



No. 04-128948- -00010-0000

Fecha: 2008-12-30 11:40:22 Dep. 2020 NUECREACIONE
Tra 11 PATENTELIYI Eje: 379 FASENACIONALI
Act. 329 CTOINFORMACION Folios: 10**FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES**

1	SOLICITUD DE: ☐ Corrección de Error Material ☒ Modificación a una solicitud	
2	SOLICITANTE Nombre: LABORATORIOS ALMIRALL, S.A. Sociedad constituida y existente bajo las leyes de España. Dirección: Ronda del General Mitre 151, 08022 Barcelona, España Domicilio: Barcelona, España Teléfono: 546 09 70 Fax: 249 40 70 E-mail: clientes@camyp.com	IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Número: _____
3	REPRESENTANTE O APODERADO Nombre: Emilio FERRERO Dirección: Carrera 4ª No. 72-35 Teléfono: 347 36 11 Fax: 217 92 11 E-mail: cavelier@cavelier.com	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: 438.019 TP 31.929
4	Número de expediente: <u>04.128.948</u>	
5	Descripción de la corrección o modificación solicitada: Atentamente informo a Su Despacho que la presente solicitud de patente ha sido transferida de la Sociedad ALMIRALL AG domiciliada en Lindenhof, Dorfstrasse 38, 6340 Baar, Suiza a la Sociedad LABORATORIOS ALMIRALL, S.A. , domiciliada en Ronda del General Mitre 151, 08022 Barcelona, España. Por lo tanto solicito la inscripción de este cambio para que el título sea expedido a favor de esta sociedad.	
6	Comprobante de pago No. <u>08-96.959</u> Fecha: <u>15 de diciembre de 2008</u>	
7	Anexos ☒ Comprobante de pago de la tasa por \$103.000, por concepto de modificaciones. ☒ Poderes, si fuere el caso ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.	
8	NOMBRE: EMILIO FERRERO	FIRMA:  C.C. 438.019 de Usaquén T.P.A. 31.929

PODER CON CESION / POWER WITH ASSIGNMENT

Por este Contrato
By this Contract

ALMIRALL AG
Lindenhof, Dorfstrasse 38
CH - 6340 Baar, Suiza

cede, vende y transfiere en toda propiedad y dominio a:
assigns, sells, and transfers in whole ownership and dominion to:

LABORATORIOS ALMIRALL, S.A.
Ronda del General Mitre, 151
08022 Barcelona, España

todos los derechos, títulos e intereses correspondientes a los siguientes derechos de propiedad industrial:
all rights, titles and interests on the following industrial property rights:

Pais	Nº solicitud	Nº concesión
COLOMBIA	04.125.580	
COLOMBIA	04.104.136	
COLOMBIA	04.128.948	
COLOMBIA	03052815	
COLOMBIA	03054214	
COLOMBIA	00052873	28393
COLOMBIA	99060536	27927

El precio de esta transferencia es la cantidad de USD \$1, libremente fijado por las partes y ya recibido por la parte cedente
The price of this transfer is the amount of USD \$1, freely fixed by the parties and already received by the assignor.

Por el presente acto el/los cesionarios aceptan dicha cesión y nombran a
The assignee accepts hereby the said assignment and appoints

Emilio FERRERO tpa 31929, Luz Clemencia de Paez tpa 23555 y Daniel PEÑA tpa 65620
CAVELIER
Edificio Siski
Carrera 4 N° 72-35
Bogotá 8, Colombia

Apoderados verdaderos y legales con poder especial amplio y suficiente para recabar de las oficinas y autoridades nacionales que correspondan en
true and legal agents with special ample and sufficient power for obtaining from
Offices and Authorities in

Colombia

la inscripción de dicha cesión, facultándolos para dar ante las autoridades mencionadas, todos los pasos necesarios al objeto indicado, con la facultad de solicitar nuevos testimonios y devoluciones.
for which purpose authorizes to take before said authorities all the necessary steps to that end, with the faculty to file petitions, effect payments and collect refunds.

Date: 11/06/2007

ASSIGNOR / CEDENTE
ALMIRALL AG

ASSIGNEE / CESIONARIA
LABORATORIOS ALMIRALL, S.A.

Herbert Trachsler Sandro Frei
Members of the Board of Directors

Pio Oriz Pedro Berga
Apoderados

LEG1.00/...



Legalización



XM
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2

Legalización oficial

Por la presente se legaliza oficialmente la autenticidad de la firma al reverso, reconocida en nuestra presencia por

señor Dr. Herbert Trachsler, ciudadano de Wetzikon/ZH, domiciliado en Küsnacht quien conocemos personalmente

y el cual esta inscrito en el Registro Mercantil como vicepresidente del consejo de administracion con poder de firma colectiva a dos de la compania

Almirall AG, con sede en Baar.

Riesbach-Zürich, 21 de enero 2008/mh

B no. 5088-50112

Tarifa: Frs. 30.--

NOTARIAT RIESBACH-ZÜRICH

M. Barmettler, notario sustituto



APOSTILLE
(Convention de La Haye du 5 octobre 1961)

1. País: Confederación Suiza, Cantón de Zurich
Confederação Suíça, Cantão de Zurique
El presente documento público / Este documento público

2. Ha sido firmado por Herv
foi assinado por Mario Barmettler

3. Actuando en calidad de Notar-Stellvertreter
na sua qualidade de

4. Se halla sellado/timbrado con/está previsto do selo/carimbo do (da)
Notariat Riesbach-Zürich

Certificado

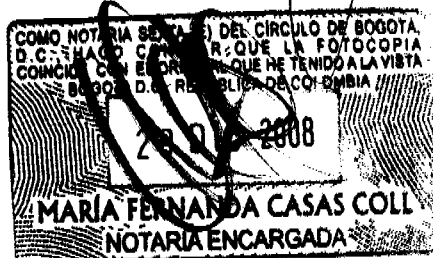
5. En/em 8090 Zurich/Zurique 6. El/no día 23. Jan. 2008

7. Por la Cancillería de Estado del Cantón de Zurich
pela Chancelaria de Estado do Cantão de Zurique

8. Con el número/sob o No. 1537/3008

9. Selo/timbre/selo/carimbo CHF 30.-

S. Giudici



Fr. 4.50



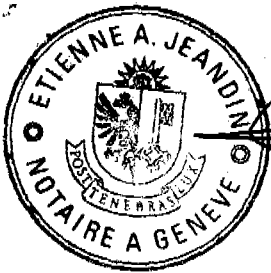
Fr. 4.50

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LEGALISATION OF SIGNATURE

I, Etienne JEANDIN, notary public at Geneva, do hereby certify that the signature of Mr. Sandro FREI which appears on this document, is the authentic signature of the above named Mr. Sandro FREI.
Geneva, 29th January 2008

xm



APOSTILLE

(Convention de la Haye du 5 octobre 1961)

1. Pays: Suisse
2. Le présent acte public a été signé par Etienne A. Jeandin
3. agissant en qualité de NOTAIRE
4. est revêtu du sceau/l'empreinte de

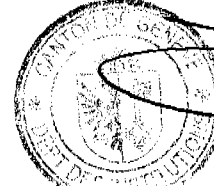
Attesté **30 JAN. 2008**

5. à Genève
6. le

République et Canton de Genève

N° 6373

Sceau / empreinte



Maria RODRIGUES
Commissaire administrative

.../...TIMACION: Yo, SALVADOR CARBALLO CASADO, Notario del Ilustre Colegio Notarial de Catalunya, con residencia en Barcelona, DOY FE:-----

Que reputo legítimas y auténticas las firmas y rúbricas que anteceden, de DON PIO ORVIZ DIAZ y DON PEDRO BERGA MARTI, por ser de mí conocidas, puestas en este documento, en su condición de apoderados de "LABORATORIOS ALMIRALL, S.A." en uso de los poderes que dicha Sociedad les tienen conferidos, los cuales están debidamente inscritos en el Registro Mercantil de Barcelona.-----

Esta legitimación se hace a los efectos previstos en el artículo 207.2 del Reglamento Notarial, en virtud de acta en la que ha quedado debidamente acreditada la representación de dichos señores en nombre de la Sociedad, de esta misma fecha y protocolo, número 517.-----

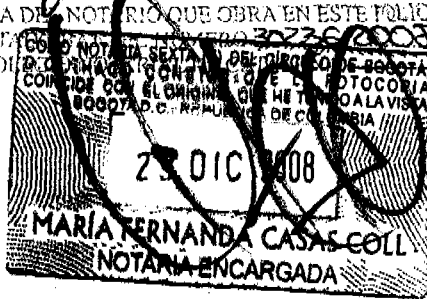
Anotado en mi Libro Indicador del año 2008 (Sección segunda), Asiento 223.-----

En Barcelona, a - 3 ABR. 2008

3 ABR. 2008



EL SIGNO, FIRMA Y RÚBRICA DEL NOTARIO QUE OBRA EN ESTE FOLIO, HA SIDO APOSTILLADO Y ANOTADO EN EL LIBRO REGISTRO DEL COLEGIO NOTARIAL DE CATALUÑA, EN EL NÚMERO 517, DEL 30 DE ENERO DE 2008, EN EL LIBRO REGISTRO DEL COLEGIO NOTARIAL DE CATALUÑA, EN EL NÚMERO 517, DEL 30 DE ENERO DE 2008.



3

COMO NORMA SEXTA (E) DEL CIRCULO DE BOGOTA.
D.C. HAY QUE CONSTAR QUE LA FOTOCOPIA
COINCIDE CON EL ORIGINAL QUE SE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA //

29 DEC 2008

MARIA FERNANDA CASAS COLL
NOTARIA ENCARGADA

011494422

10/2007

8K7127206

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A P O S T I L L E

(Convention de La Haye du 5 octobre 1961)

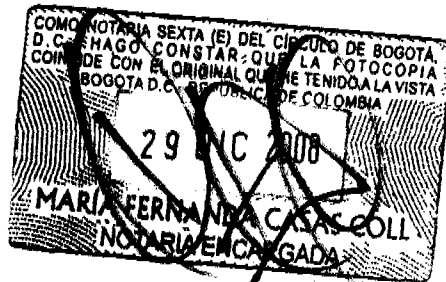
1. País **ESPAÑA**-----
- El presente documento público-----
2. ha sido firmado por D. SALVADOR CARBALLO CASADO-----
3. quien actúa en calidad de Notario, en legitimación de firmas de don Pio Orviz Díaz y don Pedro Berga Martí, en documento de----- poder con cesión, en representación de LABORATORIOS ALMIRALL,-- S.A., conforme Acta, número 617/2008, de fecha 3 de abril de--- 2008.-----
4. y está revestido del sello/timbre de su Notaría de ----- BARCELONA-----

CERTIFICADO

5. en BARCELONA-----
6. el día 16 de abril de 2008.-----
7. por DON ANTONI BOSCH I CARRERA, Censor Segundo de la Junta----- Directiva del Colegio Notarial de Cataluña-----
8. bajo el número: -30236/2008-----
9. Sello/timbre : -----
10. Firma: -----



Antoni Bosch i Carrera
Censor Segundo



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TRADUCCIÓN OFICIAL No. 12.24/08c realizada por Diego Vargas, Traductor Oficial, Resolución No. 0001 de 1999 del Ministerio de Justicia y registrado ante el Ministerio de Relaciones Exteriores de Colombia.

A continuación se traduce la legalización en inglés de un documento por medio de la cual ALMIRALL AG, domiciliada en Lindenhof, Dirfstrasse 38, CH - 6340 Bear, Suiza, cede, vende y transfiere a LABORATORIOS ALMIRALL, S.A., Ronda del General Mitre, 151, 0822 Barcelona, España, todos los derechos, títulos en intereses correspondientes a los derechos de propiedad industrial:

País	No. Solicitud	No. Concesión
COLOMBIA	04.125.580	
COLOMBIA	04.104.136	
COLOMBIA	04.128.948	
COLOMBIA	03052815	
COLOMBIA	03054214	
COLOMBIA	00052873	28393
COLOMBIA	99060536	27927



Y adicionalmente otorga poder a los Doctores Emilio Ferrero, tpa. 31929, Luz Clemencia de Páez, tpa. 23555 y Daniel Peña tpa. 65620 domiciliados en la Carrera 4, No. 72-35, Bogotá Colombia, para la inscripción de la presente cesión.

Fecha: 11/06/2007

CEDENTE

CESIONARIO

ALMIRALL AG

LABORATORIOS ALMIRALL, S.A.

