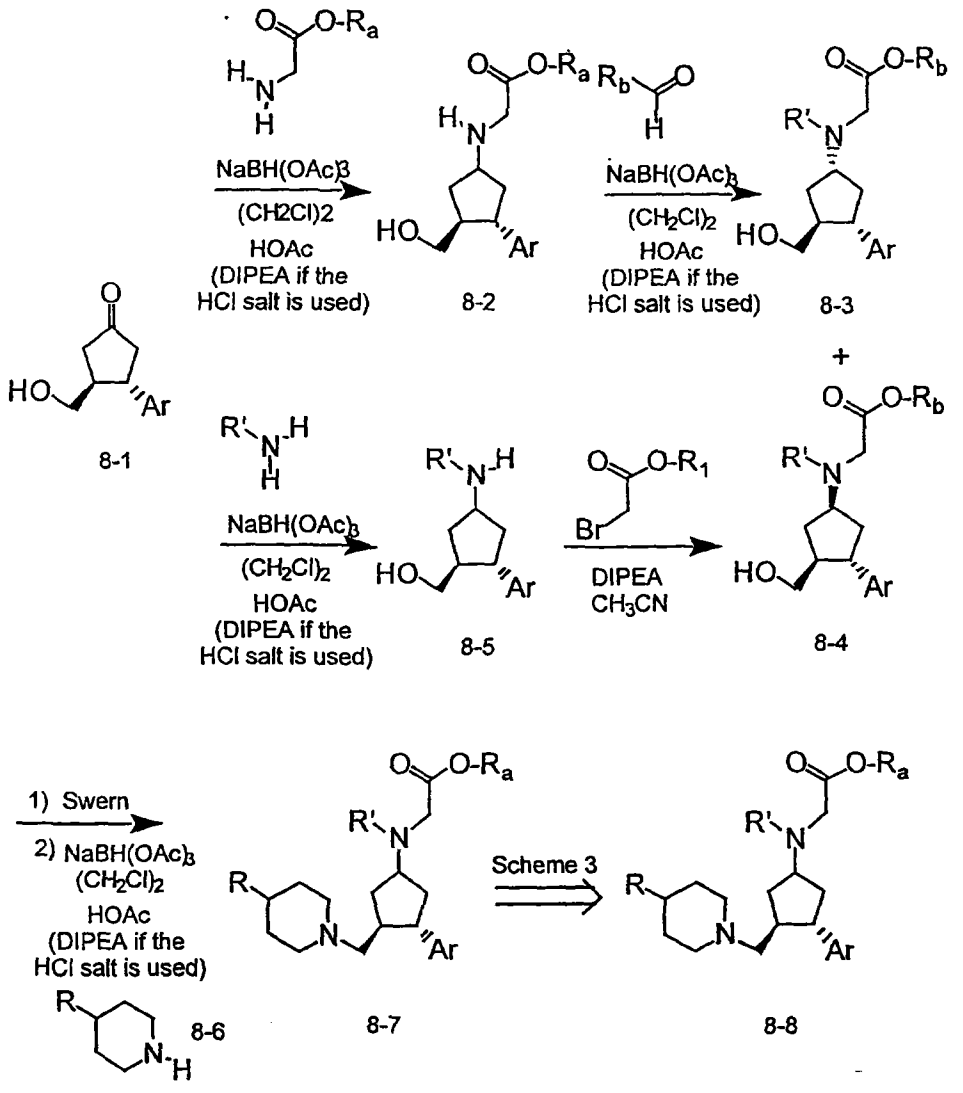
An alternative route for the preparation of some 1,3,4-trisubstituted cyclopentanes within the scope of the instant invention is given in Scheme 7. Reductive alkylation, using for example sodium triacetoxyborohydride or sodium cyanoborohydride, of an alkyl amine with the ketone 7-1 (Schemes 3 or 4) gives 7-2 as a mixture of C-1 isomers which may be separated. Alternatively, carbamate 7-3 (see Scheme 6) can be alkylated with an alkyl or allyl halide, such as 1-bromo-2-

methylprop-2-ene, and a strong base, such as sodium hydride in DMF, followed by hydrogenation under standard conditions to reduce the allyl. When R_a is Bn, removal the CBZ can occur simultaneously to give the same amine intermediate 7-2. When R_a is t-butyl, a subsequent reaction with TFA is required to give 7-2. Alkylation of the amine with t-butyl or benzyl bromoacetate affords 7-5 which can be converted to the desired final compound(s) 7-6 as described in Scheme 3.

SUBSTITUTE SHEET (RULE 26)

602

SCHEME 8



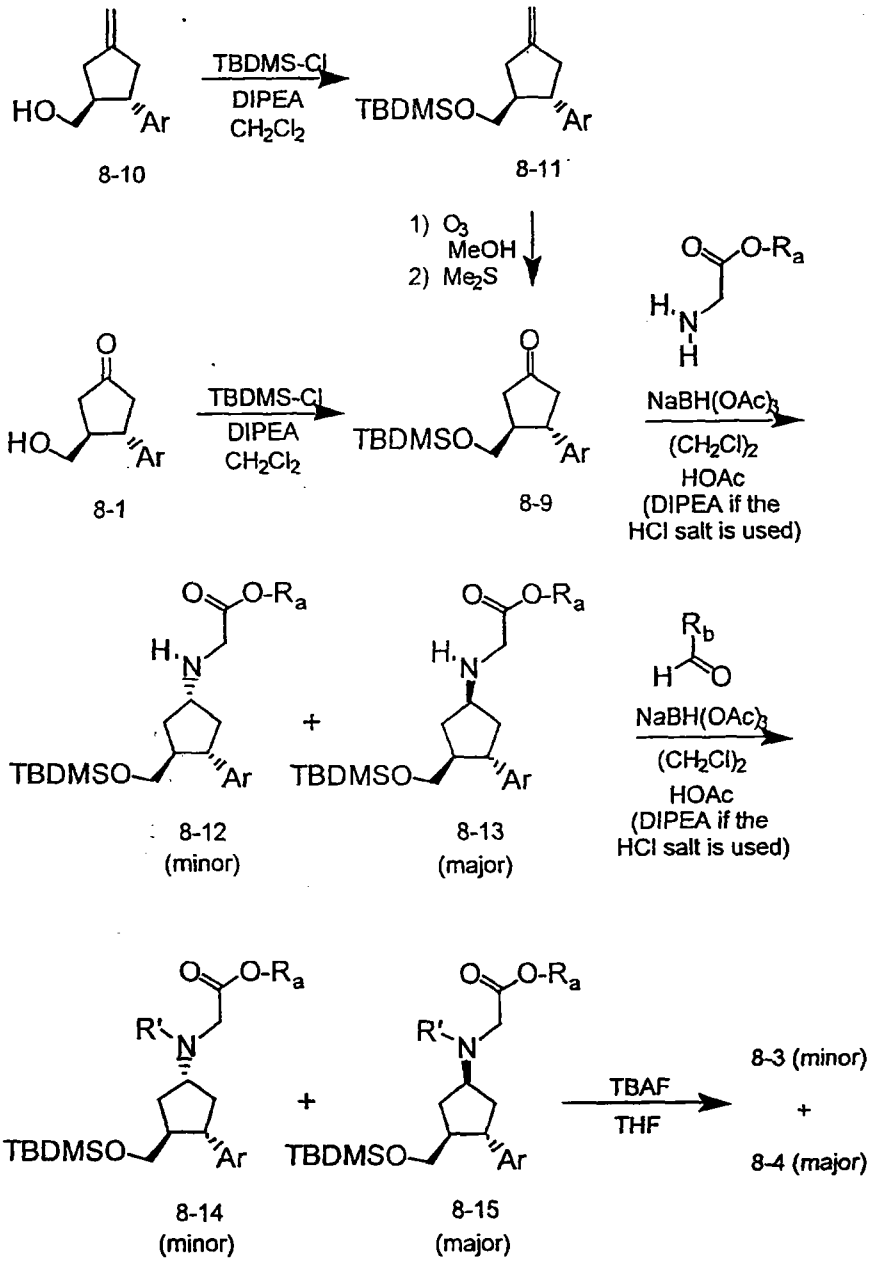
An alternative route for the preparation of some 1,3,4-trisubstituted cyclopentanes within the scope of the instant invention is given in Scheme 8. Reductive alkylation, using for example sodium triacetoxyborohydride or sodium cyanoborohydride, of glycine t-butyl, benzyl or PMB ester with the ketone-alcohol 8-1 (Scheme 4) gives 8-2 as a mixture of C-1 isomers. A second reductive alkylation

with a ketone or aldehyde affords the N-alkyl glycine derivatives 8-3 and 8-4 which can be separated chromatographically either before and/or after the second alkylation. Also, the order of the steps can be reversed such that reductive alkylation of an amine with 8-1 first to give 8-5, followed by alkylation with an alkyl or benzyl bromoacetate as in Scheme 7, affords 8-3 and 8-4. These reactions generally give 8-3 as the predominate product. Individual oxidation of the alcohols 8-3 and 8-4 can be done either under Swern conditions or using the *N*-methylmorpholine/TPAP method to give the aldehyde intermediate(s) followed by a second or third reductive alkylation of a 4-substitutedpiperidine 8-6, using for example sodium triacetoxyborohydride or sodium cyanoborohydride in a suitable solvent such as methylene chloride, 1,2-dichloroethane, THF, acetonitrile or methanol, which then provides the 3-((4-substitutedpiperidin-1-yl)methyl)cyclopentane derivative 8-7. This intermediate can then be converted to the final product(s) 8-8 as described in Scheme 3.

SUBSTITUTE SHEET (RULE 26)

604

SCHEME 8A



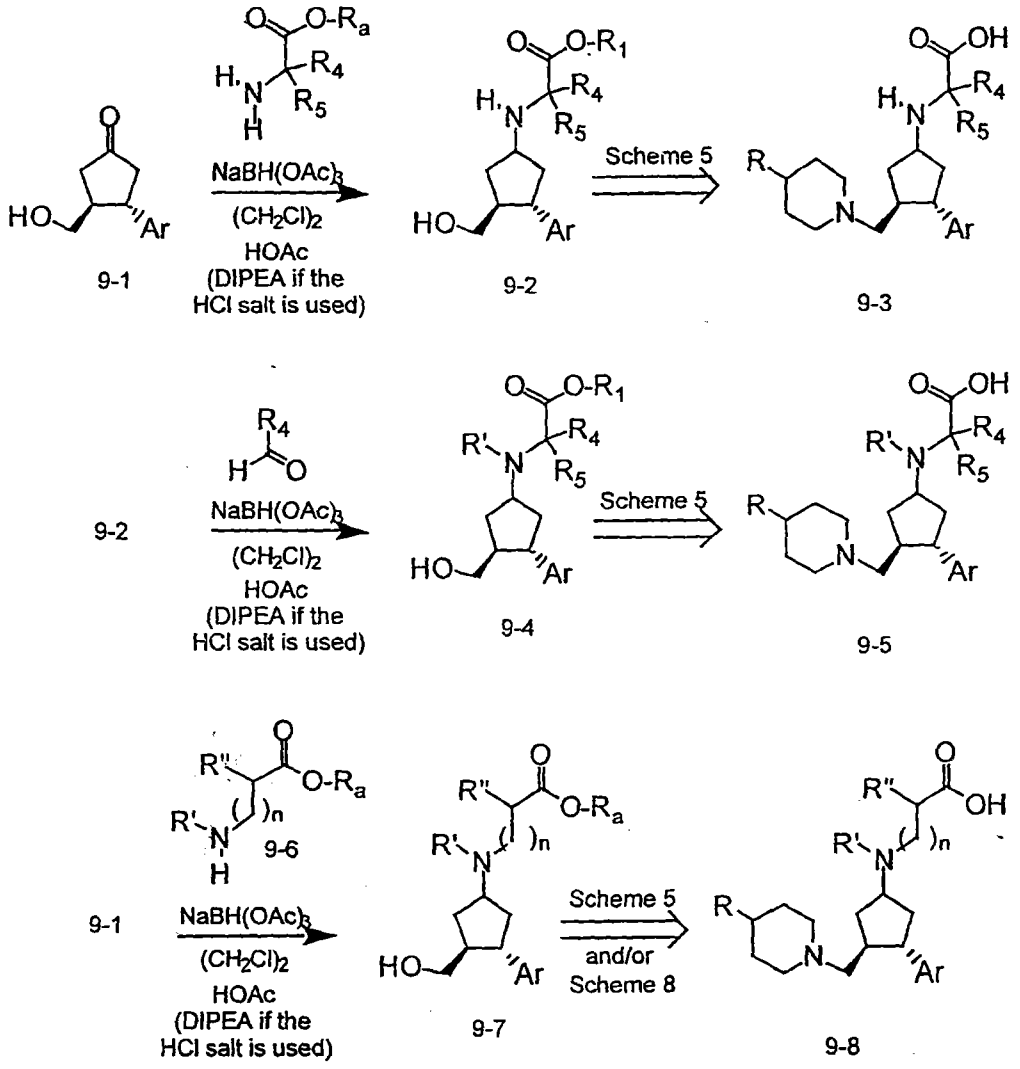
An alternative preparation of the intermediates 8-3 and 8-4 in Scheme 8 which again reverses the C-1 isomeric selectivity is shown in Scheme 8A.

Silylation of the alcohol moiety of 8-1 (Scheme 4) gives the silyl ether 8-9. Alternatively, silylation of the alcohol 8-10 (Scheme 3) gives 8-11, which on ozonolysis can also afford the silyl ether 8-9. Reductive alkylation now using the silyl ether 8-9 gives 8-12 and 8-13 followed by the second reductive alkylation with an aldehyde or ketone affords the products 8-14 and 8-15 in an essentially opposite ratio as is obtained in Scheme 8 for 8-3 and 8-4. TBAF desilylation then affords primarily 8-4. Separation of the C-1 isomers can usually be achieved at one or more of the intermediate steps. Thus, the preferred C-1 orientation can be selected for depending on the requirements of the desired final compounds.

05-20-2000 - 20461PV

606

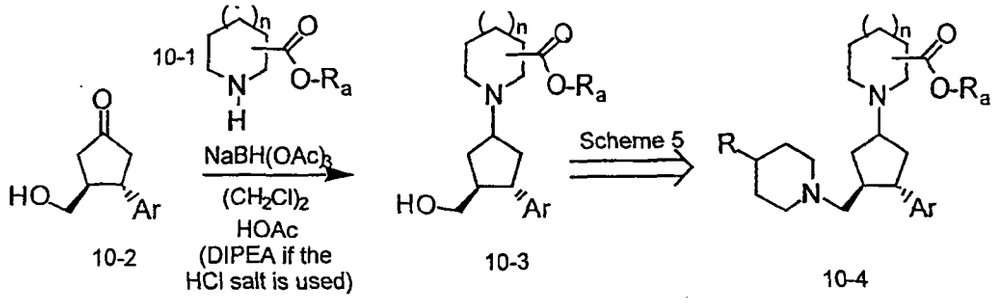
SCHEME 9



Several other alternative routes for the preparation of some 1,3,4-trisubstituted cyclopentanes within the scope of the instant invention are given in Scheme 9. Reductive alkylation, using for example sodium triacetoxyborohydride or sodium cyanoborohydride, of an amino-acid ester having dialkyl substitution with the ketone-alcohol 9-1 (Scheme 4) gives 9-2 as a mixture of C-1 isomers which may be separated and carried on to the final product(s) 9-3 individually or as a mixture as

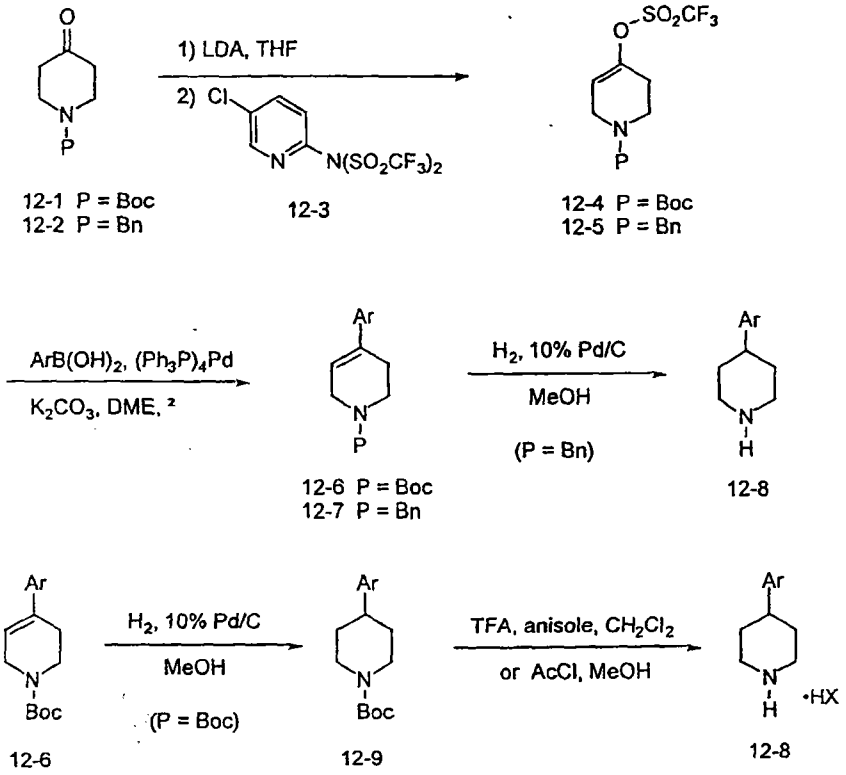
detailed in Scheme 5. Alternatively, a second reductive alkylation of 9-2 as in Scheme 8 affords 9-4 which may be separable or used as a mixture to give final product(s) 9-5. Also, more extended amino-acid esters, such as a β-alanine ester (9-6, n = 1) or 4-aminobutyrate (9-6, n = 2), which may also be substituted on the chain or on N, can be employed to give 9-7. These intermediates can then be converted to final product(s) 9-8 as described in Scheme 5 and/or 8.

SCHEME 10



An alternative route for the preparation of some 1,3,4-trisubstituted cyclopentanes within the scope of the instant invention is given in Scheme 10. Reductive alkylation, using for example sodium triacetoxyborohydride or sodium cyanoborohydride, of a cyclic secondary amino-acid 10-1, such as D- or L-proline t-butyl ester (n = 0), β-proline t-butyl ester (n = 0), 2-, 3-, and 4-t-butylcarboxypiperidine (n = 1), with the ketone-alcohol 10-2 (Scheme 4) gives 10-3 and 10-4 as a mixture of C-1 isomers which may be separated. These intermediates can then be converted to the final product(s) as described in Scheme 5.

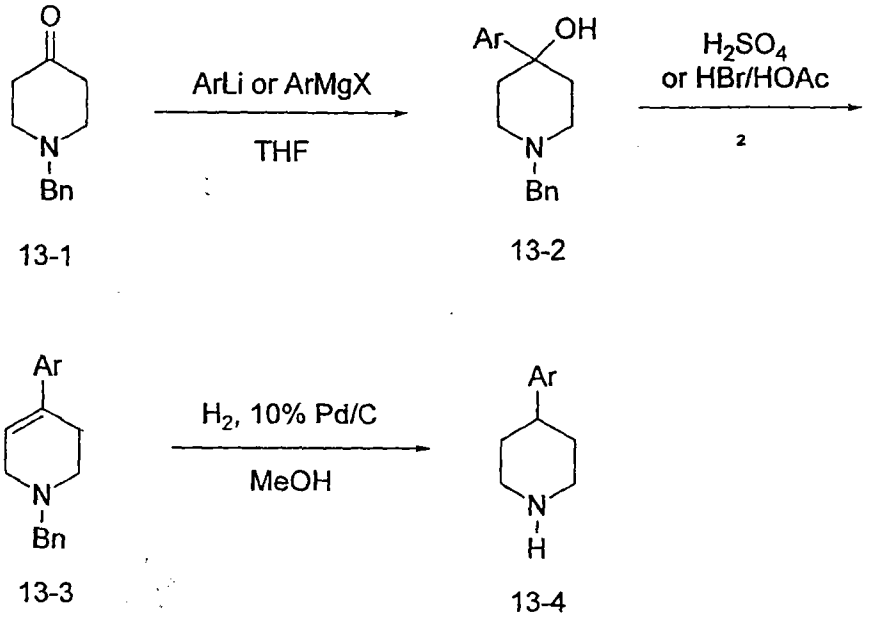
SCHEME 12



One method of generating 4-aryl piperidines as intermediates is given in Scheme 12. Reaction of commercially available 12-1 or 12-2 with a strong base, such as LDA, LHDMS, NaHMDS, KHMDS, or NaH followed by treating with a suitable triflating agent, such as 5-chloropyrid-2-yl triflimide (12-3), N-phenyl triflimide or triflic anhydride, provides enol triflates 12-4 or 12-5. Heating with commercially available aryl boronic acids in the presence of a suitable palladium(0) catalyst such as tetrakis triphenylphosphine palladium, a base (such as potassium carbonate or sodium carbonate), in a solvent such as DME, THF, dioxane or toluene/ethanol, effects coupling to provide the unsaturated products 12-6 or 12-7. In the case of 12-7, treatment with a heterogeneous palladium catalyst in methanol or ethanol in an atmosphere of hydrogen provides the desired intermediate 12-8. Alternatively, the Boc protected derivative 12-6 is hydrogenated under standard conditions to provided the saturated piperidine 12-9, which is then deprotected under

acidic conditions (such as trifluoroacetic acid and anisole in methylene chloride or HCl in methanol), to provide 12-8 as a salt, which is then utilized as the cyclic secondary amine component as shown above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

SCHEME 13



An alternative method of generating 4-aryl piperidines as intermediates is given in Scheme 13. Reaction of commercially available 13-1 with an aryl magnesium halide or with an aryllithium (in the presence or absence of anhydrous cerium trichloride) provides tertiary alcohol 13-2, which upon treatment under acidic conditions (such as sulfuric acid, HBr in acetic acid, HCl in acetic acid) or under dehydrating conditions (such as with thionyl chloride in pyridine or with phosphorus oxychloride) provides olefin 13-3. Hydrogenation under standard conditions using either hydrogen gas or a hydrogen donor (such as ammonium formate or cyclohexene) effects reduction of the double bond and cleavage of the N-benzyl group to provide the desired intermediate 13-4. Under some circumstances it may be preferable to reduce the double bond under non-hydrogenolytic conditions, for example with triethylsilane and trifluoroacetic acid or under dissolving metal conditions (for example, sodium or lithium metal in ammonia or a lower alkyl amine). If the N-

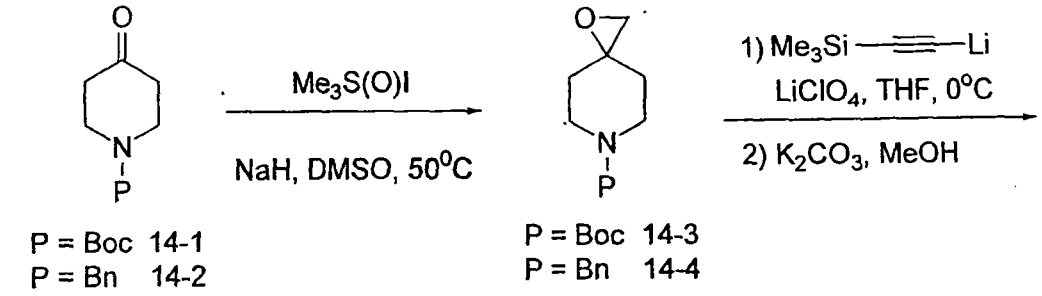
612

benzyl group is not removed under these conditions, it may be cleaved by treatment with either vinyl chloroformate and then hydrogen chloride or by treatment with 2-chloroethyl chloroformate followed by heating in methanol. The product 13-4 is then utilized as the cyclic secondary amine component as shown above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

SCHEME 14

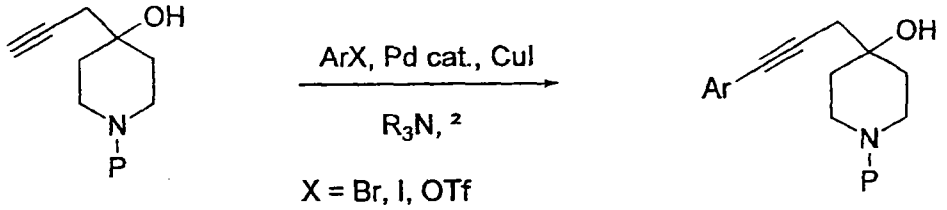
0243686-050450

613



P = Boc 14-1
P = Bn 14-2

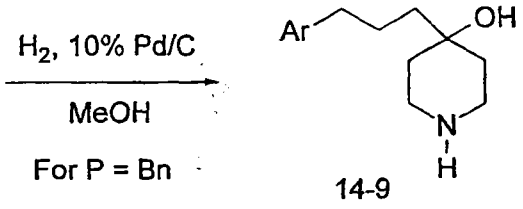
P = Boc 14-3
P = Bn 14-4



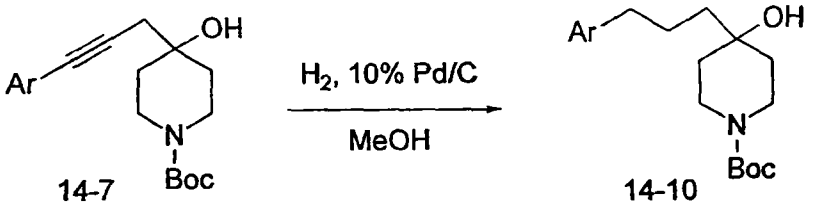
P = Boc 14-5
P = Bn 14-6

X = Br, I, OTf
Pd cat. = $(Ph_3P)_2PdCl_2$, $(Ph_3P)_2Pd(OAc)_2$
R_3N: Et_3N, Bu_3N

P = Boc 14-7
P = Bn 14-8

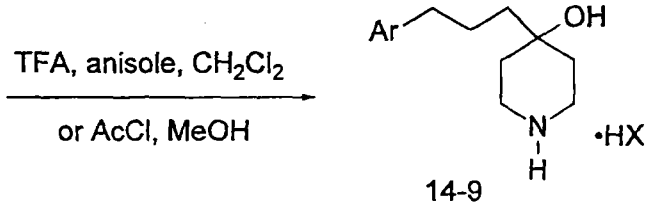


14-9



14-7

14-10

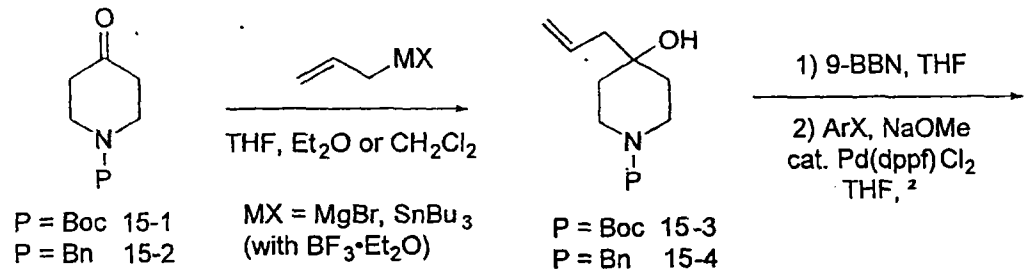


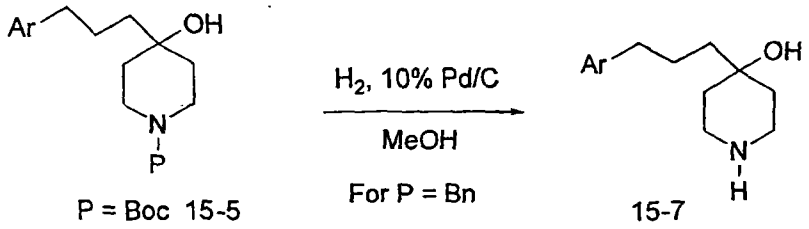
14-9

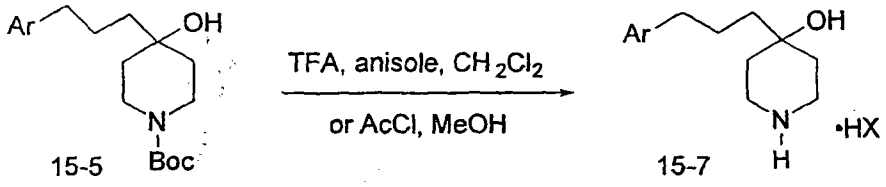
One route for the preparation of 4-hydroxy-4-(3-arylpropyl)piperidines is given in Scheme 14. Treatment of commercially available 4-piperidones 14-1 or 14-2 with trimethylsulfonium iodide and sodium hydride in dimethyl sulfoxide at or above room temperature provides spiro epoxides 14-3 or 14-4. Addition of the lithium salt of trimethylsilylacetylene to these epoxides in the presence of lithium perchlorate in THF at 0 degrees C, followed by treatment of the crude intermediate with potassium carbonate in methanol, affords the acetylenic alcohols 14-5 or 14-6. Heating of these alkynes with an aromatic halide or triflate in the presence of copper(I) iodide, a palladium catalyst such as bis(triphenylphosphine)palladium dichloride or bis(triphenylphosphine)palladium diacetate in the presence of a tertiary amine base such as triethylamine or tributylamine, then provides coupling products 14-7 or 14-8. In the case of the N-benzyl protected intermediate 14-8, hydrogenation/hydrogenolysis under standard conditions (for example 10% Pd/C in an atmosphere of hydrogen) provides desired intermediate 14-9. For the Boc protected species 14-7, hydrogenation as above provides the saturated piperidine 14-10, and treatment of this compound under anhydrous acidic conditions (for example, trifluoroacetic acid and anisole in methylene chloride, or acetyl chloride in methanol) then yields the salt of intermediate 14-9. This compound is then utilized as the cyclic secondary amine component as shown above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11. Alternatively, if 4-piperidone is attached directly to the functionalized alkylcyclopentane framework described above and no functionality in the alkylcyclopentane would be affected, then the chemistry described herein can be carried out treating the aforementioned alkylcyclopentane segment as 'P' given in Scheme 14.

615

SCHEME 15





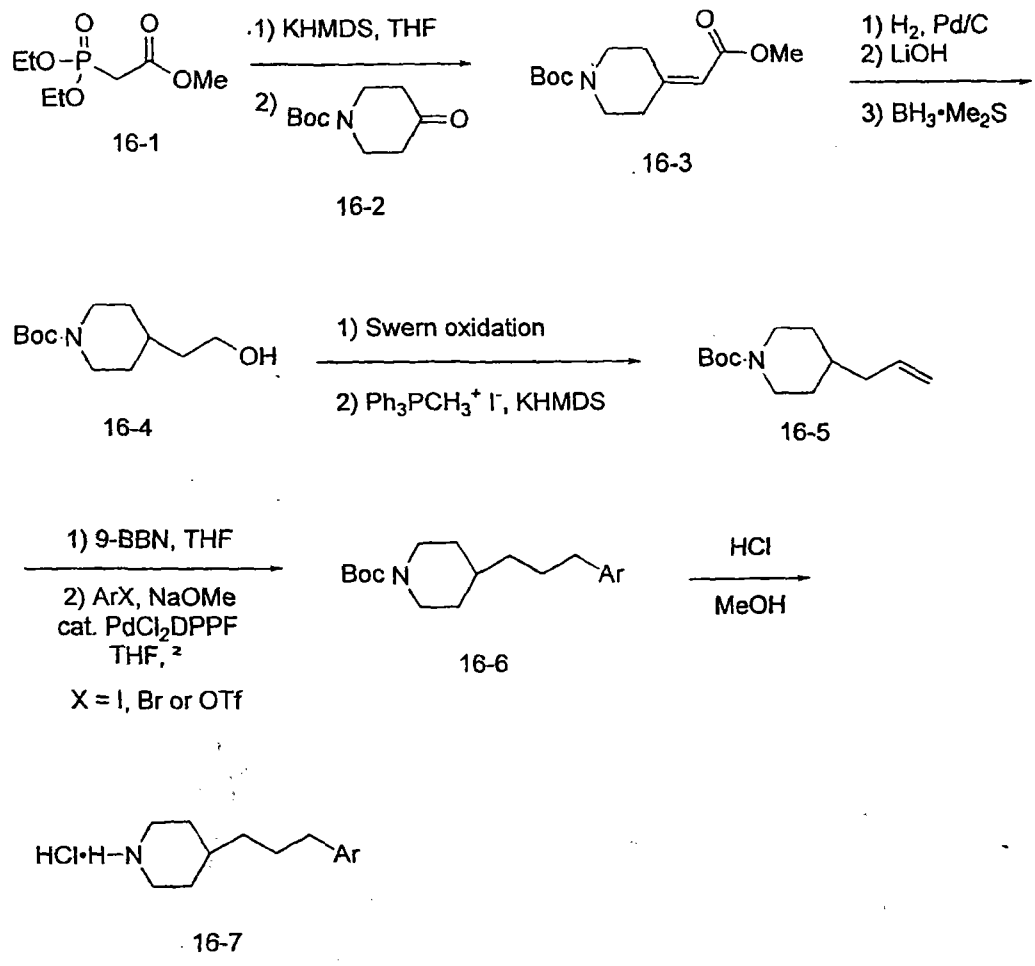


An alternative route for the preparation of 4-hydroxy-4-(3-arylpropyl)piperidines is given in Scheme 15. Treatment of commercially available 4-piperidones 15-1 or 15-2 with a suitable allyl metal compound (such as allylmagnesium bromide or allyltributylstannane (in the presence of boron trifluoride etherate) in THF, ether or dichloromethane, provides adducts 15-3 or 15-4. Hydroboration with a dialkylborane, such as 9-borabicyclo[3.3.1]nonane (9-BBN), followed by treatment with an aryl halide (the halides preferably being bromide or iodide) or aryl triflate and sodium methoxide in the presence of a suitable soluble palladium catalyst, for example $Pd(dppf)Cl_2$, in warm to refluxing THF, provides the 3-arylpropyl derivatives 15-5 and 15-6. For benzylamine 15-6, hydrogenolysis under

standard conditions provides the desired intermediate 15-7. For Boc substituted piperidine 15-5, exposure to suitable anhydrous acidic conditions (for example trifluoroacetic acid and anisole in methylene chloride or HCl in methanol at temperatures from 0-25 degrees C) affords the salt of 15-7. This compound is then utilized as the cyclic secondary amine component as shown above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11. Alternatively, if no functionality are present in the alkylcyclopentane framework that would be adversely effected by the above mentioned chemistry, then 4-piperidone may be attached directly to the alkylcyclopentane framework described above, and the chemistry described in this paragraph can be carried out equating the alkylcyclopentane segment to the group 'P' given in Scheme 15, structures 1 through 6.

EXPRESS MAIL NO. EV 339000005

SCHEME 16



A route for the preparation of 4-(3-arylpropyl)piperidines is given in Scheme 16. Treatment of phosphonoacetate 16-1 with KHMDS followed by addition of commercially available N-Boc -4-piperidone 16-2 provides unsaturated ester 16-3. Hydrogenation of 16-3 followed by hydrolysis to the acid and then reduction with borane•methyl sulfide then affords primary alcohol 16-4. Mild oxidation of 16-4 under Swern conditions provides the corresponding aldehyde, which upon treatment with the Wittig reagent prepared from methyltriphenylphosphonium iodide and KHMDS yields olefin 16-5. Hydroboration with a dialkylborane, such as 9-borabicyclo[3.3.1]nonane (9-BBN), followed by treatment with an aryl halide (the

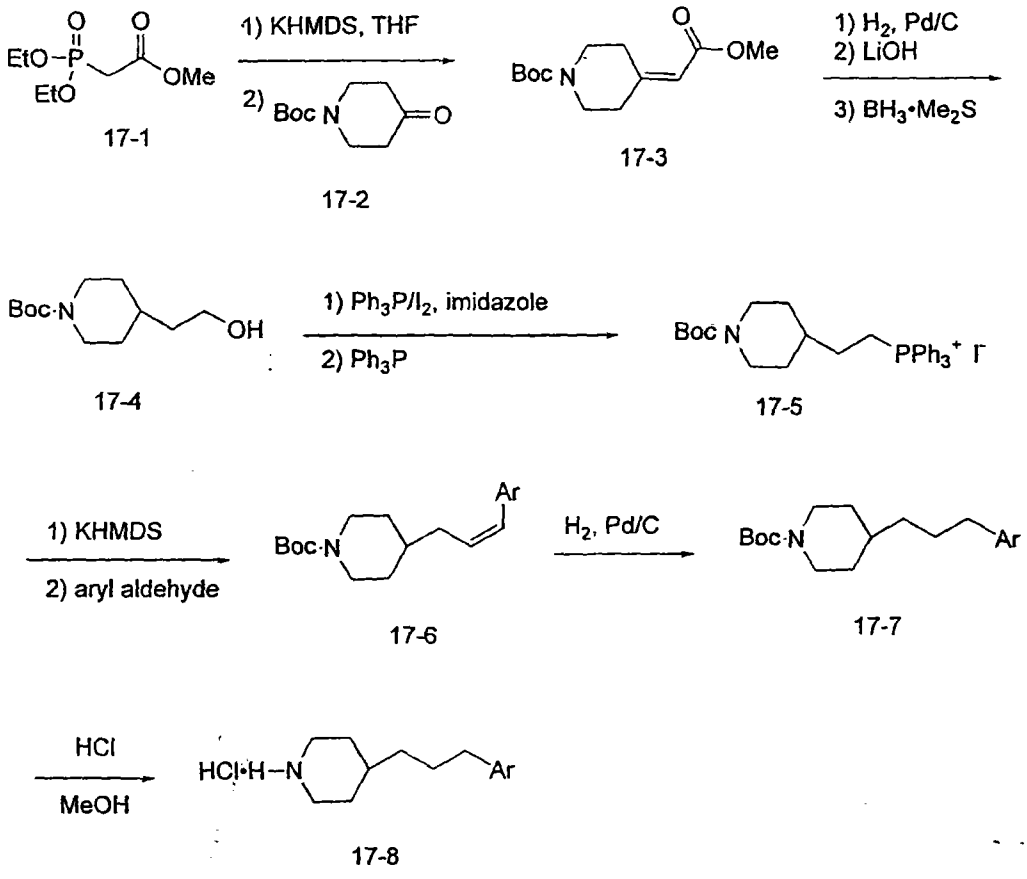
619

halides preferably being bromide or iodide) or aryl triflate in the presence of a suitable soluble palladium catalyst, for example $PdCl_2DPPF$, in warm to refluxing THF, provides the 3-arylpropyl derivative 16-6. Removal of the Boc group under acidic conditions, for example with HCl in methanol or with trifluoroacetic acid in methylene chloride, then affords the 1-unsubstituted piperidine 16-7, which can then be employed as the secondary amine component in the syntheses described above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

0043000005.061403

619

SCHEME 17



Another route for the preparation of 4-(3-arylpropyl)piperidines is given in Scheme 17. Treatment of phosphonoacetate 17-1 with KHMDS followed by addition of commercially available N-Boc -4-piperidone 17-2 provides unsaturated ester 17-3. Hydrogenation of 17-3 followed by hydrolysis to the acid and then reduction with borane•methyl sulfide then affords primary alcohol 17-4. Formation of the alkyl iodide with triphenylphosphine and iodine in the presence of imidazole followed by treatment with triphenylphosphine provides phosphonium salt 17-5. Deprotonation with a suitable base, for example, KHMDS, LiHMDS, NaHMDS, NaH, LDA, or KH affords the Wittig agent *in situ*, which upon treatment with a suitable aromatic aldehyde yields the unsaturated derivative 17-6. Hydrogenation under standard conditions provides 17-7, and removal of the Boc group with HCl in methanol or with other acidic conditions then provides the 1-unsubstituted piperidine

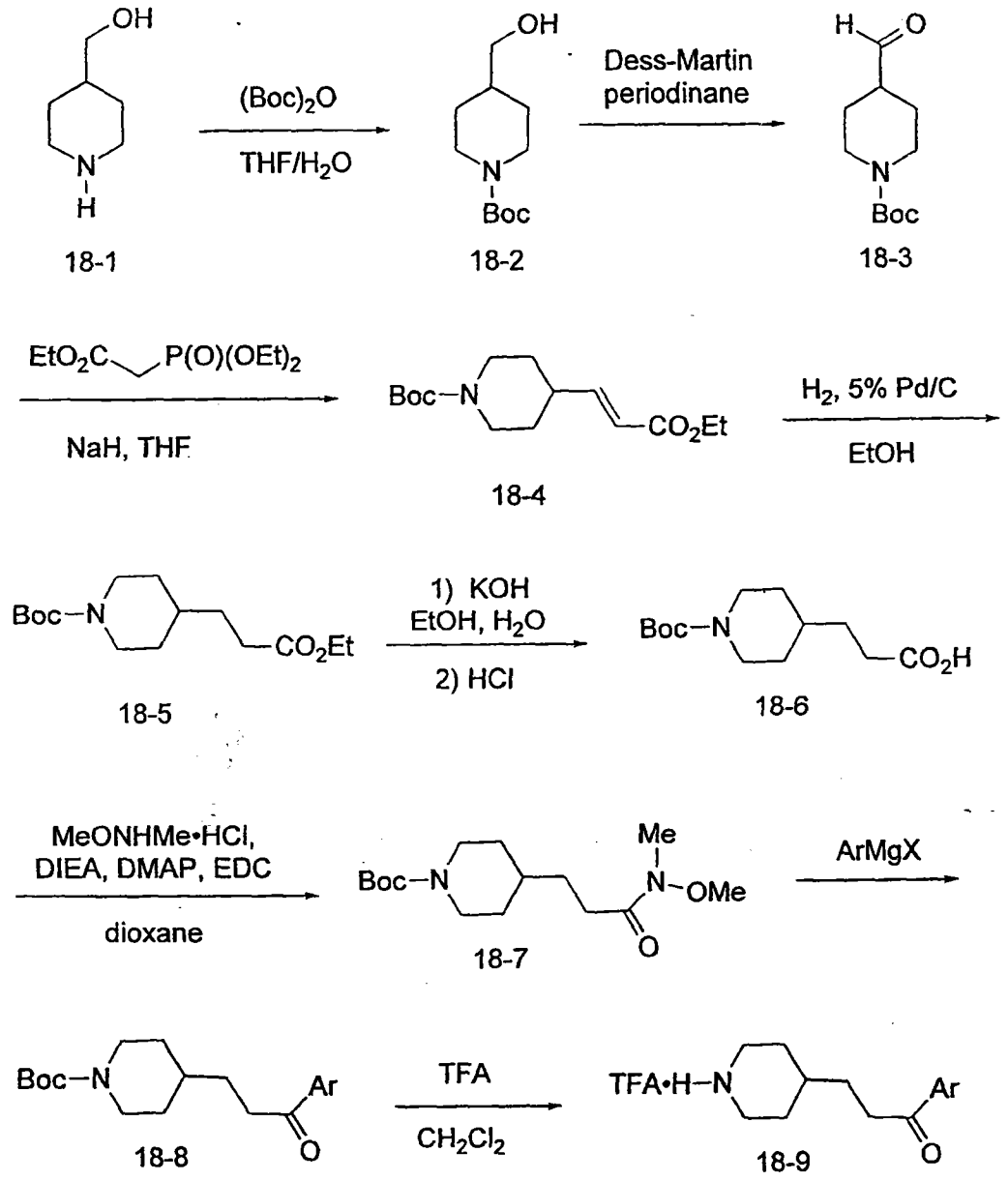
620

17-8, which can then be employed as the secondary amine component in the syntheses described above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

0074050 - 0074050

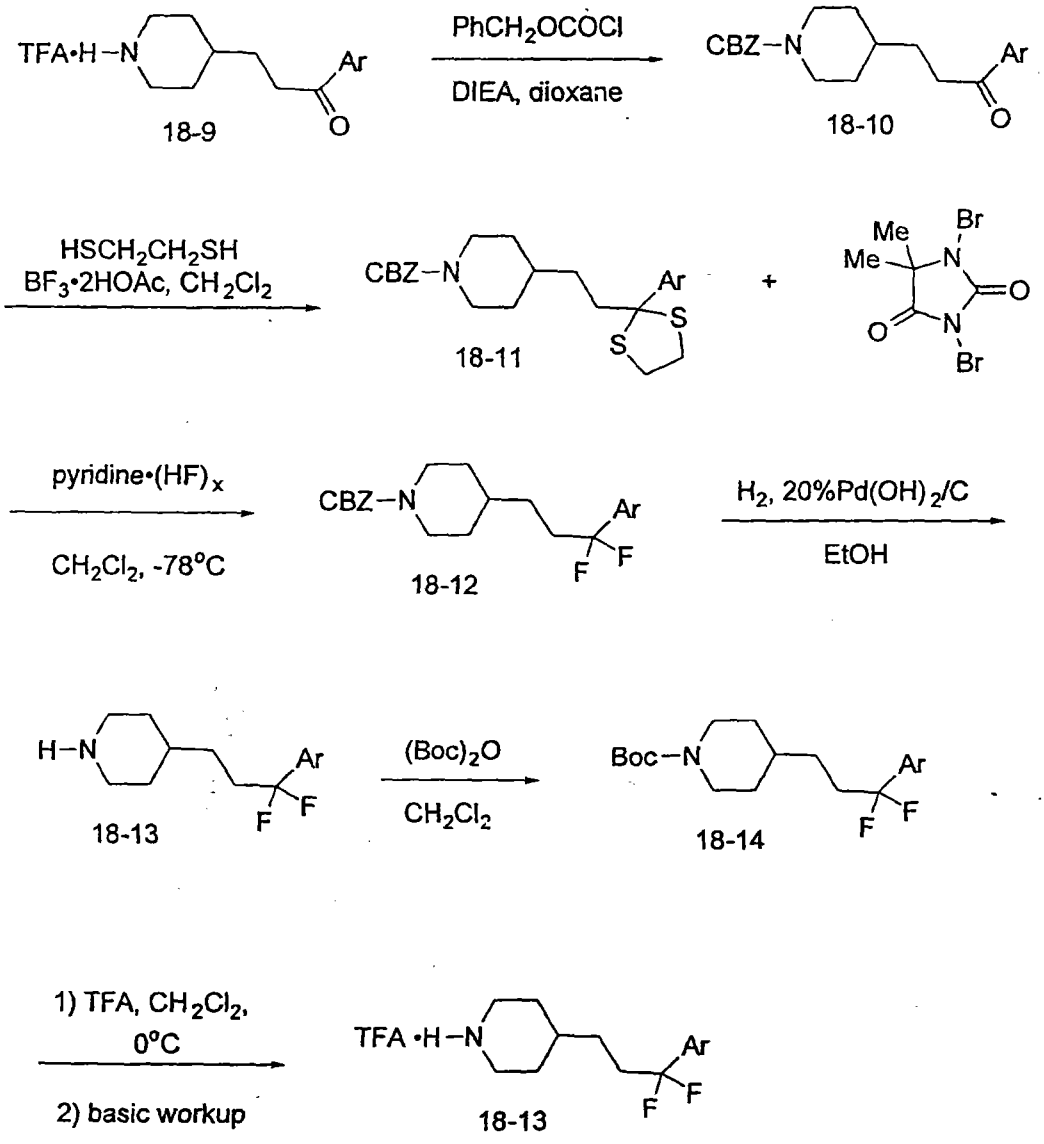
383
621

SCHEME 18



622

SCHEME 18, con't.

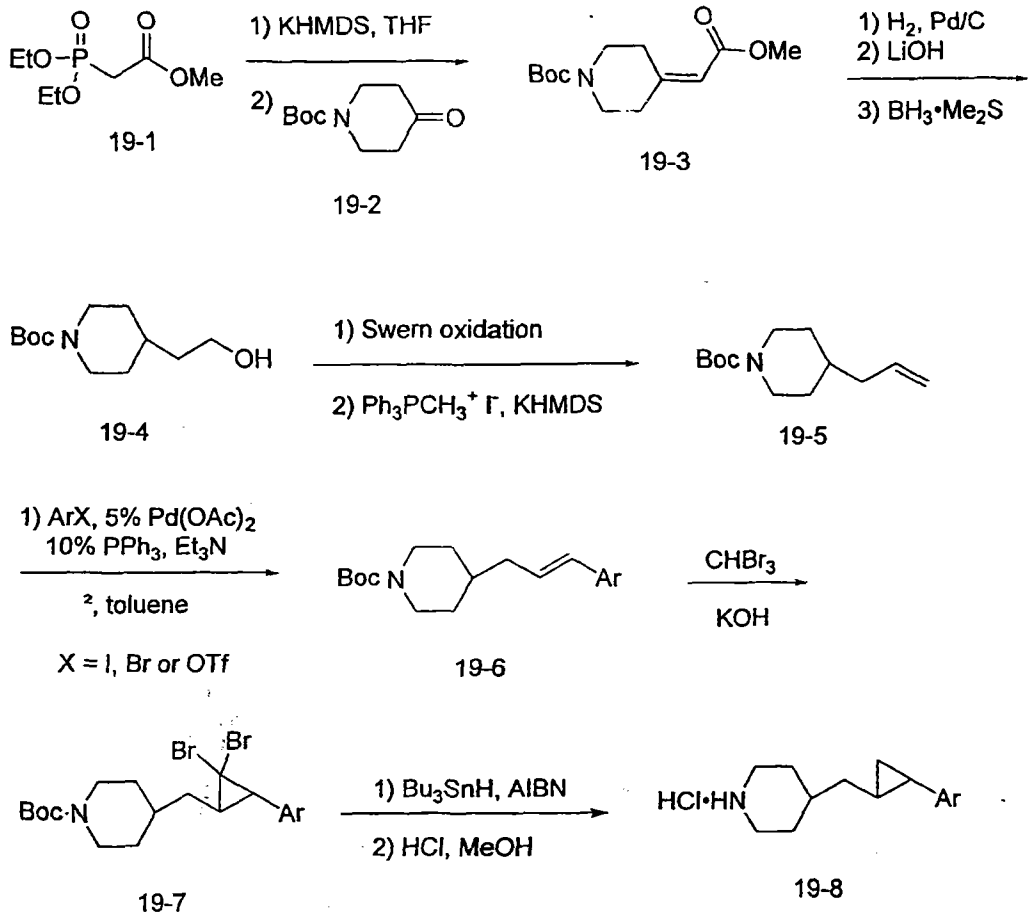


Preparation of piperidines with a 4-(3-aryl-3,3,-difluoropropyl) side chain is given in Scheme 18. Treatment of commercially available 18-1 with Boc anhydride provides

protected piperidine 18-2. Oxidation, for example with the Dess-Martin reagent, by a Swern oxidation, or other known methods provides aldehyde 18-3. Condensation under Horner-Wadsworth-Emmons conditions affords unsaturated ester 18-4, which is hydrogenated to ester 18-5 and then hydrolysed to acid 18-6. Formation of the N-methyl-N-methoxy amide 18-7 is carried out employing standard activating agents such as EDC. Weinreb amide 18-7 is then allowed to react with an arylmetal reagent, such as an aryl magnesium halide or an aryllithium, to provide ketone 18-8. Cleavage of the protecting Boc group under acidic conditions yields 18-9, which is reprotected with a carbobenzyloxy group under standard conditions, to afford 18-10. Formation of dithiolane 18-11 with ethanedithiol and boron trifluoride is followed by treatment with 1,3-dibromo-3,3-dimethylhydantoin and pyridine-hydrogen fluoride complex at or around -78 degrees C, to provide gem-difluoro derivative 18-12. Removal of the CBZ group under reductive conditions provides piperidine 18-13, which may be employed directly as the secondary amine in chemistry described above.

Alternatively, if additional purification is desired, 18-13 may be protected with a Boc group to afford 18-14. After suitable purification, the Boc group is removed under acidic conditions at or near 0 degrees C. A controlled, basic work-up then provides 18-13, suitable for use as described above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

SCHEME 19

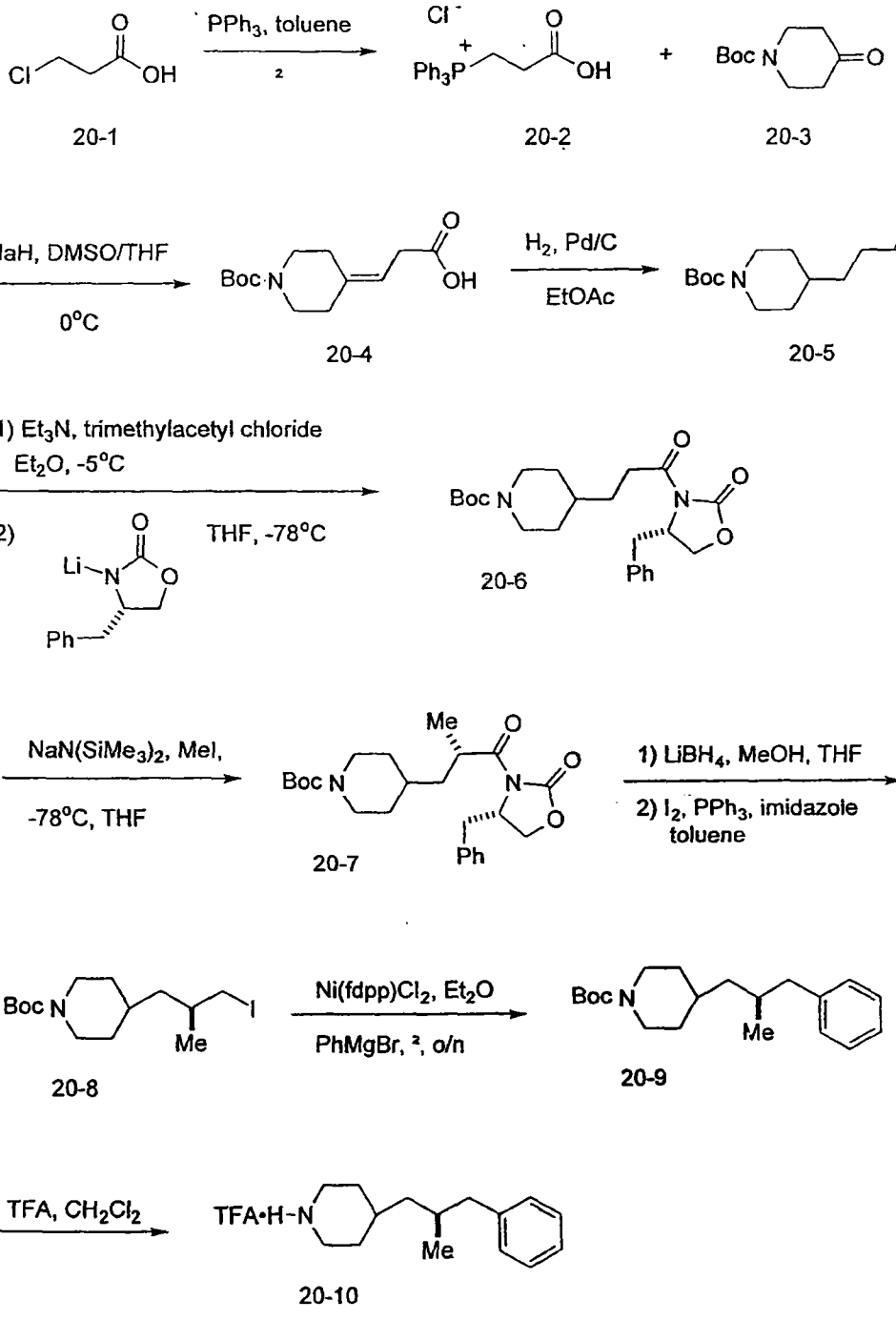


A route for the preparation of 4-(3-arylpropyl)piperidines is given in Scheme 19. Treatment of phosphonoacetate 19-1 with KHMDS followed by addition of commercially available N-Boc -4-piperidone 19-2 provides unsaturated ester 19-3. Hydrogenation of 19-3 followed by hydrolysis to the acid and then reduction with borane•methyl sulfide then affords primary alcohol 19-4. Mild oxidation of 19-4 under Swern conditions provides the corresponding aldehyde, which upon treatment with the Wittig reagent prepared from methyltriphenylphosphonium iodide and KHMDS yields olefin 19-5. Palladium-catalyzed arylation of 19-5 then affords

unsaturated derivative 19-6. Addition of dibromocarbene (generated *in situ* from bromoform and potassium hydroxide) provides cyclopropyl derivative 19-7. Debromination is carried out by slow addition of tributyltin hydride in the presence of the radical initiator AIBN. Removal of the nitrogen protecting group under acidic conditions, for example, hydrochloric acid in methanol, affords cyclopropyl piperidine 19-8, which can then be employed as the secondary amine component in the syntheses described above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

626

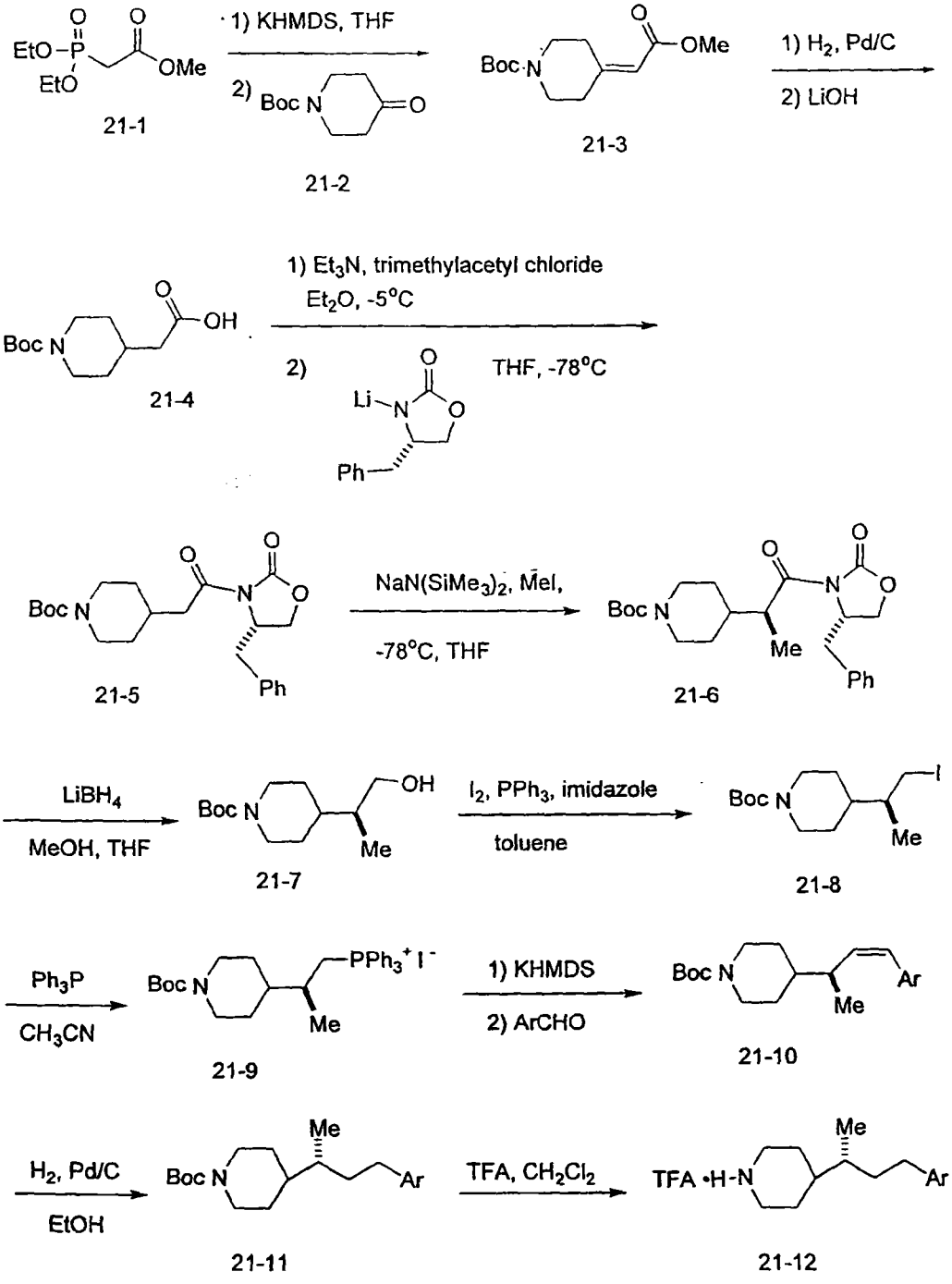
SCHEME 20



A route for the preparation of 4-(3-aryl-2-methylpropyl)piperidines is given in Scheme 20. Treatment of commercially available 3-chloropropionic acid (20-1) with triphenylphosphine in refluxing toluene provides phosphonium salt 20-2. Treatment with sodium hydride in DMSO/THF provides the ylide in situ, which upon addition of piperidone 20-3 affords the adduct 20-4. Reduction of the double bond, for example with hydrogen gas in the presence of a palladium catalyst, gives acid 20-5. Treatment of 20-5 with trimethylacetyl chloride and triethylamine generates the mixed anhydride in situ, which upon treatment with the lithium salt of 4-(S)-benzyl-2-oxazolidone yields 20-6. Deprotonation of 20-6 with sodium hexamethyldisilazide, followed by addition of methyl iodide, provides alpha-methyl derivative 20-7. Reduction of acyl-oxazolidone 20-7 with lithium borohydride produces the corresponding primary alcohol, which is converted to primary iodide 20-8 with iodine, triphenylphosphine and imidazole in toluene. Coupling with phenyl magnesium bromide in the presence of $Ni(fdpp)Cl_2$ affords aralkyl derivative 20-9, which is then deprotected under acidic conditions to provide piperidine 20-10. Piperidine 20-10 can then be employed as the secondary amine component in the syntheses described above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

628

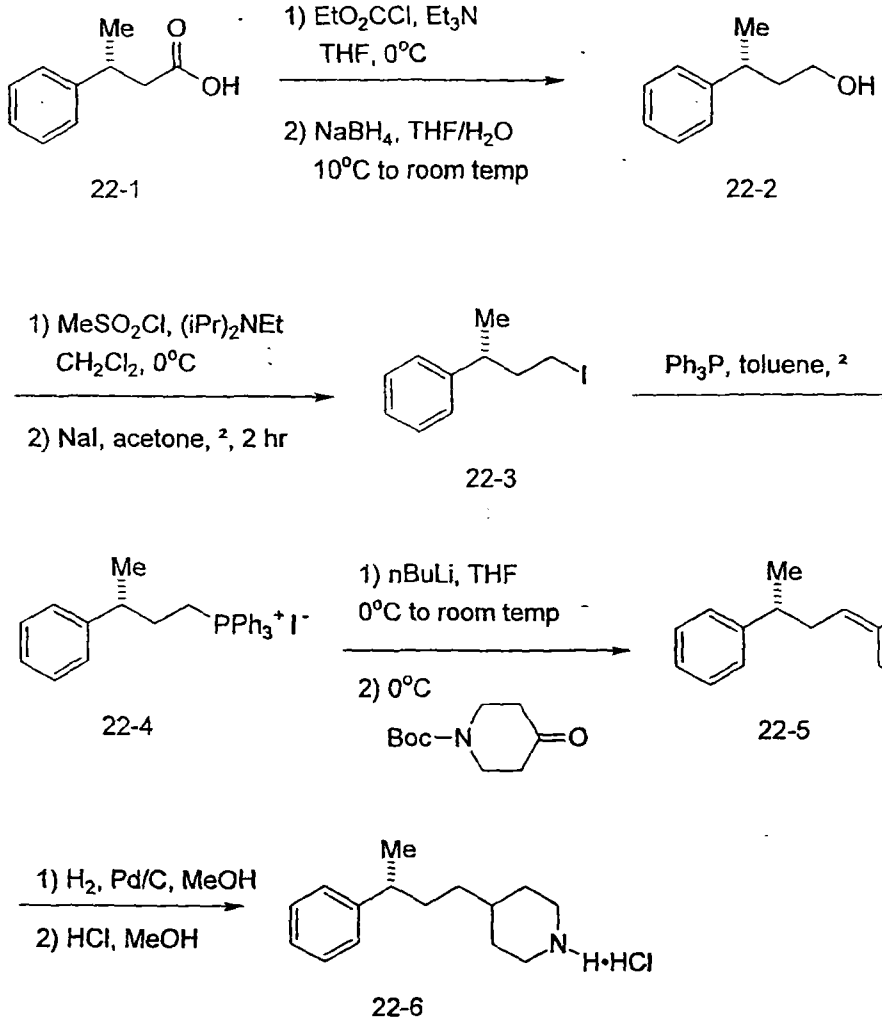
SCHEME 21



A route for the preparation of 4-(3-aryl-1-methylpropyl)piperidines is given in Scheme 21. Addition of the anion of phosphonoester 21-1 to piperidone 21-2 provides unsaturated ester 21-3. Reduction of the double bond and hydrolysis of the ester affords acid 21-4. Treatment of 21-4 with triethylamine and trimethylacetyl chloride provides the mixed anhydride in situ, which is then coupled with the lithium salt of 4-(S)-benzyl-2-oxazolidone , to yield acyl oxazolidone 21-5. Deprotonation with sodium hexamethyldisilazide followed by addition of methyl iodide provides 21-6. Reduction of 21-6 with lithium borohydride affords alcohol 21-7, which upon treatment with iodine, triphenylphosphine and imidazole in toluene is converted to iodide 21-8. Treatment with triphenylphosphine gives phosphonium salt 21-9, which is converted to the ylide with potassium hexamethyldisilazide. Addition of an aryl aldehyde generates unsaturated aryl derivative 21-10. Hydrogenation provides saturated piperidine 21-11, which is then deprotected under acidic conditions to afford 21-12, which can then be employed as the secondary amine component in the syntheses described above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

630

SCHEME 22



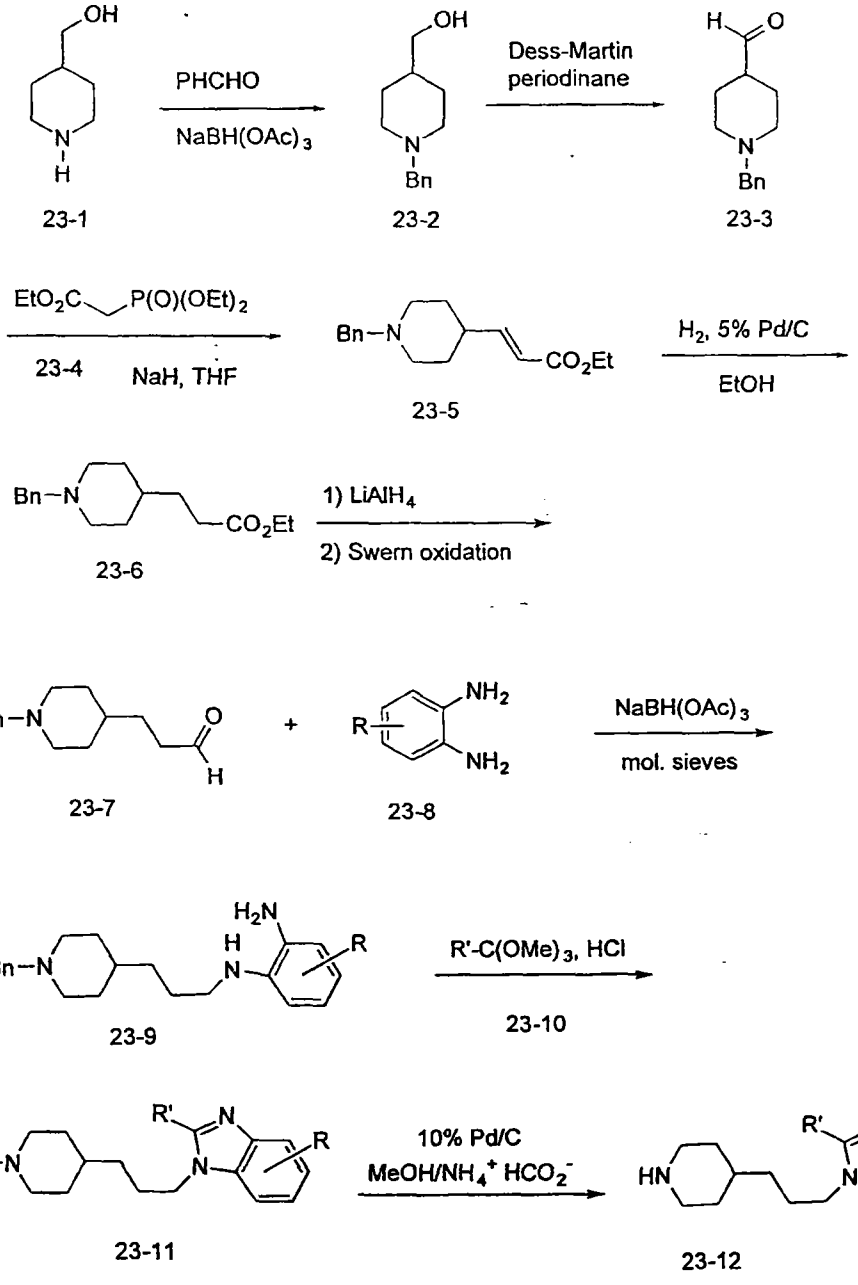
A route for the preparation of 4-(3-aryl-3-methylpropyl)piperidines is given in Scheme 22. Treatment of commercially available 4-(R)-phenylbutyric acid (22-1) with ethyl chloroformate and triethylamine forms the asymmetric anhydride in situ, which upon treatment with sodium borohydride provides primary alcohol 22-1. Alternatively, this conversion can be carried out by treatment of 22-1 with borane-THF. Activation of the hydroxy group of 22-2 with methanesulfonyl chloride in the presence of a hindered base such as N,N-(diisopropyl)ethylamine, followed by displacement with sodium iodide in refluxing acetone affords iodide 22-3. Heating

with triphenylphosphine in toluene provides the phosphonium salt 22-4. Deprotonation of this salt with a strong base, for example n-butyl lithium generates the Wittig reagent in situ, which is then allowed to react with N-Boc-4-piperidone, to yield olefin 22-5. Hydrogenation of the double bond followed by treatment with acid, for example HCl in methanol, then provides the secondary amine salt 22-6, which can then be employed as the secondary amine component in the syntheses described above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

EP1360185 - 061400

632

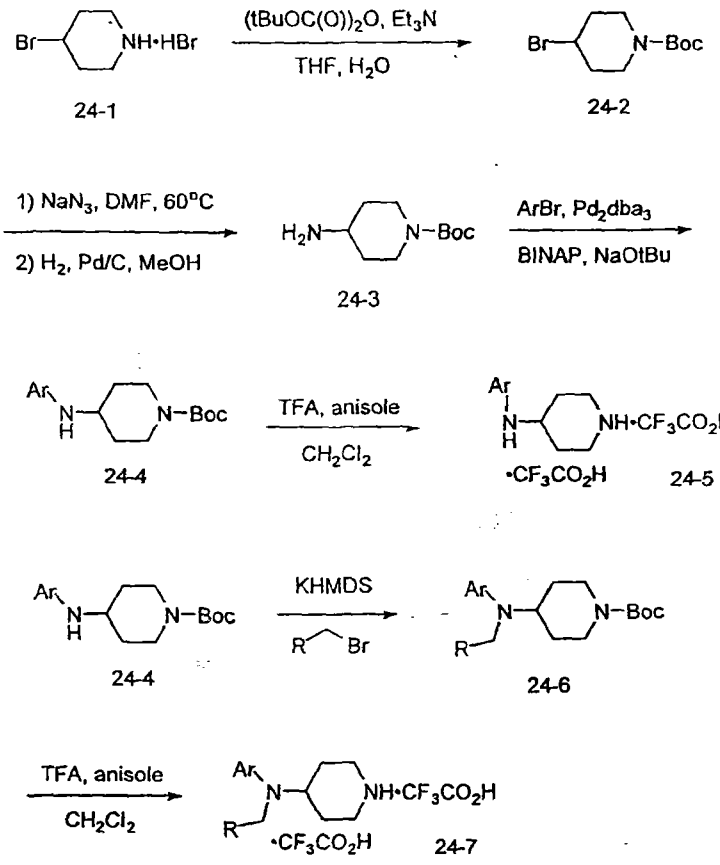
SCHEME 23



5

A route for the preparation of 4-(3-(benzimidazol-2-yl)propyl)piperidines is given in Scheme 23. Protection of piperidine 23-1 under reductive amination conditions provides benzylamine 23-2. Oxidation to aldehyde 23-3 is carried out under standard conditions, for example with the Dess-Martin periodinane. Addition of ester 23-4 provides unsaturated olefin 23-5, which upon reduction affords ester 23-6. Reduction with lithium aluminum hydride or other strong hydride reducing agents followed by mild oxidation provides aldehyde 23-7. Upon combination with diamine 23-8 under reductive alkylation conditions affords the N-alkylated derivative 23-9. Treatment with orthoformate derivative 23-10 in the presence of acid yields benzimidazole 23-11, which upon hydrogenation with palladium on carbon under transfer hydrogenation conditions generates piperidine 23-12, which can then be employed as the secondary amine component in the syntheses described above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

SCHEME 24

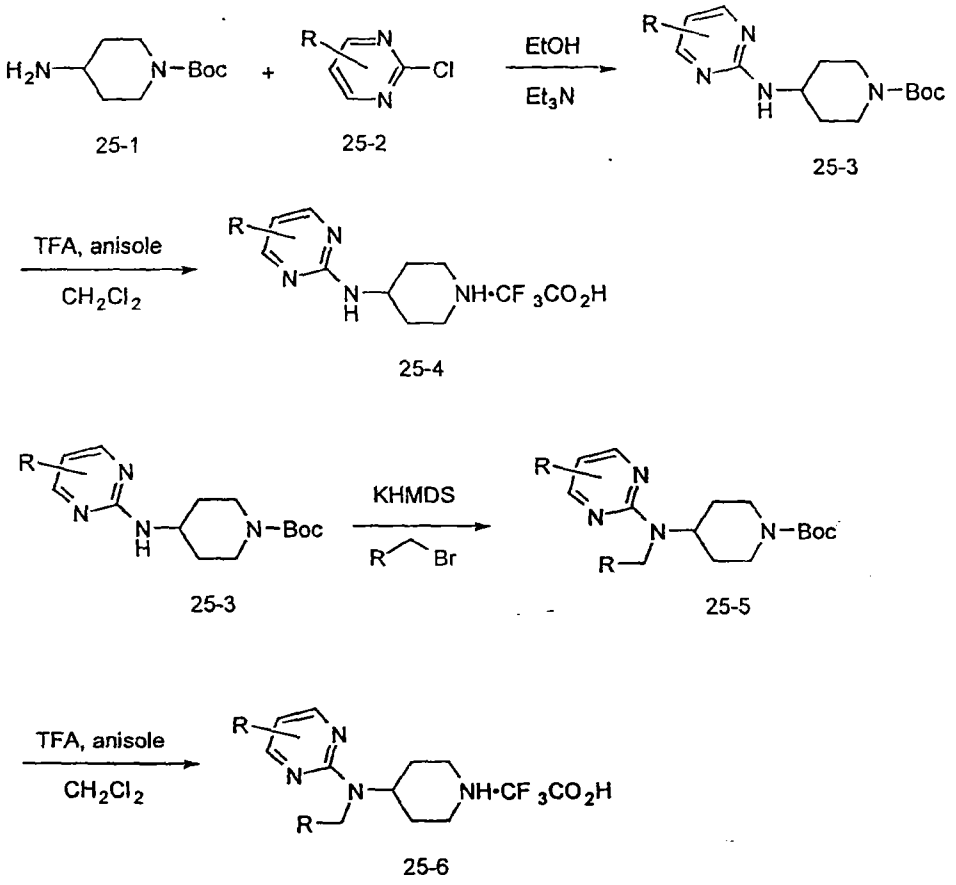


Procedures for synthesizing certain CCR5 receptor modulators containing 4-(heteroarylamino)piperidine functionality are shown in Scheme 24. After protecting commercially available 4-bromopiperidine, the bromide is displaced with sodium azide, and the azide is reduced, for example by catalytic reduction, to provide aminopiperidine 24-3. Treatment of 24-3 with an aryl or heteroaryl halide (the halide preferably being bromide) in the presence of a palladium catalyst, sodium t-butoxide and a suitable bidentate ligand (such as BINAP), according to the conditions of Buchwald et al, provides arylamine 24-4. Direct acidic deprotection of 24-4 may be carried out to provide secondary amine 24-5. Alternatively, amine 24-4 may be alkylated with a suitable alkyl, alkenyl or alkynyl halide (wherein the halide is bromo or iodo in the case of an alkyl group and chloro or bromo in the case of allylic or propargylic functionality) in the presence of a strong base, such as potassium

hexamethyldisilazide, to provide trisubstituted amine 24-6. Acidic deprotection, for example, trifluoroacetic acid and anisole in dichloromethane, or methanolic hydrochloric acid, then provides the bis ammonium salt, which in the case of trifluoroacetic acid deprotection, is compound 24-7. The secondary piperidines 24-5 and 24-7 are then utilized as the cyclic secondary amine component as shown above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

0143000 "0514 05

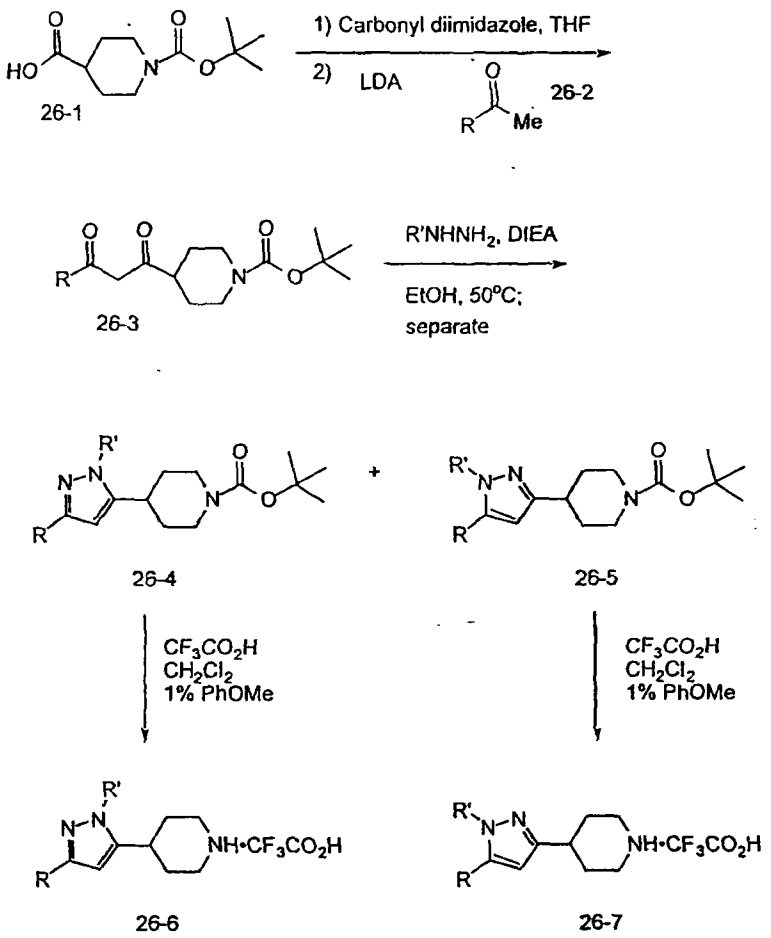
SCHEME 25



For certain aminoheterocycles, direct displacement of a halogen may provide improved access to the desired intermediates. For example, as shown in Scheme 25, unsubstituted and substituted 2-chloropyrimidines 25-2 may be coupled directly to amine 25-1 in the presence of a suitable base, such as triethylamine, to provide aminopyrimidine 25-3. Acidic deprotection then affords 25-4. Alternatively, 25-3 may be alkylated in the presence of a strong base to provide 25-5, which upon deprotection gives intermediate 25-6. The secondary piperidines 25-4 and 25-6 are then utilized as the cyclic secondary amine component as shown in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

637

SCHEME 26

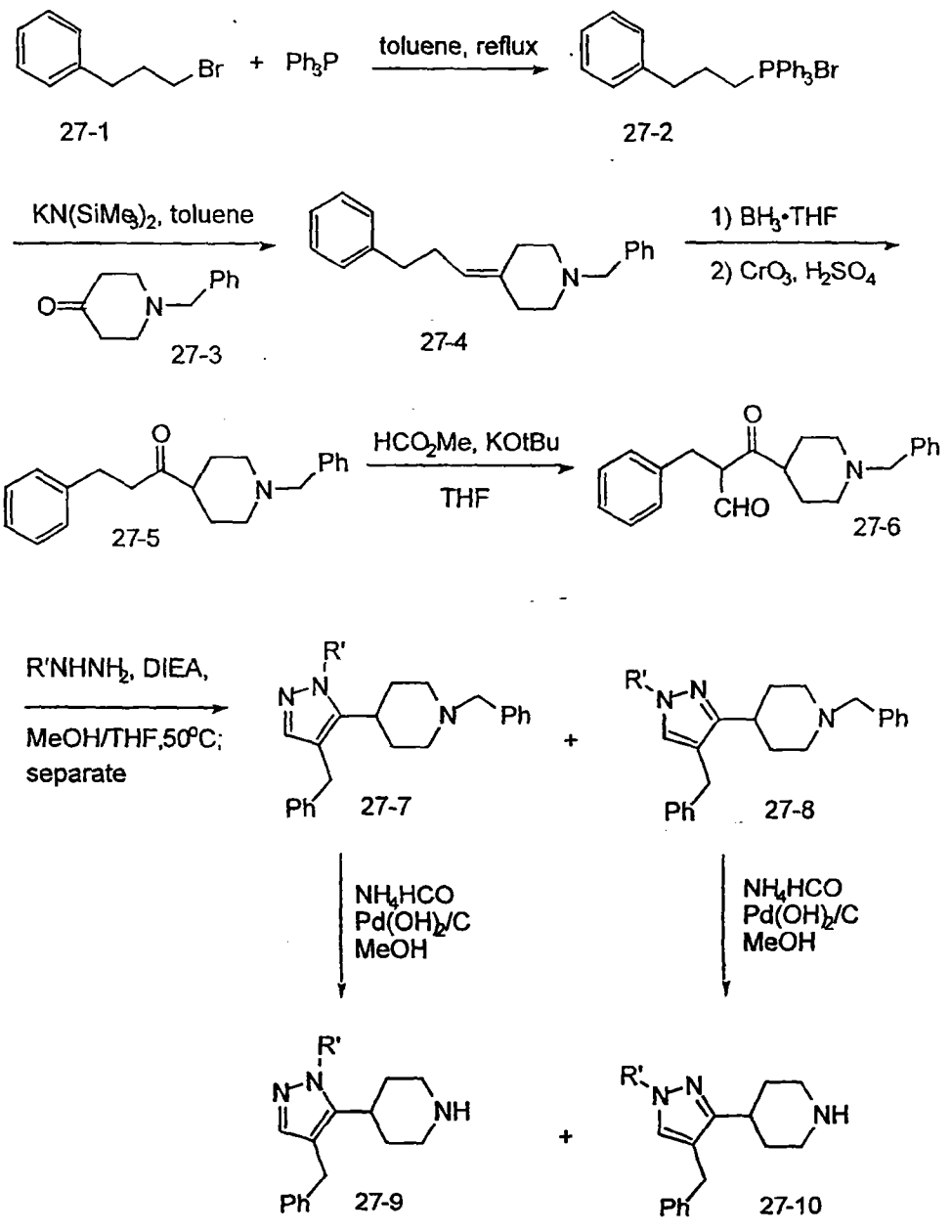


One preparation of piperidine subunits containing functionalized pyrazoles at C4 of the piperidine is given in Scheme 26. Treatment of piperidine 26-1 with carbonyldiimidazole to form the acyl imidazole, followed by addition of a dialkyl or alkyl-aryl ketone (26-2) in the presence of lithium diisopropylamide (LDA) gives the diketone 26-3. Treatment with a monoalkyhydrazine in an alcohol solvent at temperatures between 0 to 100 degrees C (preferably about 50 degrees C) in the presence of a hindered base such as DIPEA then provides a mixture of the isomeric pyrazoles 26-4 and 26-5. After separation of these compounds by chromatography or crystallization, the individual products are deblocked under acidic conditions (for example trifluoroacetic acid and anisole with or without methylene chloride as a co-

solvent) to provide the piperidine salts 26-6 and 26-7, which are then used as the cyclic secondary amine component as shown above in Scheme 2 and in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

0054000.0054030

SCHEME 27



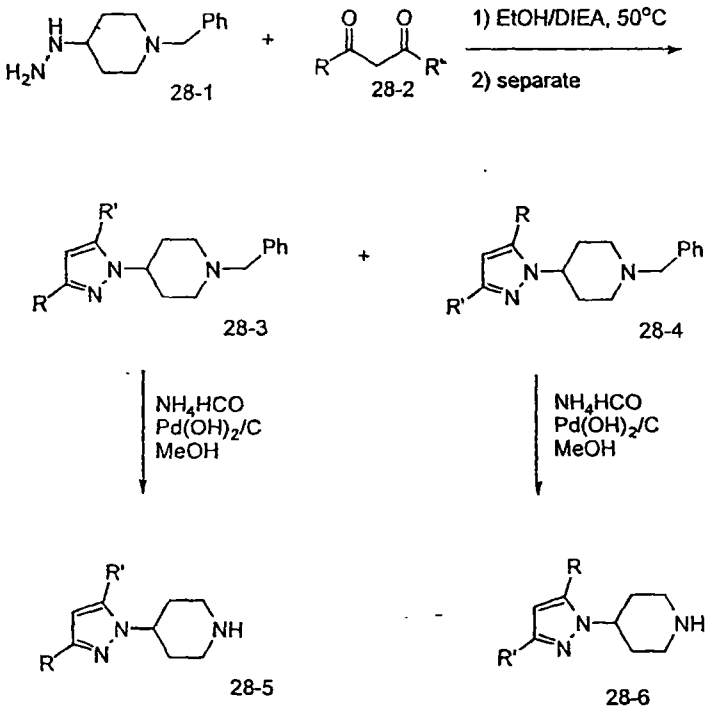
Another preparation of piperidine subunits containing functionalized pyrazoles at C4 of the piperidine is given in Scheme 27. Treatment of commercially available bromide 27-1 with triphenylphosphine in refluxing toluene provides phosphonium salt

64C

27-2, which after treatment with a strong anhydrous base such as potassium hexamethyldisilazide in toluene and the piperidine ketone 27-3 provides the olefin 27-4. Hydroboration followed by an oxidative work-up with chromic acid then affords ketone 27-5. Selective formylation of 27-5 with methyl formate in the presence of potassium t-butoxide selectively affords ketoaldehyde 27-6. Heating of 27-6 with a monoalkylhydrazine in methanol in the presence of a hindered (or insoluble) base such as DIPEA then provides a mixture of the 1,4-disubstituted pyrazoles 27-7 and 27-8. After separation by chromatography, crystallization or fractional distillation, the purified isomers are deprotected under transfer hydrogenation conditions to provide the piperidines 27-9 and 27-10, which are then utilized as the cyclic secondary amine component as shown above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

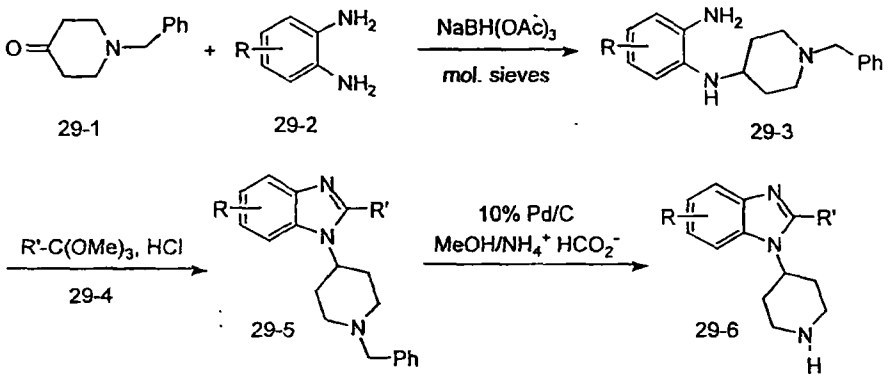
0054.0054.0000

SCHEME 28



A preparation of piperidine subunits containing 3,5-difunctionalized pyrazoles linked through N-1 to C-4 of the piperidine is given in Scheme 28. Treatment of commercially available hydrazine 28-1 with diketone 28-2 in ethanol at 0 to 90 degrees C (preferably 50 degrees C) in the presence of DIPEA provides a mixture of pyrazoles 28-3 and 28-4, which are separated under standard conditions, for example HPLC. Removal of the benzyl groups by transfer hydrogenation provides the secondary piperidines 28-5 and 28-6, which are then utilized as the cyclic secondary amine component as shown above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

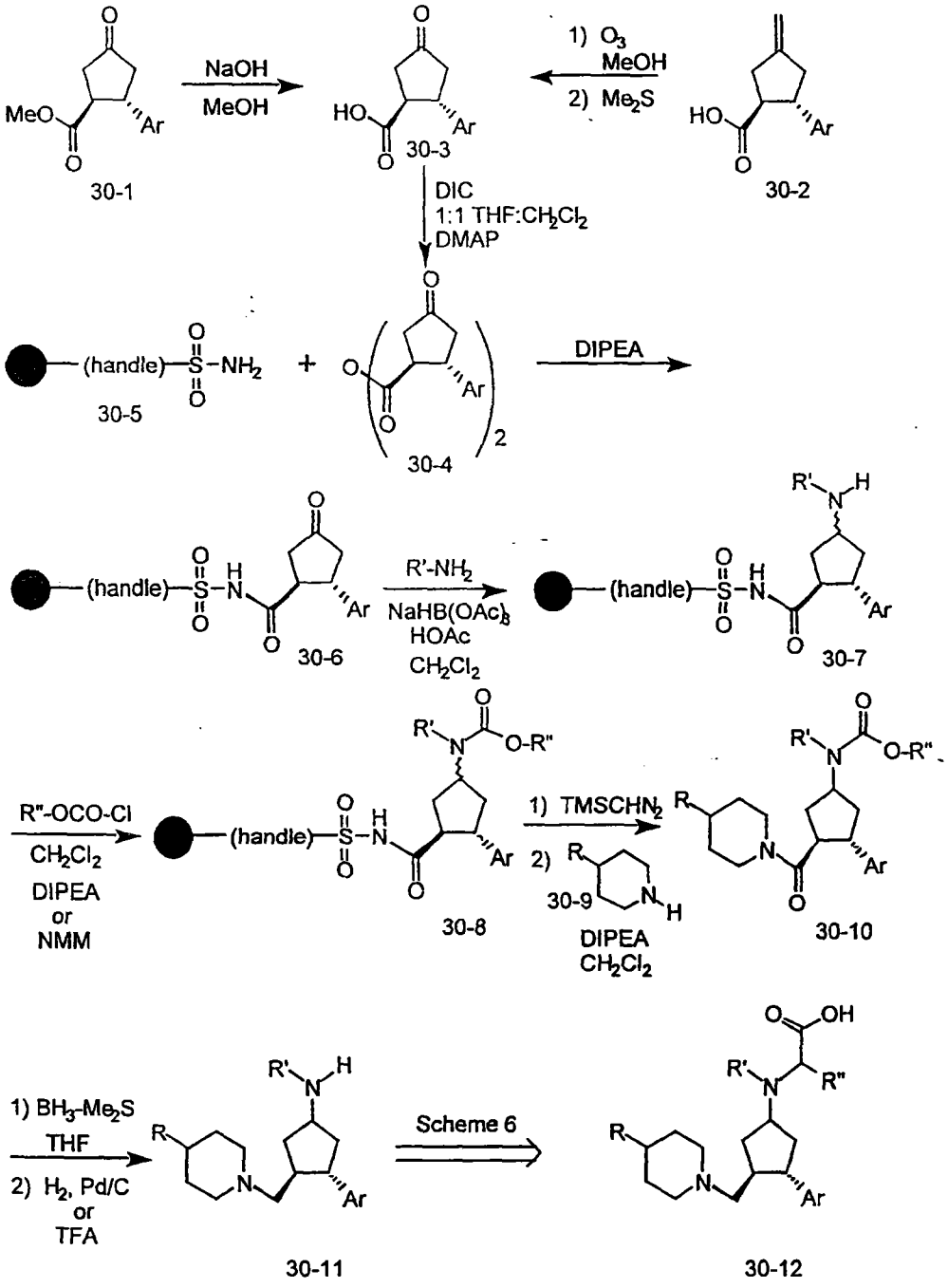
SCHEME 29



A preparation of 4-(benzimidazol-1-yl)piperidine subunits is given in Scheme 29. Combining piperidone 29-1 and diamine 29-2 in the presence of sodium triacetoxyborohydride under dehydrating conditions provides reductive amination product 29-3. Addition of a suitably substituted ortho ester 29-4 in the presence of a acid catalyst, for example concentrated hydrochloric acid, provides benzimidazole intermediate 29-5. Deprotection under reductive conditions, for example with palladium on carbon under transfer hydrogenation conditions, then provides secondary amine 29-6, which is then utilized as the cyclic secondary amine component as shown above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

643

SCHEME 30



Another method of preparing compounds within the scope of the instant invention is given in Scheme 30 in which most of the chemistry is done on a resin and thus simplifies the isolations. Thus, the keto-acid 30-3, prepared either by standard hydrolysis of the ester 30-1 or oxidation of the exo-methylene of 30-2 with ozone in methanol at -70 °C followed by treatment with dimethyl sulfide, is first activated as its anhydride 30-4 by treatment with a dehydrating agent, such as dicyclohexylcarbodiimide or diisopropylcarbodiimde, in a suitable solvent, such as THF or methylene chloride or a mixture of these, with a catalytic amount of DMAP. Reaction of 30-4 with a suitable sulfonamide linker 30-5 affords the resin-bound cyclopentanone 30-6. Reductive amination of various amines with 30-6 affords the resin-bound amino derivative 30-7. Acylation can be done under standard conditions, such as with chloroformates, usually in the presence of an amine base, such as triethylamine, diisopropylethylamine, N-methylmorpholine, or pyridine, to afford the resin-bound amine derivative 30-8. Activation of the resin sulfonamide linker with trimethylsilyldiazomethane and displacement with an amine, such as the piperidine 30-9 (see Schemes 12-29) in which R must be stable to borane-dimethyl sulfide reduction, gives the corresponding amide 30-10. Subsequent reduction of the amide 30-10 with borane-dimethyl sulfide and removal of the carbamate, such as with TFA for a Boc derivative or standard hydrogenation for a CBZ derivative, affords the amine 30-11, which can be converted to the desired final compound as detailed in Scheme 6.

In some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

GENERAL

Concentration of solutions was carried out on a rotary evaporator under reduced pressure. Flash chromatography was carried out on silica gel (230-400 mesh). NMR spectra were obtained in $CDCl_3$ solution unless otherwise noted. Coupling constants (J) are in hertz (Hz). Abbreviations: diethyl ether (ether), triethylamine (TEA), N,N-diisopropylethylamine (DIEA) saturated aqueous (sat'd), room temperature (rt), hour(s) (h), minute(s) (min).

