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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-105172- -00001-0000

Fecha: 2007-10-31 16:32:27 Dep. 2020 NUECREACION
Tra. 11 PATENTE/II Eve: 378 FASENACIONAL
Act. 538 PETICION Folios: 2

Re: P1.-ASTRAZENECA AB.-Solicitud de Patente de Invención en
Fase Nacional PCT para "DERIVADOS DE PIPERIDINA COMO
MODULADORES DEL RECEPTOR DE QUIMIOQUINA CCR5".-
Clase C07D 401/06.-Expediente número 06-105.172.-

1. Me refiero a mi solicitud de patente de 18 de Octubre de 2006.
2. De conformidad con lo dispuesto en el Artículo 5.2.12 de la Circular Externa No. 03 de 28 de Abril de 2003, y estando dentro del plazo de seis meses contados desde la fecha de la publicación de la solicitud en la Gaceta de la Propiedad Industrial número **576** de 31 de Mayo de 2007, solicito a ese Despacho proceder a realizar el examen de patentabilidad de la presente invención.
3. Me permito recordar a usted, que tal como se informó en el Petitorio de la invención, la presente solicitud corresponde a Capítulo **I**.
4. Anexo me permito acompañar recibo número 07-87.676, expedido por la Superintendencia de Industria y Comercio, que acredita el pago de la tasa que dicho examen causa.

Señor Superintendente,

ALICIA LLOREDA RICAURTE

T.P. 53.215

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 87,676
FECHA : OCTUBRE 25 DE 2007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-105172- -00001-0000

Fecha: 2007-10-31 16:32:27 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 2

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
LLOREDA Y CIA S. A	CONSIGNACION	BANCO POPULAR	050-00110-6	47999925	25/10/2007	9,104,700.00

***** CONCEPTO *****

NT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN	404,000.00
	TOTAL :	\$ 404,000.00

SON: CUATROCIENTOS CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

06-105172

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-105172

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **576** DE

FECHA **31 DE MAYO DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **31 DE AGOSTO DE 2007**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

Bogotá, D.C., 24 de febrero de 2010

Apoderado: Alicia Lloreda Ricaurte

ASUNTO	Radicación	06-105172
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	
	Folios	3072

Patente de Invención ☒

Vía PCT (fase nacional) ☒ Cap. I ☒ Cap. II ☐

No. Sol. Internacional PCT/SE2005/000574
Fecha de Presentación Internal. 20/abr/2005

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

1.1 Descripción: Folios: 40 a 172 Como se radicó inicialmente

1.2 Reivindicaciones: Folios 173 a 179 Modificado al momento de entrar en fase nacional
Folios 26 a 32 El que obra en fase internacional.

1.3 Prioridad: Folio 1: SE 0401057-5, folios 23-04-04
SE 05000

2. Modificaciones no aceptadas (artículo 34 D.486 de la C.A.N.)

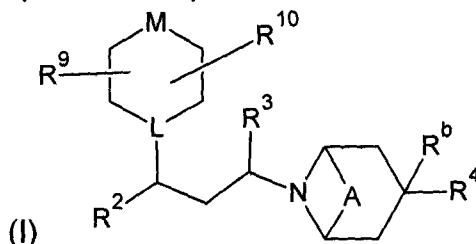
El capítulo reivindicatorio de la presente solicitud no es el mismo tal como había sido presentado en la solicitud internacional (folios 173-179). El capítulo reivindicatorio fue modificado al momento de su presentación en fase nacional, dicha modificación no está prevista en el momento de entrada a fase nacional, como lo confirman el artículo 22 y 34 del mismo Tratado, sino únicamente *después* de haberse admitido a dicha fase nacional y sólo previo diligenciamiento y presentación de un formulario único de correcciones y modificaciones y pago de la tasa estipulada para tal fin (numeral 1.2.1.6 del capítulo quinto, título X de la circular única de la Superintendencia de Industria y Comercio).

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3. Objeto de la invención

Título de la solicitud: DERIVADOS DE PIPERIDINA COMO MODULADORES DEL RECEPTOR DE QUIMOQUINA CCR5.

Definir el objeto de la invención son los derivados de 1-(3-fenil-3-heterocicliilpropil)piperidine y derivados de 8-(3-fenil-3-herocicliilpropil)-8-azabicyclo[3.2.1]octano que están representados con la fórmula Markush(I):



Reivindicaciones 1–10, 13,14: Un compuesto de la fórmula (I).

Reivindicación 11: Procedimiento de Síntesis de los compuestos de fórmula (I).

Reivindicación 12: Composiciones que los contienen.