Firma Ilegible Firma Ilegible

Firma Ilegible

Herbert Traschler Sandro Frei

Pio Orviz Pedro Berga

Miembros de la Junta Directiva

Apoderados

Diego F. Vargas
DIEGO F. VARGAS Z.

TRADUCTOR E INTERPRETE OFICIAL
ESPAÑOL - INGLES - INGLES - ESPAÑOL
RES. 0001 DE ENERO 4 DE 1999
MINISTERIO DE JUSTICIA 1

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Legalización Oficial en español de la firma del señor Herbert Träschler en el anterior documento otorgada por M. Barmettler, notario sustituto del Cantón de Zurich, Confederación Suiza.
Sello de Apostille en español expedido por la Confederación Suiza, Cantón de Zurich, y certificada en Zurich, el 23 de enero de 2008 con el No. 1537/2008.

(ANEXO)

LEGALIZACIÓN DE FIRMA

Yo, Etienne JEANDIN, notario público de Ginebra, por el presente certifico que la firma del señor Sandro FREI que aparece en este documento es la firma auténtica del susodicho Sandro FREI.
Ginebra, 29 de enero de 2008.

Sello Notarial Firma Ilegible

Sello de Apostille expedido en Suiza y certificada en Ginebra, el 30 de enero de 2008 con el No. 6373.

MINISTERIO DE
RELACIONES
EXTERIORES
132640
CUBA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

Legalización Oficial en español por parte de Salvador Carballo Casado, Notario de Catalunya, de las firmas de Pío Orviz Díaz y Pedro Berga en el anterior documento. Dado y firmado en Barcelona el 3 de abril de 2008.

NO ASUME
RESPONSABILIDAD
DEL TEXTO
2008 DEC 29 A 11:09
JEFE DE LEGALIZACIONES
BOGOTÁ D.C.

Sello de Apostille en español expedido por España en Barcelona, el 16 de abril de 2008 con el No. 30236/2008.

Es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

DVZ\DVZ\ID-141158\ -002-5

COMO NOTARIO SE CITA EN EL CIRCULO DE BOGOTÁ
D.C. SHAGO NOTARIO DE LA CIUDAD DE BOGOTÁ
CONCORDIA POR LA NACIONALIDAD DE TERCERA VISTA
BOGOTÁ D.C. REPUBLICA DE COLOMBIA
29 DEC 2008
MARÍA FERNANDA CASAS COLL
NOTARIA ENCARGADA

Diego F. Vargas Z.
DIEGO F. VARGAS Z.
TRADUCTOR E INTERPRETE OFICIAL
ESPAÑOL - INGLES - INGLES - ESPAÑOL
RES. 0001 DE ENERO 4 DE 1999
MINISTERIO DE JUSTICIA

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TRADUCCIÓN OFICIAL No. 773/08 DE UN DOCUMENTO ESCRITO EN FRANCÉS, EL CUAL PARA SU IDENTIFICACIÓN SE SELLA CON EL SELLO DEL TRADUCTOR. ESTA ES UNA TRADUCCIÓN OFICIAL EFECTUADA EL DIA 24 DE DICIEMBRE 2008 POR JEAN-JACQUES TURPIN, C.E.: 193849 DE BOGOTÁ, TRADUCTOR E INTÉRPRETE OFICIAL SEGÚN RESOLUCIÓN No. 2680/91 DEL 19 DE DICIEMBRE DE 1991, EXPEDIDA POR EL MINISTERIO DE JUSTICIA DE COLOMBIA.

Autenticaciones que se hallan a continuación de un documento de poder con cesión, conferido en español por **ALMIRALL AG**, domiciliada en Lindenhof, Dorfstrasse 38, CH-6340 Baar, Suiza, quines declaran ceder, vender y transferir a **LABORATORIOS ALMIRALL, S.A.**, domiciliada en Ronda del General Mitre, 151, 08022 Barcelona, España, todos los derechos, títulos e intereses correspondientes a los siguientes derechos de propiedad industrial: (ver lista en documento original).

APOSTILLA

(Convención de La Haya del 5 de octubre de 1961)

1. - País: Suiza

El presente documento público

2. - ha sido firmado por el Señor Étienne A. Jeandin
3. - obrando en calidad de Notario
4. - con sello de su Despacho

CERTIFICADO

5. - En Ginebra
6. - El 30 de enero 2008
7. - República y Cantón de Ginebra
8. - Bajo el número 6373
9. - Sello: Cantón de Ginebra – Departamento de las Instituciones
10. - Firma ilegible de Melissa RODRIGUES, Agente administrativo



Traducción Oficial No. 773/08
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCOIS - ESPANOL
Res. Minjusticia No. 2680/91

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APOSTILLA

(Convención de La Haya del 5 de octubre de 1961)

1. - País: Confederación Suiza, Cantón de Zurich
- El presente documento público
2. - ha sido firmado por el Señor Mario Barmettler
3. - obrando en calidad de Notario
4. - con sello de su Despacho en Riesbach-Zurich

CERTIFICADO

5. - En 8090 Zurich
6. - El 23 de enero 2008
7. - Por la Cancillería de Estado del Cantón de Zurich
8. - Bajo el número 1537/2008
9. - Sello y estampilla por valor de 30CHF
10. - Firma ilegible de S. Gludici

APOSTILLA

(Convención de La Haya del 5 de octubre de 1961)

1. - País: ESPAÑA
- El presente documento público
2. - ha sido firmado por el Señor D. SALVADOR CARBALLO
3. - obrando en calidad de Notario
4. - con sello de su Notaria en Barcelona

CERTIFICADO

5. - En Barcelona
6. - El 16 de abril 2008
7. - Por DON ANTONI BOSCH I CARRERA, Censor Segundo de la Junta Directiva del Colegio Notarial de Cataluña



Traducción Oficial No. 773/08
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCOIS - ESPANOL
Res. Minjusticia No. 2680/91

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- 8. - Bajo el número 30236/2008 ✓
- 9. - Sello y estampilla por valor de 30.15 Euro
- 10. - Firma ilegible de Antoni Bosch I. Carrera

Es traducción fiel y completa de la cual se deja copia en los archivos de esta oficina para confrontación y a la cual me remito.

Traducción oficial No. 773/08.

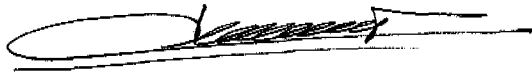
COLO : 06734-843-002-5

Traductor: Jean-Jacques Turpin

Bogotá, D.C., 24 de diciembre 2008.

Traducción Oficial No.
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCOIS - ESPAROL
Res. Minjusticia No. 2680/91

773/08



MINISTERIO DE RELACIONES EXTERIORES
RECIBO LEGALIZACION
2008

132641
COPIA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

MINISTERIO DE
RELACIONES
EXTERIORES

2008 DEC 26 A 11:11
JEFE DE LEGALIZACIONES
BOGOTA D.C.

NO ASUME
RESPONSABILIDAD
DEL TEXTO

COMO NOTARIA SEXTA (E) DEL CIRCULO DE BOGOTA
D.C. EN ACCION CONSTA QUE LA FOTOCOPIA
COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. 29 DE DICIEMBRE DE 2008
MARIA FERNANDA CUEVAS COLL
NOTARIA ENCARGADA

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 96,959
FECHA : DICIEMBRE 15 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 04-128948- -00010-0000

Fecha: 2008-12-30 11:40:22 Dep. 2020 NUECREACION
Tra. 11 PATENTE/II Lve: 379 FASENACIONALII
Act. 329 C/OINFORMACION Folios: 10

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	102218944	15/12/2008	19,210,000.00

***** CONCEPTO *****

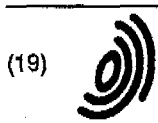
CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICA	
12		MARCAS Y LEMAS COMERCIALES	103,000.00
		TOTAL :	\$ 103,000.00

SON: CIENTO TRES MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

06734-843-003-3



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) EP 0 930 298 A1

(12)

EUROPEAN PATENT APPLICATION

published in accordance with Art. 158(3) EPC

(43) Date of publication:
21.07.1999 Bulletin 1999/29

(21) Application number: 97933037.0

(22) Date of filing: 28.07.1997

(51) Int. Cl.⁶: C07D 211/46, C07D 211/58,
C07D 213/75, C07D 401/06,
C07D 405/06, C07D 409/06,
A61K 31/445, C07C 59/56

(86) International application number:
PCT/JP97/02600

(87) International publication number:
WO 98/05641 (12.02.1998 Gazette 1998/06)

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC
NL PT SE
Designated Extension States:
LT LV RO SI

(30) Priority: 01.08.1996 JP 21943696
21.02.1997 JP 5397997

(71) Applicant:
BANYU PHARMACEUTICAL CO., LTD.
Chuo-ku, Tokyo 103-8416 (JP)

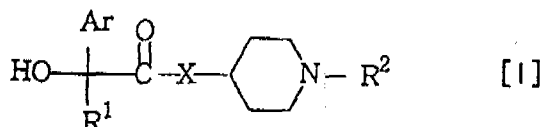
(72) Inventors:
• TSUCHIYA, Yoshimi, Banyu Pharmaceutical Co.,
Ltd.
Ibaraki 300-2611 (JP)
• NOMOTO, Takashi, Banyu Pharmaceutical Co.,
Ltd.
Menuma-machi, Osato-gun, Saltama 360-0214
(JP)

• OHSAWA, Hirokazu, Banyu Pharmaceutical Co.,
Ltd.
Ibaraki 300-2611 (JP)
• KAWAKAMI, Kumiko, Banyu Pharmaceutical
Co., Ltd.
Ibaraki 300-2611 (JP)
• OHWAKI, Kenji, Banyu Pharmaceutical Co., Ltd.
Ibaraki 300-2611 (JP)
• NISHIKIBE, Masaru, Banyu Pharmaceutical Co.,
Ltd.
Ibaraki 300-2611 (JP)

(74) Representative:
Weisert, Annekäte, Dipl.-Ing. Dr.-Ing.
Patentanwälte
Kraus Weisert & Partner
Thomas-Wimmer-Ring 15
80539 München (DE)

(54) FLUORINATED 1,4-DISUBSTITUTED PIPERIDINE DERIVATIVES

(57) This invention relates to novel fluorine-containing 1,4-disubstituted piperidine derivatives represented by a general formula [I]



and pharmaceutically acceptable salts thereof,
[wherein:

Ar represents an aryl group or a hetero-aryl group having 1 to 2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulfur (any 1 to 3 hydrogen atoms on the ring of said aryl or heteroaryl group may be substituted with lower alkyl, etc.);

R¹ represents C₃-C₆ cycloalkyl whose any 1-4 hydrogen atoms may be substituted with fluorine atoms(s);

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R² represents C₅-C₁₅ saturated or unsaturated aliphatic hydrocarbon groups whose any 1 to 6 hydrogen atoms may be substituted with fluorine atom(s), aralkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl group having 1 to 2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulfur (optionally any 1 to 3 hydrogen atoms on the ring in said aralkyl, arylalkenyl, hetero-arylalkyl or heteroarylalkenyl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxy, carbonyl, halogen, lower alkoxy or amino, etc. ; and X stands for O or NH, provided that at least either one of R¹ and R² contains one or more fluorine atoms].

The compounds of the present invention have selective antagonistic activity for muscarinic M₃ receptors, and exhibit excellent oral activity, duration of action and pharmacokinetics, so that they have little side effects and are safe and effective. Therefore they are useful for treatment or prophylaxis of respiratory diseases, urinary diseases and digestive diseases.

Description

Technical Field

[0001] This invention relates to novel fluorine-containing 1,4-disubstituted piperidine derivatives, processes for preparing them, pharmaceuticals containing them and their use as medicines, especially in the treatment or prophylaxis of various diseases of the respiratory, urinary and digestive systems.

Background Art

[0002] Antagonism to muscarinic receptors are known to cause bronchodilation, gastrointestinal hypanakinesis, gastric hyposecretion, dry mouth, mydriasis, suppression of bladder contraction, hypohidrosis, tachycardia and the like ["Basic and Clinical Pharmacology", 4th ed., APPLETON & LANGE, pp. 83-92 (1989); Drug News & Perspective, 5(6), pp. 345-352 (1992)].