HPLC CONDITIONS

HPLC A. Retention time using the following conditions: Column: YMC ODS A, 5 μ, 4.6 x 50 mm; Gradient Eluant: 10:90 to 90:10 v/v CH_3CN/H_2O + 0.5% TFA over 4.5 min, hold 30 sec; Detection: PDA, 210-400 nm; Flow Rate: 2.5 mL/min.

HPLC B. Retention time using the following conditions: Column: Analytical Sales & Services Advantage HL C18 5 μ 4.6 x 100 mm column; Gradient Eluant: 10:90 to 90:10 v/v CH_3CN/H_2O + 0.5% TFA over 10 min, hold 2 min; Detection: PDA, 200-400 nm; Flow Rate: 2.25 mL/min.

The following are representative Procedures for the preparation of the piperidines used in the following Examples or which can be substituted for the piperidines used in the following Examples which may not be commercially available.

PROCEDURE 1

4-(3-Benzyl-1-ethyl-(1H)-pyrazol-5-yl)piperidine trifluoroacetic acid salt

Step A: 1-(1-(t-Butoxycarbonyl)piperidin-4-yl)-4-phenylbutane-1,3-dioneMethod A:

n-Butyl lithium (100 mL, 0.16 mole) was added to a stirred solution of diisopropylamine (16.16 g, 22.4 mL, 0.16 mole, distilled) in THF (450 mL) at 0 °C over 45 min under nitrogen. Stirring was continued for 10 min at 0 °C after the addition was complete. After cooling to -78 °C, phenylacetone (21.45 g, 21.13 mL, 0.16 mole) in THF (100 mL) was added dropwise over 15 min with stirring. This solution was stirred at -78 °C for 1 h. Meanwhile, a solution of *N*-Boc isonipecotic acid (18.32 g, 0.080 mole) and carbonyl diimidazole (12.98 g, 0.080 mole) in THF (150 mL) was prepared. After stirring for 15 min, this solution was cannulated into the enolate solution dropwise over 15 min. The reaction was stirred at <-70 °C for 1 h and then allowed to warm to rt over 3 h. The reaction was quenched with 1M citric acid (250 mL) and stirred for 16 h. The organic layer was separated and washed with

250 mL each of saturated sodium bicarbonate solution, water and brine. After drying over sodium sulfate, the organic layer was concentrated to give an oil. The residue was purified by FC on silica gel (10% ethyl acetate in 60-80 °C petroleum ether) to give separation of the two isomers. The first higher R_f fractions afforded pure title compound as the minor product (3.5 g) as an oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.37 (m, 2 H), 7.25-7.31 (m, 3 H), 5.46 (s, 1 H), 4.11-4.17 (m, 2 H), 3.63 (s, 2 H), 2.70-2.76 (m, 2 H), 2.29 (tt, J = 11.7 and 3.7 Hz, 1 H), 1.75-1.80 (m, 2 H), 1.47-1.61 (m, 2 H), 1.47 (s, 9 H).

MS (ESI): m/z 346 (M + 1).

The lower R_f fractions contained phenylacetone and major product 1-(1-(t-butoxycarbonyl)piperidin-4-yl)-2-phenylbutane-1,3-dione from which the latter crystallized on standing to give 7 g white solid (m.p. 105-106 °C).

^{1}H NMR (360 MHz, $CDCl_3$): δ 15.23 (s, 1 H), 7.3-7.45 (m, 3 H), 7.15-7.2 (m, 2 H), 4-4.1 (m, 2 H), 2.35-2.50 (m, 2 H), 2.2-2.3 (m, 1 H), 1.87 (s, 3 H), 1.5-1.75 (m, 4 H), 1.43 (s, 9 H).

MS (ESI): m/z 346 (M + 1).

Method B:

Step B1: 1-(t-Butoxycarbonyl)piperidine-4-*N*-methyl-*N*-methoxycarboxamide

N-Boc isonipecotic acid (13.56 g, 59.2 mmol), N,O-dimethyl hydroxylamine hydrochloride (8.65 g, 88.7 mmol), and 1-hydroxybenzotriazole hydrate (15.9 g, 118 mmol) were dissolved in DMF (225 mL) in a 500 mL round-bottom flask and diisopropylethylamine (15.3 g, 20.6 mL, 118.3 mmol) was then added with stirring at rt. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (17.01 g, 88.74 mmol) was added in several portions over 10 min with stirring. After 22 h, the reaction mixture was poured into a water and ice mixture (600 mL) and was extracted with ethyl acetate (5 x 125 mL). The combined organic layers were washed with 1N HCl (2 x 200 mL), 5% sodium bicarbonate (2 x 200 mL), water and brine, dried over sodium sulfate and concentrated to give the title compound (15.58 g) as a yellowish oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.11-4.20 (m, 2 H), 3.72 (br s, 3 H), 3.20 (br s, 3 H), 2.75-2.86 (m, 3 H), 1.63-1.76 (m, 4 H), 1.47 (s, 9 H).

Step B2: 4-Acetyl-1-(t-butoxycarbonyl)piperidine

After dissolving the Weinreb amide from Step B1 in anhydrous ether (400 mL) under nitrogen and cooling the solution in an ice bath, 1.4M methyl magnesium bromide (55 mL) in 3:1 toluene and THF was added with stirring and cooling over 30 min. After stirring at 0 °C for 1 h, the reaction was poured into a mixture of ice water (400 mL) and acetic acid (8 mL, 150 mmol). The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were washed with 0.1N HCl (200 mL), 3% sodium bicarbonate (200 mL), water (200 mL) and brine (200 mL), dried over sodium sulfate, and concentrated to give the crude product (14.322 g). FC (20-80% ethyl acetate in hexanes) gave the title compound (9.440 g) as a yellowish oil. R_f: 0.27 (25% ethyl acetate in hexanes). Some starting Weinreb amide was also recovered (3.212 g). R_f: 0.10 (25% ethyl acetate in hexanes).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.07-4.14 (m, 2 H), 2.75-2.83 (m, 2 H), 2.46 (tt, J = 11.3 and 3.8 Hz, 1 H), 2.17 (s, 3 H), 1.82-1.87 (m, 2 H), 1.48-1.57 (m, 2 H), 1.46 (s, 9 H).

Step B3: 1-(1-(t-Butoxycarbonyl)piperidin-4-yl)-4-phenyl-butane-1,3-dione

To a suspension of 60% sodium hydride (1.07 g) in THF (15 mL) at 0°C was added a solution of 4-acetyl-1-(t-butoxycarbonyl)piperidine from Step B2 (3.03 g, 13.3 mmol) and methyl phenylacetate (6.01 g, 39.9 mmol) in THF (6 mL) over 20 min. The reaction was stirred for another 4 h as it was allowed to warm to rt. The mixture was diluted with ether (30 mL) and poured into 1N HCl. The layers were separated and the aqueous layer was extracted three times with ether. The combined organic layers were washed with brine (150 mL), dried over sodium sulfate and concentrated. The crude product was purified by FC (20% ethyl acetate in hexanes) to give the title compound (3.02 g). R_f: 0.30 (20% ethyl acetate in hexane). The ^{1}H NMR data was the same as that obtained from the product of Method A.

Step B: 4-(5-Benzyl-1-ethyl-(1H)-pyrazol-3-yl)-1-(t-butoxycarbonyl)piperidine (Higher R_f isomer) and 4-(3-benzyl-1-ethyl-(1H)-pyrazol-5-yl)-1-(t-butoxycarbonyl)piperidine (Lower R_f isomer)

1-(1-(t-Butoxycarbonyl)piperidin-4-yl)-4-phenyl-butane-1,3-dione from Step A, from Method A or Method B, Step B3, (0.851 g, 2.46 mmol) in methanol (25 mL) was added over 10 min to a suspension of ethylhydrazine oxalate (0.444 g, 2.96 mmol) in methanol (5 mL) in a 60 °C oil bath. After 15 h, the reaction

was concentrated in vacuo and the residue was purified by repeated FC using a gradient of 50-100% ethyl acetate in hexanes to give first 4-(5-benzyl-1-ethyl-(1H)-pyrazol-3-yl)-1-(t-butoxycarbonyl)piperidine (0.148 g total) as the higher R_f product isomer and then the title compound (0.373 g total) as the lower R_f.

Higher R_f isomer:
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.2-7.3 (m, 2 H), 7.3-7.4 (m, 1 H), 7.17 (d, J = 7.5 Hz, 2 H), 5.77 (s, 1 H), 4.0-4.25 (m, 2 H), 3.97 (q, J = 7.3 Hz, 2 H), 3.95 (s, 2 H), 2.7-2.9 (m, 2 H), 2.76 (tt, J = 11.3 and 3.8 Hz, 1 H), 1.92 (br d, J = 13 Hz, 1 H), 1.5-1.65 (m, 2 H), 1.47 (s, 9 H), 1.29 (t, J = 7.3 Hz, 3 H).

Lower R_f isomer:
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25-7.4 (m, 3 H), 7.2 (m, 2 H), 5.72 (s, 1 H), 4.1-4.3 (m, 2 H), 4.08 (q, J = 7.1 Hz, 2 H), 3.95 (s, 2 H), 2.7-2.9 (m, 2 H), 2.66 (tt, J = 11.3 and 3.8 Hz, 1 H), 1.82 (br d, J = 12.8 Hz, 1 H), 1.4-1.6 (m, 2 H), 1.48 (s, 9 H), 1.47 (t, J = 7.1 Hz, 3 H).

Step C: 4-(3-Benzyl-1-ethyl-(1H)-pyrazol-5-yl)piperidine di-TFA salt

To a solution of 4-(3-benzyl-1-ethyl-(1H)-pyrazol-5-yl)-1-(t-butoxycarbonyl)piperidine from Step B (lower R_f isomer) (0.373 g, 1.01 mmol) and anisole (0.219 mL, 2.02 mmol) in dichloromethane (15 mL) was added trifluoroacetic acid (1.555 mL, 20.2 mmol). The reaction was stirred at rt for 2.5 h and then concentrated. The residue was purified on preparative reverse-phase HPLC using 9.4 x 250 mm Semi-preparative Zorbax SB-C18 column with 17.5-35% acetonitrile gradient in water having 0.5% (v/v) TFA over 15 min at 6.05 mL per minute to give the title di-TFA salt compound as an oil. When a mixture of isomers from Step B is used, separation is also possible at this step with the above Prep HPLC conditions in which the title isomer elutes prior to 4-(5-benzyl-1-ethyl-(1H-pyrazol-3-yl))piperidine.

PROCEDURE 2

4-(3-Benzyl-(1H)-pyrazol-5-yl)piperidine trifluoroacetic acid salt

Step A: 4-(3-Benzyl-(1H)-pyrazol-5-yl)-1-(t-butoxycarbonyl)piperidine TFA salt

649

A solution of 1-(1-(t-butoxycarbonyl)piperidin-4-yl)-4-phenyl-butane-1,3-dione from Procedure 1, Step A (30 mg, 0.087 mmol), hydrazine dihydrochloride (10.9 mg, 0.1 mmol) and DIPEA (0.045 mL, 0.25 mmol) in methanol (1 mL) was heated at 50 °C for 16 h. The volatiles were then removed under reduced pressure. Purification of the residue was done on preparative reverse-phase HPLC using a 9.4 x 250 mm Semi-preparative Zorbax SB-C18 column with 35-50% MeCN gradient in water having 0.5% (v/v) TFA over 15 min to give the title compound (45.2 mg) as a gel.

Step B: 4-(3-Benzyl-(1H)-pyrazol-5-yl)piperidine TFA salt

To a solution of 4-(3-benzyl-(1H-pyrazol-5-yl))-1-(t-butoxycarbonyl)piperidine TFA salt (from Step A) in dichloromethane (1.5 mL) was added anisole (0.017 mL) and TFA (0.230 mL). After several hours at rt, volatiles were removed under reduced pressure. Purification of the residue was done by preparative reverse-phase HPLC using a 9.4 x 250 mm Semi-preparative Zorbax SB-C18 column with a 15-25% acetonitrile gradient in water having 0.5% (v/v) TFA over 15 min at 6.0 mL per minute to give the title compound (40.7 mg) as a gel.

PROCEDURE 3

4-(4-(2-Phenyleth-1-yl)-1-ethyl-(1H)-pyrazol-5-yl)piperidine

Step A: 4-Phenylbutyl bromide

To a solution of 4-phenyl-1-butanol (21.75 g) in acetonitrile (300 mL) was added triphenylphosphene dibromide (67.23 g) in portions with stirring over 10 min. After stirring over night under nitrogen, methanol (4 mL) was added and after 1.5 h, the solvent was removed under reduced pressure. Hexanes (200 mL) and ~75 g silica gel were added to the residue and the mixture was filtered and the filter cake was eluted with hexanes. The clear filtrate was concentrated to give 32.8 g of clear colorless liquid. This product was again eluted through silica gel using 1.5 L hexanes to give the title compound (24.7 g) as a colorless liquid.
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28-7.32 (m, 2 H), 7.20-7.23 (m, 3 H), 3.44 (t, J = 6.8 Hz, 2 H), 2.67 (t, J = 7.6 Hz, 2 H), 1.93-1.89 (m, 2 H), 1.77-1.84 (m, 2 H).

Step B: (4-Phenylbut-1-yl)triphenylphosphonium bromide A solution of 4-phenylbutyl bromide from the Step A (24.7 g) and triphenylphosphene (19.00 g) in toluene (100 mL) was heated at 120-130 °C for 3 days. The reaction was cooled to rt and the solid precipitate was collected by filtration, washed with toluene and air dried. The solid was dissolved in a 2:1 mixture of water and acetonitrile and gave the title compound (30.6 g) as a white solid after lyopholization.
^{1}H NMR (500 MHz, CD_3OD): δ 7.84-7.89 (m, 2 H), 7.71-7.81 (m, 15 H), 7.20-7.23 (m, 1 H), 7.11-7.15 (m, 2 H), 3.37-3.43 (m, 2 H), 2.66 (t, J = 7.5 Hz, 2 H), 1.87 (tt, J = 7.5 and 7.3 Hz, 2 H), 1.63-1.70 (m, 2 H).

Step C: 1-Benzyl-4-(4-phenylbutylidene)piperidine
A 0.62M solution of potassium bis(trimethylsilyl)amide in THF (180 mL, 112 mmol) in toluene (250 mL) was added to a mixture of (4-phenylbut-1-yl)triphenylphosphonium bromide from Step B (53 g) in toluene (250 mL) in an ice bath over 15 min with stirring under nitrogen. After stirring for a further 15 min, a solution of 1-benzyl-4-piperidone (16.9 g) in toluene (100 mL) was added over 30 min with stirring. The reaction mixture was allowed to warm to rt over 15 h. The reaction mixture was then poured into cold 1N HCl (400 mL) and the layers were separated. The organic layer was extracted with two more portions of 1N HCl. The combined cloudy HCl solution and an oil layer in between were washed with toluene (200 mL) before the aqueous layer was basified by the addition of potassium hydroxide (30 g). The aqueous layer was extracted with ether (3x150 mL) and the combined organic layers were washed with water and brine, dried over sodium sulfate and concentrated. The crude product was purified by FC (10-15% ethyl acetate in hexanes having 4% (v/v) TEA) to give the title compound (16 g) as a colorless oil.
R_f: 0.47 (20% ethyl acetate in hexanes having 4% (v/v) TEA).
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26-7.38 (m, 7 H), 7.18-7.21 (m, 3 H), 5.18 (t, J = 7.4 Hz, 1 H), 3.54 (s, 2 H), 2.61-2.64 (m, 2 H), 2.42-2.49 (m, 4 H), 2.22-2.27 (m, 4 H), 2.02-2.07 (m, 2 H), 1.65-1.71 (m, 2 H).

Step D: 1-(1-Benzylpiperidin-4-yl)-4-phenylbutan-1-one
To a solution of 4-(4-phenylbutylidene)-1-benzylpiperidine from Step C (4.37 g) in anhydrous ether (150 mL) under nitrogen with stirring was add 1M borane solution in THF (45 mL). The reaction was stirred for 3 h when water (2 mL) was added dropwise. The mixture was stirred a further 30 min and was then cooled in

an ice bath. A solution of chromic anhydride (2.5 g), concentrated sulfuric acid (5.44 mL) and water (125 mL) was added dropwise with vigorous magnetic stirring over 5 min. After another 5 min, the ice bath was removed. After 1.5 h at rt, 0.5N sodium hydroxide and ether (400 mL each) were added and the mixture was stirred until the residue dissolved. The layers were separated and the aqueous layer was extracted twice with ether. The combined ether layers were washed with an aqueous EDTA solution, water and brine (100 mL each), dried over sodium sulfate and concentrated under reduced pressure to give a colorless gel. Flash chromatography on silica gel with 30-50% ethyl acetate in hexanes with 3% (v/v) TEA gave the title compound (1 g) as a colorless gel. R_f: 0.43 (30% ethyl acetate in hexanes with 3% (v/v) TEA). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25-7.33 (m, 7 H), 7.16-7.22 (m, 3 H), 3.51 (s, 2 H), 2.89-2.93 (m, 2 H), 2.63 (t, J = 7.6 Hz, 2 H), 2.46 (t, J = 7.2 Hz, 2 H), 2.38 (tt, J = 11.5 and 3.9 Hz, 1 H), 1.99-2.03 (m, 2 H), 1.92 (tt, J = 7.2 and 7.6 Hz, 2 H), 1.76-1.81 (m, 2 H), 1.65-1.72 (m, 2 H).

Step E: 1-(1-Benzylpiperidin-4-yl)-2-formyl-4-phenylbutan-1-one

To a solution of potassium t-butoxide (0.673 g) in THF (20 mL) under nitrogen and cooled in an ice bath was added a solution of 1-(1-benzylpiperidin-4-yl)-4-phenylbutan-1-one from Step D (0.71 g) and methyl formate (3.76 mL) in THF (12 mL) over 5 minute. The reaction was stirred for 15 min before being allowed to warm to rt for 2 h. The reaction was poured into water and extracted with ether (4 x 100 mL), dichloromethane (100 mL), and TFA (100 mL). The combined organic layers were washed with water and brine, dried over sodium sulfate and concentrate under reduced pressure. The crude product was purified by FC on silica gel eluting with 5 and 20% methanol in ethyl acetate with 4% TEA to afford the title compound (0.8 g). ^{1}H NMR (500 MHz, $CDCl_3$) showed a 3:1 ratio of enol (δ 8.54 ppm) and aldehyde (δ 9.54 ppm) forms. Other signals from the two forms were only partially resolved. The title compound had a retention time of 9.47 min on a Zorbax SB-C18 column (4.6x75 mm) eluting with 20-100% gradient of acetonitrile in water with 0.1% TFA over 10 min at 1 mL per min.

Step F: 4-(4-(2-Phenyleth-1-yl)-1-ethyl-(1H)-pyrazol-5-yl)-1-benzylpiperidine di-TFA salt A solution of 1-(1-benzylpiperidin-4-yl)-2-formyl-4-phenyl-1-butanone from Step E (76.5 mg) and ethylhydrazine oxalate (45 mg) in methanol (4 mL) was heated at 45 °C for 15.5 h. The solvent was removed under

652

reduced pressure. The residue was purified by preparative reverse-phase HPLC using a 9.4x250 mm Semi-preparative Zorbax SB-C18 column with 30-50% acetonitrile gradient in water having 0.5% (v/v) TFA over 15 min at 7.1 mL per min to give the title compound (45 mg) as the faster-eluting, minor isomer.

^{1}H NMR (500 MHz, CD_3OD): δ 7.46-7.52 (m, 5 H), 7.37 (s, 1 H), 7.21-7.24 (m, 2 H), 7.12-7.15 (m, 3 H), 4.32 (s, 2 H), 4.17 (q, J = 7.2 Hz, 2 H), 3.53 (br d, J = 12.4 Hz, 2 H), 3.06-3.12 (m, 3 H), 2.79-2.88 (m, 4 H), 2.10-2.20 (m, 2 H), 1.78 (br d, J = 14.2 Hz, 2 H), 1.34 (t, J = 7.2 Hz, 3 H). The isomeric assignment was confirmed by a NOESY spectrum.

HPLC/MS (ESI): m/z 374.3 (M + 1), 2.51 min.

Step G: 4-(4-(2-Phenyleth-1-yl)-1-ethyl-(1H)-pyrazol-5-yl)piperidine di-TFA salt A mixture of ammonium formate (119 mg), 20% $Pd(OH)_2/C$ (5 mg) and 4-(4-(2-phenylethyl)-1-ethyl-(1H-pyrazol-5-yl))-1-benzylpiperidine di-TFA salt from Step F in methanol (2 mL) was heated at 60 °C for 1.5 h. The solvent was removed under reduced pressure and the residue was purified by preparative reverse-phase HPLC using a 9.4x250 mm Semi-preparative Zorbax SB-C18 column with 20-35% acetonitrile gradient in water having 0.5% (v/v) TFA over 15 min at 6.25 mL per min to give the title compound as the di-TFA salt (25 mg) as a gel.

^{1}H NMR (500 MHz, CD_3OD): δ 7.40 (s, 1 H), 7.22-7.25 (m, 2 H), 7.13-7.17 (m, 3 H), 4.20 (q, J = 7.3 Hz, 2 H), 3.42-3.46 (m, 2 H), 3.05-3.15 (m, 3 H), 2.83-2.90 (m, 4 H), 2.04-2.14 (m, 2 H), 1.74-1.79 (m, 2 H), 1.36 (t, J = 7.4 Hz, 3 H). The isomer assignment was confirmed by an NOE difference spectrum.

PROCEDURE 4A

4-(3-(4-Fluorobenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidine di-TFA

The title compound was prepared using essentially the same procedure as that described in Procedure 1, but substituting methyl 4-fluorophenylacetate for methyl phenylacetate in Step A, Method B, Step B3.

PROCEDURE 4B

4-(3-(3,4-Difluorobenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidine di-TFA

The title compound was prepared using essentially the same procedure as that described in Procedure 1, but substituting methyl 3,4-difluorophenylacetate for methyl phenylacetate in Step A, Method B.

PROCEDURE 5

(4-(3-Benzofurazan-4-yl)prop-1-yl)piperidine hydrochloride

Step A: (1-t-Butoxycarbonylpiperidin-4-yl)acetaldehyde A solution of oxalyl chloride (1.23 mL, 14.1 mmol) in methylene chloride (50 mL) was cooled to -78 °C. DMSO (2.0 mL, 28.3 mmol), was added slowly via syringe. After 10 min, 4-(2-hydroxyeth-1-yl)-1-t-butoxycarbonyl piperidine (2.7 g, 11.8 mmol) in methylene chloride (15 mL) was added. The cold mixture was stirred for an additional 20 min then TEA (8.2 mL, 59 mmol) was added. The mixture was warmed to rt and stirred for 1.5 h, then diluted with methylene chloride (300 mL). The organic phase was washed with 1M sodium hydroxide, dried over sodium sulfate and concentrated. FC (125 g silica, 2.5/1 hexanes/ethyl acetate) afforded the title compound (2.25 g).
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.1-1.2 (m, 2 H), 1.45 (s, 9 H), 1.65-1.75 (m, 2 H), 1.99-2.13 (m, 1 H), 2.38-2.4 (d, 2 H), 2.65-2.8 (m, 2 H), 4.03-4.15 (m, 2 H), 9.78 (s, 1 H)

Step B: 4-(Prop-2-en-1-yl)-1-t-butoxycarbonyl piperidine
A solution of methyltriphenylphosphonium bromide (5.3 g, 14.8 mmol) in THF (50 mL) was cooled to 0 °C under nitrogen. Potassium hexamethyl disilazide (27.7 mL, 0.5M toluene solution, 13.9 mmol) was added and the mixture was stirred for 30 min. A solution of (1-t-butoxycarbonylpiperidin-4-yl)acetaldehyde from Step A (2.25 g, 9.9 mmol) in THF (10 mL) was added and the mixture was warmed to rt. After 30 min, the reaction was complete by tlc analysis. The mixture was diluted with ethyl acetate (200 mL) and washed with water and brine (100 mL each). The organic phase was dried over sodium sulfate and concentrated to give an oil which was purified by FC (75 g silica, 10/1 hexane/ethyl acetate) to afford the title compound (1.61 g).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03-1.18 (m, 2 H), 1.45 (s, 9 H), 1.4-1.5 (m, 1 H), 1.6-1.7 (m, 2 H), 1.99-2.13 (t, 1 H), 2.62-2.75 (m, 2 H), 4.03-4.15 (m, 2 H), 4.98-5.12 (m, 2 H), 5.7-5.83 (m, 1 H).

Step C: 4-Bromobenzofurazan

To a solution of 2,6-dibromoaniline (10 g, 40 mmol) in glacial acetic acid (160 mL) was added 30% hydrogen peroxide (30 mL). The mixture was left for 48 h at which point crystals had precipitated. The crystals were collected by filtration, washed with acetic acid and water then dried under high vacuum to give 2,6-dibromonitrosobenzene (6.24 g). This material (2.6 g, 10 mmol) was dissolved in DMSO (25 mL) along with sodium azide (650 mg, 10 mmol). The mixture was heated to 100 °C for 1 h then cooled to rt and diluted with ethyl acetate and water. The layers were separated and the organic phase was washed with water and brine, then dried over sodium sulfate and concentrated. FC (75 g silica, 10/1 hexane/ethyl acetate) afforded the title compound (1.7 g).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25-7.35 (dd, 1 H), 7.6-7.65 (d, 1 H), 7.78-7.82 (d, 1 H)

Step D: 4-(3-(Benzofurazan-4-yl)prop-1-yl)piperidine hydrochloride

A solution of 4-(prop-2-en-1-yl)-1-t-butoxycarbonylpiperidine from Step B (330 mg, 1.46 mmol) in dry THF (0.5 mL) was cooled to 0 °C and a solution of 9-BBN (3.2 mL, 0.5 M in THF, 1.61 mmol) was added. The mixture was warmed to rt and stirred for 5 h. Potassium carbonate (405 mg, 2.93 mmol), 1,2-bis(diphenylphosphino)-ferrocenyl palladium dichloride (60 mg, 0.073 mmol) and 4-bromobenzofurazan (from Step C) (292 mg, 1.46 mmol) were added followed by dry DMF (5 mL). The resulting mixture was heated to 55 °C overnight then diluted with ethyl acetate. The solution was washed with water (3x) and brine, then dried over sodium sulfate and concentrated. FC (15 g silica, 5/1 hexane/ethyl acetate) afforded the title Boc derivative. Heating in 1% conc. HCl/methanol at 50 °C for 2 h followed by removal of solvent and drying under vacuum afforded the title compound as the hydrochloride (155 mg).

^{1}H NMR (300 MHz, CD_3OD): δ 1.31-1.42 (m, 4 H), 1.6-1.75 (m, 1 H), 1.84-2.0 (m, 4 H), 2.9-3.1 (m, 4 H), 3.3-3.4 (m, 2 H), 7.25-7.3 (d, 1 H), 7.4-7.5 (dd, 1 H), 7.7-7.75 (d, 1 H).

PROCEDURE 6

(4-(3-Benzofurazan-5-yl)prop-1-yl)piperidine hydrochloride

Using essentially the same methods as in Procedure 5, but substituting 2,5-dibromoaniline for 2,6-dibromoaniline in Step C, the title compound was prepared.

PROCEDURE 7

(3-(4-Cyanophenyl)prop-1-yl)piperidine hydrochloride

Starting with 4-(prop-2-en-1-yl)-1-t-butoxycarbonylpiperidine from Procedure 5, Step B (475 mg, 2.1 mmol) and using essentially the same methods as in Procedure 5, Step D, but substituting 4-bromobenzonitrile (382 mg, 2.1 mmol), the title compound (337 mg) was obtained as the hydrochloride.
^{1}H NMR (300 MHz, CD_3OD). δ 1.31-1.42 (m, 4 H), 1.58-1.75 (m, 5 H), 1.9-2.1 (m, 2 H), 2.67-2.77 (t, 2 H), 2.9-3.0 (m, 2 H), 3.3-3.4 (m, 2 H), 7.35-7.4 (d, 2 H), 7.6-7.63 (d, 2 H).

PROCEDURE 8

(3-(4-Cyano-3-fluorophenyl)prop-1-yl)piperidine hydrochloride

Starting with 4-(prop-2-en-1-yl)-1-t-butoxycarbonylpiperidine from Procedure 5, Step B and using essentially the same methods as in Procedure 5, Step D, but substituting 4-bromo-2-fluorobenzonitrile, the title compound was obtained as the hydrochloride.

PROCEDURE 9

(3-(4-Fluorophenyl)prop-1-yl)piperidine hydrochloride

Starting with 4-(prop-2-en-1-yl)-1-t-butoxycarbonylpiperidine (from Procedure 5, Step B) and using essentially the same methods as in Procedure 5, Step D, but substituting 4-bromofluorobenzene, the title compound was obtained as the hydrochloride.

PROCEDURE 10

4-(3-(Quinolin-3-yl)propyl)piperidine di-hydrochloride salt

Step A: 1-(t-Butoxycarbonyl)-4-(3-(quinolin-3-yl)propyl)piperidine

A solution of 1-(t-butoxycarbonyl)-4-(prop-2-en-1-yl)piperidine (from Procedure 5, Step B) (260 mg, 1.15 mmol) in THF (3 mL) under argon was treated with 0.5M 9-BBN solution in THF (2.30 mL, 1.15 mmol). The resulting mixture was stirred at rt for 2 h, then treated with sodium methoxide (68 mg, 1.25 mmol). The resulting mixture was stirred until it was homogeneous (~15 min) and then was treated with 3-(bromo) quinoline (0.155 mL, 1.15 mmol) and [1,1'-bis(triphenylphosphino)ferrocene)dichloropalladium · methylene chloride (41 mg, 0.05 mmol). The resulting mixture was heated at reflux for 30 min, cooled and quenched with 1N NaOH (20 mL). The quenched reaction was extracted with 2 x 50 mL of ether; the extracts were dried over magnesium sulfate, combined and concentrated. FC (15 g of silica gel, 4:1 v/v hexanes/ethyl acetate) afforded the title compound (240 mg).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00-1.16 (m, 2 H), 1.25-1.40 (m, 2 H), 1.45 (s, 9 H), 1.60-1.80 (m, 5 H), 2.62-2.72 (m, 2 H), 2.79 (t, J = 7.8, 2 H), 4.06 (br s, 2 H), 7.52 (m, 1 H), 7.66 (m, 1 H), 7.76 (dd, J = 8.0, 1.6, 1 H), 7.91 (d, J = 1.6, 1 H), 8.77 (d, J = 2.2, 1 H).

Step B: 4-(3-(Quinolin-3-yl)propyl)piperidine di-hydrochloride salt

A solution of 1-(t-butoxycarbonyl)-4-(3-(quinolin-3-yl)propyl)piperidine from Step A (240 mg, 0.68 mmol) in 1M HCl solution (8 mL) in methanol was stirred at rt for 48 h. The solution was concentrated and the residue crystallized from ethyl acetate to afford the title compound (182 mg),

^{1}H NMR (500 MHz, CD_3OD): δ 1.37-1.49 (m, 4 H), 1.67-1.74 (m, 2 H), 1.85-1.91 (m, 2 H), 1.99 (app d, J = 13.5 Hz, 2 H), 2.99 (app t, J = 11.5 Hz, 2 H), 3.05 (t, J = 8.0 Hz, 2 H), 3.38 (app d, J = 12.5 Hz, 1 H), 7.97 (t, J = 7.0 Hz, 1 H), 8.13 (dt. J = 1.0 and

7.0 Hz, 1H), 8.24 (d, J = 8.5 Hz, 1 H), 8.31 (d, J = 8.0 Hz, 1 H), 9.10 (s, 1 H), 9.21 (d, J = 1.0 Hz, 1 H).

PROCEDURE 11

4-(3-(2-Pyridyl)propyl)piperidine

Step A: 1-(t-Butoxycarbonyl)-4-(3-(2-pyridyl)propyl)piperidine

The title compound was prepared using a procedure analogous to that described in Procedure 10, Step A, substituting (2-bromo)pyridine for (3-bromo)quinoline. FC (4:1 v/v hexanes/ethyl acetate followed by 3:2 v/v hexanes/ethyl acetate) provided the title compound (135 mg, 48%).
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.05-1.81 (m, 10 H), 1.46 (s, 9 H), 2.67-2.82 (m, 2 H), 3.65 (m, 1 H), 4.08-4.16 (m, 2 H), 7.14-7.18 (m, 2 H), 7.63 (m, 1 H), 8.54 (d, J = 4.4 Hz, 1 H).
HPLC/MS (ESI): m/z 304 (M+1).

Step B: 4-(3-(2-Pyridyl)propyl)piperidine di-TFA salt

To a solution of 1-(t-butoxycarbonyl)-4-(3-(2-pyridyl)propyl)piperidine (from Step A) (128 mg, 0.42 mmol) in methylene chloride (1 mL) was added TFA (1 mL). After stirring for 2 h at rt, the reaction was concentrated to give the title compound (36 mg).
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.22-1.46 (m, 5 H), 1.73-1.79 (m, 4 H), 2.68 (t, J = 11.8 Hz, 2 H), 2.78 (t, J = 7.8 Hz, 2 H), 3.19 (d, J = 11.8 Hz, 2 H), 5.32 (br s, 1 H), 7.09-7.15 (m, 2 H), 7.59 (t, J = 7.7 Hz, 2 H), 8.52 (d, J = 4.6 Hz, 1 H).

PROCEDURE 12

4-(3-((4-Trifluoromethyl)pyrimidin-2-yl))propyl)piperidine

Step A: 1-(t-Butoxycarbonyl)-4-(3,3-dibromoprop-2-en-1-yl)piperidine

To a solution of carbon tetrabromide (286 mg, 0.86 mmol) in methylene chloride (4 mL) at –10 °C was added triphenylphosphine (339 mg, 1.29 mmol). After 10 min, a solution of ((1-t-butoxycarbonyl)piperidin-4-yl)acetaldehyde (from Procedure 5, Step A) (98 mg, 0.43 mmol) and TEA (0.060 mL, 0.43 mmol) in

methylene chloride (2 mL) was added. After stirring at rt for 2 h, the reaction mixture was concentrated. The residue was purified by FC (9:1 v/v hexanes/ethyl acetate followed by 1:1 v/v hexanes/ethyl acetate) to give the title compound (118 mg).
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.14-1.22 (m, 2 H), 1.47 (s, 9 H), 1.57-1.60 (m, 1 H), 1.67 (br d, J = 12.6 Hz, 2 H), 2.08 (t, J = 7.1 Hz, 2 H), 2.70 (t, J = 12.7 Hz, 2 H), 4.10 (br d, J = 12.6 Hz, 2 H), 6.42 (t, J = 7.4 Hz, 1 H).

Step B: 1-(t-Butoxycarbonyl)-4-(prop-2-yn-1-yl)piperidine

To a solution of 118 mg (0.31 mmol) of 1-(t-butoxycarbonyl)-4-(3,3-dibromoprop-2-en-1-yl)piperidine from Step A in THF (4 mL) at –78 °C was added a 2.5M solution of n-butyl lithium (0.370 mL, 0.92 mmol). After stirring at –78 °C for 45 min, the reaction mixture was quenched with sat'd ammonium chloride (4 mL) and diluted with ether (25 mL). After separating the phases, the aqueous layer was extracted with ether. The combined organic phases were washed with brine, dried over magnesium sulfate and concentrated. The residue was purified by FC (4:1 v/v hexanes/ether) to give the title compound (55 mg).
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.18-1.26 (m, 2 H), 1.47 (s, 9 H), 1.60-1.67 (m, 1 H), 1.77 (br d, J = 13.2 Hz, 2 H), 1.99 (t, J = 2.6 Hz, 1 H), 2.16 (dd, J = 6.6 Hz, 2.5, 2 H), 2.68-2.74 (m, 2 H), 4.12 (br d, J = 13.0 Hz, 2 H).

Step C: 1-(t-Butoxycarbonyl)-4-(3-((4-trifluoromethyl)pyrimidin-2-yl)prop-2-yn-1-yl)piperidine

To a solution of 1-(t-butoxycarbonyl)-4-(prop-2-yn-1-yl)piperidine from Step B (86 mg, 0.39 mmol) in TEA (4 mL) under argon at 0 °C was added 2-chloro-4-(trifluoromethyl)pyrimidine (0.070 mL, 0.58 mmol). After stirring at 0 °C for 5 min, dichlorobis(triphenylphosphine)palladium(II) (27 mg, 0.04 mmol), and copper iodide (4 mg, 0.02 mmol) was added and the reaction vessel was flushed with argon. After 3 h at 60 °C, the reaction mixture was cooled to rt and quenched with 1N sodium hydroxide (5 mL) and diluted with ether (25 mL). After separating the phases, the aqueous layer was extracted again with ether. The combined organic phases were washed with brine, dried over magnesium sulfate and concentrated. The residue was purified by FC (9:1 v/v hexanes/ethyl acetate followed by 2:1 v/v hexanes/ethyl acetate) to give the title compound (132 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26-1.33 (m, 2 H), 1.46 (s, 9 H), 1.80-1.88 (m, 3 H), 2.46 (d, J = 6.4 Hz, 2 H), 1.99 (br t, J = 11.2 Hz, 1 H), 4.10-4.40 (m, 2 H), 7.54 (d, J = 5.0 Hz, 1 H), 8.94 (d, J = 5.0 Hz, 1 H).

Step D: 1-(t-Butoxycarbonyl)-4-(3-((4-trifluoromethyl)pyrimidin-2-yl)prop-1-yl)piperidine

To a solution of 1-(t-butoxycarbonyl)-4-(3-((4-trifluoromethyl)pyrimidin-2-yl)prop-2-yn-1-yl)piperidine from Step C (130 mg) in methanol (4 mL) was added 10% palladium on carbon (15 mg). The mixture was hydrogenated using a Parr shaker set at 40 psi. After TLC indicated the absence of the starting material, the reaction was filtered through a 0.45 micron nylon membrane polypropylene filter and concentrated. FC (9:1 v/v hexanes/ethyl acetate followed by 2:1 v/v hexanes/ethyl acetate) of the residue afforded the title compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04-1.15 (m, 2 H), 1.27-1.49 (m, 3 H), 1.46 (s, 9 H), 1.68 (br d, J = 12.7 Hz, 2 H), 1.85-1.93 (m, 2 H), 2.68 (br t, J = 12.1 Hz, 2 H), 3.05 (t, J = 7.7 Hz, 2 H), 4.08 (br d, J = 11.5 Hz, 2 H), 7.47 (d, J = 5.0 Hz, 1 H), 8.92 (d, J = 5.0 Hz, 1 H).

Step E: 4-(3-((4-Trifluoromethyl)pyrimidin-2-yl)prop-1-yl)piperidine TFA salt

The title compound was prepared from 1-(t-butoxycarbonyl)-4-(3-((4-trifluoromethyl)pyrimidin-2-yl)prop-1-yl)piperidine (from Step D) (17 mg, 0.046 mmol) using a procedure analogous to that described in Procedure 10, Step B. FC (95:5:0.5 v/v/v methylene chloride/MeOH/ NH_4OH) afforded the title compound (22 mg).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21-3.45 (m, 15 H), 7.52 (d, J = 5.0 Hz, 1 H), 8.95 (d, J = 5.0 Hz, 1 H).

PROCEDURE 13

4-(*N*-(Pyrimidin-2-yl)-*N*-(prop-1-yl)amino)piperidine

Step A: 4-Amino-1-t-butoxycarbonylpiperidine

1-t-Butoxycarbonylpiperidin-4-one (20 g, 100 mmol), benzylamine (11 mL, 100 mmol) and sodium triacetoxyborohydride (32 g, 150 mmol) were stirred together in 1,2-dichloroethane (400 mL) for 3 h. The resulting mixture was diluted with ethyl acetate (1 L) and washed with 1M aqueous sodium hydroxide (500 mL) followed by brine (500 mL). The organic phase was dried over sodium sulfate and concentrated to afford 4-*N*-benzylamino-1-t-butoxycarbonyl piperidine (30.1 g) as a viscous oil. The oil was dissolved in methanol (400 mL) and ammonium formate (39 g, 600 mmol) was added. The vessel was purged with nitrogen and 10% palladium on carbon (6.5 g, 6 mmol) was added. The mixture was refluxed for 1 h and then filtered through celite and concentrated. Drying under vacuum afforded the title compound (20 g).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15-1.3 (m, 2 H), 1.43 (s, 9 H), 1.7-1.9 (m, 4 H), 2.65-2.72 (m, 3 H), 3.95-4.1 (m, 2 H).

Step B: 4-(*N*-(Pyrimidin-2-yl)amino)-1-t-butoxycarbonylpiperidine

4-Amino-1-t-butoxycarbonylpiperidine from Step A, (1.9 g, 9.5 mmol), 2-chloropyrimidine (1.1 g, 9.5 mmol) and DIPEA (3.3 mL, 19 mmol) were combined in isopropanol (10 mL) and the mixture was refluxed for 24 h. The mixture was cooled, diluted with methylene chloride (100 mL) and washed with water and brine. The organic phase was dried over sodium sulfate and concentrated. FC (60 g silica, 1/1 hexanes/ethyl acetate) afforded the title compound (0.97 g).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31-1.45 (m, 2 H), 1.44 (s, 9 H), 2.0-2.1 (m, 2 H), 2.9-3.0 (m, 2 H), 3.9-4.1 (m, 3 H), 5.0-5.05 (m, 1 H), 6.5-6.58, (t, 1 H), 8.15-8.2 (d, 2 H).

Step C: 4-(*N*-(Pyrimidin-2-yl)-*N*-(allyl)amino)-1-t-butoxycarbonyl- piperidine

A solution of 4-(*N*-(pyrimidin-2-yl)amino)-1-t-butoxycarbonylpiperidine from Step B (528 mg, 1.9 mmol) in dry THF (5 mL) was cooled to -78 °C and a solution of sodium hexamethyldisilazide (2.8 mL, 1.0 M in THF, 2.8 mmol) was added via syringe. The mixture was stirred cold for 20 min then allyl bromide (0.23 mL, 2.7 mmol) was added. The mixture was then warmed to rt and stirred for 1.5 h at which time TLC showed very little starting material. The solution was poured into sat'd ammonium chloride and methylene chloride. The layers were separated and the organic phase was dried over sodium sulfate and

concentrated. FC (25 g silica, 4/1 hexanes/ethyl acetate) afforded the title compound (367 mg).
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45 (s, 9 H), 1.6-1.8 (m, 4 H), 2.75-2.85 (m, 2 H), 4.1-4.3 (m, 4 H), 4.7-4.8 (m, 1 H), 5.05-5.17 (m, 2 H), 5.92-5.98 (m, 1 H), 6.45-6.5 (t, 1 H), 8.3-8.35 (d, 2 H).

Step D: 4-(*N*-(Pyrimidin-2-yl)-*N*-(prop-1-yl)amino)piperidine dihydrochloride

In a round bottom flask purged with nitrogen 4-(*N*-(pyrimidin-2-yl)-4-N-(allyl)amino)-1-t-butoxylcarbonylpiperidine from Step C (461 mg, 1.45 mmol) was dissolved in methanol (4 mL) and 10% palladium on carbon (150 mg, 0.14 mmol) was added. The mixture was stirred under 1 atm of hydrogen using a balloon for 1.5 h. The mixture was filtered through celite and concentrated. FC (20 g silica, 3/1 hexanes/ethyl acetate) afforded 4-(*N*-(pyrimidin-2-yl)-4-*N*-(prop-1-yl)amino)-1-t-butoxylcarbonylpiperidine.
^{1}H NMR (400 MHz, $CDCl_3$). δ 0.9-1.0 (t, 3 H, J=7 Hz), 1.5 (s, 9 H), 1.6-1.8 (m, 6 H), 2.8-2.9 (m, 2 H), 3.33-3.4 (m, 2 H), 4.2-4.27 (m, 2 H), 4.7-4.8 (m, 1 H), 6.42-6.45 (t, 1 H),), 8.3-8.35 (d, 2 H).

This material was dissolved in 2 % conc. HCl/methanol and heated to 50 °C for 2 h. Removal of solvent and drying under vacuum afforded the title compound as a white solid.

PROCEDURE 14

(3-(3,4-Difluorophenyl)prop-1-yl)piperidine hydrochloride

Starting with 4-(prop-2-en-1-yl)-1-t-butoxycarbonylpiperidine from Procedure 5, Step B and using essentially the same methods as in Procedure 5, Step D, but substituting 3,4-difluorobromobenzene, the title compound was obtained as the hydrochloride.

PROCEDURE 15

4-(5-Benzyl-1-(prop-1-yl)-(1H)-pyrazol-3-yl)piperidine di-hydrochloride salt (Higher R_f isomer) and 4-(3-benzyl-1-(prop-1-yl)-(1H-pyrazol-5-yl))piperidine di-hydrochloride salt (Lower R_f isomer)

Using essentially the same methods as in Procedure 1, Step B-C, but substituting propylhydrazine for ethylhydrazine in Step B, the title compounds were prepared.

PROCEDURE 16

4-(3,3-Difluoro-3-phenylprop-1-yl)piperidine

Step A: 1-(Benzyloxycarbonyl)-4-(3-oxo-3-phenylprop-1-en-1-yl)piperidine

DIPEA (4.6 mL, 3.4 g, 26 mmol) was added to a solution of 4-(hydroxymethyl)piperidine (2.00 g, 17.4 mmol) dissolved in methylene chloride (20 mL). The solution was cooled in an ice bath and benzyl chloroformate (2.5 mL, 3.0 g, 18 mmol) was added dropwise over 10 min. After warming to rt and stirring for 96 h, the mixture was diluted with ethyl acetate (50 mL) and washed in succession with 25 mL each of saturated aq. $NaHCO_3$, 2N aq. HCl, saturated aq. $NaHCO_3$, and saturated aq. NaCl. The organic layer was dried (Na_2SO_4), decanted, and evaporated to give 4.14 g of 1-(benzyloxycarbonyl)-4-(hydroxymethyl)piperidine.

1,1,1-Triacetoxy-1,1-dihydro-1,2-benzoiodoxol-3(1H)-one (1.92 g, 4.53 mmol) was added to a solution of 1-(benzyloxycarbonyl)-4-(hydroxymethyl)piperidine (1.00 g, 4.01 mmol) in methylene chloride (20 mL) and the mixture was stirred at rt for 45 min. Ether (75 mL) and 1.3 N aq. NaOH (25 mL) were added and stirring was continued for 15 min. The mixture was transferred to a separatory funnel with additional ether (30 mL) and 1.3 N aq. NaOH (20 mL). The organic layer was separated, washed with saturated aq. NaCl (20 mL), dried (Na_2SO_4), decanted, and evaporated to give 846 mg of 1-(benzyloxycarbonyl)-4-piperidine carboxaldehyde as a colorless syrup.

Diethyl (2-oxo-2-phenylethyl)phosphonate (0.96 mL, 1.1 g, 4.4 mmol) was added in one portion to a stirred suspension of sodium hydride (60% oil dispersion, 158 mg, 3.95 mmol) in THF (20 mL). After 15 min. at rt, the clear solution was cooled in an ice bath and 1-(benzyloxycarbonyl)-4-

piperidinecarboxaldehyde (840 mg, 3.40 mmol) was added in THF (1.0 mL) with additional THF (2 x 1.0 mL) for rinsing. Stirring was continued for a total of 2 h, with slow warming to rt. The mixture was then partitioned between ether (120 mL) and 2.5 N aq. NaOH (60 mL). The organic layer was washed with saturated aq. NaCl (60 mL), dried (Na_2SO_4), decanted, and evaporated. The crude product was purified by FC, eluting with 15-20% ethyl acetate in hexane, to give 0.95 g of the title compound as a colorless syrup.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 8 Hz, 2 H), 7.57 (t, J = 8 Hz, 1 H), 7.48 (t, J = 8 Hz, 2 H), 7.39-7.29 (m, 5 H), 6.99 (dd, J = 15, 6 Hz, 1 H), 6.87 (dd, J = 15 and 1 Hz, 1 H), 5.15 (s, 2 H), 2.97-2.82 (m, 2 H), 2.50-2.39 (m, 1 H), 1.89-1.77 (m, 2 H), 1.54-1.39 (m, 2 H).

MS (ESI): m/z 367 (M + NH_3 + H).

Step B: 2-(2-(1-(Benzyloxycarbonyl)piperidin-4-yl)ethyl)-2-phenyl-1,3-dithiolane

1-(Benzyloxycarbonyl)-4-(3-oxo-3-phenylprop-1-en-1-yl)piperidine from Step A (0.95 g, 2.7 mmol) was hydrogenated using 5% Pd/C (10 mg) in 95% ethanol (20 mL) at atmospheric pressure. After 3.5 h, the mixture was filtered and the catalyst was washed with 95% ethanol. Evaporation of the filtrate gave 0.95 g of 1-(benzyloxycarbonyl)-4-(3-oxo-3-phenylprop-1-yl)piperidine as a colorless syrup.

Boron trifluoride-acetic acid complex ($BF_3 \cdot 2CH_3CO_2H$, 0.370 mL, 501 mg, 2.67 mmol) was added to a solution of 1,2-ethanedithiol (0.440 mL, 494 mg, 5.25 mmol) and (1-(benzyloxycarbonyl)-4-(3-oxo-3-phenylprop-1-yl)piperidine (930 mg, 2.65 mmol) in methylene chloride (4.0 mL) at rt. After 6 h, the mixture was diluted with ether (50 mL) and washed with saturated aq. $NaHCO_3$ (2 x 25 mL), 2.5 N aq. NaOH (25 mL), and saturated aq. NaCl (25 mL). The organic layer was dried (Na_2SO_4), decanted, and evaporated. The crude product was purified by FC, eluting with 10% ethyl acetate in hexane, to give 1.05 g of the title compound as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 8 Hz, 2 H), 7.38-7.26 (m, 7 H), 7.22 (t, J = 8 Hz, 1 H), 5.10 (s, 2 H), 4.18-4.02 (m, 2 H), 3.41-3.32 (m, 2 H), 3.29-3.20 (m, 2 H), 2.79-2.62 (m, 2 H), 2.40-2.32 (m, 2 H), 1.65-1.54 (m, 2 H), 1.40-1.27 (m, 1 H), 1.24-1.16 (m, 2 H), 1.10-0.97 (m, 2 H);

HPLC/MS (ESI): m/z 428 (M + H); HPLC: 4.21 min.

664

Step C: 1-(t-Butoxycarbonyl)-4-(3,3-difluoro-3-phenylprop-1-yl)piperidine

1,3-Dibromo-5,5-dimethylhydantoin (74 mg, 0.26 mmol) was stirred with methylene chloride (0.50 mL) at rt, and the suspension was then cooled in a dry ice/2-PrOH bath. After 5 min., hydrogen fluoride·pyridine (70% HF, 0.18 mL) was added over 1 min. After 5 min., a solution of 2-(2-(1-(benzyloxycarbonyl)piperidin-4-yl)ethyl)-2-phenyl-1,3-dithiolane from Step B (100 mg, 0.234 mmol) in methylene chloride (0.20 mL) was added over 1 min. After 10 min, the reaction mixture was diluted into methylene chloride (25 mL) and washed with water (10 mL) containing $NaHSO_3$ (0.5 g). The organic layer was washed with saturated aq. $NaHCO_3$ (2 x 10 mL) followed by saturated aq. NaCl (10 mL), dried (Na_2SO_4), decanted, and evaporated to give 98 mg of colorless syrup. This material was combined with 195 mg of crude product from two similar reactions and purified by FC, eluting with 8% ethyl acetate in hexane, to give 247 mg of 1-(benzyloxycarbonyl)-4-(3,3-difluoro-3-phenylprop-1-yl)piperidine (R_f: 0.3 using 10% ethyl acetate in hexane) containing some residual impurity. .

The partially purified 1-(benzyloxycarbonyl)-4-(3,3-difluoro-3-phenylprop-1-yl)piperidine (247 mg) was hydrogenated at atmospheric pressure in 95% ethanol (4.0 mL) containing 20% $Pd(OH)_2/C$ (60 mg). After 6 h, additional 20% $Pd(OH)_2/C$ (32 mg) was added and the hydrogenation was continued for another 16 h. The mixture was filtered and the catalyst was washed with 95% ethanol. Evaporation of the filtrate gave 164 mg of crude 4-(3,3-difluoro-3-phenylprop-1-yl)piperidine as a colorless syrup.

Di-t-butyl dicarbonate (178 mg, 0.816 mmol) was transferred with methylene chloride (2 x 0.5 mL) to a solution of crude 4-(3,3-difluoro-3-phenylprop-1-yl)piperidine (164 mg) in methylene chloride (2.0 mL). After stirring at rt for 1 h, the solution was stored at -20 °C for 48 h. The mixture was then diluted into ethyl acetate (25 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL) followed by saturated aqueous NaCl (10 mL). The organic layer was dried (Na_2SO_4), decanted, and evaporated. The crude product was purified by FC, eluting with 4-5% ethyl acetate in hexane to give the title compound as 112 mg of colorless syrup. R_f: 0.25 (5% ethyl acetate in hexane).

^1H NMR (400 MHz, $CDCl_3$): δ 7.50-7.40 (m, 5 H), 4.24-3.99 (m, 2 H), 2.64 (bt, J = 12 Hz, 2 H), 2.14 (tm, J = 16 Hz, 2 H), 1.62 (bd, J = 12 Hz, 2 H), 1.45 (s, 9 H), 1.42-1.33 (m, 3 H), 1.13-1.00 (m, 2 H).

Step D: 4-(3,3-Difluoro-3-phenylprop-1-yl)piperidine

Trifluoroacetic acid (2.5 mL, 3.7 g, 32 mmol) was added dropwise to a solution of 1-(t-butoxycarbonyl)-4-(3,3-difluoro-3-phenylprop-1-yl)piperidine from Step C (42 mg, 0.12 mmol) in methylene chloride (2.5 mL) at 0 °C. After 80 min., the solution was transferred using a double-ended needle to a rapidly stirred solution of $NaHCO_3$ (5.0 g, 60 mmol) in water (50 mL). Ether (50 mL) and 2.5 N aq. NaOH (20 mL) were added, followed by solid NaCl to saturate the aqueous layer. The aqueous layer was separated and extracted with ether (50 mL). The organic layers were washed in succession with saturated aq. NaCl (20 mL), combined, dried (Na_2SO_4), decanted, and evaporated to give the title compound as 27 mg of colorless oil.

^1H NMR (400 MHz, CD_3OD): δ 7.51-7.40 (m, 5 H), 2.98 (dm, J = 12 Hz, 2 H), 2.53 (td, J = 12 and 3 Hz, 2 H), 2.24-2.10 (m, 2 H), 1.65 (bd, J = 12 Hz, 2 H), 1.42-1.26 (m, 3 H), 1.06 (qd, J = 12 and 4 Hz, 2 H).

HPLC/MS (ESI): m/z 240 (M + H); HPLC: 2.25 min.

PROCEDURE 17

4-(3,3-Difluoro-3-(4-fluorophenyl)prop-1-yl)piperidine

Step A: 1-(t-Butoxycarbonyl)-4-(hydroxymethyl)piperidine

Di-t-butyl dicarbonate (4.69 g, 21.5 mmol) was transferred in methylene chloride (9 mL) over 10 min. to a solution of 4-(hydroxymethyl)piperidine (2.47 g, 21.4 mmol) in methylene chloride (16 mL). After stirring at rt for 1 h, the solution was diluted with ether (50 mL) and washed with 2 N aq. HCl, saturated aq. $NaHCO_3$, and saturated aq. NaCl (25 mL of each). The organic layer was dried (Na_2SO_4), decanted, and evaporated to give 4.57 g of the title compound as a crystalline solid.

^1H NMR (500 MHz, CD_3OD): δ 4.08 (d, J = 14 Hz, 2 H), 3.40 (d, J = 6 Hz, 2 H), 2.81-2.67 (m, 2 H), 1.71 (d, J = 13 Hz, 2 H), 1.67-1.58 (m, 1 H), 1.44 (s, 9 H), 1.09 (qd, J = 12 and 4 Hz, 2 H).

Step B: 1-(t-Butoxycarbonyl)-4-(iodomethyl)piperidine

Methanesulfonyl chloride (4.10 mL, 6.07 g, 52.9 mmol) was added dropwise to a solution of 1-(t-butoxycarbonyl)-4-(hydroxymethyl)piperidine from

Step A (10.0 g, 46.4 mmol) and triethylamine (9.80 mL, 7.11 g, 70.3 mmol) in methylene chloride (140 mL) at 5-8 °C. After 1 h, the mixture was diluted with ethyl acetate (400 mL) and washed with water (200 mL). The aqueous layer was extracted with ethyl acetate (2 x 150 mL) and the combined organic layers were washed with 1 N aq. HCl (200 mL), saturated aq. $NaHCO_3$ (200 mL), and saturated aq. NaCl (200 mL). The organic layer was dried (Na_2SO_4), decanted, and evaporated to give 13.58 g of 1-(t-butoxycarbonyl)piperidin-4-yl methanesulfonate as a pale yellow solid.

A mixture of 1-(t-butoxycarbonyl)piperidin-4-yl methanesulfonate (13.58 g, 46.4 mmol) and sodium iodide (34.68 g, 232 mmol) in acetone (80 mL) was heated to reflux for 3 h. The mixture was partitioned between ether (350 mL) and water (350 mL). The organic layer was washed with saturated aq. NaCl (250 mL), and the aqueous layers were extracted in succession with ether (250 mL). The combined organic layers were dried (Na_2SO_4), decanted, and evaporated to give the title compound (14.8 g) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.25-4.00 (m, 2 H), 3.12 (d, J = 4 Hz, 2 H), 2.78-2.52 (m, 2 H), 1.85 (d, J = 13 Hz, 2 H), 1.68-1.56 (m, 1 H), 1.48 (s, 9 H), 1.15 (qd, J = 12 and 4 Hz, 2 H).

Step C: ((1-(t-Butoxycarbonyl)piperidin-4-yl)methyl)triphenylphosphonium iodide

A solution of triphenylphosphine (6.63 g, 25.3 mmol) and 1-(t-butoxycarbonyl)-4-(iodomethyl)piperidine from Step B (7.96 g, 24.5 mmol) in acetonitrile (40 mL) was heated to reflux for 72 h. The solution was evaporated to give 13.35 g of white solid. A portion (12.34 g) of this material was dissolved in acetonitrile (25 mL) at 65 °C. Ethyl acetate (35 mL) was added and the mixture was allowed to cool slowly to rt and then to -20 °C. The supernatant was decanted, and the colorless crystals were washed with ethyl acetate (5 x 5 mL) and dried under vacuum to give 9.25 g of the title compound.

^{1}H NMR (500 MHz, CD_3OD): δ 7.89 (t, J = 8 Hz, 3 H), 7.86 (dd, J = 12 and 8 Hz, 6 H), 7.76 (td, J = 8 and 4 Hz, 6 H), 3.91 (bd, J = 13 Hz, 2 H), 3.44 (dd, J = 14 and 6 Hz, 2 H), 2.72-2.58 (m, 2 H), 2.08-1.96 (m, 1 H), 1.49 (bd, J = 12 Hz, 2 H), 1.41 (s, 9 H), 1.43 (qd, J = 13 and 4 Hz, 2 H).

Step D: Methyl (4-fluorobenzoyl)formate

Dimethyl oxalate (5.90 g, 50 mmol) was dissolved in THF (50 mL) and ether (50 mL) in a 3-neck round bottom flask fitted with a mechanical stirrer. The solution was stirred vigorously at -65 °C as a 1.0 M THF solution of 4-fluorophenylmagnesium bromide (60 mL, 60 mmol) was added dropwise over 40 min. The mixture was stirred 30 min at -65 °C and allowed to warm to -20 °C over 30 min before being poured into 2N aq. HCl (50 mL) with stirring. The layers were separated and the aq. layer was extracted with ether (3 x 50 mL). The combined organic layers were washed with saturated aq. NaCl (2 x 50 mL), dried (Na_2SO_4), decanted, and evaporated. The residue was dissolved in ethyl acetate, dried (Na_2SO_4), filtered, and evaporated to give a yellow solid. The crude product was dissolved in warm hexane (25 mL), filtered, and cooled to -20 °C. Filtration followed by washing with cold hexane (15 mL) gave 4.95 g of the title compound as light tan crystals.

^1H NMR (500 MHz, $CDCl_3$): δ 8.11 (dd, J = 9 and 5, Hz, 2 H), 7.21 (t, J = 9 Hz, 2 H), 4.00 (s, 3 H).

Step E: Methyl difluoro(4-fluorophenyl)acetate

Methyl (4-fluorobenzoyl)formate from Step D(4.75 g, 26.1 mmol) was added to (diethylamino)sulfur trifluoride (7.0 mL, 8.5 g, 53 mmol). The mixture was stirred rapidly and an ice bath was used briefly to reduce the temperature to 15 °C. After the ice bath was removed, the reaction temperature rose to 48 °C over 10 min and then slowly returned to rt. After a total of 2.75 h, the solution was carefully poured onto crushed ice (30 g) and the mixture was extracted with methylene chloride (2 x 25 mL). The organic layers were washed in succession with saturated aq. $NaHCO_3$ (2 x 25 mL) and saturated aq. NaCl (10 mL), combined, dried (Na_2SO_4) decanted, and evaporated. The residue was distilled to give the title compound as 4.16 g of light yellow liquid, B.P. 46-48 °C (0.5 mm Hg).

^1H NMR (500 MHz, $CDCl_3$): δ 7.63 (dd, J = 9, 5 Hz, 2 H), 7.16 (d, J = 9 Hz, 2 H), 3.88 (s, 3 H).

Step F: 1-(t-Butoxycarbonyl)-4-(3,3-difluoro-3-(4-fluorophenyl)prop-1-en-1-yl)piperidine

A solution of methyl difluoro(4-fluorophenyl)acetate (2.04 g, 10.0 mmol) in CH_3OH (10.0 mL) was cooled to -60 °C. Sodium borohydride (380 mg, 10.0 mmol) was added in 5 portions at 10 to 15 min. intervals. The mixture was

cooled to -60 to -55 °C prior to each addition and allowed to warm to -45 °C following each addition. After the last addition, the mixture was stirred 1.25 h at -50 to -45 °C. The mixture was cooled to -60 °C and quenched with 1 N aq. HCl (30 mL), with the temperature rising to -20 °C near the end of the addition. After warming to 0 °C, the mixture was extracted with ether (3 x 20 mL). The combined ether layers were washed with water (2 x 20 mL), dried (Na_2SO_4), decanted, and evaporated to give 1.95 g of crude 2,2-difluoro-2-(4-fluorophenyl)-1-methoxyethanol as a pale yellow oil.

A suspension of ((1-(t-butoxycarbonyl)piperidin-4-yl)methyl)triphenylphosphonium iodide (500 mg, 0,92 mmol) in THF (7.2 mL) was stirred at rt for 30 min. A 0.5 M toluene solution of potassium bis(trimethylsilyl)amide (1.8 mL, 0.90 mmol) was added over 3 min., giving an orange suspension. After 30 min., crude 2,2-difluoro-2-(4-fluorophenyl)-1-methoxyethanol (95 mg, 0.46 mmol) was added in THF (1.0 mL). After an additional 30 min, the mixture was quenched by the addition of saturated aq. NH_4Cl (2 mL). The mixture was partitioned between ethyl acetate (50 mL) and water (75 mL), and the aqueous layer was extracted with ethyl acetate (50 mL). The organic layers were washed in succession with saturated aq. NaCl (25 mL), dried (Na_2SO_4), decanted, and evaporated. The crude product was purified by FC, eluting with 10% ether in hexane to give 117 mg of the title compound as a 95:5 mixture of cis and trans isomers, respectively.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (dd, J = 9 and 5 Hz, 2 H), 7.13 (t, J = 9 Hz, 2 H), 5.76 (q, J = 12 Hz, 1 H), 5.64 (dd, J = 12 and 10 Hz, 1 H), 4.20-3.95 (m, 2 H), 2.80-2.54 (m, 3 H), 1.54 (bd, J = 12 Hz, 2 H), 1.47 (s, 9 H), 1.26 (qd, J = 12 and 4 Hz, 2 H).

Step G: 1-(t-Butoxycarbonyl)-4-(3,3-difluoro-3-(4-fluorophenyl)propyl)piperidine

Potassium azodicarboxylate (695 mg, 3.58 mmol) was added to a solution of 1-(t-butoxycarbonyl)-4-(3,3-difluoro-3-(4-fluorophenyl)prop-1-en-1-yl)piperidine from Step F (424 mg, 1.19 mmol) in methanol (3.3 mL). The mixture was stirred at rt as a 9.0 M solution of acetic acid in methanol (0.80 mL, 7.2 mmol) was added over 3 h using a syringe pump. After 30 min., a second portion of potassium azodicarboxylate (695 mg, 3.58 mmol) was added followed by the addition of 9.0 M acetic acid in methanol (0.80 mL, 7.2 mmol) over 3 h. After 20 min, a third

portion of potassium azodicarboxylate (695 mg, 3.58 mmol) was added followed by the addition of 9.0 M acetic acid in methanol (0.80 mL, 7.2 mmol) over 3 h. After stirring for 20 h at rt, the mixture was diluted with ethyl acetate (80 mL), and washed with 2 N aq. HCl (40 mL), saturated aq. $NaHCO_3$ (40 mL), and saturated aq. NaCl (40 mL). The organic layer was dried (Na_2SO_4), decanted, and evaporated to give 417 mg of a mixture containing the title compound and 20-25% of unreduced 1-(t-butoxycarbonyl)-4-(3,3-difluoro-3-(4-fluorophenyl)prop-1-en-1-yl)piperidine.

A portion (365 mg) of the crude mixture containing residual olefin was hydrogenated at atmospheric pressure for 16 h using iridium black (30 mg) in a mixture of t-butanol (24 mL) and ethyl acetate (2.4 mL). The mixture was filtered, the catalyst was washed with methanol, and the filtrate was evaporated to give 371 mg of the title compound as a pale yellow syrup. Rf: 0.2 (5% ethyl acetate in hexane). ^1H NMR (500 MHz, $CDCl_3$): δ 7.46 (dd, J = 9 and 5 Hz, 2 H), 7.12 (t, J = 9 Hz, 2 H), 4.18-4.00 (m, 2 H), 2.73-2.61 (m, 2 H), 2.14 (tm, J = 16 Hz, 2 H), 1.64 (bd, J = 12 Hz, 2 H), 1.46 (s, 9 H), 1.46-1.33 (m, 3 H), 1.08 (qd, J = 12 and 4 Hz, 2 H).

Step H: 4-(3,3-Difluoro-3-(4-fluorophenyl)prop-1-yl)piperidine

1-(t-Butoxycarbonyl)-4-(3,3-difluoro-3-(4-fluorophenyl)prop-1-yl)piperidine from Step G (122 mg, 0.34 mmol) was dried by evaporation of a toluene solution at reduced pressure. The residue was dissolved in chloroform (7.6 mL) and iodotrimethylsilane (0.100 mL, 141 mg, 0.70 mmol) was added. After stirring 30 min at rt, the solution was poured into a mixture of saturated aqueous $NaHCO_3$ (15 mL) and 2.5 N aq. NaOH (5 mL), and extracted with ether (50 mL). The organic layer was washed with saturated aq. NaCl (15 mL), dried (Na_2SO_4), decanted, and evaporated to give the title compound as 88 mg of colorless oil.
^1H NMR (500 MHz, CD_3OD): δ 7.51 (dd, J = 9 and 5 Hz, 2 H), 7.17 (t, J = 9 Hz, 2 H), 2.98 (dm, J = 12 Hz, 2 H), 2.52 (td, J = 12, 3 Hz, 2 H), 2.17 (tm, J = 16 Hz, 2 H), 1.65 (bd, J = 13 Hz, 2 H), 1.42-1.26 (m, 3 H), 1.07 (qd, J = 12 and 4 Hz, 2 H).
HPLC/MS (ESI): m/z 258 (M + H); HPLC: 2.64 min.

EXAMPLE 1

N-(1-(SR)-3-(SR)-((4-(3-(Phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-L-leucine di-hydrochloride salt and *N*-(1-(SR)-3-(SR)-((4-(3-

(phenyl)prop-1-yl)piperidin-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-D-leucine di-hydrochloride salt

Step A: Methyl (+-)-*trans*-4-methylene-2-phenylcylopentanoate

A mixture of methyl *trans*-cinnamate (5.0 g, 31 mmol), tetrakis(triphenylphosphine) palladium(0) (2.6 g, 2.3 mmol), 1,2-bis(diphenylphosphino)ethane (0.70 g, 1.8 mmol) and 2-((trimethylsilyl)methyl)-2-propen-1-yl acetate (6.90 g, 37 mmol) in THF (60 mL) under argon was heated to reflux for 4 h. An additional aliquot of 2-((trimethylsilyl)methyl)-2-propen-1-yl acetate (3.40 g) was added and the reaction was continued for another 16 h. The volatiles were then removed *in vacuo* and the residue was purified by FC (10% ethyl acetate in hexanes) to afford the title compound (6.2 g).

^{1}H NMR ($CDCl_3$) δ: 2.52 (m, 1 H), 2.68 (m, 1 H), 2.75-2.9 (m, 2 H), 2.95 (ddd, 1 H), 3.45 (ddd, 1 H), 3.57 (s, 3 H), 4.92 (m, 2 H), 7.15-7.3 (m, 5 H).

Step B: (+-)-*trans*-1-Hydroxymethyl-4-methylene-2-phenylcylopentane

To a solution of methyl (+-)-*trans*-4-methylene-2-phenylcylopentanoate (26.0 g, 128 mmol) prepared as in Step A in THF (600 mL) under nitrogen and cooled to -10 °C was added dropwise over 15 min 1M lithium aluminum hydride (LAH) in THF (193 mL). After 1 h, the bath was removed and the reaction was stirred at RT for 16 h. The reaction was cooled in an ice/methanol bath and the excess LAH was quenched by dropwise addition of acetone. The reaction was then poured into dilute aq. HCl. The mixture was extracted twice with ether and the organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (20 - 30% ethyl acetate in hexanes) to afford the title product (23.8 g).

Step C: (+-)-*trans*-1-Hydroxymethyl-4-oxo-2-phenylcylopentane

Into a solution of (+-)-*trans*-1-hydroxymethyl-4-methylene-2-phenylcylopentane from Step B (22.7 g, 121 mmol) in methanol (300 mL) cooled in a dry ice/acetone bath was bubbled ozone until the blue color persisted. The excess ozone was removed with a stream of nitrogen and then dimethylsulfide (25 mL) was added. After 30 min, the bath was removed and the reaction was allowed to warm to RT over 16 h. The volatiles were removed in vacuo and the residue was purified by FC (15 -30% ethyl acetate in hexanes) to give the title compound (22.1 g).

671

^{1}H NMR ($CDCl_3$) δ: 2.2-2.5 (m, 4 H), 2.71 (dd, 1 H), 3.28 (m, 1 H), 3.55 (dABq, 2 H), 7.23 (m, 3 H), 7.34 (m, 2 H).

Step D: 1-(SR)-Benzylamino-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopentane and 1-(RS)-benzylamino-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopentane

To a solution of (+-)-*trans*-1-hydroxymethyl-4-oxo-2-phenylcylopentane from Step C (9.8 g, 52 mmol) in 1,2-dichloroethane (200 mL) was added benzylamine (11.3 mL, 103 mmol) and acetic acid (6.2 mL, 103 mmol). After 10 min, sodium triacetoxyborohydride (33 g, 155 mmol) was added in portions and the reaction was stirred at RT for 3 hr. The reaction was quenched into dilute aq. sodium carbonate and the mixture was extracted twice with ethyl acetate. The organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (1-5% methanol in ether) to obtain the title products (13.1 g) as a mixture of C-1 isomers.

Step E: 1-(SR)-Benzyloxycarbonylamino-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopentane (Higher R_f isomer) and 1-(RS)-benzyloxycarbonylamino-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopentane (Lower R_f isomer)

To a solution of 1-(SR)-benzylamino-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopentane and 1-(RS)-benzylamino-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopentane (13 g, 46 mmol) from Step D was added 20% palladium hydroxide (2.5 g, 50% by wt water), ammonium formate (60 g, 930 mmol) and an additional 200 mL of methanol. The reaction was heated at 60 °C for 6 h. The reaction was filtered and concentrated. The residue was taken up in water and extracted twice with methylene chloride to remove any remaining benzylamine intermediate. The aqueous layer was made basic with 2N sodium hydroxide and extracted twice with methylene chloride. The organic layers were washed with brine, dried over sodium sulfate, combined and concentrated to afford 8.1 g of crude amino-alcohol.

The above product (8.1 g, 42 mmol) was taken up in methylene chloride (200 mL), cooled in an ice bath and DIPEA (22 mL, 126 mmol) and benzyl chloroformate (6.33 mL, 44 mmol) were added. After 2.5 h at RT, the reaction was poured into dilute aq. HCl and extracted twice with methylene chloride. The organic

layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by Prep LC (30 - 75% ethyl acetate in hexanes) to afford the title compounds (4.0 g higher, 6.6 g lower).

Step F: 1-(SR)-Benzyloxycarbonylamino-3-(SR)-formyl-4-(SR)-phenylcylopentane (Higher R_f isomer) and 1-(SS)-benzyloxycarbonylamino-3-(SR)-formyl-4-(SR)-phenylcylopentane (Lower R_f isomer)

To a solution of oxalyl chloride (0.350 mL, 3.85 mmol) in methylene chloride (10 mL) at -70 °C was added dropwise DMSO (0.550 mL, 7.65 mmol). After 15 min, a solution of 1-(SR)-benzyloxycarbonylamino-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopentane (Higher R_f isomer from Step E) (500 mg, 1.53 mmol) in methylene chloride (10 mL) was added. The reaction was stirred at -70 °C for 1 h and then DIPEA (2.7 mL, 15 mmol) in methylene chloride (5 mL) was added dropwise over 5 min. After a further 10 min, the mixture was allowed to warm to RT for 1 h and then diluted with methylene chloride and poured into dilute aq. HCl. The layers were separated. The aq. layer was reextracted with a second portion of methylene chloride and the organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by FC (20 - 30% ethyl acetate in hexanes) to give the title product (465 mg) as an oil.
^{1}H NMR ($CDCl_3$) δ: 1.9-2.0 (m, 1 H, 2b-H), 2.05-2.15 (m, 2 H, both 5-H's), 2.3-2.45 (m, 1 H, 2a-H), 3.06 (q, 1 H, 3-H), 3.47 (q, 1 H, 4-H), 4.32 (br m, 1 H, 1-H), 4.94 (br s, 1 H, NH), 5.08 (s, 2 H, CH_2O), 7.1-7.4 (m, 10 H), 9.74 (s, 1 H, COH). The assignment of cis stereochemistry between C-1 and C-3 and trans between C-1 and C-4 were confirmed by 2-D NOESY NMR.

Using essentially the same procedure as above, material derived from the lower isomer from Step E (500 mg, 1.5 mmol) was also converted to the lower R_f title compound (457 mg).
^{1}H NMR ($CDCl_3$) δ: 1.71 (q, 1 H, 5a-H), 1.8-1.95 (m, 1 H, 2a-H), 2.48 (p, 1 H, 2b-H), 2.5-2.6 (m, 1 H, 5b-H), 3.0-3.1 (m, 1 H, 3-H), 3.3-3.4 (m, 1 H, 4-H), 4.0-4.2 (m, 1 H, 1-H), 4.82 (br s, 1 H, NH), 5.08 (s, 2 H, OCH_2), 7.2-7.4 (m, 10 H), 9.63 (d, 1 H, COH). The assignment of trans stereochemistry between C-1 and C-3 and cis between C-1 and C-4 were confirmed by 2-D NOESY NMR.

Step G: 1-(SR)-(Benzyloxycarbonylamino)-3-(SR)-((4-(3-phenylprop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcylopentane (Higher R_f isomer)

To a solution of 1-((SR)-(benzyloxycarbonylamino)-3-(SR)-(carbonyl)-4-(SR)-phenylcyclopentane (from Step F, derived from Higher R_f isomer in Step E) (450 mg, 0.1.4 mmol) in 1,2-dichloroethane (10 mL) was added 4-(3-phenylprop-1-yl)piperidine (424 mg, 2.1 mmol) and acetic acid (0.125 mL, 2.1 mmol). After 15 min, sodium triacetoxyborohydride (890 mg, 4.2 mmol) was added in portions over 30 min and the reaction was stirred at RT for 16 h. The reaction was diluted with methylene chloride, quenched with aq. sodium carbonate and extracted 3 times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by FC (30 - 40% ethyl acetate in hexanes) to give the title product (698 mg) as the free amine.

MS (NH_3/ESI): m/z 511 (M + 1).

Step H: 1-(SR)-(Amino)-3-(SR)-((4-(3-phenylprop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcylopentane (Higher R_f isomer)

To a solution of 1-(SR)-(benzyloxycarbonylamino)-3-(SR)-((4-(3-phenylprop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcylopentane (from Step G, derived from the Higher R_f isomer from Step E) (500 mg, 1.0 mmol) in methanol (10 mL) was added 10% Pd/C (100 mg). The mixture was hydrogenated on a Parr shaker at 40 psi for 2 h and was then filtered and concentrated to afford the crude title compound (350 mg) as an oil.

Step I: *N*-(1-(SR)-3-(SR)-((4-(3-(Phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-L-leucine di-hydrochloride salt and *N*-(1-(SR)-3-(SR)-((4-(3-(phenyl)prop-1-yl)piperidin-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-D-leucine di-hydrochloride salt

To a solution of 1-(SR)-(amino)-3-(SR)-((4-(3-phenylprop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcylopentane (from Step H, derived from the Higher R_f isomer from Step E) (25 mg, 0.067 mmol), 4-methyl-2-oxovaleric acid (17 mg, 0.13 mmol) and acetic acid (0.008 mL, 0.13 mmol) in 1,2-dichloroethane (2 mL) was added sodium triacetoxyborohydride (42 mg, 0.20 mmol). The reaction was

stirred at rt for 24 h and was then quenched into dilute aq. sodium carbonate solution and was extracted three times with ethyl acetate. The organic layers were washed with brine, dried over sodium sulfate, combined and evaporated. The residue was purified by Prep TLC (5% methanol in methylene chloride) to afford separation of the 2 title compounds. The hydrochlorides were prepared by taking up in methylene chloride, addition of excess 1M HCl in ether, and evaporation to dryness.
Higher: MS (NH_3/ESI): m/z 491 (M + 1).
Lower: MS (NH_3/ESI): m/z 491 (M + 1).

EXAMPLE 2

N-(1-(RS)-3-(SR)-((4-(3-(Phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-L-leucine di-hydrochloride salt and *N*-(1-(RS)-3-(SR)-((4-(3-(phenyl)prop-1-yl)piperidin-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-D-leucine di-hydrochloride salt

Using essentially the same procedures as in Example 1, Steps G-I, but substituting the lower R_f product from Steps E and F, the 2 title compounds were obtained after Prep TLC separation.
Higher: MS (NH_3/ESI): m/z 491 (M + 1).
Lower: MS (NH_3/ESI): m/z 491 (M + 1).

EXAMPLE 3

N-(1-(SR)-3-(SR)-((4-(3-(Phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-L-norvaline di-hydrochloride salt and *N*-(1-(SR)-3-(SR)-((4-(3-(phenyl)prop-1-yl)piperidin-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-D-norvaline di-hydrochloride salt

Using essentially the same procedure as in Example 1, Step I, but substituting 2-oxovaleric acid in Step I, the 2 title compounds were obtained as a mixture after Prep TLC purification (no separation of the diastereomers was seen in this case).
MS (NH_3/ESI): m/z 477 (M + 1).

EXAMPLE 4

N-(1-(RS)-3-(SR)-((4-(3-(Phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-L-norvaline di-hydrochloride salt and *N*-(1-(RS)-3-(SR)-((4-(3-(phenyl)prop-1-yl)piperidin-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-D-norvaline di-hydrochloride salt

Using essentially the same procedures as in Example 1, Steps G-I, but substituting the lower R_f product from Steps E and F and 2-oxovaleric acid in Step I the 2 title compounds were obtained as a mixture after Prep TLC purification (no separation of the diastereomers was seen in this case).
MS (NH_3/ESI): m/z 477 (M + 1).

EXAMPLE 5

N-(1-(RS)-3-(SR)-((4-(3-(Phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-L-phenylglycine di-hydrochloride salt and *N*-(1-(RS)-3-(SR)-((4-(3-(phenyl)prop-1-yl)piperidin-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-D-phenylglycine di-hydrochloride salt

Using essentially the same procedures as in Example 1, Steps G-I, but substituting the lower R_f product from Steps E and F and 2-oxophenylacetic acid in Step I the 2 title compounds were obtained as a mixture after Prep TLC purification (no separation of the diastereomers was seen in this case).
HPLC/MS (ESI): m/z 511 (M + 1).

Examples 6-9 illustrate the chemistry described in Schemes X-Y of the general chemistry section and were used to determine the absolute stereochemistry at the C-1, 3 and 4 positions of the cyclopentyl scaffold for the intermediates and final products. This was then applied to the preparation and assignment of stereochemistry for the subsequent Examples in this patent.

EXAMPLE 6

N-(1-(S)-3-(R)-((4-(*N*-(4-Nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-leucine (Isomer 6A), *N*-(1-(S)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-

phenylcyclopent-1-yl)-L-leucine (Isomer 6B), *N*-(1-(R)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-leucine (Isomer 6C) and *N*-(1-(R)-3-(R)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-leucine (Isomer 6D) di-TFA salts

Step A: (+-)-*trans*-4-Methylene-2-phenylcyclopentanoic acid

To a solution of methyl (+-)-*trans*-4-methylene-2-phenylcylopentanoate prepared as in Example 1, Step A (28.4 g, 131 mmol) in methanol (400 mL) was added 5N sodium hydroxide (131 mL, 656 mmol). The reaction was heated at 65 °C for 1 h then cooled and concentrated. The residue was diluted with water, acidified with 2M hydrochloric acid and extracted twice with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo to give the crude title acid (27.2 g) which was used directly in Step B.

Step B: (+-)-*trans*-1-Hydroxymethyl-4-methylene-2-phenylcylopentane

To a solution of (+-)-*trans*-4-methylene-2-phenylcylopentanoic acid (26 g, 129 mmol) from Step A in THF (600 mL) under nitrogen at -10 °C was added dropwise over 15 min 1M lithium aluminum hydride (LAH) in THF (193 mL, 193 mmol). After 16 h at rt, the excess LAH was quenched by dropwise addition of acetone and the reaction was then poured into dilute aq. HCl. The mixture was extracted twice with ether and the organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (20% ethyl acetate in hexanes) to afford the title product (23.8 g) as an oil.

Step C: (+-)-*trans*-1-Hydroxymethyl-4-oxo-2-phenylcylopentane

Into a solution of (+-)-*trans*-1-hydroxymethyl-4-methylene-2-phenylcylopentane from Step B (22.7 g, 121 mmol) in methanol (200 mL) cooled in a dry ice/acetone bath was bubbled ozone until the blue color persisted. The excess ozone was removed with a stream of nitrogen and then dimethylsulfide (20 mL) was added. After 10 min, the bath was removed and the reaction was allowed to warm to rt over 16 h. The volatiles were removed in vacuo and the residue was purified by FC (15 -30% ethyl acetate in hexanes) to give the title compound (22.1 g).

Step D: (+-)-*trans*-4-Oxo-2-phenylcylopentanecarboxaldehyde

To a solution of oxalyl chloride (1.15 mL, 13.1 mmol) in methylene chloride (30 mL) at -70 °C was added dropwise DMSO (1.87 mL, 26.3 mmol). After 15 min, a solution of (+-)-*trans*-1-hydroxymethyl-4-oxo-2-phenylcylopentane from Step C (1.0 g, 5.26 mmol) in methylene chloride (10 mL) was added. The reaction was stirred at -70 °C for 1.5 h and then DIPEA (9.25 mL, 53 mmol) in methylene chloride (10 mL) was added dropwise over 5 min. After a further 10 min, the mixture was allowed to warm to rt for 1 h and then diluted with methylene chloride and poured into dilute aq. HCl. The layers were separated. The aq. layer was reextracted with a second portion of methylene chloride and the organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by FC (30% ethyl acetate in hexanes) to give the title product (0.9 g) after vacuum drying.

Step E: 3-(SR)-((4-(*N*-(4-Nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopentan-1-one di-hydrochloride salt

To a solution of (+-)-*trans*-4-oxo-2-phenylcylopentanecarboxaldehyde from Step D (327 mg, 1.74 mmol) in 1,2-dichloroethane (20 mL) was added 4-(*N*-(4-nitrobenzyloxycarbonyl)(*N*-allyl)amino)piperidine hydrochloride (667 mg, 1.9 mmol) and DIPEA (0.36 mL, 2.1 mmol). After 5 min, sodium triacetoxyborohydride (740 mg, 3.5 mmol) was added and the reaction was stirred at rt for 4 h. The reaction was diluted with methylene chloride, quenched with aq. sodium carbonate and extracted 3 times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by FC eluting with a gradient of 35 to 75% ethyl acetate in hexanes to give the title product (365 mg) as the free amine. This was taken up in ether and 1M hydrogen chloride in ether (0.5 mL) was added to form the di-hydrochloride salt. The volatiles were removed in vacuo to give the title salt.
MS (NH_3/ESI): m/z 492 (M + 1).

Step F: *N*-(1-(S)-3-(R)-((4-(*N*-(4-Nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-leucine t-butyl ester (Isomer A), *N*-(1-(S)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-leucine t-butyl ester (Isomer B), *N*-(1-(R)-3-

(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-leucine t-butyl ester (Isomer C) and *N*-(1-(R)-3-(R)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-leucine t-butyl ester (Isomer D)

To a solution of 3-(SR)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopentan-1-one (52 mg, 0.10 mmol) from Step E, L-leucine t-butyl ester hydrochloride (65 mg, 0.29 mmol) and DIPEA (0.069 mL, 0.40 mmol) in 1,2-dichloroethane (2 mL) at rt was added sodium triacetoxyborohydride (41 mg, 0.20 mmol). The reaction was stirred at rt for 16 h and was then diluted with methylene chloride, quenched with aq. sodium carbonate and extracted 3 times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by Prep TLC eluting first with 75% ethyl acetate in hexanes to give partial separation of the four diastereomeric title products. Prep TLC was repeated with 40% ethyl acetate in hexanes for each band to give clean highest R_f product (Isomer A), a mixture of the middle R_f products (Isomers B and C), and clean lowest R_f product (Isomer D) as the free amines.

(higher R_f): HPLC/MS (ESI): m/z 663 (M + 1).

(middle R_f): HPLC/MS (ESI): m/z 663 (M + 1) (2 isomers seen).

(lower R_f): HPLC/MS (ESI): m/z 663 (M + 1).

Step G: *N*-(1-(S)-3-(R)-((4-(*N*-(4-Nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-leucine (Isomer 6A), *N*-(1-(S)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-leucine (Isomer 6B), *N*-(1-(R)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-leucine (Isomer 6C) and *N*-(1-(R)-3-(R)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-leucine (Isomer 6D) di-TFA salts

The 2 individual diastereomers and the mixed diastereomers from Step F were each taken up in 1:1 methylene chloride:ether (2 mL) and 1M hydrogen chloride in ether (1 mL) was added. After 3 days at rt the volatiles were removed

under nitrogen to give the title compounds as white solids. These were analyzed by HPLC (Advantage 4.6 x 150 mm C-18 column, using a gradient of 10% A:90% B to 35% A:65% B over 30 min; A = 0.5% TFA in water, B = 0.5% TFA in acetonitrile) and purified by Prep HPLC (Combi Prep 20 x 50 mm C-18). Evaporation of the clean fractions to dryness afforded the title compounds as their di-TFA salts.

Isomer A (from highest R_f): HPLC/MS (ESI): m/z 607 (M + 1), R_t = 25.5 min

Isomer B (from middle R_f): HPLC/MS (ESI): m/z 607 (M + 1), R_t = 25.2 min.

Isomer C (from middle R_f): HPLC/MS (ESI): m/z 607 (M + 1), R_t = 25.9 min.

Isomer D (from lowest R_f): HPLC/MS (ESI): m/z 607 (M + 1), R_t = 25.2 min.

EXAMPLE 7

N-(1-(R)-3-(S)-((4-(*N*-(4-Nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine (Isomer 7E), *N*-(1-(R)-3-(R)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-D-leucine (Isomer 7F), *N*-(1-(S)-3-(R)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-D-leucine (Isomer 7G) and *N*-(1-(S)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine (Isomer 7H) di-TFA salts

Using essentially the same procedures as in Example 6, Step F and G, but substituting D-leucine t-butyl ester hydrochloride in Step F, the four title diastereomers were obtained which were enantiomeric to those of Example 6.

Isomer E (from highest R_f): HPLC/MS (ESI): m/z 607 (M + 1), R_t = 25.5 min

Isomer F (from middle R_f): HPLC/MS (ESI): m/z 607 (M + 1), R_t = 25.2 min.

Isomer G (from middle R_f): HPLC/MS (ESI): m/z 607 (M + 1), R_t = 25.9 min.

Isomer H (from lowest R_f): HPLC/MS (ESI): m/z 607 (M + 1), R_t = 25.2 min.

EXAMPLE 8

N-(1-(S)-3-(S)-((4-(*N*-(4-Nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-leucine (Isomer 6B) and *N*-(1-(S)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine (Isomer 7H) di-TFA salts

Step A: (+-)-*trans*-4-Methylene-2-phenylcyclopentanoic acid

To a solution of methyl (+-)-*trans*-4-methylene-2-phenylcylopentanoate prepared as in Example 1, Step A (28.4 g, 131 mmol) in methanol (400 mL) was added 5N sodium hydroxide (131 mL, 656 mmol). The reaction was heated at 65 °C for 1 h then cooled and concentrated. The residue was diluted with water, acidified with 2M hydrochloric acid and extracted twice with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo to give the crude title acid (27.2 g) which was used directly in Step B.

Step B: (+)-*trans*-4-Methylene-2-phenylcyclopentanoic acid, (S)-(-)- α -methylbenzylamine salt and (-)-*trans*-4-methylene-2-phenylcylopentanoic acid, (R)-(+)- α -methylbenzylamine salt

The crude (+-)-*trans*-4-methylene-2-phenylcylopentanoic acid from Step A (assumed 131 mmol) was taken up in 2-propanol (400 mL), warmed to 80 °C and treated with (S)-(-)- α -methylbenzylamine (8.45 mL, 66 mmol). The mixture was stirred while allowed to cool to rt over 16 h and was then cooled to -10 °C for 1 h. The salt was filtered, washed with a small amount of ether to remove 2-propanol and air dried to give 6.442 g of salt. This was recrystallized twice from 2-propanol to give the title salt (4.713 g), $[\alpha]_D = +56$ (MeOH, c = 0.20).

The combined mother liquors from above were concentrated and the residue was taken up in water, acidified with 2M hydrochloric acid and extracted twice with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was taken up in 2-propanol (400 mL), warmed to 80 °C and treated with (R)-(+)- α -methylbenzylamine (9.1 mL, 70 mmol). The mixture was stirred while allowed to cool to rt over 16 h and was then cooled to -10 °C for 1 h. The salt was filtered, washed with a small amount of ether to remove 2-propanol and air dried to give 8.22 g of salt. This was recrystallized from 2-propanol to give the title salt (6.31 g), $[\alpha]_D =$ -55 (MeOH, c = 0.21).

Step C: (+)-*trans*-4-Methylene-2-phenylcylopentanoic acid and (-)-*trans*-4-methylene-2-phenylcylopentanoic acid

Method A:

The (+)-*trans*-4-methylene-2-phenylcylopentanoic acid, (S)-(-)- α -methylbenzylamine salt from Step B (4.7 g) was suspended in methylene chloride and water and acidified with 2M hydrochloric acid and extracted twice with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo to give the title (+) acid (3.1 g), $[\alpha]_D = +101$ (MeOH, c = 0.135).

Similarly, the (-)-*trans*-4-methylene-2-phenylcylopentanoic acid, (R)-(+)- α -methylbenzylamine salt (6.3 g) was converted to the free (-)-title acid (4.23 g), $[\alpha]_D = -103$ (MeOH, c = 0.23).

Method B:

Step B1: 1-(S)-(((S)-(-)-4-Benzyl-2-oxazolidin-1-yl)carbonyl)-3-methylene-2-(S)-phenylcyclopentane (higher R_f) and 1-(R)-(((S)-(-)-4-benzyl-2-oxazolidin-1-yl)carbonyl)-3-methylene-2-(R)-phenylcyclopentane (lower R_f)

A solution of (+-)-*trans*-4-methylene-2-phenylcylopentanoic acid (47.5 g, 235 mmol) in ether (1 L) and TEA (36 mL, 260 mmol) was cooled to -10 °C. Trimethylacetyl chloride (31.8 mL, 260 mmol) was then added slowly and after stirring at -10 °C for 10 min, the reaction was allowed to warm to 10 °C over 1 h. The reaction was then recooled to -60 °C.

To the above solution at -60 °C was added via a canula a solution of (S)-(-)-4-benzyl-2-oxazolidinone (45.8 g, 260 mmol) in THF (500 mL) which had been treated at -50 °C with 2.5 M n-butyl lithium (103 mL, 257 mmol) and aged at -50 °C for 45 min. The reaction was allowed to warm to rt over 16 h. The reaction was diluted with ether (1 L) and quenched with sat'd aqueous ammonium chloride (1 L). The layers were separated and the aqueous layer was reextracted with a second portion of ether. The organic layers were each washed twice with 2N hydrochloric acid, twice with 1N sodium hydroxide and brine, dried over sodium sulfate, combined and concentrated. The residue was purified by chromatography (20% ethyl acetate in

hexanes) to give the two diastereomeric products, higher R_f (18.4 g) and lower R_f (17.7 g).

Step B2: (+)-*trans*-4-Methylene-2-phenylcylopentanoic acid

A solution of 1-(S)-(((S)-(-)-4-benzyl-2-oxazolidin-1-yl)carbonyl)-3-methylene-2-(S)-phenylcyclopentane (higher R_f product from Step B1) (20.9 g, 58 mmol) in a 3 : 1 mixture of THF : water (1 L) was cooled to 5 °C. Hydrogen peroxide (30%, 39.5 mL, 350 mmol) and lithium hydroxide (4.85 g, 106 mmol) were added and the reaction was stirred for 3.5 h. The excess peroxide was quenched by dropwise addition of sodium sulfite (60 g) in water (1 L) over 1.5 h while maintaining the temperature below 5 °C. After stirring for 2 additional hours, most of the THF was removed in vacuo and the aqueous layer was washed 3 times with methylene chloride. The aqueous layer was acidified to pH = 2 with conc. HCl and reextracted twice with methylene chloride. The organic layers were washed with brine, dried and concentrated to give the (+) title product, $[\alpha]_D = +100.5$ (MeOH, c = 0.207).