Reivindicación 15: método de tratamiento que consiste en administrar un compuesto a un paciente.

Se catalogó la invención, según la Clasificación Internacional de Patentes (IPC.):C07D401/06, 401/14, 417/14, A61K31/4545, 31/496, A61P1/00, 11/00, 19/00.

4. De la solicitud de Patente

4.1. Reivindicaciones (folios 26 a 32)(artículo 30 D 486 de la C.A.N.)

-En la reivindicación 1 se debe organizar la traducción correctamente, porque existen apartes como por ejemplo “-un carbono de anillo de dicho R⁴...” o “-en donde sea posible, un nitrógeno de anillo de dicho R⁴...” o “-siempre y cuando un nitrógeno de anillo de dicho heterociclo R⁴...” etc., hace que el texto de la reivindicación no sea claro.

-La reivindicación 1 no es clara respecto al significado inequívoco del sustituyente R⁴ toda vez que es especulativo y confuso porque no son extrapolaciones estrechamente relacionadas con lo que se describió, en las reivindicaciones se acepta una generalización razonable de los ejemplos dados en la parte descriptiva, como características técnicas establecidas en la descripción-ejemplos consideradas características esenciales de la invención descrita, que deben ser las mismas que las utilizadas para definir la invención en las reivindicaciones. Entonces así las cosas, las definiciones que deben quedar son las que aparecen dentro de la reivindicación 1 folio 27 primer párrafo y folio 28 último párrafo-folio 29 primer párrafo.

Por lo tanto las reivindicaciones no cumplen con el requisito de claridad, concisión o sustento por la descripción de acuerdo al art. 30 de la Decisión 486.

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5. Unidad de invención (artículo 25 D 486 de la C.A.N.)

-La presente solicitud no cumple con el requisito de unidad inventiva a posteriori, la solicitud comprende los siguientes grupos inventivos

-Los derivados de 1-(3-fenil-3-heterociclil-propil)piperidina

-Los derivados de 8-(3-fenil-3-herociclil-propil)-8-azabicyclo[3.2.1]octano.

Cada una de estas invenciones, es una invención distinta caracterizada por su propia característica técnica especial, ya que son estructuralmente diferentes, la primera son derivados de piperidina y la segunda derivados del tropano.

6. Excepción a la patentabilidad (artículo 20 D486 literal d) de la C.A.N.)

La reivindicación 15 reclama un método de tratamiento terapéutico, por lo tanto está comprendida en el artículo 20 D486 literal d) de la C.A.N.

7. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el estado de la técnica fecha de presentación de la solicitud de la cual se reclama prioridad, 23/abr/2004.

Teniendo en cuenta la fecha indicada se realizó la búsqueda del estado de la técnica, en bases de datos donde esta oficina tiene acceso libre, para búsqueda de documentos relacionados con la materia que se reclama como nueva e inventiva en presente solicitud, encontrándose los siguientes documentos más relevantes:

N°	Documento	Título	Fecha de Publicación*
D1	WO03042205	Piperidine derivatives and their use as modulators of chemokine receptor activity (especialmente CCR5)	22-may-2003

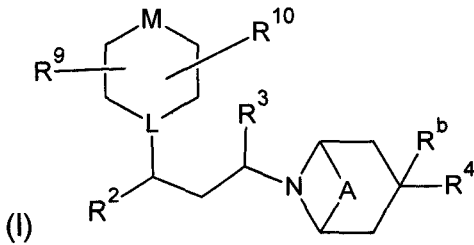
***Sólo esta analizado para la primera invención que aparece reclamada en la solicitud derivados de piperidina.**

8. Análisis de patentabilidad (artículo 14 D486)

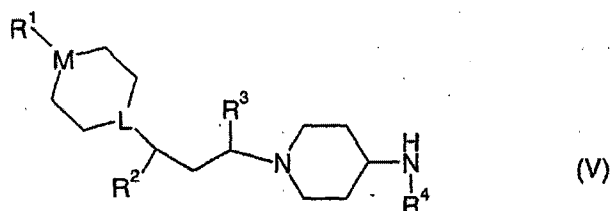
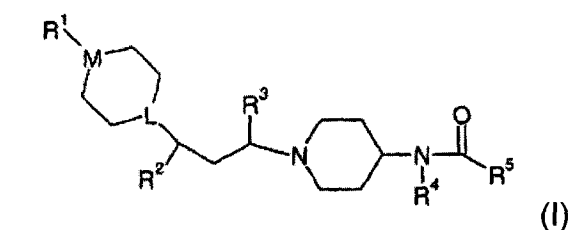
8.1. Novedad (artículo 16 D486 de la C.A.N.)