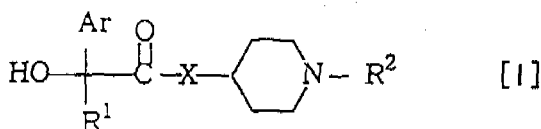
[0003] It has been made clear that there are at least three subtypes of muscarinic receptors; the M₁ receptors being present mainly in the brain, the M₂ receptors mainly in the heart, and the M₃ receptors, on smooth muscles and glandular tissues. Whereas, all of the large number of compounds heretofore known to exhibit antagonism to muscarinic receptors non-selectively antagonize the three subtypes of muscarinic receptors. Consequently, attempts to use these compounds as therapeutic or prophylactic agents for diseases of the respiratory system have caused undesirable side effects such as dry mouth, nausea and mydriasis. Still in addition, particularly serious side effects associated with the central nervous system, such as dementia, attributable to the M₁ receptors and those associated with the heart, such as tachycardia mediated by the M₂ receptors pose problems and their solution is strongly demanded.

[0004] We have disclosed, as a drug meeting the demand, 1,4-disubstituted piperidine derivatives (see: PCT WO96/33973). However, creation of even more excellent drug has been in demand.

[0005] An object of the present invention is to create even a better drug than said known compounds, whereby to provide pharmaceuticals exhibiting highly selective antagonism to M₃ receptors and minimizing adverse side effect and which, therefore, provide safe and effective pharmaceuticals for treatment or prophylaxis of diseases associated with muscarine M₃ receptors, eg., such respiratory diseases as chronic obstructive pulmonary diseases, chronic bronchitis, asthma and rhinitis; digestive diseases such as irritable bowel syndrome, convulsive colitis, diverticulitis and pain accompanying contraction of smooth muscles of the digestive system; urinary disorders like urinary incontinence and frequency in neurogenic pollakiuria, neurogenic bladder, nocturnal enuresis, unstable bladder, cystospasm and chronic cystitis; and motion sickness.

Disclosure of the Invention

[0006] According to the present invention, there are provided novel fluorine-containing 1,4-disubstituted piperidine derivatives of the general formula [I]



and pharmaceutically acceptable salts thereof, wherein:

Ar represents an aryl group or a heteroaryl group having 1 to 2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulfur (any 1 to 3 hydrogen atoms on the ring of said aryl or heteroaryl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxy, amino or lower alkylamino);

R¹ represents C₃-C₆ cycloalkyl whose any 1-4 hydrogen atoms may be substituted with fluorine atom(s);

R² represents C₅-C₁₅ saturated or unsaturated aliphatic hydrocarbon groups whose any 1 to 6 hydrogen atoms may be substituted with fluorine atom(s), aralkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl group having 1 to 2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulfur (optionally any 1 to 3 hydrogen atoms on the ring in said aralkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxy, amino or lower alkylamino); and

X stands for O or NH,
provided that at least either one of R¹ and R² contains one or more fluorine atoms.

[0007] The compounds of the above formula [I] which are provided by the present invention have potent and selective antagonistic activity for muscarinic M₃ receptors, and exhibit excellent oral activity, duration of action and pharmacokinetics, so that they have little side effects and are safe. Hence, they are very useful in the treatment or prophylaxis of diseases such respiratory diseases as chronic obstructive pulmonary diseases, chronic bronchitis, asthma and rhinitis; digestive diseases such as irritable bowel syndrome, convulsive colitis, diverticulitis and pain accompanying contraction of smooth muscles of the digestive system; urinary disorders like urinary incontinence and frequency in neurogenic polakiuria, neurogenic bladder, nocturnal enuresis, unstable bladder, cystospasm and chronic cystitis; and motion sickness.

[0008] Hereinafter the meaning of the technical terms used in the present specification are elucidated and the invention is explained in further details.

[0009] "An aryl group (any 1 to 3 hydrogen atoms on the ring in said aryl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxy, carbonyl, halogen, lower alkoxy, amino or lower alkylamino)" signifies a substituted or unsubstituted C₆-C₁₁ aryl group, examples of which including unsubstituted phenyl group, naphthyl group or those containing the above-named substituent(s).

[0010] As examples of "a heteroaryl group having 1-2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulfur (any 1 to 3 hydrogen atoms on the ring of said heteroaryl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxy, carbonyl, halogen, lower alkoxy, amino or lower alkylamino)", unsubstituted 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiazolyl, 4-thiazolyl, 2-thienyl, 3-thienyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, 2-furyl, 3-furyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 2-pyrazinyl, 3-pyridazinyl, 4-pyridazinyl, 2-quinolyl, 2-benzothienyl and 2-indolyl group; and those which are substituted with the above-named substituents can be named.

[0011] Also examples of "C₃-C₆ cycloalkyl whose 1-4 hydrogen atoms may be substituted with fluorine atom(s)" include: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-fluorocyclopropyl, 1-fluorocyclobutyl, 1-fluorocyclopentyl, 1-fluorocyclohexyl, 2-fluorocyclopropyl, 2-fluorocyclobutyl, 2-fluorocyclopentyl, 2-fluorocyclohexyl, 3-fluorocyclobutyl, 3-fluorocyclopentyl, 3-fluorocyclohexyl, 4-fluorocyclohexyl, 2,2-difluorocyclopropyl, 2,2-difluorocyclobutyl, 2,2-difluorocyclopentyl, 2,2-difluorocyclohexyl, 3,3-difluorocyclobutyl, 3,3-difluorocyclopentyl, 3,3-difluorocyclohexyl, 4,4-difluorocyclohexyl, 3,3,4,4-tetrafluorocyclopentyl, 3,3,4,4-tetrafluorocyclohexyl, 2,3-difluorocyclobutyl, 2,3-difluorocyclopentyl, 3,4-difluorocyclopentyl, 2,3-difluorocyclohexyl, 3,4-difluorocyclohexyl, 2,2,3,3-tetrafluorocyclobutyl and 2,2,3,3-tetrafluorocyclopentyl groups.

[0012] Examples of "C₅-C₁₅ saturated or unsaturated aliphatic hydrocarbon groups whose any 1 to 6 hydrogen atoms may be substituted with fluorine atoms" include C₅-C₁₅ straight chain or branched alkyl, alkenyl, alkynyl, cycloalkylidenealkyl; cycloalkylalkyl, cyclo-alkylalkenyl or cycloalkylalkynyl in which optionally hydrogen atom(s) on the cycloalkyl ring may be substituted with lower alkyl; and cycloalkenylalkyl or cyclo-alkenylalkenyl in which optionally hydrogen atom(s) on the cycloalkenyl ring may be substituted with lower alkyl; and those whose any 1 to 6 hydrogen atom(s) are substituted with fluorine atom(s).

[0013] Specific examples of such aliphatic hydrocarbon groups include:

unsubstituted or fluorine-substituted alkyl groups such as 2-methylbutyl, 3-methylbutyl, pentyl, neopentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, hexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2,4-dimethylpentyl, 2-ethylhexyl, 4,5-dimethylhexyl, 4,4-dimethylpentyl, heptyl, 4-methylheptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, 3-fluoromethylbutyl, 1-fluoropentyl, 4-fluoropentyl, 5-fluoropentyl, 1,1-difluoropentyl, 4,4-difluoropentyl, 5,5,5-trifluoropentyl, 1,1,4,4-tetrafluoropentyl, 1,1,5,5-pentafluoropentyl, 1-fluorohexyl, 5-fluorohexyl, 6-fluorohexyl, 1,1-difluorohexyl, 5,5-difluorohexyl, 6,6,6-trifluorohexyl, 1,1,5,5-tetrafluorohexyl, 1,1,6,6,6-pentafluorohexyl, 1-fluoro-4-methylpentyl, 2-fluoro-4-methylpentyl, 3-fluoro-4-methylpentyl, 4-fluoro-4-methylpentyl, 4-fluoromethylpentyl, 1,1-difluoro-4-methylpentyl, 4-trifluoromethylpentyl, 5,5,5-trifluoro-4-trifluoro-methylpentyl, 1,1-difluoro-4-trifluoromethylpentyl, 1,1,5-trifluoro-4-methylpentyl, 1-fluoro-4-methylhexyl, 4-fluoro-4-methylhexyl, 5-fluoro-4-methylhexyl, 6-fluoro-4-methylhexyl, 1,1-difluoro-4-methylhexyl, 5,5-difluoro-4-methylhexyl, 4-trifluoromethylhexyl, 6,6,6-trifluoro-4-methylhexyl, 6,6,6-trifluoro-4-trifluoro-methylhexyl, 1,1-difluoro-4-trifluoromethylhexyl and 1,1-difluoro-6,6,6-trifluoro-4-methylhexyl;

unsubstituted or fluorine-substituted alkenyl groups such as 3-methyl-2-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-pentenyl, 3-methyl-3-pentenyl, 4-methyl-2-pentenyl, 4-methyl-3-pentenyl, 4-methyl-4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 4-methyl-2-hexenyl, 4-methyl-3-hexenyl, 4-methyl-4-hexenyl, 5-methyl-2-hexenyl, 5-methyl-3-hexenyl, 5-methyl-4-hexenyl, 5-methyl-2-heptenyl, 5-methyl-3-heptenyl, 5-methyl-4-heptenyl, 5-methyl-5-heptenyl, 3,4-dimethyl-2-pentenyl, 3,4-dimethyl-3-pentenyl, 4,5-dimethyl-2-hexenyl, 4,5-dimethyl-3-hexenyl, 4,5-dimethyl-4-hexenyl, octenyl, nonenyl, decenyl, undecenyl, dodecenyl, tridecenyl, tetradecenyl, pentadecenyl, 1-

X stands for O or NH,

provided that at least either one of R¹ and R² contains one or more fluorine atoms.

[0007] The compounds of the above formula [I] which are provided by the present invention have potent and selective antagonistic activity for muscarinic M₃ receptors, and exhibit excellent oral activity, duration of action and pharmacokinetics, so that they have little side effects and are safe. Hence, they are very useful in the treatment or prophylaxis of diseases such as respiratory diseases as chronic obstructive pulmonary diseases, chronic bronchitis, asthma and rhinitis; digestive diseases such as irritable bowel syndrome, convulsive colitis, diverticulitis and pain accompanying contraction of smooth muscles of the digestive system; urinary disorders like urinary incontinence and frequency in neurogenic pollakiuria, neurogenic bladder, nocturnal enuresis, unstable bladder, cystospasm and chronic cystitis; and motion sickness.

[0008] Hereinafter the meaning of the technical terms used in the present specification are elucidated and the invention is explained in further details.

[0009] "An aryl group (any 1 to 3 hydrogen atoms on the ring in said aryl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxy, carbonyl, halogen, lower alkoxy, amino or lower alkylamino)" signifies a substituted or unsubstituted C₆-C₁₁ aryl group, examples of which including unsubstituted phenyl group, naphthyl group or those containing the above-named substituent(s).

[0010] As examples of "a heteroaryl group having 1-2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulfur (any 1 to 3 hydrogen atoms on the ring of said heteroaryl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxy, carbonyl, halogen, lower alkoxy, amino or lower alkylamino)", unsubstituted 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiazolyl, 4-thiazolyl, 2-thienyl, 3-thienyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, 2-furyl, 3-furyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 2-pyrazinyl, 3-pyridazinyl, 4-pyridazinyl, 2-quinolyl, 2-benzothienyl and 2-indolyl group; and those which are substituted with the above-named substituents can be named.

[0011] Also examples of "C₃-C₆ cycloalkyl whose 1-4 hydrogen atoms may be substituted with fluorine atom(s)" include: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-fluorocyclopropyl, 1-fluorocyclobutyl, 1-fluorocyclopentyl, 1-fluorocyclohexyl, 2-fluorocyclopropyl, 2-fluorocyclobutyl, 2-fluorocyclopentyl, 2-fluorocyclohexyl, 3-fluorocyclobutyl, 3-fluorocyclopentyl, 3-fluorocyclohexyl, 4-fluorocyclohexyl, 2,2-difluorocyclopropyl, 2,2-difluorocyclobutyl, 2,2-difluorocyclopentyl, 2,2-difluorocyclohexyl, 3,3-difluorocyclobutyl, 3,3-difluorocyclopentyl, 3,3-difluorocyclohexyl, 4,4-difluorocyclohexyl, 3,3,4,4-tetrafluorocyclopentyl, 3,3,4,4-tetrafluorocyclohexyl, 2,3-difluorocyclobutyl, 2,3-difluorocyclopentyl, 3,4-difluorocyclopentyl, 2,3-difluorocyclohexyl, 3,4-difluorocyclohexyl, 2,2,3,3-tetrafluorocyclobutyl and 2,2,3,3-tetrafluorocyclopentyl groups.