Step D: (+)-*trans*-1-Hydroxymethyl-4-methylene-2-phenylcylopentane and (-)-*trans*-1-hydroxymethyl-4-methylene-2-phenylcylopentane

Method A:

A solution of (+)-*trans*-4-methylene-2-phenylcylopentanoic acid from Step C (4.15 g, 20:5 mmol) in THF (100 mL) under nitrogen was cooled to -7 °C and 1M LAH in THF (31 mL, 31 mmol) was added dropwise over 15. The reaction was allowed to warm to rt over 16 h. The excess LAH was quenched by dropwise addition of acetone and the reaction was then poured into dilute aq. HCl. The mixture was extracted twice with ether and the organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (20% ethyl acetate in hexanes) to afford the title (+) product (3.93 g), $[\alpha]_D = +50$ (MeOH, c = 0.20).

Similarly, the (-)-*trans*-4-methylene-2-phenylcylopentanoic acid from Step C (4.23 g) was converted to the title (-) alcohol (3.75 g), $[\alpha]_D = -51$ (MeOH, c = 0.2).

Method B:

Prep-HPLC of (+-)-*trans*-4-methylene-2-phenylcylopentanoic from Example 1, Step B using a Chiracel OD column (5-10% isopropanol in hexanes) affords good separation of the title (-) enantiomer as the first eluting band and the (+) enantiomer as the second eluting band.

Step E: (+)-*trans*-1-t-Butyldimethylsilyloxymethyl-4-methylene-2-phenylcylopentane and (-)-*trans*-1-t-butyldimethylsilyloxymethyl-4-methylene-2-phenylcylopentane

To a solution of (+)-*trans*-1-hydroxymethyl-4-methylene-2-phenylcylopentane from Step D (3.9 g, 21 mmol) in methylene chloride (50 mL) was added t-butyldimethylsilyl chloride (4.7 g, 31 mmol) and DIPEA (7.3 mL, 42 mmol). The reaction was stirred at rt for 16 h, poured into dilute aq. HCl and extracted twice with ether. The organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (100% hexanes) to afford the title product (5.6 g) as a oil, $[\alpha]_D$ = +42.3 (MeOH, c = 0.18).

Similarly, (-)-*trans*-1-hydroxymethyl-4-methylene-2-phenylcylopentane from Step D (3.75 g) was converted to the title (-) silylether (5.5 g), $[\alpha]_D$ = -44.4 (MeOH, c = 0.18).

Step F: (+)-*trans*-1-Hydroxymethyl-4-oxo-2-phenylcylopentane and (-)-*trans*-1-hydroxymethyl-4-oxo-2-phenylcylopentane

Method A:

A solution of (+)-*trans*-1-t-butyldimethylsilyloxymethyl-4-methylene-2-phenylcylopentane from Step E (4.6 g, 15 mmol) in methanol (100 mL) was cooled to -70 °C in a dry-ice acetone bath and ozone was bubbled through until a blue color persisted which was discharged with a stream of nitrogen. Dimethylsulfide (10 mL) was added and after 15 min, the reaction was allowed to warm to rt over 16 h. Since by TLC (20% ethyl acetate in hexanes) indicated that there was significant loss of the silyl as well as dimethylketal formation, the methanol was mostly remove in vacuo. The residue was diluted with water and treated with sulfuric acid (6 mL) and stirred for 2 h. The mixture was extracted twice with ethyl acetate and the organic layers were washed with brine (containing some sodium bicarbonate), dried over sodium sulfate, combined and concentrated. The residue was purified by FC (15 - 30% ethyl

acetate in hexanes) to give the (+) title ketone/alcohol (2.87 g), $[\alpha]_D$ = -96 (MeOH, c = 0.2).

Similarly, (-)-*trans*-1-t-butyldimethylsilyloxymethyl-4-methylene-2-phenylcylopentane from Step E (4.4 g) was converted to the title (-) ketone/alcohol (2.8 g), $[\alpha]_D$ = +97 (MeOH, c = 0.2)..

Method B:

The title compounds can also be obtained directly from (+)-*trans*-1-hydroxymethyl-4-methylene-2-phenylcylopentane and (-)-*trans*-1-hydroxymethyl-4-methylene-2-phenylcylopentane by ozonolysis as above. Thus, (+)-*trans*-1-hydroxymethyl-4-methylene-2-phenylcylopentane (3.7 gm, 20 mmol) afforded from (+)-*trans*-1-hydroxymethyl-4-oxo-2-phenylcylopentane (3.5 g).

Step G: 1-(S)-Benzylamino-3-(S)-hydroxymethyl-4-(S)-phenylcylopentane and 1-(R)-benzylamino-3-(S)-hydroxymethyl-4-(S)-phenylcylopentane

To a solution of (+)-*trans*-1-hydroxymethyl-4-oxo-2-phenylcylopentane from Step F (1.19 g, 6.3 mmol) in 1,2-dichloroethane (25 mL) was added benzylamine (1.3 mL, 12 mmol) and acetic acid (0.75 mL, 13 mmol). After 10 min, sodium triacetoxyborohydride (2.65 g, 12.5 mmol) was added in portions and the reaction was stirred at rt for 16 hr. The reaction was quenched into dilute aq. sodium carbonate and the mixture was extracted twice with ethyl acetate. The organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (5 - 10% methanol in methylene chloride) to separate the title products (1.6 g) as a mixture of C-1 isomers.

Step H: 1-(S)-t-Butoxycarbonylamino-3-(S)-hydroxymethyl-4-(S)-phenylcylopentane (Higher R_f isomer) and 1-(R)-t-butoxycarbonylamino-3-(S)-hydroxymethyl-4-(S)-phenylcylopentane (Lower R_f isomer)

To a solution of 1-(S)-benzylamino-3-(S)-hydroxymethyl-4-(S)-phenylcylopentane and 1-(R)-benzylamino-3-(S)-hydroxymethyl-4-(S)-phenylcylopentane from Step G (1.6 g, 5.6 mmol) in methanol (40 mL) was added 20% palladium hydroxide (300 mg, 50% by wt water) and ammonium formate (7.0 g, 111 mmol). The reaction was heated at 60 °C for 6 h and rt for 16 h. The reaction

was filtered and concentrated. The residue was taken up in water and the aqueous layer was made basic with 2N sodium hydroxide and extracted twice with methylene chloride. The organic layers were washed with brine, dried over sodium sulfate, combined and concentrated to afford crude amino-alcohol.

The above product was taken up in methylene chloride (25 mL), cooled in an ice bath and DIPEA (2.9 mL, 17 mmol) and di-t-butyl dicarbonate (1.28 g, 5.8 mmol) were added. After 16 h, the reaction was poured into dilute aq. HCl and extracted twice with methylene chloride. The organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (30 - 40% ethyl acetate in hexanes) to afford separation of the two title compounds.

Higher R_f:

^{1}H NMR ($CDCl_3$) δ: 1.43 (s, 9 H), 1.45 (m, 1 H), 1.9-2.1 (m, 2 H), 2.17 (m, 1 H), 2.40 (m, 1 H), 3.01 (q, 1 H), 3.59 (dABq, 2 H), 4.20 (br m, 1 H), 5.00 (br s, 1 H), 7.15-7.3 (m, 5 H).

Lower R_f:

^{1}H NMR ($CDCl_3$) δ: 1.43 (s, 9 H), 1.58 (ddd, 1 H), 1.78.1 (ddd, 1 H), 2.02 (m, 1 H), 2.29 (m, 1 H), 2.47 (ddd, 1 H), 2.76 (ddd, 1 H), 3.54 (dABq, 2 H), 4.06 (br m, 1 H), 4.62 (br s, 1 H), 7.15-7.3 (m, 5 H).

Step I: 1-(S)-t-Butoxycarbonylamino-3-(S)-formyl-4-(S)-phenylcylopentane (Higher R_f isomer) and 1-(R)-t-butoxycarbonylamino-3-(S)-formyl-4-(S)-phenylcylopentane (Lower R_f isomer)

To a solution of oxalyl chloride (0.145 mL, 1.67 mmol) in methylene chloride (10 mL) at -70 °C was added dropwise DMSO (0.24 mL, 3.3 mmol). After 15 min, a solution of 1-(S)-t-butoxycarbonylamino-3-(S)-hydroxymethyl-4-(S)-phenylcylopentane (Higher R_f isomer from Step F) (194 mg, 0.66 mmol) in methylene chloride (5 mL) was added. The reaction was stirred at -70 °C for 1.5 h and then DIPEA (1.2 mL, 6.6 mmol) in methylene chloride (5 mL) was added dropwise over 5 min. After a further 10 min, the mixture was allowed to warm to rt for 1 h and then diluted with methylene chloride and poured into dilute aq. HCl. The layers were separated. The aq. layer was reextracted with a second portion of methylene chloride and the organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by FC (15% ethyl acetate in hexanes) to give the title product (155 mg) after vacuum drying.

Using essentially the same procedure as above, material derived from the lower isomer from Step H (0.189 g, 0.6 mmol) was also converted to the lower R_f title compound (175 mg).

Step J: 1-(S)-(t-Butoxycarbonylamino)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcylopentane (Higher R_f isomer) and 1-(R)-(t-butoxycarbonylamino)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcylopentane (Lower R_f isomer)

To a solution of 1-((S)-(t-butoxycarbonylamino)-3-(S)-(carbonyl)-4-(S)-phenylcyclopentane (from Step I, derived from Higher R_f isomer in Step G) (155 mg, 0.54 mmol) in 1,2-dichloroethane (5 mL) was added 4-(*N*-(4-nitrobenzyloxycarbonyl)(*N*-allyl)amino)piperidine hydrochloride (210 mg, 0.59 mmol) and DIPEA (0.12 mL, 0.64 mmol). After 15 min, sodium triacetoxyborohydride (230 mg, 1.1 mmol) was added and the reaction was stirred at rt for 16 h. The reaction was diluted with methylene chloride, quenched with aq. sodium carbonate and extracted 3 times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by Prep TLC eluting with 5% methanol in methylene chloride to give the title product (280 mg) as the free amine.
MS (NH_3/ESI): m/z 593 (M + 1).

Using essentially the same procedure as above, material derived from the lower isomer from Step H-I (0.175 g, 0.6 mmol) was also converted to the lower R_f title compound (275 mg).

Step K: 1-(S)-(Amino)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcylopentane di-hydrochloride salt (Higher R_f isomer) and 1-(R)-(amino)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcylopentane di-hydrochloride salt (Lower R_f isomer)

A solution of hydrogen chloride (4.6 mmol) in methanol was prepared by addition of acetyl chloride (0.325 mL, 4.6 mmol) to methanol (10 mL) and aging

for 15 min. To this was added 1-(S)-(t-butoxycarbonylamino)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcylopentane (Higher R_f isomer from Step J) (270 mg, 0.46 mmol). After 16 h, the volatiles were removed in vacuo to dryness to give the title compound as the di-hydrochloride salt (248 mg).

Using essentially the same procedure as above, material derived from the lower isomer from Step H-J (0.250 g, 0.42 mmol) was also converted to the lower R_f title compound (235 mg).

Step L: *N*-(1-(S)-3-(S)-((4-(*N*-(4-Nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-leucine (Isomer 6B) and *N*-(1-(S)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine (Isomer 7H) di-TFA salts

To a solution of 1-(S)-(amino)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcylopentane di-hydrochloride salt (derived from the higher R_f isomer in Steps H - K) (20 mg, 0.045 mmol), 4-methyl-2-oxo-valeric acid (15 mg, 0.11 mmol) and DIPEA (0.016 mL, 0.09 mmol) in 1,2-dichloroethane (2 mL) was added sodium triacetoxyborohydride (29 mg, 0.135 mmol). The reaction was stirred at 50 °C for 10 h and then at rt for another 16 h. It was then quenched with aq sodium carbonate and extracted three times with ethyl acetate. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by Prep TLC eluting with 10% methanol in methylene chloride to give the title products (8 mg) as a mixture of the free amines. HPLC analysis as in Example 6 and 7 gave only a single band corresponding to Isomers B (and enantiomeric Isomer F) and H (and enantiomeric Isomer D) which co-elute. HPLC/MS (ESI): m/z 593 (M + 1).

Example 9

N-(1-(R)-3-(S)-((4-(*N*-(4-Nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-leucine (Isomer 7E) and *N*-(1-(R)-3-(S)-

((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine (Isomer 6C) di-TFA salts

Using essentially the same procedure as in Example 8, Step L, but substituting 1-(R)-(amino)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcylopentane di-hydrochloride salt (derived from the lower R_f isomer in Steps H - K) (20 mg, 0.045 mmol), the two title compounds were prepared. HPLC analysis of the crude products as in Example 6 and 7 indicated two peaks. In this case the diastereomers were separable on Prep TLC (10% methanol in methylene chloride). HPLC analysis as in Example 6 and 7 now gave only a single peak for each sample from the Prep TLC. The higher band corresponded to Isomer E (and enantiomeric Isomer A) and the lower band corresponded to Isomer C (and enantiomeric Isomer G) which are distinct in the HPLC. The di-TFA salts were prepared by evaporation from 0.5% TFA in acetonitrile.

Higher Isomer E: HPLC/MS (ESI): m/z 593 (M + 1).

Lower Isomer C: HPLC/MS (ESI): m/z 593 (M + 1).

Example 10

Using essentially the same procedure as in Example 6, Steps E to G, but substituting 4-(3-(4-fluorophenyl)prop-1-yl)piperidine hydrochloride in Step E and L-valine t-butyl ester hydrochloride in Step F, the following diastereomers can be obtained after a combination of Prep TLC and HPLC separation.

N-(1-(S)-3-(R)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-valine di-TFA salt (Isomer A),

N-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-valine di-TFA salt (Isomer B),

N-(1-(R)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-valine di-TFA salt (Isomer C)

N-(1-(R)-3-(R)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-valine di-TFA salt (Isomer D)

Example 11

Using essentially the same procedure as in Example 6, Steps E to G, but substituting 4-(3-(4-fluorophenyl)prop-1-yl)piperidine hydrochloride (from Procedure 9) in Step E and L-leucine t-butyl ester hydrochloride in Step F, the following diastereomers can be obtained after a combination of Prep TLC and HPLC separation.

N-(1-(S)-3-(R)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-leucine di-TFA salt (Isomer A),

N-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-leucine di-TFA salt (Isomer B),

N-(1-(R)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-isoleucine di-TFA salt (Isomer C)

N-(1-(R)-3-(R)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-leucine di-TFA salt (Isomer D)

Example 12

Using essentially the same procedure as in Example 6, Steps E to G, but substituting 4-(3-(4-fluorophenyl)prop-1-yl)piperidine hydrochloride (from Procedure 9) in Step E and L-phenylglycine t-butyl ester hydrochloride in Step F, the following diastereomers can be obtained after a combination of Prep TLC and HPLC separation.

N-(1-(S)-3-(R)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-phenylglycine di-TFA salt (Isomer A),

N-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-phenylglycine di-TFA salt (Isomer B),

N-(1-(R)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-phenylglycine di-TFA salt (Isomer C)

N-(1-(R)-3-(R)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-phenylglycine di-TFA salt (Isomer D)

Example 13

Using essentially the same procedure as in Example 6, Steps E to G, but substituting 4-(3-(4-fluorophenyl)prop-1-yl)piperidine hydrochloride (from Procedure 9) in Step E and L-cyclohexylglycine t-butyl ester hydrochloride in Step F, the following diastereomers can be obtained after a combination of Prep TLC and HPLC separation.

N-(1-(S)-3-(R)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-cyclohexylglycine di-TFA salt (Isomer A),
HPLC/MS (ESI): m/z 633 (M + 1).

N-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-cyclohexylglycine di-TFA salt (Isomer B),
HPLC/MS (ESI): m/z 633 (M + 1).

N-(1-(R)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-cyclohexylglycine di-TFA salt (Isomer C)
HPLC/MS (ESI): m/z 633 (M + 1).

N-(1-(R)-3-(R)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-cyclohexylglycine di-TFA salt (Isomer D)
HPLC/MS (ESI): m/z 633 (M + 1).

Example 14

691

Using essentially the same procedures as in Example 6, Steps E to G, but substituting 4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidine hydrochloride (from Procedure 1) in Step E and L-cyclohexylglycine t-butyl ester hydrochloride in Step F and TFA in place of HCl in ether in Step G, the following diastereomers can be obtained after a combination of Prep TLC and HPLC separation.

N-(1-(S)-3-(R)-((4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-cyclohexylglycine di-TFA salt (Isomer A),

N-(1-(S)-3-(S)-((4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-cyclohexylglycine di-TFA salt (Isomer B),

N-(1-(R)-3-(S)-((4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-cyclohexylglycine di-TFA salt (Isomer C)

N-(1-(R)-3-(R)-((4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-cyclohexylglycine di-TFA salt (Isomer D)

05430005.030402

Example 15

Using essentially the same procedures as in Example 6, Steps E to G, but substituting 4-(4-fluorophenyl)piperidine hydrochloride (from Procedure 9) in Step E and L-cyclohexylglycine t-butyl ester hydrochloride in Step F and TFA in place of HCl in ether in Step G, the following diastereomers can be obtained after a combination of Prep TLC and HPLC separation.

N-(1-(S)-3-(R)-((4-(4-fluorophenyl)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-cyclohexylglycine di-TFA salt (Isomer A),

N-(1-(S)-3-(S)-((4-(4-fluorophenyl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-cyclohexylglycine di-TFA salt (Isomer B),

N-(1-(R)-3-(S)-((4-(4-fluorophenyl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-cyclohexylglycine di-TFA salt (Isomer C)

N-(1-(R)-3-(R)-((4-(4-fluorophenyl)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-cyclohexylglycine di-TFA salt (Isomer D)

Example 16

N-(1-(R)-3-(S)-((4-(3-(4-Fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine di-TFA salt

Step A: (1-(R)-3-(S)-(Hydroxymethyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine (Higher R_f) and (1-(S)-3-(S)-(hydroxymethyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine (lower R_f)

Method A:

To a solution of (+)-*trans*-1-hydroxymethyl-4-oxo-2-phenylcylopentane from Example 8, Step F (250 mg, 1.32 mmol), D-leucine t-butyl ester hydrochloride (370 mg, 2.0 mmol) and DIPEA (0.36 mL, 2.0 mmol) in 1,2-dichloroethane (10 mL) was added sodium triacetoxyborohydride (840 mg, 4.0 mmol). The reaction was stirred at rt for 4 h and was then quenched with aq sodium carbonate and extracted three times with ethyl acetate. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by FC eluting with a gradient of 5 - 25% ethyl acetate in hexanes to give the higher R_f 1-(R) title compound as the major product (280 mg) and the lower R_f 1-(S) as the minor product (160 mg mixed fractions).

Method B:

To a solution of (+)-*trans*-1-hydroxymethyl-4-oxo-2-phenylcylopentane from Example 8, Step F (3.3 g, 16 mmol) in methylene chloride (100 mL) was added t-butyldimethylsilyl chloride (11 g, 49 mmol) and DIPEA (22 mL, 74 mmol). The reaction was stirred at rt for 16 h, poured into dilute aq. HCl and extracted twice with ether. The organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (5% ethyl acetate in hexanes) to afford of (+)-*trans*-1-t-butyldimethylsilyloxymethyl-4-oxo-2-phenylcylopentane (6.3 g) as a oil, $[\alpha]_D = +97$ (MeOH, c = 0.2).

To a solution of (+)-*trans*-1-t-butyldimethylsilyloxymethyl-4-oxo-2-phenylcylopentane from above (1.0 g, 3.28 mmol), D-leucine t-butyl ester hydrochloride (2,2 g, 3.0 mmol) and DIPEA (1.8 mL, 10.2 mmol) in 1,2-dichloroethane (20 mL) was added sodium triacetoxyborohydride (2.1 g, 10 mmol). The reaction was stirred at rt for 5 h and was then quenched with aq sodium carbonate and extracted three times with ethyl acetate. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by FC eluting with 5% ethyl acetate in hexanes to give the higher R_f 1-(R) title compound as the minor product and the lower R_f 1-(S) as the major product (1.35 g as a mixture).

To a solution of the above product (1.35 g, 2.85 mmol) in THF (10 mL) was added 1M TBAF in THF (4.3 mL, 4.3 mmol). The reaction was stirred at rt for 16 h and the concentrated. The residue was purified by FC eluting with 20-25% ethyl acetate in hexanes to give the higher R_f 1-(R) title compound as the minor product (33 mg pure) and the lower R_f 1-(S) as the major product (202 mg pure, 0.70 g as a mixture).

Step B: (1-(R)-3-(S)-(Carbonyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine (Higher R_f) and (1-(S)-3-(S)-(carbonyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine (lower R_f)

Method A:

To a solution of oxalyl chloride (0.100 mL, 1.1 mmol) in methylene chloride (20 mL) at -70 °C was added dropwise DMSO (2.2 mL, 5.0 mmol). After 15 min, a solution of (1-(R)-3-(S)-(hydroxymethyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine (Higher R_f from Step A, Method A) (160 mg, 0.44 mmol) containing 1 eq. of 1M HCl in ether in methylene chloride (5 mL) was added. The reaction was stirred at -70 °C for 1.5 h and then DIPEA (0.77 mL, 4.5 mmol) in methylene chloride (5 mL) was added dropwise over 5 min. After a further 10 min, the mixture was allowed to warm to rt for 1 h and then diluted with methylene chloride and poured into dilute aq. HCl. The layers were separated. The aq. layer was reextracted with a second portion of methylene chloride and the organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by FC (20% ethyl acetate in hexanes) to give the higher R_f title product (38 mg) after vacuum drying.

Method B:

To a solution of (1-(R)-3-(S)-(hydroxymethyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine (mixture of higher and lower R_f from Step A, Method A) (142 mg, 0.39 mmol) in methylene chloride (10 mL) was added TPAP (6.9 mg, 0.020 mmol) and N-methylmorholine (70 mg, 0.60 mmol). The reaction was stirred under nitrogen at rt for 1 h and was then concentrated. The residue was purified by FC (25% ethyl acetate in hexanes) to give the title products (108 mg) after vacuum drying.

Step C: *N*-(1-(R)-3-(S)-((4-(3-(4-Fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine t-butyl ester (higher R_f) and *N*-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine t-butyl ester (lower R_f)

To a solution of (1-(R)-3-(S)-(carbonyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine (higher R_f) and (1-(S)-3-(S)-(carbonyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine (lower R_f) (from Step B, Method B) (9 mg, 0.025 mmol) in 1,2-dichloroethane (1 mL) was added 4-(3-(4-fluorophenyl)prop-1-yl)piperidine hydrochloride (from Procedure 9) (8 mg, 0.032 mmol) and DIPEA (0.006 mL, 0.033 mmol). After 15 min, sodium triacetoxyborohydride (11 mg, 0.051 mmol) was added and the reaction was stirred at rt for 16 h. The reaction was diluted with methylene chloride, quenched with aq. sodium carbonate and extracted 3 times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by Prep TLC eluting with 60% ethyl acetate in hexanes to give the title products as the free amines. (Each isomer): HPLC/MS (ES): m/z 565 (M + 1).

Step D: *N*-(1-(R)-3-(S)-((4-(3-(4-Fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine di-TFA salt (derived from higher R_f) and *N*-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine di-TFA salt (derived from lower R_f)

Each the products from Step C were taken up in TFA (5 mL) and aged at rt for 16 h. The volatiles were removed under a stream of nitrogen to afford the title products as the di-TFA salts (4 mg and 6 mg).

(Each isomer): HPLC/MS (ES): m/z 509 (M + 1).

Example 17

N-(1-(R)-3-(S)-((4-(3-(Benzofurazan-5-yl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(benzofurazan-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine di-TFA salt

Using essentially the same procedures as in Example 16, Step C and D, but substituting 4-(3-(benzofurazan-5-yl)prop-1-yl)piperidine hydrochloride (from Procedure 6) in Step C, the two diastereomeric title compounds were prepared. (Each isomer): HPLC/MS (ESI): m/z 533 (M + 1).

Example 18

N-(1-(R)-3-(S)-((4-(3-(4-Cyano-3-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(3-(4-cyano-3-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine di-TFA salt

Using essentially the same procedures as in Example 16, Step C and D, but substituting 4-(3-(4-cyano-3-fluorophenyl)prop-1-yl)piperidine hydrochloride (from Procedure 8) in Step C, the title compounds can be prepared.

Example 19

N-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine di-TFA salt
D-leucine

Using essentially the same procedures as in Example 16, Step C and D, but substituting 4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidine hydrochloride (from Procedure 1) in Step C, the title compounds can be prepared.

696

Example 20

N-(1-(R)-3-(S)-((4-(*N*-(Propyl)-*N*-(pyrrimidin-2-yl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(*N*-(propyl)-*N*-(pyrrimidin-2-yl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine di-TFA salt

Using essentially the same procedures as in Example 16, Step C and D, but substituting 4-(*N*-(propyl)-*N*-(pyrrimidin-2-yl)amino)piperidine hydrochloride (from Procedure 13) in Step C, the title compounds can be prepared.

Example 21

N-(1-(R)-3-(S)-((4-(4-Fluorophenyl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)- D-leucine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(4-fluorophenyl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)- D-leucine di-TFA salt

Using essentially the same procedures as in Example 16, Step C and D, but substituting 4-(4-fluorophenyl)piperidine hydrochloride in Step C, the title compounds can be prepared.

Example 22

N-(1-(R)-3-(S)-((4-(3-(4-Fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclohexylglycine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclohexylglycine di-TFA salt

Using essentially the same procedures as in Example 16, Step A to D, but substituting D-cyclohexylglycine t-butyl ester hydrochloride in Step A and 4-(3-(4-fluorophenyl)prop-1-yl)piperidine hydrochloride (from Procedure 9) in Step C, the title compounds were prepared.
(Each isomer): HPLC/MS (ESI): m/z 535 (M + 1).

Example 23

N-(1-(R)-3-(S)-((4-(3-(4-Cyano-3-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclohexylglycine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(3-(4-cyano-3-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclohexylglycine di-TFA salt

Using essentially the same procedures as in Example 16, Step A to D, but substituting D-cyclohexylglycine t-butyl ester hydrochloride in Step A and 4-(3-(4-cyano-3-fluorophenyl)prop-1-yl)piperidine hydrochloride (from Procedure 8) in Step C, the title compounds were prepared.
(Each isomer): HPLC/MS (ESI): m/z 560 (M + 1).

Example 24

N-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclohexylglycine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclohexylglycine di-TFA salt

Using essentially the same procedures as in Example 16, Step A to D, but substituting D-cyclohexylglycine t-butyl ester hydrochloride in Step A and 4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidine hydrochloride (from Procedure 1) in Step C, the title compounds were prepared.
(Each isomer): HPLC/MS (ESI): m/z 583 (M + 1).

Example 25

N-(1-(R)-3-(S)-((4-(*N*-(Propyl)-*N*-(pyrrimidin-2-yl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclohexylglycine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(*N*-(propyl)-*N*-(pyrrimidin-2-yl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclohexylglycine di-TFA salt

Using essentially the same procedures as in Example 16, Step A to D, but substituting D-cyclohexylglycine t-butyl ester hydrochloride in Step A and 4-(*N*-

(propyl)-*N*-(pyrrimidin-2-yl)amino)piperidine hydrochloride (from Procedure 13) in Step C, the title compounds were prepared.
(Each isomer): HPLC/MS (ESI): m/z 534 (M + 1).

Example 26

N-(1-(R)-3-(S)-((4-(4-Fluorophenyl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclohexylglycine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(4-fluorophenyl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclohexylglycine di-TFA salt

Using essentially the same procedures as in Example 16, Step A to D, but substituting D-cyclohexylglycine t-butyl ester hydrochloride in Step A and 4-(4-fluorophenyl)piperidine hydrochloride in Step C, the title compounds were prepared.
(Each isomer): HPLC/MS (ESI): m/z 493 (M + 1).

Example 27

N-(1-(R)-3-(S)-((4-(3-(4-Fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclobutylalanine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclobutylalanine di-TFA salt

Using essentially the same procedures as in Example 16, Step A to D, but substituting D/L-cyclobutylalanine t-butyl ester hydrochloride in Step A and 4-(3-(4-fluorophenyl)prop-1-yl)piperidine hydrochloride (from Procedure 9) in Step C, the title compounds can be prepared.

Example 28

N-(1-(R)-3-(S)-((4-(3-(4-Cyano-3-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D/L-cyclobutylalanine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(3-(4-cyano-3-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclobutylalanine di-TFA salt

Using essentially the same procedures as in Example 16, Step A to D, but substituting D-cyclobutylalanine t-butyl ester hydrochloride in Step A and 4-(3-(4-cyano-3-fluorophenyl)prop-1-yl)piperidine hydrochloride (from Procedure 8) in Step C, the title compounds can be prepared.

Example 29

N-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclobutylalanine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclobutylalanine di-TFA salt

Using essentially the same procedures as in Example 16, Step A to D, but substituting D/L-cyclobutylalanine t-butyl ester hydrochloride in Step A and 4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidine hydrochloride (from Procedure 1) in Step C, the title compounds were prepared.

Example 30

N-(1-(R)-3-(S)-((4-(*N*-(Propyl)-*N*-(pyrrimidin-2-yl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D/L-cyclobutylalanine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(*N*-(propyl)-*N*-(pyrrimidin-2-yl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclobutylalanine di-TFA salt

Using essentially the same procedures as in Example 16, Step A to D, but substituting D-cyclobutylalanine t-butyl ester hydrochloride in Step A and 4-(*N*-(propyl)-*N*-(pyrrimidin-2-yl)amino)piperidine hydrochloride (from Procedure 13) in Step C, the title compounds can be prepared.

Example 31

N-(1-(R)-3-(S)-((4-(3-(4-Fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclopropylalanine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclopropylalanine di-TFA salt

Using essentially the same procedures as in Example 16, Step A to D, but substituting D-cyclopropylalanine t-butyl ester hydrochloride in Step A and 4-(3-(4-fluorophenyl)prop-1-yl)piperidine hydrochloride in Step C, the title compounds can be prepared.

Example 32

N-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclopropylalanine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclopropylalanine di-TFA salt

Using essentially the same procedures as in Example 16, Step A to D, but substituting D-cyclopropylalanine t-butyl ester hydrochloride in Step A and 4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidine hydrochloride (from Procedure 1) in Step C, the title compounds were prepared.

EXAMPLE 33

N-(1-(R)-3-(S)-((4-(3-(Benzofurazan-5-yl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclohexylglycine di-hydrochloride salt

Using essentially the same procedure as in Example , Steps A to D, but substituting D-cyclohexylglycine t-butyl ester hydrochloride in Step A and 4-(3-(benzofurazan-5-yl)prop-1-yl)piperidine (from Procedure 5) in Step C, the title compound was prepared.
HPLC/MS (ESI): m/z 559 (M + 1).

EXAMPLE 34

N-(1-(R)-3-(S)-((4-(3-(4-Flurophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-leucine di-hydrochloride salt

Using essentially the same procedure as in Example 16, Steps A to D, but substituting L-leucine t-butyl ester hydrochloride in Step A and 4-(3-(4-flurophenyl)prop-1-yl)piperidine in Step F, the title compound was prepared. HPLC/MS (ESI): m/z 509 (M + 1).

EXAMPLE 35

N-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-cyclohexylglycine di-hydrochloride salt

Step A: Methyl (+-)-*trans*-4-methylene-2-(3-fluorophenyl)cylopentanoate

A mixture of methyl *trans*-3-fluorocinnamate (41.25 g, 229 mmol), tetrakis(triphenylphosphine) palladium(0) (18.5 g, 16 mmol), 1,2-bis(diphenylphosphino)ethane (5.5 g, 13.7 mmol) and 2-((trimethylsilyl)methyl)-2-propen-1-yl acetate (42.66 g, 229 mmol) in THF (300 mL) under nitrogen was heated to reflux for 6 h and then stirred at rt for 16 h. The reaction was diluted with hexane and filtered to remove yellow precipitate. The volatiles were then removed *in vacuo* and the residue was purified by FC (3 to 5% ethyl acetate in hexanes) to afford the title compound (45 g).

^{1}H NMR ($CDCl_3$) δ: 2.52 (m, 1 H), 2.68 (m, 1 H), 2.8-2.9 (m, 2 H), 2.95 (ddd, 1 H), 3.45 (ddd, 1 H), 3.63 (s, 3 H), 4.96 (m, 2 H), 6.9-7.0 (m, 2 H), 7.03 (d, 1 H), 7.2-7.3 (m, 1 H).

Step B: (+-)-*trans*-4-Methylene-2-(3-fluorophenyl)cyclopentanoic acid

To a solution of methyl (+-)-*trans*-4-methylene-2-(3-fluoro)phenylcylopentanoate prepared as in Example 33, Step A (47 g, 200 mmol) in methanol (500 mL) was added 5N sodium hydroxide (200 mL, 1000 mmol). The reaction was stirred at rt for 60 h then concentrated in vacuo. The residue was taken up in water, acidified with 2M hydrochloric acid and extracted twice with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo to give the crude title acid (40.8 g) which was used directly in Step C.

Step C: (+)-*trans*-1-Hydroxymethyl-4-methylene-2-(3-fluorophenyl)cylopentane and (-)-*trans*-1-hydroxymethyl-4-methylene-2-(3-fluorophenyl)cylopentane

A solution of (+-)-*trans*-4-methylene-2-(3-fluorophenyl)cylopentanoate (5.2 g, 23.6 mmol) from Step B in THF (100 mL) was cooled to 0 °C under nitrogen and 1M lithium aluminum hydride (LAH) in THF (35.4 mL) was added dropwise over 10 min. The reaction was stirred at rt for 16 h, the excess LAH was quenched by dropwise addition of acetone and the reaction was then poured into dilute aq. HCl. The mixture was extracted twice with ether and the organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (25% ethyl acetate in hexanes) to afford the racemic title product (4.1 g) as a an oil. Chiral Prep HPLC on a 2 cm x 25 cm Chiralcel OD column eluting with 5% isopropanol in hexanes (25 injections) afforded the (-)-enantiomer, $[\alpha]_D$ = -45.5 (MeOH, c = 0.9), as the first eluting peak (R_t = 17.5 min) and the (+)-enantiomer (1.87 g), $[\alpha]_D$ = +45.0 (MeOH, c = 1.0), as the second peak (R_t = 22.0 min).

^{1}H NMR ($CDCl_3$) δ: 2.2-2.35 (m, 2 H), 2.5 (m, 1 H), 2.65-2.85 (m, 2 H), 2.9 (m, 1 H), 3.51 and 3.68 (dABq, 2 H), 4.93 (m, 2 H), 6.9-7.0 (m, 2 H), 7.06 (d, 1 H), 7.3-7.4 (m, 1 H).

Step D: (+)-*trans*-3-Hydroxymethyl-4-(3-fluorophenyl)cylopentanone

A solution of (+)-*trans*-1-hydroxymethyl-4-methylene-2-(3-fluorophenyl)cylopentane from Step C (1.87 g, 9.0 mmol) in methanol (75 mL) was cooled in a dry ice/acetone bath and ozone was bubbled into the solution until the blue color persisted. The excess ozone was removed with a stream of nitrogen and then dimethylsulfide (5 mL) was added. After 10 min, the bath was removed and the reaction was allowed to warm to rt over 2 h. The mixture was treated with 10 drops of sulfuric acid (c) in water (2 mL) for 1 h before most of the methanol was removed in vacuo. The mixture was diluted with water and extracted twice with ethyl acetate and the organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (50% ethyl acetate in hexanes) to give the title compound (1.87 g)), $[\alpha]_D$ = +132 (MeOH, c = 1.2),.

^{1}H NMR ($CDCl_3$) δ: 2.3-2.45 (m, 2 H), 2.5 (m, 1 H), 2.61 and 2.77 (dABq, 2 H), 2.28 (ddd, 1 H), 3.61 and 3.75 (dABq, 2 H), 6.9-7.0 (m, 2 H), 7.06 (d, 1 H), 7.3-7.4 (m, 1 H).

Step E: *N*-(1-(R)-3-(S)-Hydroxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-cyclohexylglycine t-butyl ester

To a solution of (+)-*trans*-3-hydroxymethyl-4-(3-fluorophenyl)cylopentanone from Step D (500 mg, 2.4 mmol) in 1,2-dichloroethane (25 mL) was added D-cyclohexylglycine t-butyl ester (0.61 g, 2.88 mmol) and acetic acid (0.15 mL, 2.64 mmol). After 15 min, sodium triacetoxyborohydride (1.0 g, 4.8 mmol) was added and the reaction was stirred at rt for 16 h. The reaction was diluted with methylene chloride, quenched with aq. sodium carbonate and extracted 3 times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by FC eluting with 30% ethyl acetate in hexanes to give the product (936 mg) as clean major higher R_f title compound (425 mg) plus a mixture of C-1 isomers (511 mg) as the free amines.

Step F: *N*-(1-(R)-3-(S)-Formyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-cyclohexylglycine t-butyl ester

To a solution of (1-(R)-3-(S)-(hydroxymethyl)-4-(S)-(3-fluorophenyl)-cyclopent-1-yl)-D-cyclohexylglycine (higher R_f from Step E) (162 mg, 0.4 mmol) in methylene chloride (5 mL) was added TPAP (7 mg, 0.020 mmol) and N-methylmorholine (70 mg, 0.60 mmol). The reaction was stirred under nitrogen at rt for 1 h and was then concentrated. The residue was purified by FC (15% ethyl acetate in hexanes) to give the title product (115 mg) after vacuum drying.

Step G: *N*-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-cyclohexylglycine t-butyl ester

To a solution of *N*-(1-(R)-3-(S)-formyl-4-(S)-(3-fluorophenyl)-cyclopent-1-yl)-D-cyclohexylglycine t-butyl ester (13 mg, 0.032 mmol) from Step F in 1,2-dichloroethane (2 mL) was added 4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidine hydrochloride (from Procedure 1) (15 mg, 0.035 mmol) and DIPEA (0.012 mL, 0.069 mmol). After 15 min, sodium triacetoxyborohydride (14 mg, 0.064 mmol) was added and the reaction was stirred at rt for 16 h. The reaction was diluted with methylene chloride, quenched with aq. sodium carbonate and extracted 3 times with methylene chloride. The organic layers were each washed with brine, dried over

sodium sulfate, combined and concentrated in vacuo. The residue was purified by Prep TLC eluting with 5% methanol in methylene chloride to give the title product as the free amine.

Step H: *N*-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-cyclohexylglycine di-hydrochloride salt

The *N*-(1-(R)-3-(S)-((4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-cyclohexylglycine t-butyl ester from Step F was taken up in TFA (2 mL) and aged at rt for 16 h. The volatiles were evaporated under a stream of nitrogen. The residue was taken up in methanol and adsorbed onto a 500 mg Varian SCX ion-exchange resin cartridge. The resin was eluted with 2 X 3 mL of methanol, then the product was eluted with 2 X 3 mL of 2M ammonia in methanol. The product solution was concentrated under nitrogen, then 2 volumes of methylene chloride were evaporated to remove methanol and ammonia to give the free amine. The hydrochloride salt was prepared by dissolving the free amine in methylene chloride, addition of excess 1M hydrogen chloride in ether and evaporation to dryness.

HPLC/MS (ESI): m/z 601 (M + 1).

EXAMPLE 36

N-(1-(R)-3-(S)-((4-(3-(4-Cyano-3-flurophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-cyclohexylglycine di-hydrochloride salt

Using essentially the same procedure as in Example 35, Steps F and G, but substituting 4-(3-(4-cyano-3-flurophenyl)prop-1-yl)piperidine (from Procedure 8) in Step F, the title compound was prepared.

HPLC/MS (ESI): m/z 578 (M + 1).

EXAMPLE 37

N-(1-(R)-3-(S)-((4-(5-Benzylpyrazol-3-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-cyclohexylglycine di-hydrochloride salt

Using essentially the same procedure as in Example 35, Steps F and G, but substituting 4-(5-benzylpyrazol-3-yl)piperidine (from Procedure 2) in Step F, the title compound can be prepared.

EXAMPLE 38

N-(1-(R)-3-(S)-((4-(5-Benzyl-2-propylpyrazol-3-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-cyclohexylglycine di-hydrochloride salt

Using essentially the same procedure as in Example 35, Steps F and G, but substituting 4-(5-benzyl-2-propylpyrazol-3-yl)piperidine (from Procedure 15) in Step F, the title compound can be prepared.

EXAMPLE 39

Using essentially the same procedure as in Example 35, Steps E to G, but substituting the appropriate L- and/or D-aminoacid t-butyl ester in Step E, the following compounds A-D can be prepared.

EXAMPLE 39A

N-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-cyclobutylalanine di-hydrochloride salt

EXAMPLE 39B

N-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-cycloproylalanine di-hydrochloride salt

EXAMPLE 39C

N-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-leucine di-hydrochloride salt

EXAMPLE 39D

N-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine di-hydrochloride salt

EXAMPLE 40

N-(2-Methylprop-1-yl)-*N*-(1-(SR)-3-(SR)-((4-(3-(phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)glycine di-hydrochloride salt

Step A: 1-(SR)-Benzyloxycarbonylamino-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopentane (Higher R_f isomer) and 1-(RS)-benzyloxycarbonylamino-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopentane (Lower R_f isomer)

Using essentially the same procedure as in Example 1, Step F, 1-(SR and RS)-benzylamino-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopentane (13 g) was converted to the title compounds. Prep LC (30% ethyl acetate in hexanes) afforded pure minor, higher R_f product (4.0 g), then a mixture and finally pure major, lower R_f product (6.6 g).

Step B: 1-(SR)-Benzyloxycarbonylamino-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopentane (Higher R_f isomer) and 1-(RS)-benzyloxycarbonylamino-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopentane (Lower R_f isomer)

To a solution of 1-(SR)-benzyloxycarbonylamino-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopentane (Higher R_f isomer from Step A) (3.96 g, 12.2 mmol) in methylene chloride (100 mL) was added DIPEA (6.4 mL, 37 mmol) and t-butyldimethylsilyl chloride (2.0 g, 13.4 mmol). The reaction was stirred at rt for 16 h when a second portion of t-butyldimethylsilyl chloride (1.0 g, 6.7 mmol) was added. After a further 24 h, the reaction was diluted with methylene chloride and poured into dilute hydrochloric acid. The layers were separated and the organic layer

was washed with brine containing sodium bicarbonate, dried over sodium sulfate and concentrated. The residue was purified by FC (5 to 40% ethyl acetate in hexanes) to give the title compound (4.7 g). After eluting with 75% ethyl acetate in hexanes, recovered starting material was obtained.

In a similar way, 1-(RS)-benzyloxycarbonylamino-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopentane (lower R_f isomer from Step A) (6.6 g, 20.3 mmol) was converted to the lower R_f title compound (7.7 g) and recovered starting material.

Step C: 1-(SR)-*N*-(2-Methylprop-2-en-1-yl)-*N*-(benzyloxycarbonyl)amino-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopentane (Higher R_f isomer) and 1-(RS)- *N*-(2-methylprop-2-en-1-yl)-*N*-(benzyloxycarbonyl)amino -3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopentane (Lower R_f isomer)

To a solution of 1-(SR)-benzyloxycarbonylamino-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopentane (Higher R_f isomer from Steps A-B) (500 mg, 1.14 mmol) and 1-bromo-2-methylprop-2-ene (0.175 mL, 1.7 mmol) in DMF (10 mL) was added at rt in portions over 10 min 60% sodium hydride in mineral oil (68 mg, 1.7 mmol). After 3 h, the reaction was diluted with ether and quenched into water. The layers were separated and the organic layer was washed with brine containing sodium bicarbonate, dried over sodium sulfate and concentrated. The residue was purified by FC (5 to 10% ethyl acetate in hexanes) to give the title compound (0.32 g).

^{1}H NMR ($CDCl_3$): δ -0.06 (s, 3 H), -0.05 (s, 3 H), 0.84 (s, 9 H), 1.54 (s, 3 H), 1.65-1.8 (m, 3 H), 1.95-2.2 (m, 3 H), 2.8-3.0 (M, 1 H), 3.3-3.45 (m, 1 H), 3.45-3.55 (m, 1 H), 3.7-3.9 (m, 2 H), 4.80 (d, 2 H), 5.14 (br s, 2 H), 7.15 (m, 2 H), 7.25 (m, 5 H), 7.34 (m, 3 H).

In a similar way, 1-(RS)-benzyloxycarbonylamino-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopentane (lower R_f isomer from Step A-B) (1.0 g, 2.3 mmol) was converted to the lower R_f title compound (0.55 g).

Step D: 1-(SR)-*N*-(2-Methylprop-1-yl)amino-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopentane (Higher R_f

isomer) and 1-(RS)-*N*-(2-methylprop-1-yl)amino -3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopentane (Lower R_f isomer)

To a solution of 1-(SR)-*N*-(2-methylprop-2-en-1-yl)-*N*-(benzyloxycarbonyl)amino-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopentane (Higher R_f isomer from Steps A-C) (320 mg, 0.65 mmol) in methanol (5 mL) was added 10% Pd/C (50 mg) and a drop of DIPEA. The mixture was hydrogenated at 40 psi for 2 h. The reaction was filtered and the filtrate was concentrated. The residue of title compound was used directly in Step E.

^{1}H NMR ($CDCl_3$): δ -0.05 (s, 3 H), -0.04 (s, 3 H), 0.84 (s, 9 H), 0.89 (s, 3 H), 0.91 (s, 3 H), 1.35 (ddd, 1 H), 1.73 (hept, 1 H), 1.93 (m, 2 H), 2.15 (m, 1 H), 2.25 (m, 1 H), 2.38 (d, 2 H), 2.96 (q, 1 H), 3.28 (m, 1 H), 3.49 (dABq, 2 H), 7.15 (m, 3 H), 7.24 (m, 2 H).

In a similar way, 1-(RS)-*N*-(2-methylprop-2-en-1-yl)-*N*-(benzyloxycarbonyl)amino -3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopentane (lower R_f isomer from Step A-C) (0.55 g, 1.1 mmol) was converted to the lower R_f title compound (0.475 g).

Step E: *N*-(2-Methylprop-1-yl)-*N*-(1-(SR)-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopent-1-yl)-glycine (Higher R_f isomer) and *N*-(2-methylprop-1-yl)-*N*-(1-(RS)-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopent-1-yl)-glycine (Lower R_f isomer)

A solution of 1-(SR)-*N*-(2-methylprop-1-yl)amino-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopentane (Higher R_f isomer from Steps A-D) (0.65 mmol), t-butyl bromoacetate (125 mg, 0.65 mmol) and DIPEA (1.1 mL, 6.5 mmol) in acetonitrile (15 mL) was stirred at rt for 16 h. The reaction was diluted with aqueous sodium carbonate and extracted three times with ethyl acetate. The organic layers were washed with brine containing sodium bicarbonate, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (50% ethyl acetate in hexanes) to give impure product and recovered starting material (135 mg). The impure product fractions were repurified by FC (5% ethyl acetate in hexanes) to afford the title higher R_f compound (0.13 g). The recovered starting

material was recycled using the same procedure but doing the reaction at 50 °C for 16 h to afford additional title compound (140 mg).
^{1}H NMR ($CDCl_3$): δ -0.05 (s, 3 H), -0.04 (s, 3 H), 0.84 (s, 9 H), 0.86 (d, 3 H), 0.88 (d, 3 H), 1.44 (s, 9 H), 1.70 (hept, 1 H), 1.95 (m, 1 H), 2.00 (m, 1 H), 2.08 (m, 2 H), 2.38 (dABq, 2 H), 2.90 (m, 1 H), 3.26 (ABq, 2 H), 3.49 (dABq, 2 H), 3.5-3.6 (m, 1 H), 7.15 (m, 3 H), 7.24 (m, 2 H).

In a similar way, but doing the reaction at 50 °C for 20 h, 1-(RS)-*N*-(2-methylprop-1-yl)amino-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopentane (lower R_f isomer from Steps A-D) (0.375 mg) was converted to the lower R_f title compound (0.435 g).

Step F: *N*-(2-Methylprop-1-yl)-*N*-(1-(SR)-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopent-1-yl)-glycine (Higher R_f isomer) and *N*-(2-methylprop-1-yl)-*N*-(1-(RS)-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopent-1-yl)-glycine (Lower R_f isomer)

A solution of *N*-(2-methylprop-1-yl)-*N*-(1-(SR)-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopent-1-yl)-glycine (Higher R_f isomer from Steps A-E) (270 mg, 0.57 mmol) and 1M TBAF in THF (0.85 mL, 0.85 mmol) in THF (5 mL) was stirred at rt for 1 h. The reaction was concentrated and the residue was purified by FC (20% ethyl acetate in hexanes) to give the title higher R_f product (140 mg).

In a similar way, *N*-(2-methylprop-1-yl)-*N*-(1-(RS)-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopent-1-yl)-glycine (Lower R_f isomer from Steps A-E) (0.435 mg) was converted to the lower R_f title compound (0.300 mg).

Step G: *N*-(2-Methylprop-1-yl)-*N*-(1-(SR)-3-(SR)-formyl-4-(SR)-phenylcylopent-1-yl)-glycine (Higher R_f isomer) and *N*-(2-methylprop-1-yl)-*N*-(1-(RS)-3-(SR)-formyl-4-(SR)-phenylcylopent-1-yl)-glycine (Lower R_f isomer)

Using essentially the same procedure as in Example 1, Step C, *N*-(2-methylprop-1-yl)-*N*-(1-(SR)-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopent-1-yl)-glycine (Higher R_f isomer from Steps A-F) (140 mg, 0.39 mmol) was oxidized to the title compound (100 mg).

In a similar way, *N*-(2-methylprop-1-yl)-*N*-(1-(RS)-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopent-1-yl)-glycine (Lower R_f isomer from Steps A-F) (0.150 mg) was converted to the lower R_f title compound (0.140 mg).

Step H: *N*-(2-Methylprop-1-yl)-*N*-(1-(SR)-3-(SR)-((4-(3-(phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)glycine t-butyl ester (higher R_f isomer)

To a solution of *N*-(2-methylprop-1-yl)-*N*-(1-(SR)-3-(SR)-formyl-4-(SR)-phenylcylopent-1-yl)-glycine (Higher R_f isomer from Steps A-G) (25 mg, 0.070 mmol) in 1,2-dichloroethane (2 mL) was added 4-(3-(phenyl)prop-1-yl)piperidine (22 mg, 0.11 mmol) and acetic acid (0.006 mL, 0.11 mmol). After 15 min, sodium triacetoxyborohydride (45 mg, 0.21 mmol) was added and the reaction was stirred at rt for 4 h. The reaction was diluted with methylene chloride, quenched with aq. sodium carbonate and extracted 3 times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by Prep TLC eluting with 5% methanol in methylene chloride to give the title product (38 mg) as the free amine.

Step I: *N*-(2-Methylprop-1-yl)-*N*-(1-(SR)-3-(SR)-((4-(3-(phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)glycine di-TFA salt

A solution of *N*-(2-methylprop-1-yl)-*N*-(1-(SR)-3-(SR)-((4-(3-(phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)glycine t-butyl ester (higher R_f isomer from Steps A-H) (33 mg) in TFA (4 mL) was heated at 50 °C for 4 h and then the volatiles were removed under a stream of nitrogen. An additional 2 X 3 mL of methylene chloride were evaporated to dryness to afford the title compound as the di-TFA salt (50 mg).
HPLC/MS (ESI): m/z 491 (M + 1).

EXAMPLE 41

N-(2-Methylprop-1-yl)-*N*-(1-(SR)-3-(SR)-((4-(3-(4-cyanophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)glycine di-TFA salt

Using essentially the same procedure as in Example 40, Steps H and I, but substituting 4-(3-(4-cyanophenyl)prop-1-yl)piperidine (from Procedure 7) in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 516 (M + 1).

EXAMPLE 42

N-(2-Methylprop-1-yl)-*N*-(1-(SR)-3-(SR)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)glycine di-TFA salt

Using essentially the same procedure as in Example 40, Steps H and I, but substituting 4-(3-(4-fluorophenyl)prop-1-yl)piperidine (from Procedure 9) in Step H, the title compound can be prepared.

EXAMPLE 43

N-(2-Methylprop-1-yl)-*N*-(1-(RS)-3-(SR)-((4-(3-(4-cyanophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)glycine di-TFA salt

Using essentially the same procedure as in Example 40, Steps H and I, but substituting the lower R_f aldehyde from Steps A-G and 4-(3-(4-cyanophenyl)prop-1-yl)piperidine (from Procedure 7) in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 594 (M + 1).

EXAMPLE 44

N-(2-Methylprop-1-yl)-*N*-(1-(RS)-3-(SR)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)glycine di-TFA salt

Using essentially the same procedure as in Example 40, Steps H and I, but substituting the lower R_f aldehyde from Steps A-G and 4-(3-(4-fluorophenyl)prop-1-yl)piperidine (from Procedure 9) in Step H, the title compound can be prepared.

EXAMPLE 45

N-(2-Methylprop-1-yl)-*N*-(1-(RS)-3-(SR)-((4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)glycine di-TFA salt

Using essentially the same procedure as in Example 40, Steps H and I, but substituting the lower R_f aldehyde from Steps A-G and 4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidine (from Procedure 1) in Step H, the title compound can be prepared.

EXAMPLE 46

N-(Cyclobutylmethyl)-*N*-(1-(R)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

Step A: *N*-(1-(R)-3-(S)-Hydroxymethyl)-4-(S)-phenylcyclopent-1-yl)glycine and *N*-(1-(S)-3-(S)-Hydroxymethyl)-4-(S)-phenylcyclopent-1-yl)glycine

To a solution of (+)-trans-3-hydroxymethyl-4-phenylcyclopentan-1-one from Example 8, Step F, Method B (180 mg, 0.96 mmol), glycine t-butyl ester hydrochloride (241 mg, 1.44 mmol) and DIPEA (0.25 mL, 1.44 mmol) in 1,2-dichloroethane (6 mL) was added sodium triacetoxyborohydride (284 mg, 1.92 mmol). The reaction was stirred at rt for 16 h and was then diluted with aq. sodium bicarbonate and extracted three times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by FC (50 - 100% ethyl acetate in hexanes) to give the title product (196 mg) as a 2:1 mixture of C-1 free amine isomers. ^{1}H NMR ($CDCl_3$): δ 1.48 (s, 9 H), 1.6-1.7 (m, 1.3 H), 1.8-2.0 (2 m, 1.7 H), 2.23 (ddd. 0.3 H), 2.3-2.45 (m, 2 H), 2.68 (ddd, 0.7 H), 3.2-3.4 (2 m and 2 s, 3 H), 3.45-3.65 (dABq (major) and d (minor), 2 H), 3.96 (d, 1 H), 7.2-7.35 (m, 5 H).

Step B: *N*-(Cyclobutylmethyl)-*N*-(1-(R)-3-(S)-hydroxymethyl)-4-(S)-phenylcyclopent-1-yl)glycine (major, higher R_f) and *N*-(cyclobutylmethyl)-*N*-(1-(S)-3-(S)-hydroxymethyl)-4-(S)-phenylcyclopent-1-yl)glycine (minor, lower R_f)

To a solution of *N*-(1-(R and S)-3-(S)-hydroxymethyl)-4-(S)-phenylcyclopent-1-yl)glycine from Step A (180 mg, 0.59 mmol), cyclobutylaldehyde (27 mg, 0.32 mmol) and DIPEA (0.25 mL, 1.5 mmol) in 1,2-dichloroethane (6 mL) was added sodium triacetoxyborohydride (175 mg, 1.2 mmol). The reaction was stirred at rt for 16 h and was then diluted with aq. sodium bicarbonate and extracted three times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by Prep TLC (30% ethyl acetate in hexanes) to give the title 1-(R) product (45 mg pure, 31 mg mixture with the 1-(S) diastereomer) as the higher R_f C-1 isomer.

(Major, higher isomer): ^{1}H NMR ($CDCl_3$): δ 1.49 (s, 9 H), 1.6-1.85 (m, 4 H), 1.85-1.95 (m, 2 H), 2.0-2.15 (m, 2 H), 2.24 (p, 1 H), 2.2.33 (m, 1 H), 2.53 (hept, 1 H), 2.7-2.8 (m, 3 H), 3.31 (s, 2 H), 3.4-3.5 (m, 1 H), 3.48 and 3.61 (dABq, 2 H), 7.24 (tt, 1 H), 7.25-7.35 (m, 4 H).

Repurification of the mixture on Prep TLC afforded a sample of pure 1-(S) minor, lower R_f isomer.

(Minor, lower isomer): ^{1}H NMR ($CDCl_3$): δ 1.47 (s, 9 H), 1.6-1.75 (m, 3 H), 1.75-1.85 (m, 1 H), 1.9-2.0 (m, 1 H), 2.05-2.25 (m, 4 H), 2.3 (m, 1 H), 2.54 (hept, 1 H), 2.78 (ddd, 2 H), 3.09 (q, 1 H), 3.35 (ABq, 2 H), 3.55 (m, 1 H), 3.61 (dABq, 2 H), 7.24 (tt, 1 H), 7.25-7.35 (m, 4 H).

Step C: *N*-(Cyclobutylmethyl)-*N*-(1-(R)-3-(S)-formyl)-4-(S)-phenylcyclopent-1-yl)glycine

Using essentially the same procedure as in Example 1, Step C, *N*-(cyclobutylmethyl)-*N*-(1-(R)-3-(S)-hydroxymethyl)-4-(S)-phenylcyclopent-1-yl)glycine (higher R_f isomer from Steps B) (45 mg, 0.12 mmol) was oxidized to the title compound (56 mg crude without purification).

Step D: *N*-(Cyclobutylmethyl)-*N*-(1-(R)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine t-butyl ester

To a solution of *N*-(cyclobutylmethyl)-*N*-(1-(R)-3-(S)-formyl)-4-(S)-phenylcyclopent-1-yl)glycine (higher R_f isomer from Steps B-C) (22 mg, 0.059 mmol) in 1,2-dichloroethane (1 mL) was added 4-(3-(4-fluorophenyl)prop-1-yl)piperidine hydrochloride (from Procedure 9) (23 mg, 0.089 mmol) and DIPEA (0.016 mL, 0.089 mmol). After 15 min, sodium triacetoxyborohydride (18 mg, 0.12 mmol) was added and the reaction was stirred at rt for 16 h. The reaction was diluted with methylene chloride, quenched with aq. sodium carbonate and extracted 3 times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by Prep TLC eluting with 30% ethyl acetate in hexanes to give the title product (26 mg) as the free amine.

Step E: *N*-(Cyclobutylmethyl)-*N*-(1-(R)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

A solution of *N*-(cyclobutylmethyl)-*N*-(1-(R)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine t-butyl ester (higher R_f isomer from Steps B-D) in TFA (4 mL) was stirred at rt for 16 h and then the volatiles were removed under a stream of nitrogen. An additional 2 X 3 mL of toluene were evaporated and the residue was purified by Prep TLC (95:5:1:1 methylene chloride:methanol:water:NH_4OH). The free amine (5 mg) was taken up in methylene chloride and excess 1M hydrogen chloride in ether was added. The mixture was evaporated to dryness to afford the title compound as the di-HCl salt (7.3 mg).

HPLC/MS (ESI): m/z 521 (M + 1).

EXAMPLE 47

N-(Cyclopropylmethyl)-*N*-(1-(R)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

Using essentially the same procedure as in Example 46, Steps B - E, but substituting cyclopropylaldehyde in Step B, the title compound was prepared.
HPLC/MS (ESI): m/z 507 (M + 1).

EXAMPLE 48

N-(Cyclohexyl)-*N*-(1-(R)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

Using essentially the same procedure as in Example 46, Steps B - E, but substituting cyclohexanone in Step B, the title compound was prepared.
HPLC/MS (ESI): m/z 535 (M + 1).

EXAMPLE 49

N-(Cyclopentylmethyl)-*N*-(1-(R)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

Using essentially the same procedure as in Example 46, Steps B - E, but substituting cyclopentylaldehyde in Step B, the title compound was prepared.
HPLC/MS (ESI): m/z 535 (M + 1).

EXAMPLE 50

N-(Cyclobutylmethyl)-*N*-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

Using essentially the same procedure as in Example 46, Steps B - E, but substituting the lower R_f product from Step B in Steps C - E, the title compound could be prepared.
HPLC/MS (ESI): m/z 521 (M + 1).

EXAMPLE 51

N-(Cyclohexyl)-*N*-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(*S*)-phenylcyclopent-1-yl)glycine di-HCl salt

Using essentially the same procedure as in Example 46, Steps B - E, but substituting cyclohexanone in Step B and using the lower R_f product from Step B in Steps C - E, the title compound was prepared.
HPLC/MS (ESI): m/z 535 (M + 1).

EXAMPLE 52

N-(Cyclopropylmethyl)-*N*-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

Using essentially the same procedure as in Example 46, Steps B - E, but substituting cyclopropyl aldehyde in Step B and using the lower R_f product from Step B in Steps C - E, the title compound was prepared.
HPLC/MS (ESI): m/z 507 (M + 1).

EXAMPLE 53

N-(Cyclopentylmethyl)-*N*-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

Using essentially the same procedure as in Example 46, Steps B - E, but substituting cyclopentyl aldehyde in Step B and using the lower R_f product from Step B in Steps C - E, the title compound was prepared.
HPLC/MS (ESI): m/z 507 (M + 1).

EXAMPLE 54

N-(Cyclohexyl)-*N*-(1-(S)-3-(S)-((4-(3-(3,4-difluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

Step A: *N*-(1-(S)-3-(S)-t-Butyldimethylsilyloxymethyl)-4-(S)-phenylcyclopent-1-yl)glycine (major, higher R_f) and *N*-(1-(R)-3-(S)-t-

butyldimethylsilyloxymethyl)-4-(S)-phenylcyclopent-1-yl)glycine (minor, lower R_f)

To a solution of (+)-trans-3-t-butyldimethylsilyloxymethyl-4-phenylcyclopentan-1-one from Example 16, Step A, Method B (332 mg, 1.1 mmol), glycine t-butyl ester hydrochloride (275 mg, 1.64 mmol) and DIPEA (0.285 mL, 1.64 mmol) in 1,2-dichloroethane (13 mL) was added sodium triacetoxyborohydride (323 mg, 2.18 mmol). The reaction was stirred at rt for 16 h and was then diluted with aq. sodium bicarbonate and extracted three times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by FC (10% ethyl acetate in hexanes) to give the title product (437 mg) as a 2.6:1 mixture of C-1 free amine isomers. (Note: The product C-1 isomer ratio here with the silyl ether is opposite to that of Example 46 with the free alcohol. Also, note that the relative retention on TLC of the NH intermediates are opposite that of the N-alkylation products of Step B.)

Careful FC (5% ethyl acetate in hexanes) of an initial sample afforded the separated isomers.

(Major, higher isomer): ^{1}H NMR ($CDCl_3$): δ -0.05 (s, 3 H), -0.04 (s, 3 H), 0.87 (s, 9 H), 1.42 (m, 1 H), 1.50 (s, 9 H), 1.98 (dd, 2 H), 2.17 (m, 1 H), 2.27 (dt, 1 H), 3.00 (q, 1 H), 3.3-3.4 (m and s, 3 H), 3.45 and 3.60 (dABq, 2 H), 7.15-7.25 (m, 3 H), 7.25-7.35 (m, 2 H).

(Minor, lower isomer): ^{1}H NMR ($CDCl_3$): δ -0.05 (s, 3 H), -0.04 (s, 3 H), 0.87 (s, 9 H), 1.50 (s, 9 H), 1.62 (dt, 1 H), 1.75 (ddd, 1 H), 1.95 (dt, 1 H), 2.25-2.4 (2 m , 2 H), 2.85 (m, 1 H), 3.22 (m, 1 H), 3.34 (s, 2 H), 3.42 and 3.54 (dABq, 2 H), 7.24 (tt, 1 H), 7.25-7.35 (m, 4 H).

Step B: *N*-(Cyclohexyl)-*N*-(1-(S)-3-(S)-hydroxymethyl)-4-(S)-phenylcyclopent-1-yl)glycine (lower, major R_f) and *N*-(cyclohexyl)-*N*-(1-(R)-3-(S)-hydroxymethyl)-4-(S)-phenylcyclopent-1-yl)glycine (higher, minor R_f)

To a solution of *N*-(1-(R and S)-3-(S)-t-butyldimethylsilyloxymethyl)-4-(S)-phenylcyclopent-1-yl)glycine from Step A (437 mg, 1.04 mmol), cyclohexanone (0.650 mL, 6.24 mmol) and DIPEA (0.272 mL, 1.56 mmol) in 1,2-dichloroethane (10 mL) was added sodium triacetoxyborohydride (693 mg, .68

mmol). The reaction was stirred at rt for 16 h when additional cyclohexanone (0.600 mL) and sodium triacetoxyborohydride (300 mg) were added. After a further 48 h, the reaction was complete by HPLC/MS and was diluted with aq. sodium bicarbonate and extracted three times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue (2 g) was used directly in the following desilyiation.

The residue from above was taken up in THF (10 mL) and 1M TBAF in THF (5 mL, 5.0 mmol) was added. The reaction was stirred at rt for 6 h and was then poured into aq. sodium bicarbonate and extracted three times with ethyl acetate. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by FC and Prep TLC (40% ethyl acetate in hexanes) to give the title (R) product (114 mg) as the minor, higher R_f band and the title (S) product (235 mg) as the major, lower R_f band.

(Major, higher isomer): ^{1}H NMR ($CDCl_3$): δ 1.1-1.4 (m, 5 H), 1.48 (s, 9 H), 1.5-1.7 (m, 2 H), 1.7-2.0 (m, 5 H), 2.17 (m, 1 H), 2.31 (m, 1 H), 2.65-2.8 (m, 2 H), 3.24 (Abq, 2 H), 3.45-3.55 (m, 2 H), 3.6-3.7 (m, 2 H), 7.24 (tt, 1 H), 7.25-7.35 (m, 4 H).

(Minor, lower isomer): ^{1}H NMR ($CDCl_3$): δ 1.1-1.4 (m, 5 H), 1.48 (s, 9 H), 1.6-1.7 (m, 2 H), 1.7-2.0 (m, 5 H), 2.17 (m, 2 H), 2.25 (m, 1 H), 2.75 (m, 1 H), 3.10 (q, 1 H), 3.25 (Abq, 2 H), 3.55-3.65 (m and ABq, 3 H), 7.24 (tt, 1 H), 7.25-7.35 (m, 4 H).

Step C: *N*-(Cyclohexyl)-*N*-(1-(S)-3-(S)-formyl)-4-(S)-phenylcyclopent-1-yl)glycine

Using essentially the same procedure as in Example 1, Step C, *N*-(cyclohexyl)-*N*-(1-(S)-3-(S)-hydroxymethyl)-4-(S)-phenylcyclopent-1-yl)glycine (lower R_f isomer from Step B) (75 mg, 0.19 mmol) was oxidized to the title compound (84 mg crude without purification).

Step D: *N*-(Cyclohexyl)-*N*-(1-(R)-3-(S)-((4-(3-(3,4-difluorophenyl)prop-1-yl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine t-butyl ester

To a solution of *N*-(cyclohexyl)-*N*-(1-(S)-3-(S)-formyl)-4-(S)-phenylcyclopent-1-yl)glycine (lower R_f isomer from Steps B-C) (19 mg, 0.050 mmol) in 1,2-dichloroethane (1 mL) was added 4-(3-(3,4-difluorophenyl)prop-1-yl)piperidine hydrochloride (from Procedure 14) (15 mg, 0.054 mmol) and DIPEA

(0.013 mL, 0.074 mmol). After 15 min, sodium triacetoxyborohydride (15 mg, 0.10 mmol) was added and the reaction was stirred at rt for 16 h. The reaction was diluted with methylene chloride, quenched with aq. sodium carbonate and extracted 3 times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by Prep TLC eluting with 80% ethyl acetate in hexanes to give the title product (20 mg) as the free amine.

Step E: *N*-(Cyclohexyl)-*N*-(1-(R)-3-(S)-((4-(3-(3,4-difluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

A solution of *N*-(cyclohexyl)-*N*-(1-(R)-3-(S)-((4-(3-(3,4-difluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine t-butyl ester (lower R_f isomer from Steps B-D) (20 mg) in TFA (1 mL) was stirred at rt for 16 h and then the volatiles were removed under a stream of nitrogen. The residue was taken up in methanol and adsorbed onto a 500 mg Varian SCX ion-exchange resin cartridge. The resin was eluted with 2 X 3 mL of methanol, then the product was eluted with 2 X 3 mL of 2M ammonia in methanol. The product solution was concentrated under nitrogen, then 2 volumes of methylene chloride were evaporated to remove methanol and ammonia to give the free amine. The hydrochloride salt was prepared by dissolving the free amine in methylene chloride, addition of excess 1M hydrogen chloride in ether and evaporation to dryness.
HPLC/MS (ESI): m/z 553 (M + 1).

EXAMPLE 55

N-(Cyclohexyl)-*N*-(1-(S)-3-(S)-((4-(3-(4-cyanophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

Using essentially the same procedure as in Example 54, Steps D and E, but substituting 4-(3-(4-cyanophenyl)prop-1-yl)piperidine (from Procedure 7) in Step D and using the lower R_f product from Step B in Steps C - E, the title compound was prepared.
HPLC/MS (ESI): m/z 542 (M + 1).

EXAMPLE 56

N-(Cyclohexyl)-*N*-(1-(S)-3-(S)-((4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

Using essentially the same procedure as in Example 54, Steps D and E, but substituting 4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidine (from Procedure 1) in Step D and using the lower R_f product from Step B in Steps C - E, the title compound was prepared.

HPLC/MS (ESI): m/z 583 (M + 1).

EXAMPLE 57

N-(Cyclohexyl)-*N*-(1-(S)-3-(S)-((4-(*N*-propyl-*N*-(pyrrimidin-2-yl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

Using essentially the same procedure as in Example 54, Steps D and E, but substituting 4-(*N*-propyl-*N*-(pyrrimidin-2-yl)amino)piperidine (from Procedure 13) in Step D and using the lower R_f product from Step B in Steps C - E, the title compound was prepared.

HPLC/MS (ESI): m/z 534 (M + 1).

EXAMPLE 58

N-(Cyclohexyl)-*N*-(1-(S)-3-(S)-((4-(3-(quinolin-3-yl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

Using essentially the same procedure as in Example 54, Steps D and E, but substituting 4-(3-(quinolin-3-yl)prop-1-yl)amino)piperidine (from Procedure 10) in Step D and using the lower R_f product from Step B in Steps C - E, the title compound was prepared.

HPLC/MS (ESI): m/z 568 (M + 1).

EXAMPLE 59

N-(Cyclohexyl)-*N*-(1-(S)-3-(S)-((4-(4-fluorophenyl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

Using essentially the same procedure as in Example 54, Steps D and E, but substituting 4-(4-fluorophenyl)piperidine in Step D and using the lower R_f product from Step B in Steps C - E, the title compound was prepared.
HPLC/MS (ESI): m/z 493 (M + 1).

EXAMPLE 60

N-(1-(R)-3-(S)-((4-(3-(4-Fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-proline di-HCl salt

Using essentially the same procedure as in Example 46, but substituting D-proline t-butyl ester in Step A, omitting Step B, and using the higher R_f product from Step A in Steps C - E, the title compound was prepared.
HPLC/MS (ESI): m/z 493 (M + 1).

EXAMPLE 61

N-(1-(S)-3-(S)-((4-(3-(4-Fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-proline di-HCl salt

Using essentially the same procedure as in Example 46, but substituting D-proline t-butyl ester in Step A, omitting Step B, and using the lower R_f product from Step A in Steps C - E, the title compound was prepared.
HPLC/MS (ESI): m/z 493 (M + 1).

EXAMPLE 62

N-(1-(R)-3-(S)-((4-(3-(4-Fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-proline di-HCl salt

Using essentially the same procedure as in Example 46, but substituting L-proline t-butyl ester in Step A, omitting Step B, and using the higher R_f product from Step A in Steps C - E, the title compound was prepared.
HPLC/MS (ESI): m/z 493 (M + 1).

EXAMPLE 63

N-(1-(S)-3-(S)-((4-(3-(4-Fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-proline di-HCl salt

Using essentially the same procedure as in Example 46, but substituting L-proline t-butyl ester in Step A, omitting Step B, and using the lower R_f product from Step A in Steps C - E, the title compound was prepared.
HPLC/MS (ESI): m/z 493 (M + 1).

EXAMPLE 64

N-(1-(S)-3-(S)-((4-(3-Benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-proline di-HCl salt

Using essentially the same procedure as in Example 54, but substituting (+)-trans-3-hydroxymethyl-4-(3-fluorophenyl)cyclopentan-1-one from Example 35, Step E and L-proline t-butyl ester in Step A, omitting Step B, using the lower R_f product from Step A in Steps C - E and substituting 4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidine in Step F, the title compound was prepared.
HPLC/MS (ESI): m/z 559 (M + 1).

EXAMPLE 65

N-Methyl-*N*-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Step A: Methyl (+-)-*trans*-4-methylene-2-(3-fluorophenyl)cylopentanoate

A mixture of methyl *trans*-3-fluorocinnamate (41.25 g, 229 mmol), tetrakis(triphenylphosphine) palladium(0) (18.5 g, 16 mmol), 1,2-

bis(diphenylphosphino)ethane (5.5 g, 13.7 mmol) and 2-((trimethylsilyl)methyl)-2-propen-1-yl acetate (42.66 g, 229 mmol) in THF (300 mL) under nitrogen was heated to reflux for 6 h and then stirred at rt for 16 h. The reaction was diluted with hexane and filtered to remove yellow precipitate. The volatiles were then removed *in vacuo* and the residue was purified by FC (3 to 5% ethyl acetate in hexanes) to afford the title compound (45 g).

^{1}H NMR ($CDCl_3$) δ: 2.52 (m, 1 H), 2.68 (m, 1 H), 2.8-2.9 (m, 2 H), 2.95 (ddd, 1 H), 3.45 (ddd, 1 H), 3.63 (s, 3 H), 4.96 (m, 2 H), 6.9-7.0 (m, 2 H), 7.03 (d, 1 H), 7.2-7.3 (m, 1 H).

Step B: (+-)-*trans*-4-Methylene-2-(3-fluorophenyl)cyclopentanoic acid

To a solution of methyl (+-)-*trans*-4-methylene-2-(3-fluoro)phenylcylopentanoate prepared as in Example 33, Step A (47 g, 200 mmol) in methanol (500 mL) was added 5N sodium hydroxide (200 mL, 1000 mmol). The reaction was stirred at rt for 60 h then concentrated in vacuo. The residue was taken up in water, acidified with 2M hydrochloric acid and extracted twice with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo to give the crude title acid (40.8 g) which was used directly in Step C.

Step C: (+)-*trans*-1-Hydroxymethyl-4-methylene-2-(3-fluorophenyl)cylopentane and (-)-*trans*-1-hydroxymethyl-4-methylene-2-(3-fluorophenyl)cylopentane

A solution of (+-)-*trans*-4-methylene-2-(3-fluorophenyl)cylopentanoate (5.2 g, 23.6 mmol) from Step B in THF (100 mL) was cooled to 0 °C under nitrogen and 1M lithium aluminum hydride (LAH) in THF (35.4 mL) was added dropwise over 10 min. The reaction was stirred at rt for 16 h, the excess LAH was quenched by dropwise addition of acetone and the reaction was then poured into dilute aq. HCl. The mixture was extracted twice with ether and the organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (25% ethyl acetate in hexanes) to afford the racemic title product (4.1 g) as a an oil. Chiral Prep HPLC on a 2 cm x 25 cm Chiralcel OD column eluting with 5% isopropanol in hexanes (25 injections) afforded the (-)-enantiomer, $[\alpha]_D$ = -45.5 (MeOH, c = 0.9), as the first eluting peak (R_t

= 17.5 min) and the (+)-enantiomer (1.87 g), $[\alpha]_D$ = +45.0 (MeOH, c = 1.0), as the second peak (R_t = 22.0 min).
^{1}H NMR ($CDCl_3$) δ: 2.2-2.35 (m, 2 H), 2.5 (m, 1 H), 2.65-2.85 (m, 2 H), 2.9 (m, 1 H), 3.51 and 3.68 (dABq, 2 H), 4.93 (m, 2 H), 6.9-7.0 (m, 2 H), 7.06 (d, 1 H), 7.3-7.4 (m, 1 H).

Step D: (+)-*trans*-3-Hydroxymethyl-4-(3-fluorophenyl)cylopentanone

A solution of (+)-*trans*-1-hydroxymethyl-4-methylene-2-(3-fluorophenyl)cylopentane from Step C (1.87 g, 9.0 mmol) in methanol (75 mL) was cooled in a dry ice/acetone bath and ozone was bubbled into the solution until the blue color persisted. The excess ozone was removed with a stream of nitrogen and then dimethylsulfide (5 mL) was added. After 10 min, the bath was removed and the reaction was allowed to warm to rt over 2 h. The mixture was treated with 10 drops of sulfuric acid (c) in water (2 mL) for 1 h before most of the methanol was removed in vacuo. The mixture was diluted with water and extracted twice with ethyl acetate and the organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (50% ethyl acetate in hexanes) to give the title compound (1.87 g)), $[\alpha]_D$ = +132 (MeOH, c = 1.2).
^{1}H NMR ($CDCl_3$) δ: 2.3-2.45 (m, 2 H), 2.5 (m, 1 H), 2.61 and 2.77 (dABq, 2 H), 2.28 (ddd, 1 H), 3.61 and 3.75 (dABq, 2 H), 6.9-7.0 (m, 2 H), 7.06 (d, 1 H), 7.3-7.4 (m, 1 H).

Step E: *N*-(1-(R)-3-(S)-Hydroxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine t-butyl ester

To a solution of (+)-*trans*-3-hydroxymethyl-4-(3-fluorophenyl)cylopentanone from Step D (1.0 g, 4.8 mmol) in 1,2-dichloroethane (50 mL) was added D-valine t-butyl ester (0.90 g, 5.2 mmol) and acetic acid (0.330 mL, 5.8 mmol). After 15 min, sodium triacetoxyborohydride (2.0 g, 5.6 mmol) was added and the reaction was stirred at rt for 16 h. The reaction was diluted with methylene chloride, quenched with aq. sodium carbonate and extracted 3 times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by FC eluting with 30% ethyl acetate in hexanes to give the product (1.62 g) as a mixture of the higher R_f title compound and the C-1 isomer as the free amines.

Step F: *N*-Methyl-*N*-(1-(R)-3-(S)-hydroxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine t-butyl ester

To a solution of *N*-(1-(R)-3-(S)-hydroxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine t-butyl ester from Step E (1.62, 4.44 mmol) and 37 wt % formaldehyde in water (2.1 mL, 27 mmol) in methanol (35 mL) was added 10% Pd/C (200 mg). After 10 min, the mixture was placed under hydrogen and stirred at atmospheric pressure for 60 hr. The catalyst was removed by filtration and the filtrate was evaporated. The residue was purified by FC eluting with a gradient of 15 to 50% ethyl acetate in hexanes to give the higher R_f title product (1.44 g) and the lower C-1 isomer (0.17 g) as the free amines.

Step G: *N*-Methyl-*N*-(1-(R)-3-(S)-formyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine t-butyl ester

To a solution of oxalyl chloride (0.235 mL, 2.65 mmol) in methylene chloride (10 mL) at -70 °C was added dropwise DMSO (0.385 mL, 5.3 mmol). After 15 min, a solution of *N*-methyl-*N*-(1-(R)-3-(S)-hydroxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine t-butyl ester (higher R_f isomer from Step F) (400 mg, 1.05 mmol) in methylene chloride (10 mL) was added. The reaction was stirred at -70 °C for 1 h and then DIPEA (1.8 mL, 11 mmol) in methylene chloride (5 mL) was added dropwise over 5 min. After a further 10 min, the mixture was allowed to warm to RT for 1 h and then diluted with methylene chloride. The layers were separated. The aq. layer was reextracted with a second portion of methylene chloride and the organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by FC (15% ethyl acetate in hexanes) to give the title product (378 mg) as an oil.

Step H: *N*-Methyl-*N*-(1-(R)-3-(S)-((4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine t-butyl ester

To a solution of *N*-methyl-*N*-(1-(R)-3-(S)-formyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine t-butyl ester (250 mg, 0.66 mmol) from Step G in 1,2-dichloroethane (20 mL) was added 4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidine di-hydrochloride (from Procedure 1) (250 mg, 0.73 mmol) and DIPEA (0.25 mL, 0.1.46 mmol). After 15 min, sodium triacetoxyborohydride (280 mg, 0.1.33 mmol) was added and the reaction was stirred at rt for 16 h. The reaction was diluted with methylene chloride, quenched with aq. sodium carbonate and extracted 3

times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by Prep TLC eluting with 50% ethyl acetate in hexanes to give the title product as the free amine.

HPLC/MS (ESI): m/z 631 (M + 1).

Step I: *N*-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine di-hydrochloride salt

The *N*-(1-(R)-3-(S)-((4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine t-butyl ester from Step F was taken up in TFA (2 mL) and aged at rt for 16 h. The volatiles were evaporated under a stream of nitrogen. The residue was taken up in methanol and adsorbed onto a 500 mg Varian SCX ion-exchange resin cartridge. The resin was eluted with 2 X 3 mL of methanol, then the product was eluted with 2 X 3 mL of 2M ammonia in methanol. The product solution was concentrated under nitrogen, then 2 volumes of methylene chloride were evaporated to remove methanol and ammonia to give the free amine. The hydrochloride salt was prepared by dissolving the free amine in methylene chloride, addition of excess 1M hydrogen chloride in ether and evaporation to dryness.

HPLC/MS (ESI): m/z 575 (M + 1).

EXAMPLE 66A

N-Methyl-*N*-(1-(R)-3-(S)-((4-(3-(4-fluorobenzyl)-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(3-(4-fluorobenzyl)-1-ethyl-1H-pyrazol-5-yl)piperidine di-hydrochloride in Step H, the title compound was prepared.

HPLC/MS (ESI): m/z 593 (M + 1).

EXAMPLE 66B

N-Methyl-*N*-(1-(R)-3-(S)-((4-(3-(3,4-difluorobenzyl)-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(3-(3,4-difluorobenzyl)-1-ethyl-1H-pyrazol-5-yl)piperidine di-hydrochloride in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 611 (M + 1).

EXAMPLE 66C

N-Methyl-*N*-(1-(R)-3-(S)-((4-(3-(benzyl)-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(3-(benzyl)-1H-pyrazol-5-yl)piperidine di-hydrochloride in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 547 (M + 1).

EXAMPLE 66D

N-Methyl-*N*-(1-(R)-3-(S)-((4-(2-(4-fluorophenyl)sulfonyleth-1-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine di-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(2-(4-fluorophenyl)sulfonyleth-1-yl)piperidine hydrochloride in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 545 (M + 1).

EXAMPLE 66E

N-Methyl-*N*-(1-(R)-3-(S)-((4-(2-benzylthiazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(2-(benzyl)thiazol-5-yl)piperidine di-hydrochloride in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 564 (M + 1).

EXAMPLE 66F

N-Methyl-*N*-(1-(R)-3-(S)-((4-(2-benzyl-4-methylthiazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(2-benzyl-4-methylthiazol-5-yl)piperidine di-hydrochloride in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 578 (M + 1).

EXAMPLE 66G

N-Methyl-*N*-(1-(R)-3-(S)-((4-(2-benzyl-4-ethylthiazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(2-benzyl-4-ethylthiazol-5-yl)piperidine di-hydrochloride in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 592 (M + 1).

EXAMPLE 66H

N-Methyl-*N*-(1-(R)-3-(S)-((4-(3-(4-methoxybenzyl)-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(3-(4-methoxybenzyl)-1-ethyl-1H-pyrazol-5-yl)piperidine di-hydrochloride in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 605 (M + 1).

EXAMPLE 66I

N-Methyl-*N*-(1-(R)-3-(S)-((4-(3-(4-trifluoromethylbenzyl)-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(3-(4-trifluoromethylbenzyl)-1-ethyl-1H-pyrazol-5-yl)piperidine di-hydrochloride in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 643 (M + 1).

EXAMPLE 66J

N-Methyl-*N*-(1-(R)-3-(S)-((4-(3-(pyridin-3-ylmethyl)-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(3-(pyridin-3-ylmethyl)-1-ethyl-1H-pyrazol-5-yl)piperidine di-hydrochloride in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 643 (M + 1).

EXAMPLE 66K

N-Methyl-*N*-(1-(R)-3-(S)-((4-(3-(pyridin-3-ylmethyl)-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(3-(pyridin-3-ylmethyl)-1H-pyrazol-5-yl)piperidine di-hydrochloride in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 615 (M + 1).

EXAMPLE 66L

N-Methyl-*N*-(1-(R)-3-(S)-((4-(3-(4-chlorobenzyl)-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(3-(4-chlorobenzyl)-1-ethyl-1H-pyrazol-5-yl)piperidine di-hydrochloride in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 609 (M + 1), 611 (M + 3).

EXAMPLE 66M

N-Methyl-*N*-(1-(R)-3-(S)-((4-(3-(3-fluorobenzyl)-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(3-(3-fluorobenzyl)-1-ethyl-1H-pyrazol-5-yl)piperidine di-hydrochloride in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 593 (M + 1).

EXAMPLE 66N

N-Methyl-*N*-(1-(R)-3-(S)-((4-(3-(3,5-difluorobenzyl)-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(3-(3,5-difluorobenzyl)-1-ethyl-1H-pyrazol-5-yl)piperidine di-hydrochloride in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 611 (M + 1).

EXAMPLE 66O

N-Methyl-*N*-(1-(R)-3-(S)-((4-(3-benzylpyridin-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(3-benzylpyridin-5-yl)piperidine di-hydrochloride in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 558 (M + 1).

EXAMPLE 67

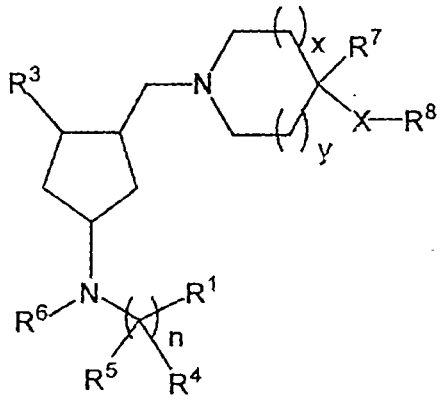
N-Methyl-*N*-(1-(S)-3-(S)-((4-(3-(benzyl)-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps G, H and I, but substituting *N*-methyl-*N*-(1-(S)-3-(S)-hydroxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine t-butyl ester (lower R_f isomer from Step F), the title compound was prepared.
HPLC/MS (ESI): m/z 575 (M + 1).

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A compound of the formula I:



I

wherein:

X is selected from: -(C_{0-6}alkyl)-Y-(C_{0-6}alkyl)-,
-(C_{0-6}alkyl)-C_{3-8} cycloalkyl-(C_{0-6}alkyl)-,
C_{2-10} alkenyl, and C_{2-10} alkynyl,
where the alkyl is unsubstituted or substituted with 1-7 substituents where the substituents are independently selected from:
(a) halo,
(b) hydroxy,
(c) -O-C_{1-3}alkyl, and
(d) trifluoromethyl,

and where Y is selected from:
a single bond, -O-, -SO_2-, -NR^{10}-, -NR^{10}-SO_2-, -SO_2-NR^{10}-, -S-, and -SO-,

and where R^{10} is independently selected from: hydrogen, C_{1-6} alkyl, benzyl, phenyl, and C_{1-6} alkyl-C_{3-6} cycloalkyl,
which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl;

R^1 is selected from:

(1) $-CO_2H$,
(2) $-NO_2$,
(3) -tetrazolyl,
(4) -hydroxyisoxazole,
(5) $-SO_2NH-(C_{0-3}$ alkyl)$-R^9$, wherein R^9 is independently selected from: hydrogen, C_{1-6} alkyl, C_{5-6} cycloalkyl, benzyl or phenyl, which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl, and
(6) $-P(O)(OH)_2$;

R^3 is selected from the group consisting of:
phenyl and heterocycle,
which is unsubstituted or substituted with 1-7 substituents where the substituents are independently selected from:
(a) halo,
(b) trifluoromethyl,
(c) hydroxy,
(d) C_{1-3}alkyl,
(e) $-O-C_{1-3}$alkyl,
(f) $-CO_2R^9$,
(g) $-NR^9R^{10}$, and
(h) $-CONR^9R^{10}$;

R^4, R^5 and R^6 are independently selected from:
hydrogen, C_{1-10} alkyl, C_{3-8} cycloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, phenyl, $-(C_{1-6}$ alkyl)-phenyl, $-(C_{1-6}$ alkyl)$-C_{3-8}$ cycloalkyl, naphthyl, biphenyl, and heterocycle,
which is unsubstituted or substituted with 1-7 of R^{11} where R^{11} is independently selected from:
(a) halo,
(b) trifluoromethyl,
(c) hydroxy,
(d) C_{1-3}alkyl,
(e) $-O-C_{1-3}$alkyl,

(f) $-CO_2R^9$,
(g) $-NR^9R^{10}$, and
(h) $-CONR^9R^{10}$,

or where R^4 and R^5 may be joined together to form a 3-8 membered saturated ring which may be unsubstituted or substituted with 1-7 of R^{11},
or where R^5 and R^6 may be joined together to form a 3-8 membered saturated ring which may be unsubstituted or substituted with 1-7 of R^{11};

R^7 is selected from:
(1) hydrogen,
(2) C_{1-6}alkyl, which is unsubstituted or substituted with 1-4 substituents where the substituents are independently selected from: hydroxy, cyano, and halo,
(3) hydroxy, and
(4) halo;

R^8 is selected from:
hydrogen, C_{3-8} cycloalkyl, phenyl, naphthyl, biphenyl, and heterocycle, which is unsubstituted or substituted with 1-7 of R^{12} where R^{12} is independently selected from:
(a) halo,
(b) cyano,
(c) hydroxy,
(d) C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 of R^{13} where R^{13} is independently selected from: halo, cyano, hydroxy, C_{1-6}alkoxy, $-CO_2H$, $-CO_2(C_{1-6}$ alkyl), trifluoromethyl, and $-NR^9R^{10}$,
(e) $-O-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-5 of R^{13},
(f) $-CF_3$,
(g) $-CHF_2$,
(h) $-CH_2F$,
(i) $-NO_2$,

(j) C_{0-6}alkyl-phenyl or C_{0-6}alkyl-heterocycle, which is unsubstituted or substituted with 1-7 substituents where the substituents are independently selected from:

(i) halo,
(ii) hydroxy,
(iii) C_{1-6}alkyl,
(iv) -O-C_{1-6}alkyl,
(v) $-CF_3$,
(vi) $-OCF_3$,
(vii) $-NO_2$,
(viii) -CN,
(ix) $-SO_2-C_{1-6}$alkyl,
(x) $-CO_2R^9$,
(xi) $-NR^9R^{10}$,
(xii) $-CONR^9R^{10}$,
(xiii) $-SO_2-NR^9R^{10}$, and
(xiv) $-NR^9-SO_2-R^{10}$;

(k) $-CO_2R^9$,
(l) tetrazolyl,
(m) $-NR^9R^{10}$,
(n) $-NR^9-COR^{10}$,
(o) $-NR^9-CO_2R^{10}$,
(p) $-CO-NR^9R^{10}$,
(q) $-OCO-NR^9R^{10}$,
(r) $-NR^9CO-NR^9R^{10}$,
(s) $-S(O)_m-R^9$, wherein m is an integer selected from 0, 1 and 2,
(t) $-S(O)_2-NR^9R^{10}$,
(u) $-NR^9S(O)_2-R^{10}$, and
(v) $-NR^9S(O)_2-NR^9R^{10}$;

n is an integer selected from 1, 2, 3 and 4;
x is an integer selected from 0, 1 and 2, and y is an integer selected from 0, 1 and 2, with the proviso that the sum of x and y is 2;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

2. The compound of Claim 1 wherein R^1 is selected from:

(1) $-CO_2H$, and

(2) -tetrazolyl.

3. The compound of Claim 1 wherein R^1 is $-CO_2H$.

4. The compound of Claim 1 wherein R^3 is selected from the group consisting of:

phenyl and thienyl,

which may be unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from:

(a) halo,

(b) trifluoromethyl,

(c) hydroxy,

(d) C_{1-3}alkyl, and

(e) $-O-C_{1-3}$alkyl.

5. The compound of Claim 1 wherein R^3 is selected from the group consisting of:

phenyl and thienyl,

which may be unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from:

(a) fluoro,

(b) chloro,

(c) trifluoromethyl,

(d) hydroxy, and

(e) C_{1-3}alkyl.

6. The compound of Claim 1 wherein R^3 is selected from the group consisting of:

phenyl, which may be unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from:

(a) fluoro, and

(b) chloro; and
unsubstituted thienyl.

7. The compound of Claim 1 wherein R^3 is unsubstituted phenyl, (3-fluoro)phenyl or 3-thienyl.

8. The compound of Claim 1 wherein R^4 is hydrogen.

9. The compound of Claim 1 wherein R^5 is selected from: hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkyl-C_{3-8} cycloalkyl, and phenyl.

10. The compound of Claim 1 wherein R^5 is selected from: hydrogen, methyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, -CH_2-cyclopropyl, -CH_2-cyclobutyl, and phenyl.

11. The compound of Claim 1 wherein R^5 is selected from: isopropyl, isobutyl, sec-butyl, and cyclohexyl.

12. The compound of Claim 1 wherein R^6 is selected from: hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkyl-C_{3-8} cycloalkyl, and phenyl.

13. The compound of Claim 1 wherein R^6 is selected from: hydrogen, methyl, n-butyl, t-butyl, isobutyl, sec-butyl, -CH_2-cyclopropyl, -CH_2-cyclobutyl, and cyclohexyl.

14. The compound of Claim 1 wherein R^6 is selected from: hydrogen, methyl, -CH_2-cyclopropyl, -CH_2-cyclobutyl, and cyclohexyl.

15. The compound of Claim 1 wherein R^7 is hydrogen, fluoro, hydroxy or C_{1-6} alkyl.

16. The compound of Claim 1 wherein R^7 is hydrogen.

17. The compound of Claim 1 wherein X is:
-(C_{0-4}alkyl)-Y-(C_{0-4}alkyl)-,

where the alkyl is unsubstituted or substituted with 1-4 substituents where the substituents are independently selected from:

(a) halo,

(b) hydroxy,

(c) -O-C_{1-3}alkyl, and

(d) trifluoromethyl,

and where Y is selected from:

a single bond, -O-, -SO_2-, -NR^{10}-, -S-, and -SO-,

and where R^{10} is independently selected from: hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, benzyl, phenyl, and C_{1-6} alkyl-C_{3-6} cycloalkyl, which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl.

18. The compound of Claim 1 wherein X is: -(C_{0-2}alkyl)-Y-(C_{0-2}alkyl)-,

where the alkyl is unsubstituted or substituted with 1-4 substituents where the substituents are independently selected from:

(a) halo,

(b) hydroxy,

(c) -O-C_{1-3}alkyl, and

(d) trifluoromethyl,

and where Y is selected from:

a single bond, -O-, -SO_2-, -NR^{10}-, -S-, and -SO-,

where R^{10} is independently selected from: hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, benzyl, phenyl, and C_{1-6} alkyl-C_{3-6} cycloalkyl, which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl.