-La solicitud en estudio reclama los derivados de fórmula Markush(I):

Derivados de 1-(3-fenil-3-heterociclil-propil)piperidina



D1 enseña derivados 1-(3-fenil-3-heterocicilil-propil)piperidina (ver todo D1):



L is CH or N; M is CH or N; provided that L and M are not both CH;

R¹ is hydrogen, C₁₋₆ alkyl [optionally substituted by phenyl {which itself optionally substituted by halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, cyano, nitro, CF₃, OCF₃, (C₁₋₄ alkyl)C(O)NH, S(O)₂NH₂, C₁₋₄ alkylthio, S(O)(C₁₋₄ alkyl) or S(O)₂(C₁₋₄ alkyl)} or heteroaryl {which itself optionally substituted by halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, cyano, nitro, CF₃, (C₁₋₄ alkyl)C(O)NH, S(O)₂NH₂, C₁₋₄ alkylthio, S(O)(C₁₋₄ alkyl) or S(O)₂(C₁₋₄ alkyl)}], phenyl {optionally substituted by halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, cyano, nitro, CF₃, OCF₃, (C₁₋₄ alkyl)C(O)NH, S(O)₂NH₂, C₁₋₄ alkylthio, S(O)(C₁₋₄ alkyl) or S(O)₂(C₁₋₄ alkyl)}, heteroaryl {optionally substituted by halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, cyano, nitro, CF₃, (C₁₋₄ alkyl)C(O)NH, S(O)₂NH₂, C₁₋₄ alkylthio, S(O)(C₁₋₄ alkyl) or S(O)₂(C₁₋₄ alkyl)}, S(O)₂R⁶, S(O)₂NR¹⁰R¹¹, C(O)R⁷, C(O)₂(C₁₋₆ alkyl) (such as *tert*-butoxycarbonyl), C(O)₂(phenyl(C₁₋₂ alkyl)) (such as benzyloxycarbonyl) or C(O)NHR⁷; and when M is CH R¹ can also be NHS(O)₂R⁶, NHS(O)₂NHR⁷, NHC(O)R⁷ or NHC(O)NHR⁷;

R² is phenyl or heteroaryl, either of which is optionally substituted by halo.

R³ is hydrogen or C₁₋₄ alkyl; In another aspect of the invention R³ is hydrogen or methyl.

R⁴ is hydrogen, methyl, ethyl, allyl or cyclopropyl;

salt thereof or a solvate thereof, in the manufacture of a medicament for use in therapy (for example modulating chemokine receptor activity (especially CCR5 receptor activity (especially rheumatoid arthritis)) in a warm blooded animal, such as man).

El elemento característico de la estructura 1-(3-fenil-3-heterocicilil-propil)piperidina con cada uno de sus sustituyentes que pudieron ser identificados inequívocamente, se encuentra una diferencia en el significados de R⁴ que en la solicitud en estudio es un heterociclo, mientras que en la solicitud en estudio la fórmula V, es un N-unido a un ciclo, o sea, la única diferencia es que el N no hace parte del ciclo, entonces por esa diferencia se considera que la solicitud es nueva.

8.2 Nivel inventivo (Artículo 18 D486 de la C.A.N.)

El D1 enseña derivados de 1-(3-fenil-3-heterocicilil-propil)piperidina al igual que la solicitud en estudio con el mismo efecto farmacológico, D1 está indicado que es

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modulador de la actividad del receptor quimoquina especialmente CCR5, pero R^4 que en la solicitud en estudio es un heterociclo, mientras que en la solicitud en estudio la fórmula V, es un N-unido a un ciclo. Pero para una persona normalmente versada en la materia podría al momento de observar la formula Markush de D1 darle el significado de heterociclo a R^4 , con enunciar por ejemplo que R^4 y R^5 formen un anillo junto con el N al cual están unidos en la fórmula (I) de D1, o enunciando que R^4 forme un heterociclo junto con el N al cual está unido, en la fórmula V. Ya que en la descripción de la solicitud no aparece en qué el salto cualitativo, respecto al arte previo D1, que evidencie que es un aporte técnico real, un avance inesperado, respecto a los conocidos compuestos descritos en D1, toda vez que son análogos los reclamados en la presente solicitud como nuevos e inventivos, con los de D1. Por lo tanto una persona del nivel medio deriva de manera evidente la presente solicitud, con las enseñanzas que existen en la anterioridad, por lo tanto no se observa el aporte al acervo tecnológico, o el salto cualitativo en la regla técnica. Por lo tanto la solicitud en estudio no cumple con el requisito exigido en el Artículo 18 D486 de la C.A.N

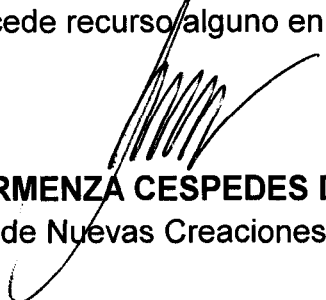
9- Conclusión

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento Nº	Reivindicaciones Afectadas	Requisito que Afecta
D1	WO03042205	1-15	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiéndole que contra él no procede recurso alguno en la vía gubernativa.


ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha
_____ 05 MAR. 2010

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
22 May 2003 (22.05.2003)

PCT

(10) International Publication Number
WO 03/042205 A1(51) International Patent Classification: C07D 401/06,
401/14, 403/06, 417/14, A61K 31/4545, 31/496, A61P
11/00, 17/00, 19/00, 29/00, 37/00SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US,
UZ, VC, VN, YU, ZA, ZM, ZW.

(21) International Application Number: PCT/SE02/02055

(22) International Filing Date:
12 November 2002 (12.11.2002)

(25) Filing Language: English

(26) Publication Language: English

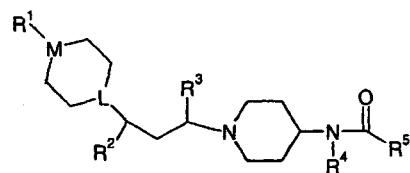
(30) Priority Data:
0103818-1 15 November 2001 (15.11.2001) SE(71) Applicant (for all designated States except US): AS-
TRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE).(72) Inventor; and
(75) Inventor/Applicant (for US only): TUCKER, Howard
[GB/GB]; AstraZeneca R & D Alderley, Alderley Park,
Macclesfield, Cheshire SK10 4TG (GB).(74) Agent: GLOBAL INTELLECTUAL PROPERTY; As-
traZeneca AB, S-151 85 Södertälje (SE).(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE,(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK,
TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— as to applicant's entitlement to apply for and be granted
a patent (Rule 4.17(ii)) for the following designations AE,
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA,
CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES,
FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT,
RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT,
TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent
(GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR),
OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
ML, MR, NE, SN, TD, TG)

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.(54) Title: PIPERIDINE DERIVATIVES AND THEIR USE AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY (ES-
PECIALLY CCR5)

(I)

(57) Abstract: Compounds of formula
(I): wherein L is CH or N; M is CH or N;
provided that L and M are not both CH;
compositions comprising them, processes
for preparing them and their use in medical
therapy (for example modulating CCR5
receptor activity in a warm blooded animal).PIPERIDINE DERIVATIVES AND THEIR USE AS MODULATORS OF CHEMOKINE
RECEPTOR ACTIVITY (ESPECIALLY CCR5)

The present invention relates to heterocyclic derivatives having pharmaceutical activity, to processes for preparing such derivatives, to pharmaceutical compositions comprising such derivatives and to the use of such derivatives as active therapeutic agents.

Pharmaceutically active piperidine derivatives are disclosed in PCT/SE01/01053, EP-A1-1013276, WO00/08013, WO99/38514 and WO99/04794.

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 and also play a rôle in the maturation of cells of the immune system. Chemokines play an important rôle in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C, or α) and Cys-Cys (C-C, or β) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1 α and 1 β (MIP-1 α and MIP-1 β).

Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

The CCR5 receptor is expressed on T-lymphocytes, monocytes, macrophages, dendritic cells, microglia and other cell types. These detect and respond to several

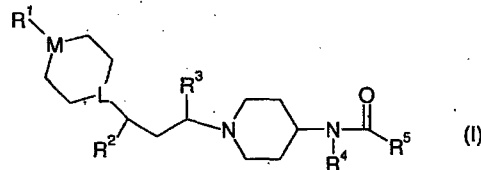
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chemokines, principally "regulated on activation normal T-cell expressed and secreted" (RANTES), macrophage inflammatory proteins (MIP) MIP-1 α and MIP-1 β and monocyte chemoattractant protein-2 (MCP-2).

This results in the recruitment of cells of the immune system to sites of disease. In many diseases it is the cells expressing CCR5 which contribute, directly or indirectly, to tissue damage. Consequently, inhibiting the recruitment of these cells is beneficial in a wide range of diseases.

CCR5 is also a co-receptor for HIV-1 and other viruses, allowing these viruses to enter cells. Blocking the receptor with a CCR5 antagonist or inducing receptor internalisation with a CCR5 agonist protects cells from viral infection.