[0012] Examples of "C₅-C₁₅ saturated or unsaturated aliphatic hydrocarbon groups whose any 1 to 6 hydrogen atoms may be substituted with fluorine atoms" include C₅-C₁₅ straight chain or branched alkyl, alkenyl, alkynyl, cycloalkylidenealkyl; cycloalkylalkyl, cycloalkylalkenyl or cycloalkylalkynyl in which optionally hydrogen atom(s) on the cycloalkyl ring may be substituted with lower alkyl; and cycloalkenylalkyl or cycloalkenylalkenyl in which optionally hydrogen atom(s) on the cycloalkenyl ring may be substituted with lower alkyl; and those whose any 1 to 6 hydrogen atom(s) are substituted with fluorine atom(s).

[0013] Specific examples of such aliphatic hydrocarbon groups include:

unsubstituted or fluorine-substituted alkyl groups such as 2-methylbutyl, 3-methylbutyl, pentyl, neopentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, hexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2,4-dimethylpentyl, 2-ethylhexyl, 4,5-dimethylhexyl, 4,4-dimethylpentyl, heptyl, 4-methylheptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, 3-fluoromethylbutyl, 1-fluoro-pentyl, 4-fluoropentyl, 5-fluoropentyl, 1,1-difluoro-pentyl, 4,4-difluoropentyl, 5,5,5-trifluoropentyl, 1,1,4,4-tetrafluoropentyl, 1,1,5,5,5-pentafluoropentyl, 1-fluorohexyl, 5-fluorohexyl, 6-fluorohexyl, 1,1-difluorohexyl, 5,5-difluorohexyl, 6,6,6-trifluorohexyl, 1,1,5,5,5-tetrafluorohexyl, 1,1,6,6,6-pentafluorohexyl, 1-fluoro-4-methylpentyl, 2-fluoro-4-methylpentyl, 3-fluoro-4-methylpentyl, 4-fluoro-4-methylpentyl, 4-fluoromethylpentyl, 1,1-difluoro-4-methylpentyl, 4-trifluoromethylpentyl, 5,5,5-trifluoro-4-trifluoro-methylpentyl, 1,1-difluoro-4-trifluoromethylpentyl, 1,1,5-trifluoro-4-methylpentyl, 1-fluoro-4-methylhexyl, 4-fluoro-4-methylhexyl, 5-fluoro-4-methylhexyl, 6-fluoro-4-methylhexyl, 1,1-difluoro-4-methylhexyl, 5,5-difluoro-4-methylhexyl, 4-trifluoromethylhexyl, 6,6,6-trifluoro-4-methylhexyl, 6,6,6-trifluoro-4-trifluoro-methylhexyl, 1,1-difluoro-4-trifluoromethylhexyl and 1,1-difluoro-6,6,6-trifluoro-4-methylhexyl;

unsubstituted or fluorine-substituted alkenyl groups such as 3-methyl-2-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-pentenyl, 3-methyl-3-pentenyl, 4-methyl-2-pentenyl, 4-methyl-3-pentenyl, 4-methyl-4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 4-methyl-2-hexenyl, 4-methyl-3-hexenyl, 4-methyl-4-hexenyl, 5-methyl-2-hexenyl, 5-methyl-3-hexenyl, 5-methyl-4-hexenyl, 5-methyl-2-heptenyl, 5-methyl-3-heptenyl, 5-methyl-4-heptenyl, 5-methyl-5-heptenyl, 3,4-dimethyl-2-pentenyl, 3,4-dimethyl-3-pentenyl, 4,5-dimethyl-2-hexenyl, 4,5-dimethyl-3-hexenyl, 4,5-dimethyl-4-hexenyl, octenyl, nonenyl, decenyl, undecenyl, dodecenyl, tridecenyl, tetradecenyl, pentadecenyl, 1-

fluoro-4-methyl-3-pentenyl, 2-fluoro-4-methyl-3-pentenyl, (E)-4-fluoro-methyl-3-pentenyl, (Z)-4-fluoromethyl-3-pentenyl, 1,1-difluoro-4-methyl-3-pentenyl, 2,2-difluoro-4-methyl-3-pentenyl, (E)-4-trifluoromethyl-3-pentenyl, (Z)-4-trifluoromethyl-3-pentenyl, (E)-1,1-difluoro-4-trifluoro-methyl-3-pentenyl, (Z)-1,1-difluoro-4-trifluoromethyl-3-pentenyl, 5,5,5-trifluoro-4-trifluoromethyl-3-pentenyl, 1-fluoro-4-methyl-2-pentenyl, 4-fluoro-4-methyl-2-pentenyl, 4-fluoromethyl-2-pentenyl, 1,1-difluoro-4-methyl-2-pentenyl, 4-trifluoromethyl-2-pentenyl, 4-fluoro-1,1-difluoro-4-methyl-2-pentenyl, 1,1-difluoro-4-trifluoro-methyl-2-pentenyl, 1-fluoro-4-methyl-4-pentenyl, 2-fluoro-4-methyl-4-pentenyl, 3-fluoro-4-methyl-4-pentenyl, 4-fluoromethyl-4-pentenyl, 1,1-difluoro-4-methyl-4-pentenyl, 2,2-difluoro-4-methyl-4-pentenyl, 3,3-difluoro-4-methyl-4-pentenyl, 4-trifluoromethyl-4-pentenyl, 1,1-difluoro-4-trifluoromethyl-4-pentenyl, 1,1,3,3-tetrafluoro-4-methyl-4-pentenyl, 1-fluoro-4-methyl-3-hexenyl, 2-fluoro-4-methyl-3-hexenyl, 4-fluoro-methyl-3-hexenyl, 6-fluoro-4-methyl-3-hexenyl, 4-trifluoromethyl-3-hexenyl, 1,1-difluoro-4-methyl-3-hexenyl, 2,2-difluoro-4-methyl-3-hexenyl, 4-trifluoromethyl-3-hexenyl, 5,5-difluoromethyl-3-hexenyl, 6,6,6-trifluoro-4-methyl-3-hexenyl, 1,1-difluoro-4-trifluoromethyl-3-hexenyl, 1,1,1-difluoro-6,6,6-trifluoromethyl-3-hexenyl and 6,6,6-trifluoro-4-trifluoromethyl-3-hexenyl;

2-pentynyl, 3-pentynyl, 4-pentynyl, 4-methyl-2-pentynyl, octynyl, nonynyl, decynyl, undecynyl, dodecynyl, tridecynyl, tetradecynyl and pentadecynyl, and those alkynyl groups in which optionally any 1 to 6 hydrogen atoms are substituted with fluorine atom(s);

unsubstituted and fluorine-substituted cyclo-alkylalkyl groups in which any of hydrogen atom(s) on the cycloalkyl ring may be substituted with lower alkyl, such as cyclopropylethyl, cyclopropylpropyl, cyclo-propylbutyl, cyclopropylpentyl, cyclopropylhexyl, cyclo-propylheptyl, cyclobutylmethyl, cyclobutylethyl, cyclo-butylpropyl, cyclobutylbutyl, cyclobutylpentyl, cyclo-pentylmethyl, cyclopentylethyl, cyclopentylpropyl, cyclopentylbutyl, cyclohexylmethyl, cyclohexylethyl, cyclohexylpropyl, cyclohexylbutyl, cycloheptylmethyl, cycloheptylethyl, cycloheptylpropyl, cycloheptylbutyl, cyclooctylmethyl, cyclooctylethyl, cyclooctylpropyl, cyclooctylbutyl, 1-methylcyclopentylmethyl, 2-methyl-cyclopentylmethyl, 3-methylcyclopentylmethyl, 1-ethyl-cyclopentylmethyl, 2-ethylcyclopentylmethyl, 3-ethyl-cyclopentylmethyl, 2-cyclopentylethyl, 2-(1-methylcyclopentyl)ethyl, 2-(2-methylcyclopentyl)ethyl, 2-(3-methylcyclopentyl)ethyl, 2-(1-ethylcyclopentyl)ethyl, 2-(2-ethylcyclopentyl)ethyl, 2-(3-ethylcyclopentyl)ethyl, 1-methylcyclohexylmethyl, 2-methylcyclohexylmethyl, 3-methylcyclohexylmethyl, 4-methylcyclohexylmethyl, 1-ethylcyclohexylmethyl, 2-ethylcyclohexylmethyl, 3-ethylcyclohexylmethyl, 4-ethylcyclohexylmethyl, cyclo-hexylethyl, 2-(1-methylcyclohexyl)ethyl, 2-(2-methyl-cyclohexyl)ethyl, 2-(3-methylcyclohexyl)ethyl, 2-(4-methylcyclohexyl)ethyl, 2-(1-ethylcyclohexyl)ethyl, 2-(2-ethylcyclohexyl)ethyl, 2-(3-ethylcyclohexyl)ethyl, 2-(4-ethylcyclohexyl)ethyl, 1-methylcycloheptylmethyl, 2-methylcycloheptylmethyl, 3-methylcycloheptylmethyl, 4-methylcycloheptylmethyl, 1-ethylcycloheptylmethyl, 2-ethylcycloheptylmethyl, 3-ethylcycloheptylmethyl, 4-ethylcycloheptylmethyl, 2-cycloheptylethyl, 2-(1-methylcycloheptyl)ethyl, 2-(2-methylcycloheptyl)ethyl, 2-(3-methylcycloheptyl)ethyl, 2-(4-methylcycloheptyl)ethyl, 2-(1-ethylcycloheptyl)ethyl, 2-(2-ethylcycloheptyl)ethyl, 2-(3-ethylcycloheptyl)ethyl, 2-(4-ethylcycloheptyl)ethyl, 1-methylcyclooctylmethyl, 2-methyl-cyclooctylmethyl, 3-methylcyclooctylmethyl, 4-methyl-cyclooctylmethyl, 5-methylcyclooctylmethyl, 1-ethyl-cyclooctylmethyl, 2-ethylcyclooctylmethyl, 3-ethyl-cyclooctylmethyl, 4-ethylcyclooctylmethyl, 5-ethyl-cyclooctylmethyl, 2-(1-methylcyclooctyl)ethyl, 2-(2-methylcyclooctyl)ethyl, 2-(3-methylcyclooctyl)ethyl, 2-(4-methylcyclooctyl)ethyl, 2-(5-methylcyclooctyl)ethyl, 2-(1-ethylcyclooctyl)ethyl, 2-(2-ethylcyclooctyl)ethyl, 2-(3-ethylcyclooctyl)ethyl, 2-(4-ethylcyclooctyl)ethyl, 2-(5-ethylcyclooctyl)ethyl, 1-fluoro-1-cyclohexylmethyl, 2-fluorocyclohexylmethyl, 3-fluorocyclohexylmethyl, 4-fluorocyclohexylmethyl, 1,1-difluoro-1-cyclohexylmethyl, 2,2-difluorocyclohexylmethyl, 3,3-difluorocyclohexyl-methyl, 4,4-difluorocyclohexylmethyl, 1-fluoro-1-cyclo-heptylmethyl, 2-fluorocycloheptylmethyl, 3-fluorocyclo-heptylmethyl, 4-fluorocycloheptylmethyl, 1,1-difluoro-1-cycloheptylmethyl, 2,2-difluorocycloheptylmethyl, 3,3-difluorocycloheptylmethyl, 4,4-difluorocycloheptylmethyl, 1-fluoro-1-(3-methylcyclohexyl)methyl, 2-fluoro-3-methylcyclohexylmethyl, 3-fluoro-3-methylcyclohexylmethyl, 4-fluoro-3-methylcyclohexylmethyl, 1,1-difluoro-1-(3-methylcyclohexyl)methyl, 2,2-difluoro-3-methylcyclohexylmethyl, 3-trifluoromethylcyclohexylmethyl, 4,4-difluoro-3-methylcyclohexylmethyl, 1-fluoro-2-cyclopentylethyl, 2-(2-fluorocyclopentyl)ethyl, 2-(3-fluorocyclopentyl)ethyl, 1,1-difluoro-2-cyclopentyl-ethyl, 2-(2,2-difluorocyclopentyl)ethyl, 2-(3,3-difluorocyclopentyl)ethyl, 1,1-difluoro-2-(2,2-difluoro-cyclopentyl)ethyl and 1,1-difluoro-2-(3,3-difluorocyclopentyl)ethyl;