19. The compound of Claim 1 wherein X is selected from: -(C_{0-2}alkyl)-Y-(C_{0-2}alkyl)-, where the alkyl is unsubstituted or substituted with fluoro,

and where Y is selected from:

a single bond, $-SO_2-$, -SO-, and $-NR^{10}-$, .

where R^{10} is independently selected from: hydrogen, C_{1-3} alkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl.

20. The compound of Claim 1 wherein X is selected from:

(1) a single bond,
(2) $-CH_2CH_2-$,
(3) $-CH_2CH_2CH_2-$,
(4) $-CH_2CH_2-CF_2-$,
(5) $-CH_2CH_2-SO_2-$, and
(6) $-CH_2CH_2-SO-$.

21. The compound of Claim 1 wherein R^8 is selected from: phenyl, naphthyl, cyclohexyl, benzoimidazolyl, benzofurazanyl, imidazopyridyl, imidazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidyl, thiazolyl and tetrazolopyridyl,

which is unsubstituted or substituted with 1-7 substituents where the substituents are independently selected from:

(a) halo,
(b) cyano,
(c) hydroxy,
(d) C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 of R^{13} where R^{13} is independently selected from: halo, cyano, hydroxy, C_{1-6}alkoxy, $-CO_2H$, $-CO_2(C_{1-6}$ alkyl), trifluoromethyl, and $-NR^9R^{10}$, wherein R^9 and R^{10} are independently selected from: hydrogen, C_{1-6} alkyl, C_{5-6} cycloalkyl, benzyl or phenyl, which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl;
(e) $-O-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-5 of R^{13},
(f) $-CF_3$,
(g) $-CHF_2$,

74C

(h) $-CH_2F$,
(i) $-NO_2$,
(j) C_{0-6}alkyl-phenyl or C_{0-6}alkyl-heterocycle, which is unsubstituted or substituted with 1-7 substituents where the substituents are independently selected from:
(i) halo,
(ii) hydroxy,
(iii) C_{1-6}alkyl,
(iv) $-O-C_{1-6}$alkyl,
(v) $-CF_3$,
(vi) $-OCF_3$,
(vii) $-NO_2$,
(viii) -CN,
(ix) $-SO_2-C_{1-6}$alkyl,
(x) $-CO_2R^9$,
(xi) $-NR^9R^{10}$,
(xii) $-CONR^9R^{10}$,
(xiii) $-SO_2-NR^9R^{10}$, and
(xiv) $-NR^9-SO_2-R^{10}$;
(k) $-CO_2R^9$,
(l) tetrazolyl,
(m) $-NR^9R^{10}$,
(n) $-NR^9-COR^{10}$,
(o) $-NR^9-CO_2R^{10}$,
(p) $-CO-NR^9R^{10}$,
(q) $-OCO-NR^9R^{10}$,
(r) $-NR^9CO-NR^9R^{10}$,
(s) $-S(O)_m-R^9$, wherein m is an integer selected from 0, 1 and 2,
(t) $-S(O)_2-NR^9R^{10}$,
(u) $-NR^9S(O)_2-R^{10}$, and
(v) $-NR^9S(O)_2-NR^9R^{10}$.

22. The compound of Claim 1 wherein R^8 is selected from: phenyl, imidazopyridyl, imidazolyl, oxazolyl, pyrazolyl, pyridyl, and thiazolyl;

which is unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from:

(a) halo,
(b) cyano,
(c) $-NO_2$,
(d) $-CF_3$,
(e) $-CHF_2$,
(f) $-CH_2F$,
(h) C_{1-6}alkyl,
(i) C_{1-3}alkyl-phenyl or C_{1-3}alkyl-pyridyl, which is unsubstituted or substituted with 1-4 substituents where the substituents are independently selected from:
  (i) halo,
  (ii) C_{1-6}alkyl,
  (iii) $-O-C_{1-6}$alkyl,
  (iv) $-CF_3$,
  (vi) $-OCF_3$,
  (vii) -CN, and
(j) $-O-C_{1-6}$alkyl.

23. The compound of Claim 1 wherein R^8 is selected from: imidazolyl, oxazolyl, pyrazolyl, and thiazolyl;
which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from:

(a) fluoro,
(b) cyano,
(c) C_{1-3}alkyl,
(d) $-CH_2$-phenyl, which is unsubstituted or substituted with 1-4 substituents where the substituents are independently selected from:
  (i) fluoro,
  (ii) chloro,
  (iii) $-O-CH_3$,
  (iv) $-CF_3$,
  (v) -CN, and

(e) $-CF_3$.

24. The compound of Claim 1 wherein R^8 is selected from: 5-(3-benzyl)pyrazolyl, 5-(1-methyl-3-benzyl)pyrazolyl, 5-(1-ethyl-3-benzyl)pyrazolyl, 5-(2-benyl)thiazolyl, 5-(2-benyl-4-methyl)thiazolyl, and 5-(2-benyl-4-ethyl)thiazolyl).

25. The compound of Claim 1 wherein n is an integer which is 1.

26. The compound of Claim 1 wherein x is an integer which is 1 and y is an integer which is 1.

27. A pharmaceutical composition which comprises an inert carrier and a compound of Claim 1.

28. A method for modulation of chemokine receptor activity in a mammal which comprises the administration of an effective amount of the compound of Claim 1.

29. A method for preventing infection by HIV, treating infection by HIV, delaying of the onset of AIDS, or treating AIDS comprising the administration to a patient of an effective amount of the compound of Claim 1.

30. A method for the prevention or treatment of an inflammatory and immunoregulatory disorder or disease which comprises the administration to a patient of an effective amount of the compound of Claim 1.

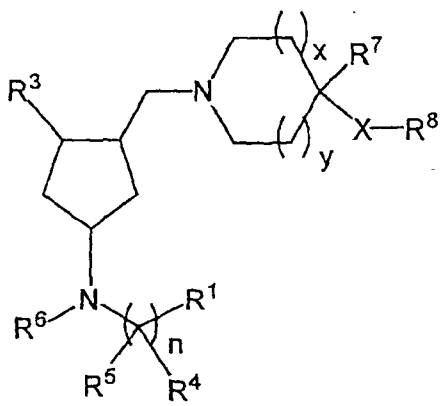
31. A method for the prevention or treatment of asthma, allergic rhinitis, dermatitis, conjunctivitis, atherosclerosis or rheumatoid arthritis which comprises the administration to a patient of an effective amount of the compound of Claim 1.

TITLE OF THE INVENTION

N-CYCLOPENTYL MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY

ABSTRACT OF THE INVENTION

The present invention is directed to compounds of the formula I:



I

(wherein R^1, R^3, R^4, R^5, R^6, R^7, R^8, X, n, x and y are defined herein) which are useful as modulators of chemokine receptor activity. In particular, these compounds are useful as modulators of the chemokine receptors CCR-5 and/or CCR-3.

Junio 19, 2000
Traducción Oficial No. 0277
REF:MERCK & CO;INC
Patente No.: 09/330,810

Merck & Co; Inc
Caso -20461Y

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS
OFICINA DE MARCAS Y PATENTES

Junio 01, 2000

Por medio del presente documento se certifica que adjunto se encuentra una fiel copia de los registros de la Oficina de Marcas y Patentes de los Estados Unidos, correspondientes a los documentos para la solicitud tal como se presentaron, con el fin de asignarle una fecha de registro bajo la norma del código 35 USC 111.

Número de Solicitud:09/330,810
Fecha de Registro:Junio 11,1999

Autorizado por:
COMISIONADO DE MARCAS Y PATENTES
Firma: T.Wallace
Funcionario Encargado de Certificaciones
Hay sello de la Oficina de Marcas y Patentes realzado de color dorado.

Eduardo Calvo A

OFICINA DE MARCAS Y PATENTES

Assistant Commisioner for Patents
Washington, D. C. 20231

No. de Cuenta Corriente: 13-2755
MERCK & CO., INC
No. de Caso: 20461Y

Estimados Señores:

La presente es una petición para registro de una SOLICITUD PROVISIONAL de solicitud de Patente de los siguientes inventores bajo el código 37 CFR 1.53(b): PAUL E. FINKE, KEVIN CHAPMAN. KERRY A. HILFIKER, JENNIFER L. LOEBACH, MALCOM MACCOSS, SANDER MILLS, BRYAN OATES.

TITULO DE LA INVENCIÓN (280 Caracteres máximo)

MODULADORES DE N-CICLOPENTILO DE RECEPTORES DE ACTIVIDAD KEMOQUINA

Para	Cantidad Registrada		Números Extras	
Total Reivindicaciones	31	-20=	11	X
Reivindicaciones independientes	1	-3=	0	
Reivindicaciones				X

Eduardo Calabrese

dependientes múltiples.

Atentamente:

Por: J. ERIC THIES

Abogado para solitante (s)

No de Registro: 35,382

Merck & Co., Inc
Patent Department -
P.O. Box 2000
Rahway, N.J 07065-0907
(732) 594-3904
Fecha: Junio 11, 1999

CERTIFICADO DE ENVIÓ POSTAL

Fecha de envío:Junio 11, 1999

Correo Inmediato Certificado No: EM358364308 US

Yo, por medio del presente documento certifico que ha sido enviado por Correo Certificado como Correo Postal al Destinatario antes de las 5 P.M. en la fecha anteriormente mencionada en un sobre rotulado al Comisionado Asistente para Patentes, Box Patent Application, Washington, DC., 20231.

Firma: Enviado por:Barbara Reilly

Eduardo Calvado

REIVINDICACIONES:

1. Un compuesto de acuerdo a la formula I:

I

en la cual:

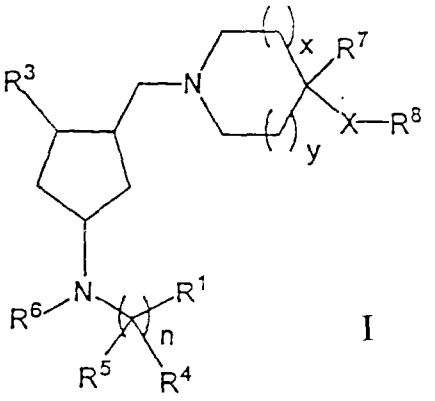
X es seleccionado de: -(C0-6alquilo)-Y-(C0-6alquilo)-,
-(C0-6alquilo-C3-8 cicloalquilo-(C0-6alquilo)-,
C2-10 alquenilo y C2-10 alquinilo,
en el cual el alquilo es sustituido o no sustituido
con 1-7 substitutos en el cual los substitutos son
seleccionados independientemente de:

(a) halo,
(b) hidroxi,
(c) -O-C1-3alquilo, y
(d) trifluorometilo,

Eduardo Calado

REIVINDICACIONES:

1. Un compuesto de acuerdo a la formula I:



I

en la cual:

X es seleccionado de: -(C0-6alquilo)-Y-(C0-6alquilo)-,

-(C0-6alquilo-C3-8 cicloalquilo-(C0-6alquilo)-,

C2-10 alquenilo y C2-10 alquinilo,

en el cual el alquilo es sustituido o no sustituido con 1-7 substitutos en el cual los substitutos son seleccionados independientemente de:

(a) halo,

(b) hidroxi,

(c) -O-C1-3alquilo, y

(d) trifluorometilo,

Eduardo Collado L

en el cual Y es seleccionado de:

un enlace único, -O-, SO2-, -NR10-, -NR10-SO2-, -SO2-NR10-, -S-, y -SO-,

en el cual R10 es seleccionado independientemente de: hidrógeno, C1-6-alquilo, bencilo, fenilo y C1-6 alquilo-C3-6 cicloalquilo,

el cual es substituido o no substituido con 1-3 substitutos donde los substitutos son seleccionados independientemente de: halo, C1-3 alquilo, C1-3 alcoxi y trifluorometilo;

R1 es seleccionado de;

(1) -CO2H,

(2) -NO2,

(3) tetrazolil,

(4) -hidroxiisoxazol,

(5) -SO2NH-(C0-3 alquilo)-R9 es seleccionado independientemente de:

hidrógeno, C1-6 alquilo, C5-6 cicloalquilo, bencilo o fenilo, el cual es substituido o no substituido con 1-3 substitutos en el

Eduardo Calado

cual los substitutos son seleccionados independientemente de:

halo, C1-3 alquilo, C1-3 alcoxi y trifluorometilo, y

(6) -P(O)(OH)2;

R3 es seleccionado de un grupo que consiste de:

fenilo y heterociclo,

el cual es substituido o no substituido con 1-7 substitutos en el cual los substitutos son seleccionados independientemente de:

(a) halo,

(b) trifluorometilo,

(c) hidroxi,

(d) C1-3 alquilo,

(e) -O-C1-3alquilo,

(f) -CO2R9,

(g) -NR9R10, y

(h) -CONR9R10;

R4, R5 y R6 son seleccionados independientemente de:

hidrógeno, C1-10 alquilo, C3-8 cicloalquilo, C2-10 alquenilo, C2-10 alquinilo, fenilo, -(C1-6 alquilo)-C3-8 cicloalquilo,

Eduardo Calado

naftilo, bifenilo y heterociclo, el cual es substituido o no substituido con 1-7 o R11 son independientemente seleccionados de:

(a) halo,

(b) trifluorometilo,

(c) hidroxi,

(d) C1-3 alquilo,

(e) -O-C1-3alquilo,

(f) -CO2R9,

(g) -NR9R10, y

(h) -CONR9R10;

o donde R4 y R5 pueden ser unidos para formar un anillo saturado de 3-8 miembros el cual puede ser substituido o no substituido con 1-7 o R11,

o donde R5 y R6 pueden ser unidos para formar un anillo saturado de 3-8 miembros el cual puede ser substituido o no substituido con 1-7 o R11;

R7 es seleccionado de:

Eduardo Calvo

(1) hidrógeno,

(2) C1-6 alquilo, el cual es substituido o no substituido con 1-4 substitutos en el cual los substitutos son seleccionados independientemente de: hidróxi, ciano y halo,

(3) hidróxi, y

(4) halo;

R8 es seleccionado de:

hidrogeno, C1-8 cicloaqluilo, fenilo, naftilo, bifenilo y heterociclo, el cual es substituido o no substituido con 1-7 de R12 donde R12 es seleccionado independientemente de:

(a) halo,

(b) ciano,

(c) hidroxi,

(d) C1-6alquilo, el cual es substituido o no substituido con 1-5 de R13 donde R13 es seleccionado independientemente de: halo, ciano,hidroxi, C1-6 alcoxi, -CO2H, -CO2(C1-6alquilo), trifluorometilo y -NR9R10,

(e) -O-C1-6alquilo, el cual es substituido o no substituido con 1-5 de R13,

Eduardo Calado A

(f) -CF3,

(g) -CHF2,

(h) -CH2F,

(i) -NO2,

(j) C0-6alquilo-fenilo o C0-6 alquilo-heterociclo, el cual es substituido o no substituido con 1-7 substitutos los cuales son seleccionados independientemente de:

(i) halo,

(ii) hidroxi,

(iii) C1-6 alquilo,

(iv) -O-C1-6alquilo,

(v) -CF3,

(vi) -OCF3,

(vii) -NO2,

(viii) -CN,

(ix) -SO2-C1-6alquilo,

(x) -CO2R9,

(xi) -NR9R10,

(xii) -CONR9R10,

(xiii) -SO2-NR9R10, y

(xiv) -NR9-SO2-R10;

Eduardo Cabrales

(k) -CO2R9,

(l) tetrazolil,

(m) -NR9R10,

(n) -NR9-COR10,

(o) -NR9 CO2R10

(p) -CO-NR9R10,

(q) -OCO-NR9R10,

(r) -NR9CO-NR9R10,

(s) -S(O)m-R9, en el cual m es un número entero seleccionado de 0, 1 y 2,

(t) -S(O)2-NR9R10,

(u) -NR9S(O)2-R10, y

(v) -NR9S(O)2-NR9R10;

n es un número entero seleccionado de 1,2,3 y 4;

x es un número entero seleccionado de 0, 1 y 2, e

y es un número entero seleccionado de 0, 1 y 2, siempre y cuando que la suma de x e y sea 2;

y sales farmacéuticamente aceptables del mismo e diastereomeros del mismo.

Eduardo Calado L.

2. El compuesto de acuerdo a la reivindicación 1 en la cual R1 es seleccionado de:

(1) -CO2H, y

(2) -tetrazolil.

3. El compuesto de acuerdo a la reivindicación 1 en la cual R1 es -CO2H.

4. El compuesto de acuerdo a la reivindicación 1 en la cual R3 es seleccionado de un grupo que consiste de:

fenilo e tienilo,

el cual puede ser substituido o no substituido con 1-5 substitutos en el cual los substitutos son independientemente seleccionados de:

(a) halo,

(b) trifluorometilo,

(c) hidroxi,

(d) C1-3alquilo, y

Eduardo Calvo L

(e) -O-C1-3alquilo.

5. El compuesto de acuerdo a la reivindicación 1 en el cual R3 es seleccionado de un grupo que consiste de:

fenilo e tienilo,

el cual puede ser substituido o no substituido con 1-5 substitutos en el cual los substitutos son seleccionados independientemente de:

(a) flúor,

(b) cloro,

(c) trifluorometilo,

(d) hidroxi, y

(e) C1-3alquilo.

6. El compuesto de acuerdo a la reivindicación 1 en la cual R3 es seleccionado de un grupo que consiste de:

fenilo, el cual puede ser substituido o no substituido con 1-5 substitutos en el cual los substitutos son seleccionados independientemente de:

(a) flúor, y

Eduardo Calvo A

(b) cloro; y

tienilo no substituido.

7. El compuesto de acuerdo a la reivindicación 1 en la cual R3 es fenilo no substituido, (3-flúor) fenilo o 3-tienilo.

8. El compuesto de acuerdo a la Reivindicación 1 en la cual R4 es hidrógeno.

9. El compuesto de acuerdo a la Reivindicación 1 en el cual R5 es seleccionado de: hidrógeno, C1-6 alquilo, C3-8 cicloalquilo, C1-6 alquilo-C3-8 cicloalquilo y fenilo.

10. El compuesto de acuerdo a la reivindicación 1 en la cual R5 es seleccionado de: hidrógeno, metilo, n-propilo, isopropilo, n-butilo, t-butilo, isobutilo, sec-butilo, ciclohexilo, -CH2-ciclopropilo, -CH2-ciclobutilo y fenilo.

11. El compuesto de acuerdo a la Reivindicación 1 en el cual R5 es seleccionado de: isopropilo, isobutilo, sec-butilo y ciclohexilo.

Eduardo Calesdo A

12. El compuesto de acuerdo a la reivindicación 1 en el cual R6 es seleccionado de: hidrógeno, C1-6 alquilo, C3-8 cicloalquilo, C1-6 alquilo-C3-8 cicloalquilo y fenilo.

13. El compuesto de acuerdo a la reivindicación 1 en el cual R6 es seleccionado de: hidrógeno, metilo, n-butilo, t-butilo, isobutilo, sec-butilo, -CH2-ciclopropilo, -CH2-ciclopropilo, -CH2-ciclobutilo e ciclohexilo.

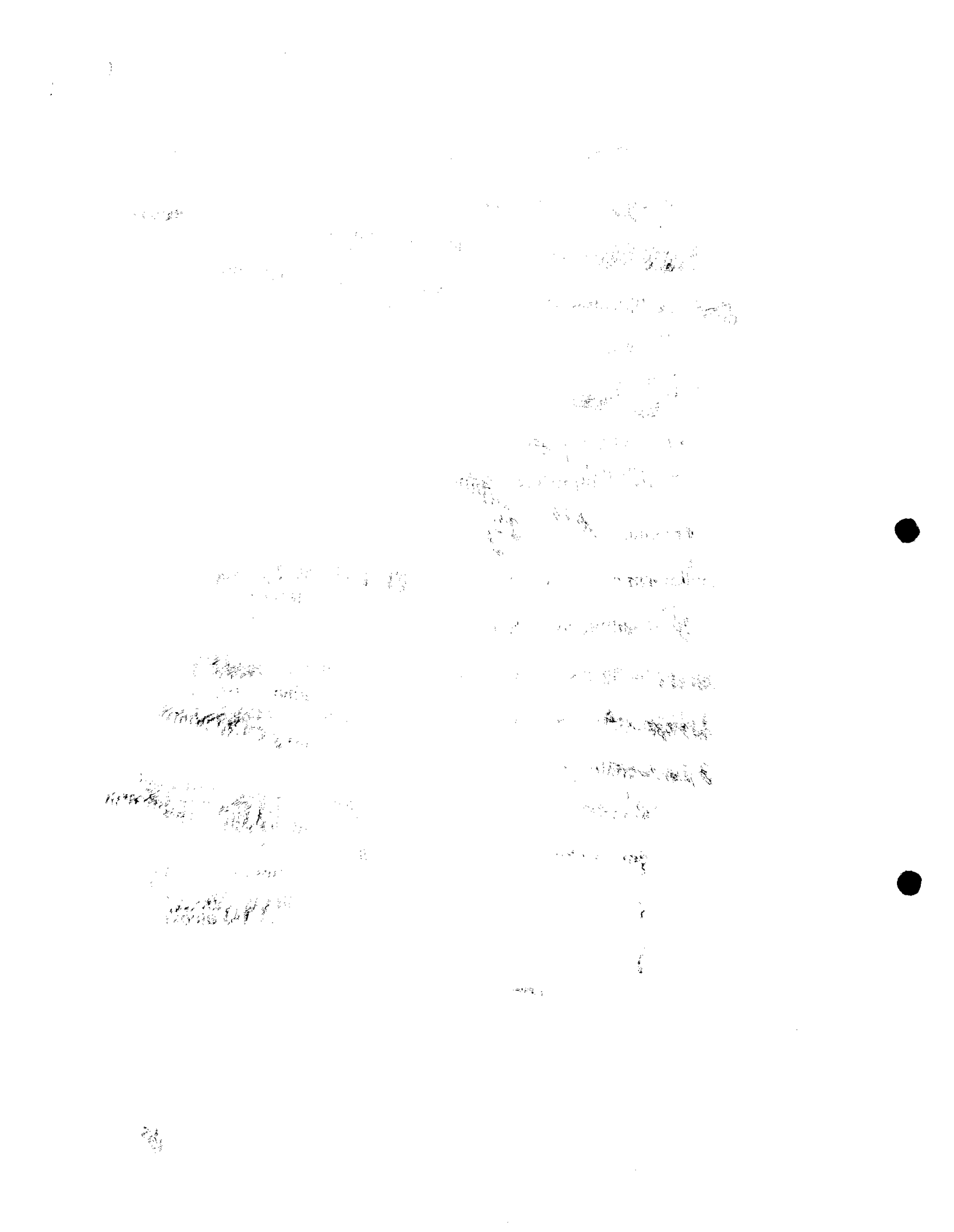
14. El compuesto de acuerdo a la reivindicación 1 en el cual R6 es seleccionado de: hidrógeno, metilo, -CH2-ciclopropilo, -CH2-ciclobutilo y ciclohexilo.

15. El compuesto de acuerdo a la Reivindicación 1 en el cual R7 es hidrógeno, flúor, hidróxi o C1-6 alquilo.

16. El compuesto de acuerdo a la Reivindicación 1 en el cual R7 es hidrógeno.

17. El compuesto de acuerdo a la reivindicación 1 en el cual X es:

Eduardo Calado



-(C0-4alquilo)-Y-(C0-4alquilo),

en el cual el alquilo es substituido o no substituido con 1-4 substitutos donde los substitutos son seleccionados independientemente de:

(a) halo,

(b) hidroxi,

(c) -O-C1-3alquilo, y

(d) trifluorometilo,

en el cual Y es seleccionado de:

un enlace único, -O-, SO2-, -NR10-, -NR10-SO2-, -SO2-NR10-, -S-, y -SO-,

en el cual R10 es seleccionado independientemente de: hidrógeno, C1-6-alquilo, bencilo, fenilo y C1-6 alquilo-C3-6 cicloalquilo,

el cual es substituido o no substituido con 1-3 substitutos donde los substitutos son seleccionados independientemente de: halo, C1-3 alquilo, C1-3 alcoxi y trifluorometilo;

Eduardo Calado

18. El compuesto de acuerdo a la reivindicación 1 en la cual X es:

-(C0-4alquilo)-Y-(C0-4alquilo),

en el cual el alquilo es substituido o no substituido con 1-4 substitutos donde los substitutos son seleccionados independientemente de:

(a) halo,

(b) hidroxi,

(c) -O-C1-3alquilo, y

(d) trifluorometilo,

en el cual Y es seleccionado de:

un enlace único, -O-, SO2-, -NR10-, -NR10-SO2-,

-SO2-NR10-, -S-, y -SO-,

en el cual R10 es seleccionado independientemente de:

hidrógeno, C1-6-alquilo, bencilo, fenilo y C1-6 alquilo-C3-6 cicloalquilo,

el cual es substituido o no substituido con 1-3 substitutos donde los substitutos son seleccionados independientemente de: halo, C1-3 alquilo, C1-3 alcoxi y trifluorometilo;

Eduardo Calado

19. El compuesto de acuerdo a la Reivindicación 1 en la cual X es seleccionado de:

-(C0-4alquilo)-Y-(C0-4alquilo),

en el cual el alquilo es substituido o no substituido con flúor,

y en el cual Y es seleccionado de:

un único enlace, -SO2-, -SO-, y -NR10-,

donde R10 es seleccionado independientemente de: hidrógeno, C1-3 alquilo, C2-3 alquenilo y c2-3 alquinilo.

20. El compuesto de acuerdo a la reivindicación 1 en el cual X es seleccionado de:

(1) un enlace único,

(2) -CH2CH2-,

(3) -CH2CH2CH2-,

(4) -CH2CH2-CF2-,

(5) - CH2CH2-SO2-, y

(6) -CH2CH2-SO-

21. El compuesto de acuerdo a la reivindicación 1 en al cual R8 es seleccionado de: fenilo, naftilo, ciclohexilo, benzoimidazolil, benzofurazanil, imidazopiridilo, imidazolil, isoxazolil, oxazolil,

Eduardo Calado

pirazinilo, piridazinilo, piridilo, pirimidilo, tiazolil y tetrazolopiridilo,

el cual es substituido o no substituido con 1-7 substitutos en el cual los substitutos son independientemente seleccionados de:

(a) halo,

(b) ciano,

(c) hidróxi,

(d) C1-6alquilo, el cual es substituido o no substituido con 1-5 de R13 donde R13 es seleccionado independientemente de: halo, ciano,hidroxi, C1-6 alcoxi, -CO2H, -CO2(C1-6alquilo), trifluorometilo y -NR9R10, en el cual R9 y R10 son seleccionados independientemente de: hidrógeno, C1-6 alquilo, C5-6 cicloalquilo, bencilo, o fenilo, el cual es substituido o no substituido con 1-3 substitutos, en el cual el substituto es seleccionado independientemente de; halo, C1-3 alquilo, C1-3 alcoxi y trifluorometilo;

Eduardo Calado M.

(e) -O-C1-6alquilo, el cual es substituido o no substituido con 1-5 de R13,

(f) -CF3,

(g) -CHF2,

(h) -CH2F,

(i) -NO2,

(j) C0-6alquilo-fenilo o C0-6 alquilo-heterociclo, el cual es substituido o no substituido con 1-7 substitutos los cuales son seleccionados independientemente de:

(i) halo,

(ii) hidroxi,

(iii) C1-6 alquilo,

(iv) -O-C1-6alquilo,

(v) -CF3,

(vi) -OCF3,

(vii) -NO2,

(viii) -CN,

(ix) -SO2-C1-6alquilo,

(x) -CO2R9,

(xi) -NR9R10,

(xii) -CONR9R10,

Eduardo Collado M.

(xiii) -SO2-NR9R10, y

(xiv) -NR9-SO2-R10;

(k) -CO2R9,

(l) tetrazolil,

(m) -NR9R10,

(n) -NR9-COR10,

(o) -NR9 CO2R10

(p) -CO-NR9R10,

(q) -OCO-NR9R10,

(r) -NR9CO-NR9R10,

(s) -S(O)m-R9, en el cual m es un número entero seleccionado de 0, 1 y 2,

(t) -S(O)2-NR9R10,

(u) -NR9S(O)2-R10, y

(v) -NR9S(O)2-NR9R10;

22. El compuesto de acuerdo a la reivindicación 1 en el cual R8 es seleccionado de: fenilo, imidazopirridilo, imidazolil, oxazolil, pirazolil, pirridilo y tiazolil.

el cual es substituido o no substituido con 1-5 substitutos en el cual los substitutos son independientemente seleccionados de:

Eduardo Calado A.

(a) halo,

(b) ciano,

(c) -NO2,

(d) -CF3,

(e) -CHF2,

(f) -CH2F,

(h) C1-6alquilo

(i) C1-3 alquilo-fenilo o C1-3alquilo-pirridilo el cual es substituido o no substituido con 1-4 substitutos en el cual dichos substitutos son seleccionados independientemente de:

(i) halo;

(ii) C1-6 alquilo,

(iii) -O-C1 alquilo,

(iv) -CF3,

(vi) -OCF3,

(vii) -CN, y

(j) -O-C1-6 alquilo.

23. El compuesto de acuerdo a la reivindicación 1 en el cual R8 es seleccionado de: imidazolil, oxazolil, pirazolil y tiazolil;

Eduardo Calado L

el cual es substituido o no substituido con 1-3 substitutos y dichos substitutos son seleccionados independientemente de:

(a) flúor,

(b) ciano,

(c) C1-3 alquilo,

(d) -CH2 fenilo, el cual es substituido o no substituido con 1-4 substitutos en el cual dichos substitutos son independientemente seleccionados de:

(i) flúor,

(ii) cloro,

(iii) -O-CH3,

(iv) -CF3,

(v) -CN, y

(e) -CF3.

24. El compuesto de acuerdo a la reivindicación 1 en el cual R8 es seleccionado de: 5-(3-bencilo)pirazolil, 5-(1-metilo-3-bencilo)pirazolil, 5--(1-etilo-3-bencilo)pirazolil, 5-(2-bencilo)tiazolil, 5-(2-benilo-4-metilo)tiazolil, y 5-(2-benilo-4-etilo)tiazolil).

Eduardo Calad 22

25. El compuesto de acuerdo a la Reivindicación 1 en el cual n es un número entero el cual es 1.

26. El compuesto de acuerdo a la Reivindicación 1 en el cual x es un número entero, el cual es 1 e y es un número entero el cual es 1.

27. Una composición farmacéutica la cual consiste de un portador inerte y un compuesto de acuerdo a la reivindicación 1.

28. Un método para la modulación de actividad receptora de kemoquina en un mamífero el cual consiste en el suministro de una cantidad eficaz del compuesto de acuerdo a la reivindicación 1.

29. Un método para la prevención de infecciones de HIV positivo, el cual consiste en tratar la infección de HIV que retarda el comienzo del SIDA o el tratamiento del SIDA el cual consiste en suministrar a un paciente que necesita dicha cantidad eficaz del compuesto de la reivindicación 1.

30. Un método para la prevención o tratamiento de un trastorno inflamatorio o inmunoregulador o enfermedad a un paciente que

Eduardo Salado A.

necesite dicho tratamiento el cual consiste en el suministro de una cantidad eficaz del compuesto de acuerdo a la Reivindicación 1.

31. Un método para la prevención o tratamiento para el asma, rinitis alérgica, dermatitis, conjuntivitis, artereosclerosis o artritis reumatoide, el cual consiste en el suministro de una cantidad eficaz del compuesto de acuerdo a la reivindicación 1 a un paciente que necesite dicho tratamiento.

Eduardo Calado A.

PA 254687

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

June 01, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: ***09/330,810***
FILING DATE: ***June 11, 1999***

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

T. WALLACE
Certifying Officer

PATENT

771

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Assistant Commissioner for Patents
Washington, D.C. 20231

Deposit Acct. 13-2755
MERCK & CO., INC.
Our Case Docket No. 20461

Sir:

Transmitted herewith for filing under 37 C.F.R. §1.53(b) is the patent application of Inventor(s):
PAUL E. FINKE, KEVIN CHAPMAN, KERRY A. HILFIKER, JENNIFER L. LOEBACH, MALCOLM MACCOSS, SANDER MILLS, BRYAN OATES

For: N-CYCLOPENTYL MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY

For	Number Filed		Number Extra			
Total Claims	31	- 20 =	11	X		
Independent Claims	1	- 3 =	0	X		
Multiple Dependent Claims				X		

EXPRESS MAIL CERTIFICATE

DATE OF DEPOSIT JUNE 11, 1999

EXPRESS MAIL NO. EM358364308US

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS EXPRESS MAIL "POST OFFICE TO ADDRESSEE" BEFORE 5 P.M. ON THE ABOVE DATE IN AN ENVELOPE ADDRESSED TO ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, D.C. 20231.

MAILED BY Barbara Reilly DATE 6-11-99

Respectfully,

By: J. ERIC THIES
Attorney For Applicant(s)
Reg. No. 35,382
MERCK & CO., INC.
Patent Dept.
P.O. Box 2000
Rahway, N.J. 07065-0907
(732) 594- 3904

Date: June 11, 1999

IN DUPLICATE

Computer generated form "Transmittal Letter", Merck & Co., Inc., 11/17/98

TITLE OF THE INVENTION

N-CYCLOPENTYL MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY

BACKGROUND OF THE INVENTION

Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation (reviewed in Schall, Cytokine, 3, 165-183 (1991) and Murphy, Rev. Immun., 12, 593-633 (1994)). There are two classes of chemokines, C-X-C (α) and C-C (β), depending on whether the first two cysteines are separated by a single amino acid (C-X-C) or are adjacent (C-C). The α-chemokines, such as interleukin-8 (IL-8), neutrophil-activating protein-2 (NAP-2) and melanoma growth stimulatory activity protein (MGSA) are chemotactic primarily for neutrophils, whereas β-chemokines, such as RANTES, MIP-1α, MIP-1β, monocyte chemotactic protein-1 (MCP-1), MCP-2, MCP-3 and eotaxin are chemotactic for macrophages, T-cells, eosinophils and basophils (Deng, et al., Nature, 381, 661-666 (1996)).

The chemokines bind specific cell-surface receptors belonging to the family of G-protein-coupled seven-transmembrane-domain proteins (reviewed in Horuk, Trends Pharm. Sci., 15, 159-165 (1994)) which are termed "chemokine receptors." On binding their cognate ligands, chemokine receptors transduce an intracellular signal though the associated trimeric G protein, resulting in a rapid increase in intracellular calcium concentration. There are at least seven human chemokine receptors that bind or respond to β-chemokines with the following characteristic pattern: CCR-1 (or "CKR-1" or "CC-CKR-1") [MIP-1α, MIP-1β, MCP-3, RANTES] (Ben-Barruch, et al., J. Biol. Chem., 270, 22123-22128 (1995); Beote, et al, Cell, 72, 415-425 (1993)); CCR-2A and CCR-2B (or "CKR-2A"/"CKR-2A" or "CC-CKR-2A"/"CC-CKR-2A") [MCP-1, MCP-3, MCP-4]; CCR-3 (or "CKR-3" or "CC-CKR-3") [eotaxin, RANTES, MCP-3] (Combadiere, et al., J. Biol. Chem., 270, 16491-16494 (1995); CCR-4 (or "CKR-4" or "CC-CKR-4") [MIP-1α, RANTES, MCP-1] (Power, et al., J. Biol. Chem., 270, 19495-19500 (1995)); CCR-5 (or "CKR-5" or "CC-CKR-5") [MIP-1α, RANTES, MIP-1β] (Sanson, et al., Biochemistry, 35, 3362-3367 (1996)); and the Duffy blood-group antigen [RANTES, MCP-1] (Chaudhun, et al., J. Biol. Chem., 269, 7835-7838 (1994)). The β-chemokines include eotaxin, MIP ("macrophage inflammatory protein"), MCP ("monocyte chemoattractant protein") and RANTES ("regulation-upon-activation, normal T expressed and secreted").

Chemokine receptors, such as CCR-1, CCR-2, CCR-2A, CCR-2B, CCR-3, CCR-4, CCR-5, CXCR-3, CXCR-4, have been implicated as being important mediators of inflammatory and immunoregulatory disorders and diseases, including asthma, rhinitis and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. Humans who are homozygous for the 32-basepair deletion in the CCR-5 gene appear to have less susceptibility to rheumatoid arthritis (Gomez, et al., Arthritis & Rheumatism, 42, 989-992 (1999)). A review of the role of chemokines in allergic inflammation is provided by Kita, H., et al., J. Exp. Med. 183, 2421-2426 (1996). Accordingly, agents which modulate chemokine receptors would be useful in such disorders and diseases. Compounds which modulate chemokine receptors would be especially useful in the treatment and prevention of atopic conditions including allergic rhinitis, dermatitis, conjunctivitis, and particularly bronchial asthma.

A retrovirus designated human immunodeficiency virus (HIV-1) is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous system. This virus was previously known as LAV, HTLV-III, or ARV.

Certain compounds have been demonstrated to inhibit the replication of HIV, including soluble CD4 protein and synthetic derivatives (Smith, et al., Science, 238, 1704-1707 (1987)), dextran sulfate, the dyes Direct Yellow 50, Evans Blue, and certain azo dyes (U.S. Patent No. 5,468,469). Some of these antiviral agents have been shown to act by blocking the binding of gp120, the coat protein of HIV, to its target, the CD4 glycoprotein of the cell.

Entry of HIV-1 into a target cell requires cell-surface CD4 and additional host cell cofactors. Fusin has been identified as a cofactor required for infection with virus adapted for growth in transformed T-cells, however, fusin does not promote entry of macrophagetropic viruses which are believed to be the key pathogenic strains of HIV in vivo. It has recently been recognized that for efficient entry into target cells, human immunodeficiency viruses require a chemokine receptors, most probably CCR-5 or CXCR-4, as well as the primary receptor CD4 (Levy, N. Engl. J. Med., 335(20), 1528-1530 (Nov. 14 1996). The principal cofactor for entry mediated by the envelope glycoproteins of primary macrophage-trophic strains of HIV-1 is CCR5, a receptor for the β-chemokines RANTES, MIP-1α and MIP-1β (Deng, et al., Nature, 381, 661-666 (1996)). HIV attaches to the CD4

molecule on cells through a region of its envelope protein, gp120. It is believed that the CD-4 binding site on the gp120 of HIV interacts with the CD4 molecule on the cell surface, and undergoes conformational changes which allow it to bind to another cell-surface receptor, such as CCR5 and/or CXCR-4. This brings the viral envelope closer to the cell surface and allows interaction between gp41 on the viral envelope and a fusion domain on the cell surface, fusion with the cell membrane, and entry of the viral core into the cell. It has been shown that β-chemokine ligands prevent HIV-1 from fusing with the cell (Dragic, et al., Nature, 381, 667-673 (1996)). It has further been demonstrated that a complex of gp120 and soluble CD4 interacts specifically with CCR-5 and inhibits the binding of the natural CCR-5 ligands MIP-1α and MIP-1β (Wu, et al., Nature, 384, 179-183 (1996); Trkola, et al., Nature, 384, 184-187 (1996)).

Humans who are homozygous for mutant CCR-5 receptors which do not serve as co-receptors for HIV-1 in vitro appear to be unusually resistant to HIV-1 infection and are not immuno-compromised by the presence of this genetic variant (Nature, 382, 722-725 (1996)). Absence of CCR-5 appears to confer substantial protection from HIV-1 infection (Nature, 382, 668-669 (1996)). Other chemokine receptors may be used by some strains of HIV-1 or may be favored by non-sexual routes of transmission. Although most HIV-1 isolates studied to date utilize CCR-5 or fusin, some can use both as well as the related CCR-2B and CCR-3 as co-receptors (Nature Medicine, 2(11), 1240-1243 (1996)). Nevertheless, drugs targeting chemokine receptors may not be unduly compromised by the genetic diversity of HIV-1 (Zhang, et al., Nature, 383, 768 (1996)). Accordingly, an agent which could block chemokine receptors in humans who possess normal chemokine receptors should prevent infection in healthy individuals and slow or halt viral progression in infected patients. By focusing on the host's cellular immune response to HIV infection, better therapies towards all subtypes of HIV may be provided. These results indicate that inhibition of chemokine receptors presents a viable method for the prevention or treatment of infection by HIV and the prevention or treatment of AIDS.

The peptides eotaxin, RANTES, MIP-1α, MIP-1β, MCP-1, and MCP-3 are known to bind to chemokine receptors. A compound from Takeda, TAK-779, reportedly is a nonpeptidal CCR5 antagonist with anti-HIV-1 activity (Baba, et al., Proc. Nat'l Acad. Sci., USA, 96, 5698-5703 (1999)). As noted above, the inhibitors of HIV-1 replication present in supernatants of CD8+ T cells have been characterized as the β-chemokines RANTES, MIP-1α and MIP-1β.

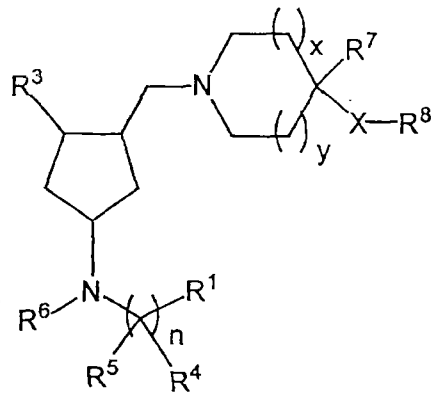
SUMMARY OF THE INVENTION

The present invention is directed to compounds which inhibit the entry of human immunodeficiency virus (HIV) into target cells and are of value in the prevention of infection by HIV, the treatment of infection by HIV and the prevention and/or treatment of the resulting acquired immune deficiency syndrome (AIDS). The present invention also relates to pharmaceutical compositions containing the compounds and to a method of use of the present compounds and other agents for the prevention and treatment of AIDS and viral infection by HIV.

The present invention is further directed to compounds which are modulators of chemokine receptor activity and are useful in the prevention or treatment of certain inflammatory and immunoregulatory disorders and diseases, allergic diseases, atopic conditions including allergic rhinitis, dermatitis, conjunctivitis, and asthma, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which chemokine receptors are involved.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds of formula I:



I

wherein:

X is selected from: -(C_{0-6}alkyl)-Y-(C_{0-6}alkyl)-,
-(C_{0-6}alkyl)-C_{3-8} cycloalkyl-(C_{0-6}alkyl)-,
C_{2-10} alkenyl, and C_{2-10} alkynyl,
where the alkyl is unsubstituted or substituted with 1-7 substituents where the substituents are independently selected from:
(a) halo,
(b) hydroxy,
(c) -O-C_{1-3}alkyl, and
(d) trifluoromethyl,

and where Y is selected from:
a single bond, -O-, -SO_2-, -NR^{10}-, -NR^{10}-SO_2-, -SO_2-NR^{10}-,
-S-, and -SO-,

and where R^{10} is independently selected from: hydrogen, C_{1-6} alkyl, benzyl, phenyl, and C_{1-6} alkyl-C_{3-6} cycloalkyl,
which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl;

R^1 is selected from:

(1) $-CO_2H$,
(2) $-NO_2$,
(3) -tetrazolyl,
(4) -hydroxyisoxazole,
(5) $-SO_2NH-(C_{0-3}$ alkyl)-R^9, wherein R^9 is independently selected from: hydrogen, C_{1-6} alkyl, C_{5-6} cycloalkyl, benzyl or phenyl, which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl, and
(6) $-P(O)(OH)_2$;

R^3 is selected from the group consisting of:
phenyl and heterocycle,
which is unsubstituted or substituted with 1-7 substituents where the substituents are independently selected from:
(a) halo,
(b) trifluoromethyl,
(c) hydroxy,
(d) C_{1-3}alkyl,
(e) $-O-C_{1-3}$alkyl,
(f) $-CO_2R^9$,
(g) $-NR^9R^{10}$, and
(h) $-CONR^9R^{10}$;

R^4, R^5 and R^6 are independently selected from:
hydrogen, C_{1-10} alkyl, C_{3-8} cycloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, phenyl, $-(C_{1-6}$ alkyl)-phenyl, $-(C_{1-6}$ alkyl)-C_{3-8} cycloalkyl, naphthyl, biphenyl, and heterocycle,
which is unsubstituted or substituted with 1-7 of R^{11} where R^{11} is independently selected from:
(a) halo,
(b) trifluoromethyl,
(c) hydroxy,
(d) C_{1-3}alkyl,
(e) $-O-C_{1-3}$alkyl,

(f) $-CO_2R^9$,

(g) $-NR^9R^{10}$, and

(h) $-CONR^9R^{10}$,

or where R^4 and R^5 may be joined together to form a 3-8 membered saturated ring which may be unsubstituted or substituted with 1-7 of R^{11},

or where R^5 and R^6 may be joined together to form a 3-8 membered saturated ring which may be unsubstituted or substituted with 1-7 of R^{11};

R^7 is selected from:

(1) hydrogen,

(2) C_{1-6}alkyl, which is unsubstituted or substituted with 1-4 substituents where the substituents are independently selected from: hydroxy, cyano, and halo,

(3) hydroxy, and

(4) halo;

R^8 is selected from:

hydrogen, C_{3-8} cycloalkyl, phenyl, naphthyl, biphenyl, and heterocycle, which is unsubstituted or substituted with 1-7 of R^{12} where R^{12} is independently selected from:

(a) halo,

(b) cyano,

(c) hydroxy,

(d) C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 of R^{13} where R^{13} is independently selected from: halo, cyano, hydroxy, C_{1-6}alkoxy, $-CO_2H$, $-CO_2(C_{1-6}$ alkyl), trifluoromethyl, and $-NR^9R^{10}$,

(e) $-O-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-5 of R^{13},

(f) $-CF_3$,

(g) $-CHF_2$,

(h) $-CH_2F$,

(i) $-NO_2$,

(j) C_{0-6}alkyl-phenyl or C_{0-6}alkyl-heterocycle, which is unsubstituted or substituted with 1-7 substituents where the substituents are independently selected from:

(i) halo,
(ii) hydroxy,
(iii) C_{1-6}alkyl,
(iv) -O-C_{1-6}alkyl,
(v) $-CF_3$,
(vi) $-OCF_3$,
(vii) $-NO_2$,
(viii) -CN,
(ix) $-SO_2-C_{1-6}$alkyl,
(x) $-CO_2R^9$,
(xi) $-NR^9R^{10}$,
(xii) $-CONR^9R^{10}$,
(xiii) $-SO_2-NR^9R^{10}$, and
(xiv) $-NR^9-SO_2-R^{10}$;

(k) $-CO_2R^9$,

(l) tetrazolyl,

(m) $-NR^9R^{10}$,

(n) $-NR^9-COR^{10}$,

(o) $-NR^9-CO_2R^{10}$,

(p) $-CO-NR^9R^{10}$,

(q) $-OCO-NR^9R^{10}$,

(r) $-NR^9CO-NR^9R^{10}$,

(s) $-S(O)_m-R^9$, wherein m is an integer selected from 0, 1 and 2,

(t) $-S(O)_2-NR^9R^{10}$,

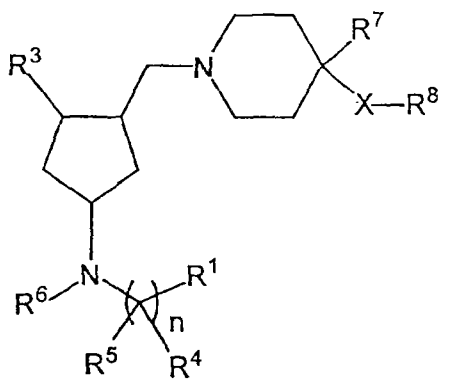
(u) $-NR^9S(O)_2-R^{10}$, and

(v) $-NR^9S(O)_2-NR^9R^{10}$;

n is an integer selected from 1, 2, 3 and 4;
x is an integer selected from 0, 1 and 2, and y is an integer selected from 0, 1 and 2, with the proviso that the sum of x and y is 2;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

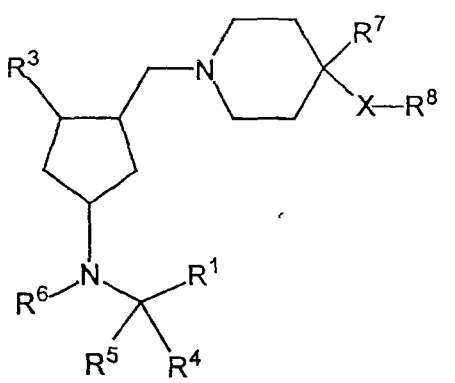
Preferred compounds of the present invention include those of formula Ia:



Ia

wherein R^1, R^3, R^4, R^5, R^6, R^7, R^8, X and n are defined herein;
and pharmaceutically acceptable salts and individual diastereomers thereof.

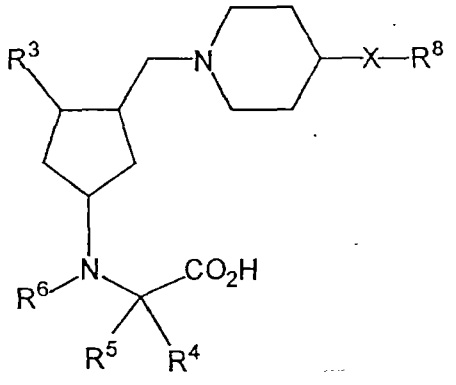
More preferred compounds of the present invention include those of formula Ic:



Ic

wherein R^1, R^3, R^4, R^5, R^6, R^7, R^8 and X are defined herein;
and pharmaceutically acceptable salts and individual diastereomers thereof.

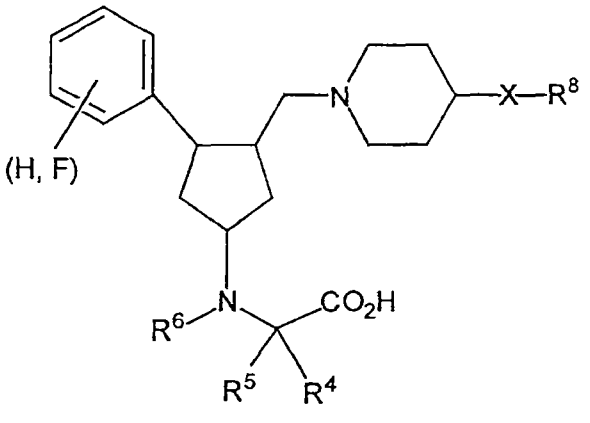
Highly preferred compounds of the present invention include those of formula Id:



Id

wherein R^3, R^4, R^5, R^6, R^8 and X are defined herein;
and pharmaceutically acceptable salts and individual diastereomers thereof.

More highly preferred compounds of the present invention include those of formula Ie:



Ie

wherein R^4, R^5, R^6, R^8 and X are defined herein;
and pharmaceutically acceptable salts and individual diastereomers thereof.

In the present invention it is preferred that R^1 is selected from:

(1) $-CO_2H$,

(2) $-P(O)(OH)_2$, and

(3) -tetrazolyl.

In the present invention it is more preferred that R^1 is selected from:

(1) $-CO_2H$, and

(2) -tetrazolyl.

In the present invention it is even more preferred that R^1 is $-CO_2H$.

In the present invention it is preferred that R^3 is selected from the group consisting of:

phenyl and thienyl,

which may be unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from:

(a) halo,

(b) trifluoromethyl,

(c) hydroxy,

(d) C_{1-3}alkyl, and

(e) $-O-C_{1-3}$alkyl.

In the present invention it is more preferred that R^3 is selected from the group consisting of:

phenyl and thienyl,

which may be unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from:

(a) fluoro,

(b) chloro,

(c) trifluoromethyl,

(d) hydroxy, and

(e) C_{1-3}alkyl.

In the present invention it is even more preferred that R^3 is selected from the group consisting of:

phenyl, which may be unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from:

(a) fluoro, and

(b) chloro; and

unsubstituted thienyl.

In the present invention it is still more preferred that R^3 is unsubstituted phenyl, (3-fluoro)phenyl or 3-thienyl.

In the present invention it is preferred that R^4 is hydrogen or C_{1-6} alkyl.

In the present invention it is more preferred that R^4 is hydrogen.

In the present invention it is preferred that R^5 is selected from: hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkyl-C_{3-8} cycloalkyl, and phenyl.

In the present invention it is more preferred that R^5 is selected from: hydrogen, methyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, -CH_2-cyclopropyl, -CH_2-cyclobutyl, and phenyl.

In the present invention it is still more preferred that R^5 is selected from: isopropyl, isobutyl, sec-butyl, and cyclohexyl.

In the present invention it is preferred that R^6 is selected from: hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkyl-C_{3-8} cycloalkyl, and phenyl.

In the present invention it is more preferred that R^6 is selected from: hydrogen, methyl, n-butyl, t-butyl, isobutyl, sec-butyl, -CH_2-cyclopropyl, -CH_2-cyclobutyl, and cyclohexyl.

In the present invention it is still more preferred that R^6 is selected from: hydrogen, methyl, -CH_2-cyclopropyl, -CH_2-cyclobutyl, and cyclohexyl.

In an alternate embodiment of the present invention it is preferred that R^5 and R^6 are joined together to form a C_{3-8} cycloalkyl ring.

In an alternate embodiment of the present invention it is more preferred that R^5 and R^6 are joined together to form a pyrrolidine ring.

In the present invention it is preferred that R^7 is hydrogen, fluoro, hydroxy or C_{1-6} alkyl.

In the present invention it is more preferred that R^7 is hydrogen or fluoro.

In the present invention it is even more preferred that R^7 is hydrogen.

In the present invention it is preferred that X is: $-(C_{0-4}alkyl)-Y-(C_{0-4}alkyl)-$,

where the alkyl is unsubstituted or substituted with 1-4 substituents where the substituents are independently selected from:

(a) halo,

(b) hydroxy,

(c) $-O-C_{1-3}alkyl$, and

(d) trifluoromethyl,

and where Y is selected from:

a single bond, -O-, $-SO_2-$, $-NR^{10}-$, -S-, and -SO-,

and where R^{10} is independently selected from: hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, benzyl, phenyl, and C_{1-6} alkyl-C_{3-6} cycloalkyl, which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl.

In the present invention it is more preferred that X is: $-(C_{0-2}alkyl)-Y-(C_{0-2}alkyl)-$,

where the alkyl is unsubstituted or substituted with 1-4 substituents where the substituents are independently selected from:

(a) halo,

(b) hydroxy,

(c) $-O-C_{1-3}alkyl$, and

(d) trifluoromethyl,

and where Y is selected from:

a single bond, -O-, $-SO_2-$, $-NR^{10}-$, -S-, and -SO-,

where R^{10} is independently selected from: hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, benzyl, phenyl, and C_{1-6} alkyl-C_{3-6} cycloalkyl, which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl.

In the present invention it is even more preferred that X is selected from:

-(C_{0-2}alkyl)-Y-(C_{0-2}alkyl)-, where the alkyl is unsubstituted or substituted with fluoro,

and where Y is selected from:

a single bond, $-SO_2-$, -SO-, and $-NR^{10}-$,

where R^{10} is independently selected from: hydrogen, C_{1-3} alkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl.

In the present invention it is still more preferred that X is selected from:

(1) a single bond,
(2) $-CH_2CH_2-$,
(3) $-CH_2CH_2CH_2-$,
(4) $-CH_2CH_2-CF_2-$,
(5) $-CH_2CH_2-SO_2-$, and
(6) $-CH_2CH_2-SO-$.

In the present invention it is preferred that R^8 is selected from: phenyl, naphthyl, cyclohexyl, benzoimidazolyl, benzofurazanyl, imidazopyridyl, imidazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidyl, thiazolyl and tetrazolopyridyl,

which is unsubstituted or substituted with 1-7 substituents where the substituents are independently selected from:

(a) halo,
(b) cyano,
(c) hydroxy,

(d) C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 of R^{13} where R^{13} is independently selected from: halo, cyano, hydroxy, C_{1-6}alkoxy, $-CO_2H$, $-CO_2(C_{1-6}$ alkyl), trifluoromethyl, and $-NR^9R^{10}$, wherein R^9 and R^{10} are independently selected from: hydrogen, C_{1-6} alkyl, C_{5-6} cycloalkyl, benzyl or phenyl, which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl;

(e) $-O-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-5 of R^{13},

(f) $-CF_3$,

(g) $-CHF_2$,

(h) $-CH_2F$,

(i) $-NO_2$,

(j) C_{0-6}alkyl-phenyl or C_{0-6}alkyl-heterocycle, which is unsubstituted or substituted with 1-7 substituents where the substituents are independently selected from:

(i) halo,
(ii) hydroxy,
(iii) C_{1-6}alkyl,
(iv) $-O-C_{1-6}$alkyl,
(v) $-CF_3$,
(vi) $-OCF_3$,
(vii) $-NO_2$,
(viii) $-CN$,
(ix) $-SO_2-C_{1-6}$alkyl,
(x) $-CO_2R^9$,
(xi) $-NR^9R^{10}$,
(xii) $-CONR^9R^{10}$,
(xiii) $-SO_2-NR^9R^{10}$, and
(xiv) $-NR^9-SO_2-R^{10}$;

(k) $-CO_2R^9$,

(l) tetrazolyl,

(m) $-NR^9R^{10}$,

(n) $-NR^9-COR^{10}$,
(o) $-NR^9-CO_2R^{10}$,
(p) $-CO-NR^9R^{10}$,
(q) $-OCO-NR^9R^{10}$,
(r) $-NR^9CO-NR^9R^{10}$,
(s) $-S(O)_m-R^9$, wherein m is an integer selected from 0, 1 and 2,
(t) $-S(O)_2-NR^9R^{10}$,
(u) $-NR^9S(O)_2-R^{10}$, and
(v) $-NR^9S(O)_2-NR^9R^{10}$.

In the present invention it is more preferred that R^8 is selected from: phenyl, imidazopyridyl, imidazolyl, oxazolyl, pyrazolyl, pyridyl, and thiazolyl;

which is unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from:

(a) halo,
(b) cyano,
(c) $-NO_2$,
(d) $-CF_3$,
(e) $-CHF_2$,
(f) $-CH_2F$,
(h) C_{1-6}alkyl,
(i) C_{1-3}alkyl-phenyl or C_{1-3}alkyl-pyridyl, which is unsubstituted or substituted with 1-4 substituents where the substituents are independently selected from:
  (i) halo,
  (ii) C_{1-6}alkyl,
  (iii) $-O-C_{1-6}$alkyl,
  (iv) $-CF_3$,
  (vi) $-OCF_3$,
  (vii) -CN, and
(j) $-O-C_{1-6}$alkyl.

In the present invention it is even more preferred that R^8 is selected from: imidazolyl, oxazolyl, pyrazolyl, and thiazolyl;

which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from:

(a) fluoro,
(b) cyano,
(c) C_{1-3}alkyl,
(d) $-CH_2$-phenyl, which is unsubstituted or substituted with 1-4 substituents where the substituents are independently selected from:
  (i) fluoro,
  (ii) chloro,
  (iii) $-O-CH_3$,
  (iv) $-CF_3$,
  (v) -CN, and
(e) $-CF_3$.

In the present invention it is still more preferred that R^8 is selected from: 5-(3-benzyl)pyrazolyl, 5-(1-methyl-3-benzyl)pyrazolyl, 5-(1-ethyl-3-benzyl)pyrazolyl, 5-(2-benyl)thiazolyl, 5-(2-benyl-4-methyl)thiazolyl, and 5-(2-benyl-4-ethyl)thiazolyl).

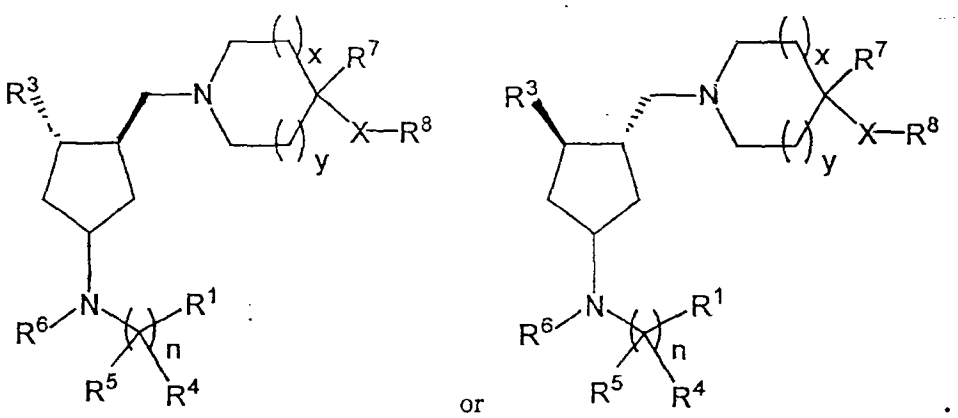
In the present invention it is preferred that n is an integer selected from 1, 2 and 3.

In the present invention it is more preferred that n is an integer which is 1.

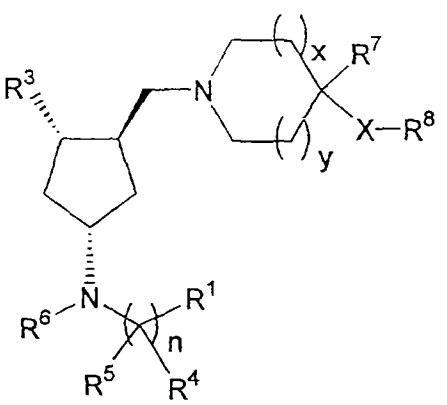
In the present invention it is preferred that x is an integer which is 1 and y is an integer which is 1.

The compounds of the instant invention have at least two asymmetric centers at the ring junction of the substitutents bearing the piperidine and R^3. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified

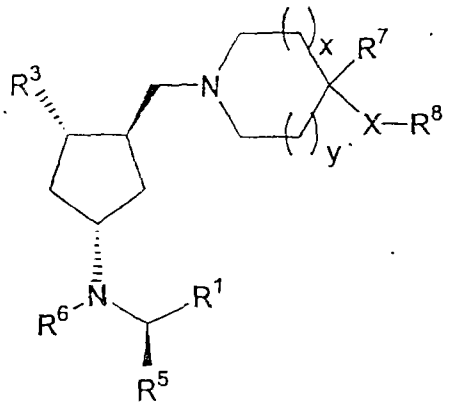
compounds are included within the ambit of this invention. The relative configurations of the more preferred compounds of this invention are of the trans orientation, i.e. as depicted:



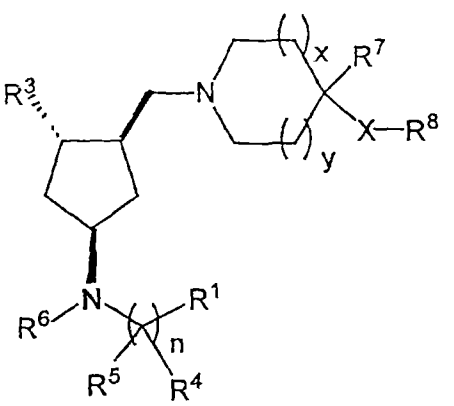
The relative configurations of the even more preferred compounds of this invention wherein R^6 is hydrogen, methyl or wherein R^5 and R^6 form a pyrrolidine ring with respect to the configuration of the nitrogen substituent on the cyclopentane ring is cis to the orientation of R^3 as depicted:



The relative configurations of the most preferred compounds of this invention wherein R^6 is hydrogen or methyl with respect to the configuration of the nitrogen substituent on the cyclopentane ring is is cis to the orientation of R^3 and with the (R)-stereochemistry of the nitrogen side chain of the orientation as depicted:



The relative configurations of the even more preferred compounds of this invention wherein R^6 is other than hydrogen or methyl with respect to the configuration of the nitrogen substituent on the cyclopentane ring is 1,3-cis of the orientation as depicted:

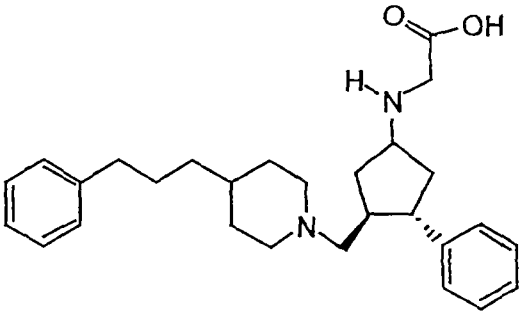


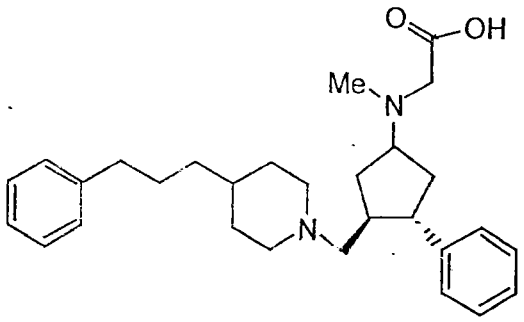
The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

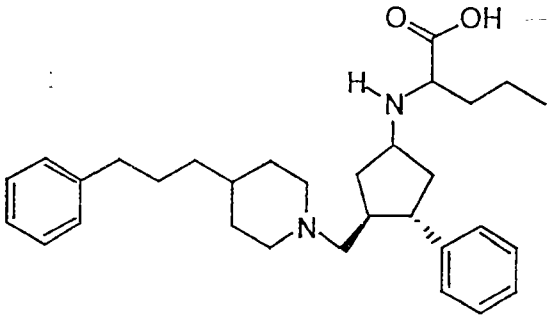
As appreciated by those of skill in the art, halo or halogen as used herein are intended to include chloro, fluoro, bromo and iodo. Similarly, C_{1-8}, as in C_{1-8}alkyl is defined to identify the group as having 1, 2, 3, 4, 5, 6, 7 or 8 carbons in a

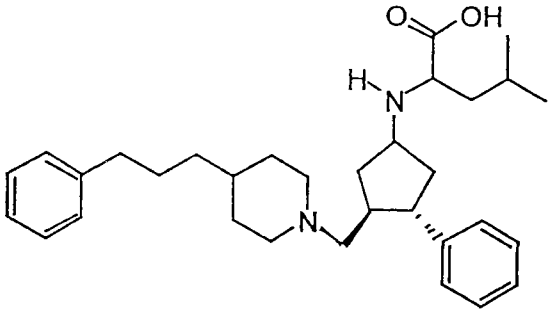
linear or branched arrangement, such that C_{1-8}alkyl specifically includes methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl and octyl. Likewise, C_0, as in C_0alkyl is defined to identify the presence of a direct covalent bond. The term "heterocycle" as used herein is intended to include the following groups: benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof. Exemplifying the invention is the use of the compounds disclosed in the Examples and herein.

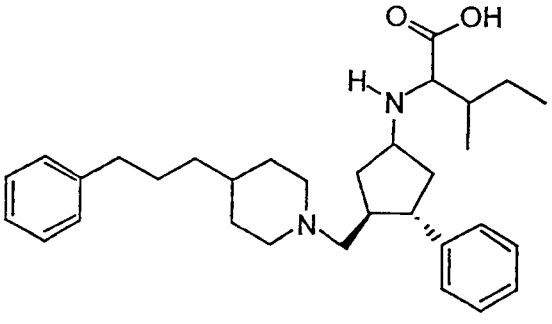
Specific compounds within the present invention include a compound which selected from the group consisting of:





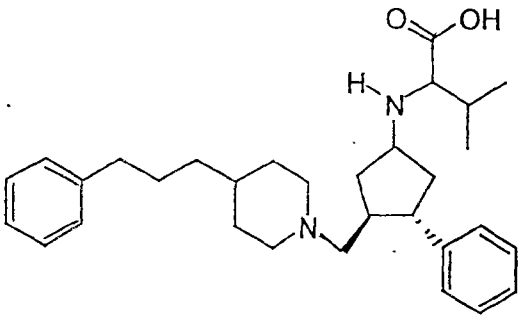


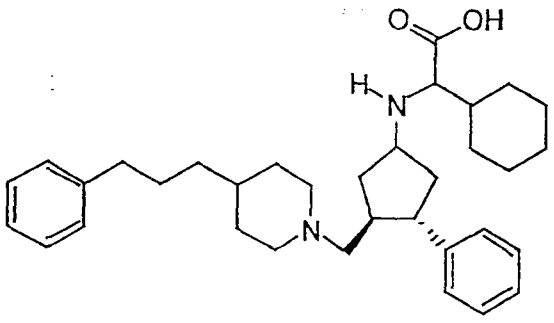


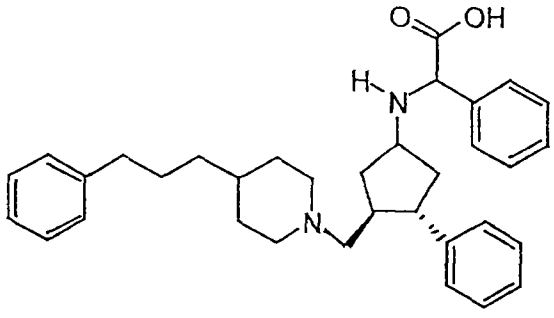


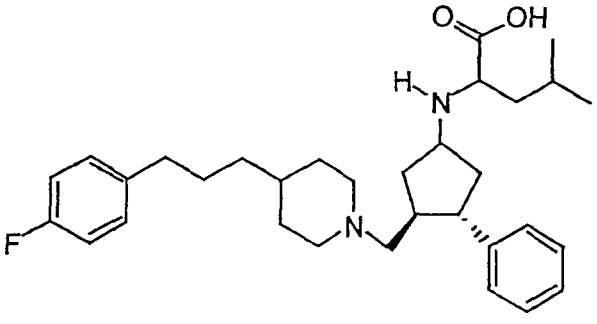
09-11-99 09:44 99 09 4 09 09 09 09

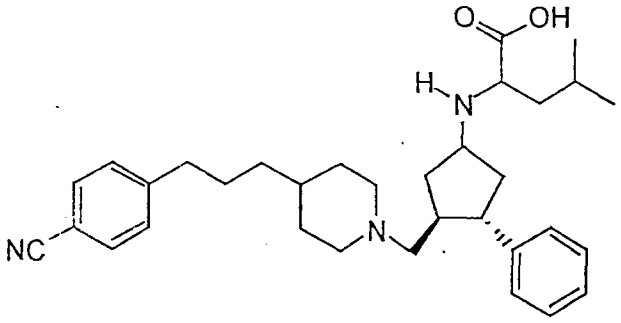
5

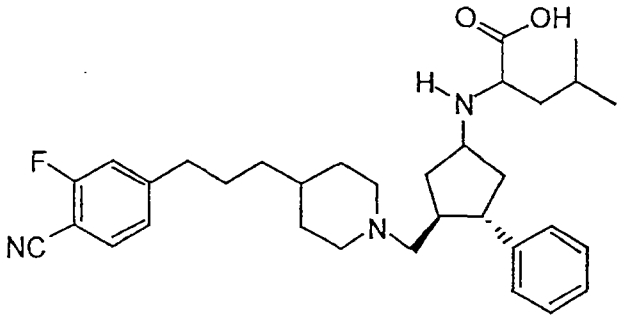


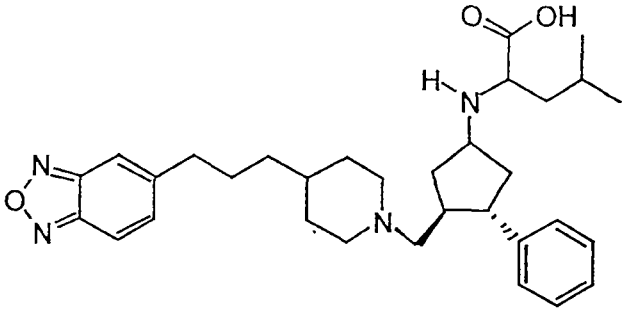


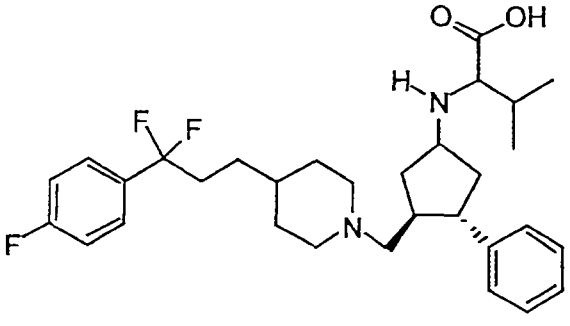




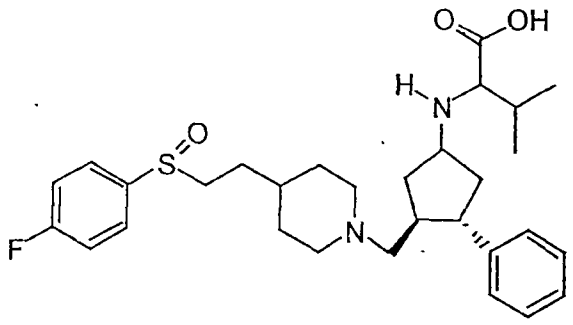


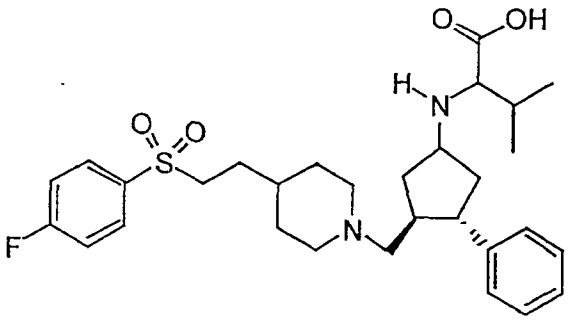


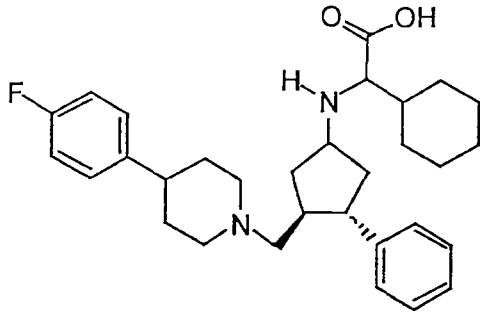


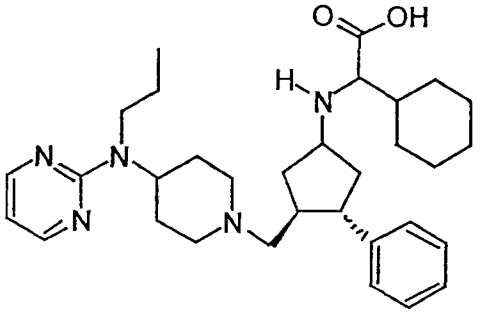


SUBSTITUTE SHEET (RULE 26)



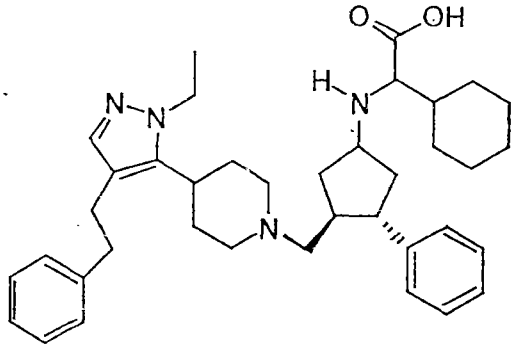


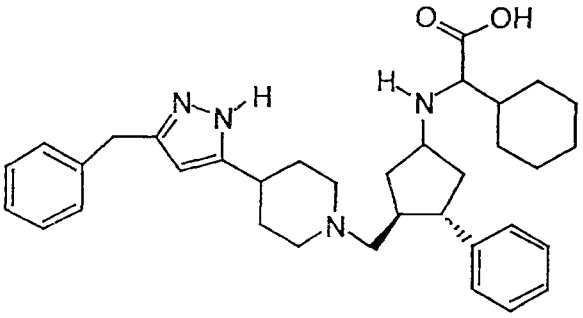


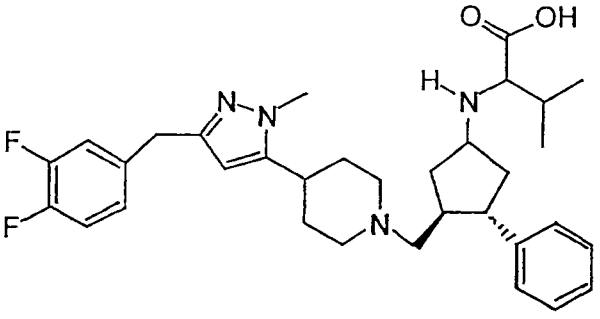


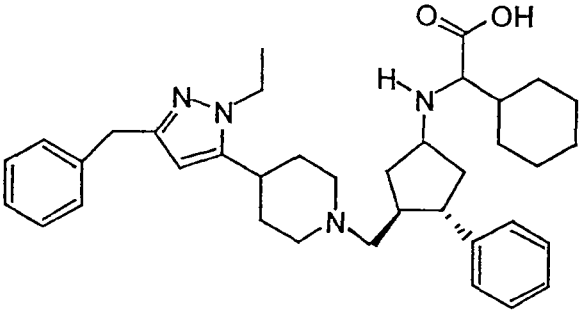
CLAIMS AMENDED

5

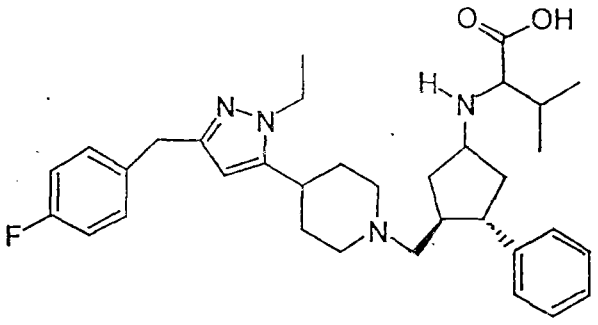


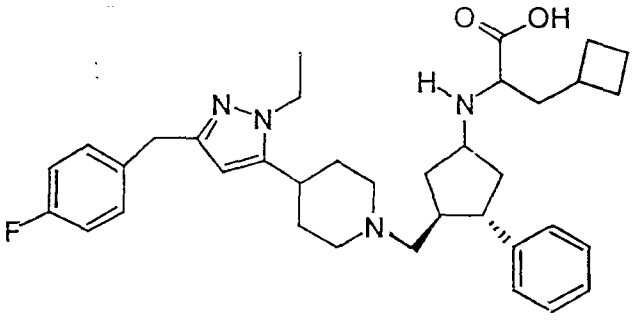


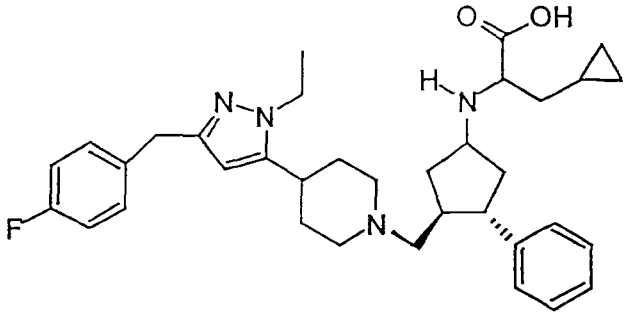


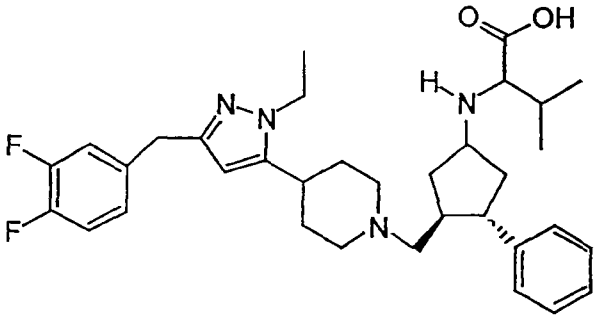


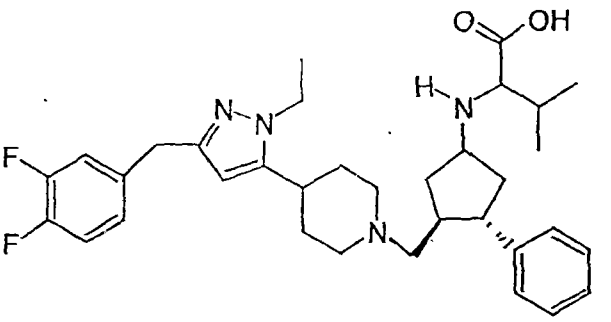
05 14 05 09 14 05 09 05 09

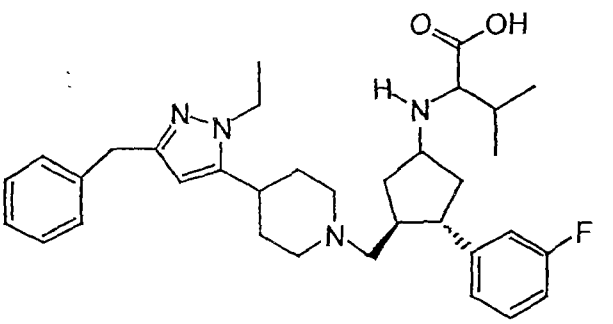


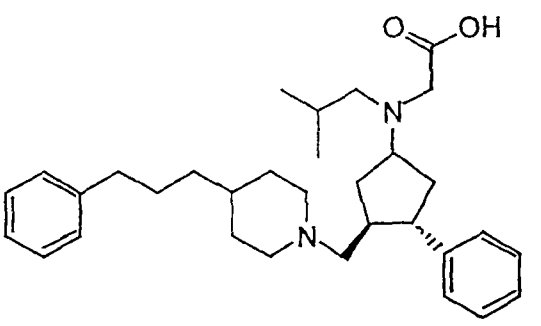


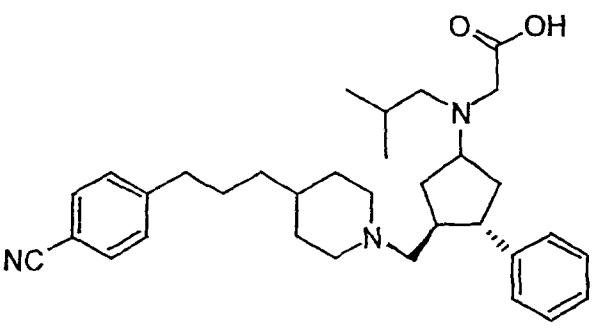


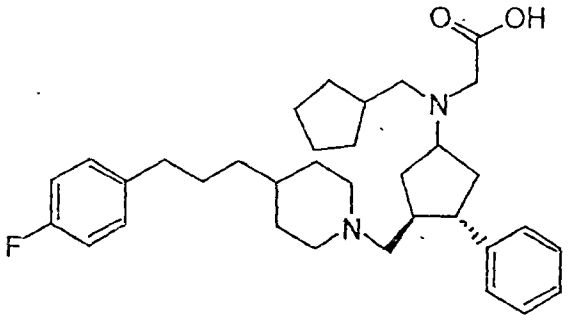


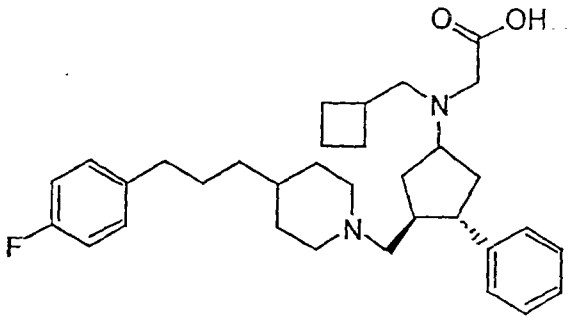


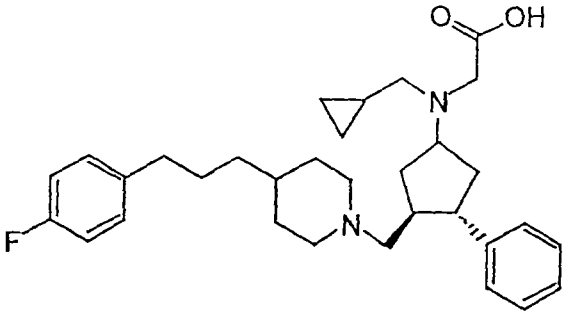




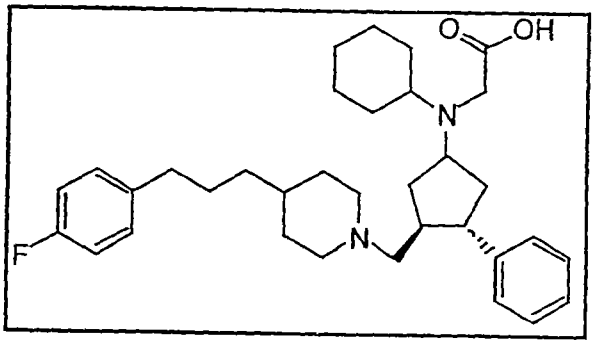


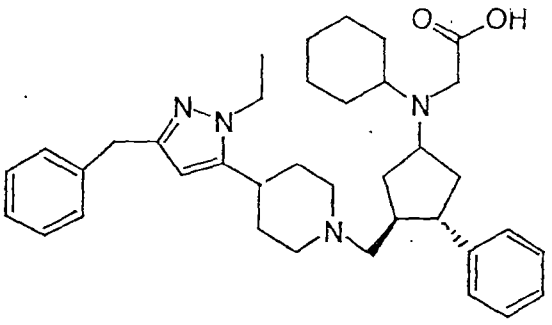


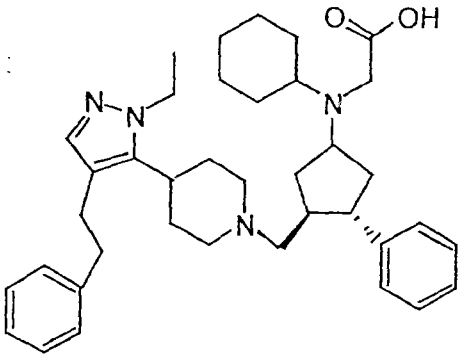


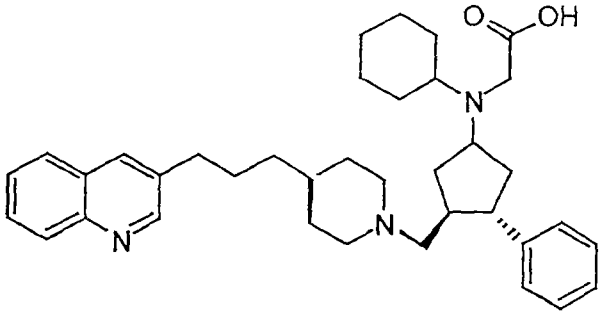


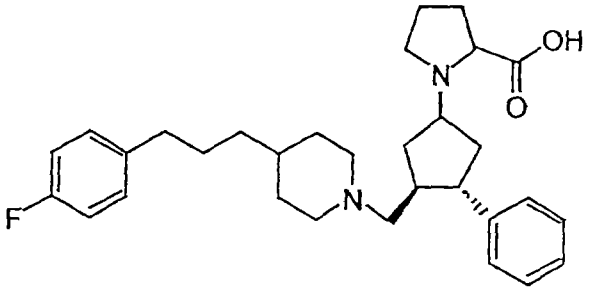
5

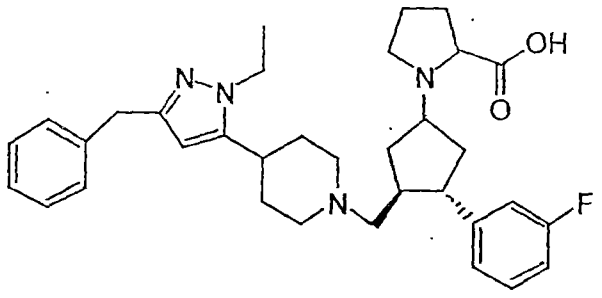


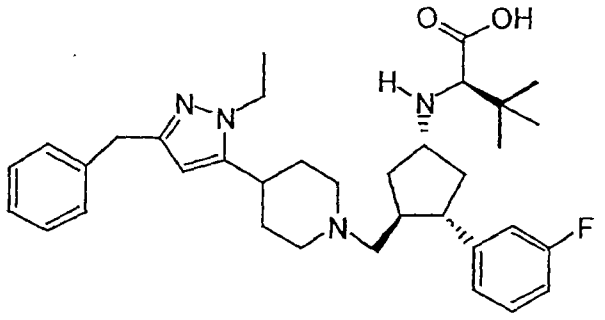


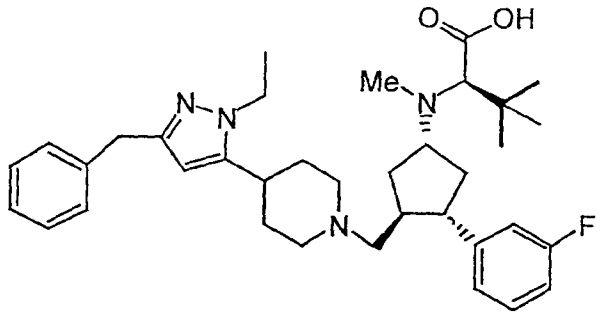


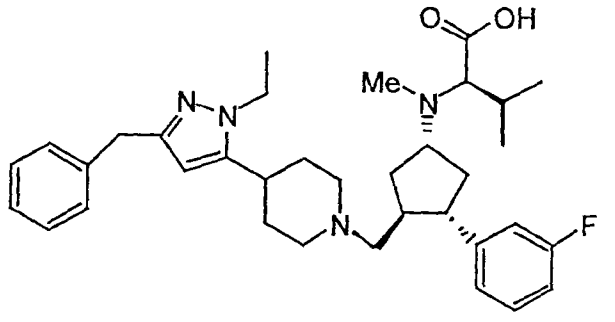


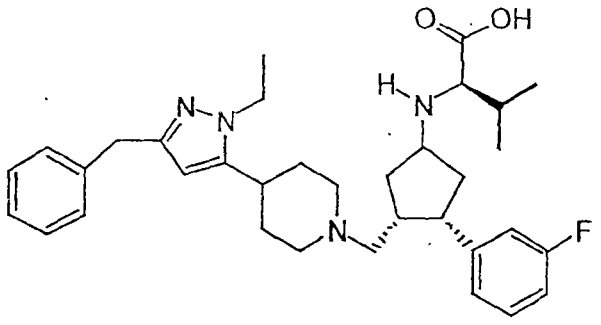


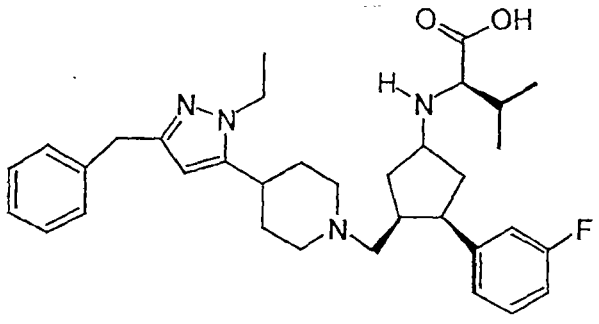


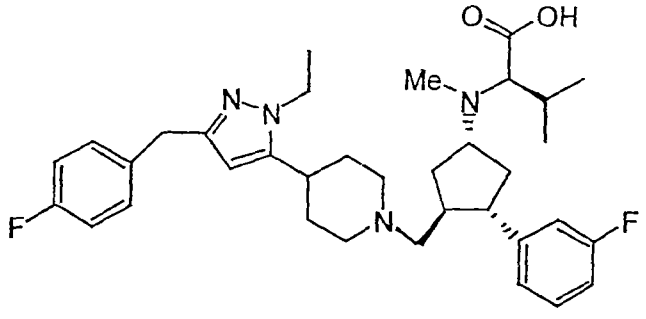


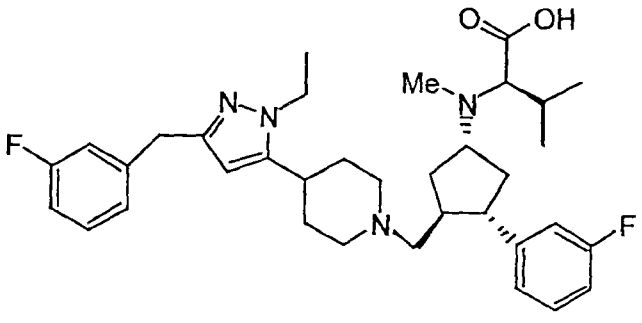


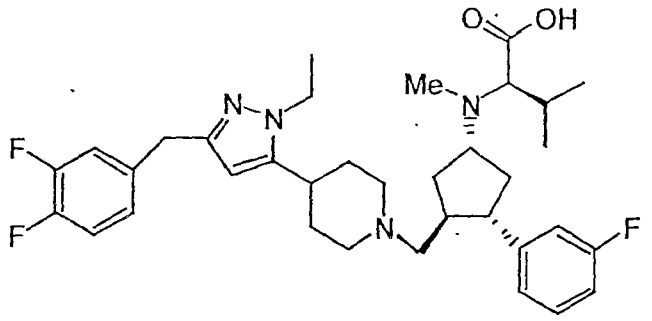


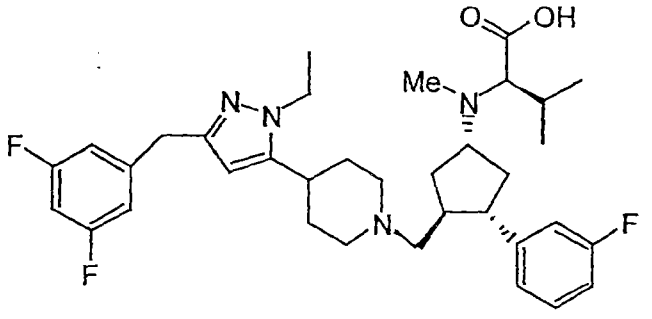


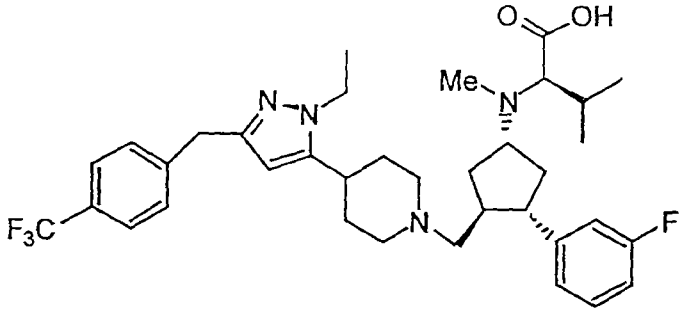


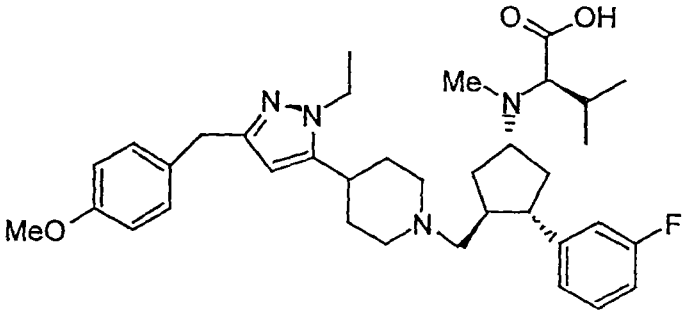








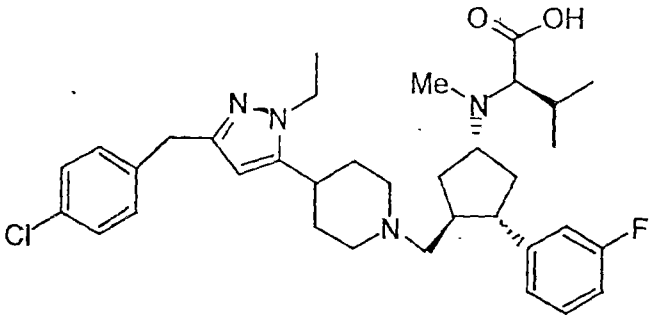


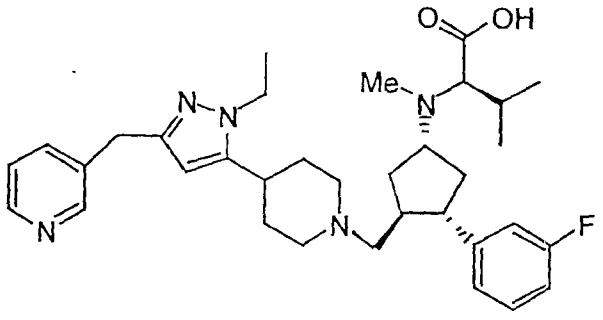


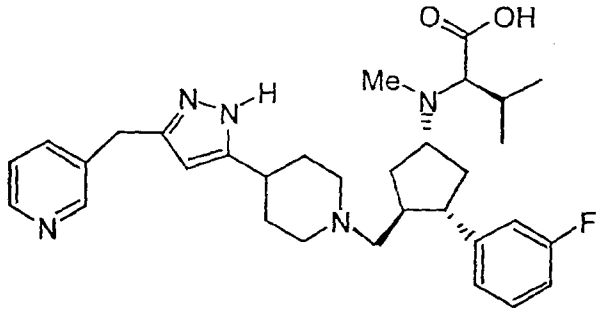
EP 1 950 209 A1

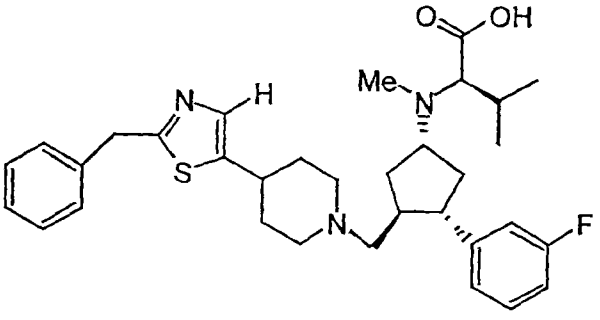
5

804

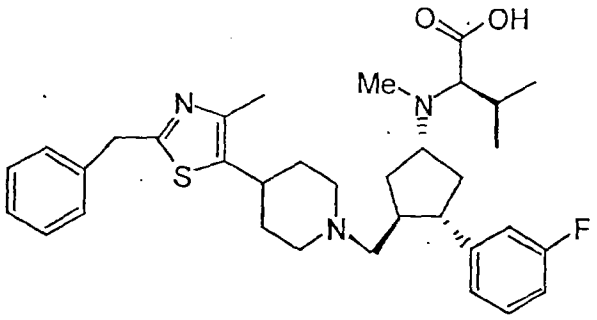


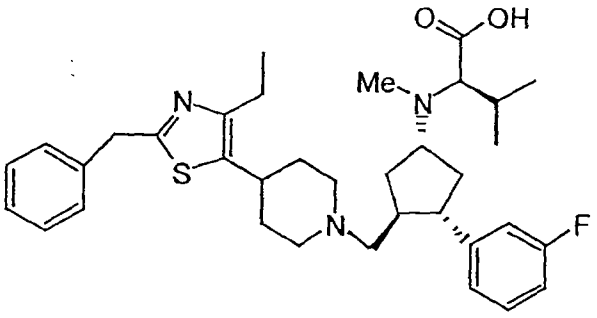


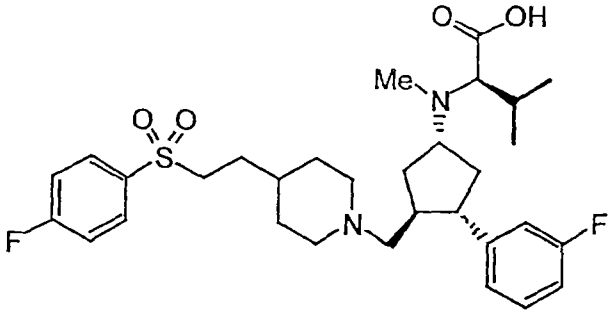


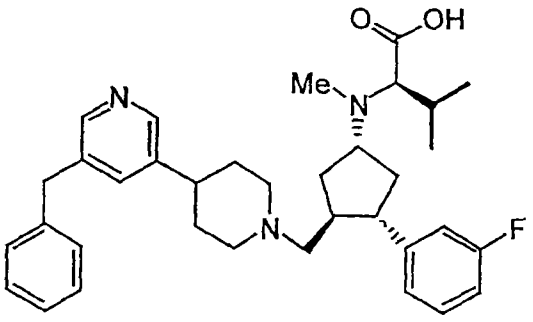


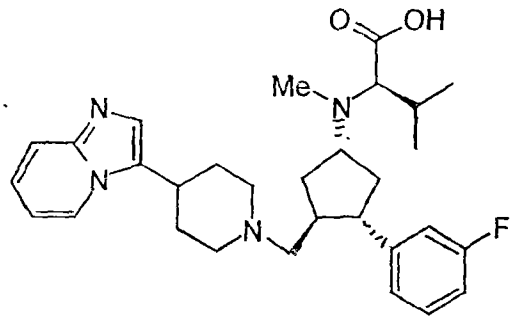
60754503.1 20461PV











and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

The subject compounds are useful in a method of modulating chemokine receptor activity in a patient in need of such modulation comprising the administration of an effective amount of the compound.