The present invention provides a compound of formula (I):



wherein

L is CH or N; M is CH or N; provided that L and M are not both CH;

- 15 R¹ is hydrogen, C₁₋₆ alkyl [optionally substituted by phenyl {which itself optionally substituted by halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, cyano, nitro, CF₃, OCF₃, (C₁₋₄ alkyl)C(O)NH, S(O)₂NH₂, C₁₋₄ alkylthio, S(O)(C₁₋₄ alkyl) or S(O)₂(C₁₋₄ alkyl)} or heteroaryl {which itself optionally substituted by halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, cyano, nitro, CF₃, (C₁₋₄ alkyl)C(O)NH, S(O)₂NH₂, C₁₋₄ alkylthio, S(O)(C₁₋₄ alkyl) or S(O)₂(C₁₋₄ alkyl)}], phenyl {optionally substituted by halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, cyano, nitro, CF₃, OCF₃, (C₁₋₄ alkyl)C(O)NH, S(O)₂NH₂, C₁₋₄ alkylthio, S(O)(C₁₋₄ alkyl) or S(O)₂(C₁₋₄ alkyl)}, heteroaryl {optionally substituted by halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, cyano, nitro, CF₃, (C₁₋₄ alkyl)C(O)NH, S(O)₂NH₂, C₁₋₄ alkylthio, S(O)(C₁₋₄ alkyl) or S(O)₂(C₁₋₄ alkyl)}, S(O)₂R⁶, S(O)₂NR¹⁰R¹¹, C(O)R⁷, C(O)₂(C₁₋₆ alkyl) (such as tert-butoxycarbonyl), C(O)₂(phenyl(C₁₋₂ alkyl)) (such as benzyloxycarbonyl) or C(O)NHR⁷; and when M is CH R¹ can also be NHS(O)₂R⁶, NHS(O)₂NHR⁷, NHC(O)R⁷ or NHC(O)NHR⁷;
- 20 R² is phenyl or heteroaryl, either of which is optionally substituted by halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, S(O)_n(C₁₋₄ alkyl), nitro, cyano or CF₃;

R³ is hydrogen or C₁₋₄ alkyl;

R⁴ is hydrogen, methyl, ethyl, allyl or cyclopropyl;

R⁵ is phenyl, heteroaryl, phenylNH, heteroarylNH, phenyl(C₁₋₂)alkyl, heteroaryl(C₁₋₂)alkyl, phenyl(C₁₋₂ alkyl)NH or heteroaryl(C₁₋₂ alkyl)NH; wherein the phenyl and heteroaryl rings of

- 5 R⁵ are optionally substituted by halo, cyano, nitro, hydroxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, S(O)_k(C₁₋₄ alkyl), S(O)₂NR⁸R⁹, NHS(O)₂(C₁₋₄ alkyl), NH₂, NH(C₁₋₄ alkyl), N(C₁₋₄ alkyl)₂, NHC(O)NH₂, C(O)NH₂, C(O)NH(C₁₋₄ alkyl), NHC(O)(C₁₋₄ alkyl), CO₂H, CO₂(C₁₋₄ alkyl), C(O)(C₁₋₄ alkyl), CF₃, CHF₂, CH₂F, CH₂CF₃ or OCF₃;

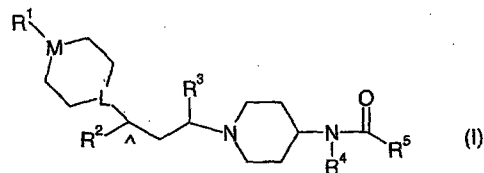
k, m and n are, independently, 0, 1 or 2;