cycloalkylidenealkyl groups such as cyclopropylideneethyl, cyclopropylidenepropyl, cyclopropylidenebutyl, cyclopropylidenepentyl, cyclobutylideneethyl, cyclobutylidenepropyl, cyclobutylidenebutyl, cyclo-butylidenepentyl, cyclopentylideneethyl, cyclopentylidenepropyl, cyclopentylidenebutyl, cyclohexylideneethyl, cyclohexylidenepropyl, cyclohexylidenebutyl, cycloheptylideneethyl, cycloheptylidenepropyl, cycloheptylidenepentyl, cyclooctylideneethyl, cyclooctylidenepropyl, cyclooctylidenebutyl and cyclo-octylidenepentyl, and those cycloalkylidene alkyl groups in which optionally any 1 to 6 hydrogen atoms are substituted with fluorine atom(s);

cycloalkylalkenyl groups in which any of hydrogen atom(s) on the cycloalkyl ring may be substituted with lower alkyl, such as cyclopropylpropenyl, cyclopropylbutenyl, cyclopropylpentenyl, cyclopropylhexenyl, cyclopropylheptenyl, cyclobutylpropenyl, cyclobutylbutenyl, cyclobutylpentenyl, cyclopentylpropenyl, cyclopentylbutenyl,

cyclopentylpropenyl, cyclohexylpropenyl, cyclohexylbutenyl, cyclohexylpentenyl, cycloheptylpropenyl and cyclooctylpropenyl, and those cycloalkylalkenyl groups in which optionally any 1 to 6 hydrogen atoms are substituted with fluorine atom(s);

cycloalkylalkynyl groups in which any of hydrogen atom(s) on the cycloalkyl ring may be substituted with lower alkyl, such as cyclopropylpropynyl, cyclopropylbutynyl, cyclopropylpentynyl, cyclopropyl-hexynyl, cyclopropylheptyn-
 5 nyl, cyclobutylpropynyl, cyclobutylbutynyl, cyclobutylpentynyl, cyclopentylpropynyl, cyclopentylbutynyl, cyclopentylpentynyl, cyclohexylpropynyl, cyclohexylbutynyl and cyclohexylpentynyl, and those cycloalkylalkynyl groups in which optionally any 1 to 6 hydrogen atoms are substituted with fluorine atom(s);

cycloalkenylalkyl groups in which any optional hydrogen atom(s) on the cycloalkenyl ring may be replaced by a
 10 lower alkyl group(s), such as cyclopropenylethyl, cyclopropenylpropyl, cyclopropenylbutyl, cyclopropenylpentyl, cyclopropenylhexyl, cyclopropenylheptyl, cyclobutenylmethyl, cyclobutenylethyl, cyclobutenylpropyl, cyclopentenylmethyl, cyclohexenylmethyl, cyclohexenylethyl, cycloheptenylmethyl, cycloheptenylethyl, cyclooctenylmethyl, cyclooctenylethyl, (1-methyl-2-cyclopentenyl)methyl, (1-methyl-3-cyclopentenyl)methyl, (2-methyl-1-cyclopentenyl)methyl, (2-methyl-2-cyclopentenyl)methyl, (2-methyl-3-cyclopentenyl)methyl, (5-methyl-2-cyclopentenyl)methyl, (5-methyl-1-cyclopentenyl)methyl, (3-methyl-1-cyclopentenyl)methyl, (3-methyl-2-cyclopentenyl)methyl, (3-methyl-3-cyclopentenyl)methyl, (4-methyl-2-cyclopentenyl)methyl, (4-methyl-1-cyclopentenyl)methyl, (1-methyl-2-cyclohexenyl)methyl, (1-methyl-3-cyclohexenyl)methyl, (2-methyl-1-cyclohexenyl)methyl, (2-methyl-2-cyclohexenyl)methyl, (2-methyl-3-cyclohexenyl)methyl, (6-methyl-3-cyclohexenyl)methyl, (6-methyl-2-cyclohexenyl)methyl, (6-methyl-1-cyclohexenyl)methyl, (3-methyl-1-cyclohexenyl)methyl, (3-methyl-2-cyclohexenyl)methyl, (3-methyl-3-cyclohexenyl)methyl, (5-methyl-3-cyclohexenyl)methyl, (5-methyl-2-cyclohexenyl)methyl, (5-methyl-1-cyclohexenyl)methyl, (4-methyl-1-cyclohexenyl)methyl, (4-methyl-2-cyclohexenyl)methyl, (4-methyl-3-cyclohexenyl)methyl, (1-methyl-2-cycloheptenyl)methyl, (1-methyl-3-cycloheptenyl)methyl, (1-methyl-4-cycloheptenyl)methyl, (2-methyl-1-cycloheptenyl)methyl, (2-methyl-2-cycloheptenyl)methyl, (2-methyl-3-cycloheptenyl)methyl, (2-methyl-4-cycloheptenyl)methyl, (7-methyl-3-cycloheptenyl)methyl, (7-methyl-2-cycloheptenyl)methyl, (7-methyl-1-cycloheptenyl)methyl, (3-methyl-1-cycloheptenyl)methyl, (3-methyl-2-cycloheptenyl)methyl, (3-methyl-3-cycloheptenyl)methyl, (3-methyl-4-cycloheptenyl)methyl, (6-methyl-3-cycloheptenyl)methyl, (6-methyl-2-cycloheptenyl)methyl, (6-methyl-1-cycloheptenyl)methyl, (4-methyl-1-cycloheptenyl)methyl, (4-methyl-2-cycloheptenyl)methyl, (4-methyl-3-cycloheptenyl)methyl, (4-methyl-4-cycloheptenyl)methyl, (5-methyl-3-cycloheptenyl)methyl, (5-methyl-2-cycloheptenyl)methyl, (5-methyl-1-cycloheptenyl)methyl, (1-methyl-2-cyclooctenyl)methyl, (1-methyl-3-cyclooctenyl)methyl, (1-methyl-4-cyclooctenyl)methyl, (2-methyl-1-cyclooctenyl)methyl, (2-methyl-2-cyclooctenyl)methyl, (2-methyl-3-cyclooctenyl)methyl, (2-methyl-4-cyclooctenyl)methyl, (8-methyl-4-cyclooctenyl)methyl, (8-methyl-3-cyclooctenyl)methyl, (8-methyl-2-cyclooctenyl)methyl, (8-methyl-1-cyclooctenyl)methyl, (3-methyl-1-cyclooctenyl)methyl, (3-methyl-2-cyclooctenyl)methyl, (3-methyl-3-cyclooctenyl)methyl, (3-methyl-4-cyclooctenyl)methyl, (7-methyl-4-cyclooctenyl)methyl, (7-methyl-3-cyclooctenyl)methyl, (7-methyl-2-cyclooctenyl)methyl, (7-methyl-1-cyclooctenyl)methyl, (4-methyl-1-cyclooctenyl)methyl, (4-methyl-2-cyclooctenyl)methyl, (4-methyl-3-cyclooctenyl)methyl, (4-methyl-4-cyclooctenyl)methyl, (6-methyl-4-cyclooctenyl)methyl, (6-methyl-2-cyclooctenyl)methyl, (6-methyl-1-cyclooctenyl)methyl, (5-methyl-1-cyclooctenyl)methyl, (5-methyl-2-cyclooctenyl)methyl, (5-methyl-3-cyclooctenyl)methyl and (5-methyl-4-cyclooctenyl)methyl, and those cycloalkenylalkyl groups in which optionally any 1 to 6 hydrogen atoms are substituted with fluorine atom(s); and

cycloalkenylalkenyl groups in which any of hydrogen atoms on the cycloalkenyl ring may be substituted with lower alkyl such as cyclopropenylpropenyl, cyclopropenylbutenyl, cyclobutenylbutenyl, cyclopentenylpropenyl, cyclopentenylbutenyl, cyclopropenylpentenyl, cyclopropenylhexenyl, cyclopropenylheptenyl, cyclobutenylpropenyl, cyclohexenylpropenyl and cyclohexenylbutenyl, and those cycloalkenylalkenyl groups in which optionally any 1 to
 45 6 hydrogen atoms are substituted with fluorine atom(s).

[0014] "Aralkyl (optionally any 1 to 3 hydrogen atoms on the ring in the aralkyl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxy, amino or lower alkylamino)" signifies unsubstituted or substituted C₇-C₁₂ aralkyl groups. As their examples, unsubstituted benzyl, phenethyl, phenylpropyl and naphthylmethyl, and those substituted with above-listed substituents may be named.

[0015] "Arylalkenyl (optionally any 1-3 hydrogen atoms on the ring in the arylalkenyl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxy, amino or lower alkylamino)" signifies unsubstituted or substituted C₈-C₁₂ arylalkenyl groups, examples of which include unsubstituted phenylpropenyl and naphthylpropenyl, and those substituted with above-listed substituents.

[0016] Examples of "heteroarylalkyl having 1 to 2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulfur (optionally any 1-3 hydrogen atoms on the ring in the heteroarylalkyl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxy, amino or lower alkylamino)" include unsubstituted 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-thiazolylmethyl, 4-thiazolylmethyl, 2-thienyl-

methyl, 3-thienylmethyl, 1-imidazolymethyl, 2-imidazolymethyl, 2-imidazolymethyl, 4-imidazolymethyl, 3-pyrazolymethyl, 4-pyrazolymethyl, 2-furylmethyl, 3-furylmethyl, 2-pyrrolylmethyl, 3-pyrrolylmethyl, 2-pyrimidinylmethyl, 4-pyrimidinylmethyl, 5-pyrimidinylmethyl, pyrazinylmethyl, 3-pyridazinylmethyl, 4-pyridazinylmethyl, 3-quinolylmethyl, 4-quinolylmethyl, 5-quinolylmethyl, 6-quinolylmethyl, 7-quinolylmethyl, 8-quinolylmethyl, 1-isoquinolylmethyl, 3-isoquinolylmethyl, 4-isoquinolylmethyl, 5-isoquinolylmethyl, 6-isoquinolylmethyl, 7-isoquinolylmethyl, 8-isoquinolylmethyl, 2-benzothienylmethyl, 3-benzothienylmethyl, 4-benzothienylmethyl, 5-benzothienylmethyl, 6-benzothienylmethyl, 7-benzothienylmethyl, 2-indolylmethyl, 3-indolylmethyl, 4-indolylmethyl, 5-indolylmethyl, 6-indolylmethyl, 7-indolylmethyl, 2-benzimidazolymethyl, 4-benzimidazolymethyl, 5-benzimidazolymethyl, 2-benzothiazolymethyl, 4-benzothiazolymethyl, 5-benzothiazolymethyl, 6-benzothiazolymethyl, 7-benzothiazolymethyl, 2-benzoxazolymethyl, 4-benzoxazolymethyl, 5-benzoxazolymethyl, 6-benzoxazolymethyl, 7-benzoxazolymethyl, 2-benzofuranylmethyl, 3-benzofuranylmethyl, 4-benzofuranylmethyl, 5-benzofuranylmethyl, 6-benzofuranylmethyl, 7-benzofuranylmethyl, 2-pyridylethyl, 2-pyridylpropyl, 3-pyridylethyl, 4-pyridylethyl, 2-thiazolylethyl, 2-thienylethyl, 3-thienylethyl, 1-imidazolylethyl, 2-imidazolylethyl, 3-pyrazolylethyl, 4-pyrazolylethyl, 2-furylethyl, 3-furylethyl, 2-pyrrolylethyl, 3-pyrrolylethyl, 2-pyrimidinylethyl, 4-pyrimidinylethyl, 5-pyrimidinylethyl, pyrazinylethyl, 3-pyridazinylethyl, 4-pyridazinylethyl, 2-quinizylethyl, 2-benzothienylethyl, 3-benzothienylethyl, 4-benzothienylethyl, 5-benzothienylethyl, 6-benzothienylethyl, 7-benzothienylethyl, 2-indolylethyl, 3-indolylethyl, 4-indolylethyl, 5-indolylethyl, 6-indolylethyl, 7-indolylethyl, 2-benzimidazolylethyl, 4-benzimidazolylethyl, 5-benzimidazolylethyl, 2-benzothiazolylethyl, 4-benzothiazolylethyl, 5-benzothiazolylethyl, 6-benzothiazolylethyl, 7-benzothiazolylethyl, 2-benzoxazolylethyl, 4-benzoxazolylethyl, 5-benzoxazolylethyl, 6-benzoxazolylethyl, 7-benzoxazolylethyl, 2-benzofuranylethyl, 3-benzofuranylethyl, 4-benzofuranylethyl, 5-benzofuranylethyl, 6-benzofuranylethyl and 7-benzofuranylethyl, and those which are substituted with above-listed substituents.