The present invention is directed to the use of the foregoing compounds as modulators of chemokine receptor activity. In particular, these compounds are useful as modulators of the chemokine receptors, including CCR-5 and/or CCR-3.

The utility of the compounds in accordance with the present invention as modulators of chemokine receptor activity may be demonstrated by methodology known in the art, such as the assay for chemokine binding as disclosed by Van Riper, et al., J. Exp. Med., 177, 851-856 (1993) which may be readily adapted for measurement of CCR-5 binding, and the assay for CCR-3 binding as disclosed by Daugherty, et al., J. Exp. Med., 183, 2349-2354 (1996). Cell lines for expressing the receptor of interest include those naturally expressing the receptor, such as EOL-3 or THP-1, or a cell engineered to express a recombinant receptor, such as CHO, RBL-2H3, HEK-293. For example, a CCR3 transfected AML14.3D10 cell line has been placed on restricted deposit with American Type Culture Collection in Rockville, Maryland as ATCC No. CRL-12079, on April 5, 1996. The utility of the compounds in accordance with the present invention as inhibitors of the spread of HIV infection in cells may be demonstrated by methodology known in the art, such as the HIV quantitation assay disclosed by Nunberg, et al., J. Virology, 65 (9), 4887-4892 (1991).

In particular, the compounds of the following examples had activity in binding to the CCR-5 or the CCR-3 receptor in the aforementioned assays, generally with an IC_{50} of less than about 1 μM. Such a result is indicative of the intrinsic activity of the compounds in use as modulators of chemokine receptor activity.

Mammalian chemokine receptors provide a target for interfering with or promoting eosinophil and/or lymphocyte function in a mammal, such as a human. Compounds which inhibit or promote chemokine receptor function, are particularly useful for modulating eosinophil and/or lymphocyte function for therapeutic purposes. Accordingly, the present invention is directed to compounds which are useful in the prevention and/or treatment of a wide variety of inflammatory and immunoregulatory disorders and diseases, allergic diseases, atopic conditions including allergic rhinitis, dermatitis, conjunctivitis, and asthma, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis.

For example, an instant compound which inhibits one or more functions of a mammalian chemokine receptor (e.g., a human chemokine receptor) may be administered to inhibit (i.e., reduce or prevent) inflammation. As a result, one or more inflammatory processes, such as leukocyte emigration, chemotaxis, exocytosis (e.g., of enzymes, histamine) or inflammatory mediator release, is inhibited. For example, eosinophilic infiltration to inflammatory sites (e.g., in asthma) can be inhibited according to the present method.

Similarly, an instant compound which promotes one or more functions of a mammalian chemokine receptor (e.g., a human chemokine) is administered to stimulate (induce or enhance) an inflammatory response, such as leukocyte emigration, chemotaxis, exocytosis (e.g., of enzymes, histamine) or inflammatory mediator release, resulting in the beneficial stimulation of inflammatory processes. For example, eosinophils can be recruited to combat parasitic infections.

In addition to primates, such as humans, a variety of other mammals can be treated according to the method of the present invention. For instance, mammals including, but not limited to, cows, sheep, goats, horses, dogs, cats, guinea pigs, rats or other bovine, ovine, equine, canine, feline, rodent or murine species can be treated. However, the method can also be practiced in other species, such as avian species (e.g., chickens).

Diseases and conditions associated with inflammation and infection can be treated using the method of the present invention. In a preferred embodiment, the disease or condition is one in which the actions of eosinophils and/or lymphocytes are to be inhibited or promoted, in order to modulate the inflammatory response.

Diseases or conditions of humans or other species which can be treated with inhibitors of chemokine receptor function, include, but are not limited to: inflammatory or allergic diseases and conditions, including respiratory allergic

diseases such as asthma, particularly bronchial asthma, allergic rhinitis, hypersensitivity lung diseases, hypersensitivity pneumonitis, eosinophilic pneumonias (e.g., Loeffler's syndrome, chronic eosinophilic pneumonia), delayed-type hypersentitivity, interstitial lung diseases (ILD) (e.g., idiopathic pulmonary fibrosis, or ILD associated with rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, systemic sclerosis, Sjogren's syndrome, polymyositis or dermatomyositis); systemic anaphylaxis or hypersensitivity responses, drug allergies (e.g., to penicillin, cephalosporins), insect sting allergies; autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus, myasthenia gravis, juvenile onset diabetes; glomerulonephritis, autoimmune thyroiditis, Behcet's disease; graft rejection (e.g., in transplantation), including allograft rejection or graft-versus-host disease; inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis; spondyloarthropathies; scleroderma; psoriasis (including T-cell mediated psoriasis) and inflammatory dermatoses such an dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria; vasculitis (e.g., necrotizing, cutaneous, and hypersensitivity vasculitis); eosinphilic myositis, eosinophilic fasciitis; cancers with leukocyte infiltration of the skin or organs. Other diseases or conditions in which undesirable inflammatory responses are to be inhibited can be treated, including, but not limited to, reperfusion injury, atherosclerosis, certain hematologic malignancies, cytokine-induced toxicity (e.g., septic shock, endotoxic shock), polymyositis, dermatomyositis.

Diseases or conditions of humans or other species which can be treated with promoters of chemokine receptor function, include, but are not limited to: immunosuppression, such as that in individuals with immunodeficiency syndromes such as AIDS, individuals undergoing radiation therapy, chemotherapy, therapy for autoimmune disease or other drug therapy (e.g., corticosteroid therapy), which causes immunosuppression; immunosuppression due congenital deficiency in receptor function or other causes; and infectious diseases, such as parasitic diseases, including, but not limited to helminth infections, such as nematodes (round worms); (Trichuriasis, Enterobiasis, Ascariasis, Hookworm, Strongyloidiasis, Trichinosis, filariasis); trematodes (flukes) (Schistosomiasis, Clonorchiasis), cestodes (tape worms) (Echinococcosis, Taeniasis saginata, Cysticercosis); visceral worms, visceral larva migrans (e.g., Toxocara), eosinophilic gastroenteritis (e.g., Anisaki spp., *Phocanema ssp.),* cutaneous larva migrans (*Ancylostona braziliense, Ancylostoma caninum*).

The compounds of the present invention are accordingly useful in the prevention and treatment of a wide variety of inflammatory and immunoregulatory disorders and diseases, allergic conditions, atopic conditions, as well as autoimmune pathologies.

In another aspect, the instant invention may be used to evaluate putative specific agonists or antagonists of chemokine receptors, including CCR-5 and/or CCR-3. Accordingly, the present invention is directed to the use of these compounds in the preparation and execution of screening assays for compounds which modulate the activity of chemokine receptors. For example, the compounds of this invention are useful for isolating receptor mutants, which are excellent screening tools for more potent compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other compounds to chemokine receptors, e.g., by competitive inhibition. The compounds of the instant invention are also useful for the evaluation of putative specific modulators of the chemokine receptors, including CCR-5 and/or CCR-3. As appreciated in the art, thorough evaluation of specific agonists and antagonists of the above chemokine receptors has been hampered by the lack of availability of non-peptidyl (metabolically resistant) compounds with high binding affinity for these receptors. Thus the compounds of this invention are commercial products to be sold for these purposes.

The present invention is further directed to a method for the manufacture of a medicament for modulating chemokine receptor activity in humans and animals comprising combining a compound of the present invention with a pharmaceutical carrier or diluent.

The present invention is further directed to the use of these compounds in the prevention or treatment of infection by a retrovirus, in particular, the human immunodeficiency virus (HIV) and the treatment of, and delaying of the onset of consequent pathological conditions such as AIDS. Treating AIDS or preventing or treating infection by HIV is defined as including, but not limited to, treating a wide range of states of HIV infection: AIDS, ARC (AIDS related complex), both symptomatic and asymptomatic, and actual or potential exposure to HIV. For example, the compounds of this invention are useful in treating infection by HIV after suspected past exposure to HIV by, e.g., blood transfusion, organ transplant, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

810

In a preferred aspect of the present invention, a subject compound may be used in a method of inhibiting the binding of a chemokine to a chemokine receptor, such as CCR-5 or CCR-3, of a target cell, which comprises contacting the target cell with an amount of the compound which is effective at inhibiting the binding of the chemokine to the chemokine receptor.

The subject treated in the methods above is a mammal, preferably a human being, male or female, in whom modulation of chemokine receptor activity is desired. "Modulation" as used herein is intended to encompass antagonism, agonism, partial antagonism, inverse agonism and/or partial agonism. In a preferred aspect of the present invention, modulation refers to antagonism of chemokine receptor activity. The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention to the individual in need of treatment.

Combined therapy to modulate chemokine receptor activity and thereby prevent and treat inflammatory and immunoregulatory disorders and diseases, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis, and those pathologies noted above is illustrated by the combination of the compounds of this invention and other compounds which are known for such utilities.

For example, in the treatment or prevention of inflammation, the present compounds may be used in conjunction with an antiinflammatory or analgesic agent such as an opiate agonist, a lipoxygenase inhibitor, such as an inhibitor of 5-lipoxygenase, a cyclooxygenase inhibitor, such as a cyclooxygenase-2 inhibitor, an interleukin inhibitor, such as an interleukin-1 inhibitor, an NMDA antagonist, an inhibitor of nitric oxide or an inhibitor of the synthesis of nitric oxide, a non-steroidal

antiinflammatory agent, or a cytokine-suppressing antiinflammatory agent, for example with a compound such as acetaminophen, asprin, codiene, fentanyl, ibuprofen, indomethacin, ketorolac, morphine, naproxen, phenacetin, piroxicam, a steroidal analgesic, sufentanyl, sunlindac, tenidap, and the like. Similarly, the instant compounds may be administered with a pain reliever; a potentiator such as caffeine, an H2-antagonist, simethicone, aluminum or magnesium hydroxide; a decongestant such as phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxy-ephedrine; an antiitussive such as codeine, hydrocodone, caramiphen, carbetapentane, or dextramethorphan; a diuretic; and a sedating or non-sedating antihistamine. Likewise, compounds of the present invention may be used in combination with other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which compounds of the pressent invention are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention. Examples of other active ingredients that may be combined with a compound of the present invention, either administered separately or in the same pharmaceutical compositions, include, but are not limited to: (a) VLA-4 antagonists such as those described in US 5,510,332, WO95/15973, WO96/01644, WO96/06108, WO96/20216, WO96/22966, WO96/31206, WO96/40781, WO97/03094, WO97/02289, WO 98/42656, WO98/53814, WO98/53817, WO98/53818, WO98/54207, and WO98/58902; (b) steroids such as beclomethasone, methylprednisolone, betamethasone, prednisone, dexamethasone, and hydrocortisone; (c) immunosuppressants such as cyclosporin, tacrolimus, rapamycin and other FK-506 type immunosuppressants; (d) antihistamines (H1-histamine antagonists) such as bromopheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripelennamine, hydroxyzine, methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, antazoline, pheniramine pyrilamine, astemizole, terfenadine, loratadine, cetirizine, fexofenadine, descarboethoxyloratadine, and the like; (e) non-steroidal anti-asthmatics such as β2-

agonists (terbutaline, metaproterenol, fenoterol, isoetharine, albuterol, bitolterol, and pirbuterol), theophylline, cromolyn sodium, atropine, ipratropium bromide, leukotriene antagonists (zafirlukast, montelukast, pranlukast, iralukast, pobilukast, SKB-106,203), leukotriene biosynthesis inhibitors (zileuton, BAY-1005); (f) non-steroidal antiinflammatory agents (NSAIDs) such as propionic acid derivatives (alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, pirprofen, pranoprofen, suprofen, tiaprofenic acid, and tioxaprofen), acetic acid derivatives (indomethacin, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin, and zomepirac), fenamic acid derivatives (flufenamic acid, meclofenamic acid, mefenamic acid, niflumic acid and tolfenamic acid), biphenylcarboxylic acid derivatives (diflunisal and flufenisal), oxicams (isoxicam, piroxicam, sudoxicam and tenoxican), salicylates (acetyl salicylic acid, sulfasalazine) and the pyrazolones (apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone, phenylbutazone); (g) cyclooxygenase-2 (COX-2) inhibitors; (h) inhibitors of phosphodiesterase type IV (PDE-IV); (i) other antagonists of the chemokine receptors, especially CCR-1, CCR-2, CCR-3 and CCR-5; (j) cholesterol lowering agents such as HMG-CoA reductase inhibitors (lovastatin, simvastatin and pravastatin, fluvastatin, atorvastatin, and other statins), sequestrants (cholestyramine and colestipol), nicotinic acid, fenofibric acid derivatives (gemfibrozil, clofibrat, fenofibrate and benzafibrate), and probucol; (k) anti-diabetic agents such as insulin, sulfonylureas, biguanides (metformin), α-glucosidase inhibitors (acarbose) and glitazones (troglitazone and pioglitazone); (l) preparations of interferon beta (interferon beta-1α, interferon beta-1β); (m) other compounds such as 5-aminosalicylic acid and prodrugs thereof, antimetabolites such as azathioprine and 6-mercaptopurine, and cytotoxic cancer chemotherapeutic agents. The weight ratio of the compound of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with an NSAID the weight ratio of the compound of the present invention to the NSAID will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be

within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

The present invention is further directed to combinations of the present compounds with one or more agents useful in the prevention or treatment of AIDS. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of the AIDS antivirals, immunomodulators, anti-infectives, or vaccines known to those of ordinary skill in the art.

ANTIVIRALS

Drug Name	Manufacturer	Indication
097	Hoechst/Bayer	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
141 W94	Glaxo Wellcome	HIV infection, AIDS, ARC (protease inhibitor)
1592U89	Glaxo Wellcome	HIV infection, AIDS, ARC
Acemannan	Carrington Labs (Irving, TX)	ARC
Acyclovir	Burroughs Wellcome	HIV infection, AIDS, ARC, in combination with AZT
AD-439	Tanox Biosystems	HIV infection, AIDS, ARC
AD-519	Tanox Biosystems	HIV infection, AIDS, ARC
Adefovir dipivoxil	Gilead Sciences	HIV infection

AL-721	Ethigen (Los Angeles, CA)	ARC, PGL HIV positive, AIDS
Alpha Interferon	Glaxo Wellcome	Kaposi's sarcoma, HIV in combination w/Retrovir
Ansamycin LM 427	Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT)	ARC
Antibody which neutralizes pH labile alpha aberrant Interferon	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC
AR177	Aronex Pharm	HIV infection, AIDS, ARC
beta-fluoro-ddA	Nat'l Cancer Institute	AIDS-associated diseases
(-) 6-Chloro-4(S)-cyclopropylethynyl-4(S)-trifluoro-methyl-1,4-dihydro-2H-3,1-benzoxazin-2-one	Merck	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
CI-1012	Warner-Lambert	HIV-1 infection
Cidofovir	Gilead Science	CMV retinitis, herpes, papillomavirus
Curdlan sulfate	AJI Pharma USA	HIV infection
Cytomegalovirus immune globin	MedImmune	CMV retinitis
Cytovene Ganciclovir	Syntex	sight threatening CMV peripheral CMV retinitis
Delaviridine	Pharmacia-Upjohn	HIV infection, AIDS, ARC (protease inhibitor)

Dextran Sulfate	Ueno Fine Chem. Ind. Ltd. (Osaka, Japan)	AIDS, ARC, HIV positive asymptomatic
ddC Dideoxycytidine	Hoffman-La Roche	HIV infection, AIDS, ARC
ddI Dideoxyinosine	Bristol-Myers Squibb	HIV infection, AIDS, ARC; combination with AZT/d4T
DMP-450	AVID (Camden, NJ)	HIV infection, AIDS, ARC (protease inhibitor)
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
Efavirenz, DMP-266	DuPont-Merck Pharmaceuticals	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
Famciclovir	Smith Kline	herpes zoster, herpes simplex
FTC	Emory University	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
GS 840	Gilead	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
GW 141	Glaxo Welcome	HIV infection, AIDS, ARC (protease inhibitor)
GW 1592	Glaxo Welcome	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)

HBY097	Hoechst Marion Roussel	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
Hypericin	VIMRx Pharm.	HIV infection, AIDS, ARC
Recombinant Human Interferon Beta	Triton Biosciences (Almeda, CA)	AIDS, Kaposi's sarcoma, ARC
Interferon alfa-n3	Interferon Sciences	ARC, AIDS
Indinavir	Merck	HIV infection, AIDS, ARC, asymptomatic HIV positive, also in combination with AZT/ddI/ddC
ISIS 2922	ISIS Pharmaceuticals	CMV retinitis
KNI-272	Nat'l Cancer Institute	HIV-assoc. diseases
Lamivudine, 3TC	Glaxo Wellcome	HIV infection, AIDS, ARC (reverse transcriptase inhibitor); also with AZT
Lobucavir	Bristol-Myers Squibb	CMV infection
Nelfinavir	Agouron Pharmaceuticals	HIV infection, AIDS, ARC (protease inhibitor)
Nevirapine	Boeheringer Ingleheim	HIV infection, AIDS, ARC (protease inhibitor)
Novapren	Novaferon Labs, Inc. (Akron, OH)	HIV inhibitor
Peptide T Octapeptide Sequence	Peninsula Labs (Belmont, CA)	AIDS

Trisodium Phosphonoformate	Astra Pharm. Products, Inc	CMV retinitis, HIV infection, other CMV infections
PNU-140690	Pharmacia Upjohn	HIV infection, AIDS, ARC (protease inhibitor)
Probucol	Vyrex	HIV infection, AIDS
RBC-CD4	Sheffield Med. Tech (Houston TX)	HIV infection, AIDS, ARC
Ritonavir	Abbott	HIV infection, AIDS, ARC (protease inhibitor)
Saquinavir	Hoffmann-LaRoche	HIV infection, AIDS, ARC (protease inhibitor)
Stavudine; d4T Didehydrodeoxy-thymidine	Bristol-Myers Squibb	HIV infection, AIDS, ARC
T-20	Trimeris	HIV infection, AIDS, ARC
Valaciclovir	Glaxo Wellcome	genital HSV & CMV infections
Virazole Ribavirin	Viratek/ICN (Costa Mesa, CA)	asymptomatic HIV positive, LAS, ARC
Amprenivir VX-478	Vertex	HIV infection, AIDS, ARC
Zalcitabine	Hoffmann-La Roche	HIV infection, AIDS, ARC, with AZT
Zidovudine; AZT	Glaxo Wellcome	HIV infection, AIDS, ARC, Kaposi's sarcoma, in combination with other therapies

IMMUNO-MODULATORS

818

Drug Name	Manufacturer	Indication
AS-101	Wyeth-Ayerst	AIDS
Bropirimine	Pharmacia Upjohn	advanced AIDS
Acemannan	Carrington Labs, Inc. (Irving, TX)	AIDS, ARC
CL246,738	American Cyanamid Lederle Labs	AIDS, Kaposi's sarcoma
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
Gamma Interferon	Genentech	ARC, in combination w/TNF (tumor necrosis factor)
Granulocyte Macrophage Colony Stimulating Factor	Genetics Institute Sandoz	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Hoeschst-Roussel Immunex	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Schering-Plough	AIDS, combination w/AZT
HIV Core Particle Immunostimulant	Rorer	seropositive HIV
IL-2 Interleukin-2	Cetus	AIDS, in combination w/AZT
IL-2 Interleukin-2	Hoffman-La Roche Immunex	AIDS, ARC, HIV, in combination w/AZT
IL-2 Interleukin-2 (aldeslukin)	Chiron	AIDS, increase in CD4 cell counts

Immune Globulin Intravenous (human)	Cutter Biological (Berkeley, CA)	pediatric AIDS, in combination w/AZT
IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
Imuthiol Diethyl Dithio Carbamate	Merieux Institute	AIDS, ARC
Alpha-2 Interferon	Schering Plough	Kaposi's sarcoma w/AZT, AIDS
Methionine-Enkephalin	TNI Pharmaceutical (Chicago, IL)	AIDS, ARC
MTP-PE Muramyl-Tripeptide	Ciba-Geigy Corp.	Kaposi's sarcoma
Granulocyte Colony Stimulating Factor	Amgen	AIDS, in combination w/AZT
Remune	Immune Response Corp.	immunotherapeutic
rCD4	Genentech	AIDS, ARC
Recombinant Soluble Human CD4		
rCD4-IgG hybrids		AIDS, ARC
Recombinant Soluble Human CD4	Biogen	AIDS, ARC
Interferon Alfa 2a	Hoffman-La Roche	Kaposi's sarcoma AIDS, ARC, in combination w/AZT
SK&F106528 Soluble T4	Smith Kline	HIV infection
TAK-779	Takeda	HIV infection
Thymopentin	Immunobiology Research Institute	HIV infection

820

Tumor Necrosis Factor; TNF	Genentech	ARC, in combination w/gamma Interferon

ANTI-INFECTIVES

Drug Name	Manufacturer	Indication
Clindamycin with Primaquine	Pharmacia Upjohn	PCP
Fluconazole	Pfizer	cryptococcal meningitis, candidiasis
Pastille Nystatin Pastille	Squibb Corp.	prevention of oral candidiasis
Ornidyl Eflornithine	Merrell Dow	PCP
Pentamidine Isethionate (IM & IV)	LyphoMed (Rosemont, IL)	PCP treatment
Trimethoprim		antibacterial
Trimethoprim/sulfa		antibacterial
Piritrexim	Burroughs Wellcome	PCP treatment
Pentamidine isethionate for inhalation	Fisons Corporation	PCP prophylaxis
Spiramycin	Rhone-Poulenc	cryptosporidial diarrhea
Intraconazole-R51211	Janssen Pharm.	histoplasmosis; cryptococcal meningitis
Trimetrexate	Warner-Lambert	PCP

OTHER

Drug Name	Manufacturer	Indication
Daunorubicin	NeXstar, Sequus	Karposi's sarcoma

Recombinant Human Erythropoietin	Ortho Pharm. Corp.	severe anemia assoc. with AZT therapy
Recombinant Human Growth Hormone	Serono	AIDS-related wasting, cachexia
Leukotriene B4 Receptor Antagonist	-	HIV infection
Megestrol Acetate	Bristol-Myers Squibb	treatment of anorexia assoc. w/AIDS
Soluble CD4 Protein and Derivatives	-	HIV infection
Testosterone	Alza, Smith Kline	AIDS-related wasting
Total Enteral Nutrition	Norwich Eaton Pharmaceuticals	diarrhea and malabsorption related to AIDS

It will be understood that the scope of combinations of the compounds of this invention with AIDS antivirals, immunomodulators, anti-infectives or vaccines is not limited to the list in the above Table, but includes in principle any combination with any pharmaceutical composition useful for the treatment of AIDS.

Preferred combinations are simultaneous or alternating treatments with a compound of the present invention and an inhibitor of HIV protease and/or a non-nucleoside inhibitor of HIV reverse transcriptase. An optional fourth component in the combination is a nucleoside inhibitor of HIV reverse transcriptase, such as AZT, 3TC, ddC or ddI. Preferred agents for combination therapy include: Zidovudine, Lamivudine, Stavudine, Efavirenz, Ritonavir, Nelfinavir, Abacavir, Indinavir, 141-W94 (4-amino-N-((2 syn,3S)-2-hydroxy-4-phenyl-3-((S)-tetrahydrofuran-3-yloxycarbonylamino)-butyl)-N-isobutyl-benzenesulfonamide), N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(2-benzo[b]furanylmethyl)-2(S)-N'(t-butylcarbox-amido)-piperazinyl))-pentaneamide, and Delavirdine. A preferred inhibitor of HIV protease is indinavir, which is the sulfate salt of N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(3-pyridyl-methyl)-2(S)-N'-(t-butylcarbo-xamido)-piperazinyl))-pentane-amide ethanolate, and is synthesized according to U.S. 5,413,999. Indinavir is generally administered at a dosage of 800

mg three times a day. Other preferred inhibitors of HIV protease include nelfinavir and ritonavir. Preferred non-nucleoside inhibitors of HIV reverse transcriptase include (-) 6-chloro-4(S)-cyclopropylethynyl-4(S)-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one, which may be prepared by methods disclosed in EP 0,582,455. The preparation of ddC, ddI and AZT are also described in EPO 0,484,071. These combinations may have unexpected effects on limiting the spread and degree of infection of HIV. Preferred combinations with the compounds of the present invention include the following: (1) Zidovudine and Lamivudine; (2) Stavudine and Lamivudine; (3) Efavirenz; (4) Ritoavir; (5) Nelfinavir; (6) Abacavir; (7) Indinavir; (8) 141-W94; and (9) Delavirdine. Preferred combinations with the compounds of the present invention further include the following (1) indinavir, with efavirenz or (-) 6-chloro-4(S)-cyclopropylethynyl-4(S)-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one, and, optionally, AZT and/or 3TC and/or ddI and/or ddC; (2) indinavir, and any of AZT and/or ddI and/or ddC.

In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

The compounds of the present invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, monkeys, etc., the compounds of the invention are effective for use in humans.

The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In

the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Patents 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy- propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum

tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally- occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the present invention are employed. (For purposes of this application, topical application shall include mouthwashes and gargles.)

The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions.

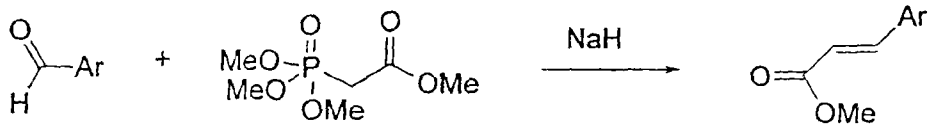
In the treatment or prevention of conditions which require chemokine receptor modulation an appropriate dosage level will generally be about 0.01 to 500 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.1 to about 250 mg/kg per day; more preferably about 0.5 to about 100 mg/kg per day. A suitable dosage level may be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage may be 0.05 to 0.5, 0.5 to 5 or 5 to 50 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active

ingredient, particularly 1.0, 5.0, 10.0, 15.0. 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples. Starting materials are made from known procedures or as illustrated.

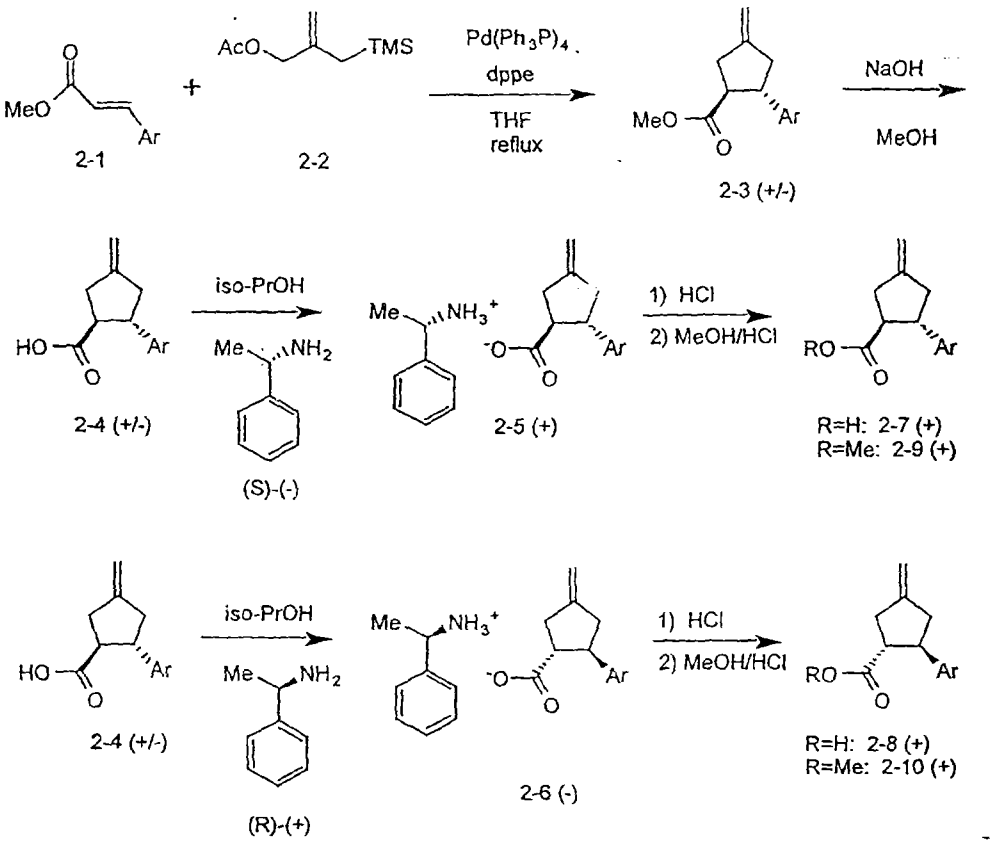
SCHEME 1



1-1 1-2 1-3

The preparation of cinnamate esters such as 1-3 as intermediates that can be used for the synthesis of compounds within the scope of the instant invention is detailed in Scheme 1. Cinnamate esters of structure 1-3 can be obtained commercially or can be synthesized by reacting a suitable aromatic aldehyde 1-1 with a phosphonoacetate such as 1-2 in the presence of sodium hydride or other bases such as sodium, lithium or potassium hexamethyldisilazide, potassium t-butoxide, and the like. The aldehyde 1-1 can be obtained commercially or can be prepared in a variety of ways from commercial materials (see March J. "Advanced Organic Chemistry", 4th ed., John Wiley & Sons, New York, pp. 1270-1271 (1992)).

SCHEME 2

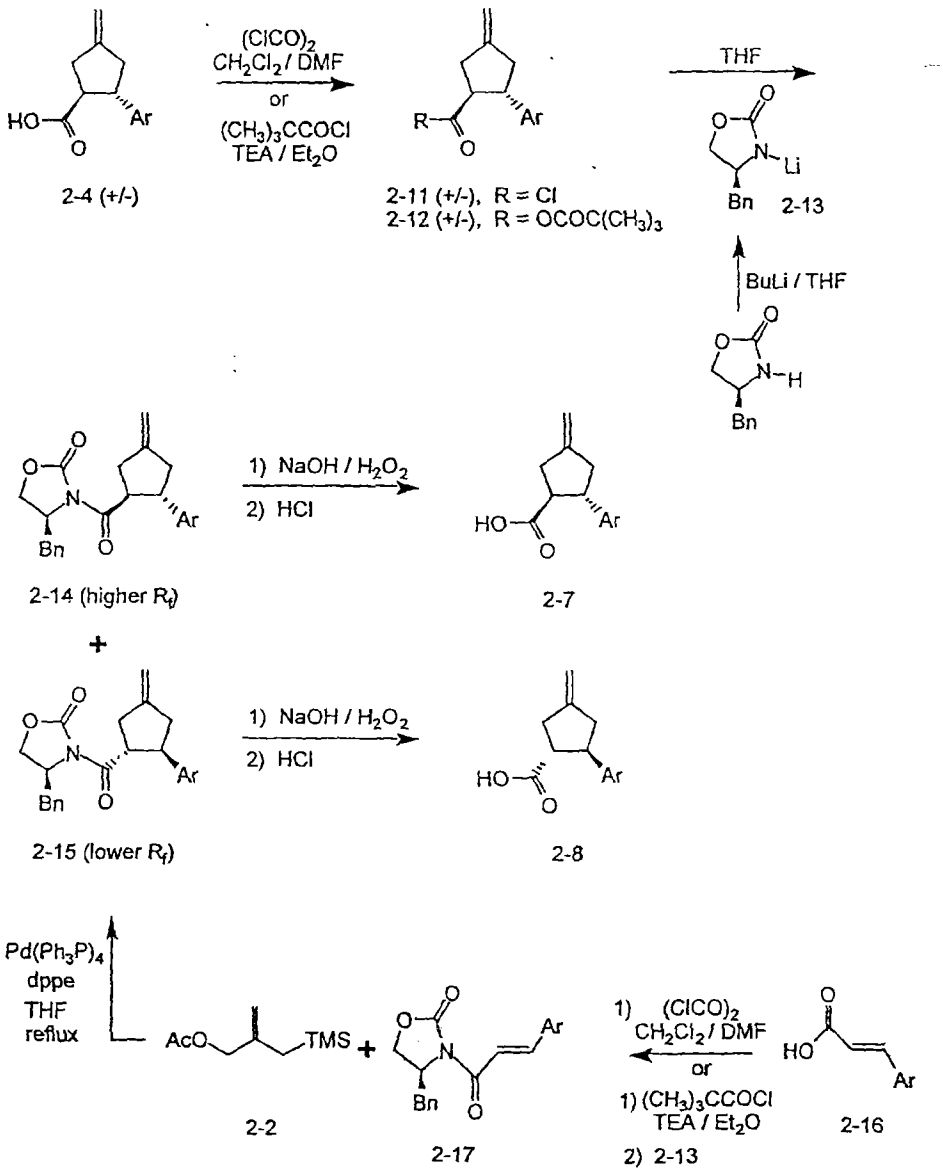


A preparation of cyclopentane intermediates having a C-4 aryl substituent within the scope of the instant invention is detailed in Scheme 2 and can be used to prepare non-racemic cyclopentane derivatives when the resolution steps are done. Treatment of a *trans*-cinnamic ester such as 2-1 (see Scheme 1) with 2-((trimethylsilyl)methyl)-2-propen-1-yl acetate (2-2) in the presence of a catalytic amount of tetrakis(triphenylphosphine) palladium (0) and 1,2-bis(diphenylphosphino)ethane in THF at reflux afforded the exo-methylene cyclopentane 2-3. Hydrolysis of the ester can be done several ways, such as with aqueous sodium or lithium hydroxide in methanol or THF, to obtain the racemic acid 2-4. Resolution of the enantiomers can be accomplished by fractional crystallization from isopropanol, or other suitable solvents, of the salts with either (R)-(+)- or (S)-(-)-α-methylbenzyl amine to give the salts 2-5 and 2-6. The non-racemic acids 2-7 and

2-8 are recovered by acidification and extraction. Reesterification to non-racemic 2-9 and 2-10 can be done in a variety of ways, such as with trimethylsilyldiazomethane or acid catalyzed esterification in methanol.

05754 05355 05356 05357 05358 05359

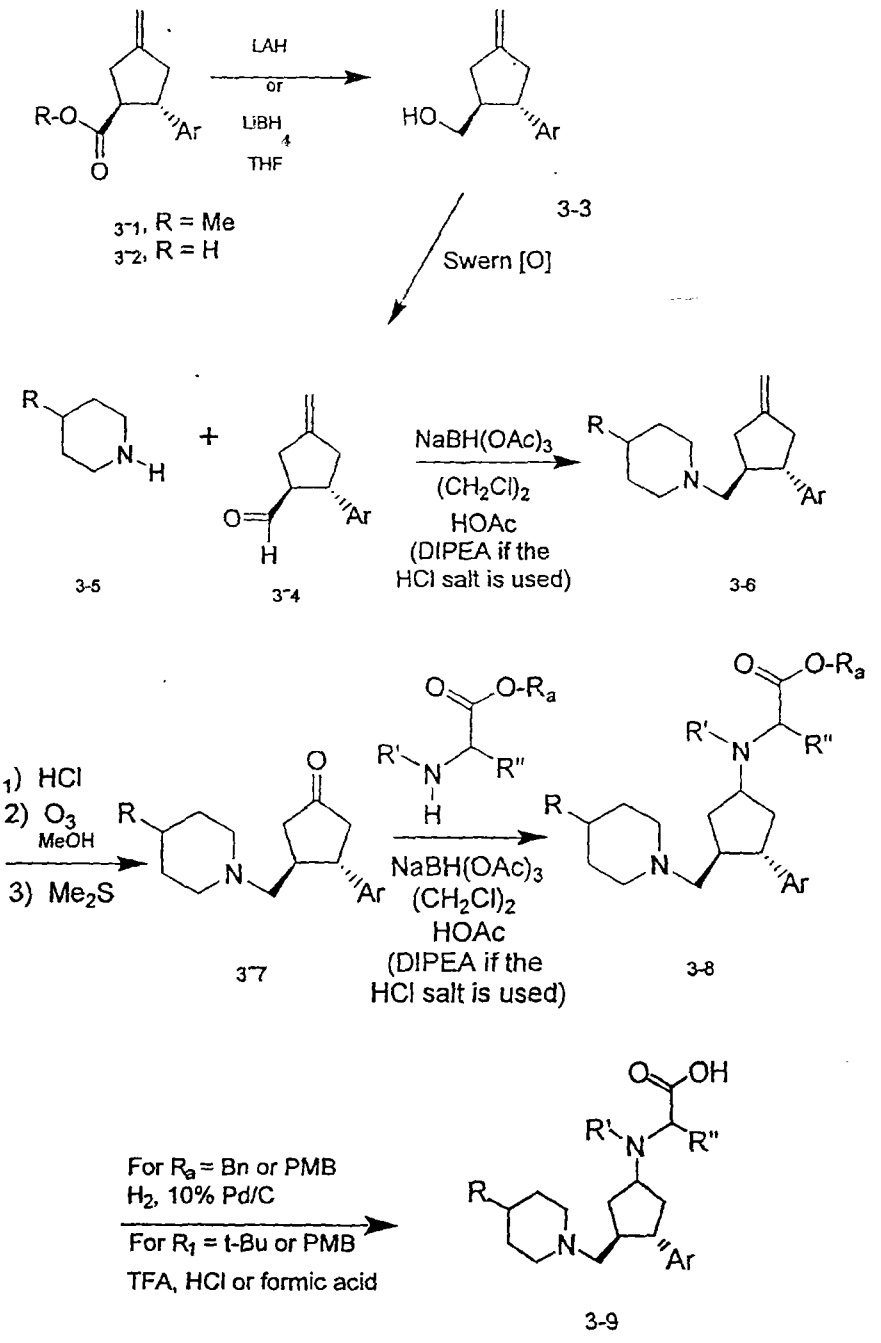
SCHEME 2A



An alternative preparation of non-racemic cyclopentane intermediates having a C-4 aryl substituent within the scope of the instant invention is detailed in Scheme 2A. Conversion of the cyclopentane acid 2-4 to the acid chloride 2-11 under standard conditions, such as with oxalyl chloride in methylene chloride with a catalytic amount of DMF, or to the mixed anhydride 2-12, prepared in situ with

trimethylacetyl chloride in ether with TEA as base, followed by reaction with the preformed lithium salt of (S)-(-)-4-benzyl-2-oxazolidinone 2-13, afforded the two non-racemic diastereomeric products 2-14 and 2-15, which are then separable by chromatography. Hydrolysis of each diastereomer under standard conditions, such as with lithium hydroxide and hydrogen peroxide or trimethylamine-N-oxide, affords the two non-racemic acids 2-7 and 2-8. Alternatively, in order to obtain an enhanced amount of the desired diastereomer 2-14 before separation, similar conversion of the starting *trans* -cinnamic acid 2-16 (Scheme 1) to the chiral *trans* -cinnamate 2-17 followed by the ring formation reaction with 2-((trimethylsilyl)methyl)-2-propen-1-yl acetate (2-2) as detailed in Scheme 2 affords a 60 : 40 product mixture of 2-14 : 2-15.

SCHEME 3

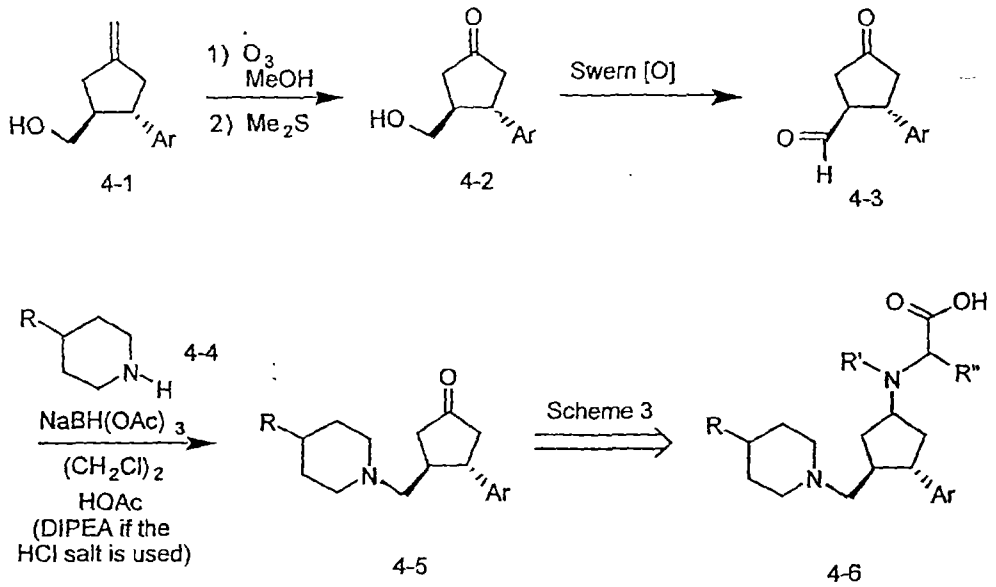

LAH
or
LiBH4
THF
R-O
Ar
O
HO
3-1, R = Me
3-2, R = H
3-3
Swern [O]
R
N
H
3-5
O
H
3-4
NaBH(OAc)3
(CH2Cl)2
HOAc
(DIPEA if the
HCl salt is used)
3-6
1) HCl
2) O3
MeOH
3) Me2S
3-7
O-Ra
R'
R"
3-8
For Ra = Bn or PMB
H2, 10% Pd/C
For R1 = t-Bu or PMB
TFA, HCl or formic acid
OH
3-9

Preparation of some 1,3,4-trisubstituted cyclopentanes within the scope of the instant invention is given in Scheme 3. Reduction of ester 3-1 (either racemic or non-racemic) (Scheme 2), for example, with lithium borohydride, diisobutylaluminum hydride, lithium aluminium hydride, or sodium bis(2-methoxyethoxy)aluminum hydride in a suitable solvent, such as ether or THF, provides the primary alcohol 3-3. Alternatively, reduction of the acid 3-2 (either racemic or non-racemic) (Scheme 2 or 2A), for example with lithium aluminium hydride in THF, will also afford the alcohol 3-3. In cases where the Ar moiety is not amenable to salt resolution as detailed in Scheme 2, an alternative resolution can often be achieved using chiral HPLC methods to separate the enantiomers of 3-3. Oxidation of 3-3 to the aldehyde 3-4 can be carried out under numerous conditions, such as with DMSO and oxalyl chloride at low temperature, followed by triethylamine (Swern oxidation), with the Dess-Martin periodinane, with *N*-methylmorpholine in the presence of a catalytic amount of TPAP, or with various chromium trioxide-based reagents (see March J. "Advanced Organic Chemistry", 4th ed., John Wiley & Sons, New York, pp. 1167-1171 (1992)). Reductive alkylation of a cyclic amine, such as piperidine 3-5 (see Schemes 12 to 29), using for example sodium triacetoxyborohydride or sodium cyanoborohydride in a suitable solvent such as methylene chloride, 1,2-dichloroethane, THF, acetonitrile or methanol, with 3-4 then provides a 3-((4-substitutedpiperidin-1-yl)methyl)cyclopentane derivative 3-6. In the cases where the R group of the piperidine is stable to ozone, ozonolysis of the exo-methylene followed by a reductive work-up with dimethyl sulfide affords the ketone 3-7. Alternatively, 3-7 can be obtained from 3-6 through a stepwise oxidation using catalytic osmium tetroxide in the presence of N-methylmorpholine-N-oxide followed by sodium periodate cleavage of the intermediate diol. A second reductive alkylation of a D- and/or L-amino-acid ester, such as the methyl, ethyl, t-butyl, benzyl or 4-methoxybenzyl ester of glycine (R" = H), alanine (R" = Me), valine (R" = iso-Pr), leucine (R" = iso-Bu), isoleucine (R' = sec-Bu), cyclopropylalanine (R" = CH_2cycPr), cyclobutylalanine (R" = CH_2cycBu), cyclohexylglycine (R" = cycHex) or a *N*-alkyl amino-acid, such as N-methyl glycine (R' = Me), or a cyclic amino-acid, such as proline (R'R" = -$(CH_2)_3$-), with 3-7 as described above with sodium triacetoxyborohydride or sodium cyanoborohydride affords 3-8. Final deprotection of the ester under conditions to which the R group is stable, such as HCl in ether, TFA or formic acid for t-butyl and 4-methoxybenzyl esters, hydrogenation for benzyl esters or

standard hydrolysis for alkyl or benzyl esters, affords the final product(s) 3-9 which are within the scope of the instant invention and which can be chemokine receptor modulators. The two individual C-1 isomers (four diastereomers when either the cyclopentyl scaffold or the amino-acid are racemic) can be separated by flash chromatography, Prep TLC or HPLC methods as either the penultimate esters 3-8 and/or the final compounds 3-9.

SUBSTITUTE SHEET (RULE 26)

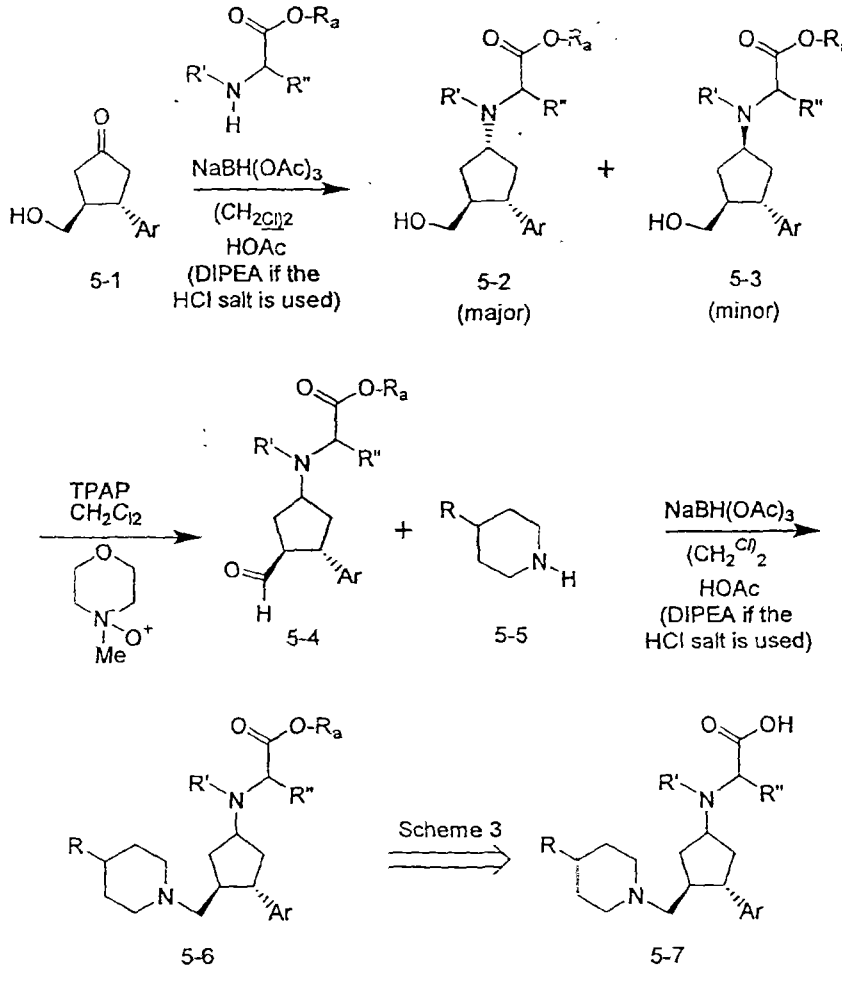
SCHEME 4



An alternative route for the preparation of some 1,3,4-trisubstituted cyclopentanes within the scope of the instant invention is given in Scheme 4. In the cases where the R group of the piperidine in Scheme 3 is not stable to ozone or the osmium tetroxide/sodium periodate sequence, oxidation of the exo-methylene can be done prior to the reductive alkylation of the piperidine. Thus, ozonolysis of the alcohol 4-1 (Scheme 3) followed by a reductive work-up with dimethyl sulfide affords the ketone-alcohol 4-2. Oxidation to the ketone-aldehyde 4-3 can be done as described for Scheme 3 with *N*-methylmorpholine/TPAP or under Swern conditions. Selective reductive alkylation of the 4-substitutedpiperidine 4-4 (see Schemes 12 to 29) with the aldehyde of 4-3, using for example sodium triacetoxyborohydride or sodium cyanoborohydride in a suitable solvent such as methylene chloride, 1,2-dichloroethane, THF, acetonitrile or methanol, then provides the 3-((4-substitutedpiperidin-1-yl)methyl)cyclopentane derivative 4-5 (same as 3-7). This can then be converted to the final product(s) 4-6 as described in Scheme 3.

SCHEME 5

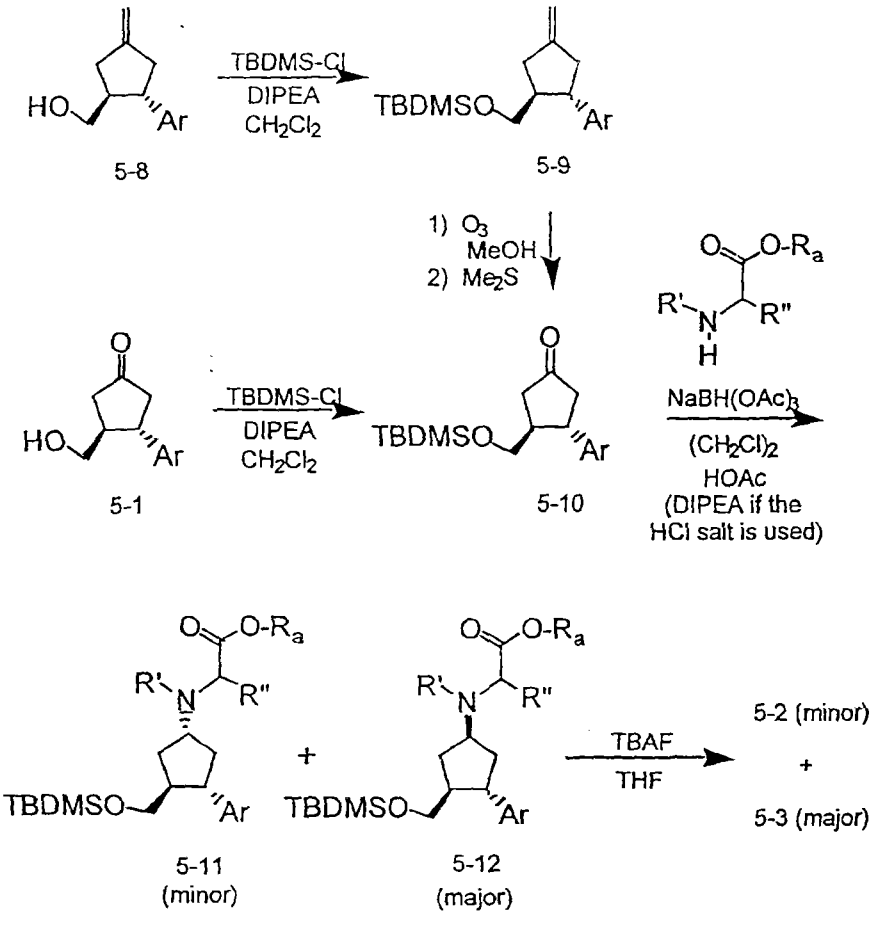
635



An alternative route for the preparation of some 1,3,4-trisubstituted cyclopentanes within the scope of the instant invention is given in Scheme 5. Reductive alkylation with ketone alcohol 5-1 (Scheme 4) of a variety of amino-acid esters (See Scheme 3) affords the alcohols 5-2 and 5-3, of which 5-2 is the major product (lower R_f when R" is (S), higher R_f when R" is (R)) and 5-3 is the minor product (higher R_f when R" is (S), lower R_f when R" is (R)). Separation of the individual diastereomers (2 when both reactants are non-racemic, 4 when only one is non-racemic) can be done at this intermediate or at a later step. Oxidation of 5-2 and/or 5-3 to the aldehyde(s) 5-4 can be done as described in Scheme 3, preferably

now with *N*-methylmorpholine/TPAP due to the presence of the secondary N-H. Reductive alkylation of a 4-substitutedpiperidine 5-5 (see Schemes 12 to 29) with the aldehyde of 5-4, using for example sodium triacetoxyborohydride or sodium cyanoborohydride in a suitable solvent such as methylene chloride, 1,2-dichloroethane, THF, acetonitrile or methanol, then provides the 3-((4-substitutedpiperidin-1-yl)methyl)cyclopentane derivative 5-6. The intermediate ester(s) 5-6 can then be converted to the final product(s) 5-7 as described in Scheme 3.

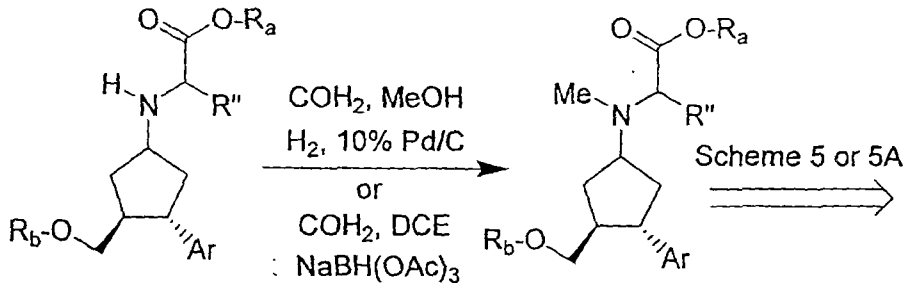
SCHEME 5A



An alternative preparation of the intermediates 5-2 and 5-3 in Scheme 5 which reverses the C-1 isomeric selectivity is shown in Scheme 5A. Silylation of the alcohol moiety of 5-1 (Scheme 4) gives the silyl ether 5-10. Alternatively, silylation of the alcohol 5-8 (Scheme 3) gives 5-9 which on ozonolysis can also afford the silyl ether 5-10. Reductive alkylation of the aforementioned amino-acid esters now using the silyl ether 5-10 affords the products 5-11 and 5-12 in an essentially opposite ratio as is obtained in Scheme 5 for 5-2 and 5-3. TBAF desilylation then affords primarily 5-3. Thus, the preferred C-1 orientation can be selected for depending on the requirements of the desired final compounds.

836

SCHEME 5B



5-13

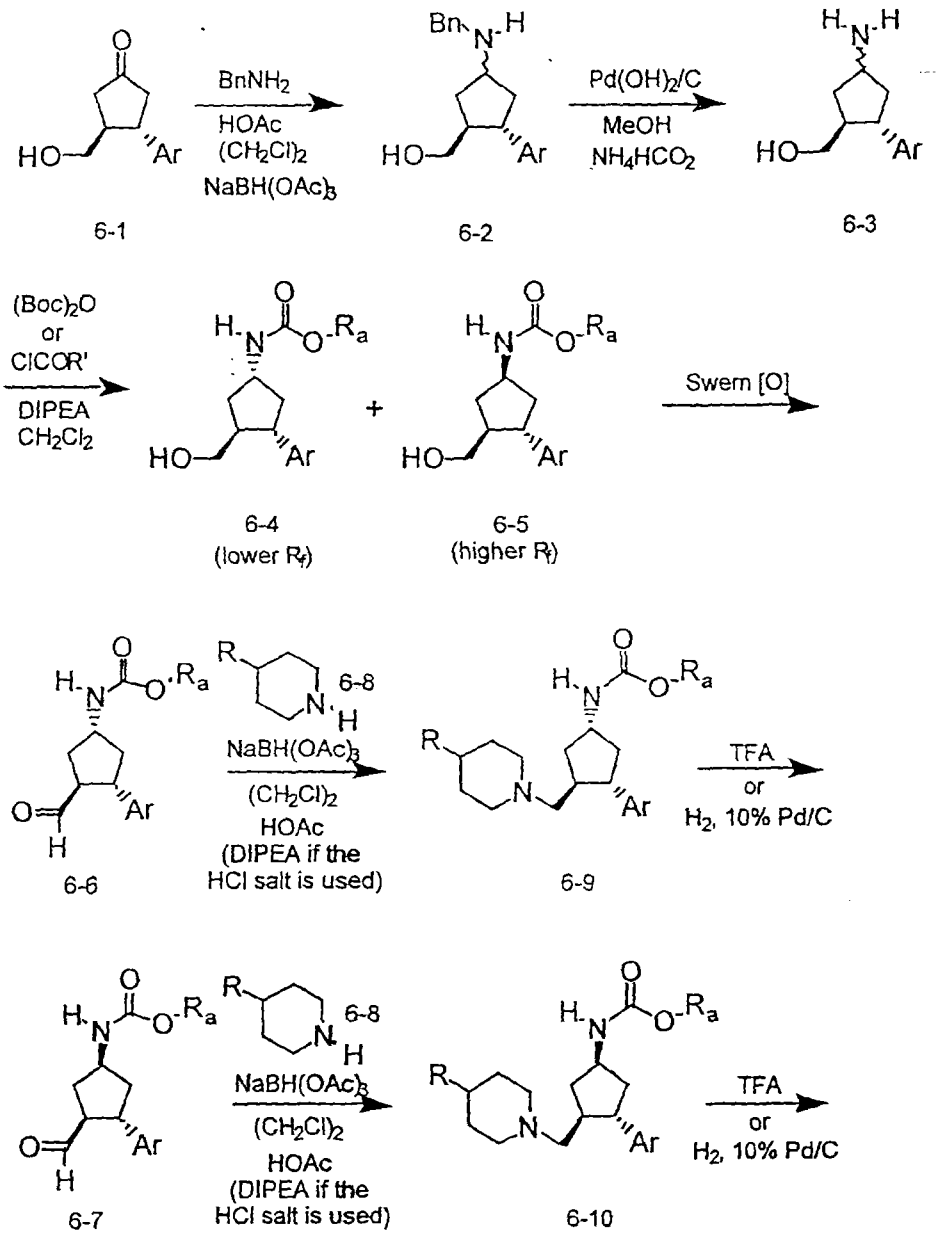
R_b = H or TBDMS

5-14

Rb = H or TBDMS

An alternative preparation of the intermediates 5-2 or 5-3 in Scheme 5 and intermediates 5-11 and 5-12 in Scheme 5A when R' is Me is shown in Scheme 5B. When 5-13 is formed in the reductive amination with ketones 5-1 (R_b = H) or 5-10 (R_b = TBDMS), a second reductive amination of 5-13 with formaldehyde, either in the presence of hydrogen and a suitable catalyst, such as 10% Pd/C or Pearlman's catalyst, in methanol or standard reaction with sodium triacetoxyborohydride in 1,2-dichloroehthane, affords the methylated intermediates 5-14. These intermediates can be further elaborated to the final products as described in Scheme 5 and/or 5A.

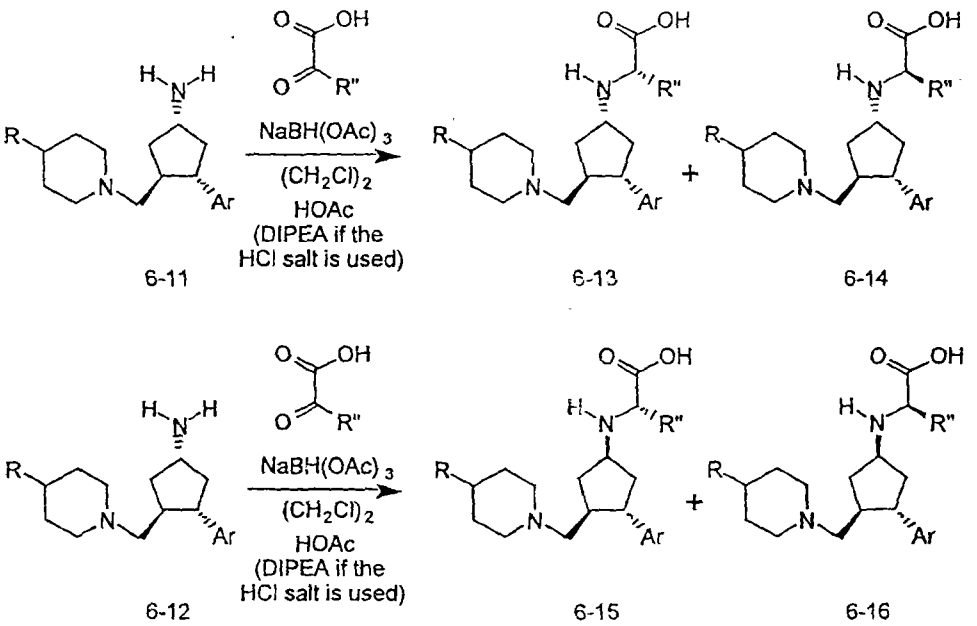
SCHEME 6


BnNH2
HOAc
(CH2Cl)2
NaBH(OAc)3
Pd(OH)2/C
MeOH
NH4HCO2
6-1
6-2
6-3
(Boc)2O
or
ClCOR'
DIPEA
CH2Cl2
Swern [O]
6-4
(lower Rf)
6-5
(higher Rf)
6-8
NaBH(OAc)3
(CH2Cl)2
HOAc
(DIPEA if the
HCl salt is used)
TFA
or
H2, 10% Pd/C
6-6
6-9
6-7
6-10

5

840

SCHEME 6 (cont'd)

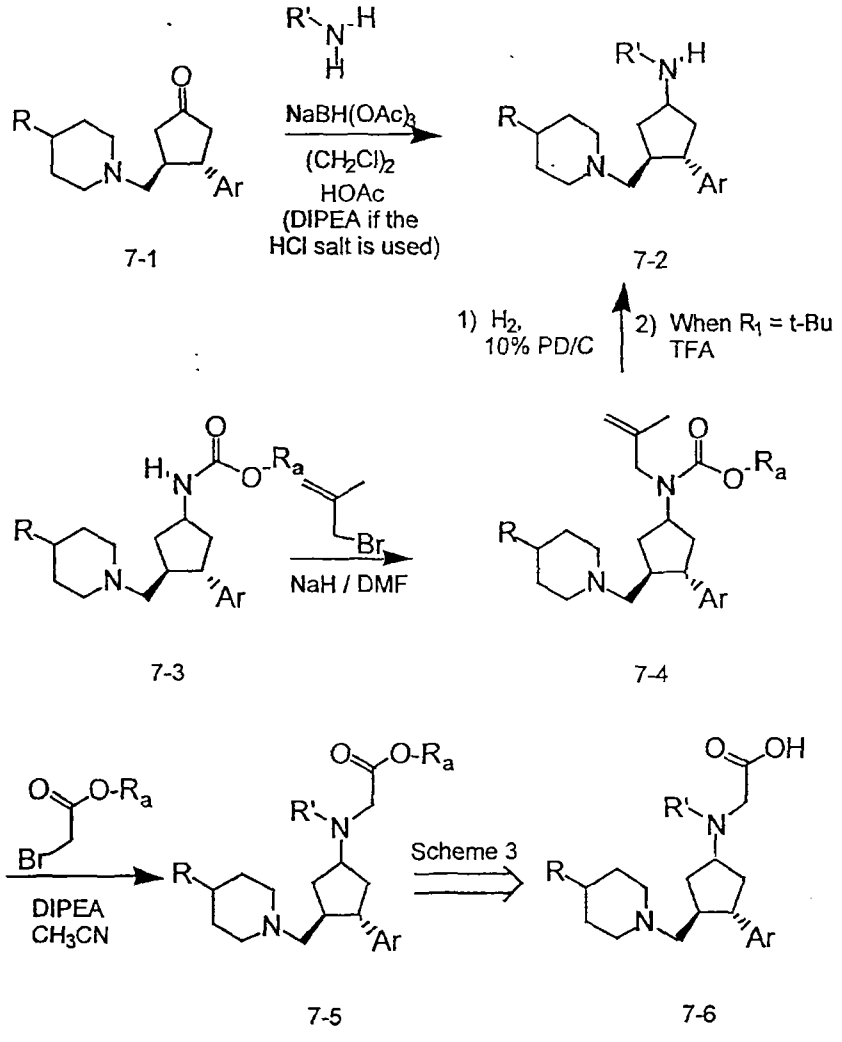


An alternative route for the preparation of some 1,3,4-trisubstituted cyclopentanes within the scope of the instant invention is given in Scheme 6. Reductive alkylation of benzylamine with ketone-alcohol 6-1 (Scheme 4, either racemic or non-racemic), using for example sodium triacetoxyborohydride or sodium cyanoborohydride, gives 6-2 which can be hydrogenated under standard conditions in methanol in the presence of a palladium catalyst, for example Pd/C or Pearlman's catalyst and using either hydrogen under pressure or ammonium formate at reflux, to afford the primary amine 6-3. Reaction of the amine with CBZ chloride or Boc anhydride gives the amine protected carbamates 6-4 and 6-5 as a mixture of C-1 isomers which can be separated. Oxidation to the aldehydes 6-6 and 6-7 is carried out under Swern conditions or with *N*-methylmorpholine/TPAP. The relative stereochemistry of the C-1 to the C-3 and C-4 substituents was determined by NMR Noe experiments on either the alcohols 6-4 and 6-5 or the aldehydes 6-6 and 6-7. Reductive alkylation of a 4-substitutedpiperidine 6-8 with the individual aldehydes 6-6 and 6-7, using for example sodium triacetoxyborohydride or sodium cyanoborohydride in a suitable solvent such as methylene chloride, 1,2-dichloroethane, THF, acetonitrile or methanol, then provides each of the C-1 amino-

protected isomeric 3-((4-substitutedpiperidin-1-yl)methyl)cyclopentane derivatives 6-9 and 6-10. Deprotection of the C-1 amino with either TFA (for R_a = t-butyl) or standard hydrogenation (for R_a = Bn) depending on the stability of the piperidine R group affords the amines 6-11 and 6-12. These amines can then be individually reductively alkylated as above with 2-oxo-acetic acids, such as 2-oxovaleric (R" = n-Pr), 4-methyl-2-oxovaleric (R" = iso-Bu), 2-oxophenylacetic (R" = Ph), to afford the final compounds 6-13 and 6-14 and 6-15 and 6-16 as mixtures of the R" isomers. In the case of R" = iso-Bu and non-racemic cyclopentyl scaffold, comparison of the HPLC of these products with those obtained in Scheme 5 allowed the stereochemical assignments of all the final products and intermediates.

SUBSTITUTE SHEET (RULE 26)

SCHEME 7

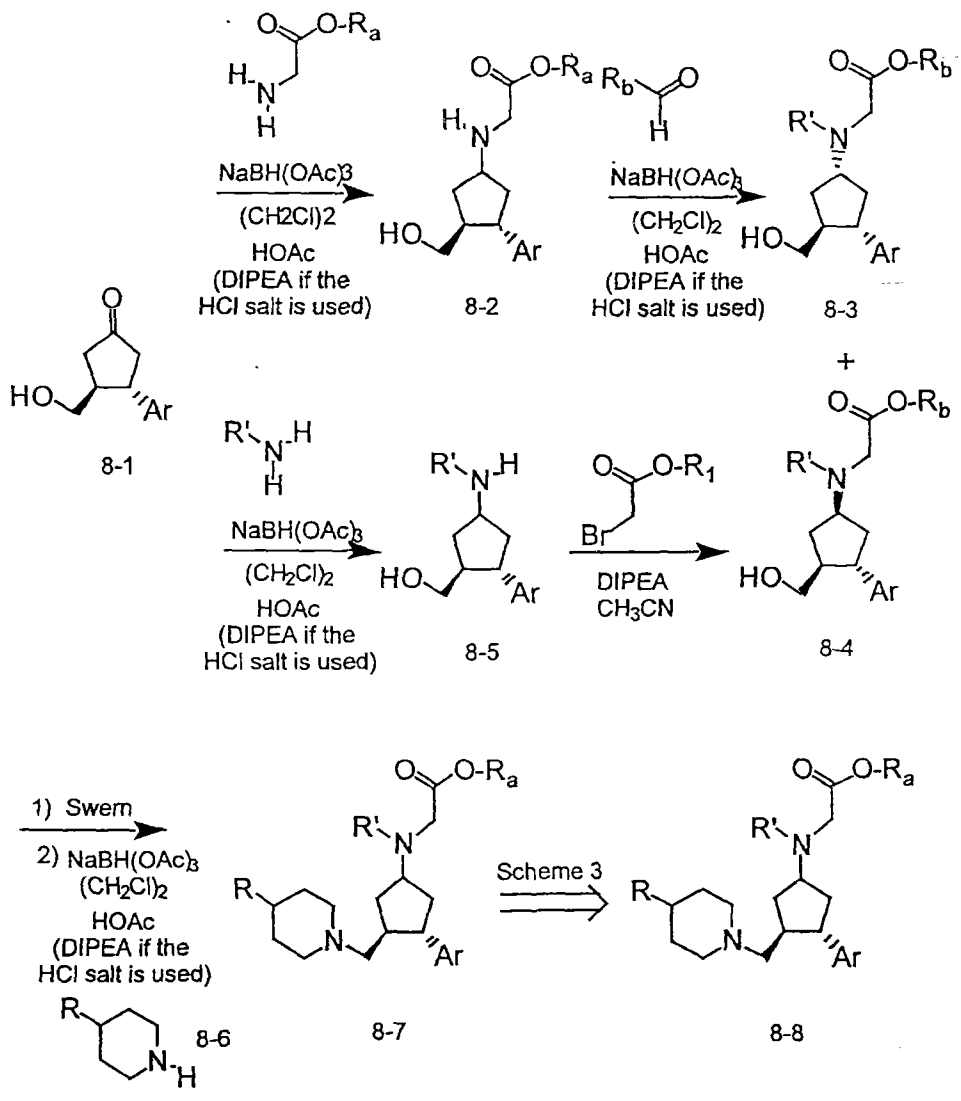


An alternative route for the preparation of some 1,3,4-trisubstituted cyclopentanes within the scope of the instant invention is given in Scheme 7. Reductive alkylation, using for example sodium triacetoxyborohydride or sodium cyanoborohydride, of an alkyl amine with the ketone 7-1 (Schemes 3 or 4) gives 7-2 as a mixture of C-1 isomers which may be separated. Alternatively, carbamate 7-3 (see Scheme 6) can be alkylated with an alkyl or allyl halide, such as 1-bromo-2-

methylprop-2-ene, and a strong base, such as sodium hydride in DMF, followed by hydrogenation under standard conditions to reduce the allyl. When R_a is Bn, removal the CBZ can occur simultaneously to give the same amine intermediate 7-2. When R_a is t-butyl, a subsequent reaction with TFA is required to give 7-2. Alkylation of the amine with t-butyl or benzyl bromoacetate affords 7-5 which can be converted to the desired final compound(s) 7-6 as described in Scheme 3.

09202004-09504-95

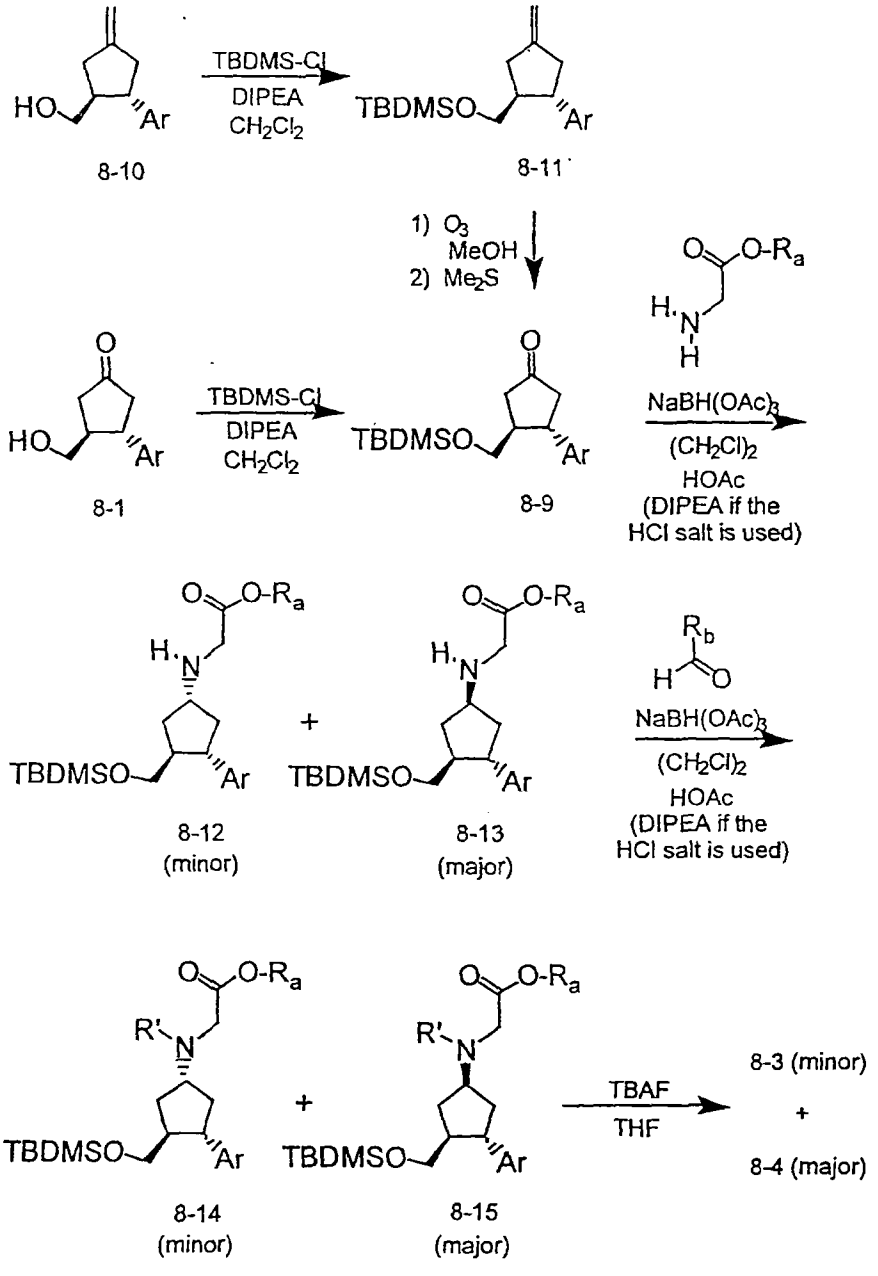
SCHEME 8



An alternative route for the preparation of some 1,3,4-trisubstituted cyclopentanes within the scope of the instant invention is given in Scheme 8. Reductive alkylation, using for example sodium triacetoxyborohydride or sodium cyanoborohydride, of glycine t-butyl, benzyl or PMB ester with the ketone-alcohol 8-1 (Scheme 4) gives 8-2 as a mixture of C-1 isomers. A second reductive alkylation

with a ketone or aldehyde affords the N-alkyl glycine derivatives 8-3 and 8-4 which can be separated chromatographically either before and/or after the second alkylation. Also, the order of the steps can be reversed such that reductive alkylation of an amine with 8-1 first to give 8-5, followed by alkylation with an alkyl or benzyl bromoacetate as in Scheme 7, affords 8-3 and 8-4. These reactions generally give 8-3 as the predominate product. Individual oxidation of the alcohols 8-3 and 8-4 can be done either under Swern conditions or using the *N*-methylmorpholine/TPAP method to give the aldehyde intermediate(s) followed by a second or third reductive alkylation of a 4-substitutedpiperidine 8-6, using for example sodium triacetoxyborohydride or sodium cyanoborohydride in a suitable solvent such as methylene chloride, 1,2-dichloroethane, THF, acetonitrile or methanol, which then provides the 3-((4-substitutedpiperidin-1-yl)methyl)cyclopentane derivative 8-7. This intermediate can then be converted to the final product(s) 8-8 as described in Scheme 3.

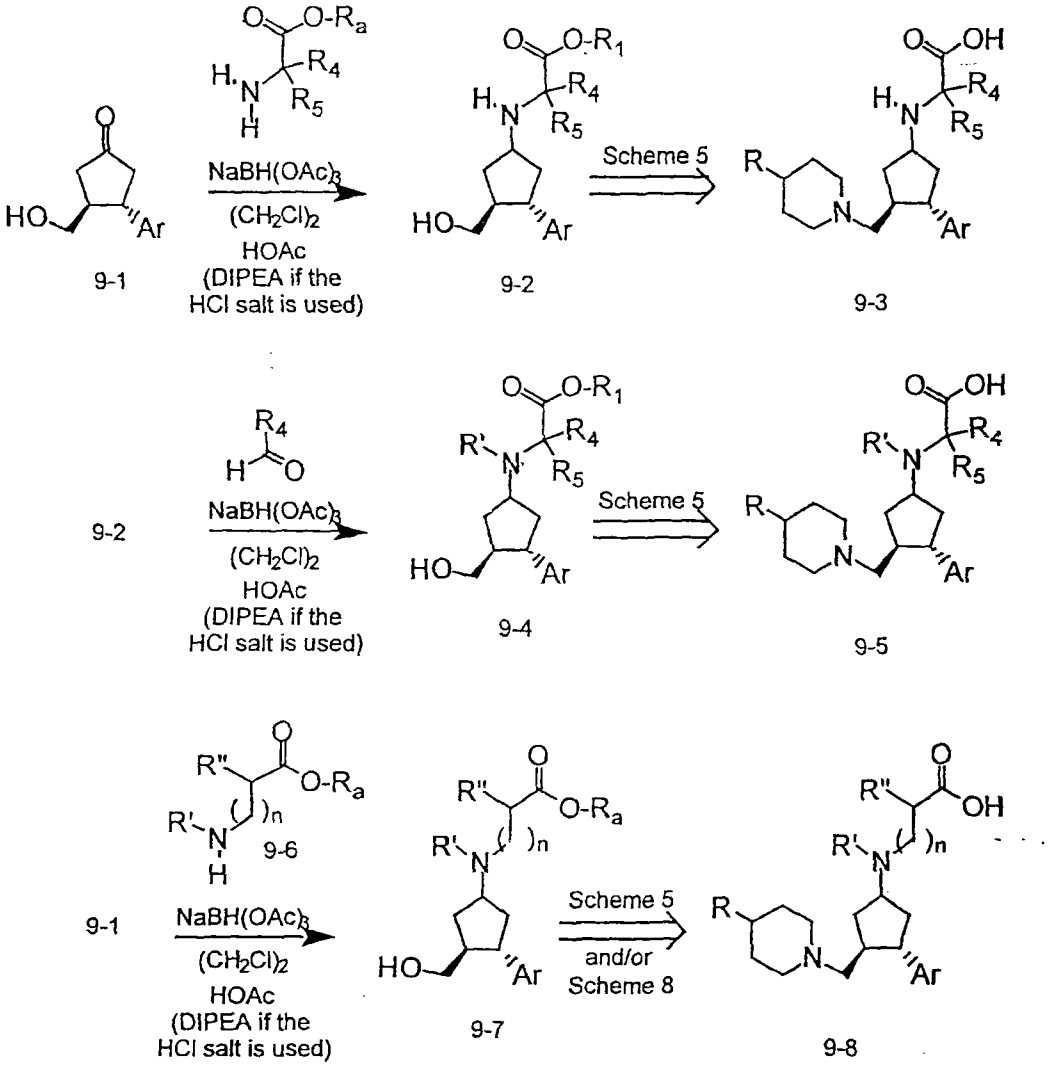
SCHEME 8A



An alternative preparation of the intermediates 8-3 and 8-4 in Scheme 8 which again reverses the C-1 isomeric selectivity is shown in Scheme 8A.

Silylation of the alcohol moiety of 8-1 (Scheme 4) gives the silyl ether 8-9. Alternatively, silylation of the alcohol 8-10 (Scheme 3) gives 8-11, which on ozonolysis can also afford the silyl ether 8-9. Reductive alkylation now using the silyl ether 8-9 gives 8-12 and 8-13 followed by the second reductive alkylation with an aldehyde or ketone affords the products 8-14 and 8-15 in an essentially opposite ratio as is obtained in Scheme 8 for 8-3 and 8-4. TBAF desilylation then affords primarily 8-4. Separation of the C-1 isomers can usually be achieved at one or more of the intermediate steps. Thus, the preferred C-1 orientation can be selected for depending on the requirements of the desired final compounds.

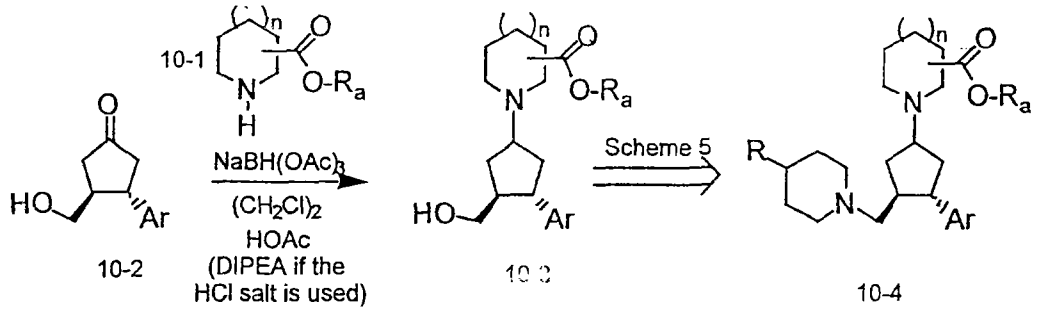
SCHEME 9



Several other alternative routes for the preparation of some 1,3,4-trisubstituted cyclopentanes within the scope of the instant invention are given in Scheme 9. Reductive alkylation, using for example sodium triacetoxyborohydride or sodium cyanoborohydride, of an amino-acid ester having dialkyl substitution with the ketone-alcohol 9-1 (Scheme 4) gives 9-2 as a mixture of C-1 isomers which may be separated and carried on to the final product(s) 9-3 individually or as a mixture as

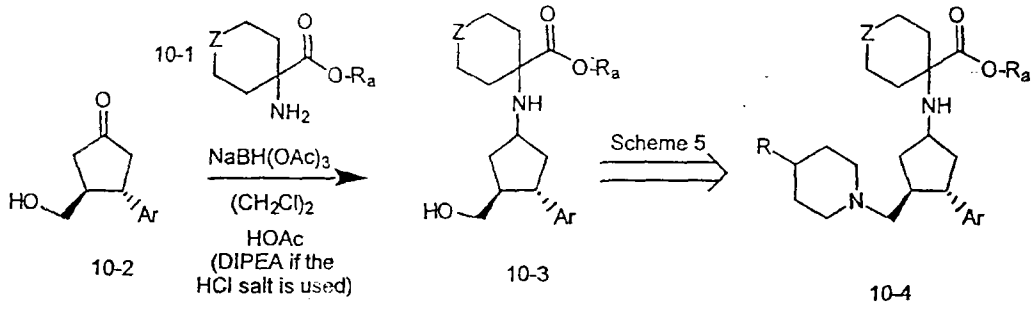
detailed in Scheme 5. Alternatively, a second reductive alkylation of 9-2 as in Scheme 8 affords 9-4 which may be separable or used as a mixture to give final product(s) 9-5. Also, more extended amino-acid esters, such as a β-alanine ester (9-6, n = 1) or 4-aminobutyrate (9-6, n = 2), which may also be substituted on the chain or on N, can be employed to give 9-7. These intermediates can then be converted to final product(s) 9-8 as described in Scheme 5 and/or 8.

SCHEME 10



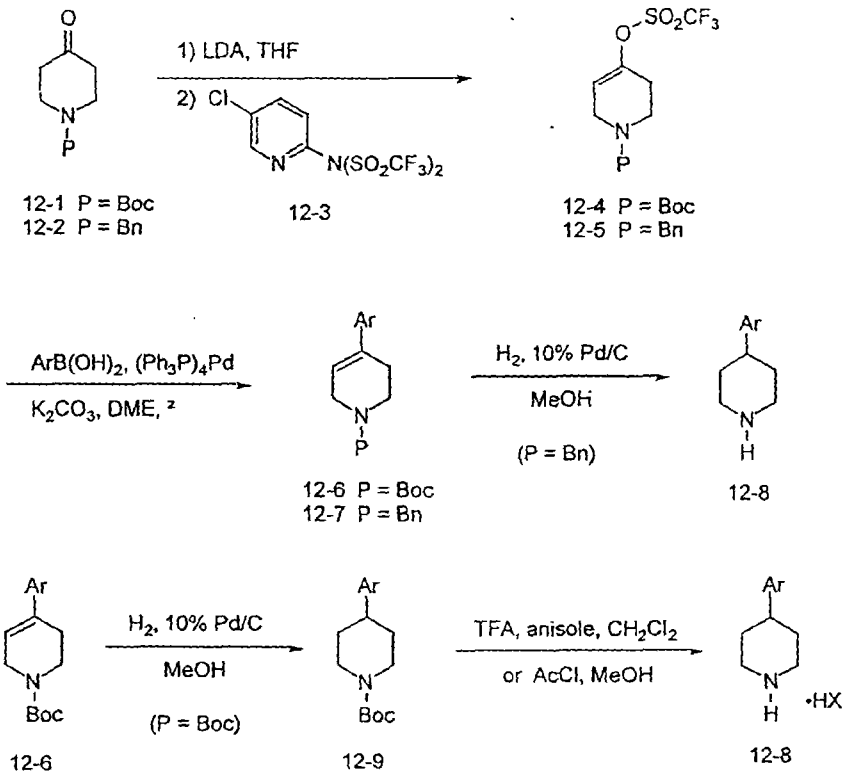
An alternative route for the preparation of some 1,3,4-trisubstituted cyclopentanes within the scope of the instant invention is given in Scheme 10. Reductive alkylation, using for example sodium triacetoxyborohydride or sodium cyanoborohydride, of a cyclic secondary amino-acid 10-1, such as D- or L-proline t-butyl ester (n = 0), β-proline t-butyl ester (n = 0), 2-, 3-, and 4-t-butylcarboxypiperidine (n = 1), with the ketone-alcohol 10-2 (Scheme 4) gives 10-3 and 10-4 as a mixture of C-1 isomers which may be separated. These intermediates can then be converted to the final product(s) as described in Scheme 5.

SCHEME 11



An alternative route for the preparation of some 1,3,4-trisubstituted cyclopentanes within the scope of the instant invention is given in Scheme 11. Reductive alkylation, using for example sodium triacetoxyborohydride or sodium cyanoborohydride, of a cycloalkyl amino-acid 11-1, such as 1-aminocyclopentane carboxylic acid t-butyl ester (Z = single bond) or a heterocyclic amino-acid, such as 4-aminomorpholin-2-yl carboxylic acid t-butyl ester (Z = O) with the ketone-alcohol 11-2 (Scheme 4) gives 11-3 and 11-4 as a mixture of C-1 isomers which may be separated. These intermediates can then be converted to the final product(s) as described in Scheme 5.