- 10 R⁶ is C₁₋₆ alkyl [optionally substituted by halo (such as fluoro), C₁₋₄ alkoxy, phenyl {which itself optionally substituted by halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, cyano, nitro, CF₃, OCF₃, (C₁₋₄ alkyl)C(O)NH, S(O)₂NH₂, C₁₋₄ alkylthio, S(O)(C₁₋₄ alkyl) or S(O)₂(C₁₋₄ alkyl)} or heteroaryl {which itself optionally substituted by halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, cyano, nitro, CF₃, (C₁₋₄ alkyl)C(O)NH, S(O)₂NH₂, C₁₋₄ alkylthio, S(O)(C₁₋₄ alkyl) or S(O)₂(C₁₋₄ alkyl)}], C₃₋₇ cycloalkyl, pyranil, phenyl {optionally substituted by halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, cyano, nitro, CF₃, OCF₃, (C₁₋₄ alkyl)C(O)NH, S(O)₂NH₂, C₁₋₄ alkylthio, S(O)(C₁₋₄ alkyl) or S(O)₂(C₁₋₄ alkyl)} or heteroaryl {optionally substituted by halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, cyano, nitro, CF₃, (C₁₋₄ alkyl)C(O)NH, S(O)₂NH₂, C₁₋₄ alkylthio, S(O)(C₁₋₄ alkyl) or S(O)₂(C₁₋₄ alkyl)}];
- 15 R⁷ is hydrogen, C₁₋₆ alkyl [optionally substituted by halo (such as fluoro), C₁₋₄ alkoxy, phenyl {which itself optionally substituted by halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, cyano, nitro, CF₃, OCF₃, (C₁₋₄ alkyl)C(O)NH, S(O)₂NH₂, C₁₋₄ alkylthio, S(O)(C₁₋₄ alkyl) or S(O)₂(C₁₋₄ alkyl)} or heteroaryl {which itself optionally substituted by halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, cyano, nitro, CF₃, OCF₃, (C₁₋₄ alkyl)C(O)NH, S(O)₂NH₂, C₁₋₄ alkylthio, S(O)(C₁₋₄ alkyl) or S(O)₂(C₁₋₄ alkyl)} or heteroaryl {which itself optionally substituted by halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, cyano, nitro, CF₃, (C₁₋₄ alkyl)C(O)NH, S(O)₂NH₂, C₁₋₄ alkylthio, S(O)(C₁₋₄ alkyl) or S(O)₂(C₁₋₄ alkyl)}];
- 20 R⁸ and R⁹ are, independently, hydrogen or C₁₋₄ alkyl, or together with a nitrogen or oxygen atom, may join to form a 5- or 6-membered ring which is optionally substituted with C₁₋₄ alkyl, C(O)H or C(O)(C₁₋₄ alkyl);
- 25 R¹⁰ and R¹¹ are, independently, hydrogen or C₁₋₄ alkyl, or may join to form a 5- or 6-membered ring which is optionally substituted with C₁₋₄ alkyl or phenyl (wherein the phenyl ring is optionally substituted by halo, cyano, nitro, hydroxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, S(O)_mC₁₋₄

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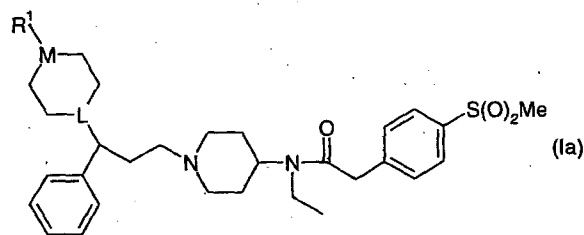
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The carbon labelled ^ in the representation of formula (I) shown below, is always chiral.



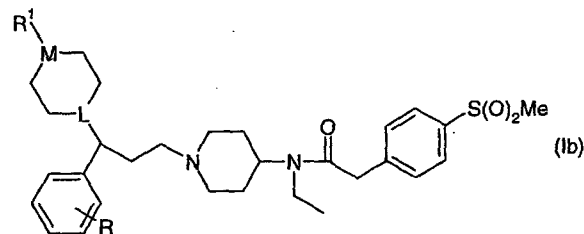
When L is N the carbon labelled ^ has, for example, the S absolute configuration. When L is CH the carbon labelled ^ has, for example, the R absolute configuration.

In another aspect the present invention provides a compound of formula (Ia):



wherein L, M and R¹ are as defined above.

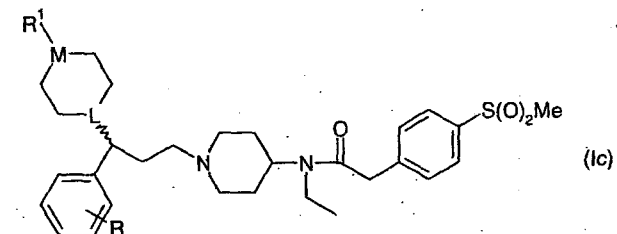
In a further aspect the present invention provides a compound of formula (Ib):



wherein L, M and R¹ are as defined above; and R is hydrogen, one or two fluorine atoms, S(O)_n(C₁₋₄ alkyl) or C₁₋₄ alkoxy; and n is 0, 1 or 2 (for example, 2).