[0017] As examples of "heteroarylalkenyl having 1-2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur (any 1 to 3 hydrogen atoms on the ring of said heteroarylalkenyl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxycarbonyl, halogen, lower alkoxy, amino or lower alkylamino)", unsubstituted 2-pyridylpropenyl, 3-pyridylpropenyl, 4-pyridylpropenyl, 2-thiazolylpropenyl, 2-thienylpropenyl, 3-thienylpropenyl, 1-imidasolylbutenyl, 2-imidazolylpropenyl, 3-pyrazolylpropenyl, 4-pyrazolylpropenyl, 2-furylpropenyl, 3-furylpropenyl, 2-pyrrolylpropenyl, 3-pyrrolylpropenyl, 2-pyrimidinylpropenyl, 4-pyrimidinylpropenyl, 5-pyrimidinylpropenyl, pyrazinylpropenyl, 3-pyridazinylpropenyl, 4-pyridazinylpropenyl, 2-quinidylpropenyl, 2-benzothienylpropenyl and 2-indolylpropenyl, and those substituted with above-named substituents may be named.

[0018] "Halogen" include fluorine, chlorine, bromine and iodine.

[0019] "Lower alkyl" signifies C₁-C₆ straight chain or branched alkyl groups, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, hexyl and isohexyl groups.

[0020] "Lower alkoxy" signifies C₁-C₆ straight chain or branched alkoxy groups, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, sec-butoxy, isobutoxy, t-butoxy, pentyloxy, isopentyloxy, hexyloxy and isohexyl-oxy groups.

[0021] "Lower alkoxycarbonyl" signifies C₁-C₇ straight chain or branched alkoxycarbonyl groups, for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, sec-butoxy-carbonyl, isobutoxycarbonyl, t-butoxycarbonyl, pentyloxycarbonyl, isopentyloxycarbonyl, hexyloxycarbonyl and isohexyloxycarbonyl groups.

[0022] "Aralkyloxycarbonyl" signifies C₇-C₁₀ aralkyloxycarbonyl groups, for example, benzyloxycarbonyl and phenethyloxycarbonyl groups.

[0023] "Lower alkylamino" signifies C₁-C₆ straight chain or branched alkylamino groups, for example, methylamino, ethylamino, propylamino, isopropylamino, butylamino, sec-butylamino, t-butylamino, pentylamino, isopentylamino, hexylamino, isohexylamino, dimethylamino, diethylamino and dipropylamino groups.

[0024] "Protected hydroxyl groups" signify hydroxyl groups which are protected with acyl such as acetyl, alkylsilyl such as trimethylsilyl and t-butyldimethylsilyl, aralkyl such as benzyl and trityl, ether group such as methoxymethyl, and in the form of alkylideneketal such as isopropylideneketal.

[0025] "Protected oxo groups" signify oxo groups which are protected in the form of acetal or ketal such as ethylene ketal, trimethylene ketal and dimethyl ketal.

[0026] "Protected amino or lower alkylamino groups" signify amino or lower alkylamino groups which are protected with, for example, aralkyl groups such as benzyl, p-methoxybenzyl, p-nitrobenzyl, benzhydryl and trityl; lower alkanoyl groups such as formyl, acetyl and propionyl; arylalkanoyl groups such as phenylacetyl and phenoxyacetyl; lower alkoxycarbonyl groups such as methoxycarbonyl, ethoxycarbonyl, isobutoxycarbonyl and t-butoxycarbonyl; alkenyloxycarbonyl groups such as 2-propenyloxycarbonyl; aralkyloxycarbonyl groups such as benzyloxycarbonyl and p-nitrobenzyloxycarbonyl, and lower alkylsilyl groups such as trimethylsilyl and t-butyldimethylsilyl. In particular, amino or lower alkylamino groups which are protected with t-butoxycarbonyl and benzyloxycarbonyl groups are preferred.

[0027] Also "deprotection" signifies removal of protective groups by the means conventionally used in the field of organic chemistry, such as hydrolysis, hydrogenolysis and the like.

[0028] Referring to the general formula [I],

(1) Ar represents an aryl group or a heteroaryl group having 1 to 2 hetero atoms selected from a group consisting

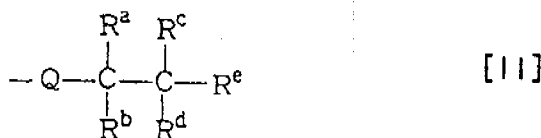
of nitrogen, oxygen and sulfur (any 1 to 3 hydrogen atoms on the ring of said aryl or heteroaryl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxycarbonyl, halogen, lower alkoxy, amino or lower alkylamino). In particular, unsubstituted phenyl or substituted phenyl having above-named substituents are preferred.

(2) R^1 is a C_3 - C_6 cycloalkyl which may have 1 to 4 fluorine atoms on the ring; cyclobutyl, cyclopentyl, cyclohexyl, 2-fluorocyclobutyl, 3-fluorocyclobutyl, 2,2-difluorocyclobutyl, 3,3-difluorocyclobutyl, 2-fluorocyclopentyl, 3-fluorocyclopentyl, 2,2-difluorocyclopentyl, 3,3-difluorocyclopentyl, 2,2,3,3-tetrafluorocyclopentyl, 3,3,4,4-tetrafluorocyclopentyl, 2-fluorocyclohexyl, 3-fluorocyclohexyl, 4-fluorocyclohexyl, 2,2-difluorocyclohexyl, 3,3-difluorocyclohexyl and 4,4-difluorocyclohexyl being preferred.

Of these, particularly 2-fluorocyclobutyl, 3-fluorocyclobutyl, 2,2-difluorocyclobutyl, 3,3-difluorocyclobutyl, 2-fluorocyclopentyl, 3-fluorocyclopentyl, 2,2-difluorocyclopentyl, 3,3-difluorocyclopentyl, 2,2,3,3-tetrafluorocyclopentyl, 3,3,4,4-tetrafluorocyclopentyl, 2-fluorocyclohexyl, 3-fluorocyclohexyl, 4-fluorocyclohexyl, 2,2-difluorocyclohexyl, 3,3-difluorocyclohexyl and 4,4-difluorocyclohexyl are preferred. 3,3-Difluorocyclopentyl is the best preferred.

(3) X represents O or NH, NH being the preferred.

(4) R^2 represents C_5 - C_{15} saturated or unsaturated aliphatic hydrocarbon groups whose any 1 to 6 hydrogen atoms may be substituted with fluorine atom(s), aralkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl group having 1 to 2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulfur (optionally any 1 to 3 hydrogen atoms on the ring in said aralkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxycarbonyl, halogen, lower alkoxy, amino or lower alkylamino). Of these, the groups expressed by the following formula [II], in which any 1 to 6 hydrogen atoms may be substituted with fluorine atom(s),



[in which

Q represents methylene, ethylene, trimethylene or tetramethylene;

R^a and R^c each represents a hydrogen atom or are combined to form a single bond; and

R^b , R^d and R^e may be the same or different and each represents a hydrogen atom, a lower alkyl group, C_3 - C_8 cycloalkyl or cycloalkenyl, or R^b and R^d , or R^d and R^e together form each a C_3 - C_8 cycloalkyl or cycloalkenyl],

benzyl, phenethyl, phenylpropyl, phenylpropenyl or 2-pyridylmethyl, 2-pyridylethyl, 2-pyridylpropyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-thiazolylmethyl, 2-thienylmethyl, 3-thienylmethyl, 1-imidazolylmethyl, 2-imidazolylmethyl, 4-imidazolylmethyl, 2-furylmethyl, 3-furylmethyl, 2-pyrrolylmethyl, 3-pyrrolylmethyl (any 1 to 3 hydrogen atoms on the ring of said benzyl, phenethyl, phenylpropyl, phenylpropenyl or heteroarylalkyl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxycarbonyl, halogen, lower alkoxy, amino or lower alkylamino) are preferred.

[0029] In particular, 2-thienylmethyl, 3-thienylmethyl, 2-furylmethyl, 3-furylmethyl, 2-pyridylmethyl or benzyl (any 1-3 hydrogen atoms on the ring in the thienylmethyl, furylmethyl, pyridylmethyl or benzyl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxycarbonyl, halogen, amino, lower alkylamino or lower alkoxy) are preferred, *inter alia*, 6-aminopyridin-2-ylmethyl group is preferred.

[0030] According to the manner of substitution, the compounds of the present invention may exist in the form of stereoisomers such as optical isomers, diastereoisomers and geometrical isomers. It is to be understood that the compounds of the present invention also include all such stereoisomers and mixtures thereof.

[0031] Moreover, the compounds of the present invention may exist in the form of pharmaceutically acceptable salts. Such salts include inorganic acid salts such as hydrochlorides, sulfates, nitrates, phosphates and perchlorates; organic carboxylic acid salts such as maleates, fumarates, succinates, tartrates, citrates and ascorbates; organic sulfonic acid salts such as methanesulfonates, isethionates, benzenesulfonates and p-toluenesulfonates; and the like.

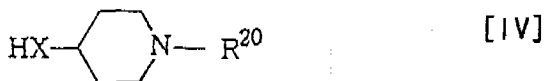
[0032] The compounds of the above general formula [I] in accordance with the present invention can be prepared, for example, by:

(a) reacting a carboxylic acid of the general formula [III]



[wherein Ar represents an aryl group or a heteroaryl group having 1 to 2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulfur (any 1 to 3 hydrogen atoms on the ring of said aryl or heteroaryl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxy, amino or lower alkylamino); and R¹⁰ represents a C₃-C₆ cycloalkyl in which any 1 to 4 hydrogen atoms may be substituted with fluorine atom(s) or a C₃-C₆ cycloalkyl having 1 to 2 protected or unprotected hydroxyl or oxo group(s)]

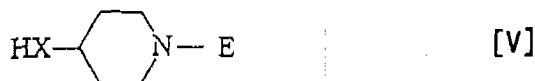
or a reactive derivative thereof with a compound of the general formula [IV]



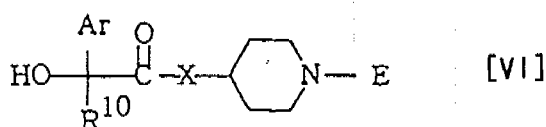
[wherein R²⁰ represents a C₅-C₁₅ saturated or unsaturated aliphatic hydrocarbon group in which any 1 to 6 hydrogen atoms may be substituted with fluorine atom(s), C₅-C₁₅ saturated or unsaturated aliphatic hydrocarbon group having 1-2 protected or unprotected hydroxyl or oxo group(s), aralkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl group having 1 to 2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulfur (optionally any 1 to 3 hydrogen atoms on the ring in said aralkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxy, amino, unprotected or protected lower alkylamino or aralkyloxycarbonyl group) and X stands for NH or O] or a salt thereof;

and when either R¹⁰ or R²⁰ has unprotected or protected 1 to 2 hydroxyl or oxo group(s) converting said hydroxyl or oxo groups to fluorine atom(s) either as they are or after removing the protective group(s); when R¹⁰ or R²⁰ has protected amino or protected lower alkylamino group(s), removing the protective group(s); and when R¹⁰ or R²⁰ has lower alkoxy, amino, unprotected or protected lower alkylamino or aralkyloxycarbonyl, converting the same to amino; or

(b) reacting a carboxylic acid of the above general formula [III] or a reactive derivative thereof with a compound of the general formula [V]



[wherein E is a protective group for the imino group, and X is as defined above] or a salt thereof; deprotecting the resulting compound of the general formula [VI]



[wherein Ar, R¹⁰, X and E are as defined above] hereafter reacting the same with a compound of the general formula [VII]



[wherein L represents a leaving group, and R²⁰ is as defined above]

in the presence of a base, if necessary, and again if necessary conducting a conversion reaction of R¹⁰ and R²⁰ similar to the above; or

(c) deprotecting a compound of the above general formula [VI] and subjecting it to a reductive alkylation reaction with a compound of the general formula [VIII]



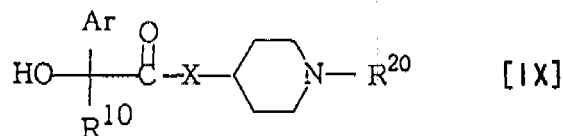
[wherein R²¹ represents a C₄-C₁₄ saturated or unsaturated aliphatic hydrocarbon group in which any 1 to 6 hydrogen atom(s) may be substituted with fluorine atom(s), C₄-C₁₄ saturated or unsaturated aliphatic hydrocarbon group having unprotected or protected 1 to 2 hydroxyl or oxo group(s), aryl, aralkyl, arylalkenyl or heteroaryl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulfur (optionally any 1-3 hydrogen atoms on the ring in said aryl, aralkyl, arylalkenyl, heteroaryl, heteroarylalkyl or heteroarylalkenyl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxy, unprotected or protected amino, unprotected or protected lower alkylamino or aralkyloxycarbonyl)],

and if necessary conducting the conversion reaction of R¹⁰ and R²¹ similar to the foregoing.