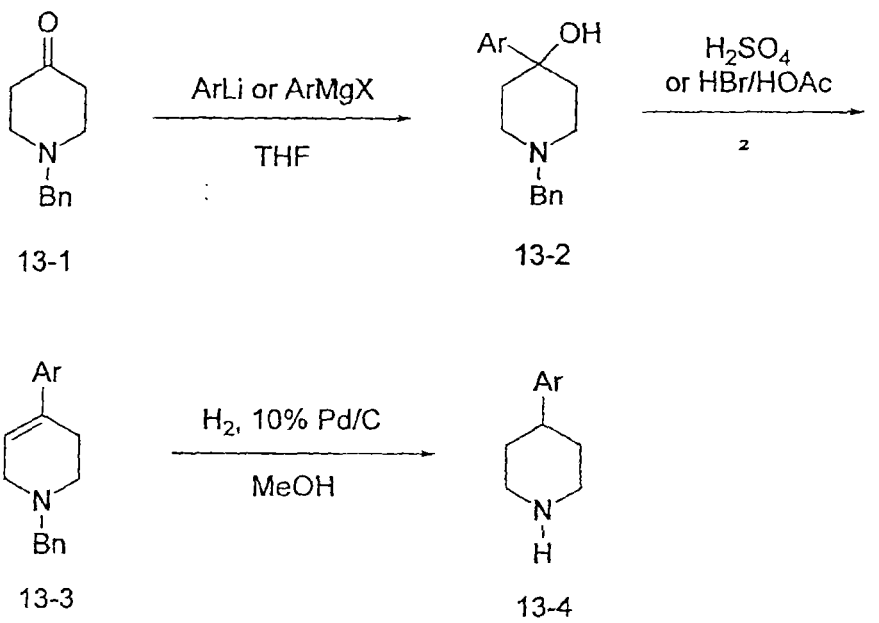
SCHEME 12



One method of generating 4-aryl piperidines as intermediates is given in Scheme 12. Reaction of commercially available 12-1 or 12-2 with a strong base, such as LDA, LHDMS, NaHMDS, KHMDS, or NaH followed by treating with a suitable triflating agent, such as 5-chloropyrid-2-yl triflimide (12-3), N-phenyl triflimide or triflic anhydride, provides enol triflates 12-4 or 12-5. Heating with commercially available aryl boronic acids in the presence of a suitable palladium(0) catalyst such as tetrakis triphenylphosphine palladium, a base (such as potassium carbonate or sodium carbonate), in a solvent such as DME, THF, dioxane or toluene/ethanol, effects coupling to provide the unsaturated products 12-6 or 12-7. In the case of 12-7, treatment with a heterogeneous palladium catalyst in methanol or ethanol in an atmosphere of hydrogen provides the desired intermediate 12-8. Alternatively, the Boc protected derivative 12-6 is hydrogenated under standard conditions to provided the saturated piperidine 12-9, which is then deprotected under

acidic conditions (such as trifluoroacetic acid and anisole in methylene chloride or HCl in methanol), to provide 12-8 as a salt, which is then utilized as the cyclic secondary amine component as shown above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

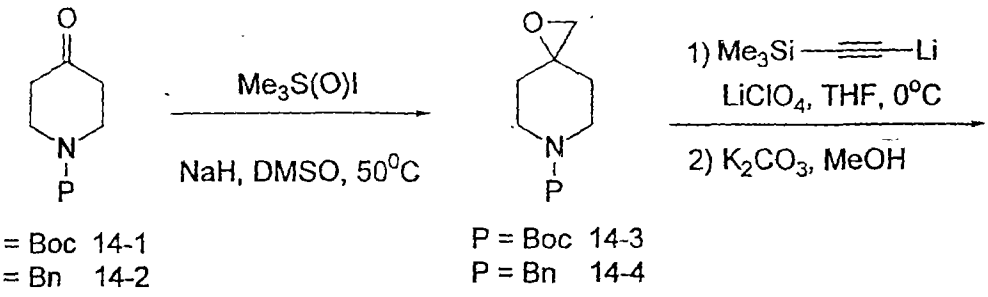
SCHEME 13



An alternative method of generating 4-aryl piperidines as intermediates is given in Scheme 13. Reaction of commercially available 13-1 with an aryl magnesium halide or with an aryllithium (in the presence or absence of anhydrous cerium trichloride) provides tertiary alcohol 13-2, which upon treatment under acidic conditions (such as sulfuric acid, HBr in acetic acid, HCl in acetic acid) or under dehydrating conditions (such as with thionyl chloride in pyridine or with phosphorus oxychloride) provides olefin 13-3. Hydrogenation under standard conditions using either hydrogen gas or a hydrogen donor (such as ammonium formate or cyclohexene) effects reduction of the double bond and cleavage of the N-benzyl group to provide the desired intermediate 13-4. Under some circumstances it may be preferable to reduce the double bond under non-hydrogenolytic conditions, for example with triethylsilane and trifluoroacetic acid or under dissolving metal conditions (for example, sodium or lithium metal in ammonia or a lower alkyl amine). If the N-

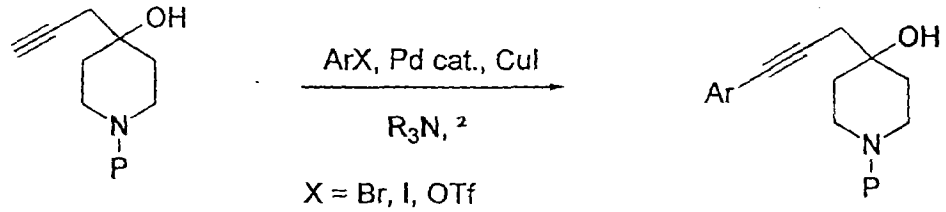
benzyl group is not removed under these conditions, it may be cleaved by treatment with either vinyl chloroformate and then hydrogen chloride or by treatment with 2-chloroethyl chloroformate followed by heating in methanol. The product 13-4 is then utilized as the cyclic secondary amine component as shown above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

SCHEME 14



P = Boc 14-1
P = Bn 14-2

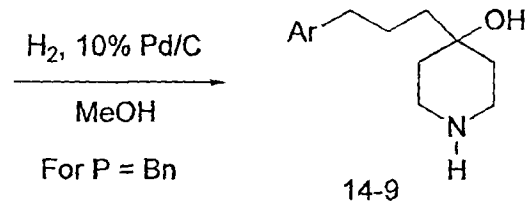
P = Boc 14-3
P = Bn 14-4



P = Boc 14-5
P = Bn 14-6

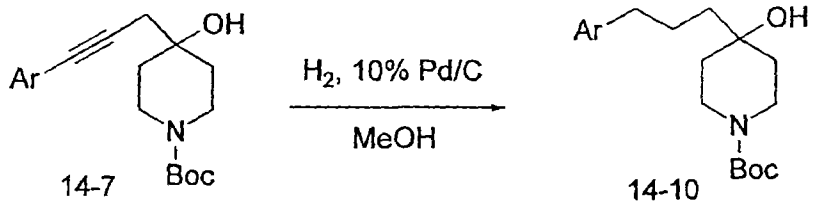
X = Br, I, OTf
Pd cat. = $(Ph_3P)_2PdCl_2$, $(Ph_3P)_2Pd(OAc)_2$
R_3N: Et_3N, Bu_3N

P = Boc 14-7
P = Bn 14-8



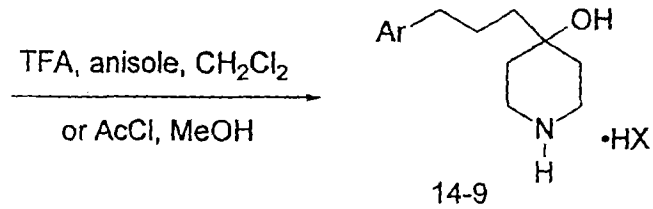
For P = Bn

14-9



14-7

14-10

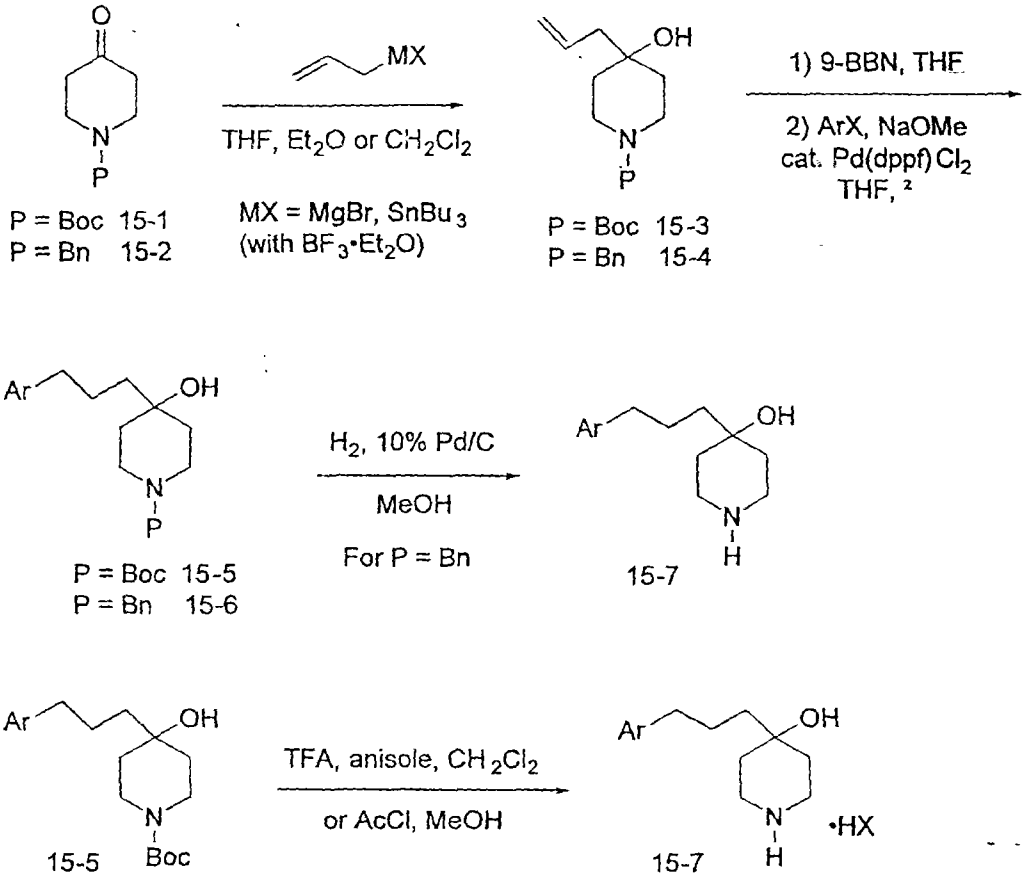


14-9

856

One route for the preparation of 4-hydroxy-4-(3-arylpropyl)piperidines is given in Scheme 14. Treatment of commercially available 4-piperidones 14-1 or 14-2 with trimethylsulfonium iodide and sodium hydride in dimethyl sulfoxide at or above room temperature provides spiro epoxides 14-3 or 14-4. Addition of the lithium salt of trimethylsilylacetylene to these epoxides in the presence of lithium perchlorate in THF at 0 degrees C, followed by treatment of the crude intermediate with potassium carbonate in methanol, affords the acetylenic alcohols 14-5 or 14-6. Heating of these alkynes with an aromatic halide or triflate in the presence of copper(I) iodide, a palladium catalyst such as bis(triphenylphosphine)palladium dichloride or bis(triphenylphosphine)palladium diacetate in the presence of a tertiary amine base such as triethylamine or tributylamine, then provides coupling products 14-7 or 14-8. In the case of the N-benzyl protected intermediate 14-8, hydrogenation/hydrogenolysis under standard conditions (for example 10% Pd/C in an atmosphere of hydrogen) provides desired intermediate 14-9. For the Boc protected species 14-7, hydrogenation as above provides the saturated piperidine 14-10, and treatment of this compound under anhydrous acidic conditions (for example, trifluoroacetic acid and anisole in methylene chloride, or acetyl chloride in methanol) then yields the salt of intermediate 14-9. This compound is then utilized as the cyclic secondary amine component as shown above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11. Alternatively, if 4-piperidone is attached directly to the functionalized alkylcyclopentane framework described above and no functionality in the alkylcyclopentane would be affected, then the chemistry described herein can be carried out treating the aforementioned alkylcyclopentane segment as 'P' given in Scheme 14.

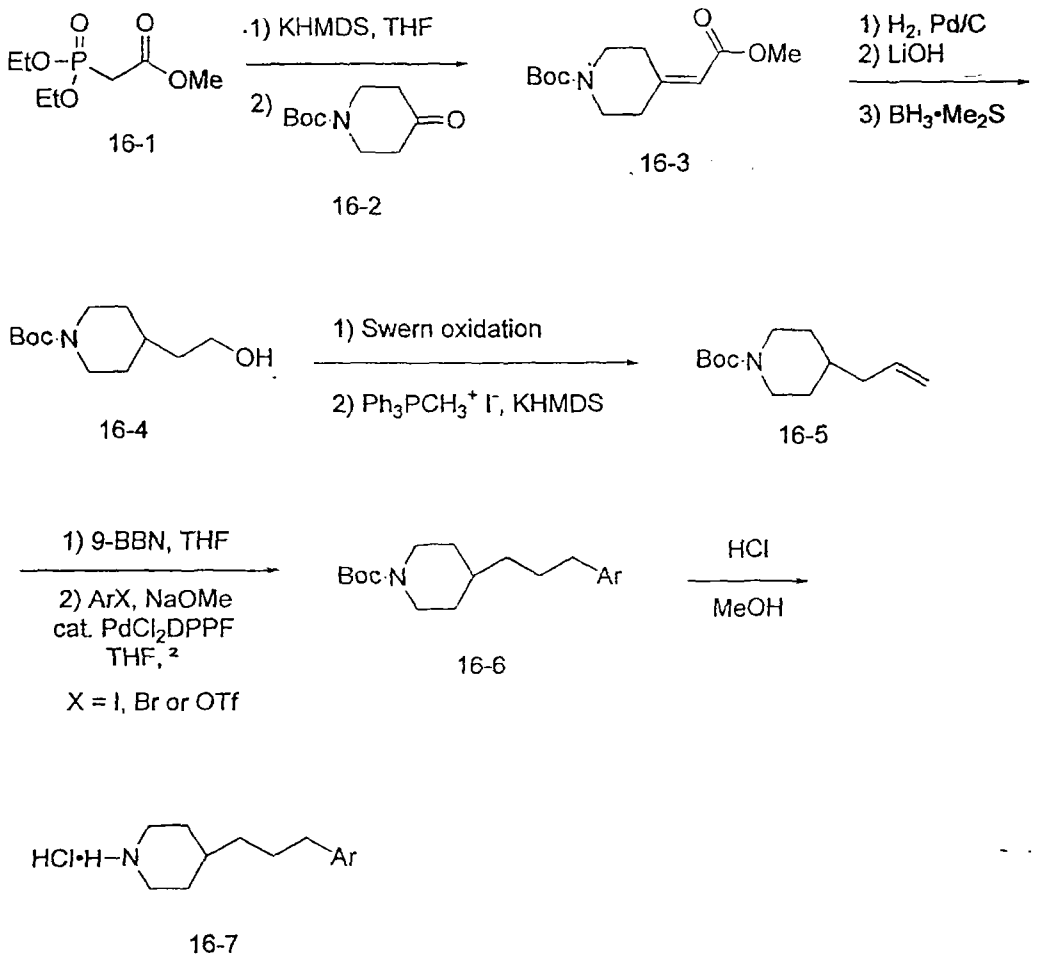
SCHEME 15



An alternative route for the preparation of 4-hydroxy-4-(3-arylpropyl)piperidines is given in Scheme 15. Treatment of commercially available 4-piperidones 15-1 or 15-2 with a suitable allyl metal compound (such as allylmagnesium bromide or allyltributylstannane (in the presence of boron trifluoride etherate) in THF, ether or dichloromethane, provides adducts 15-3 or 15-4. Hydroboration with a dialkylborane, such as 9-borabicyclo[3.3.1]nonane (9-BBN), followed by treatment with an aryl halide (the halides preferably being bromide or iodide) or aryl triflate and sodium methoxide in the presence of a suitable soluble palladium catalyst, for example $Pd(dppf)Cl_2$, in warm to refluxing THF, provides the 3-arylpropyl derivatives 15-5 and 15-6. For benzylamine 15-6, hydrogenolysis under

standard conditions provides the desired intermediate 15-7. For Boc substituted piperidine 15-5, exposure to suitable anhydrous acidic conditions (for example trifluoroacetic acid and anisole in methylene chloride or HCl in methanol at temperatures from 0-25 degrees C) affords the salt of 15-7. This compound is then utilized as the cyclic secondary amine component as shown above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11. Alternatively, if no functionality are present in the alkylcyclopentane framework that would be adversely effected by the above mentioned chemistry, then 4-piperidone may be attached directly to the alkylcyclopentane framework described above, and the chemistry described in this paragraph can be carried out equating the alkylcyclopentane segment to the group 'P' given in Scheme 15, structures 1 through 6.

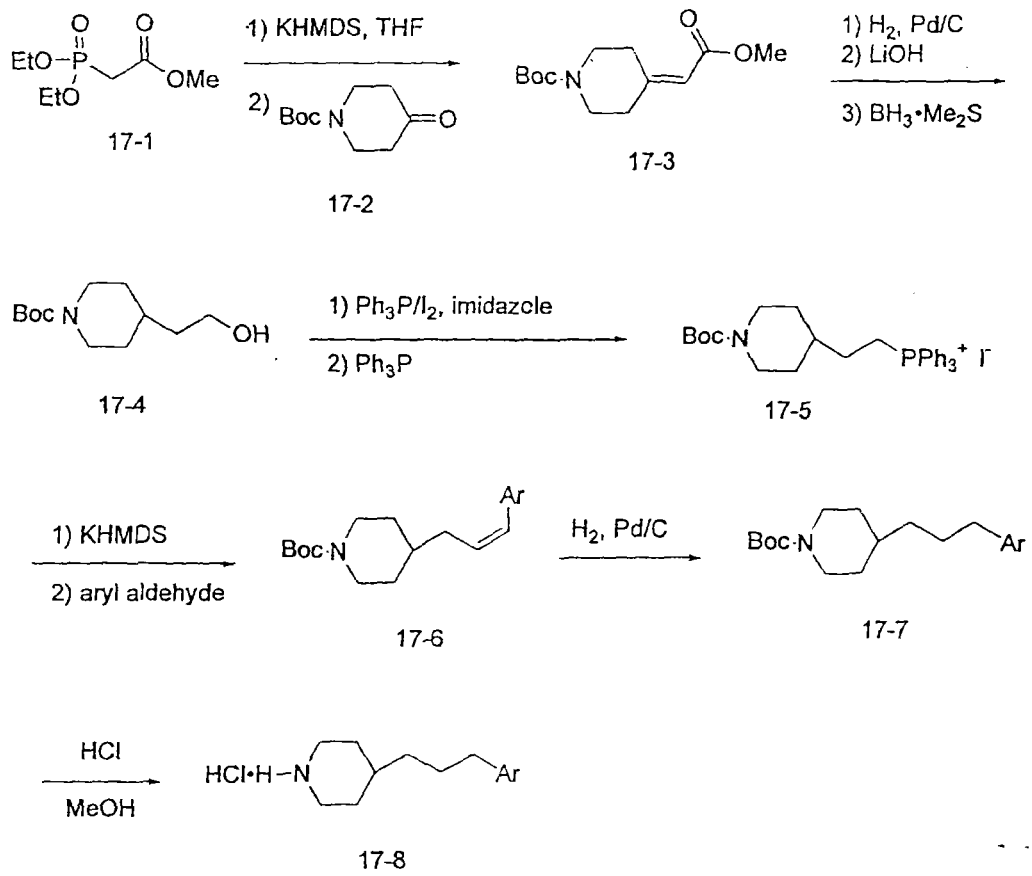
SCHEME 16



A route for the preparation of 4-(3-arylpropyl)piperidines is given in Scheme 16. Treatment of phosphonoacetate 16-1 with KHMDS followed by addition of commercially available N-Boc -4-piperidone 16-2 provides unsaturated ester 16-3. Hydrogenation of 16-3 followed by hydrolysis to the acid and then reduction with borane•methyl sulfide then affords primary alcohol 16-4. Mild oxidation of 16-4 under Swern conditions provides the corresponding aldehyde, which upon treatment with the Wittig reagent prepared from methyltriphenylphosphonium iodide and KHMDS yields olefin 16-5. Hydroboration with a dialkylborane, such as 9-borabicyclo[3.3.1]nonane (9-BBN), followed by treatment with an aryl halide (the

halides preferably being bromide or iodide) or aryl triflate in the presence of a suitable soluble palladium catalyst, for example $PdCl_2DPPF$, in warm to refluxing THF, provides the 3-arylpropyl derivative 16-6. Removal of the Boc group under acidic conditions, for example with HCl in methanol or with trifluoroacetic acid in methylene chloride, then affords the 1-unsubstituted piperidine 16-7, which can then be employed as the secondary amine component in the syntheses described above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

SCHEME 17

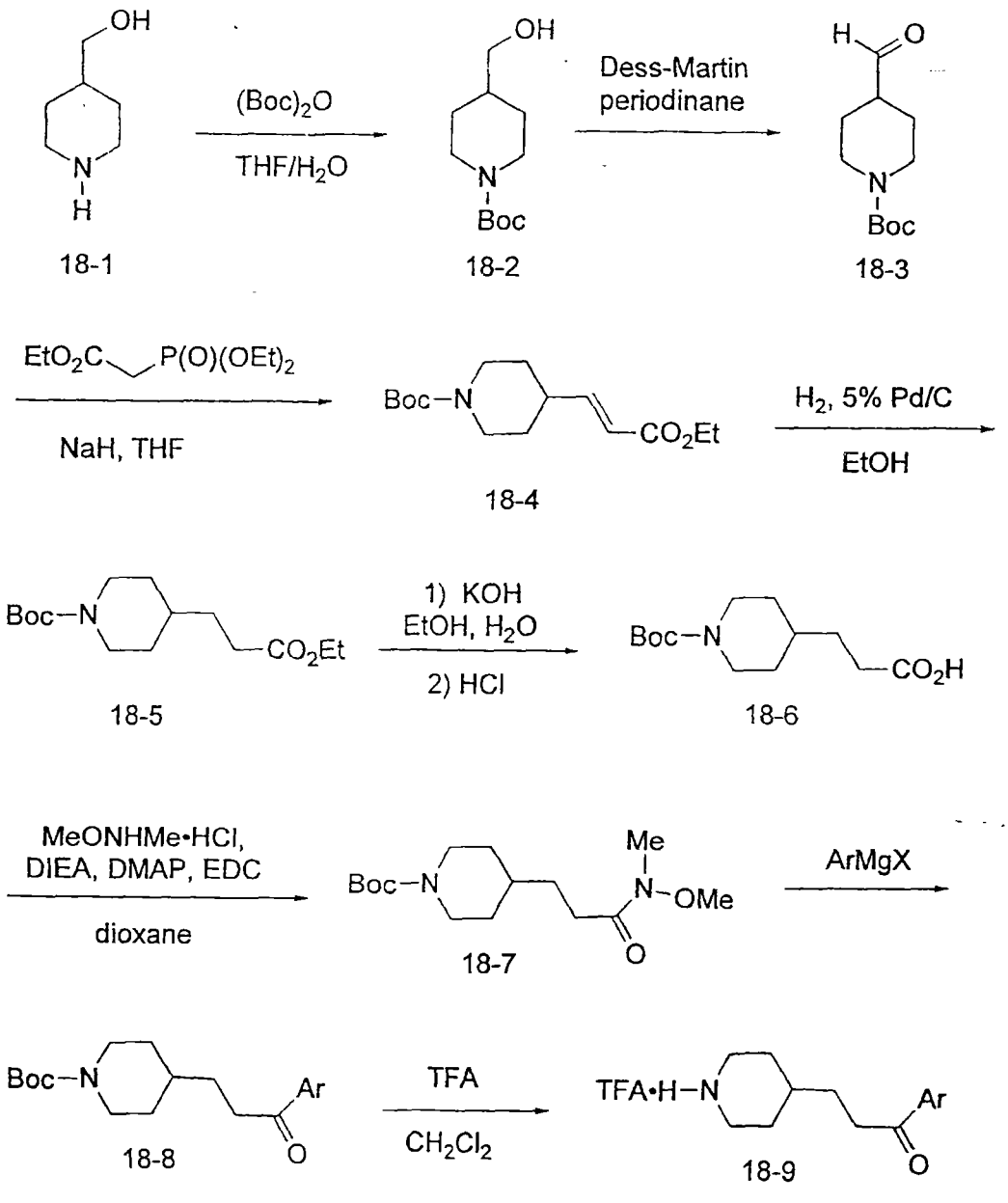


Another route for the preparation of 4-(3-arylpropyl)piperidines is given in Scheme 17. Treatment of phosphonoacetate 17-1 with KHMDS followed by addition of commercially available N-Boc -4-piperidone 17-2 provides unsaturated ester 17-3. Hydrogenation of 17-3 followed by hydrolysis to the acid and then reduction with borane•methyl sulfide then affords primary alcohol 17-4. Formation of the alkyl iodide with triphenylphosphine and iodine in the presence of imidazole followed by treatment with triphenylphosphine provides phosphonium salt 17-5. Deprotonation with a suitable base, for example, KHMDS, LiHMDS, NaHMDS, NaH, LDA, or KH affords the Wittig agent *in situ*, which upon treatment with a suitable aromatic aldehyde yields the unsaturated derivative 17-6. Hydrogenation under standard conditions provides 17-7, and removal of the Boc group with HCl in methanol or with other acidic conditions then provides the 1-unsubstituted piperidine

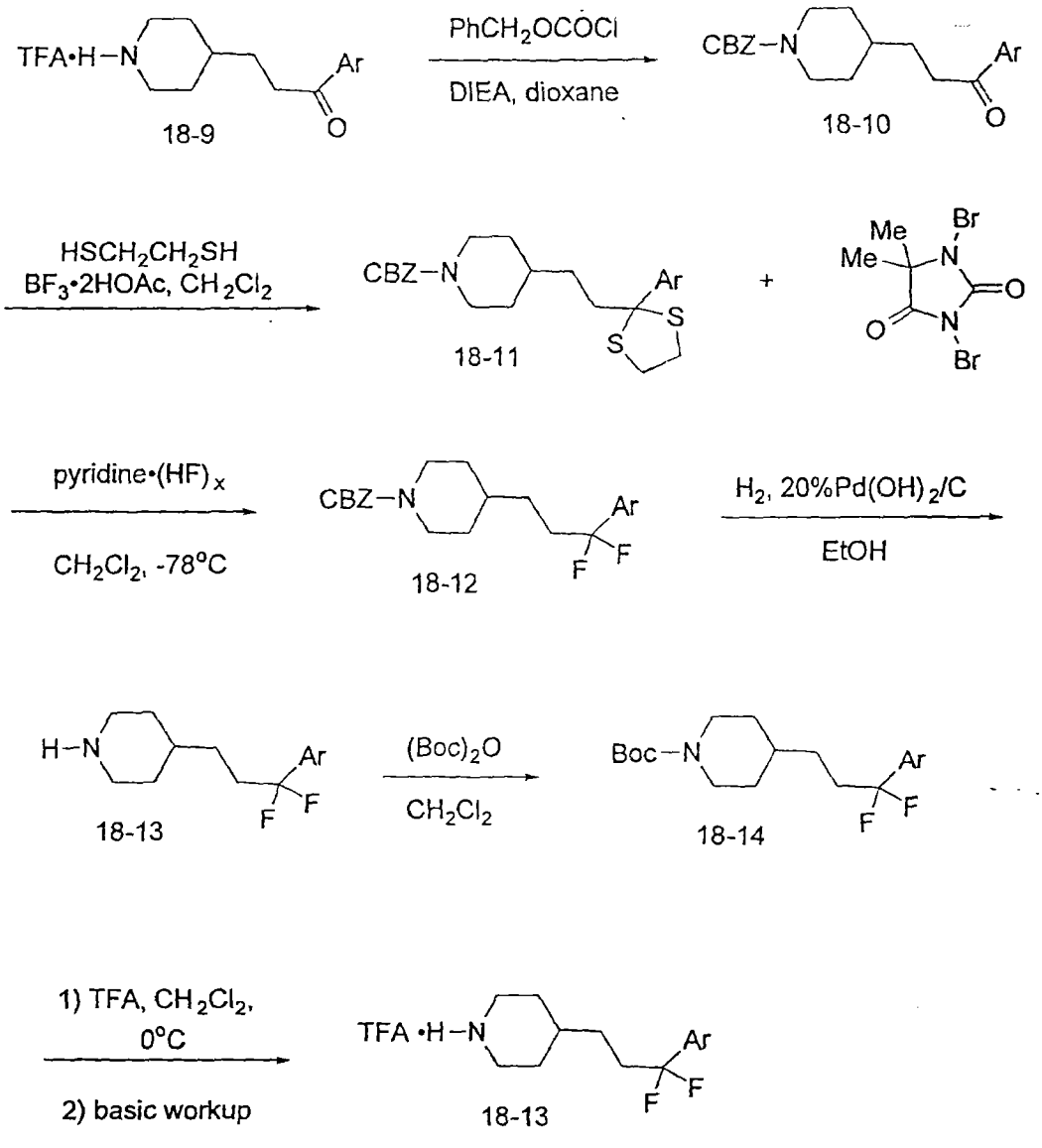
862

17-8, which can then be employed as the secondary amine component in the syntheses described above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

SCHEME 18


OH
N
H
18-1
(Boc)2O
THF/H2O
OH
N
Boc
18-2
Dess-Martin
periodinane
H
O
N
Boc
18-3
EtO2C
P(O)(OEt)2
NaH, THF
Boc–N
CO2Et
18-4
H2, 5% Pd/C
EtOH
Boc–N
CO2Et
18-5
1) KOH
EtOH, H2O
2) HCl
Boc–N
CO2H
18-6
MeONHMe•HCl,
DIEA, DMAP, EDC
dioxane
Boc–N
Me
N–OMe
O
18-7
ArMgX
Boc–N
Ar
O
18-8
TFA
CH2Cl2
TFA•H–N
Ar
O
18-9

SCHEME 18, con't.

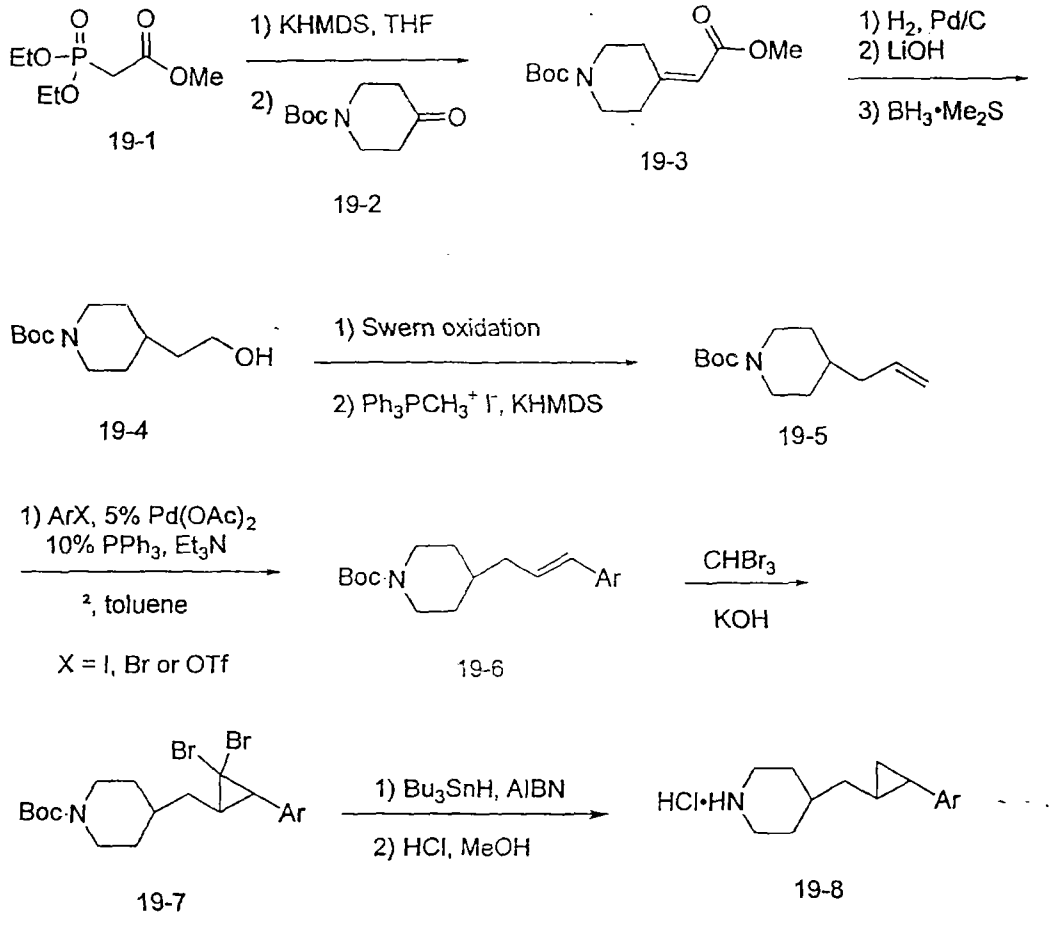


Preparation of piperidines with a 4-(3-aryl-3,3,-difluoropropyl) side chain is given in Scheme 18. Treatment of commercially available 18-1 with Boc anhydride provides

protected piperidine 18-2. Oxidation, for example with the Dess-Martin reagent, by a Swern oxidation, or other known methods provides aldehyde 18-3. Condensation under Horner-Wadsworth-Emmons conditions affords unsaturated ester 18-4, which is hydrogenated to ester 18-5 and then hydrolysed to acid 18-6. Formation of the N-methyl-N-methoxy amide 18-7 is carried out employing standard activating agents such as EDC. Weinreb amide 18-7 is then allowed to react with an arylmetal reagent, such as an aryl magnesium halide or an aryllithium, to provide ketone 18-8. Cleavage of the protecting Boc group under acidic conditions yields 18-9, which is reprotected with a carbobenzyloxy group under standard conditions, to afford 18-10. Formation of dithiolane 18-11 with ethanedithiol and boron trifluoride is followed by treatment with 1,3-dibromo-3,3-dimethylhydantoin and pyridine-hydrogen fluoride complex at or around -78 degrees C, to provide gem-difluoro derivative 18-12. Removal of the CBZ group under reductive conditions provides piperidine 18-13, which may be employed directly as the secondary amine in chemistry described above.

Alternatively, if additional purification is desired, 18-13 may be protected with a Boc group to afford 18-14. After suitable purification, the Boc group is removed under acidic conditions at or near 0 degrees C. A controlled, basic work-up then provides 18-13, suitable for use as described above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

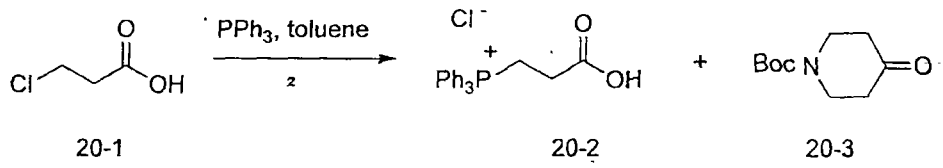
SCHEME 19



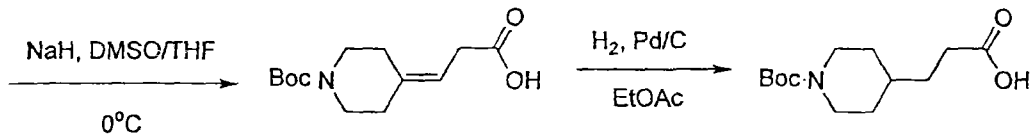
A route for the preparation of 4-(3-arylpropyl)piperidines is given in Scheme 19. Treatment of phosphonoacetate 19-1 with KHMDS followed by addition of commercially available N-Boc -4-piperidone 19-2 provides unsaturated ester 19-3. Hydrogenation of 19-3 followed by hydrolysis to the acid and then reduction with borane•methyl sulfide then affords primary alcohol 19-4. Mild oxidation of 19-4 under Swern conditions provides the corresponding aldehyde, which upon treatment with the Wittig reagent prepared from methyltriphenylphosphonium iodide and KHMDS yields olefin 19-5. Palladium-catalyzed arylation of 19-5 then affords

unsaturated derivative 19-6. Addition of dibromocarbene (generated *in situ* from bromoform and potassium hydroxide) provides cyclopropyl derivative 19-7. Debromination is carried out by slow addition of tributyltin hydride in the presence of the radical initiator AIBN. Removal of the nitrogen protecting group under acidic conditions, for example, hydrochloric acid in methanol, affords cyclopropyl piperidine 19-8, which can then be employed as the secondary amine component in the syntheses described above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

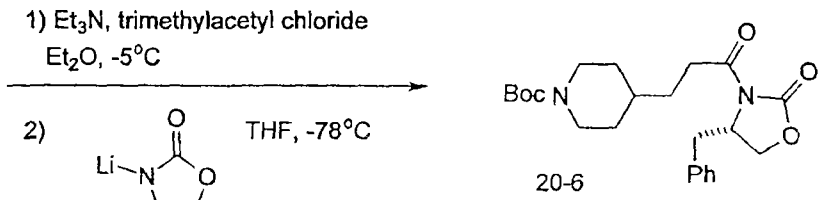
SCHEME 20



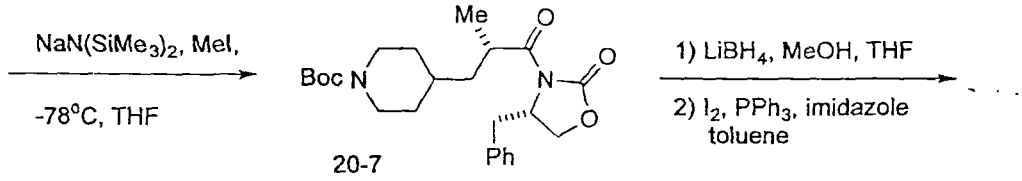
20-1 20-2 20-3



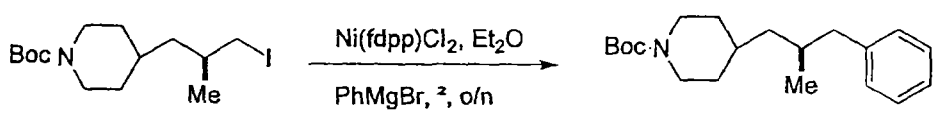
20-4 20-5



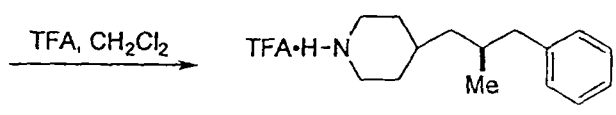
20-6



20-7



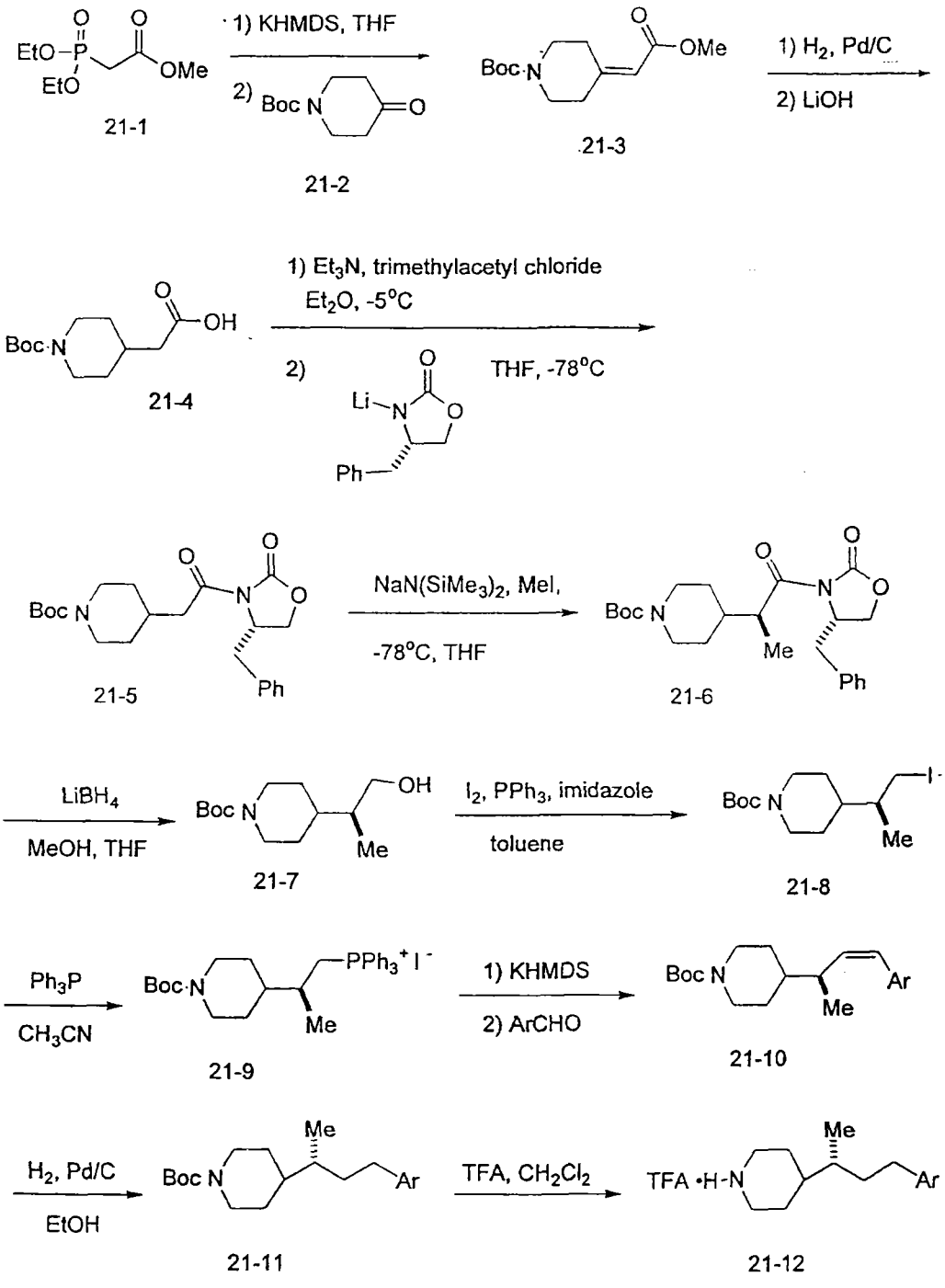
20-8 20-9



20-10

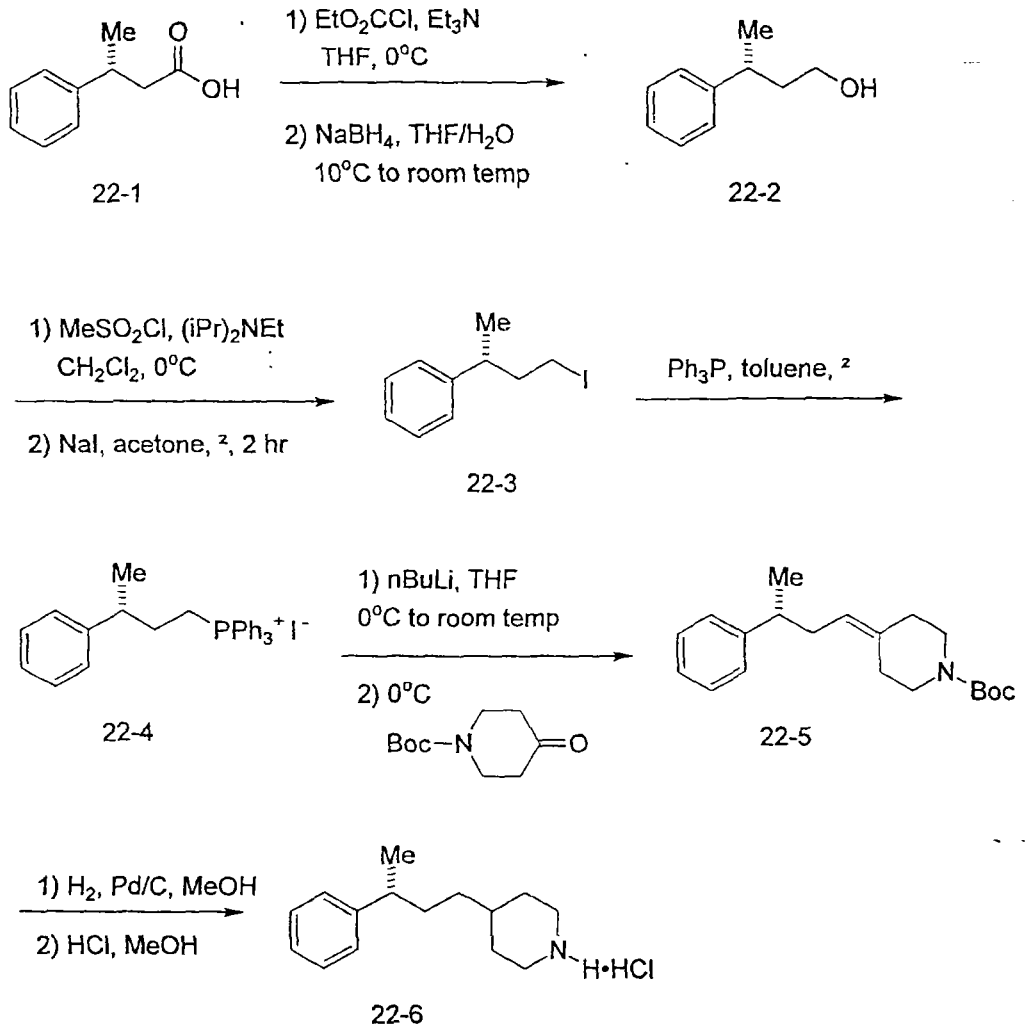
A route for the preparation of 4-(3-aryl-2-methylpropyl)piperidines is given in Scheme 20. Treatment of commercially available 3-chloropropionic acid (20-1) with triphenylphosphine in refluxing toluene provides phosphonium salt 20-2. Treatment with sodium hydride in DMSO/THF provides the ylide in situ, which upon addition of piperidone 20-3 affords the adduct 20-4. Reduction of the double bond, for example with hydrogen gas in the presence of a palladium catalyst, gives acid 20-5. Treatment of 20-5 with trimethylacetyl chloride and triethylamine generates the mixed anhydride in situ, which upon treatment with the lithium salt of 4-(S)-benzyl-2-oxazolidone yields 20-6. Deprotonation of 20-6 with sodium hexamethyldisilazide, followed by addition of methyl iodide, provides alpha-methyl derivative 20-7. Reduction of acyl-oxazolidone 20-7 with lithium borohydride produces the corresponding primary alcohol, which is converted to primary iodide 20-8 with iodine, triphenylphosphine and imidazole in toluene. Coupling with phenyl magnesium bromide in the presence of $Ni(fdpp)Cl_2$ affords aralkyl derivative 20-9, which is then deprotected under acidic conditions to provide piperidine 20-10. Piperidine 20-10 can then be employed as the secondary amine component in the syntheses described above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

SCHEME 21


EtO–P(O)(EtO)–CH2–C(=O)–OMe
21-1
1) KHMDS, THF
2) Boc N=O
21-2
Boc-N
OMe
21-3
1) H2, Pd/C
2) LiOH
Boc-N
OH
21-4
1) Et3N, trimethylacetyl chloride
Et2O, -5°C
2)
THF, -78°C
Li-N
Ph
Boc N
Ph
21-5
NaN(SiMe3)2, MeI,
-78°C, THF
Me
21-6
LiBH4
MeOH, THF
OH
21-7
I2, PPh3, imidazole
toluene
I
21-8
Ph3P
CH3CN
PPh3+ I-
21-9
1) KHMDS
2) ArCHO
Ar
21-10
H2, Pd/C
EtOH
21-11
TFA, CH2Cl2
TFA •H-N
21-12

A route for the preparation of 4-(3-aryl-1-methylpropyl)piperidines is given in Scheme 21. Addition of the anion of phosphonoester 21-1 to piperidone 21-2 provides unsaturated ester 21-3. Reduction of the double bond and hydrolysis of the ester affords acid 21-4. Treatment of 21-4 with triethylamine and trimethylacetyl chloride provides the mixed anhydride in situ, which is then coupled with the lithium salt of 4-(S)-benzyl-2-oxazolidone , to yield acyl oxazolidone 21-5. Deprotonation with sodium hexamethyldisilazide followed by addition of methyl iodide provides 21-6. Reduction of 21-6 with lithium borohydride affords alcohol 21-7, which upon treatment with iodine, triphenylphosphine and imidazole in toluene is converted to iodide 21-8. Treatment with triphenylphosphine gives phosphonium salt 21-9, which is converted to the ylide with potassium hexamethyldisilazide. Addition of an aryl aldehyde generates unsaturated aryl derivative 21-10. Hydrogenation provides saturated piperidine 21-11, which is then deprotected under acidic conditions to afford 21-12, which can then be employed as the secondary amine component in the syntheses described above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

SCHEME 22

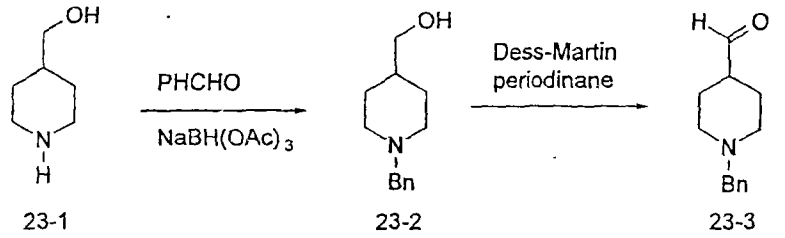


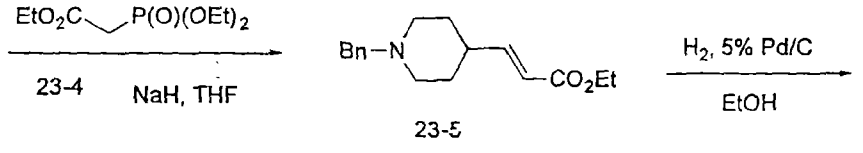
A route for the preparation of 4-(3-aryl-3-methylpropyl)piperidines is given in Scheme 22. Treatment of commercially available 4-(R)-phenylbutyric acid (22-1) with ethyl chloroformate and triethylamine forms the asymmetric anhydride in situ, which upon treatment with sodium borohydride provides primary alcohol 22-1. Alternatively, this conversion can be carried out by treatment of 22-1 with borane-THF. Activation of the hydroxy group of 22-2 with methanesulfonyl chloride in the presence of a hindered base such as N,N-(diisopropyl)ethylamine, followed by displacement with sodium iodide in refluxing acetone affords iodide 22-3. Heating

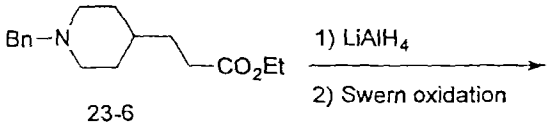
with triphenylphosphine in toluene provides the phosphonium salt 22-4. Deprotonation of this salt with a strong base, for example n-butyl lithium generates the Wittig reagent in situ, which is then allowed to react with N-Boc-4-piperidone, to yield olefin 22-5. Hydrogenation of the double bond followed by treatment with acid, for example HCl in methanol, then provides the secondary amine salt 22-6, which can then be employed as the secondary amine component in the syntheses described above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

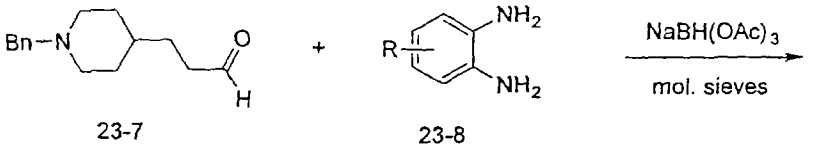
SUBSTITUTE SHEET (RULE 26)

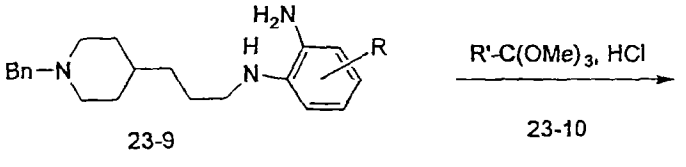
SCHEME 23

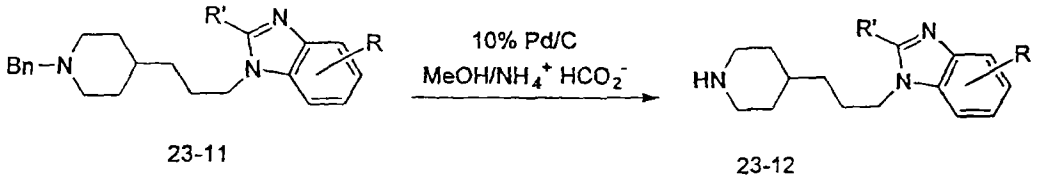

OH
PHCHO
NaBH(OAc)3
N
H
23-1
OH
N
Bn
23-2
Dess-Martin
periodinane
H
O
N
Bn
23-3


EtO2C
P(O)(OEt)2
23-4
NaH, THF
Bn–N
CO2Et
23-5
H2, 5% Pd/C
EtOH


Bn–N
CO2Et
23-6
1) LiAlH4
2) Swern oxidation


Bn–N
O
H
23-7
+
R
NH2
NH2
23-8
NaBH(OAc)3
mol. sieves

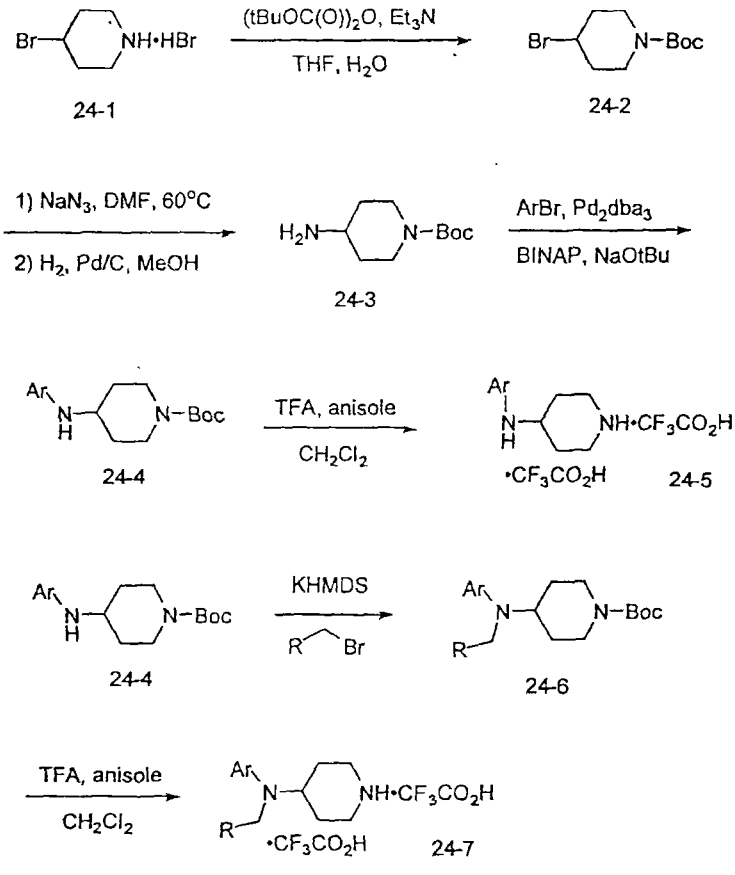

H2N
H
Bn–N
N
R
23-9
R'-C(OMe)3, HCl
23-10


R'
N
Bn–N
N
R
23-11
10% Pd/C
MeOH/NH4+ HCO2-
HN
23-12

5

A route for the preparation of 4-(3-(benzimidazol-2-yl)propyl)piperidines is given in Scheme 23. Protection of piperidine 23-1 under reductive amination conditions provides benzylamine 23-2. Oxidation to aldehyde 23-3 is carried out under standard conditions, for example with the Dess-Martin periodinane. Addition of ester 23-4 provides unsaturated olefin 23-5, which upon reduction affords ester 23-6. Reduction with lithium aluminum hydride or other strong hydride reducing agents followed by mild oxidation provides aldehyde 23-7. Upon combination with diamine 23-8 under reductive alkylation conditions affords the N-alkylated derivative 23-9. Treatment with orthoformate derivative 23-10 in the presence of acid yields benzimidazole 23-11, which upon hydrogenation with palladium on carbon under transfer hydrogenation conditions generates piperidine 23-12, which can then be employed as the secondary amine component in the syntheses described above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

SCHEME 24

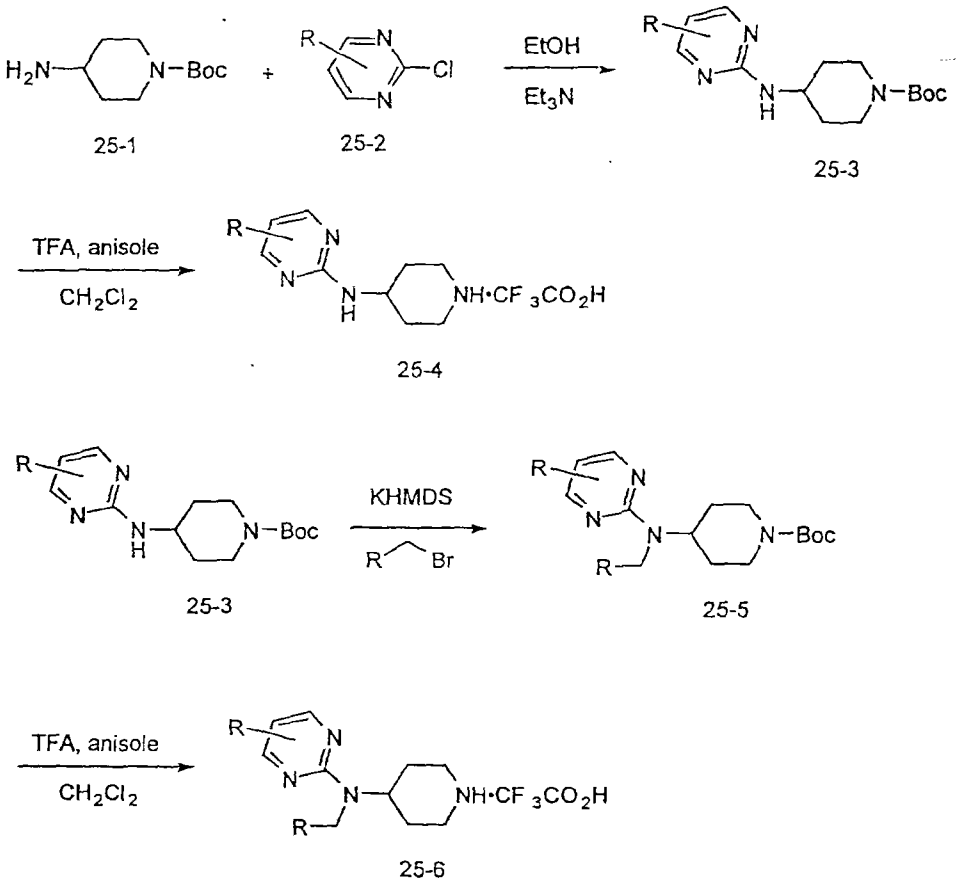


Procedures for synthesizing certain CCR5 receptor modulators containing 4-(heteroarylamino)piperidine functionality are shown in Scheme 24. After protecting commercially available 4-bromopiperidine, the bromide is displaced with sodium azide, and the azide is reduced, for example by catalytic reduction, to provide aminopiperidine 24-3. Treatment of 24-3 with an aryl or heteroaryl halide (the halide preferably being bromide) in the presence of a palladium catalyst, sodium t-butoxide and a suitable bidentate ligand (such as BINAP), according to the conditions of Buchwald et al, provides arylamine 24-4. Direct acidic deprotection of 24-4 may be carried out to provide secondary amine 24-5. Alternatively, amine 24-4 may be alkylated with a suitable alkyl, alkenyl or alkynyl halide (wherein the halide is bromo or iodo in the case of an alkyl group and chloro or bromo in the case of allylic or propargylic functionality) in the presence of a strong base, such as potassium

hexamethyldisilazide, to provide trisubstituted amine 24-6. Acidic deprotection, for example, trifluoroacetic acid and anisole in dichloromethane, or methanolic hydrochloric acid, then provides the bis ammonium salt, which in the case of trifluoroacetic acid deprotection, is compound 24-7. The secondary piperidines 24-5 and 24-7 are then utilized as the cyclic secondary amine component as shown above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

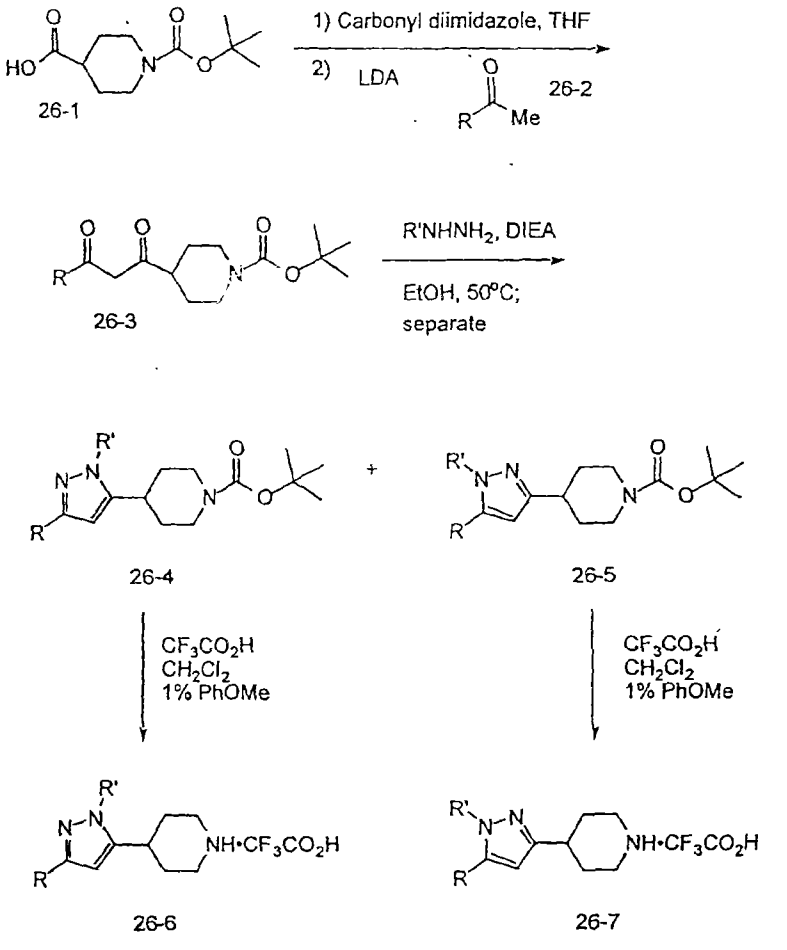
SUBSTITUTE SHEET (RULE 26)

SCHEME 25



For certain aminoheterocycles, direct displacement of a halogen may provide improved access to the desired intermediates. For example, as shown in Scheme 25, unsubstituted and substituted 2-chloropyrimidines 25-2 may be coupled directly to amine 25-1 in the presence of a suitable base, such as triethylamine, to provide aminopyrimidine 25-3. Acidic deprotection then affords 25-4. Alternatively, 25-3 may be alkylated in the presence of a strong base to provide 25-5, which upon deprotection gives intermediate 25-6. The secondary piperidines 25-4 and 25-6 are then utilized as the cyclic secondary amine component as shown in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

SCHEME 26



One preparation of piperidine subunits containing functionalized pyrazoles at C4 of the piperidine is given in Scheme 26. Treatment of piperidine 26-1 with carbonyldiimidazole to form the acyl imidazole, followed by addition of a dialkyl or alkyl-aryl ketone (26-2) in the presence of lithium diisopropylamide (LDA) gives the diketone 26-3. Treatment with a monoalkyhydrazine in an alcohol solvent at temperatures between 0 to 100 degrees C (preferably about 50 degrees C) in the presence of a hindered base such as DIPEA then provides a mixture of the isomeric pyrazoles 26-4 and 26-5. After separation of these compounds by chromatography or crystallization, the individual products are deblocked under acidic conditions (for example trifluoroacetic acid and anisole with or without methylene chloride as a co-

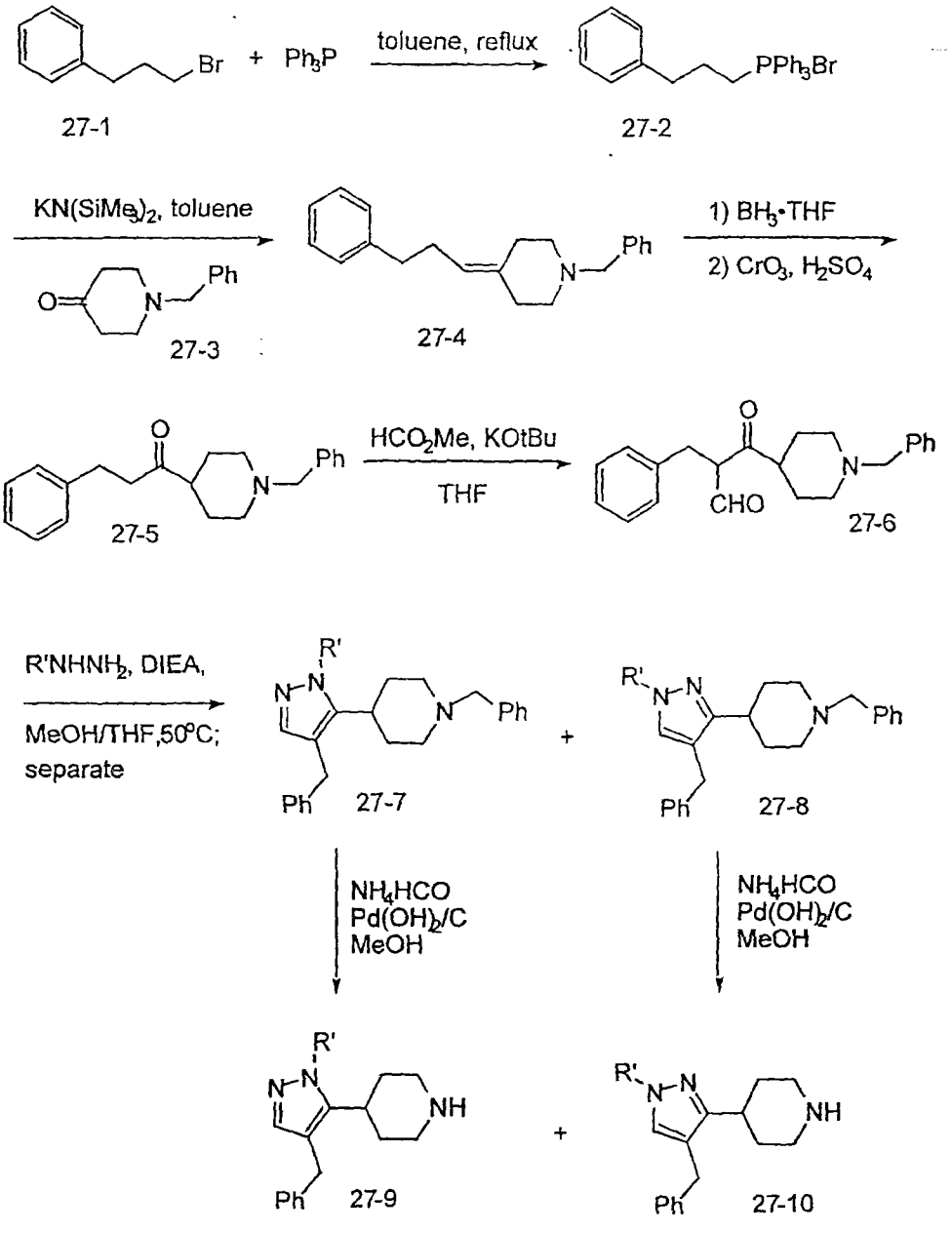
4-50

solvent) to provide the piperidine salts 26-6 and 26-7, which are then used as the cyclic secondary amine component as shown above in Scheme 2 and in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

copied from 09/445,626

09/14/2005 15:50 FAX 609 734 6949

SCHEME 27



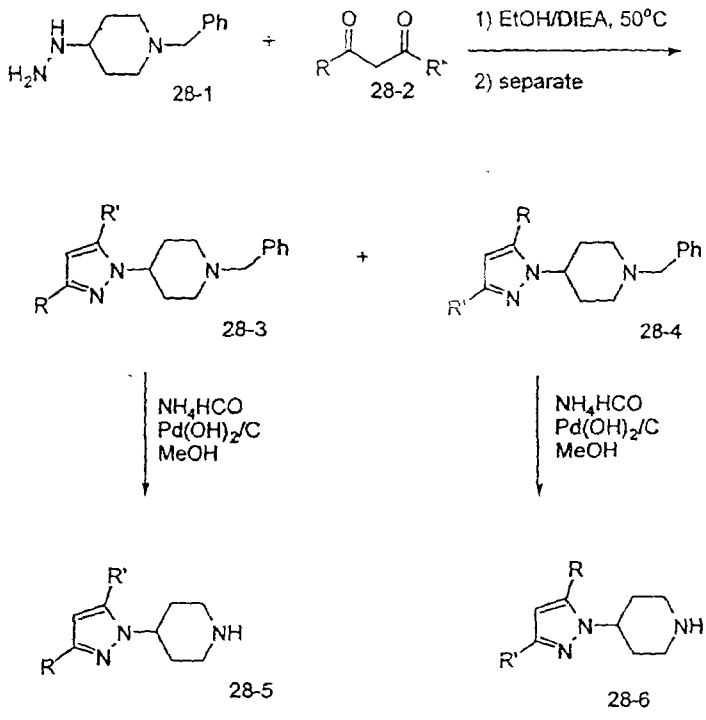
Another preparation of piperidine subunits containing functionalized pyrazoles at C4 of the piperidine is given in Scheme 27. Treatment of commercially available bromide 27-1 with triphenylphosphine in refluxing toluene provides phosphonium salt

882

27-2, which after treatment with a strong anhydrous base such as potassium hexamethyldisilazide in toluene and the piperidine ketone 27-3 provides the olefin 27-4. Hydroboration followed by an oxidative work-up with chromic acid then affords ketone 27-5. Selective formylation of 27-5 with methyl formate in the presence of potassium t-butoxide selectively affords ketoaldehyde 27-6. Heating of 27-6 with a monoalkylhydrazine in methanol in the presence of a hindered (or insoluble) base such as DIPEA then provides a mixture of the 1,4-disubstituted pyrazoles 27-7 and 27-8. After separation by chromatography, crystallization or fractional distillation, the purified isomers are deprotected under transfer hydrogenation conditions to provide the piperidines 27-9 and 27-10, which are then utilized as the cyclic secondary amine component as shown above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

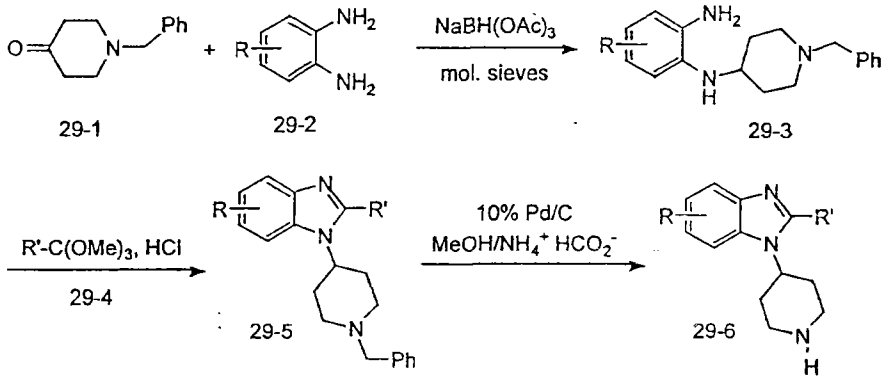
SUBSTITUTE SHEET (RULE 26)

SCHEME 28



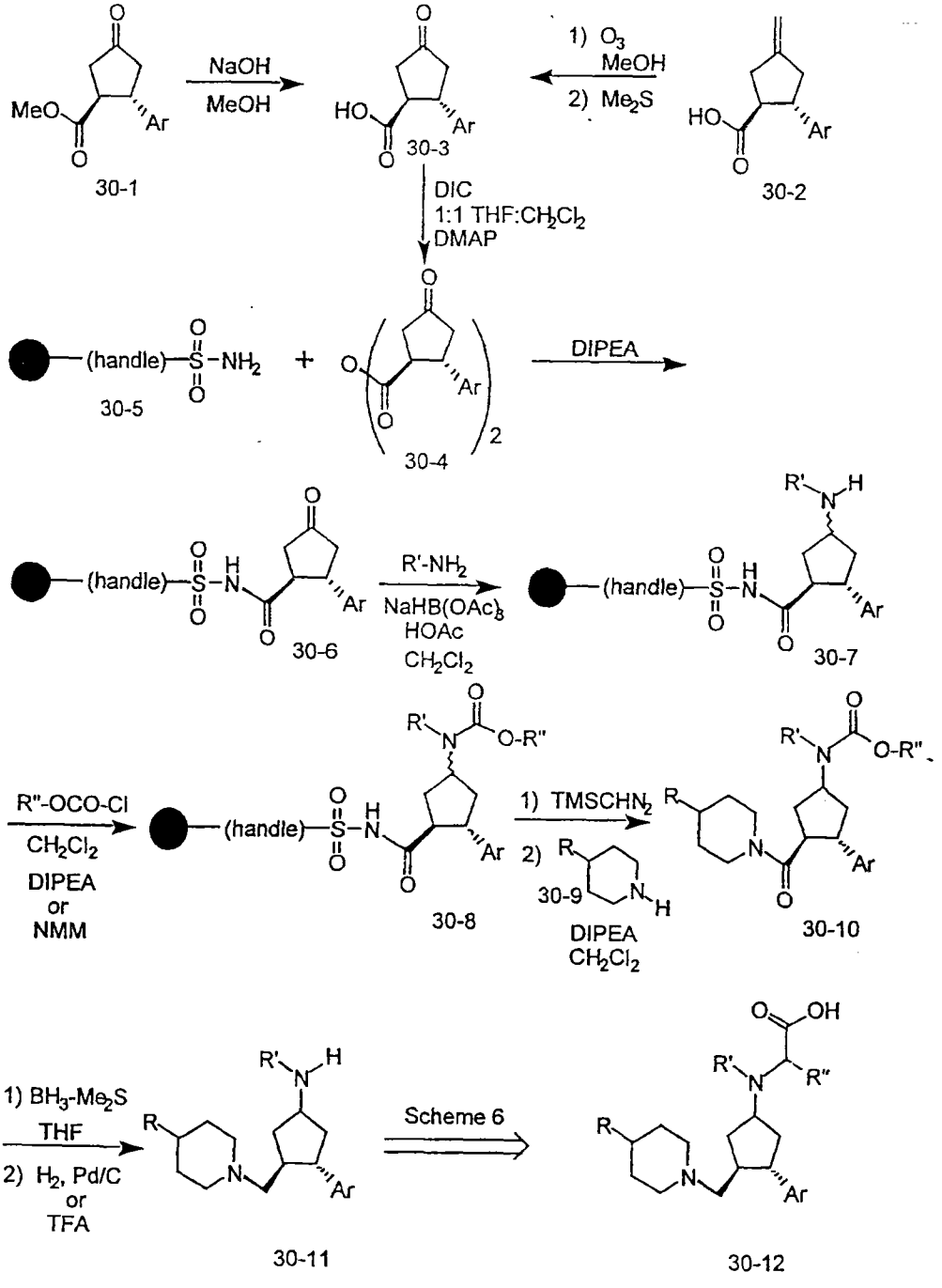
A preparation of piperidine subunits containing 3,5-difunctionalized pyrazoles linked through N-1 to C-4 of the piperidine is given in Scheme 28. Treatment of commercially available hydrazine 28-1 with diketone 28-2 in ethanol at 0 to 90 degrees C (preferably 50 degrees C) in the presence of DIPEA provides a mixture of pyrazoles 28-3 and 28-4, which are separated under standard conditions, for example HPLC. Removal of the benzyl groups by transfer hydrogenation provides the secondary piperidines 28-5 and 28-6, which are then utilized as the cyclic secondary amine component as shown above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

SCHEME 29



A preparation of 4-(benzimidazol-1-yl)piperidine subunits is given in Scheme 29. Combining piperidone 29-1 and diamine 29-2 in the presence of sodium triacetoxyborohydride under dehydrating conditions provides reductive amination product 29-3. Addition of a suitably substituted ortho ester 29-4 in the presence of a acid catalyst, for example concentrated hydrochloric acid, provides benzimidazole intermediate 29-5. Deprotection under reductive conditions, for example with palladium on carbon under transfer hydrogenation conditions, then provides secondary amine 29-6, which is then utilized as the cyclic secondary amine component as shown above in Schemes 3, 4, 5, 6, 8, 9, 10 and 11.

SCHEME 30


MeO
Ar
O
30-1
NaOH
MeOH
HO
30-3
1) O_3
MeOH
2) Me_2S
30-2
DIC
1:1 THF:CH_2Cl_2
DMAP
(handle)
NH_2
30-5
30-4
DIPEA
R'-NH_2
$NaHB(OAc)_3$
HOAc
CH_2Cl_2
30-6
30-7
R"-OCO-Cl
CH_2Cl_2
DIPEA
or
NMM
30-8
1) $TMSCHN_2$
2)
30-9
DIPEA
CH_2Cl_2
30-10
1) BH_3-Me_2S
THF
2) H_2, Pd/C
or
TFA
30-11
Scheme 6
30-12

Another method of preparing compounds within the scope of the instant invention is given in Scheme 30 in which most of the chemistry is done on a resin and thus simplifies the isolations. Thus, the keto-acid 30-3, prepared either by standard hydrolysis of the ester 30-1 or oxidation of the exo-methylene of 30-2 with ozone in methanol at -70 °C followed by treatment with dimethyl sulfide, is first activated as its anhydride 30-4 by treatment with a dehydrating agent, such as dicyclohexylcarbodiimide or diisopropylcarbodiimde, in a suitable solvent, such as THF or methylene chloride or a mixture of these, with a catalytic amount of DMAP. Reaction of 30-4 with a suitable sulfonamide linker 30-5 affords the resin-bound cyclopentanone 30-6. Reductive amination of various amines with 30-6 affords the resin-bound amino derivative 30-7. Acylation can be done under standard conditions, such as with chloroformates, usually in the presence of an amine base, such as triethylamine, diisopropylethylamine, N-methylmorpholine, or pyridine, to afford the resin-bound amine derivative 30-8. Activation of the resin sulfonamide linker with trimethylsilyldiazomethane and displacement with an amine, such as the piperidine 30-9 (see Schemes 12-29) in which R must be stable to borane-dimethyl sulfide reduction, gives the corresponding amide 30-10. Subsequent reduction of the amide 30-10 with borane-dimethyl sulfide and removal of the carbamate, such as with TFA for a Boc derivative or standard hydrogenation for a CBZ derivative, affords the amine 30-11, which can be converted to the desired final compound as detailed in Scheme 6.

In some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

GENERAL

Concentration of solutions was carried out on a rotary evaporator under reduced pressure. Flash chromatography was carried out on silica gel (230-400 mesh). NMR spectra were obtained in $CDCl_3$ solution unless otherwise noted. Coupling constants (J) are in hertz (Hz). Abbreviations: diethyl ether (ether), triethylamine (TEA), N,N-diisopropylethylamine (DIEA) saturated aqueous (sat'd), room temperature (rt), hour(s) (h), minute(s) (min).

HPLC CONDITIONS

HPLC A. Retention time using the following conditions: Column: YMC ODS A, 5 μ, 4.6 x 50 mm; Gradient Eluant: 10:90 to 90:10 v/v CH_3CN/H_2O + 0.5% TFA over 4.5 min, hold 30 sec; Detection: PDA, 210-400 nm; Flow Rate: 2.5 mL/min.

HPLC B. Retention time using the following conditions: Column: Analytical Sales & Services Advantage HL C18 5 μ 4.6 x 100 mm column; Gradient Eluant: 10:90 to 90:10 v/v CH_3CN/H_2O + 0.5% TFA over 10 min, hold 2 min; Detection: PDA, 200-400 nm; Flow Rate: 2.25 mL/min.

The following are representative Procedures for the preparation of the piperidines used in the following Examples or which can be substituted for the piperidines used in the following Examples which may not be commercially available.

PROCEDURE 1

4-(3-Benzyl-1-ethyl-(1H)-pyrazol-5-yl)piperidine trifluoroacetic acid salt

Step A: 1-(1-(t-Butoxycarbonyl)piperidin-4-yl)-4-phenylbutane-1,3-dioneMethod A:

n-Butyl lithium (100 mL, 0.16 mole) was added to a stirred solution of diisopropylamine (16.16 g, 22.4 mL, 0.16 mole, distilled) in THF (450 mL) at 0 °C over 45 min under nitrogen. Stirring was continued for 10 min at 0 °C after the addition was complete. After cooling to -78 °C, phenylacetone (21.45 g, 21.13 mL, 0.16 mole) in THF (100 mL) was added dropwise over 15 min with stirring. This solution was stirred at -78 °C for 1 h. Meanwhile, a solution of *N*-Boc isonipecotic acid (18.32 g, 0.080 mole) and carbonyl diimidazole (12.98 g, 0.080 mole) in THF (150 mL) was prepared. After stirring for 15 min, this solution was cannulated into the enolate solution dropwise over 15 min. The reaction was stirred at <-70 °C for 1 h and then allowed to warm to rt over 3 h. The reaction was quenched with 1M citric acid (250 mL) and stirred for 16 h. The organic layer was separated and washed with

250 mL each of saturated sodium bicarbonate solution, water and brine. After drying over sodium sulfate, the organic layer was concentrated to give an oil. The residue was purified by FC on silica gel (10% ethyl acetate in 60-80 °C petroleum ether) to give separation of the two isomers. The first higher R_f fractions afforded pure title compound as the minor product (3.5 g) as an oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.37 (m, 2 H), 7.25-7.31 (m, 3 H), 5.46 (s, 1 H), 4.11-4.17 (m, 2 H), 3.63 (s, 2 H), 2.70-2.76 (m, 2 H), 2.29 (tt, J = 11.7 and 3.7 Hz, 1 H), 1.75-1.80 (m, 2 H), 1.47-1.61 (m, 2 H), 1.47 (s, 9 H).

MS (ESI): m/z 346 (M + 1).

The lower R_f fractions contained phenylacetone and major product 1-(1-(t-butoxycarbonyl)piperidin-4-yl)-2-phenylbutane-1,3-dione from which the latter crystallized on standing to give 7 g white solid (m.p. 105-106 °C).

^{1}H NMR (360 MHz, $CDCl_3$): δ 15.23 (s, 1 H), 7.3-7.45 (m, 3 H), 7.15-7.2 (m, 2 H), 4-4.1 (m, 2 H), 2.35-2.50 (m, 2 H), 2.2-2.3 (m, 1 H), 1.87 (s, 3 H), 1.5-1.75 (m, 4 H), 1.43 (s, 9 H).

MS (ESI): m/z 346 (M + 1).

Method B:

Step B1: 1-(t-Butoxycarbonyl)piperidine-4-*N*-methyl-*N*-methoxycarboxamide

N-Boc isonipecotic acid (13.56 g, 59.2 mmol), N,O-dimethyl hydroxylamine hydrochloride (8.65 g, 88.7 mmol), and 1-hydroxybenzotriazole hydrate (15.9 g, 118 mmol) were dissolved in DMF (225 mL) in a 500 mL round-bottom flask and diisopropylethylamine (15.3 g, 20.6 mL, 118.3 mmol) was then added with stirring at rt. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (17.01 g, 88.74 mmol) was added in several portions over 10 min with stirring. After 22 h, the reaction mixture was poured into a water and ice mixture (600 mL) and was extracted with ethyl acetate (5 x 125 mL). The combined organic layers were washed with 1N HCl (2 x 200 mL), 5% sodium bicarbonate (2 x 200 mL), water and brine, dried over sodium sulfate and concentrated to give the title compound (15.58 g) as a yellowish oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.11-4.20 (m, 2 H), 3.72 (br s, 3 H), 3.20 (br s, 3 H), 2.75-2.86 (m, 3 H), 1.63-1.76 (m, 4 H), 1.47 (s, 9 H).

Step B2: 4-Acetyl-1-(t-butoxycarbonyl)piperidine

After dissolving the Weinreb amide from Step B1 in anhydrous ether (400 mL) under nitrogen and cooling the solution in an ice bath, 1.4M methyl magnesium bromide (55 mL) in 3:1 toluene and THF was added with stirring and cooling over 30 min. After stirring at 0 °C for 1 h, the reaction was poured into a mixture of ice water (400 mL) and acetic acid (8 mL, 150 mmol). The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were washed with 0.1N HCl (200 mL), 3% sodium bicarbonate (200 mL), water (200 mL) and brine (200 mL), dried over sodium sulfate, and concentrated to give the crude product (14.322 g). FC (20-80% ethyl acetate in hexanes) gave the title compound (9.440 g) as a yellowish oil. R_f: 0.27 (25% ethyl acetate in hexanes). Some starting Weinreb amide was also recovered (3.212 g). R_f: 0.10 (25% ethyl acetate in hexanes).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.07-4.14 (m, 2 H), 2.75-2.83 (m, 2 H), 2.46 (tt, J = 11.3 and 3.8 Hz, 1 H), 2.17 (s, 3 H), 1.82-1.87 (m, 2 H), 1.48-1.57 (m, 2 H), 1.46 (s, 9 H).

Step B3: 1-(1-(t-Butoxycarbonyl)piperidin-4-yl)-4-phenyl-butane-1,3-dione

To a suspension of 60% sodium hydride (1.07 g) in THF (15 mL) at 0°C was added a solution of 4-acetyl-1-(t-butoxycarbonyl)piperidine from Step B2 (3.03 g, 13.3 mmol) and methyl phenylacetate (6.01 g, 39.9 mmol) in THF (6 mL) over 20 min. The reaction was stirred for another 4 h as it was allowed to warm to rt. The mixture was diluted with ether (30 mL) and poured into 1N HCl. The layers were separated and the aqueous layer was extracted three times with ether. The combined organic layers were washed with brine (150 mL), dried over sodium sulfate and concentrated. The crude product was purified by FC (20% ethyl acetate in hexanes) to give the title compound (3.02 g). R_f: 0.30 (20% ethyl acetate in hexane). The ^{1}H NMR data was the same as that obtained from the product of Method A.

Step B: 4-(5-Benzyl-1-ethyl-(1H)-pyrazol-3-yl)-1-(t-butoxycarbonyl)piperidine (Higher R_f isomer) and 4-(3-benzyl-1-ethyl-(1H)-pyrazol-5-yl)-1-(t-butoxycarbonyl)piperidine (Lower R_f isomer)

1-(1-(t-Butoxycarbonyl)piperidin-4-yl)-4-phenyl-butane-1,3-dione from Step A, from Method A or Method B, Step B3, (0.851 g, 2.46 mmol) in methanol (25 mL) was added over 10 min to a suspension of ethylhydrazine oxalate (0.444 g, 2.96 mmol) in methanol (5 mL) in a 60 °C oil bath. After 15 h, the reaction

was concentrated in vacuo and the residue was purified by repeated FC using a gradient of 50-100% ethyl acetate in hexanes to give first 4-(5-benzyl-1-ethyl-(1H)-pyrazol-3-yl)-1-(t-butoxycarbonyl)piperidine (0.148 g total) as the higher R_f product isomer and then the title compound (0.373 g total) as the lower R_f.

Higher R_f isomer:
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.2-7.3 (m, 2 H), 7.3-7.4 (m, 1 H), 7.17 (d, J = 7.5 Hz, 2 H), 5.77 (s, 1 H), 4.0-4.25 (m, 2 H), 3.97 (q, J = 7.3 Hz, 2 H), 3.95 (s, 2 H), 2.7-2.9 (m, 2 H), 2.76 (tt, J = 11.3 and 3.8 Hz, 1 H), 1.92 (br d, J = 13 Hz, 1 H), 1.5-1.65 (m, 2 H), 1.47 (s, 9 H), 1.29 (t, J = 7.3 Hz, 3 H).

Lower R_f isomer:
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25-7.4 (m, 3 H), 7.2 (m, 2 H), 5.72 (s, 1 H), 4.1-4.3 (m, 2 H), 4.08 (q, J = 7.1 Hz, 2 H), 3.95 (s, 2 H), 2.7-2.9 (m, 2 H), 2.66 (tt, J = 11.3 and 3.8 Hz, 1 H), 1.82 (br d, J = 12.8 Hz, 1 H), 1.4-1.6 (m, 2 H), 1.48 (s, 9 H), 1.47 (t, J = 7.1 Hz, 3 H).

Step C: 4-(3-Benzyl-1-ethyl-(1H)-pyrazol-5-yl)piperidine di-TFA salt

To a solution of 4-(3-benzyl-1-ethyl-(1H)-pyrazol-5-yl)-1-(t-butoxycarbonyl)piperidine from Step B (lower R_f isomer) (0.373 g, 1.01 mmol) and anisole (0.219 mL, 2.02 mmol) in dichloromethane (15 mL) was added trifluoroacetic acid (1.555 mL, 20.2 mmol). The reaction was stirred at rt for 2.5 h and then concentrated. The residue was purified on preparative reverse-phase HPLC using 9.4 x 250 mm Semi-preparative Zorbax SB-C18 column with 17.5-35% acetonitrile gradient in water having 0.5% (v/v) TFA over 15 min at 6.05 mL per minute to give the title di-TFA salt compound as an oil. When a mixture of isomers from Step B is used, separation is also possible at this step with the above Prep HPLC conditions in which the title isomer elutes prior to 4-(5-benzyl-1-ethyl-(1H-pyrazol-3-yl))piperidine.

PROCEDURE 2

4-(3-Benzyl-(1H)-pyrazol-5-yl)piperidine trifluoroacetic acid salt

Step A: 4-(3-Benzyl-(1H)-pyrazol-5-yl)-1-(t-butoxycarbonyl)piperidine TFA salt

891

A solution of 1-(1-(t-butoxycarbonyl)piperidin-4-yl)-4-phenyl-butane-1,3-dione from Procedure 1, Step A (30 mg, 0.087 mmol), hydrazine dihydrochloride (10.9 mg, 0.1 mmol) and DIPEA (0.045 mL, 0.25 mmol) in methanol (1 mL) was heated at 50 °C for 16 h. The volatiles were then removed under reduced pressure. Purification of the residue was done on preparative reverse-phase HPLC using a 9.4 x 250 mm Semi-preparative Zorbax SB-C18 column with 35-50% MeCN gradient in water having 0.5% (v/v) TFA over 15 min to give the title compound (45.2 mg) as a gel.

Step B: 4-(3-Benzyl-(1H)-pyrazol-5-yl)piperidine TFA salt

To a solution of 4-(3-benzyl-(1H-pyrazol-5-yl))-1-(t-butoxycarbonyl)piperidine TFA salt (from Step A) in dichloromethane (1.5 mL) was added anisole (0.017 mL) and TFA (0.230 mL). After several hours at rt, volatiles were removed under reduced pressure. Purification of the residue was done by preparative reverse-phase HPLC using a 9.4 x 250 mm Semi-preparative Zorbax SB-C18 column with a 15-25% acetonitrile gradient in water having 0.5% (v/v) TFA over 15 min at 6.0 mL per minute to give the title compound (40.7 mg) as a gel.

PROCEDURE 3

4-(4-(2-Phenyleth-1-yl)-1-ethyl-(1H)-pyrazol-5-yl)piperidine

Step A: 4-Phenylbutyl bromide

To a solution of 4-phenyl-1-butanol (21.75 g) in acetonitrile (300 mL) was added triphenylphosphene dibromide (67.23 g) in portions with stirring over 10 min. After stirring over night under nitrogen, methanol (4 mL) was added and after 1.5 h, the solvent was removed under reduced pressure. Hexanes (200 mL) and ~75 g silica gel were added to the residue and the mixture was filtered and the filter cake was eluted with hexanes. The clear filtrate was concentrated to give 32.8 g of clear colorless liquid. This product was again eluted through silica gel using 1.5 L hexanes to give the title compound (24.7 g) as a colorless liquid.
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28-7.32 (m, 2 H), 7.20-7.23 (m, 3 H), 3.44 (t, J = 6.8 Hz, 2 H), 2.67 (t, J = 7.6 Hz, 2 H), 1.93-1.89 (m, 2 H), 1.77-1.84 (m, 2 H).

892

Step B: (4-Phenylbut-1-yl)triphenylphosphonium bromide A solution of 4-phenylbutyl bromide from the Step A (24.7 g) and triphenylphosphene (19.00 g) in toluene (100 mL) was heated at 120-130 °C for 3 days. The reaction was cooled to rt and the solid precipitate was collected by filtration, washed with toluene and air dried. The solid was dissolved in a 2:1 mixture of water and acetonitrile and gave the title compound (30.6 g) as a white solid after lyopholization.
^{1}H NMR (500 MHz, CD_3OD): δ 7.84-7.89 (m, 2 H), 7.71-7.81 (m, 15 H), 7.20-7.23 (m, 1 H), 7.11-7.15 (m, 2 H), 3.37-3.43 (m, 2 H), 2.66 (t, J = 7.5 Hz, 2 H), 1.87 (tt, J = 7.5 and 7.3 Hz, 2 H), 1.63-1.70 (m, 2 H).

Step C: 1-Benzyl-4-(4-phenylbutylidene)piperidine
A 0.62M solution of potassium bis(trimethylsilyl)amide in THF (180 mL, 112 mmol) in toluene (250 mL) was added to a mixture of (4-phenylbut-1-yl)triphenylphosphonium bromide from Step B (53 g) in toluene (250 mL) in an ice bath over 15 min with stirring under nitrogen. After stirring for a further 15 min, a solution of 1-benzyl-4-piperidone (16.9 g) in toluene (100 mL) was added over 30 min with stirring. The reaction mixture was allowed to warm to rt over 15 h. The reaction mixture was then poured into cold 1N HCl (400 mL) and the layers were separated. The organic layer was extracted with two more portions of 1N HCl. The combined cloudy HCl solution and an oil layer in between were washed with toluene (200 mL) before the aqueous layer was basified by the addition of potassium hydroxide (30 g). The aqueous layer was extracted with ether (3x150 mL) and the combined organic layers were washed with water and brine, dried over sodium sulfate and concentrated. The crude product was purified by FC (10-15% ethyl acetate in hexanes having 4% (v/v) TEA) to give the title compound (16 g) as a colorless oil.
R_f: 0.47 (20% ethyl acetate in hexanes having 4% (v/v) TEA).
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26-7.38 (m, 7 H), 7.18-7.21 (m, 3 H), 5.18 (t, J = 7.4 Hz, 1 H), 3.54 (s, 2 H), 2.61-2.64 (m, 2 H), 2.42-2.49 (m, 4 H), 2.22-2.27 (m, 4 H), 2.02-2.07 (m, 2 H), 1.65-1.71 (m, 2 H).

Step D: 1-(1-Benzylpiperidin-4-yl)-4-phenylbutan-1-one
To a solution of 4-(4-phenylbutylidene)-1-benzylpiperidine from Step C (4.37 g) in anhydrous ether (150 mL) under nitrogen with stirring was add 1M borane solution in THF (45 mL). The reaction was stirred for 3 h when water (2 mL) was added dropwise. The mixture was stirred a further 30 min and was then cooled in

an ice bath. A solution of chromic anhydride (2.5 g), concentrated sulfuric acid (5.44 mL) and water (125 mL) was added dropwise with vigorous magnetic stirring over 5 min. After another 5 min, the ice bath was removed. After 1.5 h at rt, 0.5N sodium hydroxide and ether (400 mL each) were added and the mixture was stirred until the residue dissolved. The layers were separated and the aqueous layer was extracted twice with ether. The combined ether layers were washed with an aqueous EDTA solution, water and brine (100 mL each), dried over sodium sulfate and concentrated under reduced pressure to give a colorless gel. Flash chromatography on silica gel with 30-50% ethyl acetate in hexanes with 3% (v/v) TEA gave the title compound (1 g) as a colorless gel. Rf: 0.43 (30% ethyl acetate in hexanes with 3% (v/v) TEA). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25-7.33 (m, 7 H), 7.16-7.22 (m, 3 H), 3.51 (s, 2 H), 2.89-2.93 (m, 2 H), 2.63 (t, J = 7.6 Hz, 2 H), 2.46 (t, J = 7.2 Hz, 2 H), 2.38 (tt, J = 11.5 and 3.9 Hz, 1 H), 1.99-2.03 (m, 2 H), 1.92 (tt, J = 7.2 and 7.6 Hz, 2 H), 1.76-1.81 (m, 2 H), 1.65-1.72 (m, 2 H).