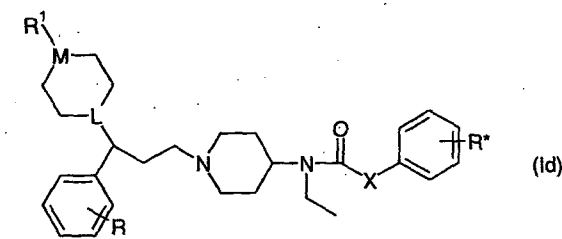
In another aspect the present invention provides a compound of formula (Ic):

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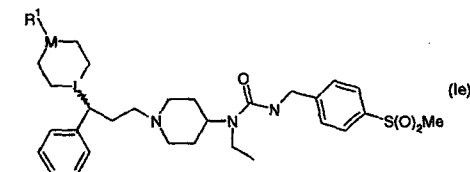
wherein L, M and R¹ are as defined above; and R is hydrogen, one or two fluorine atoms, S(O)_n(C₁₋₄ alkyl) or C₁₋₄ alkoxy; and n is 0, 1 or 2 (for example, 2).

In a still further aspect the present invention provides a compound of formula (Id):



wherein L, M and R¹ are as defined above; R is hydrogen, one or two fluorine atoms, S(O)_n(C₁₋₄ alkyl) or C₁₋₄ alkoxy; X is NHCH₂, NH or CH₂; n is 0, 1 or 2 (for example, 2); and R* is halo (such as fluoro, chloro or bromo), cyano, C₁₋₄ alkyl (such as methyl), C₁₋₄ alkoxy (such as methoxy) or S(O)₂C₁₋₄ alkyl (such as S(O)₂CH₃).

In another aspect the present invention provides a compound of formula (Ie):

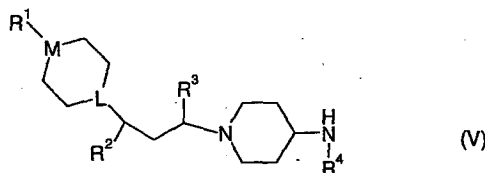


wherein L, M and R¹ are as defined above.

In yet another aspect the present invention provides a compound of formula (If):

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Alternatively, a compound of the invention can be prepared by coupling a compound of formula (V):



wherein L, M, R¹, R², R³ and R⁴ are as defined above, with:

- 5 a) an acid of formula R⁵CO₂H in the presence of a suitable coupling agent (for example PyBrOP or HATU) in the presence of a suitable base (such as a tri(C₁₋₆ alkyl)amine, for example diisopropylethylamine) in a suitable solvent (for example *N*-methylpyrrolidinone or a chlorinated solvent, such as dichloromethane) at room temperature (for example 10-30°C); or,
- 10 b) an acid chloride of formula R⁵C(O)Cl, in the presence of a suitable base (such as a tri(C₁₋₆ alkyl)amine, for example triethylamine or diisopropylethylamine) in a suitable solvent (for example a chlorinated solvent, such as dichloromethane) at room temperature (for example 10-30°C).

The starting materials for these processes are either commercially available or can be prepared by literature methods, adapting literature methods or by following or adapting Methods herein described.

In a further aspect the invention provides an intermediate of formula (V).

In a still further aspect the invention provides processes for preparing the compounds of formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If) and (Ig). Many of the intermediates in the processes are novel and these are provided as further features of the invention.

The compounds of the invention have activity as pharmaceuticals, in particular as modulators (such as agonists, partial agonists, inverse agonists or antagonists) of chemokine receptor (especially CCR5) activity, and may be used in the treatment of autoimmune, inflammatory, proliferative or hyperproliferative diseases, or immunologically-mediated diseases (including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS)).

The compounds of the present invention are also of value in inhibiting the entry of viruses (such as human immunodeficiency virus (HIV)) into target cells and, therefore, are of

value in the prevention of infection by viruses (such as HIV), the treatment of infection by viruses (such as HIV) and the prevention and/or treatment of acquired immune deficiency syndrome (AIDS).

According to a further feature of the invention there is provided a compound of the formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If) or (Ig) (such as (I) or (Ia)), or a pharmaceutically acceptable salt thereof or a solvate thereof, for use in a method of treatment of a warm blooded animal (such as man) by therapy (including prophylaxis).

According to a further feature of the present invention there is provided a method for modulating chemokine receptor activity (especially CCR5 receptor activity) in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof or a solvate thereof.

The present invention also provides the use of a compound of the formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If) or (Ig) (such as (I) or (Ia)), or a pharmaceutically acceptable salt thereof or a solvate thereof, as a medicament, especially a medicament for the treatment of transplant rejection, respiratory disease, psoriasis or rheumatoid arthritis (especially rheumatoid arthritis). [Respiratory disease is, for example, COPD, asthma (such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)) or rhinitis (acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis); and is particularly asthma or rhinitis].