[0033] In the above formula [VII], "leaving groups" represented by L include, for example, halogen atoms such as chlorine, bromine and iodine; alkylsulfonyloxy groups such as methanesulfonyloxy; and arylsulfonyloxy groups such as p-toluenesulfonyloxy.

[0034] In the above formulae [V] and [VI], "protective groups for the imino group" represented by E signify similar protective groups to those for amino as above.

[0035] In the above-described process variant (a), a carboxylic acid of formula [III] is reacted with a compound of formula [IV] or a salt thereof in the presence of a suitable condensing agent. Thus, there is obtained a coupled compound of the general formula [IX]



[wherein Ar, R¹⁰, X and R²⁰ are as defined above].

[0036] The carboxylic acid of formula [III] used as a starting material in the above condensation reaction can be prepared, for example, by the method as described in Referential Examples.

[0037] The condensing agent to be used in the above-described reaction may be any of those which are commonly

used in the field of organic synthetic chemistry for condensation reactions of carboxyl groups with hydroxyl or amino groups, and examples thereof include N,N'-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethyl-aminopropyl)carbodiimide, diphenylphosphoryl azide and dipyridyl disulfide-triphenylphosphine. Of these, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide is preferred.

5 [0038] Use rate of these condensing agents are subject to no critical limitation, while normally it may be within a range of 1 to 5 equivalents, preferably 1 to 2 equivalents, per mole of the compound of formula [III].

[0039] If necessary, the above-described condensation reaction may be carried out in the presence of a base. Bases which can be used for this purpose include, for example, aliphatic tertiary amines such as triethylamine and diisopropylethylamine; and aromatic amines such as pyridine, 4-dimethylaminopyridine, quinoline. 4-Dimethylaminopyridine is particularly preferred.

10 [0040] The condensation reaction is preferably carried out in an inert solvent. Suitable inert organic solvents include, for example, diethyl ether, tetrahydrofuran, N,N-dimethylformamide, dioxane, benzene, toluene, chlorobenzene, methylene chloride, chloroform, carbon tetrachloride, dichloroethane, trichloroethylene and mixtures of the foregoing solvents. Of these, diethyl ether, tetrahydrofuran, N,N-dimethylformamide and dioxane are preferred.

15 [0041] The reaction temperature may usually range from -70°C to the boiling point of the solvent used for the reaction and preferably from -20°C to 100°C. Under these conditions, the reaction can usually be completed in a period of time ranging from 5 minutes to 7 days and preferably from 10 minutes to 24 hours.

[0042] The proportion of the compound of formula [IV] or a salt thereof to the compound of formula [III] is not critical and may vary according to the kinds of individual compounds, the reaction conditions employed and other factors. 20 Whereas, the compound of formula [IV] or a salt thereof may usually be used in an amount of 1 to 5 moles, preferably 1 to 2 moles, per mole of the compound of formula [III].

[0043] The coupled compound of the above formula [IX] can also be obtained by converting the carboxylic acid of formula [III] into a reactive derivative thereof and condensing it with the compound of formula [IV] or a salt thereof.

25 [0044] Suitable reactive derivatives of the carboxylic acid of formula [III] include, for example, compounds which are commonly used in the field of organic synthetic chemistry for activation of carboxyl group(s) in an esterification or amidation reaction, such as mixed acid anhydrides, active esters and active amides.

[0045] Mixed acid anhydrides of the carboxylic acid of formula [III] can be obtained by reacting the carboxylic acid of formula [III] with an alkyl chlorocarbonate, e.g., ethyl chlorocarbonate, an aliphatic carboxylic acid chloride, e.g., acetyl chloride, pivaloyl chloride or the like according to conventional method. Reactive esters thereof can be obtained by 30 reacting the carboxylic acid of formula [III] with an N-hydroxy compound, e.g., N-hydroxysuccinimide, N-hydroxyphthalimide or 1-hydroxybenzotriazole; or a phenol compound, e.g., 4-nitrophenol, 2,4-dinitrophenol, 2,4,5-trichlorophenol, pentachlorophenol or the like; in the presence of a condensing agent, e.g., N,N'-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, diphenylphosphoryl azide or dipyridyl disulfide-triphenylphosphine, according to conventional method. Reactive amides thereof can be obtained by reacting the carboxylic acid of formula [III] with 35 1,1'-carbonyl-diimidazole, 1,1'-carbonylbis(2-methylimidazole) or the like according to conventional method.

[0046] The condensation reaction of a reactive derivative of a carboxylic acid of formula [III] with a compound of formula [IV] or a salt thereof is preferably carried out in an inert solvent. Suitable inert organic solvents include, for example, diethyl ether, tetrahydrofuran, N,N-dimethylformamide, dioxane, benzene, toluene, chlorobenzene, methylene chloride, chloroform, carbon tetrachloride, dichloroethane, trichloroethylene and mixtures of the foregoing solvents. Of 40 these, diethyl ether, chloroform, tetrahydrofuran, N,N-dimethylformamide and dioxane are preferred.

[0047] The reaction temperature may usually range from -70°C to the boiling point of the solvent used for the reaction and preferably from -20°C to 100°C.

[0048] The proportion of the compound of formula [IV] or a salt thereof to the reactive derivative of a carboxylic acid of formula [III] is not critical and may vary according to the kind of the reactive derivative and other factors, while the 45 compound of formula [IV] or a salt thereof may usually be used in an amount of 1 to 5 moles, preferably 1 to 2 moles, per mole of the reactive derivative of the carboxylic acid of formula [III].

[0049] In the coupled compounds expressed by the general formula [IX], when R¹⁰ is a C₃-C₆ cycloalkyl group having 1-2 unprotected or protected hydroxyl or oxo group(s), or R²⁰ is an aliphatic hydrocarbon group having 1-2 unprotected or protected hydroxyl or oxo group(s), the hydroxyl or oxo group(s) are converted to fluorine atom(s) either as they are 50 or after removing the protective group(s).

[0050] Removal of protective groups from hydroxyl and oxo groups which are protected in the form of ketals in the compounds of formula [IX] can normally be effected in aqueous solvent, using an inorganic acid, an organic acid, a weakly acidic salt or the like. Suitable inorganic acids include, for example, hydrochloric acid and sulfuric acid; suitable organic acids include, for example, p-toluenesulfonic acid, benzenesulfonic acid, camphor-sulfonic acid and acetic acid; 55 and suitable weakly acidic salts include, for example, ammonium chloride and pyridinium p-toluenesulfonate. Preferred aqueous solvents include aqueous methanol, aqueous ethanol, aqueous tetrahydrofuran, aqueous dioxane and the like. The reaction may usually be carried out in the presence of a catalytic amount to 5 equivalents, preferably a catalytic amount to 1 equivalent, of such an acid or salt at a temperature ranging from 0°C to 100°C and preferably from room

temperature to 80°C.

[0051] Conversion of the hydroxyl or oxo group(s) to fluorine atom(s) can normally be effected by causing the compound to react in an inert solvent which is not detrimental to the reaction, e.g., methylene chloride, chloroform, tetrahydrofuran, methanol, acetonitrile, dimethylsulfoxide or pyridine, or in the absence of a solvent, using one equivalent to an excessive amount, preferably 1-2 equivalents, of a fluorinating agent such as sulfur tetrafluoride, diethylaminosulfur trifluoride, cesium fluorosulfate, tetrabutylammonium fluoride, tris(dimethylamino)sulfonium-difluorotrimethylsilicate, hydrogen fluoride or tosyl fluoride, preferably at temperatures ranging -80°C - 180°C for 10 minutes to 72 hours.

[0052] When R²⁰ in the compounds expressed by general formula [IV] or [IX] has protected amino group(s) or protected lower alkylamino group(s), the protective group(s) are removed if necessary; when lower alkoxy carbonyl or aryloxy carbonyl group(s) are present, the functional group(s) are suitably converted to amino group(s). Removal of amino-protective groups can be effected by processes known *per se*, for example, any of those described in Protective Groups in Organic Synthesis, T.W. Greene, John Wiley & Sons Co. (1981) or methods analogous thereto, for example, solvolysis using an acid or base, chemical reduction using a metal hydride complex or the like and catalytic reduction using palladium-on-carbon, Raney-nickel or the like.

[0053] Solvolysis with an acid can normally be carried out by treating the compound with an acid such as formic acid, trifluoroacetic acid, hydrochloric acid or sulfuric acid, in an inert solvent such as methylene chloride, anisole, tetrahydrofuran, dioxane, methanol or ethanol or a mixture of such a solvent and water, or in the absence of solvent, preferably at a temperature in the range from about 0° to about 100°C, for a period of time ranging from 10 minutes to 24 hours.

[0054] Solvolysis with a base can normally be carried out by treating the compound with an alkali metal hydroxide, e.g., lithium hydroxide, sodium hydroxide or potassium hydroxide; an alkali metal carbonate, e.g., sodium carbonate or potassium carbonate, in an inert solvent which exerts no adverse effect on the reaction, e.g., methanol, ethanol, isopropanol, tetrahydrofuran or dioxane or a mixture of such a solvent and water, preferably at a temperature in the range of from about -20 to about 80°C, for a period of time ranging from 10 minutes to 24 hours.

[0055] Catalytic reduction can normally be carried out in the presence of a catalyst such as palladium-on-carbon, palladium hydroxide, Raney nickel or platinum oxide, in an inert solvent, e.g., methanol, ethanol, water or acetic acid or a mixture of such solvents, preferably under a pressure of hydrogen of about 1 to about 20 kg/cm², preferably at a temperature in the range of from about 0 to about 40°C, for a period of time ranging from 10 minutes to 24 hours.

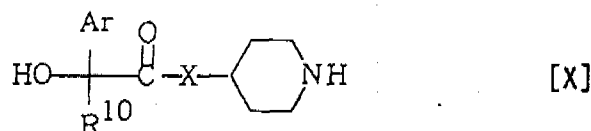
[0056] Conversion of the lower alkoxy carbonyl or aryloxy carbonyl to amino can be conducted by either reacting the compound with hydrazine to form an acid hydrazide and thereafter converting it to the corresponding acid azide; or converting the compound to a carboxylic acid by hydrolysis, then to an acid azide, followed by rearrangement and hydrolysis.

[0057] In the process variant (b), the condensation reaction of a carboxylic acid of formula [III] or a reactive derivative thereof with a piperidine derivative of formula [V] in the first stage can be practiced in the manner similar to the condensation reaction of a carboxylic acid of formula [III] or a reactive derivative thereof with a compound of formula [IV] in the process variant (a).

[0058] The compound of the foregoing formula [VI] obtained through this condensation reaction is then removed of the protective group(s) of imino group(s).

[0059] Removal of said imino-protective groups from a compound of formula [VI] can be effected in the manner similar to above-described removal of amino-protective groups.

[0060] Thus obtained compounds of the general formula



[wherein Ar, R¹⁰ and X are as defined above] is reacted with a compound of formula [VII] in the second stage, if necessary in the presence of a base.

[0061] The reaction of the compound of formula [X] with the compound of formula [VII] is usually carried out in a suitable solvent by using the compounds in substantially equimolar amounts or using either of the compounds in slight excess (e.g., using the compound of formula [VII] in an amount of 1 to 1.3 moles per mole of the compound of formula [X]). If desired, however, either of the compounds may be used in large excess. Moreover, a suitable base and/or an

additive may be used.

[0062] Suitable solvents include, for example, ethers such as diethyl ether, tetrahydrofuran and dioxane; aromatic hydrocarbons such as benzene, toluene, chlorobenzene and xylene; aprotic polar solvents such as dimethyl sulfoxide, N,N-dimethylformamide, acetonitrile and hexamethylphosphoric triamide; and mixtures thereof.