Step E: 1-(1-Benzylpiperidin-4-yl)-2-formyl-4-phenylbutan-1-one

To a solution of potassium t-butoxide (0.673 g) in THF (20 mL) under nitrogen and cooled in an ice bath was added a solution of 1-(1-benzylpiperidin-4-yl)-4-phenylbutan-1-one from Step D (0.71 g) and methyl formate (3.76 mL) in THF (12 mL) over 5 minute. The reaction was stirred for 15 min before being allowed to warm to rt for 2 h. The reaction was poured into water and extracted with ether (4 x 100 mL), dichloromethane (100 mL), and TFA (100 mL). The combined organic layers were washed with water and brine, dried over sodium sulfate and concentrate under reduced pressure. The crude product was purified by FC on silica gel eluting with 5 and 20% methanol in ethyl acetate with 4% TEA to afford the title compound (0.8 g). ^{1}H NMR (500 MHz, $CDCl_3$) showed a 3:1 ratio of enol (δ 8.54 ppm) and aldehyde (δ 9.54 ppm) forms. Other signals from the two forms were only partially resolved. The title compound had a retention time of 9.47 min on a Zorbax SB-C18 column (4.6x75 mm) eluting with 20-100% gradient of acetonitrile in water with 0.1% TFA over 10 min at 1 mL per min.

Step F: 4-(4-(2-Phenyleth-1-yl)-1-ethyl-(1H)-pyrazol-5-yl)-1-benzylpiperidine di-TFA salt A solution of 1-(1-benzylpiperidin-4-yl)-2-formyl-4-phenyl-1-butanone from Step E (76.5 mg) and ethylhydrazine oxalate (45 mg) in methanol (4 mL) was heated at 45 °C for 15.5 h. The solvent was removed under

reduced pressure. The residue was purified by preparative reverse-phase HPLC using a 9.4x250 mm Semi-preparative Zorbax SB-C18 column with 30-50% acetonitrile gradient in water having 0.5% (v/v) TFA over 15 min at 7.1 mL per min to give the title compound (45 mg) as the faster-eluting, minor isomer.

^{1}H NMR (500 MHz, CD_3OD): δ 7.46-7.52 (m, 5 H), 7.37 (s, 1 H), 7.21-7.24 (m, 2 H), 7.12-7.15 (m, 3 H), 4.32 (s, 2 H), 4.17 (q, J = 7.2 Hz, 2 H), 3.53 (br d, J = 12.4 Hz, 2 H), 3.06-3.12 (m, 3 H), 2.79-2.88 (m, 4 H), 2.10-2.20 (m, 2 H), 1.78 (br d, J = 14.2 Hz, 2 H), 1.34 (t, J = 7.2 Hz, 3 H). The isomeric assignment was confirmed by a NOESY spectrum.

HPLC/MS (ESI): m/z 374.3 (M + 1), 2.51 min.

Step G: 4-(4-(2-Phenyleth-1-yl)-1-ethyl-(1H)-pyrazol-5-yl)piperidine di-TFA salt A mixture of ammonium formate (119 mg), 20% $Pd(OH)_2/C$ (5 mg) and 4-(4-(2-phenylethyl)-1-ethyl-(1H-pyrazol-5-yl))-1-benzylpiperidine di-TFA salt from Step F in methanol (2 mL) was heated at 60 °C for 1.5 h. The solvent was removed under reduced pressure and the residue was purified by preparative reverse-phase HPLC using a 9.4x250 mm Semi-preparative Zorbax SB-C18 column with 20-35% acetonitrile gradient in water having 0.5% (v/v) TFA over 15 min at 6.25 mL per min to give the title compound as the di-TFA salt (25 mg) as a gel.

^{1}H NMR (500 MHz, CD_3OD): δ 7.40 (s, 1 H), 7.22-7.25 (m, 2 H), 7.13-7.17 (m, 3 H), 4.20 (q, J = 7.3 Hz, 2 H), 3.42-3.46 (m, 2 H), 3.05-3.15 (m, 3 H), 2.83-2.90 (m, 4 H), 2.04-2.14 (m, 2 H), 1.74-1.79 (m, 2 H), 1.36 (t, J = 7.4 Hz, 3 H). The isomer assignment was confirmed by an NOE difference spectrum.

PROCEDURE 4A

4-(3-(4-Fluorobenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidine di-TFA

The title compound was prepared using essentially the same procedure as that described in Procedure 1, but substituting methyl 4-fluorophenylacetate for methyl phenylacetate in Step A, Method B, Step B3.

PROCEDURE 4B

4-(3-(3,4-Difluorobenzyl)-1-ethyl-(1H)-pyrazol-5-yl)piperidine di-TFA

The title compound was prepared using essentially the same procedure as that described in Procedure 1, but substituting methyl 3,4-difluorophenylacetate for methyl phenylacetate in Step A, Method B.

PROCEDURE 5

(4-(3-Benzofurazan-4-yl)prop-1-yl)piperidine hydrochloride

Step A: (1-t-Butoxycarbonylpiperidin-4-yl)acetaldehyde A solution of oxalyl chloride (1.23 mL, 14.1 mmol) in methylene chloride (50 mL) was cooled to -78 °C. DMSO (2.0 mL, 28.3 mmol), was added slowly via syringe. After 10 min, 4-(2-hydroxyeth-1-yl)-1-t-butoxycarbonyl piperidine (2.7 g, 11.8 mmol) in methylene chloride (15 mL) was added. The cold mixture was stirred for an additional 20 min then TEA (8.2 mL, 59 mmol) was added. The mixture was warmed to rt and stirred for 1.5 h, then diluted with methylene chloride (300 mL). The organic phase was washed with 1M sodium hydroxide, dried over sodium sulfate and concentrated. FC (125 g silica, 2.5/1 hexanes/ethyl acetate) afforded the title compound (2.25 g).
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.1-1.2 (m, 2 H), 1.45 (s, 9 H), 1.65-1.75 (m, 2 H), 1.99-2.13 (m, 1 H), 2.38-2.4 (d, 2 H), 2.65-2.8 (m, 2 H), 4.03-4.15 (m, 2 H), 9.78 (s, 1 H)

Step B: 4-(Prop-2-en-1-yl)-1-t-butoxycarbonyl piperidine
A solution of methyltriphenylphosphonium bromide (5.3 g, 14.8 mmol) in THF (50 mL) was cooled to 0 °C under nitrogen. Potassium hexamethyl disilazide (27.7 mL, 0.5M toluene solution, 13.9 mmol) was added and the mixture was stirred for 30 min. A solution of (1-t-butoxycarbonylpiperidin-4-yl)acetaldehyde from Step A (2.25 g, 9.9 mmol) in THF (10 mL) was added and the mixture was warmed to rt. After 30 min, the reaction was complete by tlc analysis. The mixture was diluted with ethyl acetate (200 mL) and washed with water and brine (100 mL each). The organic phase was dried over sodium sulfate and concentrated to give an oil which was purified by FC (75 g silica, 10/1 hexane/ethyl acetate) to afford the title compound (1.61 g).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03-1.18 (m, 2 H), 1.45 (s, 9 H), 1.4-1.5 (m, 1 H), 1.6-1.7 (m, 2 H), 1.99-2.13 (t, 1 H), 2.62-2.75 (m, 2 H), 4.03-4.15 (m, 2 H), 4.98-5.12 (m, 2 H), 5.7-5.83 (m, 1 H).

Step C: 4-Bromobenzofurazan

To a solution of 2,6-dibromoaniline (10 g, 40 mmol) in glacial acetic acid (160 mL) was added 30% hydrogen peroxide (30 mL). The mixture was left for 48 h at which point crystals had precipitated. The crystals were collected by filtration, washed with acetic acid and water then dried under high vacuum to give 2,6-dibromonitrosobenzene (6.24 g). This material (2.6 g, 10 mmol) was dissolved in DMSO (25 mL) along with sodium azide (650 mg, 10 mmol). The mixture was heated to 100 °C for 1 h then cooled to rt and diluted with ethyl acetate and water. The layers were separated and the organic phase was washed with water and brine, then dried over sodium sulfate and concentrated. FC (75 g silica, 10/1 hexane/ethyl acetate) afforded the title compound (1.7 g).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25-7.35 (dd, 1 H), 7.6-7.65 (d, 1 H), 7.78-7.82 (d, 1 H)

Step D: 4-(3-(Benzofurazan-4-yl)prop-1-yl)piperidine hydrochloride

A solution of 4-(prop-2-en-1-yl)-1-t-butoxycarbonylpiperidine from Step B (330 mg, 1.46 mmol) in dry THF (0.5 mL) was cooled to 0 °C and a solution of 9-BBN (3.2 mL, 0.5 M in THF, 1.61 mmol) was added. The mixture was warmed to rt and stirred for 5 h. Potassium carbonate (405 mg, 2.93 mmol), 1,2-bis(diphenylphosphino)-ferrocenyl palladium dichloride (60 mg, 0.073 mmol) and 4-bromobenzofurazan (from Step C) (292 mg, 1.46 mmol) were added followed by dry DMF (5 mL). The resulting mixture was heated to 55 °C overnight then diluted with ethyl acetate. The solution was washed with water (3x) and brine, then dried over sodium sulfate and concentrated. FC (15 g silica, 5/1 hexane/ethyl acetate) afforded the title Boc derivative. Heating in 1% conc. HCl/methanol at 50 °C for 2 h followed by removal of solvent and drying under vacuum afforded the title compound as the hydrochloride (155 mg).

^{1}H NMR (300 MHz, CD_3OD): δ 1.31-1.42 (m, 4 H), 1.6-1.75 (m, 1 H), 1.84-2.0 (m, 4 H), 2.9-3.1 (m, 4 H), 3.3-3.4 (m, 2 H), 7.25-7.3 (d, 1 H), 7.4-7.5 (dd, 1 H), 7.7-7.75 (d, 1 H).

PROCEDURE 6

(4-(3-Benzofurazan-5-yl)prop-1-yl)piperidine hydrochloride

Using essentially the same methods as in Procedure 5, but substituting 2,5-dibromoaniline for 2,6-dibromoaniline in Step C, the title compound was prepared.

PROCEDURE 7

(3-(4-Cyanophenyl)prop-1-yl)piperidine hydrochloride

Starting with 4-(prop-2-en-1-yl)-1-t-butoxycarbonylpiperidine from Procedure 5, Step B (475 mg, 2.1 mmol) and using essentially the same methods as in Procedure 5, Step D, but substituting 4-bromobenzonitrile (382 mg, 2.1 mmol), the title compound (337 mg) was obtained as the hydrochloride.
^{1}H NMR (300 MHz, CD_3OD). δ 1.31-1.42 (m, 4 H), 1.58-1.75 (m, 5 H), 1.9-2.1 (m, 2 H), 2.67-2.77 (t, 2 H), 2.9-3.0 (m, 2 H), 3.3-3.4 (m, 2 H), 7.35-7.4 (d, 2 H), 7.6-7.63 (d, 2 H).

PROCEDURE 8

(3-(4-Cyano-3-fluorophenyl)prop-1-yl)piperidine hydrochloride

Starting with 4-(prop-2-en-1-yl)-1-t-butoxycarbonylpiperidine from Procedure 5, Step B and using essentially the same methods as in Procedure 5, Step D, but substituting 4-bromo-2-fluorobenzonitrile, the title compound was obtained as the hydrochloride.

PROCEDURE 9

(3-(4-Fluorophenyl)prop-1-yl)piperidine hydrochloride

Starting with 4-(prop-2-en-1-yl)-1-t-butoxycarbonylpiperidine (from Procedure 5, Step B) and using essentially the same methods as in Procedure 5, Step D, but substituting 4-bromofluorobenzene, the title compound was obtained as the hydrochloride.

PROCEDURE 10

4-(3-(Quinolin-3-yl)propyl)piperidine di-hydrochloride salt

Step A: 1-(t-Butoxycarbonyl)-4-(3-(quinolin-3-yl)propyl)piperidine

A solution of 1-(t-butoxycarbonyl)-4-(prop-2-en-1-yl)piperidine (from Procedure 5, Step B) (260 mg, 1.15 mmol) in THF (3 mL) under argon was treated with 0.5M 9-BBN solution in THF (2.30 mL, 1.15 mmol). The resulting mixture was stirred at rt for 2 h, then treated with sodium methoxide (68 mg, 1.25 mmol). The resulting mixture was stirred until it was homogeneous (~15 min) and then was treated with 3-(bromo) quinoline (0.155 mL, 1.15 mmol) and [1,1'-bis(triphenylphosphino)ferrocene)dichloropalladium · methylene chloride (41 mg, 0.05 mmol). The resulting mixture was heated at reflux for 30 min, cooled and quenched with 1N NaOH (20 mL). The quenched reaction was extracted with 2 x 50 mL of ether; the extracts were dried over magnesium sulfate, combined and concentrated. FC (15 g of silica gel, 4:1 v/v hexanes/ethyl acetate) afforded the title compound (240 mg).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00-1.16 (m, 2 H), 1.25-1.40 (m, 2 H), 1.45 (s, 9 H), 1.60-1.80 (m, 5 H), 2.62-2.72 (m, 2 H), 2.79 (t, J = 7.8, 2 H), 4.06 (br s, 2 H), 7.52 (m, 1 H), 7.66 (m, 1 H), 7.76 (dd, J = 8.0, 1.6, 1 H), 7.91 (d, J = 1.6, 1 H), 8.77 (d, J = 2.2, 1 H).

Step B: 4-(3-(Quinolin-3-yl)propyl)piperidine di-hydrochloride salt

A solution of 1-(t-butoxycarbonyl)-4-(3-(quinolin-3-yl)propyl)piperidine from Step A (240 mg, 0.68 mmol) in 1M HCl solution (8 mL) in methanol was stirred at rt for 48 h. The solution was concentrated and the residue crystallized from ethyl acetate to afford the title compound (182 mg),

^{1}H NMR (500 MHz, CD_3OD): δ 1.37-1.49 (m, 4 H), 1.67-1.74 (m, 2 H), 1.85-1.91 (m, 2 H), 1.99 (app d, J = 13.5 Hz, 2 H), 2.99 (app t, J = 11.5 Hz, 2 H), 3.05 (t, J = 8.0 Hz, 2 H), 3.38 (app d, J = 12.5 Hz, 1 H), 7.97 (t, J = 7.0 Hz, 1 H), 8.13 (dt. J = 1.0 and

7.0 Hz, 1H), 8.24 (d, J = 8.5 Hz, 1 H), 8.31 (d, J = 8.0 Hz, 1 H), 9.10 (s, 1 H), 9.21 (d, J = 1.0 Hz, 1 H).

PROCEDURE 11

4-(3-(2-Pyridyl)propyl)piperidine

Step A: 1-(t-Butoxycarbonyl)-4-(3-(2-pyridyl)propyl)piperidine

The title compound was prepared using a procedure analogous to that described in Procedure 10, Step A, substituting (2-bromo)pyridine for (3-bromo)quinoline. FC (4:1 v/v hexanes/ethyl acetate followed by 3:2 v/v hexanes/ethyl acetate) provided the title compound (135 mg, 48%).
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.05-1.81 (m, 10 H), 1.46 (s, 9 H), 2.67-2.82 (m, 2 H), 3.65 (m, 1 H), 4.08-4.16 (m, 2 H), 7.14-7.18 (m, 2 H), 7.63 (m, 1 H), 8.54 (d, J = 4.4 Hz, 1 H).
HPLC/MS (ESI): m/z 304 (M+1).

Step B: 4-(3-(2-Pyridyl)propyl)piperidine di-TFA salt

To a solution of 1-(t-butoxycarbonyl)-4-(3-(2-pyridyl)propyl)piperidine (from Step A) (128 mg, 0.42 mmol) in methylene chloride (1 mL) was added TFA (1 mL). After stirring for 2 h at rt, the reaction was concentrated to give the title compound (36 mg).
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.22-1.46 (m, 5 H), 1.73-1.79 (m, 4 H), 2.68 (t, J = 11.8 Hz, 2 H), 2.78 (t, J = 7.8 Hz, 2 H), 3.19 (d, J = 11.8 Hz, 2 H), 5.32 (br s, 1 H), 7.09-7.15 (m, 2 H), 7.59 (t, J = 7.7 Hz, 2 H), 8.52 (d, J = 4.6 Hz, 1 H).

PROCEDURE 12

4-(3-((4-Trifluoromethyl)pyrimidin-2-yl))propyl)piperidine

Step A: 1-(t-Butoxycarbonyl)-4-(3,3-dibromoprop-2-en-1-yl)piperidine

To a solution of carbon tetrabromide (286 mg, 0.86 mmol) in methylene chloride (4 mL) at –10 °C was added triphenylphosphine (339 mg, 1.29 mmol). After 10 min, a solution of ((1-t-butoxycarbonyl)piperidin-4-yl)acetaldehyde (from Procedure 5, Step A) (98 mg, 0.43 mmol) and TEA (0.060 mL, 0.43 mmol) in

methylene chloride (2 mL) was added. After stirring at rt for 2 h, the reaction mixture was concentrated. The residue was purified by FC (9:1 v/v hexanes/ethyl acetate followed by 1:1 v/v hexanes/ethyl acetate) to give the title compound (118 mg).
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.14-1.22 (m, 2 H), 1.47 (s, 9 H), 1.57-1.60 (m, 1 H), 1.67 (br d, J = 12.6 Hz, 2 H), 2.08 (t, J = 7.1 Hz, 2 H), 2.70 (t, J = 12.7 Hz, 2 H), 4.10 (br d, J = 12.6 Hz, 2 H), 6.42 (t, J = 7.4 Hz, 1 H).

Step B: 1-(t-Butoxycarbonyl)-4-(prop-2-yn-1-yl)piperidine

To a solution of 118 mg (0.31 mmol) of 1-(t-butoxycarbonyl)-4-(3,3-dibromoprop-2-en-1-yl)piperidine from Step A in THF (4 mL) at –78 °C was added a 2.5M solution of n-butyl lithium (0.370 mL, 0.92 mmol). After stirring at –78 °C for 45 min, the reaction mixture was quenched with sat'd ammonium chloride (4 mL) and diluted with ether (25 mL). After separating the phases, the aqueous layer was extracted with ether. The combined organic phases were washed with brine, dried over magnesium sulfate and concentrated. The residue was purified by FC (4:1 v/v hexanes/ether) to give the title compound (55 mg).
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.18-1.26 (m, 2 H), 1.47 (s, 9 H), 1.60-1.67 (m, 1 H), 1.77 (br d, J = 13.2 Hz, 2 H), 1.99 (t, J = 2.6 Hz, 1 H), 2.16 (dd, J = 6.6 Hz, 2.5, 2 H), 2.68-2.74 (m, 2 H), 4.12 (br d, J = 13.0 Hz, 2 H).

Step C: 1-(t-Butoxycarbonyl)-4-(3-((4-trifluoromethyl)pyrimidin-2-yl)prop-2-yn-1-yl)piperidine

To a solution of 1-(t-butoxycarbonyl)-4-(prop-2-yn-1-yl)piperidine from Step B (86 mg, 0.39 mmol) in TEA (4 mL) under argon at 0 °C was added 2-chloro-4-(trifluoromethyl)pyrimidine (0.070 mL, 0.58 mmol). After stirring at 0 °C for 5 min, dichlorobis(triphenylphosphine)palladium(II) (27 mg, 0.04 mmol), and copper iodide (4 mg, 0.02 mmol) was added and the reaction vessel was flushed with argon. After 3 h at 60 °C, the reaction mixture was cooled to rt and quenched with 1N sodium hydroxide (5 mL) and diluted with ether (25 mL). After separating the phases, the aqueous layer was extracted again with ether. The combined organic phases were washed with brine, dried over magnesium sulfate and concentrated. The residue was purified by FC (9:1 v/v hexanes/ethyl acetate followed by 2:1 v/v hexanes/ethyl acetate) to give the title compound (132 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26-1.33 (m, 2 H), 1.46 (s, 9 H), 1.80-1.88 (m, 3 H), 2.46 (d, J = 6.4 Hz, 2 H), 1.99 (br t, J = 11.2 Hz, 1 H), 4.10-4.40 (m, 2 H), 7.54 (d, J = 5.0 Hz, 1 H), 8.94 (d, J = 5.0 Hz, 1 H).

Step D: 1-(t-Butoxycarbonyl)-4-(3-((4-trifluoromethyl)pyrimidin-2-yl)prop-1-yl)piperidine

To a solution of 1-(t-butoxycarbonyl)-4-(3-((4-trifluoromethyl)pyrimidin-2-yl)prop-2-yn-1-yl)piperidine from Step C (130 mg) in methanol (4 mL) was added 10% palladium on carbon (15 mg). The mixture was hydrogenated using a Parr shaker set at 40 psi. After TLC indicated the absence of the starting material, the reaction was filtered through a 0.45 micron nylon membrane polypropylene filter and concentrated. FC (9:1 v/v hexanes/ethyl acetate followed by 2:1 v/v hexanes/ethyl acetate) of the residue afforded the title compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04-1.15 (m, 2 H), 1.27-1.49 (m, 3 H), 1.46 (s, 9 H), 1.68 (br d, J = 12.7 Hz, 2 H), 1.85-1.93 (m, 2 H), 2.68 (br t, J = 12.1 Hz, 2 H), 3.05 (t, J = 7.7 Hz, 2 H), 4.08 (br d, J = 11.5 Hz, 2 H), 7.47 (d, J = 5.0 Hz, 1 H), 8.92 (d, J = 5.0 Hz, 1 H).

Step E: 4-(3-((4-Trifluoromethyl)pyrimidin-2-yl)prop-1-yl)piperidine TFA salt

The title compound was prepared from 1-(t-butoxycarbonyl)-4-(3-((4-trifluoromethyl)pyrimidin-2-yl)prop-1-yl)piperidine (from Step D) (17 mg, 0.046 mmol) using a procedure analogous to that described in Procedure 10, Step B. FC (95:5:0.5 v/v/v methylene chloride/MeOH/ NH_4OH) afforded the title compound (22 mg).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21-3.45 (m, 15 H), 7.52 (d, J = 5.0 Hz, 1 H), 8.95 (d, J = 5.0 Hz, 1 H).

PROCEDURE 13

4-(*N*-(Pyrimidin-2-yl)-*N*-(prop-1-yl)amino)piperidine

Step A: 4-Amino-1-t-butoxycarbonylpiperidine

1-t-Butoxycarbonylpiperidin-4-one (20 g, 100 mmol), benzylamine (11 mL, 100 mmol) and sodium triacetoxyborohydride (32 g, 150 mmol) were stirred together in 1,2-dichloroethane (400 mL) for 3 h. The resulting mixture was diluted with ethyl acetate (1 L) and washed with 1M aqueous sodium hydroxide (500 mL) followed by brine (500 mL). The organic phase was dried over sodium sulfate and concentrated to afford 4-*N*-benzylamino-1-t-butoxycarbonyl piperidine (30.1 g) as a viscous oil. The oil was dissolved in methanol (400 mL) and ammonium formate (39 g, 600 mmol) was added. The vessel was purged with nitrogen and 10% palladium on carbon (6.5 g, 6 mmol) was added. The mixture was refluxed for 1 h and then filtered through celite and concentrated. Drying under vacuum afforded the title compound (20 g).
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15-1.3 (m, 2 H), 1.43 (s, 9 H), 1.7-1.9 (m, 4 H), 2.65-2.72 (m, 3 H), 3.95-4.1 (m, 2 H).

Step B: 4-(*N*-(Pyrimidin-2-yl)amino)-1-t-butoxycarbonylpiperidine

4-Amino-1-t-butoxycarbonylpiperidine from Step A, (1.9 g, 9.5 mmol), 2-chloropyrimidine (1.1 g, 9.5 mmol) and DIPEA (3.3 mL, 19 mmol) were combined in isopropanol (10 mL) and the mixture was refluxed for 24 h. The mixture was cooled, diluted with methylene chloride (100 mL) and washed with water and brine. The organic phase was dried over sodium sulfate and concentrated. FC (60 g silica, 1/1 hexanes/ethyl acetate) afforded the title compound (0.97 g).
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31-1.45 (m, 2 H), 1.44 (s, 9 H), 2.0-2.1 (m, 2 H), 2.9-3.0 (m, 2 H), 3.9-4.1 (m, 3 H), 5.0-5.05 (m, 1 H), 6.5-6.58, (t, 1 H), 8.15-8.2 (d, 2 H).

Step C: 4-(*N*-(Pyrimidin-2-yl)-*N*-(allyl)amino)-1-t-butoxycarbonyl- piperidine

A solution of 4-(*N*-(pyrimidin-2-yl)amino)-1-t-butoxycarbonylpiperidine from Step B (528 mg, 1.9 mmol) in dry THF (5 mL) was cooled to -78 °C and a solution of sodium hexamethyldisilazide (2.8 mL, 1.0 M in THF, 2.8 mmol) was added via syringe. The mixture was stirred cold for 20 min then allyl bromide (0.23 mL, 2.7 mmol) was added. The mixture was then warmed to rt and stirred for 1.5 h at which time TLC showed very little starting material. The solution was poured into sat'd ammonium chloride and methylene chloride. The layers were separated and the organic phase was dried over sodium sulfate and

concentrated. FC (25 g silica, 4/1 hexanes/ethyl acetate) afforded the title compound (367 mg).

^{1}H NMR (300 MHz, CDCl$_3$): δ 1.45 (s, 9 H), 1.6-1.8 (m, 4 H), 2.75-2.85 (m, 2 H), 4.1-4.3 (m, 4 H), 4.7-4.8 (m, 1 H), 5.05-5.17 (m, 2 H), 5.92-5.98 (m, 1 H), 6.45-6.5 (t, 1 H), 8.3-8.35 (d, 2 H).

Step D: 4-(*N*-(Pyrimidin-2-yl)-*N*-(prop-1-yl)amino)piperidine dihydrochloride

In a round bottom flask purged with nitrogen 4-(*N*-(pyrimidin-2-yl)-4-N-(allyl)amino)-1-t-butoxylcarbonylpiperidine from Step C (461 mg, 1.45 mmol) was dissolved in methanol (4 mL) and 10% palladium on carbon (150 mg, 0.14 mmol) was added. The mixture was stirred under 1 atm of hydrogen using a balloon for 1.5 h. The mixture was filtered through celite and concentrated. FC (20 g silica, 3/1 hexanes/ethyl acetate) afforded 4-(*N*-(pyrimidin-2-yl)-4-*N*-(prop-1-yl)amino)-1-t-butoxylcarbonylpiperidine.

^{1}H NMR (400 MHz, CDCl$_3$). δ 0.9-1.0 (t, 3 H, J=7 Hz), 1.5 (s, 9 H), 1.6-1.8 (m, 6 H), 2.8-2.9 (m, 2 H), 3.33-3.4 (m, 2 H), 4.2-4.27 (m, 2 H), 4.7-4.8 (m, 1 H), 6.42-6.45 (t, 1 H),), 8.3-8.35 (d, 2 H).

This material was dissolved in 2 % conc. HCl/methanol and heated to 50 °C for 2 h. Removal of solvent and drying under vacuum afforded the title compound as a white solid.

PROCEDURE 14

(3-(3,4-Difluorophenyl)prop-1-yl)piperidine hydrochloride

Starting with 4-(prop-2-en-1-yl)-1-t-butoxycarbonylpiperidine from Procedure 5, Step B and using essentially the same methods as in Procedure 5, Step D, but substituting 3,4-difluorobromobenzene, the title compound was obtained as the hydrochloride.

PROCEDURE 15

4-(5-Benzyl-1-(prop-1-yl)-(1H)-pyrazol-3-yl)piperidine di-hydrochloride salt (Higher R_f isomer) and 4-(3-benzyl-1-(prop-1-yl)-(1H-pyrazol-5-yl))piperidine di-hydrochloride salt (Lower R_f isomer)

Using essentially the same methods as in Procedure 1, Step B-C, but substituting propylhydrazine for ethylhydrazine in Step B, the title compounds were prepared.

PROCEDURE 16

4-(3,3-Difluoro-3-phenylprop-1-yl)piperidine

Step A: 1-(Benzyloxycarbonyl)-4-(3-oxo-3-phenylprop-1-en-1-yl)piperidine

DIPEA (4.6 mL, 3.4 g, 26 mmol) was added to a solution of 4-(hydroxymethyl)piperidine (2.00 g, 17.4 mmol) dissolved in methylene chloride (20 mL). The solution was cooled in an ice bath and benzyl chloroformate (2.5 mL, 3.0 g, 18 mmol) was added dropwise over 10 min. After warming to rt and stirring for 96 h, the mixture was diluted with ethyl acetate (50 mL) and washed in succession with 25 mL each of saturated aq. $NaHCO_3$, 2N aq. HCl, saturated aq. $NaHCO_3$, and saturated aq. NaCl. The organic layer was dried (Na_2SO_4), decanted, and evaporated to give 4.14 g of 1-(benzyloxycarbonyl)-4-(hydroxymethyl)piperidine.

1,1,1-Triacetoxy-1,1-dihydro-1,2-benzoiodoxol-3(1H)-one (1.92 g, 4.53 mmol) was added to a solution of 1-(benzyloxycarbonyl)-4-(hydroxymethyl)piperidine (1.00 g, 4.01 mmol) in methylene chloride (20 mL) and the mixture was stirred at rt for 45 min. Ether (75 mL) and 1.3 N aq. NaOH (25 mL) were added and stirring was continued for 15 min. The mixture was transferred to a separatory funnel with additional ether (30 mL) and 1.3 N aq. NaOH (20 mL). The organic layer was separated, washed with saturated aq. NaCl (20 mL), dried (Na_2SO_4), decanted, and evaporated to give 846 mg of 1-(benzyloxycarbonyl)-4-piperidine carboxaldehyde as a colorless syrup.

Diethyl (2-oxo-2-phenylethyl)phosphonate (0.96 mL, 1.1 g, 4.4 mmol) was added in one portion to a stirred suspension of sodium hydride (60% oil dispersion, 158 mg, 3.95 mmol) in THF (20 mL). After 15 min. at rt, the clear solution was cooled in an ice bath and 1-(benzyloxycarbonyl)-4-

piperidinecarboxaldehyde (840 mg, 3.40 mmol) was added in THF (1.0 mL) with additional THF (2 x 1.0 mL) for rinsing. Stirring was continued for a total of 2 h, with slow warming to rt. The mixture was then partitioned between ether (120 mL) and 2.5 N aq. NaOH (60 mL). The organic layer was washed with saturated aq. NaCl (60 mL), dried (Na_2SO_4), decanted, and evaporated. The crude product was purified by FC, eluting with 15-20% ethyl acetate in hexane, to give 0.95 g of the title compound as a colorless syrup.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 8 Hz, 2 H), 7.57 (t, J = 8 Hz, 1 H), 7.48 (t, J = 8 Hz, 2 H), 7.39-7.29 (m, 5 H), 6.99 (dd, J = 15, 6 Hz, 1 H), 6.87 (dd, J = 15 and 1 Hz, 1 H), 5.15 (s, 2 H), 2.97-2.82 (m, 2 H), 2.50-2.39 (m, 1 H), 1.89-1.77 (m, 2 H), 1.54-1.39 (m, 2 H).

MS (ESI): m/z 367 (M + NH_3 + H).

Step B: 2-(2-(1-(Benzyloxycarbonyl)piperidin-4-yl)ethyl)-2-phenyl-1,3-dithiolane

1-(Benzyloxycarbonyl)-4-(3-oxo-3-phenylprop-1-en-1-yl)piperidine from Step A (0.95 g, 2.7 mmol) was hydrogenated using 5% Pd/C (10 mg) in 95% ethanol (20 mL) at atmospheric pressure. After 3.5 h, the mixture was filtered and the catalyst was washed with 95% ethanol. Evaporation of the filtrate gave 0.95 g of 1-(benzyloxycarbonyl)-4-(3-oxo-3-phenylprop-1-yl)piperidine as a colorless syrup.

Boron trifluoride-acetic acid complex (BF_3·$2CH_3CO_2H$, 0.370 mL, 501 mg, 2.67 mmol) was added to a solution of 1,2-ethanedithiol (0.440 mL, 494 mg, 5.25 mmol) and (1-(benzyloxycarbonyl)-4-(3-oxo-3-phenylprop-1-yl)piperidine (930 mg, 2.65 mmol) in methylene chloride (4.0 mL) at rt. After 6 h, the mixture was diluted with ether (50 mL) and washed with saturated aq. $NaHCO_3$ (2 x 25 mL), 2.5 N aq. NaOH (25 mL), and saturated aq. NaCl (25 mL). The organic layer was dried (Na_2SO_4), decanted, and evaporated. The crude product was purified by FC, eluting with 10% ethyl acetate in hexane, to give 1.05 g of the title compound as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 8 Hz, 2 H), 7.38-7.26 (m, 7 H), 7.22 (t, J = 8 Hz, 1 H), 5.10 (s, 2 H), 4.18-4.02 (m, 2 H), 3.41-3.32 (m, 2 H), 3.29-3.20 (m, 2 H), 2.79-2.62 (m, 2 H), 2.40-2.32 (m, 2 H), 1.65-1.54 (m, 2 H), 1.40-1.27 (m, 1 H), 1.24-1.16 (m, 2 H), 1.10-0.97 (m, 2 H);

HPLC/MS (ESI): m/z 428 (M + H); HPLC: 4.21 min.

Step C: 1-(t-Butoxycarbonyl)-4-(3,3-difluoro-3-phenylprop-1-yl)piperidine

1,3-Dibromo-5,5-dimethylhydantoin (74 mg, 0.26 mmol) was stirred with methylene chloride (0.50 mL) at rt, and the suspension was then cooled in a dry ice/2-PrOH bath. After 5 min., hydrogen fluoride·pyridine (70% HF, 0.18 mL) was added over 1 min. After 5 min., a solution of 2-(2-(1-(benzyloxycarbonyl)piperidin-4-yl)ethyl)-2-phenyl-1,3-dithiolane from Step B (100 mg, 0.234 mmol) in methylene chloride (0.20 mL) was added over 1 min. After 10 min, the reaction mixture was diluted into methylene chloride (25 mL) and washed with water (10 mL) containing $NaHSO_3$ (0.5 g). The organic layer was washed with saturated aq. $NaHCO_3$ (2 x 10 mL) followed by saturated aq. NaCl (10 mL), dried (Na_2SO_4), decanted, and evaporated to give 98 mg of colorless syrup. This material was combined with 195 mg of crude product from two similar reactions and purified by FC, eluting with 8% ethyl acetate in hexane, to give 247 mg of 1-(benzyloxycarbonyl)-4-(3,3-difluoro-3-phenylprop-1-yl)piperidine (R_f: 0.3 using 10% ethyl acetate in hexane) containing some residual impurity. .

The partially purified 1-(benzyloxycarbonyl)-4-(3,3-difluoro-3-phenylprop-1-yl)piperidine (247 mg) was hydrogenated at atmospheric pressure in 95% ethanol (4.0 mL) containing 20% $Pd(OH)_2/C$ (60 mg). After 6 h, additional 20% $Pd(OH)_2/C$ (32 mg) was added and the hydrogenation was continued for another 16 h. The mixture was filtered and the catalyst was washed with 95% ethanol. Evaporation of the filtrate gave 164 mg of crude 4-(3,3-difluoro-3-phenylprop-1-yl)piperidine as a colorless syrup.

Di-t-butyl dicarbonate (178 mg, 0.816 mmol) was transferred with methylene chloride (2 x 0.5 mL) to a solution of crude 4-(3,3-difluoro-3-phenylprop-1-yl)piperidine (164 mg) in methylene chloride (2.0 mL). After stirring at rt for 1 h, the solution was stored at -20 °C for 48 h. The mixture was then diluted into ethyl acetate (25 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL) followed by saturated aqueous NaCl (10 mL). The organic layer was dried (Na_2SO_4), decanted, and evaporated. The crude product was purified by FC, eluting with 4-5% ethyl acetate in hexane to give the title compound as 112 mg of colorless syrup. R_f: 0.25 (5% ethyl acetate in hexane).

^1H NMR (400 MHz, $CDCl_3$): δ 7.50-7.40 (m, 5 H), 4.24-3.99 (m, 2 H), 2.64 (bt, J = 12 Hz, 2 H), 2.14 (tm, J = 16 Hz, 2 H), 1.62 (bd, J = 12 Hz, 2 H), 1.45 (s, 9 H), 1.42-1.33 (m, 3 H), 1.13-1.00 (m, 2 H).

Step D: 4-(3,3-Difluoro-3-phenylprop-1-yl)piperidine

Trifluoroacetic acid (2.5 mL, 3.7 g, 32 mmol) was added dropwise to a solution of 1-(t-butoxycarbonyl)-4-(3,3-difluoro-3-phenylprop-1-yl)piperidine from Step C (42 mg, 0.12 mmol) in methylene chloride (2.5 mL) at 0 °C. After 80 min., the solution was transferred using a double-ended needle to a rapidly stirred solution of $NaHCO_3$ (5.0 g, 60 mmol) in water (50 mL). Ether (50 mL) and 2.5 N aq. NaOH (20 mL) were added, followed by solid NaCl to saturate the aqueous layer. The aqueous layer was separated and extracted with ether (50 mL). The organic layers were washed in succession with saturated aq. NaCl (20 mL), combined, dried (Na_2SO_4), decanted, and evaporated to give the title compound as 27 mg of colorless oil.

^1H NMR (400 MHz, CD_3OD): δ 7.51-7.40 (m, 5 H), 2.98 (dm, J = 12 Hz, 2 H), 2.53 (td, J = 12 and 3 Hz, 2 H), 2.24-2.10 (m, 2 H), 1.65 (bd, J = 12 Hz, 2 H), 1.42-1.26 (m, 3 H), 1.06 (qd, J = 12 and 4 Hz, 2 H).

HPLC/MS (ESI): m/z 240 (M + H); HPLC: 2.25 min.

PROCEDURE 17

4-(3,3-Difluoro-3-(4-fluorophenyl)prop-1-yl)piperidine

Step A: 1-(t-Butoxycarbonyl)-4-(hydroxymethyl)piperidine

Di-t-butyl dicarbonate (4.69 g, 21.5 mmol) was transferred in methylene chloride (9 mL) over 10 min. to a solution of 4-(hydroxymethyl)piperidine (2.47 g, 21.4 mmol) in methylene chloride (16 mL). After stirring at rt for 1 h, the solution was diluted with ether (50 mL) and washed with 2 N aq. HCl, saturated aq. $NaHCO_3$, and saturated aq. NaCl (25 mL of each). The organic layer was dried (Na_2SO_4), decanted, and evaporated to give 4.57 g of the title compound as a crystalline solid.

^1H NMR (500 MHz, CD_3OD): δ 4.08 (d, J = 14 Hz, 2 H), 3.40 (d, J = 6 Hz, 2 H), 2.81-2.67 (m, 2 H), 1.71 (d, J = 13 Hz, 2 H), 1.67-1.58 (m, 1 H), 1.44 (s, 9 H), 1.09 (qd, J = 12 and 4 Hz, 2 H).

Step B: 1-(t-Butoxycarbonyl)-4-(iodomethyl)piperidine

Methanesulfonyl chloride (4.10 mL, 6.07 g, 52.9 mmol) was added dropwise to a solution of 1-(t-butoxycarbonyl)-4-(hydroxymethyl)piperidine from

Step A (10.0 g, 46.4 mmol) and triethylamine (9.80 mL, 7.11 g, 70.3 mmol) in methylene chloride (140 mL) at 5-8 °C. After 1 h, the mixture was diluted with ethyl acetate (400 mL) and washed with water (200 mL). The aqueous layer was extracted with ethyl acetate (2 x 150 mL) and the combined organic layers were washed with 1 N aq. HCl (200 mL), saturated aq. $NaHCO_3$ (200 mL), and saturated aq. NaCl (200 mL). The organic layer was dried (Na_2SO_4), decanted, and evaporated to give 13.58 g of 1-(t-butoxycarbonyl)piperidin-4-yl methanesulfonate as a pale yellow solid.

A mixture of 1-(t-butoxycarbonyl)piperidin-4-yl methanesulfonate (13.58 g, 46.4 mmol) and sodium iodide (34.68 g, 232 mmol) in acetone (80 mL) was heated to reflux for 3 h. The mixture was partitioned between ether (350 mL) and water (350 mL). The organic layer was washed with saturated aq. NaCl (250 mL), and the aqueous layers were extracted in succession with ether (250 mL). The combined organic layers were dried (Na_2SO_4), decanted, and evaporated to give the title compound (14.8 g) as a pale yellow oil.

^1H NMR (500 MHz, $CDCl_3$): δ 4.25-4.00 (m, 2 H), 3.12 (d, J = 4 Hz, 2 H), 2.78-2.52 (m, 2 H), 1.85 (d, J = 13 Hz, 2 H), 1.68-1.56 (m, 1 H), 1.48 (s, 9 H), 1.15 (qd, J = 12 and 4 Hz, 2 H).

Step C: ((1-(t-Butoxycarbonyl)piperidin-4-yl)methyl)triphenylphosphonium iodide

A solution of triphenylphosphine (6.63 g, 25.3 mmol) and 1-(t-butoxycarbonyl)-4-(iodomethyl)piperidine from Step B (7.96 g, 24.5 mmol) in acetonitrile (40 mL) was heated to reflux for 72 h. The solution was evaporated to give 13.35 g of white solid. A portion (12.34 g) of this material was dissolved in acetonitrile (25 mL) at 65 °C. Ethyl acetate (35 mL) was added and the mixture was allowed to cool slowly to rt and then to -20 °C. The supernatant was decanted, and the colorless crystals were washed with ethyl acetate (5 x 5 mL) and dried under vacuum to give 9.25 g of the title compound.

^1H NMR (500 MHz, CD_3OD): δ 7.89 (t, J = 8 Hz, 3 H), 7.86 (dd, J = 12 and 8 Hz, 6 H), 7.76 (td, J = 8 and 4 Hz, 6 H), 3.91 (bd, J = 13 Hz, 2 H), 3.44 (dd, J = 14 and 6 Hz, 2 H), 2.72-2.58 (m, 2 H), 2.08-1.96 (m, 1 H), 1.49 (bd, J = 12 Hz, 2 H), 1.41 (s, 9 H), 1.43 (qd, J = 13 and 4 Hz, 2 H).

Step D: Methyl (4-fluorobenzoyl)formate

Dimethyl oxalate (5.90 g, 50 mmol) was dissolved in THF (50 mL) and ether (50 mL) in a 3-neck round bottom flask fitted with a mechanical stirrer. The solution was stirred vigorously at -65 °C as a 1.0 M THF solution of 4-fluorophenylmagnesium bromide (60 mL, 60 mmol) was added dropwise over 40 min. The mixture was stirred 30 min at -65 °C and allowed to warm to -20 °C over 30 min before being poured into 2N aq. HCl (50 mL) with stirring. The layers were separated and the aq. layer was extracted with ether (3 x 50 mL). The combined organic layers were washed with saturated aq. NaCl (2 x 50 mL), dried (Na_2SO_4), decanted, and evaporated. The residue was dissolved in ethyl acetate, dried (Na_2SO_4), filtered, and evaporated to give a yellow solid. The crude product was dissolved in warm hexane (25 mL), filtered, and cooled to -20 °C. Filtration followed by washing with cold hexane (15 mL) gave 4.95 g of the title compound as light tan crystals.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (dd, J = 9 and 5, Hz, 2 H), 7.21 (t, J = 9 Hz, 2 H), 4.00 (s, 3 H).

Step E: Methyl difluoro(4-fluorophenyl)acetate

Methyl (4-fluorobenzoyl)formate from Step D(4.75 g, 26.1 mmol) was added to (diethylamino)sulfur trifluoride (7.0 mL, 8.5 g, 53 mmol). The mixture was stirred rapidly and an ice bath was used briefly to reduce the temperature to 15 °C. After the ice bath was removed, the reaction temperature rose to 48 °C over 10 min and then slowly returned to rt. After a total of 2.75 h, the solution was carefully poured onto crushed ice (30 g) and the mixture was extracted with methylene chloride (2 x 25 mL). The organic layers were washed in succession with saturated aq. $NaHCO_3$ (2 x 25 mL) and saturated aq. NaCl (10 mL), combined, dried (Na_2SO_4) decanted, and evaporated. The residue was distilled to give the title compound as 4.16 g of light yellow liquid, B.P. 46-48 °C (0.5 mm Hg).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (dd, J = 9, 5 Hz, 2 H), 7.16 (d, J = 9 Hz, 2 H), 3.88 (s, 3 H).

Step F: 1-(t-Butoxycarbonyl)-4-(3,3-difluoro-3-(4-fluorophenyl)prop-1-en-1-yl)piperidine

A solution of methyl difluoro(4-fluorophenyl)acetate (2.04 g, 10.0 mmol) in CH_3OH (10.0 mL) was cooled to -60 °C. Sodium borohydride (380 mg, 10.0 mmol) was added in 5 portions at 10 to 15 min. intervals. The mixture was

Step C: (+)-*trans*-4-Methylene-2-phenylcylopentanoic acid and (-)-*trans*-4-methylene-2-phenylcylopentanoic acid

Method A:

The (+)-*trans*-4-methylene-2-phenylcylopentanoic acid, (S)-(-)- α -methylbenzylamine salt from Step B (4.7 g) was suspended in methylene chloride and water and acidified with 2M hydrochloric acid and extracted twice with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo to give the title (+) acid (3.1 g), $[\alpha]_D = +101$ (MeOH, c = 0.135).

Similarly, the (-)-*trans*-4-methylene-2-phenylcylopentanoic acid, (R)-(+)- α -methylbenzylamine salt (6.3 g) was converted to the free (-)-title acid (4.23 g), $[\alpha]_D = -103$ (MeOH, c = 0.23).

Method B:

Step B1: 1-(S)-(((S)-(-)-4-Benzyl-2-oxazolidin-1-yl)carbonyl)-3-methylene-2-(S)-phenylcyclopentane (higher R_f) and 1-(R)-(((S)-(-)-4-benzyl-2-oxazolidin-1-yl)carbonyl)-3-methylene-2-(R)-phenylcyclopentane (lower R_f)

A solution of (+-)-*trans*-4-methylene-2-phenylcylopentanoic acid (47.5 g, 235 mmol) in ether (1 L) and TEA (36 mL, 260 mmol) was cooled to -10 °C. Trimethylacetyl chloride (31.8 mL, 260 mmol) was then added slowly and after stirring at -10 °C for 10 min, the reaction was allowed to warm to 10 °C over 1 h. The reaction was then recooled to -60 °C.

To the above solution at -60 °C was added via a canula a solution of (S)-(-)-4-benzyl-2-oxazolidinone (45.8 g, 260 mmol) in THF (500 mL) which had been treated at -50 °C with 2.5 M n-butyl lithium (103 mL, 257 mmol) and aged at -50 °C for 45 min. The reaction was allowed to warm to rt over 16 h. The reaction was diluted with ether (1 L) and quenched with sat'd aqueous ammonium chloride (1 L). The layers were separated and the aqueous layer was reextracted with a second portion of ether. The organic layers were each washed twice with 2N hydrochloric acid, twice with 1N sodium hydroxide and brine, dried over sodium sulfate, combined and concentrated. The residue was purified by chromatography (20% ethyl acetate in

cooled to -60 to -55 °C prior to each addition and allowed to warm to -45 °C following each addition. After the last addition, the mixture was stirred 1.25 h at -50 to -45 °C. The mixture was cooled to -60 °C and quenched with 1 N aq. HCl (30 mL), with the temperature rising to -20 °C near the end of the addition. After warming to 0 °C, the mixture was extracted with ether (3 x 20 mL). The combined ether layers were washed with water (2 x 20 mL), dried (Na_2SO_4), decanted, and evaporated to give 1.95 g of crude 2,2-difluoro-2-(4-fluorophenyl)-1-methoxyethanol as a pale yellow oil.

A suspension of ((1-(t-butoxycarbonyl)piperidin-4-yl)methyl)triphenylphosphonium iodide (500 mg, 0,92 mmol) in THF (7.2 mL) was stirred at rt for 30 min. A 0.5 M toluene solution of potassium bis(trimethylsilyl)amide (1.8 mL, 0.90 mmol) was added over 3 min., giving an orange suspension. After 30 min., crude 2,2-difluoro-2-(4-fluorophenyl)-1-methoxyethanol (95 mg, 0.46 mmol) was added in THF (1.0 mL). After an additional 30 min, the mixture was quenched by the addition of saturated aq. NH_4Cl (2 mL). The mixture was partitioned between ethyl acetate (50 mL) and water (75 mL), and the aqueous layer was extracted with ethyl acetate (50 mL). The organic layers were washed in succession with saturated aq. NaCl (25 mL), dried (Na_2SO_4), decanted, and evaporated. The crude product was purified by FC, eluting with 10% ether in hexane to give 117 mg of the title compound as a 95:5 mixture of cis and trans isomers, respectively.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (dd, J = 9 and 5 Hz, 2 H), 7.13 (t, J = 9 Hz, 2 H), 5.76 (q, J = 12 Hz, 1 H), 5.64 (dd, J = 12 and 10 Hz, 1 H), 4.20-3.95 (m, 2 H), 2.80-2.54 (m, 3 H), 1.54 (bd, J = 12 Hz, 2 H), 1.47 (s, 9 H), 1.26 (qd, J = 12 and 4 Hz, 2 H).

Step G: 1-(t-Butoxycarbonyl)-4-(3,3-difluoro-3-(4-fluorophenyl)propyl)piperidine

Potassium azodicarboxylate (695 mg, 3.58 mmol) was added to a solution of 1-(t-butoxycarbonyl)-4-(3,3-difluoro-3-(4-fluorophenyl)prop-1-en-1-yl)piperidine from Step F (424 mg, 1.19 mmol) in methanol (3.3 mL). The mixture was stirred at rt as a 9.0 M solution of acetic acid in methanol (0.80 mL, 7.2 mmol) was added over 3 h using a syringe pump. After 30 min., a second portion of potassium azodicarboxylate (695 mg, 3.58 mmol) was added followed by the addition of 9.0 M acetic acid in methanol (0.80 mL, 7.2 mmol) over 3 h. After 20 min, a third

portion of potassium azodicarboxylate (695 mg, 3.58 mmol) was added followed by the addition of 9.0 M acetic acid in methanol (0.80 mL, 7.2 mmol) over 3 h. After stirring for 20 h at rt, the mixture was diluted with ethyl acetate (80 mL), and washed with 2 N aq. HCl (40 mL), saturated aq. $NaHCO_3$ (40 mL), and saturated aq. NaCl (40 mL). The organic layer was dried (Na_2SO_4), decanted, and evaporated to give 417 mg of a mixture containing the title compound and 20-25% of unreduced 1-(t-butoxycarbonyl)-4-(3,3-difluoro-3-(4-fluorophenyl)prop-1-en-1-yl)piperidine.

A portion (365 mg) of the crude mixture containing residual olefin was hydrogenated at atmospheric pressure for 16 h using iridium black (30 mg) in a mixture of t-butanol (24 mL) and ethyl acetate (2.4 mL). The mixture was filtered, the catalyst was washed with methanol, and the filtrate was evaporated to give 371 mg of the title compound as a pale yellow syrup. Rf: 0.2 (5% ethyl acetate in hexane). ^1H NMR (500 MHz, $CDCl_3$): δ 7.46 (dd, J = 9 and 5 Hz, 2 H), 7.12 (t, J = 9 Hz, 2 H), 4.18-4.00 (m, 2 H), 2.73-2.61 (m, 2 H), 2.14 (tm, J = 16 Hz, 2 H), 1.64 (bd, J = 12 Hz, 2 H), 1.46 (s, 9 H), 1.46-1.33 (m, 3 H), 1.08 (qd, J = 12 and 4 Hz, 2 H).

Step H: 4-(3,3-Difluoro-3-(4-fluorophenyl)prop-1-yl)piperidine

1-(t-Butoxycarbonyl)-4-(3,3-difluoro-3-(4-fluorophenyl)prop-1-yl)piperidine from Step G (122 mg, 0.34 mmol) was dried by evaporation of a toluene solution at reduced pressure. The residue was dissolved in chloroform (7.6 mL) and iodotrimethylsilane (0.100 mL, 141 mg, 0.70 mmol) was added. After stirring 30 min at rt, the solution was poured into a mixture of saturated aqueous $NaHCO_3$ (15 mL) and 2.5 N aq. NaOH (5 mL), and extracted with ether (50 mL). The organic layer was washed with saturated aq. NaCl (15 mL), dried (Na_2SO_4), decanted, and evaporated to give the title compound as 88 mg of colorless oil.
^1H NMR (500 MHz, CD_3OD): δ 7.51 (dd, J = 9 and 5 Hz, 2 H), 7.17 (t, J = 9 Hz, 2 H), 2.98 (dm, J = 12 Hz, 2 H), 2.52 (td, J = 12, 3 Hz, 2 H), 2.17 (tm, J = 16 Hz, 2 H), 1.65 (bd, J = 13 Hz, 2 H), 1.42-1.26 (m, 3 H), 1.07 (qd, J = 12 and 4 Hz, 2 H).
HPLC/MS (ESI): m/z 258 (M + H); HPLC: 2.64 min.

EXAMPLE 1

N-(1-(SR)-3-(SR)-((4-(3-(Phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-L-leucine di-hydrochloride salt and *N*-(1-(SR)-3-(SR)-((4-(3-

(phenyl)prop-1-yl)piperidin-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-D-leucine di-hydrochloride salt

Step A: Methyl (+-)-*trans*-4-methylene-2-phenylcylopentanoate

A mixture of methyl *trans*-cinnamate (5.0 g, 31 mmol), tetrakis(triphenylphosphine) palladium(0) (2.6 g, 2.3 mmol), 1,2-bis(diphenylphosphino)ethane (0.70 g, 1.8 mmol) and 2-((trimethylsilyl)methyl)-2-propen-1-yl acetate (6.90 g, 37 mmol) in THF (60 mL) under argon was heated to reflux for 4 h. An additional aliquot of 2-((trimethylsilyl)methyl)-2-propen-1-yl acetate (3.40 g) was added and the reaction was continued for another 16 h. The volatiles were then removed *in vacuo* and the residue was purified by FC (10% ethyl acetate in hexanes) to afford the title compound (6.2 g).

^{1}H NMR ($CDCl_3$) δ: 2.52 (m, 1 H), 2.68 (m, 1 H), 2.75-2.9 (m, 2 H), 2.95 (ddd, 1 H), 3.45 (ddd, 1 H), 3.57 (s, 3 H), 4.92 (m, 2 H), 7.15-7.3 (m, 5 H).

Step B: (+-)-*trans*-1-Hydroxymethyl-4-methylene-2-phenylcylopentane

To a solution of methyl (+-)-*trans*-4-methylene-2-phenylcylopentanoate (26.0 g, 128 mmol) prepared as in Step A in THF (600 mL) under nitrogen and cooled to -10 °C was added dropwise over 15 min 1M lithium aluminum hydride (LAH) in THF (193 mL). After 1 h, the bath was removed and the reaction was stirred at RT for 16 h. The reaction was cooled in an ice/methanol bath and the excess LAH was quenched by dropwise addition of acetone. The reaction was then poured into dilute aq. HCl. The mixture was extracted twice with ether and the organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (20 - 30% ethyl acetate in hexanes) to afford the title product (23.8 g).

Step C: (+-)-*trans*-1-Hydroxymethyl-4-oxo-2-phenylcylopentane

Into a solution of (+-)-*trans*-1-hydroxymethyl-4-methylene-2-phenylcylopentane from Step B (22.7 g, 121 mmol) in methanol (300 mL) cooled in a dry ice/acetone bath was bubbled ozone until the blue color persisted. The excess ozone was removed with a stream of nitrogen and then dimethylsulfide (25 mL) was added. After 30 min, the bath was removed and the reaction was allowed to warm to RT over 16 h. The volatiles were removed in vacuo and the residue was purified by FC (15 -30% ethyl acetate in hexanes) to give the title compound (22.1 g).

^{1}H NMR ($CDCl_3$) δ: 2.2-2.5 (m, 4 H), 2.71 (dd, 1 H), 3.28 (m, 1 H), 3.55 (dABq, 2 H), 7.23 (m, 3 H), 7.34 (m, 2 H).

Step D: 1-(SR)-Benzylamino-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopentane and 1-(RS)-benzylamino-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopentane

To a solution of (+-)-*trans*-1-hydroxymethyl-4-oxo-2-phenylcylopentane from Step C (9.8 g, 52 mmol) in 1,2-dichloroethane (200 mL) was added benzylamine (11.3 mL, 103 mmol) and acetic acid (6.2 mL, 103 mmol). After 10 min, sodium triacetoxyborohydride (33 g, 155 mmol) was added in portions and the reaction was stirred at RT for 3 hr. The reaction was quenched into dilute aq. sodium carbonate and the mixture was extracted twice with ethyl acetate. The organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (1-5% methanol in ether) to obtain the title products (13.1 g) as a mixture of C-1 isomers.

Step E: 1-(SR)-Benzyloxycarbonylamino-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopentane (Higher R_f isomer) and 1-(RS)-benzyloxycarbonylamino-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopentane (Lower R_f isomer)

To a solution of 1-(SR)-benzylamino-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopentane and 1-(RS)-benzylamino-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopentane (13 g, 46 mmol) from Step D was added 20% palladium hydroxide (2.5 g, 50% by wt water), ammonium formate (60 g, 930 mmol) and an additional 200 mL of methanol. The reaction was heated at 60 °C for 6 h. The reaction was filtered and concentrated. The residue was taken up in water and extracted twice with methylene chloride to remove any remaining benzylamine intermediate. The aqueous layer was made basic with 2N sodium hydroxide and extracted twice with methylene chloride. The organic layers were washed with brine, dried over sodium sulfate, combined and concentrated to afford 8.1 g of crude amino-alcohol.

The above product (8.1 g, 42 mmol) was taken up in methylene chloride (200 mL), cooled in an ice bath and DIPEA (22 mL, 126 mmol) and benzyl chloroformate (6.33 mL, 44 mmol) were added. After 2.5 h at RT, the reaction was poured into dilute aq. HCl and extracted twice with methylene chloride. The organic

layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by Prep LC (30 - 75% ethyl acetate in hexanes) to afford the title compounds (4.0.g higher, 6.6 g lower).

Step F: 1-(SR)-Benzyloxycarbonylamino-3-(SR)-formyl-4-(SR)-phenylcylopentane (Higher R_f isomer) and 1-(SS)-benzyloxycarbonylamino-3-(SR)-formyl-4-(SR)-phenylcylopentane (Lower R_f isomer)

To a solution of oxalyl chloride (0.350 mL, 3.85 mmol) in methylene chloride (10 mL) at -70 °C was added dropwise DMSO (0.550 mL, 7.65 mmol). After 15 min, a solution of 1-(SR)-benzyloxycarbonylamino-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopentane (Higher R_f isomer from Step E) (500 mg, 1.53 mmol) in methylene chloride (10 mL) was added. The reaction was stirred at -70 °C for 1 h and then DIPEA (2.7 mL, 15 mmol) in methylene chloride (5 mL) was added dropwise over 5 min. After a further 10 min, the mixture was allowed to warm to RT for 1 h and then diluted with methylene chloride and poured into dilute aq. HCl. The layers were separated. The aq. layer was reextracted with a second portion of methylene chloride and the organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by FC (20 - 30% ethyl acetate in hexanes) to give the title product (465 mg) as an oil. ^{1}H NMR ($CDCl_3$) δ: 1.9-2.0 (m, 1 H, 2b-H), 2.05-2.15 (m, 2 H, both 5-H's), 2.3-2.45 (m, 1 H, 2a-H), 3.06 (q, 1 H, 3-H), 3.47 (q, 1 H, 4-H), 4.32 (br m, 1 H, 1-H), 4.94 (br s, 1 H, NH), 5.08 (s, 2 H, CH_2O), 7.1-7.4 (m, 10 H), 9.74 (s, 1 H, COH). The assignment of cis stereochemistry between C-1 and C-3 and trans between C-1 and C-4 were confirmed by 2-D NOESY NMR.

Using essentially the same procedure as above, material derived from the lower isomer from Step E (500 mg, 1.5 mmol) was also converted to the lower R_f title compound (457 mg).

^{1}H NMR ($CDCl_3$) δ: 1.71 (q, 1 H, 5a-H), 1.8-1.95 (m, 1 H, 2a-H), 2.48 (p, 1 H, 2b-H), 2.5-2.6 (m, 1 H, 5b-H), 3.0-3.1 (m, 1 H, 3-H), 3.3-3.4 (m, 1 H, 4-H), 4.0-4.2 (m, 1 H, 1-H), 4.82 (br s, 1 H, NH), 5.08 (s, 2 H, OCH_2), 7.2-7.4 (m, 10 H), 9.63 (d, 1 H, COH). The assignment of trans stereochemistry between C-1 and C-3 and cis between C-1 and C-4 were confirmed by 2-D NOESY NMR.

Step G: 1-(SR)-(Benzyloxycarbonylamino)-3-(SR)-((4-(3-phenylprop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcylopentane (Higher R_f isomer)

To a solution of 1-((SR)-(benzyloxycarbonylamino)-3-(SR)-(carbonyl)-4-(SR)-phenylcyclopentane (from Step F, derived from Higher R_f isomer in Step E) (450 mg, 0.1.4 mmol) in 1,2-dichloroethane (10 mL) was added 4-(3-phenylprop-1-yl)piperidine (424 mg, 2.1 mmol) and acetic acid (0.125 mL, 2.1 mmol). After 15 min, sodium triacetoxyborohydride (890 mg, 4.2 mmol) was added in portions over 30 min and the reaction was stirred at RT for 16 h. The reaction was diluted with methylene chloride, quenched with aq. sodium carbonate and extracted 3 times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by FC (30 - 40% ethyl acetate in hexanes) to give the title product (698 mg) as the free amine.

MS (NH_3/ESI): m/z 511 (M + 1).

Step H: 1-(SR)-(Amino)-3-(SR)-((4-(3-phenylprop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcylopentane (Higher R_f isomer)

To a solution of 1-(SR)-(benzyloxycarbonylamino)-3-(SR)-((4-(3-phenylprop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcylopentane (from Step G, derived from the Higher R_f isomer from Step E) (500 mg, 1.0 mmol) in methanol (10 mL) was added 10% Pd/C (100 mg). The mixture was hydrogenated on a Parr shaker at 40 psi for 2 h and was then filtered and concentrated to afford the crude title compound (350 mg) as an oil.

Step I: *N*-(1-(SR)-3-(SR)-((4-(3-(Phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-L-leucine di-hydrochloride salt and *N*-(1-(SR)-3-(SR)-((4-(3-(phenyl)prop-1-yl)piperidin-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-D-leucine di-hydrochloride salt

To a solution of 1-(SR)-(amino)-3-(SR)-((4-(3-phenylprop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcylopentane (from Step H, derived from the Higher R_f isomer from Step E) (25 mg, 0.067 mmol), 4-methyl-2-oxovaleric acid (17 mg, 0.13 mmol) and acetic acid (0.008 mL, 0.13 mmol) in 1,2-dichloroethane (2 mL) was added sodium triacetoxyborohydride (42 mg, 0.20 mmol). The reaction was

stirred at rt for 24 h and was then quenched into dilute aq. sodium carbonate solution and was extracted three times with ethyl acetate. The organic layers were washed with brine, dried over sodium sulfate, combined and evaporated. The residue was purified by Prep TLC (5% methanol in methylene chloride) to afford separation of the 2 title compounds. The hydrochlorides were prepared by taking up in methylene chloride, addition of excess 1M HCl in ether, and evaporation to dryness.
Higher: MS (NH_3/ESI): m/z 491 (M + 1).
Lower: MS (NH_3/ESI): m/z 491 (M + 1).

EXAMPLE 2

N-(1-(RS)-3-(SR)-((4-(3-(Phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-L-leucine di-hydrochloride salt and *N*-(1-(RS)-3-(SR)-((4-(3-(phenyl)prop-1-yl)piperidin-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-D-leucine di-hydrochloride salt

Using essentially the same procedures as in Example 1, Steps G-I, but substituting the lower R_f product from Steps E and F, the 2 title compounds were obtained after Prep TLC separation.
Higher: MS (NH_3/ESI): m/z 491 (M + 1).
Lower: MS (NH_3/ESI): m/z 491 (M + 1).

EXAMPLE 3

N-(1-(SR)-3-(SR)-((4-(3-(Phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-L-norvaline di-hydrochloride salt and *N*-(1-(SR)-3-(SR)-((4-(3-(phenyl)prop-1-yl)piperidin-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-D-norvaline di-hydrochloride salt

Using essentially the same procedure as in Example 1, Step I, but substituting 2-oxovaleric acid in Step I, the 2 title compounds were obtained as a mixture after Prep TLC purification (no separation of the diastereomers was seen in this case).
MS (NH_3/ESI): m/z 477 (M + 1).

EXAMPLE 4

N-(1-(RS)-3-(SR)-((4-(3-(Phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-L-norvaline di-hydrochloride salt and *N*-(1-(RS)-3-(SR)-((4-(3-(phenyl)prop-1-yl)piperidin-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-D-norvaline di-hydrochloride salt

Using essentially the same procedures as in Example 1, Steps G-I, but substituting the lower R_f product from Steps E and F and 2-oxovaleric acid in Step I the 2 title compounds were obtained as a mixture after Prep TLC purification (no separation of the diastereomers was seen in this case).
MS (NH_3/ESI): m/z 477 (M + 1).

EXAMPLE 5

N-(1-(RS)-3-(SR)-((4-(3-(Phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-L-phenylglycine di-hydrochloride salt and *N*-(1-(RS)-3-(SR)-((4-(3-(phenyl)prop-1-yl)piperidin-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)-D-phenylglycine di-hydrochloride salt

Using essentially the same procedures as in Example 1, Steps G-I, but substituting the lower R_f product from Steps E and F and 2-oxophenylacetic acid in Step I the 2 title compounds were obtained as a mixture after Prep TLC purification (no separation of the diastereomers was seen in this case).
HPLC/MS (ESI): m/z 511 (M + 1).

Examples 6-9 illustrate the chemistry described in Schemes X-Y of the general chemistry section and were used to determine the absolute stereochemistry at the C-1, 3 and 4 positions of the cyclopentyl scaffold for the intermediates and final products. This was then applied to the preparation and assignment of stereochemistry for the subsequent Examples in this patent.

EXAMPLE 6

N-(1-(S)-3-(R)-((4-(*N*-(4-Nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-leucine (Isomer 6A), *N*-(1-(S)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-

phenylcyclopent-1-yl)-L-leucine (Isomer 6B), *N*-(1-(R)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-leucine (Isomer 6C) and *N*-(1-(R)-3-(R)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-leucine (Isomer 6D) di-TFA salts

Step A: (+-)-*trans*-4-Methylene-2-phenylcyclopentanoic acid

To a solution of methyl (+-)-*trans*-4-methylene-2-phenylcylopentanoate prepared as in Example 1, Step A (28.4 g, 131 mmol) in methanol (400 mL) was added 5N sodium hydroxide (131 mL, 656 mmol). The reaction was heated at 65 °C for 1 h then cooled and concentrated. The residue was diluted with water, acidified with 2M hydrochloric acid and extracted twice with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo to give the crude title acid (27.2 g) which was used directly in Step B.

Step B: (+-)-*trans*-1-Hydroxymethyl-4-methylene-2-phenylcylopentane

To a solution of (+-)-*trans*-4-methylene-2-phenylcylopentanoic acid (26 g, 129 mmol) from Step A in THF (600 mL) under nitrogen at -10 °C was added dropwise over 15 min 1M lithium aluminum hydride (LAH) in THF (193 mL, 193 mmol). After 16 h at rt, the excess LAH was quenched by dropwise addition of acetone and the reaction was then poured into dilute aq. HCl. The mixture was extracted twice with ether and the organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (20% ethyl acetate in hexanes) to afford the title product (23.8 g) as an oil.

Step C: (+-)-*trans*-1-Hydroxymethyl-4-oxo-2-phenylcylopentane

Into a solution of (+-)-*trans*-1-hydroxymethyl-4-methylene-2-phenylcylopentane from Step B (22.7 g, 121 mmol) in methanol (200 mL) cooled in a dry ice/acetone bath was bubbled ozone until the blue color persisted. The excess ozone was removed with a stream of nitrogen and then dimethylsulfide (20 mL) was added. After 10 min, the bath was removed and the reaction was allowed to warm to rt over 16 h. The volatiles were removed in vacuo and the residue was purified by FC (15 -30% ethyl acetate in hexanes) to give the title compound (22.1 g).

919

Step D: (+-)-*trans*-4-Oxo-2-phenylcylopentanecarboxaldehyde

To a solution of oxalyl chloride (1.15 mL, 13.1 mmol) in methylene chloride (30 mL) at -70 °C was added dropwise DMSO (1.87 mL, 26.3 mmol). After 15 min, a solution of (+-)-*trans*-1-hydroxymethyl-4-oxo-2-phenylcylopentane from Step C (1.0 g, 5.26 mmol) in methylene chloride (10 mL) was added. The reaction was stirred at -70 °C for 1.5 h and then DIPEA (9.25 mL, 53 mmol) in methylene chloride (10 mL) was added dropwise over 5 min. After a further 10 min, the mixture was allowed to warm to rt for 1 h and then diluted with methylene chloride and poured into dilute aq. HCl. The layers were separated. The aq. layer was reextracted with a second portion of methylene chloride and the organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by FC (30% ethyl acetate in hexanes) to give the title product (0.9 g) after vacuum drying.

Step E: 3-(SR)-((4-(*N*-(4-Nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopentan-1-one di-hydrochloride salt

To a solution of (+-)-*trans*-4-oxo-2-phenylcylopentanecarboxaldehyde from Step D (327 mg, 1.74 mmol) in 1,2-dichloroethane (20 mL) was added 4-(*N*-(4-nitrobenzyloxycarbonyl)(*N*-allyl)amino)piperidine hydrochloride (667 mg, 1.9 mmol) and DIPEA (0.36 mL, 2.1 mmol). After 5 min, sodium triacetoxyborohydride (740 mg, 3.5 mmol) was added and the reaction was stirred at rt for 4 h. The reaction was diluted with methylene chloride, quenched with aq. sodium carbonate and extracted 3 times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by FC eluting with a gradient of 35 to 75% ethyl acetate in hexanes to give the title product (365 mg) as the free amine. This was taken up in ether and 1M hydrogen chloride in ether (0.5 mL) was added to form the di-hydrochloride salt. The volatiles were removed in vacuo to give the title salt.

MS (NH_3/ESI): m/z 492 (M + 1).

Step F: *N*-(1-(S)-3-(R)-((4-(*N*-(4-Nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-leucine t-butyl ester (Isomer A), *N*-(1-(S)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-leucine t-butyl ester (Isomer B), *N*-(1-(R)-3-

(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-leucine t-butyl ester (Isomer C) and *N*-(1-(R)-3-(R)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-leucine t-butyl ester (Isomer D)

To a solution of 3-(SR)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopentan-1-one (52 mg, 0.10 mmol) from Step E, L-leucine t-butyl ester hydrochloride (65 mg, 0.29 mmol) and DIPEA (0.069 mL, 0.40 mmol) in 1,2-dichloroethane (2 mL) at rt was added sodium triacetoxyborohydride (41 mg, 0.20 mmol). The reaction was stirred at rt for 16 h and was then diluted with methylene chloride, quenched with aq. sodium carbonate and extracted 3 times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by Prep TLC eluting first with 75% ethyl acetate in hexanes to give partial separation of the four diastereomeric title products. Prep TLC was repeated with 40% ethyl acetate in hexanes for each band to give clean highest R_f product (Isomer A), a mixture of the middle R_f products (Isomers B and C), and clean lowest R_f product (Isomer D) as the free amines.

(higher R_f): HPLC/MS (ESI): m/z 663 (M + 1).

(middle R_f): HPLC/MS (ESI): m/z 663 (M + 1) (2 isomers seen).

(lower R_f): HPLC/MS (ESI): m/z 663 (M + 1).

Step G: *N*-(1-(S)-3-(R)-((4-(*N*-(4-Nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-leucine (Isomer 6A), *N*-(1-(S)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-*L*-leucine (Isomer 6B), *N*-(1-(R)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-leucine (Isomer 6C) and *N*-(1-(R)-3-(R)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-leucine (Isomer 6D) di-TFA salts

The 2 individual diastereomers and the mixed diastereomers from Step F were each taken up in 1:1 methylene chloride:ether (2 mL) and 1M hydrogen chloride in ether (1 mL) was added. After 3 days at rt the volatiles were removed

under nitrogen to give the title compounds as white solids. These were analyzed by HPLC (Advantage 4.6 x 150 mm C-18 column, using a gradient of 10% A:90% B to 35% A:65% B over 30 min; A = 0.5% TFA in water, B = 0.5% TFA in acetonitrile) and purified by Prep HPLC (Combi Prep 20 x 50 mm C-18). Evaporation of the clean fractions to dryness afforded the title compounds as their di-TFA salts.

Isomer A (from highest R_f): HPLC/MS (ESI): m/z 607 (M + 1), R_t = 25.5 min
Isomer B (from middle R_f): HPLC/MS (ESI): m/z 607 (M + 1), R_t = 25.2 min.
Isomer C (from middle R_f): HPLC/MS (ESI): m/z 607 (M + 1), R_t = 25.9 min.
Isomer D (from lowest R_f): HPLC/MS (ESI): m/z 607 (M + 1), R_t = 25.2 min.

EXAMPLE 7

N-(1-(R)-3-(S)-((4-(*N*-(4-Nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine (Isomer 7E), *N*-(1-(R)-3-(R)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-D-leucine (Isomer 7F), *N*-(1-(S)-3-(R)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-D-leucine (Isomer 7G) and *N*-(1-(S)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine (Isomer 7H) di-TFA salts

Using essentially the same procedures as in Example 6, Step F and G, but substituting D-leucine t-butyl ester hydrochloride in Step F, the four title diastereomers were obtained which were enantiomeric to those of Example 6.

Isomer E (from highest R_f): HPLC/MS (ESI): m/z 607 (M + 1), R_t = 25.5 min
Isomer F (from middle R_f): HPLC/MS (ESI): m/z 607 (M + 1), R_t = 25.2 min.
Isomer G (from middle R_f): HPLC/MS (ESI): m/z 607 (M + 1), R_t = 25.9 min.
Isomer H (from lowest R_f): HPLC/MS (ESI): m/z 607 (M + 1), R_t = 25.2 min.

EXAMPLE 8

N-(1-(S)-3-(S)-((4-(*N*-(4-Nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-leucine (Isomer 6B) and *N*-(1-(S)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine (Isomer 7H) di-TFA salts

Step A: (+-)-*trans*-4-Methylene-2-phenylcyclopentanoic acid

To a solution of methyl (+-)-*trans*-4-methylene-2-phenylcylopentanoate prepared as in Example 1, Step A (28.4 g, 131 mmol) in methanol (400 mL) was added 5N sodium hydroxide (131 mL, 656 mmol). The reaction was heated at 65 °C for 1 h then cooled and concentrated. The residue was diluted with water, acidified with 2M hydrochloric acid and extracted twice with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo to give the crude title acid (27.2 g) which was used directly in Step B.

Step B: (+)-*trans*-4-Methylene-2-phenylcyclopentanoic acid, (S)-(-)- α -methylbenzylamine salt and (-)-*trans*-4-methylene-2-phenylcylopentanoic acid, (R)-(+)- α -methylbenzylamine salt

The crude (+-)-*trans*-4-methylene-2-phenylcylopentanoic acid from Step A (assumed 131 mmol) was taken up in 2-propanol (400 mL), warmed to 80 °C and treated with (S)-(-)- α -methylbenzylamine (8.45 mL, 66 mmol). The mixture was stirred while allowed to cool to rt over 16 h and was then cooled to -10 °C for 1 h. The salt was filtered, washed with a small amount of ether to remove 2-propanol and air dried to give 6.442 g of salt. This was recrystallized twice from 2-propanol to give the title salt (4.713 g), $[\alpha]_D = +56$ (MeOH, c = 0.20).

The combined mother liquors from above were concentrated and the residue was taken up in water, acidified with 2M hydrochloric acid and extracted twice with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was taken up in 2-propanol (400 mL), warmed to 80 °C and treated with (R)-(+)- α -methylbenzylamine (9.1 mL, 70 mmol). The mixture was stirred while allowed to cool to rt over 16 h and was then cooled to -10 °C for 1 h. The salt was filtered, washed with a small amount of ether to remove 2-propanol and air dried to give 8.22 g of salt. This was recrystallized from 2-propanol to give the title salt (6.31 g), $[\alpha]_D =$ -55 (MeOH, c = 0.21).

hexanes) to give the two diastereomeric products, higher R_f (18.4 g) and lower R_f (17.7 g).

Step B2: (+)-*trans*-4-Methylene-2-phenylcylopentanoic acid

A solution of 1-(S)-(((S)-(-)-4-benzyl-2-oxazolidin-1-yl)carbonyl)-3-methylene-2-(S)-phenylcyclopentane (higher R_f product from Step B1) (20.9 g, 58 mmol) in a 3 : 1 mixture of THF : water (1 L) was cooled to 5 °C. Hydrogen peroxide (30%, 39.5 mL, 350 mmol) and lithium hydroxide (4.85 g, 106 mmol) were added and the reaction was stirred for 3.5 h. The excess peroxide was quenched by dropwise addition of sodium sulfite (60 g) in water (1 L) over 1.5 h while maintaining the temperature below 5 °C. After stirring for 2 additional hours, most of the THF was removed in vacuo and the aqueous layer was washed 3 times with methylene chloride. The aqueous layer was acidified to pH = 2 with conc. HCl and reextracted twice with methylene chloride. The organic layers were washed with brine, dried and concentrated to give the (+) title product, $[\alpha]_D$ = +100.5 (MeOH, c = 0.207).

Step D: (+)-*trans*-1-Hydroxymethyl-4-methylene-2-phenylcylopentane and (-)-*trans*-1-hydroxymethyl-4-methylene-2-phenylcylopentane

Method A:

A solution of (+)-*trans*-4-methylene-2-phenylcylopentanoic acid from Step C (4.15 g, 20.5 mmol) in THF (100 mL) under nitrogen was cooled to -7 °C and 1M LAH in THF (31 mL, 31 mmol) was added dropwise over 15. The reaction was allowed to warm to rt over 16 h. The excess LAH was quenched by dropwise addition of acetone and the reaction was then poured into dilute aq. HCl. The mixture was extracted twice with ether and the organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (20% ethyl acetate in hexanes) to afford the title (+) product (3.93 g), $[\alpha]_D$ = +50 (MeOH, c = 0.20).

Similarly, the (-)-*trans*-4-methylene-2-phenylcylopentanoic acid from Step C (4.23 g) was converted to the title (-) alcohol (3.75 g), $[\alpha]_D$ = -51 (MeOH, c = 0.2).

Method B:

925

Prep-HPLC of (+-)-*trans*-4-methylene-2-phenylcylopentanoic from Example 1, Step B using a Chiracel OD column (5-10% isopropanol in hexanes) affords good separation of the title (-) enantiomer as the first eluting band and the (+) enantiomer as the second eluting band.

Step E: (+)-*trans*-1-t-Butyldimethylsilyloxymethyl-4-methylene-2-phenylcylopentane and (-)-*trans*-1-t-butyldimethylsilyloxymethyl-4-methylene-2-phenylcylopentane

To a solution of (+)-*trans*-1-hydroxymethyl-4-methylene-2-phenylcylopentane from Step D (3.9 g, 21 mmol) in methylene chloride (50 mL) was added t-butyldimethylsilyl chloride (4.7 g, 31 mmol) and DIPEA (7.3 mL, 42 mmol). The reaction was stirred at rt for 16 h, poured into dilute aq. HCl and extracted twice with ether. The organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (100% hexanes) to afford the title product (5.6 g) as a oil, $[\alpha]_D$ = +42.3 (MeOH, c = 0.18).

Similarly, (-)-*trans*-1-hydroxymethyl-4-methylene-2-phenylcylopentane from Step D (3.75 g) was converted to the title (-) silylether (5.5 g), $[\alpha]_D$ = -44.4 (MeOH, c = 0.18).

Step F: (+)-*trans*-1-Hydroxymethyl-4-oxo-2-phenylcylopentane and (-)-*trans*-1-hydroxymethyl-4-oxo-2-phenylcylopentane

Method A:

A solution of (+)-*trans*-1-t-butyldimethylsilyloxymethyl-4-methylene-2-phenylcylopentane from Step E (4.6 g, 15 mmol) in methanol (100 mL) was cooled to -70 °C in a dry-ice acetone bath and ozone was bubbled through until a blue color persisted which was discharged with a stream of nitrogen. Dimethylsulfide (10 mL) was added and after 15 min, the reaction was allowed to warm to rt over 16 h. Since by TLC (20% ethyl acetate in hexanes) indicated that there was significant loss of the silyl as well as dimethylketal formation, the methanol was mostly remove in vacuo. The residue was diluted with water and treated with sulfuric acid (6 mL) and stirred for 2 h. The mixture was extracted twice with ethyl acetate and the organic layers were washed with brine (containing some sodium bicarbonate), dried over sodium sulfate, combined and concentrated. The residue was purified by FC (15 - 30% ethyl

acetate in hexanes) to give the (+) title ketone/alcohol (2.87 g), $[\alpha]_D$ = -96 (MeOH, c = 0.2).

Similarly, (-)-*trans*-1-t-butyldimethylsilyloxymethyl-4-methylene-2-phenylcylopentane from Step E (4.4 g) was converted to the title (-) ketone/alcohol (2.8 g), $[\alpha]_D$ = +97 (MeOH, c = 0.2)..

Method B:

The title compounds can also be obtained directly from (+)-*trans*-1-hydroxymethyl-4-methylene-2-phenylcylopentane and (-)-*trans*-1-hydroxymethyl-4-methylene-2-phenylcylopentane by ozonolysis as above. Thus, (+)-*trans*-1-hydroxymethyl-4-methylene-2-phenylcylopentane (3.7 gm, 20 mmol) afforded from (+)-*trans*-1-hydroxymethyl-4-oxo-2-phenylcylopentane (3.5 g).

Step G: 1-(S)-Benzylamino-3-(S)-hydroxymethyl-4-(S)-phenylcylopentane and 1-(R)-benzylamino-3-(S)-hydroxymethyl-4-(S)-phenylcylopentane

To a solution of (+)-*trans*-1-hydroxymethyl-4-oxo-2-phenylcylopentane from Step F (1.19 g, 6.3 mmol) in 1,2-dichloroethane (25 mL) was added benzylamine (1.3 mL, 12 mmol) and acetic acid (0.75 mL, 13 mmol). After 10 min, sodium triacetoxyborohydride (2.65 g, 12.5 mmol) was added in portions and the reaction was stirred at rt for 16 hr. The reaction was quenched into dilute aq. sodium carbonate and the mixture was extracted twice with ethyl acetate. The organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (5 - 10% methanol in methylene chloride) to separate the title products (1.6 g) as a mixture of C-1 isomers.

Step H: 1-(S)-t-Butoxycarbonylamino-3-(S)-hydroxymethyl-4-(S)-phenylcylopentane (Higher R_f isomer) and 1-(R)-t-butoxycarbonylamino-3-(S)-hydroxymethyl-4-(S)-phenylcylopentane (Lower R_f isomer)

To a solution of 1-(S)-benzylamino-3-(S)-hydroxymethyl-4-(S)-phenylcylopentane and 1-(R)-benzylamino-3-(S)-hydroxymethyl-4-(S)-phenylcylopentane from Step G (1.6 g, 5.6 mmol) in methanol (40 mL) was added 20% palladium hydroxide (300 mg, 50% by wt water) and ammonium formate (7.0 g, 111 mmol). The reaction was heated at 60 °C for 6 h and rt for 16 h. The reaction

927

was filtered and concentrated. The residue was taken up in water and the aqueous layer was made basic with 2N sodium hydroxide and extracted twice with methylene chloride. The organic layers were washed with brine, dried over sodium sulfate, combined and concentrated to afford crude amino-alcohol.

The above product was taken up in methylene chloride (25 mL), cooled in an ice bath and DIPEA (2.9 mL, 17 mmol) and di-t-butyl dicarbonate (1.28 g, 5.8 mmol) were added. After 16 h, the reaction was poured into dilute aq. HCl and extracted twice with methylene chloride. The organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (30 - 40% ethyl acetate in hexanes) to afford separation of the two title compounds.

Higher R_f:

^{1}H NMR ($CDCl_3$) δ: 1.43 (s, 9 H), 1.45 (m, 1 H), 1.9-2.1 (m, 2 H), 2.17 (m, 1 H), 2.40 (m, 1 H), 3.01 (q, 1 H), 3.59 (dABq, 2 H), 4.20 (br m, 1 H), 5.00 (br s, 1 H), 7.15-7.3 (m, 5 H).

Lower R_f:

^{1}H NMR ($CDCl_3$) δ: 1.43 (s, 9 H), 1.58 (ddd, 1 H), 1.78.1 (ddd, 1 H), 2.02 (m, 1 H), 2.29 (m, 1 H), 2.47 (ddd, 1 H), 2.76 (ddd, 1 H), 3.54 (dABq, 2 H), 4.06 (br m, 1 H), 4.62 (br s, 1 H), 7.15-7.3 (m, 5 H).

Step I: 1-(S)-t-Butoxycarbonylamino-3-(S)-formyl-4-(S)-phenylcylopentane (Higher R_f isomer) and 1-(R)-t-butoxycarbonylamino-3-(S)-formyl-4-(S)-phenylcylopentane (Lower R_f isomer)

To a solution of oxalyl chloride (0.145 mL, 1.67 mmol) in methylene chloride (10 mL) at -70 °C was added dropwise DMSO (0.24 mL, 3.3 mmol). After 15 min, a solution of 1-(S)-t-butoxycarbonylamino-3-(S)-hydroxymethyl-4-(S)-phenylcylopentane (Higher R_f isomer from Step F) (194 mg, 0.66 mmol) in methylene chloride (5 mL) was added. The reaction was stirred at -70 °C for 1.5 h and then DIPEA (1.2 mL, 6.6 mmol) in methylene chloride (5 mL) was added dropwise over 5 min. After a further 10 min, the mixture was allowed to warm to rt for 1 h and then diluted with methylene chloride and poured into dilute aq. HCl. The layers were separated. The aq. layer was reextracted with a second portion of methylene chloride and the organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by FC (15% ethyl acetate in hexanes) to give the title product (155 mg) after vacuum drying.

Using essentially the same procedure as above, material derived from the lower isomer from Step H (0.189 g, 0.6 mmol) was also converted to the lower R_f title compound (175 mg).

Step J: 1-(S)-(t-Butoxycarbonylamino)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcylopentane (Higher R_f isomer) and 1-(R)-(t-butoxycarbonylamino)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcylopentane (Lower R_f isomer)

To a solution of 1-((S)-(t-butoxycarbonylamino)-3-(S)-(carbonyl)-4-(S)-phenylcyclopentane (from Step I, derived from Higher R_f isomer in Step G) (155 mg, 0.54 mmol) in 1,2-dichloroethane (5 mL) was added 4-(*N*-(4-nitrobenzyloxycarbonyl)(*N*-allyl)amino)piperidine hydrochloride (210 mg, 0.59 mmol) and DIPEA (0.12 mL, 0.64 mmol). After 15 min, sodium triacetoxyborohydride (230 mg, 1.1 mmol) was added and the reaction was stirred at rt for 16 h. The reaction was diluted with methylene chloride, quenched with aq. sodium carbonate and extracted 3 times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by Prep TLC eluting with 5% methanol in methylene chloride to give the title product (280 mg) as the free amine.
MS (NH_3/ESI): m/z 593 (M + 1).

Using essentially the same procedure as above, material derived from the lower isomer from Step H-I (0.175 g, 0.6 mmol) was also converted to the lower R_f title compound (275 mg).

Step K: 1-(S)-(Amino)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcylopentane di-hydrochloride salt (Higher R_f isomer) and 1-(R)-(amino)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcylopentane di-hydrochloride salt (Lower R_f isomer)

A solution of hydrogen chloride (4.6 mmol) in methanol was prepared by addition of acetyl chloride (0.325 mL, 4.6 mmol) to methanol (10 mL) and aging

for 15 min. To this was added 1-(S)-(t-butoxycarbonylamino)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcylopentane (Higher R_f isomer from Step J) (270 mg, 0.46 mmol). After 16 h, the volatiles were removed in vacuo to dryness to give the title compound as the di-hydrochloride salt (248 mg).

Using essentially the same procedure as above, material derived from the lower isomer from Step H-J (0.250 g, 0.42 mmol) was also converted to the lower R_f title compound (235 mg).

Step L: *N*-(1-(S)-3-(S)-((4-(*N*-(4-Nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-leucine (Isomer 6B) and *N*-(1-(S)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine (Isomer 7H) di-TFA salts

To a solution of 1-(S)-(amino)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcylopentane di-hydrochloride salt (derived from the higher R_f isomer in Steps H - K) (20 mg, 0.045 mmol), 4-methyl-2-oxo-valeric acid (15 mg, 0.11 mmol) and DIPEA (0.016 mL, 0.09 mmol) in 1,2-dichloroethane (2 mL) was added sodium triacetoxyborohydride (29 mg, 0.135 mmol). The reaction was stirred at 50 °C for 10 h and then at rt for another 16 h. It was then quenched with aq sodium carbonate and extracted three times with ethyl acetate. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by Prep TLC eluting with 10% methanol in methylene chloride to give the title products (8 mg) as a mixture of the free amines. HPLC analysis as in Example 6 and 7 gave only a single band corresponding to Isomers B (and enantiomeric Isomer F) and H (and enantiomeric Isomer D) which co-elute. HPLC/MS (ESI): m/z 593 (M + 1).

Example 9

N-(1-(R)-3-(S)-((4-(*N*-(4-Nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-leucine (Isomer 7E) and *N*-(1-(R)-3-(S)-

((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine (Isomer 6C) di-TFA salts

Using essentially the same procedure as in Example 8, Step L, but substituting 1-(R)-(amino)-3-(S)-((4-(*N*-(4-nitrobenzyloxycarbonyl)-*N*-(allyl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcylopentane di-hydrochloride salt (derived from the lower R_f isomer in Steps H - K) (20 mg, 0.045 mmol), the two title compounds were prepared. HPLC analysis of the crude products as in Example 6 and 7 indicated two peaks. In this case the diastereomers were separable on Prep TLC (10% methanol in methylene chloride). HPLC analysis as in Example 6 and 7 now gave only a single peak for each sample from the Prep TLC. The higher band corresponded to Isomer E (and enantiomeric Isomer A) and the lower band corresponded to Isomer C (and enantiomeric Isomer G) which are distinct in the HPLC. The di-TFA salts were prepared by evaporation from 0.5% TFA in acetonitrile.

Higher Isomer E: HPLC/MS (ESI): m/z 593 (M + 1).

Lower Isomer C: HPLC/MS (ESI): m/z 593 (M + 1).

Example 10

Using essentially the same procedure as in Example 6, Steps E to G, but substituting 4-(3-(4-fluorophenyl)prop-1-yl)piperidine hydrochloride in Step E and L-valine t-butyl ester hydrochloride in Step F, the following diastereomers can be obtained after a combination of Prep TLC and HPLC separation.

N-(1-(S)-3-(R)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-valine di-TFA salt (Isomer A),

N-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-valine di-TFA salt (Isomer B),

N-(1-(R)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-valine di-TFA salt (Isomer C)

N-(1-(R)-3-(R)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-valine di-TFA salt (Isomer D)

Example 11

Using essentially the same procedure as in Example 6, Steps E to G, but substituting 4-(3-(4-fluorophenyl)prop-1-yl)piperidine hydrochloride (from Procedure 9) in Step E and L-leucine t-butyl ester hydrochloride in Step F, the following diastereomers can be obtained after a combination of Prep TLC and HPLC separation.

N-(1-(S)-3-(R)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-leucine di-TFA salt (Isomer A),

N-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-leucine di-TFA salt (Isomer B),

N-(1-(R)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-isoleucine di-TFA salt (Isomer C)

N-(1-(R)-3-(R)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-leucine di-TFA salt (Isomer D)

Example 12

Using essentially the same procedure as in Example 6, Steps E to G, but substituting 4-(3-(4-fluorophenyl)prop-1-yl)piperidine hydrochloride (from Procedure 9) in Step E and L-phenylglycine t-butyl ester hydrochloride in Step F, the following diastereomers can be obtained after a combination of Prep TLC and HPLC separation.

N-(1-(S)-3-(R)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-phenylglycine di-TFA salt (Isomer A),

N-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-phenylglycine di-TFA salt (Isomer B),

N-(1-(R)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-phenylglycine di-TFA salt (Isomer C)

N-(1-(R)-3-(R)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-phenylglycine di-TFA salt (Isomer D)

Example 13

Using essentially the same procedure as in Example 6, Steps E to G, but substituting 4-(3-(4-fluorophenyl)prop-1-yl)piperidine hydrochloride (from Procedure 9) in Step E and L-cyclohexylglycine t-butyl ester hydrochloride in Step F, the following diastereomers can be obtained after a combination of Prep TLC and HPLC separation.

N-(1-(S)-3-(R)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-cyclohexylglycine di-TFA salt (Isomer A),
HPLC/MS (ESI): m/z 633 (M + 1).

N-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-cyclohexylglycine di-TFA salt (Isomer B),
HPLC/MS (ESI): m/z 633 (M + 1).

N-(1-(R)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-cyclohexylglycine di-TFA salt (Isomer C)
HPLC/MS (ESI): m/z 633 (M + 1).

N-(1-(R)-3-(R)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-cyclohexylglycine di-TFA salt (Isomer D)
HPLC/MS (ESI): m/z 633 (M + 1).

Example 14

Using essentially the same procedures as in Example 6, Steps E to G, but substituting 4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidine hydrochloride (from Procedure 1) in Step E and L-cyclohexylglycine t-butyl ester hydrochloride in Step F and TFA in place of HCl in ether in Step G, the following diastereomers can be obtained after a combination of Prep TLC and HPLC separation.

N-(1-(S)-3-(R)-((4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-cyclohexylglycine di-TFA salt (Isomer A),

N-(1-(S)-3-(S)-((4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-cyclohexylglycine di-TFA salt (Isomer B),

N-(1-(R)-3-(S)-((4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-cyclohexylglycine di-TFA salt (Isomer C)

N-(1-(R)-3-(R)-((4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-cyclohexylglycine di-TFA salt (Isomer D)

Example 15

Using essentially the same procedures as in Example 6, Steps E to G, but substituting 4-(4-fluorophenyl)piperidine hydrochloride (from Procedure 9) in Step E and L-cyclohexylglycine t-butyl ester hydrochloride in Step F and TFA in place of HCl in ether in Step G, the following diastereomers can be obtained after a combination of Prep TLC and HPLC separation.