In another aspect the present invention provides the use of a compound of the formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If) or (Ig) (such as (I) or (Ia)), or a pharmaceutically acceptable salt thereof or a solvate thereof, in the manufacture of a medicament for use in therapy (for example modulating chemokine receptor activity (especially CCR5 receptor activity (especially rheumatoid arthritis)) in a warm blooded animal, such as man).

The invention also provides a compound of the formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If) or (Ig) (such as (I) or (Ia)), or a pharmaceutically acceptable salt thereof or a solvate thereof, for use as a medicament, especially a medicament for the treatment of rheumatoid arthritis.

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In another aspect the present invention provides the use of a compound of the formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If) or (Ig) (such as (I) or (Ia)), or a pharmaceutically acceptable salt thereof or a solvate thereof, in the manufacture of a medicament for use in therapy (for example modulating chemokine receptor activity (especially CCR5 receptor activity (5 (especially rheumatoid arthritis)) in a warm blooded animal, such as man).

The invention further provides the use of a compound of formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If) or (Ig) (such as (I) or (Ia)), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of:

- (1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); asthma (such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)); bronchitis (such as eosinophilic bronchitis); acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa;
- 15 membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung or idiopathic interstitial pneumonia;
- (2) (bone and joints) arthrides including rheumatic, infectious, autoimmune, seronegative spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behçet's disease, Sjogren's syndrome or systemic sclerosis;
- 20 (3) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, Alopecia areata or vernal conjunctivitis;
- (4) (gastrointestinal tract) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (for example migraine, rhinitis or eczema);
- 30 (5) (Allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea; or chronic graft versus host disease; and/or

(6) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), Lupus disorders (such as lupus erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (such as lepromatous leprosy), Peridontal disease, Sezary syndrome, idiopathic thrombocytopenia purpura or disorders of the menstrual cycle;

5 in a warm blooded animal, such as man.

The present invention further provides a method of treating a chemokine mediated disease state (especially a CCR5 mediated disease state) in a warm blooded animal, such as man, which comprises administering to a mammal in need of such treatment an effective amount of a compound of formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If) or (Ig) (such as (I) or (Ia)), or a pharmaceutically acceptable salt thereof or solvate thereof.

In order to use a compound of the invention, or a pharmaceutically acceptable salt thereof or solvate thereof, for the therapeutic treatment of a warm blooded animal, such as man, in particular modulating chemokine receptor (for example CCR5 receptor) activity, said ingredient is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If) or (Ig) (such as (I) or (Ia)), or a pharmaceutically acceptable salt thereof or a solvate thereof (active ingredient), and a pharmaceutically acceptable adjuvant, diluent or carrier. In a further aspect the present invention provides a process for the preparation of said composition which comprises mixing active ingredient with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by topical (such as to the lung and/or airways or to the skin), oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, aerosols, dry powder formulations, tablets, capsules, syrups, powders, granules, aqueous or oily solutions or suspensions, (lipid) emulsions, dispersible

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powders, suppositories, ointments, creams, drops and sterile injectable aqueous or oily solutions or suspensions.

A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between

5 0.1mg and 1g of active ingredient.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection.

Each patient may receive, for example, an intravenous, subcutaneous or intramuscular dose of 0.01mgkg^{-1} to 100mgkg^{-1} of the compound, preferably in the range of 0.1mgkg^{-1} to
10 20mgkg^{-1} of this invention, the composition being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient will receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to
15 4 times per day.

The following illustrate representative pharmaceutical dosage forms containing the compound of formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If) or (Ig) (such as (I) or (Ia)), or a pharmaceutically acceptable salt thereof or a solvent thereof (hereafter Compound X), for therapeutic or prophylactic use in humans:

20 (a)

Tablet I	mg/tablet
Compound X	100
Lactose Ph.Eur.	179
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

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X

- a) (i) $(\text{EtO})_2\text{P}(=\text{O})\text{CH}_2\text{CO}_2\text{Et}$, base; (ii) hydrogenation (e.g. $\text{Pd}(\text{OH})_2$, H_2)
- b) Reduction (e.g. LiAlH_4) (R^3 is H)
- c) (i) Reduction to aldehyde (e.g. DIBAL-H); (ii) R^3MgBr
- d) Oxidation (e.g. Dess-Martin periodinane)
- e) (i) MeONHMe , AlMe_3 ; (ii) Reduction (R^3 is H) or R^3MgBr
- f) Reductive amination ($\text{NaBH}(\text{OAc})_3$, AcOH)
- g) HCl or TFA
- h) Amide formation (acid & coupling reagent or acid halide, base)
- i) Sulfonamide formation (sulfonyl chloride, base)
- j) Reductive amination (aldehyde, $\text{NaBH}(\text{OAc})_3$)

process =