N-(1-(S)-3-(R)-((4-(4-fluorophenyl)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-cyclohexylglycine di-TFA salt (Isomer A),

N-(1-(S)-3-(S)-((4-(4-fluorophenyl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-cyclohexylglycine di-TFA salt (Isomer B),

N-(1-(R)-3-(S)-((4-(4-fluorophenyl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-cyclohexylglycine di-TFA salt (Isomer C)

N-(1-(R)-3-(R)-((4-(4-fluorophenyl)piperidin-1-yl)methyl)-4-(R)-phenylcyclopent-1-yl)-L-cyclohexylglycine di-TFA salt (Isomer D)

Example 16

N-(1-(R)-3-(S)-((4-(3-(4-Fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine di-TFA salt

Step A: (1-(R)-3-(S)-(Hydroxymethyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine (Higher R_f) and (1-(S)-3-(S)-(hydroxymethyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine (lower R_f)

Method A:

To a solution of (+)-*trans*-1-hydroxymethyl-4-oxo-2-phenylcylopentane from Example 8, Step F (250 mg, 1.32 mmol), D-leucine t-butyl ester hydrochloride (370 mg, 2.0 mmol) and DIPEA (0.36 mL, 2.0 mmol) in 1,2-dichloroethane (10 mL) was added sodium triacetoxyborohydride (840 mg, 4.0 mmol). The reaction was stirred at rt for 4 h and was then quenched with aq sodium carbonate and extracted three times with ethyl acetate. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by FC eluting with a gradient of 5 - 25% ethyl acetate in hexanes to give the higher R_f 1-(R) title compound as the major product (280 mg) and the lower R_f 1-(S) as the minor product (160 mg mixed fractions).

Method B:

To a solution of (+)-*trans*-1-hydroxymethyl-4-oxo-2-phenylcylopentane from Example 8, Step F (3.3 g, 16 mmol) in methylene chloride (100 mL) was added t-butyldimethylsilyl chloride (11 g, 49 mmol) and DIPEA (22 mL, 74 mmol). The reaction was stirred at rt for 16 h, poured into dilute aq. HCl and extracted twice with ether. The organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (5% ethyl acetate in hexanes) to afford of (+)-*trans*-1-t-butyldimethylsilyloxymethyl-4-oxo-2-phenylcylopentane (6.3 g) as a oil, $[\alpha]_D = +97$ (MeOH, c = 0.2).

To a solution of (+)-*trans*-1-t-butyldimethylsilyloxymethyl-4-oxo-2-phenylcylopentane from above (1.0 g, 3.28 mmol), D-leucine t-butyl ester hydrochloride (2,2 g; 3.0 mmol) and DIPEA (1.8 mL, 10.2 mmol) in 1,2-dichloroethane (20 mL) was added sodium triacetoxyborohydride (2.1 g, 10 mmol). The reaction was stirred at rt for 5 h and was then quenched with aq sodium carbonate and extracted three times with ethyl acetate. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by FC eluting with 5% ethyl acetate in hexanes to give the higher R_f 1-(R) title compound as the minor product and the lower R_f 1-(S) as the major product (1.35 g as a mixture).

To a solution of the above product (1.35 g, 2.85 mmol) in THF (10 mL) was added 1M TBAF in THF (4.3 mL, 4.3 mmol). The reaction was stirred at rt for 16 h and the concentrated. The residue was purified by FC eluting with 20-25% ethyl acetate in hexanes to give the higher R_f 1-(R) title compound as the minor product (33 mg pure) and the lower R_f 1-(S) as the major product (202 mg pure, 0.70 g as a mixture).

Step B: (1-(R)-3-(S)-(Carbonyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine (Higher R_f) and (1-(S)-3-(S)-(carbonyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine (lower R_f)

Method A:

To a solution of oxalyl chloride (0.100 mL, 1.1 mmol) in methylene chloride (20 mL) at -70 °C was added dropwise DMSO (2.2 mL, 5.0 mmol). After 15 min, a solution of (1-(R)-3-(S)-(hydroxymethyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine (Higher R_f from Step A, Method A) (160 mg, 0.44 mmol) containing 1 eq. of 1M HCl in ether in methylene chloride (5 mL) was added. The reaction was stirred at -70 °C for 1.5 h and then DIPEA (0.77 mL, 4.5 mmol) in methylene chloride (5 mL) was added dropwise over 5 min. After a further 10 min, the mixture was allowed to warm to rt for 1 h and then diluted with methylene chloride and poured into dilute aq. HCl. The layers were separated. The aq. layer was reextracted with a second portion of methylene chloride and the organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by FC (20% ethyl acetate in hexanes) to give the higher R_f title product (38 mg) after vacuum drying.

Method B:

To a solution of (1-(R)-3-(S)-(hydroxymethyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine (mixture of higher and lower R_f from Step A, Method A) (142 mg, 0.39 mmol) in methylene chloride (10 mL) was added TPAP (6.9 mg, 0.020 mmol) and N-methylmorholine (70 mg, 0.60 mmol). The reaction was stirred under nitrogen at rt for 1 h and was then concentrated. The residue was purified by FC (25% ethyl acetate in hexanes) to give the title products (108 mg) after vacuum drying.

Step C: *N*-(1-(R)-3-(S)-((4-(3-(4-Fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine t-butyl ester (higher R_f) and *N*-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine t-butyl ester (lower R_f)

To a solution of (1-(R)-3-(S)-(carbonyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine (higher R_f) and (1-(S)-3-(S)-(carbonyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine (lower R_f) (from Step B, Method B) (9 mg, 0.025 mmol) in 1,2-dichloroethane (1 mL) was added 4-(3-(4-fluorophenyl)prop-1-yl)piperidine hydrochloride (from Procedure 9) (8 mg, 0.032 mmol) and DIPEA (0.006 mL, 0.033 mmol). After 15 min, sodium triacetoxyborohydride (11 mg, 0.051 mmol) was added and the reaction was stirred at rt for 16 h. The reaction was diluted with methylene chloride, quenched with aq. sodium carbonate and extracted 3 times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by Prep TLC eluting with 60% ethyl acetate in hexanes to give the title products as the free amines. (Each isomer): HPLC/MS (ES): m/z 565 (M + 1).

Step D: *N*-(1-(R)-3-(S)-((4-(3-(4-Fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine di-TFA salt (derived from higher R_f) and *N*-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine di-TFA salt (derived from lower R_f)

Each the products from Step C were taken up in TFA (5 mL) and aged at rt for 16 h. The volatiles were removed under a stream of nitrogen to afford the title products as the di-TFA salts (4 mg and 6 mg).

(Each isomer): HPLC/MS (ES): m/z 509 (M + 1).

Example 17

N-(1-(R)-3-(S)-((4-(3-(Benzofurazan-5-yl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(benzofurazan-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine di-TFA salt

Using essentially the same procedures as in Example 16, Step C and D, but substituting 4-(3-(benzofurazan-5-yl)prop-1-yl)piperidine hydrochloride (from Procedure 6) in Step C, the two diastereomeric title compounds were prepared. (Each isomer): HPLC/MS (ESI): m/z 533 (M + 1).

Example 18

N-(1-(R)-3-(S)-((4-(3-(4-Cyano-3-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(3-(4-cyano-3-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine di-TFA salt

Using essentially the same procedures as in Example 16, Step C and D, but substituting 4-(3-(4-cyano-3-fluorophenyl)prop-1-yl)piperidine hydrochloride (from Procedure 8) in Step C, the title compounds can be prepared.

Example 19

N-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine di-TFA salt
D-leucine

Using essentially the same procedures as in Example 16, Step C and D, but substituting 4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidine hydrochloride (from Procedure 1) in Step C, the title compounds can be prepared.

Example 20

N-(1-(R)-3-(S)-((4-(*N*-(Propyl)-*N*-(pyrrimidin-2-yl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(*N*-(propyl)-*N*-(pyrrimidin-2-yl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-leucine di-TFA salt

Using essentially the same procedures as in Example 16, Step C and D, but substituting 4-(*N*-(propyl)-*N*-(pyrrimidin-2-yl)amino)piperidine hydrochloride (from Procedure 13) in Step C, the title compounds can be prepared.

Example 21

N-(1-(R)-3-(S)-((4-(4-Fluorophenyl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)- D-leucine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(4-fluorophenyl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)- D-leucine di-TFA salt

Using essentially the same procedures as in Example 16, Step C and D, but substituting 4-(4-fluorophenyl)piperidine hydrochloride in Step C, the title compounds can be prepared.

Example 22

N-(1-(R)-3-(S)-((4-(3-(4-Fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclohexylglycine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclohexylglycine di-TFA salt

Using essentially the same procedures as in Example 16, Step A to D, but substituting D-cyclohexylglycine t-butyl ester hydrochloride in Step A and 4-(3-(4-fluorophenyl)prop-1-yl)piperidine hydrochloride (from Procedure 9) in Step C, the title compounds were prepared.
(Each isomer): HPLC/MS (ESI): m/z 535 (M + 1).

Example 23

939

N-(1-(R)-3-(S)-((4-(3-(4-Cyano-3-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclohexylglycine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(3-(4-cyano-3-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclohexylglycine di-TFA salt

Using essentially the same procedures as in Example 16, Step A to D, but substituting D-cyclohexylglycine t-butyl ester hydrochloride in Step A and 4-(3-(4-cyano-3-fluorophenyl)prop-1-yl)piperidine hydrochloride (from Procedure 8) in Step C, the title compounds were prepared.
(Each isomer): HPLC/MS (ESI): m/z 560 (M + 1).

Example 24

N-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclohexylglycine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclohexylglycine di-TFA salt

Using essentially the same procedures as in Example 16, Step A to D, but substituting D-cyclohexylglycine t-butyl ester hydrochloride in Step A and 4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidine hydrochloride (from Procedure 1) in Step C, the title compounds were prepared.
(Each isomer): HPLC/MS (ESI): m/z 583 (M + 1).

Example 25

N-(1-(R)-3-(S)-((4-(*N*-(Propyl)-*N*-(pyrrimidin-2-yl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclohexylglycine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(*N*-(propyl)-*N*-(pyrrimidin-2-yl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclohexylglycine di-TFA salt

Using essentially the same procedures as in Example 16, Step A to D, but substituting D-cyclohexylglycine t-butyl ester hydrochloride in Step A and 4-(*N*-

(propyl)-*N*-(pyrrimidin-2-yl)amino)piperidine hydrochloride (from Procedure 13) in Step C, the title compounds were prepared.
(Each isomer): HPLC/MS (ESI): m/z 534 (M + 1).

Example 26

N-(1-(R)-3-(S)-((4-(4-Fluorophenyl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclohexylglycine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(4-fluorophenyl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclohexylglycine di-TFA salt

Using essentially the same procedures as in Example 16, Step A to D, but substituting D-cyclohexylglycine t-butyl ester hydrochloride in Step A and 4-(4-fluorophenyl)piperidine hydrochloride in Step C, the title compounds were prepared.
(Each isomer): HPLC/MS (ESI): m/z 493 (M + 1).

Example 27

N-(1-(R)-3-(S)-((4-(3-(4-Fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclobutylalanine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclobutylalanine di-TFA salt

Using essentially the same procedures as in Example 16, Step A to D, but substituting D/L-cyclobutylalanine t-butyl ester hydrochloride in Step A and 4-(3-(4-fluorophenyl)prop-1-yl)piperidine hydrochloride (from Procedure 9) in Step C, the title compounds can be prepared.

Example 28

N-(1-(R)-3-(S)-((4-(3-(4-Cyano-3-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D/L-cyclobutylalanine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(3-(4-cyano-3-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclobutylalanine di-TFA salt

Using essentially the same procedures as in Example 16, Step A to D, but substituting D-cyclobutylalanine t-butyl ester hydrochloride in Step A and 4-(3-(4-cyano-3-fluorophenyl)prop-1-yl)piperidine hydrochloride (from Procedure 8) in Step C, the title compounds can be prepared.

Example 29

N-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclobutylalanine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclobutylalanine di-TFA salt

Using essentially the same procedures as in Example 16, Step A to D, but substituting D/L-cyclobutylalanine t-butyl ester hydrochloride in Step A and 4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidine hydrochloride (from Procedure 1) in Step C, the title compounds were prepared.

Example 30

N-(1-(R)-3-(S)-((4-(*N*-(Propyl)-*N*-(pyrrimidin-2-yl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D/L-cyclobutylalanine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(*N*-(propyl)-*N*-(pyrrimidin-2-yl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclobutylalanine di-TFA salt

Using essentially the same procedures as in Example 16, Step A to D, but substituting D-cyclobutylalanine t-butyl ester hydrochloride in Step A and 4-(*N*-(propyl)-*N*-(pyrrimidin-2-yl)amino)piperidine hydrochloride (from Procedure 13) in Step C, the title compounds can be prepared.

Example 31

N-(1-(R)-3-(S)-((4-(3-(4-Fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclopropylalanine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclopropylalanine di-TFA salt

Using essentially the same procedures as in Example 16, Step A to D, but substituting D-cyclopropylalanine t-butyl ester hydrochloride in Step A and 4-(3-(4-fluorophenyl)prop-1-yl)piperidine hydrochloride in Step C, the title compounds can be prepared.

Example 32

N-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclopropylalanine di-TFA salt and *N*-(1-(S)-3-(S)-((4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclopropylalanine di-TFA salt

Using essentially the same procedures as in Example 16, Step A to D, but substituting D-cyclopropylalanine t-butyl ester hydrochloride in Step A and 4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidine hydrochloride (from Procedure 1) in Step C, the title compounds were prepared.

EXAMPLE 33

N-(1-(R)-3-(S)-((4-(3-(Benzofurazan-5-yl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-cyclohexylglycine di-hydrochloride salt

Using essentially the same procedure as in Example , Steps A to D, but substituting D-cyclohexylglycine t-butyl ester hydrochloride in Step A and 4-(3-(benzofurazan-5-yl)prop-1-yl)piperidine (from Procedure 5) in Step C, the title compound was prepared.
HPLC/MS (ESI): m/z 559 (M + 1).

EXAMPLE 34

N-(1-(R)-3-(S)-((4-(3-(4-Flurophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-leucine di-hydrochloride salt

Using essentially the same procedure as in Example 16, Steps A to D, but substituting L-leucine t-butyl ester hydrochloride in Step A and 4-(3-(4-flurophenyl)prop-1-yl)piperidine in Step F, the title compound was prepared. HPLC/MS (ESI): m/z 509 (M + 1).

EXAMPLE 35

N-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-cyclohexylglycine di-hydrochloride salt

Step A: Methyl (+-)-*trans*-4-methylene-2-(3-fluorophenyl)cylopentanoate

A mixture of methyl *trans*-3-fluorocinnamate (41.25 g, 229 mmol), tetrakis(triphenylphosphine) palladium(0) (18.5 g, 16 mmol), 1,2-bis(diphenylphosphino)ethane (5.5 g, 13.7 mmol) and 2-((trimethylsilyl)methyl)-2-propen-1-yl acetate (42.66 g, 229 mmol) in THF (300 mL) under nitrogen was heated to reflux for 6 h and then stirred at rt for 16 h. The reaction was diluted with hexane and filtered to remove yellow precipitate. The volatiles were then removed *in vacuo* and the residue was purified by FC (3 to 5% ethyl acetate in hexanes) to afford the title compound (45 g).

^{1}H NMR ($CDCl_3$) δ: 2.52 (m, 1 H), 2.68 (m, 1 H), 2.8-2.9 (m, 2 H), 2.95 (ddd, 1 H), 3.45 (ddd, 1 H), 3.63 (s, 3 H), 4.96 (m, 2 H), 6.9-7.0 (m, 2 H), 7.03 (d, 1 H), 7.2-7.3 (m, 1 H).

Step B: (+-)-*trans*-4-Methylene-2-(3-fluorophenyl)cyclopentanoic acid

To a solution of methyl (+-)-*trans*-4-methylene-2-(3-fluoro)phenylcylopentanoate prepared as in Example 33, Step A (47 g, 200 mmol) in methanol (500 mL) was added 5N sodium hydroxide (200 mL, 1000 mmol). The reaction was stirred at rt for 60 h then concentrated in vacuo. The residue was taken up in water, acidified with 2M hydrochloric acid and extracted twice with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo to give the crude title acid (40.8 g) which was used directly in Step C.

Step C: (+)-*trans*-1-Hydroxymethyl-4-methylene-2-(3-fluorophenyl)cylopentane and (-)-*trans*-1-hydroxymethyl-4-methylene-2-(3-fluorophenyl)cylopentane

A solution of (+-)-*trans*-4-methylene-2-(3-fluorophenyl)cylopentanoate (5.2 g, 23.6 mmol) from Step B in THF (100 mL) was cooled to 0 °C under nitrogen and 1M lithium aluminum hydride (LAH) in THF (35.4 mL) was added dropwise over 10 min. The reaction was stirred at rt for 16 h, the excess LAH was quenched by dropwise addition of acetone and the reaction was then poured into dilute aq. HCl. The mixture was extracted twice with ether and the organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (25% ethyl acetate in hexanes) to afford the racemic title product (4.1 g) as a an oil. Chiral Prep HPLC on a 2 cm x 25 cm Chiralcel OD column eluting with 5% isopropanol in hexanes (25 injections) afforded the (-)-enantiomer, $[\alpha]_D$ = -45.5 (MeOH, c = 0.9), as the first eluting peak (R_t = 17.5 min) and the (+)-enantiomer (1.87 g), $[\alpha]_D$ = +45.0 (MeOH, c = 1.0), as the second peak (R_t = 22.0 min).

^{1}H NMR ($CDCl_3$) δ: 2.2-2.35 (m, 2 H), 2.5 (m, 1 H), 2.65-2.85 (m, 2 H), 2.9 (m, 1 H), 3.51 and 3.68 (dABq, 2 H), 4.93 (m, 2 H), 6.9-7.0 (m, 2 H), 7.06 (d, 1 H), 7.3-7.4 (m, 1 H).

Step D: (+)-*trans*-3-Hydroxymethyl-4-(3-fluorophenyl)cylopentanone

A solution of (+)-*trans*-1-hydroxymethyl-4-methylene-2-(3-fluorophenyl)cylopentane from Step C (1.87 g, 9.0 mmol) in methanol (75 mL) was cooled in a dry ice/acetone bath and ozone was bubbled into the solution until the blue color persisted. The excess ozone was removed with a stream of nitrogen and then dimethylsulfide (5 mL) was added. After 10 min, the bath was removed and the reaction was allowed to warm to rt over 2 h. The mixture was treated with 10 drops of sulfuric acid (c) in water (2 mL) for 1 h before most of the methanol was removed in vacuo. The mixture was diluted with water and extracted twice with ethyl acetate and the organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (50% ethyl acetate in hexanes) to give the title compound (1.87 g)), $[\alpha]_D$ = +132 (MeOH, c = 1.2),.

^{1}H NMR ($CDCl_3$) δ: 2.3-2.45 (m, 2 H), 2.5 (m, 1 H), 2.61 and 2.77 (dABq, 2 H), 2.28 (ddd, 1 H), 3.61 and 3.75 (dABq, 2 H), 6.9-7.0 (m, 2 H), 7.06 (d, 1 H), 7.3-7.4 (m, 1 H).

Step E: *N*-(1-(R)-3-(S)-Hydroxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-cyclohexylglycine t-butyl ester

To a solution of (+)-*trans*-3-hydroxymethyl-4-(3-fluorophenyl)cylopentanone from Step D (500 mg, 2.4 mmol) in 1,2-dichloroethane (25 mL) was added D-cyclohexylglycine t-butyl ester (0.61 g, 2.88 mmol) and acetic acid (0.15 mL, 2.64 mmol). After 15 min, sodium triacetoxyborohydride (1.0 g, 4.8 mmol) was added and the reaction was stirred at rt for 16 h. The reaction was diluted with methylene chloride, quenched with aq. sodium carbonate and extracted 3 times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by FC eluting with 30% ethyl acetate in hexanes to give the product (936 mg) as clean major higher R_f title compound (425 mg) plus a mixture of C-1 isomers (511 mg) as the free amines.

Step F: *N*-(1-(R)-3-(S)-Formyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-cyclohexylglycine t-butyl ester

To a solution of (1-(R)-3-(S)-(hydroxymethyl)-4-(S)-(3-fluorophenyl)-cyclopent-1-yl)-D-cyclohexylglycine (higher R_f from Step E) (162 mg, 0.4 mmol) in methylene chloride (5 mL) was added TPAP (7 mg, 0.020 mmol) and N-methylmorholine (70 mg, 0.60 mmol). The reaction was stirred under nitrogen at rt for 1 h and was then concentrated. The residue was purified by FC (15% ethyl acetate in hexanes) to give the title product (115 mg) after vacuum drying.

Step G: *N*-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-cyclohexylglycine t-butyl ester

To a solution of *N*-(1-(R)-3-(S)-formyl-4-(S)-(3-fluorophenyl)-cyclopent-1-yl)-D-cyclohexylglycine t-butyl ester (13 mg, 0.032 mmol) from Step F in 1,2-dichloroethane (2 mL) was added 4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidine hydrochloride (from Procedure 1) (15 mg, 0.035 mmol) and DIPEA (0.012 mL, 0.069 mmol). After 15 min, sodium triacetoxyborohydride (14 mg, 0.064 mmol) was added and the reaction was stirred at rt for 16 h. The reaction was diluted with methylene chloride, quenched with aq. sodium carbonate and extracted 3 times with methylene chloride. The organic layers were each washed with brine, dried over

sodium sulfate, combined and concentrated in vacuo. The residue was purified by Prep TLC eluting with 5% methanol in methylene chloride to give the title product as the free amine.

Step H: *N*-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-cyclohexylglycine di-hydrochloride salt

The *N*-(1-(R)-3-(S)-((4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-cyclohexylglycine t-butyl ester from Step F was taken up in TFA (2 mL) and aged at rt for 16 h. The volatiles were evaporated under a stream of nitrogen. The residue was taken up in methanol and adsorbed onto a 500 mg Varian SCX ion-exchange resin cartridge. The resin was eluted with 2 X 3 mL of methanol, then the product was eluted with 2 X 3 mL of 2M ammonia in methanol. The product solution was concentrated under nitrogen, then 2 volumes of methylene chloride were evaporated to remove methanol and ammonia to give the free amine. The hydrochloride salt was prepared by dissolving the free amine in methylene chloride, addition of excess 1M hydrogen chloride in ether and evaporation to dryness.

HPLC/MS (ESI): m/z 601 (M + 1).

EXAMPLE 36

N-(1-(R)-3-(S)-((4-(3-(4-Cyano-3-flurophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-cyclohexylglycine di-hydrochloride salt

Using essentially the same procedure as in Example 35, Steps F and G, but substituting 4-(3-(4-cyano-3-flurophenyl)prop-1-yl)piperidine (from Procedure 8) in Step F, the title compound was prepared.

HPLC/MS (ESI): m/z 578 (M + 1).

EXAMPLE 37

N-(1-(R)-3-(S)-((4-(5-Benzylpyrazol-3-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-cyclohexylglycine di-hydrochloride salt

9A7

Using essentially the same procedure as in Example 35, Steps F and G, but substituting 4-(5-benzylpyrazol-3-yl)piperidine (from Procedure 2) in Step F, the title compound can be prepared.

EXAMPLE 38

N-(1-(R)-3-(S)-((4-(5-Benzyl-2-propylpyrazol-3-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-cyclohexylglycine di-hydrochloride salt

Using essentially the same procedure as in Example 35, Steps F and G, but substituting 4-(5-benzyl-2-propylpyrazol-3-yl)piperidine (from Procedure 15) in Step F, the title compound can be prepared.

EXAMPLE 39

Using essentially the same procedure as in Example 35, Steps E to G, but substituting the appropriate L- and/or D-aminoacid t-butyl ester in Step E, the following compounds A-D can be prepared.

EXAMPLE 39A

N-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-cyclobutylalanine di-hydrochloride salt

EXAMPLE 39B

N-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-cycloproylalanine di-hydrochloride salt

EXAMPLE 39C

N-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-leucine di-hydrochloride salt

EXAMPLE 39D

N-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine di-hydrochloride salt

EXAMPLE 40

N-(2-Methylprop-1-yl)-*N*-(1-(SR)-3-(SR)-((4-(3-(phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)glycine di-hydrochloride salt

Step A: 1-(SR)-Benzyloxycarbonylamino-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopentane (Higher R_f isomer) and 1-(RS)-benzyloxycarbonylamino-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopentane (Lower R_f isomer)

Using essentially the same procedure as in Example 1, Step F, 1-(SR and RS)-benzylamino-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopentane (13 g) was converted to the title compounds. Prep LC (30% ethyl acetate in hexanes) afforded pure minor, higher R_f product (4.0 g), then a mixture and finally pure major, lower R_f product (6.6 g).

Step B: 1-(SR)-Benzyloxycarbonylamino-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopentane (Higher R_f isomer) and 1-(RS)-benzyloxycarbonylamino-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopentane (Lower R_f isomer)

To a solution of 1-(SR)-benzyloxycarbonylamino-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopentane (Higher R_f isomer from Step A) (3.96 g, 12.2 mmol) in methylene chloride (100 mL) was added DIPEA (6.4 mL, 37 mmol) and t-butyldimethylsilyl chloride (2.0 g, 13.4 mmol). The reaction was stirred at rt for 16 h when a second portion of t-butyldimethylsilyl chloride (1.0 g, 6.7 mmol) was added. After a further 24 h, the reaction was diluted with methylene chloride and poured into dilute hydrochloric acid. The layers were separated and the organic layer

was washed with brine containing sodium bicarbonate, dried over sodium sulfate and concentrated. The residue was purified by FC (5 to 40% ethyl acetate in hexanes) to give the title compound (4.7 g). After eluting with 75% ethyl acetate in hexanes, recovered starting material was obtained.

In a similar way, 1-(RS)-benzyloxycarbonylamino-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopentane (lower R_f isomer from Step A) (6.6 g, 20.3 mmol) was converted to the lower R_f title compound (7.7 g) and recovered starting material.

Step C: 1-(SR)-*N*-(2-Methylprop-2-en-1-yl)-*N*-(benzyloxycarbonyl)amino-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopentane (Higher R_f isomer) and 1-(RS)- *N*-(2-methylprop-2-en-1-yl)-*N*-(benzyloxycarbonyl)amino -3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopentane (Lower R_f isomer)

To a solution of 1-(SR)-benzyloxycarbonylamino-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopentane (Higher R_f isomer from Steps A-B) (500 mg, 1.14 mmol) and 1-bromo-2-methylprop-2-ene (0.175 mL, 1.7 mmol) in DMF (10 mL) was added at rt in portions over 10 min 60% sodium hydride in mineral oil (68 mg, 1.7 mmol). After 3 h, the reaction was diluted with ether and quenched into water. The layers were separated and the organic layer was washed with brine containing sodium bicarbonate, dried over sodium sulfate and concentrated. The residue was purified by FC (5 to 10% ethyl acetate in hexanes) to give the title compound (0.32 g).

^{1}H NMR ($CDCl_3$): δ -0.06 (s, 3 H), -0.05 (s, 3 H), 0.84 (s, 9 H), 1.54 (s, 3 H), 1.65-1.8 (m, 3 H), 1.95-2.2 (m, 3 H), 2.8-3.0 (M, 1 H), 3.3-3.45 (m, 1 H), 3.45-3.55 (m, 1 H), 3.7-3.9 (m, 2 H), 4.80 (d, 2 H), 5.14 (br s, 2 H), 7.15 (m, 2 H), 7.25 (m, 5 H), 7.34 (m, 3 H).

In a similar way, 1-(RS)-benzyloxycarbonylamino-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopentane (lower R_f isomer from Step A-B) (1.0 g, 2.3 mmol) was converted to the lower R_f title compound (0.55 g).

Step D: 1-(SR)-*N*-(2-Methylprop-1-yl)amino-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopentane (Higher R_f

isomer) and 1-(RS)-*N*-(2-methylprop-1-yl)amino -3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopentane (Lower R_f isomer)

To a solution of 1-(SR)-*N*-(2-methylprop-2-en-1-yl)-*N*-(benzyloxycarbonyl)amino-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopentane (Higher R_f isomer from Steps A-C) (320 mg, 0.65 mmol) in methanol (5 mL) was added 10% Pd/C (50 mg) and a drop of DIPEA. The mixture was hydrogenated at 40 psi for 2 h. The reaction was filtered and the filtrate was concentrated. The residue of title compound was used directly in Step E.

^{1}H NMR ($CDCl_3$): δ -0.05 (s, 3 H), -0.04 (s, 3 H), 0.84 (s, 9 H), 0.89 (s, 3 H), 0.91 (s, 3 H), 1.35 (ddd, 1 H), 1.73 (hept, 1 H), 1.93 (m, 2 H), 2.15 (m, 1 H), 2.25 (m, 1 H), 2.38 (d, 2 H), 2.96 (q, 1 H), 3.28 (m, 1 H), 3.49 (dABq, 2 H), 7.15 (m, 3 H), 7.24 (m, 2 H).

In a similar way, 1-(RS)-*N*-(2-methylprop-2-en-1-yl)-*N*-(benzyloxycarbonyl)amino -3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopentane (lower R_f isomer from Step A-C) (0.55 g, 1.1 mmol) was converted to the lower R_f title compound (0.475 g).

Step E: *N*-(2-Methylprop-1-yl)-*N*-(1-(SR)-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopent-1-yl)-glycine (Higher R_f isomer) and *N*-(2-methylprop-1-yl)-*N*-(1-(RS)-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopent-1-yl)-glycine (Lower R_f isomer)

A solution of 1-(SR)-*N*-(2-methylprop-1-yl)amino-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopentane (Higher R_f isomer from Steps A-D) (0.65 mmol), t-butyl bromoacetate (125 mg, 0.65 mmol) and DIPEA (1.1 mL, 6.5 mmol) in acetonitrile (15 mL) was stirred at rt for 16 h. The reaction was diluted with aqueous sodium carbonate and extracted three times with ethyl acetate. The organic layers were washed with brine containing sodium bicarbonate, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (50% ethyl acetate in hexanes) to give impure product and recovered starting material (135 mg). The impure product fractions were repurified by FC (5% ethyl acetate in hexanes) to afford the title higher R_f compound (0.13 g). The recovered starting

material was recycled using the same procedure but doing the reaction at 50 °C for 16 h to afford additional title compound (140 mg).
^{1}H NMR ($CDCl_3$): δ -0.05 (s, 3 H), -0.04 (s, 3 H), 0.84 (s, 9 H), 0.86 (d, 3 H), 0.88 (d, 3 H), 1.44 (s, 9 H), 1.70 (hept, 1 H), 1.95 (m, 1 H), 2.00 (m, 1 H), 2.08 (m, 2 H), 2.38 (dABq, 2 H), 2.90 (m, 1 H), 3.26 (ABq, 2 H), 3.49 (dABq, 2 H), 3.5-3.6 (m, 1 H), 7.15 (m, 3 H), 7.24 (m, 2 H).

In a similar way, but doing the reaction at 50 °C for 20 h, 1-(RS)-*N*-(2-methylprop-1-yl)amino-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopentane (lower R_f isomer from Steps A-D) (0.375 mg) was converted to the lower R_f title compound (0.435 g).

Step F: *N*-(2-Methylprop-1-yl)-*N*-(1-(SR)-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopent-1-yl)-glycine (Higher R_f isomer) and *N*-(2-methylprop-1-yl)-*N*-(1-(RS)-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopent-1-yl)-glycine (Lower R_f isomer)

A solution of *N*-(2-methylprop-1-yl)-*N*-(1-(SR)-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopent-1-yl)-glycine (Higher R_f isomer from Steps A-E) (270 mg, 0.57 mmol) and 1M TBAF in THF (0.85 mL, 0.85 mmol) in THF (5 mL) was stirred at rt for 1 h. The reaction was concentrated and the residue was purified by FC (20% ethyl acetate in hexanes) to give the title higher R_f product (140 mg).

In a similar way, *N*-(2-methylprop-1-yl)-*N*-(1-(RS)-3-(SR)-t-butyldimethylsilyloxymethyl-4-(SR)-phenylcylopent-1-yl)-glycine (Lower R_f isomer from Steps A-E) (0.435 mg) was converted to the lower R_f title compound (0.300 mg).

Step G: *N*-(2-Methylprop-1-yl)-*N*-(1-(SR)-3-(SR)-formyl-4-(SR)-phenylcylopent-1-yl)-glycine (Higher R_f isomer) and *N*-(2-methylprop-1-yl)-*N*-(1-(RS)-3-(SR)-formyl-4-(SR)-phenylcylopent-1-yl)-glycine (Lower R_f isomer)

Using essentially the same procedure as in Example 1, Step C, *N*-(2-methylprop-1-yl)-*N*-(1-(SR)-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopent-1-yl)-glycine (Higher R_f isomer from Steps A-F) (140 mg, 0.39 mmol) was oxidized to the title compound (100 mg).

In a similar way, *N*-(2-methylprop-1-yl)-*N*-(1-(RS)-3-(SR)-hydroxymethyl-4-(SR)-phenylcylopent-1-yl)-glycine (Lower R_f isomer from Steps A-F) (0.150 mg) was converted to the lower R_f title compound (0.140 mg).

Step H: *N*-(2-Methylprop-1-yl)-*N*-(1-(SR)-3-(SR)-((4-(3-(phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)glycine t-butyl ester (higher R_f isomer)

To a solution of *N*-(2-methylprop-1-yl)-*N*-(1-(SR)-3-(SR)-formyl-4-(SR)-phenylcylopent-1-yl)-glycine (Higher R_f isomer from Steps A-G) (25 mg, 0.070 mmol) in 1,2-dichloroethane (2 mL) was added 4-(3-(phenyl)prop-1-yl)piperidine (22 mg, 0.11 mmol) and acetic acid (0.006 mL, 0.11 mmol). After 15 min, sodium triacetoxyborohydride (45 mg, 0.21 mmol) was added and the reaction was stirred at rt for 4 h. The reaction was diluted with methylene chloride, quenched with aq. sodium carbonate and extracted 3 times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by Prep TLC eluting with 5% methanol in methylene chloride to give the title product (38 mg) as the free amine.

Step I: *N*-(2-Methylprop-1-yl)-*N*-(1-(SR)-3-(SR)-((4-(3-(phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)glycine di-TFA salt

A solution of *N*-(2-methylprop-1-yl)-*N*-(1-(SR)-3-(SR)-((4-(3-(phenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)glycine t-butyl ester (higher R_f isomer from Steps A-H) (33 mg) in TFA (4 mL) was heated at 50 °C for 4 h and then the volatiles were removed under a stream of nitrogen. An additional 2 X 3 mL of methylene chloride were evaporated to dryness to afford the title compound as the di-TFA salt (50 mg).
HPLC/MS (ESI): m/z 491 (M + 1).

EXAMPLE 41

N-(2-Methylprop-1-yl)-*N*-(1-(SR)-3-(SR)-((4-(3-(4-cyanophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)glycine di-TFA salt

Using essentially the same procedure as in Example 40, Steps H and I, but substituting 4-(3-(4-cyanophenyl)prop-1-yl)piperidine (from Procedure 7) in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 516 (M + 1).

EXAMPLE 42

N-(2-Methylprop-1-yl)-*N*-(1-(SR)-3-(SR)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)glycine di-TFA salt

Using essentially the same procedure as in Example 40, Steps H and I, but substituting 4-(3-(4-fluorophenyl)prop-1-yl)piperidine (from Procedure 9) in Step H, the title compound can be prepared.

EXAMPLE 43

N-(2-Methylprop-1-yl)-*N*-(1-(RS)-3-(SR)-((4-(3-(4-cyanophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)glycine di-TFA salt

Using essentially the same procedure as in Example 40, Steps H and I, but substituting the lower R_f aldehyde from Steps A-G and 4-(3-(4-cyanophenyl)prop-1-yl)piperidine (from Procedure 7) in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 594 (M + 1).

EXAMPLE 44

N-(2-Methylprop-1-yl)-*N*-(1-(RS)-3-(SR)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)glycine di-TFA salt

Using essentially the same procedure as in Example 40, Steps H and I, but substituting the lower R_f aldehyde from Steps A-G and 4-(3-(4-fluorophenyl)prop-1-yl)piperidine (from Procedure 9) in Step H, the title compound can be prepared.

EXAMPLE 45

N-(2-Methylprop-1-yl)-*N*-(1-(RS)-3-(SR)-((4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(SR)-phenylcyclopent-1-yl)glycine di-TFA salt

Using essentially the same procedure as in Example 40, Steps H and I, but substituting the lower R_f aldehyde from Steps A-G and 4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidine (from Procedure 1) in Step H, the title compound can be prepared.

EXAMPLE 46

N-(Cyclobutylmethyl)-*N*-(1-(R)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

Step A: *N*-(1-(R)-3-(S)-Hydroxymethyl)-4-(S)-phenylcyclopent-1-yl)glycine and *N*-(1-(S)-3-(S)-Hydroxymethyl)-4-(S)-phenylcyclopent-1-yl)glycine

To a solution of (+)-trans-3-hydroxymethyl-4-phenylcyclopentan-1-one from Example 8, Step F, Method B (180 mg, 0.96 mmol), glycine t-butyl ester hydrochloride (241 mg, 1.44 mmol) and DIPEA (0.25 mL, 1.44 mmol) in 1,2-dichloroethane (6 mL) was added sodium triacetoxyborohydride (284 mg, 1.92 mmol). The reaction was stirred at rt for 16 h and was then diluted with aq. sodium bicarbonate and extracted three times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by FC (50 - 100% ethyl acetate in hexanes) to give the title product (196 mg) as a 2:1 mixture of C-1 free amine isomers. ^{1}H NMR ($CDCl_3$): δ 1.48 (s, 9 H), 1.6-1.7 (m, 1.3 H), 1.8-2.0 (2 m, 1.7 H), 2.23 (ddd. 0.3 H), 2.3-2.45 (m, 2 H), 2.68 (ddd, 0.7 H), 3.2-3.4 (2 m and 2 s, 3 H), 3.45-3.65 (dABq (major) and d (minor), 2 H), 3.96 (d, 1 H), 7.2-7.35 (m, 5 H).

Step B: *N*-(Cyclobutylmethyl)-*N*-(1-(R)-3-(S)-hydroxymethyl)-4-(S)-phenylcyclopent-1-yl)glycine (major, higher R_f) and *N*-(cyclobutylmethyl)-*N*-(1-(S)-3-(S)-hydroxymethyl)-4-(S)-phenylcyclopent-1-yl)glycine (minor, lower R_f)

To a solution of *N*-(1-(R and S)-3-(S)-hydroxymethyl)-4-(S)-phenylcyclopent-1-yl)glycine from Step A (180 mg, 0.59 mmol), cyclobutylaldehyde (27 mg, 0.32 mmol) and DIPEA (0.25 mL, 1.5 mmol) in 1,2-dichloroethane (6 mL) was added sodium triacetoxyborohydride (175 mg, 1.2 mmol). The reaction was stirred at rt for 16 h and was then diluted with aq. sodium bicarbonate and extracted three times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by Prep TLC (30% ethyl acetate in hexanes) to give the title 1-(R) product (45 mg pure, 31 mg mixture with the 1-(S) diastereomer) as the higher R_f C-1 isomer.

(Major, higher isomer): ^{1}H NMR ($CDCl_3$): δ 1.49 (s, 9 H), 1.6-1.85 (m, 4 H), 1.85-1.95 (m, 2 H), 2.0-2.15 (m, 2 H), 2.24 (p, 1 H), 2.2.33 (m, 1 H), 2.53 (hept, 1 H), 2.7-2.8 (m, 3 H), 3.31 (s, 2 H), 3.4-3.5 (m, 1 H), 3.48 and 3.61 (dABq, 2 H), 7.24 (tt, 1 H), 7.25-7.35 (m, 4 H).

Repurification of the mixture on Prep TLC afforded a sample of pure 1-(S) minor, lower R_f isomer.

(Minor, lower isomer): ^{1}H NMR ($CDCl_3$): δ 1.47 (s, 9 H), 1.6-1.75 (m, 3 H), 1.75-1.85 (m, 1 H), 1.9-2.0 (m, 1 H), 2.05-2.25 (m, 4 H), 2.3 (m, 1 H), 2.54 (hept, 1 H), 2.78 (ddd, 2 H), 3.09 (q, 1 H), 3.35 (ABq, 2 H), 3.55 (m, 1 H), 3.61 (dABq, 2 H), 7.24 (tt, 1 H), 7.25-7.35 (m, 4 H).

Step C: *N*-(Cyclobutylmethyl)-*N*-(1-(R)-3-(S)-formyl)-4-(S)-phenylcyclopent-1-yl)glycine

Using essentially the same procedure as in Example 1, Step C, *N*-(cyclobutylmethyl)-*N*-(1-(R)-3-(S)-hydroxymethyl)-4-(S)-phenylcyclopent-1-yl)glycine (higher R_f isomer from Steps B) (45 mg, 0.12 mmol) was oxidized to the title compound (56 mg crude without purification).

Step D: *N*-(Cyclobutylmethyl)-*N*-(1-(R)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine t-butyl ester

To a solution of *N*-(cyclobutylmethyl)-*N*-(1-(R)-3-(S)-formyl)-4-(S)-phenylcyclopent-1-yl)glycine (higher R_f isomer from Steps B-C) (22 mg, 0.059 mmol) in 1,2-dichloroethane (1 mL) was added 4-(3-(4-fluorophenyl)prop-1-yl)piperidine hydrochloride (from Procedure 9) (23 mg, 0.089 mmol) and DIPEA (0.016 mL, 0.089 mmol). After 15 min, sodium triacetoxyborohydride (18 mg, 0.12 mmol) was added and the reaction was stirred at rt for 16 h. The reaction was diluted with methylene chloride, quenched with aq. sodium carbonate and extracted 3 times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by Prep TLC eluting with 30% ethyl acetate in hexanes to give the title product (26 mg) as the free amine.

Step E: *N*-(Cyclobutylmethyl)-*N*-(1-(R)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

A solution of *N*-(cyclobutylmethyl)-*N*-(1-(R)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine t-butyl ester (higher R_f isomer from Steps B-D) in TFA (4 mL) was stirred at rt for 16 h and then the volatiles were removed under a stream of nitrogen. An additional 2 X 3 mL of toluene were evaporated and the residue was purified by Prep TLC (95:5:1:1 methylene chloride:methanol:water:NH_4OH). The free amine (5 mg) was taken up in methylene chloride and excess 1M hydrogen chloride in ether was added. The mixture was evaporated to dryness to afford the title compound as the di-HCl salt (7.3 mg).

HPLC/MS (ESI): m/z 521 (M + 1).

EXAMPLE 47

N-(Cyclopropylmethyl)-*N*-(1-(R)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

Using essentially the same procedure as in Example 46, Steps B - E, but substituting cyclopropylaldehyde in Step B, the title compound was prepared.
HPLC/MS (ESI): m/z 507 (M + 1).

EXAMPLE 48

N-(Cyclohexyl)-*N*-(1-(R)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

Using essentially the same procedure as in Example 46, Steps B - E, but substituting cyclohexanone in Step B, the title compound was prepared.
HPLC/MS (ESI): m/z 535 (M + 1).

EXAMPLE 49

N-(Cyclopentylmethyl)-*N*-(1-(R)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

Using essentially the same procedure as in Example 46, Steps B - E, but substituting cyclopentylaldehyde in Step B, the title compound was prepared.
HPLC/MS (ESI): m/z 535 (M + 1).

EXAMPLE 50

N-(Cyclobutylmethyl)-*N*-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

Using essentially the same procedure as in Example 46, Steps B - E, but substituting the lower R_f product from Step B in Steps C - E, the title compound could be prepared.
HPLC/MS (ESI): m/z 521 (M + 1).

EXAMPLE 51

N-(Cyclohexyl)-*N*-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

Using essentially the same procedure as in Example 46, Steps B - E, but substituting cyclohexanone in Step B and using the lower R_f product from Step B in Steps C - E, the title compound was prepared.
HPLC/MS (ESI): m/z 535 (M + 1).

EXAMPLE 52

N-(Cyclopropylmethyl)-*N*-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

Using essentially the same procedure as in Example 46, Steps B - E, but substituting cyclopropyl aldehyde in Step B and using the lower R_f product from Step B in Steps C - E, the title compound was prepared.
HPLC/MS (ESI): m/z 507 (M + 1).

EXAMPLE 53

N-(Cyclopentylmethyl)-*N*-(1-(S)-3-(S)-((4-(3-(4-fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

Using essentially the same procedure as in Example 46, Steps B - E, but substituting cyclopentyl aldehyde in Step B and using the lower R_f product from Step B in Steps C - E, the title compound was prepared.
HPLC/MS (ESI): m/z 507 (M + 1).

EXAMPLE 54

N-(Cyclohexyl)-*N*-(1-(S)-3-(S)-((4-(3-(3,4-difluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

Step A: *N*-(1-(S)-3-(S)-t-Butyldimethylsilyloxymethyl)-4-(S)-phenylcyclopent-1-yl)glycine (major, higher R_f) and *N*-(1-(R)-3-(S)-t-

butyldimethylsilyloxymethyl)-4-(S)-phenylcyclopent-1-yl)glycine (minor, lower R_f)

To a solution of (+)-trans-3-t-butyldimethylsilyloxymethyl-4-phenylcyclopentan-1-one from Example 16, Step A, Method B (332 mg, 1.1 mmol), glycine t-butyl ester hydrochloride (275 mg, 1.64 mmol) and DIPEA (0.285 mL, 1.64 mmol) in 1,2-dichloroethane (13 mL) was added sodium triacetoxyborohydride (323 mg, 2.18 mmol). The reaction was stirred at rt for 16 h and was then diluted with aq. sodium bicarbonate and extracted three times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by FC (10% ethyl acetate in hexanes) to give the title product (437 mg) as a 2.6:1 mixture of C-1 free amine isomers. (Note: The product C-1 isomer ratio here with the silyl ether is opposite to that of Example 46 with the free alcohol. Also, note that the relative retention on TLC of the NH intermediates are opposite that of the N-alkylation products of Step B.)

Careful FC (5% ethyl acetate in hexanes) of an initial sample afforded the separated isomers.

(Major, higher isomer): ^{1}H NMR ($CDCl_3$): δ -0.05 (s, 3 H), -0.04 (s, 3 H), 0.87 (s, 9 H), 1.42 (m, 1 H), 1.50 (s, 9 H), 1.98 (dd, 2 H), 2.17 (m, 1 H), 2.27 (dt, 1 H), 3.00 (q, 1 H), 3.3-3.4 (m and s, 3 H), 3.45 and 3.60 (dABq, 2 H), 7.15-7.25 (m, 3 H), 7.25-7.35 (m, 2 H).

(Minor, lower isomer): ^{1}H NMR ($CDCl_3$): δ -0.05 (s, 3 H), -0.04 (s, 3 H), 0.87 (s, 9 H), 1.50 (s, 9 H), 1.62 (dt, 1 H), 1.75 (ddd, 1 H), 1.95 (dt, 1 H), 2.25-2.4 (2 m , 2 H), 2.85 (m, 1 H), 3.22 (m, 1 H), 3.34 (s, 2 H), 3.42 and 3.54 (dABq, 2 H), 7.24 (tt, 1 H), 7.25-7.35 (m, 4 H).

Step B: *N*-(Cyclohexyl)-*N*-(1-(S)-3-(S)-hydroxymethyl)-4-(S)-phenylcyclopent-1-yl)glycine (lower, major R_f) and *N*-(cyclohexyl)-*N*-(1-(R)-3-(S)-hydroxymethyl)-4-(S)-phenylcyclopent-1-yl)glycine (higher, minor R_f)

To a solution of *N*-(1-(R and S)-3-(S)-t-butyldimethylsilyloxymethyl)-4-(S)-phenylcyclopent-1-yl)glycine from Step A (437 mg, 1.04 mmol), cyclohexanone (0.650 mL, 6.24 mmol) and DIPEA (0.272 mL, 1.56 mmol) in 1,2-dichloroethane (10 mL) was added sodium triacetoxyborohydride (693 mg, .68

960

mmol). The reaction was stirred at rt for 16 h when additional cyclohexanone (0.600 mL) and sodium triacetoxyborohydride (300 mg) were added. After a further 48 h, the reaction was complete by HPLC/MS and was diluted with aq. sodium bicarbonate and extracted three times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue (2 g) was used directly in the following desilylation.

The residue from above was taken up in THF (10 mL) and 1M TBAF in THF (5 mL, 5.0 mmol) was added. The reaction was stirred at rt for 6 h and was then poured into aq. sodium bicarbonate and extracted three times with ethyl acetate. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by FC and Prep TLC (40% ethyl acetate in hexanes) to give the title (R) product (114 mg) as the minor, higher R_f band and the title (S) product (235 mg) as the major, lower R_f band.

(Major, higher isomer): ^{1}H NMR ($CDCl_3$): δ 1.1-1.4 (m, 5 H), 1.48 (s, 9 H), 1.5-1.7 (m, 2 H), 1.7-2.0 (m, 5 H), 2.17 (m, 1 H), 2.31 (m, 1 H), 2.65-2.8 (m, 2 H), 3.24 (Abq, 2 H), 3.45-3.55 (m, 2 H), 3.6-3.7 (m, 2 H), 7.24 (tt, 1 H), 7.25-7.35 (m, 4 H).

(Minor, lower isomer): ^{1}H NMR ($CDCl_3$): δ 1.1-1.4 (m, 5 H), 1.48 (s, 9 H), 1.6-1.7 (m, 2 H), 1.7-2.0 (m, 5 H), 2.17 (m, 2 H), 2.25 (m, 1 H), 2.75 (m, 1 H), 3.10 (q, 1 H), 3.25 (Abq, 2 H), 3.55-3.65 (m and ABq, 3 H), 7.24 (tt, 1 H), 7.25-7.35 (m, 4 H).

Step C: *N*-(Cyclohexyl)-*N*-(1-(S)-3-(S)-formyl)-4-(S)-phenylcyclopent-1-yl)glycine

Using essentially the same procedure as in Example 1, Step C, *N*-(cyclohexyl)-*N*-(1-(S)-3-(S)-hydroxymethyl)-4-(S)-phenylcyclopent-1-yl)glycine (lower R_f isomer from Step B) (75 mg, 0.19 mmol) was oxidized to the title compound (84 mg crude without purification).

Step D: *N*-(Cyclohexyl)-*N*-(1-(R)-3-(S)-((4-(3-(3,4-difluorophenyl)prop-1-yl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine t-butyl ester

To a solution of *N*-(cyclohexyl)-*N*-(1-(S)-3-(S)-formyl)-4-(S)-phenylcyclopent-1-yl)glycine (lower R_f isomer from Steps B-C) (19 mg, 0.050 mmol) in 1,2-dichloroethane (1 mL) was added 4-(3-(3,4-difluorophenyl)prop-1-yl)piperidine hydrochloride (from Procedure 14) (15 mg, 0.054 mmol) and DIPEA

(0.013 mL, 0.074 mmol). After 15 min, sodium triacetoxyborohydride (15 mg, 0.10 mmol) was added and the reaction was stirred at rt for 16 h. The reaction was diluted with methylene chloride, quenched with aq. sodium carbonate and extracted 3 times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by Prep TLC eluting with 80% ethyl acetate in hexanes to give the title product (20 mg) as the free amine.

Step E: *N*-(Cyclohexyl)-*N*-(1-(R)-3-(S)-((4-(3-(3,4-difluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

A solution of *N*-(cyclohexyl)-*N*-(1-(R)-3-(S)-((4-(3-(3,4-difluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine t-butyl ester (lower R_f isomer from Steps B-D) (20 mg) in TFA (1 mL) was stirred at rt for 16 h and then the volatiles were removed under a stream of nitrogen. The residue was taken up in methanol and adsorbed onto a 500 mg Varian SCX ion-exchange resin cartridge. The resin was eluted with 2 X 3 mL of methanol, then the product was eluted with 2 X 3 mL of 2M ammonia in methanol. The product solution was concentrated under nitrogen, then 2 volumes of methylene chloride were evaporated to remove methanol and ammonia to give the free amine. The hydrochloride salt was prepared by dissolving the free amine in methylene chloride, addition of excess 1M hydrogen chloride in ether and evaporation to dryness.
HPLC/MS (ESI): m/z 553 (M + 1).

EXAMPLE 55

N-(Cyclohexyl)-*N*-(1-(S)-3-(S)-((4-(3-(4-cyanophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

Using essentially the same procedure as in Example 54, Steps D and E, but substituting 4-(3-(4-cyanophenyl)prop-1-yl)piperidine (from Procedure 7) in Step D and using the lower R_f product from Step B in Steps C - E, the title compound was prepared.
HPLC/MS (ESI): m/z 542 (M + 1).

EXAMPLE 56

N-(Cyclohexyl)-*N*-(1-(S)-3-(S)-((4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

Using essentially the same procedure as in Example 54, Steps D and E, but substituting 4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidine (from Procedure 1) in Step D and using the lower R_f product from Step B in Steps C - E, the title compound was prepared.

HPLC/MS (ESI): m/z 583 (M + 1).

EXAMPLE 57

N-(Cyclohexyl)-*N*-(1-(S)-3-(S)-((4-(*N*-propyl-*N*-(pyrimidin-2-yl)amino)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

Using essentially the same procedure as in Example 54, Steps D and E, but substituting 4-(*N*-propyl-*N*-(pyrimidin-2-yl)amino)piperidine (from Procedure 13) in Step D and using the lower R_f product from Step B in Steps C - E, the title compound was prepared.

HPLC/MS (ESI): m/z 534 (M + 1).

EXAMPLE 58

N-(Cyclohexyl)-*N*-(1-(S)-3-(S)-((4-(3-(quinolin-3-yl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

Using essentially the same procedure as in Example 54, Steps D and E, but substituting 4-(3-(quinolin-3-yl)prop-1-yl)amino)piperidine (from Procedure 10) in Step D and using the lower R_f product from Step B in Steps C - E, the title compound was prepared.

HPLC/MS (ESI): m/z 568 (M + 1).

EXAMPLE 59

N-(Cyclohexyl)-*N*-(1-(S)-3-(S)-((4-(4-fluorophenyl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)glycine di-HCl salt

Using essentially the same procedure as in Example 54, Steps D and E, but substituting 4-(4-fluorophenyl)piperidine in Step D and using the lower R_f product from Step B in Steps C - E, the title compound was prepared.
HPLC/MS (ESI): m/z 493 (M + 1).

EXAMPLE 60

N-(1-(R)-3-(S)-((4-(3-(4-Fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-proline di-HCl salt

Using essentially the same procedure as in Example 46, but substituting D-proline t-butyl ester in Step A, omitting Step B, and using the higher R_f product from Step A in Steps C - E, the title compound was prepared.
HPLC/MS (ESI): m/z 493 (M + 1).

EXAMPLE 61

N-(1-(S)-3-(S)-((4-(3-(4-Fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-proline di-HCl salt

Using essentially the same procedure as in Example 46, but substituting D-proline t-butyl ester in Step A, omitting Step B, and using the lower R_f product from Step A in Steps C - E, the title compound was prepared.
HPLC/MS (ESI): m/z 493 (M + 1).

EXAMPLE 62

N-(1-(R)-3-(S)-((4-(3-(4-Fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-L-proline di-HCl salt

Using essentially the same procedure as in Example 46, but substituting L-proline t-butyl ester in Step A, omitting Step B, and using the higher R_f product from Step A in Steps C - E, the title compound was prepared.
HPLC/MS (ESI): m/z 493 (M + 1).

EXAMPLE 63

N-(1-(S)-3-(S)-((4-(3-(4-Fluorophenyl)prop-1-yl)piperidin-1-yl)methyl)-4-(S)-phenylcyclopent-1-yl)-D-proline di-HCl salt

Using essentially the same procedure as in Example 46, but substituting L-proline t-butyl ester in Step A, omitting Step B, and using the lower R_f product from Step A in Steps C - E, the title compound was prepared.
HPLC/MS (ESI): m/z 493 (M + 1).

EXAMPLE 64

N-(1-(S)-3-(S)-((4-(3-Benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-proline di-HCl salt

Using essentially the same procedure as in Example 54, but substituting (+)-trans-3-hydroxymethyl-4-(3-fluorophenyl)cyclopentan-1-one from Example 35, Step E and L-proline t-butyl ester in Step A, omitting Step B, using the lower R_f product from Step A in Steps C - E and substituting 4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidine in Step F, the title compound was prepared.
HPLC/MS (ESI): m/z 559 (M + 1).

EXAMPLE 65

N-Methyl-*N*-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Step A: Methyl (+-)-*trans*-4-methylene-2-(3-fluorophenyl)cylopentanoate

A mixture of methyl *trans*-3-fluorocinnamate (41.25 g, 229 mmol), tetrakis(triphenylphosphine) palladium(0) (18.5 g, 16 mmol), 1,2-

bis(diphenylphosphino)ethane (5.5 g, 13.7 mmol) and 2-((trimethylsilyl)methyl)-2-propen-1-yl acetate (42.66 g, 229 mmol) in THF (300 mL) under nitrogen was heated to reflux for 6 h and then stirred at rt for 16 h. The reaction was diluted with hexane and filtered to remove yellow precipitate. The volatiles were then removed *in vacuo* and the residue was purified by FC (3 to 5% ethyl acetate in hexanes) to afford the title compound (45 g).

^{1}H NMR ($CDCl_3$) δ: 2.52 (m, 1 H), 2.68 (m, 1 H), 2.8-2.9 (m, 2 H), 2.95 (ddd, 1 H), 3.45 (ddd, 1 H), 3.63 (s, 3 H), 4.96 (m, 2 H), 6.9-7.0 (m, 2 H), 7.03 (d, 1 H), 7.2-7.3 (m, 1 H).

Step B: (+-)-*trans*-4-Methylene-2-(3-fluorophenyl)cyclopentanoic acid

To a solution of methyl (+-)-*trans*-4-methylene-2-(3-fluoro)phenylcylopentanoate prepared as in Example 33, Step A (47 g, 200 mmol) in methanol (500 mL) was added 5N sodium hydroxide (200 mL, 1000 mmol). The reaction was stirred at rt for 60 h then concentrated in vacuo. The residue was taken up in water, acidified with 2M hydrochloric acid and extracted twice with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo to give the crude title acid (40.8 g) which was used directly in Step C.

Step C: (+)-*trans*-1-Hydroxymethyl-4-methylene-2-(3-fluorophenyl)cylopentane and (-)-*trans*-1-hydroxymethyl-4-methylene-2-(3-fluorophenyl)cylopentane

A solution of (+-)-*trans*-4-methylene-2-(3-fluorophenyl)cylopentanoate (5.2 g, 23.6 mmol) from Step B in THF (100 mL) was cooled to 0 °C under nitrogen and 1M lithium aluminum hydride (LAH) in THF (35.4 mL) was added dropwise over 10 min. The reaction was stirred at rt for 16 h, the excess LAH was quenched by dropwise addition of acetone and the reaction was then poured into dilute aq. HCl. The mixture was extracted twice with ether and the organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (25% ethyl acetate in hexanes) to afford the racemic title product (4.1 g) as a an oil. Chiral Prep HPLC on a 2 cm x 25 cm Chiralcel OD column eluting with 5% isopropanol in hexanes (25 injections) afforded the (-)-enantiomer, $[\alpha]_D$ = -45.5 (MeOH, c = 0.9), as the first eluting peak (R_t

= 17.5 min) and the (+)-enantiomer (1.87 g), $[\alpha]_D$ = +45.0 (MeOH, c = 1.0), as the second peak (R_t = 22.0 min).

^{1}H NMR ($CDCl_3$) δ: 2.2-2.35 (m, 2 H), 2.5 (m, 1 H), 2.65-2.85 (m, 2 H), 2.9 (m, 1 H), 3.51 and 3.68 (dABq, 2 H), 4.93 (m, 2 H), 6.9-7.0 (m, 2 H), 7.06 (d, 1 H), 7.3-7.4 (m, 1 H).

Step D: (+)-*trans*-3-Hydroxymethyl-4-(3-fluorophenyl)cylopentanone

A solution of (+)-*trans*-1-hydroxymethyl-4-methylene-2-(3-fluorophenyl)cylopentane from Step C (1.87 g, 9.0 mmol) in methanol (75 mL) was cooled in a dry ice/acetone bath and ozone was bubbled into the solution until the blue color persisted. The excess ozone was removed with a stream of nitrogen and then dimethylsulfide (5 mL) was added. After 10 min, the bath was removed and the reaction was allowed to warm to rt over 2 h. The mixture was treated with 10 drops of sulfuric acid (c) in water (2 mL) for 1 h before most of the methanol was removed in vacuo. The mixture was diluted with water and extracted twice with ethyl acetate and the organic layers were washed with brine, dried over sodium sulfate, combined and concentrated. The residue was purified by FC (50% ethyl acetate in hexanes) to give the title compound (1.87 g)), $[\alpha]_D$ = +132 (MeOH, c = 1.2).

^{1}H NMR ($CDCl_3$) δ: 2.3-2.45 (m, 2 H), 2.5 (m, 1 H), 2.61 and 2.77 (dABq, 2 H), 2.28 (ddd, 1 H), 3.61 and 3.75 (dABq, 2 H), 6.9-7.0 (m, 2 H), 7.06 (d, 1 H), 7.3-7.4 (m, 1 H).

Step E: *N*-(1-(R)-3-(S)-Hydroxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine t-butyl ester

To a solution of (+)-*trans*-3-hydroxymethyl-4-(3-fluorophenyl)cylopentanone from Step D (1.0 g, 4.8 mmol) in 1,2-dichloroethane (50 mL) was added D-valine t-butyl ester (0.90 g, 5.2 mmol) and acetic acid (0.330 mL, 5.8 mmol). After 15 min, sodium triacetoxyborohydride (2.0 g, 5.6 mmol) was added and the reaction was stirred at rt for 16 h. The reaction was diluted with methylene chloride, quenched with aq. sodium carbonate and extracted 3 times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by FC eluting with 30% ethyl acetate in hexanes to give the product (1.62 g) as a mixture of the higher R_f title compound and the C-1 isomer as the free amines.

Step F: *N*-Methyl-*N*-(1-(R)-3-(S)-hydroxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine t-butyl ester

To a solution of *N*-(1-(R)-3-(S)-hydroxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine t-butyl ester from Step E (1.62, 4.44 mmol) and 37 wt % formaldehyde in water (2.1 mL, 27 mmol) in methanol (35 mL) was added 10% Pd/C (200 mg). After 10 min, the mixture was placed under hydrogen and stirred at atmospheric pressure for 60 hr. The catalyst was removed by filtration and the filtrate was evaporated. The residue was purified by FC eluting with a gradient of 15 to 50% ethyl acetate in hexanes to give the higher R_f title product (1.44 g) and the lower C-1 isomer (0.17 g) as the free amines.

Step G: *N*-Methyl-*N*-(1-(R)-3-(S)-formyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine t-butyl ester

To a solution of oxalyl chloride (0.235 mL, 2.65 mmol) in methylene chloride (10 mL) at -70 °C was added dropwise DMSO (0.385 mL, 5.3 mmol). After 15 min, a solution of *N*-methyl-*N*-(1-(R)-3-(S)-hydroxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine t-butyl ester (higher R_f isomer from Step F) (400 mg, 1.05 mmol) in methylene chloride (10 mL) was added. The reaction was stirred at -70 °C for 1 h and then DIPEA (1.8 mL, 11 mmol) in methylene chloride (5 mL) was added dropwise over 5 min. After a further 10 min, the mixture was allowed to warm to RT for 1 h and then diluted with methylene chloride. The layers were separated. The aq. layer was reextracted with a second portion of methylene chloride and the organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by FC (15% ethyl acetate in hexanes) to give the title product (378 mg) as an oil.

Step H: *N*-Methyl-*N*-(1-(R)-3-(S)-((4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine t-butyl ester

To a solution of *N*-methyl-*N*-(1-(R)-3-(S)-formyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine t-butyl ester (250 mg, 0.66 mmol) from Step G in 1,2-dichloroethane (20 mL) was added 4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidine di-hydrochloride (from Procedure 1) (250 mg, 0.73 mmol) and DIPEA (0.25 mL, 0.1.46 mmol). After 15 min, sodium triacetoxyborohydride (280 mg, 0.1.33 mmol) was added and the reaction was stirred at rt for 16 h. The reaction was diluted with methylene chloride, quenched with aq. sodium carbonate and extracted 3

times with methylene chloride. The organic layers were each washed with brine, dried over sodium sulfate, combined and concentrated in vacuo. The residue was purified by Prep TLG eluting with 50% ethyl acetate in hexanes to give the title product as the free amine.

HPLC/MS (ESI): m/z 631 (M + 1).

Step I: *N*-(1-(R)-3-(S)-((4-(3-Benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine di-hydrochloride salt

The *N*-(1-(R)-3-(S)-((4-(3-benzyl-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine t-butyl ester from Step F was taken up in TFA (2 mL) and aged at rt for 16 h. The volatiles were evaporated under a stream of nitrogen. The residue was taken up in methanol and adsorbed onto a 500 mg Varian SCX ion-exchange resin cartridge. The resin was eluted with 2 X 3 mL of methanol, then the product was eluted with 2 X 3 mL of 2M ammonia in methanol. The product solution was concentrated under nitrogen, then 2 volumes of methylene chloride were evaporated to remove methanol and ammonia to give the free amine. The hydrochloride salt was prepared by dissolving the free amine in methylene chloride, addition of excess 1M hydrogen chloride in ether and evaporation to dryness.

HPLC/MS (ESI): m/z 575 (M + 1).

EXAMPLE 66A

N-Methyl-*N*-(1-(R)-3-(S)-((4-(3-(4-fluorobenzyl)-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(3-(4-fluorobenzyl)-1-ethyl-1H-pyrazol-5-yl)piperidine di-hydrochloride in Step H, the title compound was prepared.

HPLC/MS (ESI): m/z 593 (M + 1).

EXAMPLE 66B

N-Methyl-*N*-(1-(R)-3-(S)-((4-(3-(3,4-difluorobenzyl)-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(3-(3,4-difluorobenzyl)-1-ethyl-1H-pyrazol-5-yl)piperidine di-hydrochloride in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 611 (M + 1).

EXAMPLE 66C

N-Methyl-*N*-(1-(R)-3-(S)-((4-(3-(benzyl)-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(3-(benzyl)-1H-pyrazol-5-yl)piperidine di-hydrochloride in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 547 (M + 1).

EXAMPLE 66D

N-Methyl-*N*-(1-(R)-3-(S)-((4-(2-(4-fluorophenyl)sulfonyleth-1-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine di-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(2-(4-fluorophenyl)sulfonyleth-1-yl)piperidine hydrochloride in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 545 (M + 1).

EXAMPLE 66E

N-Methyl-*N*-(1-(R)-3-(S)-((4-(2-benzylthiazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(2-(benzyl)thiazol-5-yl)piperidine di-hydrochloride in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 564 (M + 1).

EXAMPLE 66F

N-Methyl-*N*-(1-(R)-3-(S)-((4-(2-benzyl-4-methylthiazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(2-benzyl-4-methylthiazol-5-yl)piperidine di-hydrochloride in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 578 (M + 1).

EXAMPLE 66G

N-Methyl-*N*-(1-(R)-3-(S)-((4-(2-benzyl-4-ethylthiazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(2-benzyl-4-ethylthiazol-5-yl)piperidine di-hydrochloride in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 592 (M + 1).

EXAMPLE 66H

N-Methyl-*N*-(1-(R)-3-(S)-((4-(3-(4-methoxybenzyl)-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(3-(4-methoxybenzyl)-1-ethyl-1H-pyrazol-5-yl)piperidine di-hydrochloride in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 605 (M + 1).

EXAMPLE 66I

N-Methyl-*N*-(1-(R)-3-(S)-((4-(3-(4-trifluoromethylbenzyl)-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(3-(4-trifluoromethylbenzyl)-1-ethyl-1H-pyrazol-5-yl)piperidine di-hydrochloride in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 643 (M + 1).

EXAMPLE 66J

N-Methyl-*N*-(1-(R)-3-(S)-((4-(3-(pyridin-3-ylmethyl)-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(3-(pyridin-3-ylmethyl)-1-ethyl-1H-pyrazol-5-yl)piperidine di-hydrochloride in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 643 (M + 1).

EXAMPLE 66K

N-Methyl-*N*-(1-(R)-3-(S)-((4-(3-(pyridin-3-ylmethyl)-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(3-(pyridin-3-ylmethyl)-1H-pyrazol-5-yl)piperidine di-hydrochloride in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 615 (M + 1).

EXAMPLE 66L

N-Methyl-*N*-(1-(R)-3-(S)-((4-(3-(4-chlorobenzyl)-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(3-(4-chlorobenzyl)-1-ethyl-1H-pyrazol-5-yl)piperidine di-hydrochloride in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 609 (M + 1), 611 (M + 3).

EXAMPLE 66M

N-Methyl-*N*-(1-(R)-3-(S)-((4-(3-(3-fluorobenzyl)-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(3-(3-fluorobenzyl)-1-ethyl-1H-pyrazol-5-yl)piperidine di-hydrochloride in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 593 (M + 1).

EXAMPLE 66N

N-Methyl-*N*-(1-(R)-3-(S)-((4-(3-(3,5-difluorobenzyl)-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(3-(3,5-difluorobenzyl)-1-ethyl-1H-pyrazol-5-yl)piperidine di-hydrochloride in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 611 (M + 1).

EXAMPLE 66O

N-Methyl-*N*-(1-(R)-3-(S)-((4-(3-benzylpyridin-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps H and I, but substituting 4-(3-benzylpyridin-5-yl)piperidine di-hydrochloride in Step H, the title compound was prepared.
HPLC/MS (ESI): m/z 558 (M + 1).

EXAMPLE 67

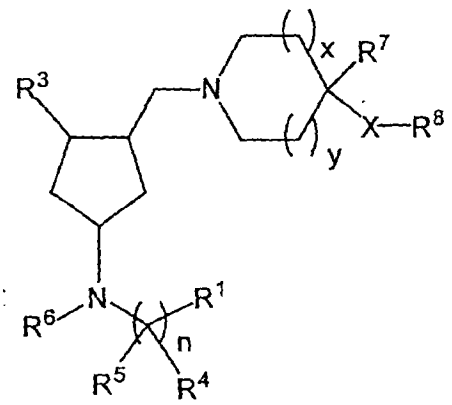
N-Methyl-*N*-(1-(S)-3-(S)-((4-(3-(benzyl)-1-ethyl-1H-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine tri-hydrochloride salt

Using essentially the same procedures as in Example 65, Steps G, H and I, but substituting *N*-methyl-*N*-(1-(S)-3-(S)-hydroxymethyl-4-(S)-(3-fluorophenyl)cyclopent-1-yl)-D-valine t-butyl ester (lower R_f isomer from Step F), the title compound was prepared.
HPLC/MS (ESI): m/z 575 (M + 1).

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A compound of the formula I:



I

wherein:

X is selected from: -(C_{0-6}alkyl)-Y-(C_{0-6}alkyl)-,

-(C_{0-6}alkyl)-C_{3-8} cycloalkyl-(C_{0-6}alkyl)-,

C_{2-10} alkenyl, and C_{2-10} alkynyl,

where the alkyl is unsubstituted or substituted with 1-7 substituents where the substituents are independently selected from:

(a) halo,

(b) hydroxy,

(c) -O-C_{1-3}alkyl, and

(d) trifluoromethyl,

and where Y is selected from:

a single bond, -O-, -SO_2-, -NR^{10}-, -NR^{10}-SO_2-, -SO_2-NR^{10}-,

-S-, and -SO-,

and where R^{10} is independently selected from: hydrogen, C_{1-6} alkyl, benzyl, phenyl, and C_{1-6} alkyl-C_{3-6} cycloalkyl,

which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl;

R^1 is selected from:

(1) $-CO_2H$,
(2) $-NO_2$,
(3) -tetrazolyl,
(4) -hydroxyisoxazole,
(5) $-SO_2NH-(C_{0-3}\ alkyl)-R^9$, wherein R^9 is independently selected from: hydrogen, C_{1-6} alkyl, C_{5-6} cycloalkyl, benzyl or phenyl, which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl, and
(6) $-P(O)(OH)_2$;

R^3 is selected from the group consisting of:
phenyl and heterocycle,
which is unsubstituted or substituted with 1-7 substituents where the substituents are independently selected from:
(a) halo,
(b) trifluoromethyl,
(c) hydroxy,
(d) C_{1-3}alkyl,
(e) $-O-C_{1-3}$alkyl,
(f) $-CO_2R^9$,
(g) $-NR^9R^{10}$, and
(h) $-CONR^9R^{10}$;

R^4, R^5 and R^6 are independently selected from:
hydrogen, C_{1-10} alkyl, C_{3-8} cycloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, phenyl, $-(C_{1-6}$ alkyl)-phenyl, $-(C_{1-6}$ alkyl)-C_{3-8} cycloalkyl, naphthyl, biphenyl, and heterocycle,
which is unsubstituted or substituted with 1-7 of R^{11} where R^{11} is independently selected from:
(a) halo,
(b) trifluoromethyl,
(c) hydroxy,
(d) C_{1-3}alkyl,
(e) $-O-C_{1-3}$alkyl,

2. The compound of Claim 1 wherein R^1 is selected from:

(1) $-CO_2H$, and

(2) -tetrazolyl.

3. The compound of Claim 1 wherein R^1 is $-CO_2H$.

4. The compound of Claim 1 wherein R^3 is selected from the group consisting of:

phenyl and thienyl,

which may be unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from:

(a) halo,

(b) trifluoromethyl,

(c) hydroxy,

(d) C_{1-3}alkyl, and

(e) $-O-C_{1-3}$alkyl.

5. The compound of Claim 1 wherein R^3 is selected from the group consisting of:

phenyl and thienyl,

which may be unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from:

(a) fluoro,

(b) chloro,

(c) trifluoromethyl,

(d) hydroxy, and

(e) C_{1-3}alkyl.

6. The compound of Claim 1 wherein R^3 is selected from the group consisting of:

phenyl, which may be unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from:

(a) fluoro, and

(b) chloro; and
unsubstituted thienyl.

7. The compound of Claim 1 wherein R^3 is unsubstituted phenyl, (3-fluoro)phenyl or 3-thienyl.

8. The compound of Claim 1 wherein R^4 is hydrogen.

9. The compound of Claim 1 wherein R^5 is selected from: hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkyl-C_{3-8} cycloalkyl, and phenyl.

10. The compound of Claim 1 wherein R^5 is selected from: hydrogen, methyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, -CH_2-cyclopropyl, -CH_2-cyclobutyl, and phenyl.

11. The compound of Claim 1 wherein R^5 is selected from: isopropyl, isobutyl, sec-butyl, and cyclohexyl.

12. The compound of Claim 1 wherein R^6 is selected from: hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkyl-C_{3-8} cycloalkyl, and phenyl.

13. The compound of Claim 1 wherein R^6 is selected from: hydrogen, methyl, n-butyl, t-butyl, isobutyl, sec-butyl, -CH_2-cyclopropyl, -CH_2-cyclobutyl, and cyclohexyl.

14. The compound of Claim 1 wherein R^6 is selected from: hydrogen, methyl, -CH_2-cyclopropyl, -CH_2-cyclobutyl, and cyclohexyl.

15. The compound of Claim 1 wherein R^7 is hydrogen, fluoro, hydroxy or C_{1-6} alkyl.

16. The compound of Claim 1 wherein R^7 is hydrogen.

17. The compound of Claim 1 wherein X is: -(C_{0-4}alkyl)-Y-(C_{0-4}alkyl)-,

where the alkyl is unsubstituted or substituted with 1-4 substituents where the substituents are independently selected from:

(a) halo,

(b) hydroxy,

(c) -O-C_{1-3}alkyl, and

(d) trifluoromethyl,

and where Y is selected from:

a single bond, -O-, -SO_2-, -NR^{10}-, -S-, and -SO-,

and where R^{10} is independently selected from: hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, benzyl, phenyl, and C_{1-6} alkyl-C_{3-6} cycloalkyl, which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl.

18. The compound of Claim 1 wherein X is:

-(C_{0-2}alkyl)-Y-(C_{0-2}alkyl)-,

where the alkyl is unsubstituted or substituted with 1-4 substituents where the substituents are independently selected from:

(a) halo,

(b) hydroxy,

(c) -O-C_{1-3}alkyl, and

(d) trifluoromethyl,

and where Y is selected from:

a single bond, -O-, -SO_2-, -NR^{10}-, -S-, and -SO-,

where R^{10} is independently selected from: hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, benzyl, phenyl, and C_{1-6} alkyl-C_{3-6} cycloalkyl, which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl.

19. The compound of Claim 1 wherein X is selected from: -(C_{0-2}alkyl)-Y-(C_{0-2}alkyl)-, where the alkyl ~~is~~ unsubstituted or substituted with fluoro,

and where Y is selected from:

a single bond, $-SO_2-$, -SO-, and $-NR^{10}-$, .

where R^{10} is independently selected from: hydrogen, C_{1-3} alkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl.

20. The compound of Claim 1 wherein X is selected from:

(1) a single bond,
(2) $-CH_2CH_2-$,
(3) $-CH_2CH_2CH_2-$,
(4) $-CH_2CH_2-CF_2-$,
(5) $-CH_2CH_2-SO_2-$, and
(6) $-CH_2CH_2-SO-$.

21. The compound of Claim 1 wherein R^8 is selected from: phenyl, naphthyl, cyclohexyl, benzoimidazolyl, benzofurazanyl, imidazopyridyl, imidazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidyl, thiazolyl and tetrazolopyridyl,

which is unsubstituted or substituted with 1-7 substituents where the substituents are independently selected from:

(a) halo,
(b) cyano,
(c) hydroxy,
(d) C_{1-6}alkyl, which is unsubstituted or substituted with 1-5 of R^{13} where R^{13} is independently selected from: halo, cyano, hydroxy, C_{1-6}alkoxy, $-CO_2H$, $-CO_2(C_{1-6}$ alkyl), trifluoromethyl, and $-NR^9R^{10}$, wherein R^9 and R^{10} are independently selected from: hydrogen, C_{1-6} alkyl, C_{5-6} cycloalkyl, benzyl or phenyl, which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from: halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl;
(e) $-O-C_{1-6}$alkyl, which is unsubstituted or substituted with 1-5 of R^{13},
(f) $-CF_3$,
(g) $-CHF_2$,

(h) $-CH_2F$,
(i) $-NO_2$,
(j) C_{0-6}alkyl-phenyl or C_{0-6}alkyl-heterocycle, which is unsubstituted or substituted with 1-7 substituents where the substituents are independently selected from:
  (i) halo,
  (ii) hydroxy,
  (iii) C_{1-6}alkyl,
  (iv) $-O-C_{1-6}$alkyl,
  (v) $-CF_3$,
  (vi) $-OCF_3$,
  (vii) $-NO_2$,
  (viii) -CN,
  (ix) $-SO_2-C_{1-6}$alkyl,
  (x) $-CO_2R^9$,
  (xi) $-NR^9R^{10}$,
  (xii) $-CONR^9R^{10}$,
  (xiii) $-SO_2-NR^9R^{10}$, and
  (xiv) $-NR^9-SO_2-R^{10}$;
(k) $-CO_2R^9$,
(l) tetrazolyl,
(m) $-NR^9R^{10}$,
(n) $-NR^9-COR^{10}$,
(o) $-NR^9-CO_2R^{10}$,
(p) $-CO-NR^9R^{10}$,
(q) $-OCO-NR^9R^{10}$,
(r) $-NR^9CO-NR^9R^{10}$,
(s) $-S(O)_m-R^9$, wherein m is an integer selected from 0, 1 and 2,
(t) $-S(O)_2-NR^9R^{10}$,
(u) $-NR^9S(O)_2-R^{10}$, and
(v) $-NR^9S(O)_2-NR^9R^{10}$.

22. The compound of Claim 1 wherein R^8 is selected from: phenyl, imidazopyridyl, imidazolyl, oxazolyl, pyrazolyl, pyridyl, and thiazolyl;

which is unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from:

(a) halo,
(b) cyano,
(c) $-NO_2$,
(d) $-CF_3$,
(e) $-CHF_2$,
(f) $-CH_2F$,
(h) C_{1-6}alkyl,
(i) C_{1-3}alkyl-phenyl or C_{1-3}alkyl-pyridyl, which is unsubstituted or substituted with 1-4 substituents where the substituents are independently selected from:
  (i) halo,
  (ii) C_{1-6}alkyl,
  (iii) $-O-C_{1-6}$alkyl,
  (iv) $-CF_3$,
  (vi) $-OCF_3$,
  (vii) -CN, and
(j) $-O-C_{1-6}$alkyl.

23. The compound of Claim 1 wherein R^8 is selected from: imidazolyl, oxazolyl, pyrazolyl, and thiazolyl;
which is unsubstituted or substituted with 1-3 substituents where the substituents are independently selected from:

(a) fluoro,
(b) cyano,
(c) C_{1-3}alkyl,
(d) $-CH_2$-phenyl, which is unsubstituted or substituted with 1-4 substituents where the substituents are independently selected from:
  (i) fluoro,
  (ii) chloro,
  (iii) $-O-CH_3$,
  (iv) $-CF_3$,
  (v) -CN, and

(e) $-CF_3$.

24. The compound of Claim 1 wherein R^8 is selected from: 5-(3-benzyl)pyrazolyl, 5-(1-methyl-3-benzyl)pyrazolyl, 5-(1-ethyl-3-benzyl)pyrazolyl, 5-(2-benyl)thiazolyl, 5-(2-benyl-4-methyl)thiazolyl, and 5-(2-benyl-4-ethyl)thiazolyl).

25. The compound of Claim 1 wherein n is an integer which is 1.

26. The compound of Claim 1 wherein x is an integer which is 1 and y is an integer which is 1.

27. A pharmaceutical composition which comprises an inert carrier and a compound of Claim 1.

28. A method for modulation of chemokine receptor activity in a mammal which comprises the administration of an effective amount of the compound of Claim 1.

29. A method for preventing infection by HIV, treating infection by HIV, delaying of the onset of AIDS, or treating AIDS comprising the administration to a patient of an effective amount of the compound of Claim 1.

30. A method for the prevention or treatment of an inflammatory and immunoregulatory disorder or disease which comprises the administration to a patient of an effective amount of the compound of Claim 1.

31. A method for the prevention or treatment of asthma, allergic rhinitis, dermatitis, conjunctivitis, atherosclerosis or rheumatoid arthritis which comprises the administration to a patient of an effective amount of the compound of Claim 1.

Señor

SUPERINTENDENTE DE INDUSTRIA Y COI

DIVISION DE NUEVAS CREACIONES

E. S. D.

Re: P1.-**MERCK & CO., INC.**-Solicitud de Patente de Invención para **"DERIVADOS DE N-[3-((PIPERIDIN-1-IL)METIL)-4-(FENIL O HETEROCICLIL) CICLOPENT-1-IL]AMINA UTILES COMO MODULADORES DE LA ACTIVIDAD DEL RECEPTOR DE LA QUIMIOQUINA".**-Clase A. 61-Expediente número 00-042.774.-

1. Me refiero a mi solicitud de 8 de Junio de 2000 y al auto dictado por ese Despacho notificado por estado el 7 de Octubre del mismo año.

2. Por medio del presente atentamente manifiesto a usted que, debidamente autorizado por mi poderdante, modifico el título de la solicitud con el objeto de dar cumplimiento a las exigencias del señor Examinador, para que quede como sigue:

"DERIVADOS DE N-[3-((PIPERIDIN-1-IL)METIL)-4-(FENIL O HETEROCICLIL) CICLOPENT-1-IL]AMINA UTILES COMO MODULADORES DE LA ACTIVIDAD DEL RECEPTOR DE LA QUIMIOQUINA"

3. Anexos me permito presentar a usted:

(1) Nuevo Resumen, Objeto y Finalidad de la Invención, **que reemplaza el originalmente presentado,** el cual incluye el nuevo título;

(2) Nueva página 2 del texto de la descripción **que reemplaza la originalmente presentada** bajo el mismo número en la cual se ha modificado el título de la solicitud:

(3) En original y dos copias, una de ellas de 6cm x 6cm, Arte Final de la figura característica del invento, para la publicación en la Gaceta de la Propiedad Industrial; y

(4) Nuevo extracto en sus dos formas, **que reemplaza el originalmente presentado,** el cual incluye el nuevo título de la solicitud.

4. Llamo su atención al hecho de que las copias debidamente certificadas de las primeras solicitudes presentadas para el invento arriba nombrado **respecto de las cuales reclamo prioridad,** a saber las solicitudes estadinenses números 60/138,886 y 09/330,810 ambas de 11 de Junio de 1999, junto con la traducción correspondiente a las reivindicaciones y legalizaciones, fueron presentadas a ese Despacho mediante memorial de 22 de Agosto de 2000.

5. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,

JOSE ANTONIO LLOREDA
T.P. 10.784
Código 231

OBSERVACIONES: Se retiraron folios

990 → tarjeta de propietarios
991 → tarjeta temática
992 - 994 → extracto para publicación.
Del folio 989 se tomó arte final tamaño
6x6cm y 12x12cm.

202041

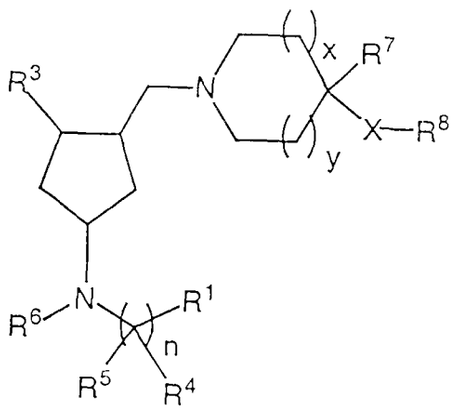
21 marzo /02

995

RESUMEN OBJETO Y FINALIDAD DE LA INVENCIÓN

"DERIVADOS DE N-[3-((PIPERIDIN-1-IL)METIL)-4-(FENIL O HETEROCICLIL)CICLOPENT-1-IL]AMINA UTILES COMO MODULADORES DE LA ACTIVIDAD DEL RECEPTOR DE LA QUIMIOQUINA"

El presente invento se refiere a compuestos de la formula I:



I

(donde R^1, R^3, R^4, R^5, R^6, R^7, R^8, X, n x y y se definen en el presente documento) que son útiles como moduladores de la actividad receptora de la quimioquina. En particular, estos compuestos son útiles como moduladores de los receptores de la quimioquina CCR-5 y/o CCR-3.

Industria y Comercio
SUPERINTENDENCIA

2do. EXAMEN DE FORMA PATENTE DE INVENCION

Folio 997

Radicación no 00-42774

Concepto Técnico no 505 Clasificación Internacional de Patentes A61K 31/195, 31/015, 31/445

Practicado el examen de acuerdo a lo establecido en el Art. 38 de la Decisión 486 se determinó que esta solicitud de **Patente de Invención:**

SI [X]	NO [ ]	Contiene un resumen de la invención (Art.26-e).
SI [X]	NO [ ]	Contiene el título o nombre de la invención (Art.27-d).
SI [X]	NO [ ]	Contiene la descripción de la invención (Art.26-b).
SI [X]	NO [ ]	NO ES APLICABLE [ ] Contiene los dibujos necesarios para comprender la invención (Art.26-d)
SI [X]	NO [ ]	Contiene una o más reivindicaciones. (Art.26-c).
SI [ ]	NO [ ]	NO ES APLICABLE [X] Han sido desarrollados los productos y/o procedimientos a partir de recursos genéticos o de sus productos derivados de los que cualquiera de los Países Miembros es país de origen. (Art. 26- h).
SI [ ]	NO [ ]	NO ES APLICABLE [X]Los productos y/o procedimientos han sido obtenidos o desarrollados a partir de los conocimientos tradicionales de las comunidades indígenas, afroamericanas, o locales de los países miembros, de acuerdo a lo establecido en la Decisión 391 y sus modificaciones y reglamentaciones vigentes.(Art.26-i).
SI [ ]	NO [X]	La invención se refiere a un producto relativo a un material biológico. (Art.26-J).
SI [X]	NO [ ]	La prioridad coincide con la materia reivindicada.
SI [X]	**NO [ ]**	**CUMPLE LOS REQUISITOS TÉCNICOS**

OBSERVACIONES Y OTROS: SI [ ] NO [ ] ver hoja(s) anexa(s)

1. Modifica el título inicialmente presentado por el consignado en el folio 987.
2. Anexa nuevo resumen (folio 995) nueva página 2 del texto de la descripción, que reemplaza la originalmente presentada, folio 996, arte final (folio 989) nuevo extracto para publicación (folios 992 a 994) Tarjetas temática (991) y de propietarios (folio 990).

EXAMINADOR TÉCNICO
202041

Bogotá D. C., 21 marzo /02

Carrera 13 No. 27-00 Piso 5 y 10
Conmutador: 334 12 21-2-3-4
Fax: 281 31 25 e-mail: info@sic.gov.co
Santa Fe de Bogotá D.C. - Colombia

998

Industria y Comercio
SUPERINTENDENCIA

Folio **998**

2020
Bogotá, D.C.

Doctor(a)
JOSE ANTONIO LLOREDA
Apoderado(a)

REFERENCIA:	Radicación No.	**00-42774**
	Trámite	002
	Evento	001
	Actuación	416
	Oficio No.	**654**
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486 de la Comisión de la comunidad andina, y en las demás disposiciones vigentes sobre la materia, se envía el extracto de la solicitud a la Oficina de comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo establece el artículo 40 de la misma Decisión.

Cúmplase
Dado en Bogotá, D.C., a los

ALIX CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

Bogotá, D.C., Feb. 2003 El extracto de esta solicitud fue publicado en el número 518 de la Gaceta de Propiedad Industrial, de fecha 30-07-2002 . El término hábil señalado por la ley expiró el 25-Oct-2002 y SI__ NO X se presentaron oposiciones por parte de terceros.

202041

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador: 382 0840
Fax: 382 2695
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., (

994

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

EDICTO No. **00003625**

RADICACION: 00 42774

LA SECRETARIA GENERAL AD - HOC
HACE SABER:

Que esta Superintendencia profirió la Resolución No. 3550 de 19 FEB. 2003. Que el contenido de la parte resolutiva es como sigue: El Superintendente de Industria y Comercio, en ejercicio de sus facultades legales y CONSIDERANDO....

RESUELVE

ARTICULO PRIMERO: Declarar abandonada la solicitud de privilegio de patente de invención contenida en el expediente de la referencia.

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución al doctor José Antonio Lloreda, o a quien haga sus veces, quien actúa como apoderado de Merck & Co., Inc., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 dias hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE
Dada en Bogotá, D.C., a los 19 FEB. 2003

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO (E),

CARLOS GERMÁN CAYCEDO ESPINEL

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:30 a.m. de hoy.

Secretaria General Ad - Hoc 18 MAR. 2003

Este edicto se desfija hoy 01 ABR. 2003 a las cinco (5:00 p.m.)

Secretaria General Ad - Hoc

*/

1000

Industria y Comercio

SUPERINTENDENCIA

AVISO DE NOTIFICACION

0103/

CORREO CERTIFICADO

Bogotá D.C.

Doctor(a)
LLOREDA JOSE ANTONIO
CALLE 72 A 5-83 PISO 6
BOGOTA

SUPERINDUSTRIA Y COMERCIO
Radicacion : 00042774 00000004
Fecha : 06/03/2003 10:57:25 AM Folios
Tramite : 2 PATENTES 1 REGISTRO/ 432 RESOLUCIO
Dependencia : 103 Solicita : LLOREDA JOSE ANTONIO

REF: RESOLUCION No. 3550
FECHA: 19/02/2003
EXPEDIENTE No. 0 42774 000
Tramite: 2 PATENTES DE INVENCION
Evento : 1 REGISTRO/DEPOSITO/CONCESION
Actuac.: 432 RESOLUCION

Estimado doctor(a):

Comedidamente le solicito presentarse a este Despacho ubicado en la Carrera 13 No. 27 - 00 Piso Quinto(5), de Bogotá D.C., dentro del término de cinco (5) días hábiles contados a partir del envío de la presente citación, en horario de 8:30 a.m. a 5:00 p.m., jornada continua con el fin de notificarle personalmente el contenido de la resolución y expediente citados en la referencia.

De no hacerse presente en el término indicado anteriormente, la providencia en mención se notificará por edicto.

Secretaría General
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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

Industria y Comercio
SUPERINTENDENCIA

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION 03550

Por la cual se declara abandonada una solicitud

Rad. Exp. N° 00-42774

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO (E)
en ejercicio de sus facultades legales, en especial de las que se confirieron en el artículo 4, numeral 5 del decreto 2153 de 1992, y

CONSIDERANDO:

PRIMERO: El artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina, establece que: "Dentro del plazo de seis meses contados desde la publicación de la solicitud, independientemente que se hubieren presentado oposiciones, el solicitante deberá pedir que se examine si la invención es patentable. Los Países Miembros podrán cobrar una tasa para la realización de este examen. Si transcurriera dicho plazo sin que el solicitante hubiera pedido que se realice el examen, la solicitud caerá en abandono".

SEGUNDO: El extracto de esta solicitud fue publicado en la Gaceta de la Propiedad Industrial N° 518 del 30 de julio de 2002. Contados seis meses desde la publicación de la misma, no se presentó petición de parte del interesado, para efectuar el examen de fondo.

De conformidad con lo anterior, se considera abandonada la solicitud en los términos del mencionado artículo 44.

RESUELVE:

ARTICULO PRIMERO: Declarar abandonada la solicitud de privilegio de patente de invención contenida en el expediente de la referencia.

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución al doctor José Antonio Lloreda, o a quien haga sus veces, quien actúa como apoderado de Merck & Co., Inc., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE
Dada en Bogotá, D.C., a los 19 FEB. 2003

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO (E),

CARLOS GERMÁN CAYCEDO ESPINEL

Doctor
JOSÉ ANTONIO LLOREDA
Calle 72 N° 5 – 83 Piso 6.
Bogotá, D.C.

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

Industria y Comercio
SUPERINTENDENCIA

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION 03550

Por la cual se declara abandonada una solicitud

Rad. Exp. N° 00-42774

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO (E)
en ejercicio de sus facultades legales, en especial de las que se confirieron en el artículo 4, numeral 5 del decreto 2153 de 1992, y

CONSIDERANDO:

PRIMERO: El artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina, establece que: "Dentro del plazo de seis meses contados desde la publicación de la solicitud, independientemente que se hubieren presentado oposiciones, el solicitante deberá pedir que se examine si la invención es patentable. Los Países Miembros podrán cobrar una tasa para la realización de este examen. Si transcurriera dicho plazo sin que el solicitante hubiera pedido que se realice el examen, la solicitud caerá en abandono".

SEGUNDO: El extracto de esta solicitud fue publicado en la Gaceta de la Propiedad Industrial N° 518 del 30 de julio de 2002. Contados seis meses desde la publicación de la misma, no se presentó petición de parte del interesado, para efectuar el examen de fondo.

De conformidad con lo anterior, se considera abandonada la solicitud en los términos del mencionado artículo 44.

RESUELVE:

ARTICULO PRIMERO: Declarar abandonada la solicitud de privilegio de patente de invención contenida en el expediente de la referencia.

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución al doctor José Antonio Lloreda, o a quien haga sus veces, quien actúa como apoderado de Merck & Co., Inc., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE
Dada en Bogotá, D.C., a los 19 FEB. 2003

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO (E),

CARLOS GERMÁN CAYCEDO ESPINEL

Doctor
JOSÉ ANTONIO LLOREDA
Calle 72 N° 5 – 83 Piso 6.
Bogotá, D.C.

202021

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