5 [0063] Bases which can be used for above-described reaction include, for example, alkali metal bicarbonates such as sodium hydrogen carbonate and potassium hydrogen carbonate; alkali metal carbonates such as sodium carbonate and potassium carbonate; tertiary aliphatic amines such as trimethylamine, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N-methylpyrrolidine, N-methylpiperidine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN); and aromatic amines such as pyridine, 4-dimethylaminopyridine, 10 picoline, lutidine, quinoline and isoquinoline. Of these, N,N-diisopropylethylamine and potassium carbonate are preferred.

[0064] Additives which can be used for above-described reaction include, for example, alkali metal iodides such as lithium iodide, sodium iodide and potassium iodide. Of these, potassium iodide is preferred.

15 [0065] The reaction temperature may usually range from about 0°C to the boiling point of the solvent, and the reaction time may usually range from 10 minutes to 48 hours. If desired, however, reaction conditions beyond these limits may be used.

[0066] If necessary, furthermore, conversion reactions of R¹⁰ and R²⁰ as described as to the process variant (a) are conducted.

20 [0067] The reductive alkylation reaction of a compound of the above formula [X] with an aldehyde of formula [VIII] according to the process variant (c) is normally carried out in an inert solvent which exerts no adverse effect on the reaction. Suitable inert solvents include, for example, alcohols such as methanol and ethanol; ethers such as diethyl ether, tetrahydrofuran and dioxane; aromatic hydrocarbons such as benzene and toluene; and mixtures thereof. Of these, methanol, ethanol, tetrahydrofuran and toluene are preferred.

25 [0068] The reaction temperature may usually range from about -30°C to about 200°C and preferably from about 0°C to about 100°C. The reaction time may usually range from 10 minutes to 7 days and preferably from 10 minutes to 24 hours.

[0069] The above-described reductive alkylation reaction is preferably carried out under weakly acidic conditions which facilitate formation of Schiff bases. Acids which can be used for the necessary pH control include, for example, p-toluenesulfonic acid, hydrochloric acid, acetic acid and trifluoroacetic acid.

30 [0070] The reductive alkylation can be effected, for example, using a metal hydride complex such as sodium borohydride, sodium cyanoborohydride, lithium aluminum hydride or sodium triacetoxyborohydride, or by catalytic reduction using a palladium-on-carbon catalyst, a Raney nickel catalyst or the like. Preferably, it is effected using a metal hydride complex such as sodium borohydride or sodium cyanoborohydride. Especially when the reductive alkylation is carried out under weakly acidic conditions which facilitate formation of Schiff bases, it is preferable to use sodium cyanoboro- 35 hydride or the like which are relatively stable in the acidic pH range.

[0071] When a metal hydride complex is used as the reducing agent, the amount of reducing agent used may usually range from 1 mole to excessive moles, preferably from 1 to 10 moles, per mole of the compound of formula [X].

[0072] If necessary, then the conversion reactions of R¹⁰ and R²¹ as described as to the process variant (a) are carried out.

40 [0073] The compounds of formula [I] which are obtained according to the above-described process variants (a), (b) and (c) can be isolated and purified by those methods known per se, i.e. such customarily used separation means as column chromatography using silica gel, adsorbent resin or the like, liquid chromatography, thin-layer chromatography, solvent extraction or recrystallization and reprecipitation.

45 [0074] The compounds of the present invention and intermediates thereof exist in stereoisomeric forms such as enantiomeric isomers, diastereoisomers and geometrical isomers. It is to be understood that the compounds of the present invention also include all such stereoisomerically pure substances and mixtures thereof. When the compounds of the present invention and intermediates thereof are racemates, their optical resolution can be achieved by conventional means such as high-performance liquid chromatography using a chiral carrier or fractional crystallization of a diastereomeric salt.

50 [0075] The compounds of formula [I] obtained in the above-described manner may be converted into pharmaceutically acceptable salts thereof according to usual manner. Conversely, such salts may also be converted into the corresponding free amines according to usual manner.

55 [0076] The compounds of formula [I] in accordance with the present invention exhibit potent and selective inhibitory activity for binding to muscarinic receptors, a potent and selective antagonism to muscarinic receptors *in vitro* and, furthermore, potent and durable bronchodilatory action *in vivo*. These activities exhibited by the compounds of the present invention are demonstrated by the following tests on the inhibition of binding to muscarinic receptors and tests on antagonism against various muscarinic receptors.

Tests on inhibition of binding to muscarinic receptors

[0077] These tests were performed according to a modification of the method of Hargreaves et al. (Br. J. Pharmacol. 107: 494-501, 1992). Muscarinic receptors m1-m5 expressed in CHO cells (Receptor Biology, Inc.) were incubated with 0.2 nM [³H]-N-methylscopolamine (84Ci/mmol, New England Nuclear, Inc.) and a test compound to be tested in 0.5 ml of 50 mM Tris-HCl - 10 mM MgCl₂ - 1 mM EDTA (pH 7.4) for 120 minutes at room temperature (about 20-25°C), followed by suction filtration over glass filters (UniFilter-GF/C; Packard). Then the filter was washed four times with 1 ml of ice-cold Tris-HCl buffer and dried at 50°C for an hour. After adding a scintillator (Microscinti O; Packard), the radioactivity of [³H]-N-methylscopolamine binding to the filter was counted by a microplate scintillation counter (TopCount™; Packard). Non-specific binding of [³H]-N-methylscopolamine was measured by adding 1 μM N-methylscopolamine. According to the method of Cheng and Prusoff (Biochem. Pharmacol. 22: 3099-3108, 1973), the binding affinity (K_i value) of a compound of the present invention for muscarinic receptors was calculated from the concentration of the test compound which achieved 50% inhibition of binding of [³H]-N-methylscopolamine, labeled ligand (IC₅₀ value).

Table 1

Inhibitory Effects on Binding to Muscarinic m ₂ and m ₃ Receptors			
	K _i (nM)		m ₂ /m ₃
	m ₂	m ₃	
Compound of Example 1	3200	5.5	590
Compound of Example 10	17000	8.9	1900
Compound of Example 11	460	3.2	140
Compound of Example 12	8600	30	290
Compound of Example 14	1400	10	140
Compound of Example 15	1000	3.5	290
Compound of Example 20	550	3.0	180
Compound of Example 21	50000	22	2300
Compound of Example 22	13000	19	680
Compound of Example 26	24000	22	1100
Compound of Example 27	4200	20	210
Compound of Example 31	10000	19	520

[0078] As is clear from the results indicated in above Table 1, those compounds of the present invention exhibited far higher binding-inhibitory activity to m₃ receptor, than to m₂ receptor.

Tests for Antagonism to Muscarinic Receptors (in vitro)1) Tests for antagonism to M₂ receptor in an isolated rat right atrium

[0079] These tests were performed according to a conventional method. A male SD strain rat (weighing 300-500 g) was killed by exsanguination, and the right atrium was isolated. This preparation was isometrically suspended in organ bath filled with 20 ml of Krebs-Henseleit solution (gassed with 95% O₂ - 5% CO₂ and kept at 32°C) with an initial tension of 0.5 g. The heart rate was recorded with a heart rate counter. After the preparation was equilibrated for 30 minutes, carbachol (10⁻⁹ to 10⁻⁶ M) was cumulatively administered in three-fold increasing doses. Thus, a decrease in heart rate was measured to obtain a dose-response curve for the control experiment. After the preparation was washed with fresh solution to restore the heart rate, a test compound was administered thereto. Ten minutes later, carbachol was cumulatively administered again. Responses to carbachol were expressed as percentages based on the heart rate before administration of carbachol as 100%. The antagonistic potency (K_B value) of the test compound was determined from the degree of shift of the dose-response curve obtained by treatment with individual test compound of the present invention.

2) Tests for antagonism to the airway M_3 receptor in an isolated rat trachea

[0080] These tests were performed according to a conventional method. A male SD strain rat (weighing 300-500 g) was killed by exsanguination, and the trachea was isolated. Annular segments (2 mm wide) were cut out from the trachea and cut transversely at the anterior cartilage part to make open ring preparation. A preparation was suspended in a Magnus tube filled with 5 ml of Krebs-Henseleit solution (gassed with 95% O_2 - 5% CO_2 and kept at 32°C) with an initial tension of 1.0 g and a resting tension of 0.6 g. The tension of the preparation was recorded isometrically. After being equilibrated for an hour, the preparation was made to contract twice by treatment with 10^{-4} M carbachol, and the second contraction induced by carbachol was used as the reference contraction. After the preparation was washed with fresh solution to be restored to the base line, a test compound was administered thereto (or no treatment was given). Ten minutes later, carbachol (10^{-8} to 10^{-3} M) was cumulatively administered in three-fold increasing doses to obtain a dose-response curve. The dose-response curve was plotted by expressing responses as percentages based on the reference contraction of the preparation as 100%. The antagonistic potency (K_B value) of the test compound was determined from the degree of shift of the dose-response curve obtained by treatment with the test compound.

TABLE 2

Antagonism to Muscarinic Receptors (in vitro)			
	K_B (nM)		M_2/M_3
	right atrium M_2	Trachea M_3	
Compound of Example 1	1000	6.3	160
Compound of Example 11	610	0.95	640
Compound of Example 20	2100	1.6	630

[0081] As is clear from the results indicated in above Table 2, the compounds of the present invention exhibited far more powerful antagonism to the trachea M_3 receptor than to the right atrium M_2 receptor. Therefore, the compounds of the present invention are more selective for trachea M_3 receptor.

Tests for antagonism against muscarinic M_3 receptor (in vivo)

1-A) Tests for bronchodilation in rats (i.v.)

[0082] Eight- to eleven-weeks-old male rats of the Sprague-Dawley strain, weighing 380-420 g, were anesthetized with urethane (750 mg/kg, i.p.) and α -chloralose (37.5 mg/kg, i.p.). The bronchus of each rat was intubated, and the right jugular vein was cannulated for drug administration. After spontaneous respiration was fully suppressed by succinylcholine (5 mg/body, s.c.), the airway resistance was measured under artificial ventilation by means of a Pulmonary Mechanics Model 6 (Buxco). The acetylcholine (50 μ g/kg, i.v.)-induced airway resistance increase was measured 5 minutes before and 5 minutes after administration of test compound, and the ratio of the airway resistance of the latter to the former was calculated. In controls, isotonic sodium chloride solution was used in place of the test compounds and otherwise identical procedures were repeated, the calculated ratio of the airway resistance being set to be 100%. A dose that inhibited the acetylcholine-induced increase in airway resistance in the control groups by 50% was defined to be ED_{50} , and the ED_{50} values of the test compounds were calculated by probit analysis of their dose-response curves.

1-B) Tests for bronchodilation in rats (p.o.)

[0083] Eight- to eleven-weeks-old male rats of Sprague-Dawley strain weighing 380-420 g were orally administered with a test compound. The rats were treated in the identical manner as in the i.v. test, starting 30 minutes after the administration, and their airway resistance values were measured. The acetylcholine-(50 μ g/kg, i.v.) induced airway resistance increase were measured 60 minutes after the administration of test compounds. In controls, isotonic sodium chloride solution was used in place of the test compounds and otherwise identical procedures were repeated, the airway resistance values being set to be 100%. A dose that inhibited the acetylcholine-induced increase in airway resistance in the control groups by 50% was defined to be ED_{50} , and the ED_{50} values of the test compounds were calculated by probit analysis of their dose-response curves.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
EMILIO FERRERO
Apoderado

ASUNTO

Radicación 04128948
Trámite 011
Evento 379
Actuación 430
Oficio **Nº 01815**
Folios 258

Patente de Invención ☒

Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒

Cap. I ☐

Cap. II ☒

No. Sol. Internacional

PCT/EP2003/006708

Fecha de Presentación Internal.

15/01/2004

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

Descripción: Folios: 87 a 135

Reivindicaciones: Folios 136 a 145 como se radicó inicialmente

Folios 213 a 223 modificadas como respuesta del solicitante.

Prioridad: Fecha: 2/07/2002, país: ES y número: P 200201539

Respuesta del solicitante: Folios: 207 a 211 y 224 a 227

2. Objeto de la invención

- Título de la solicitud: **NUEVOS DERIVADOS DE QUINUCLIDINA-AMIDA.**
Número de folio: 1

El problema planteado en esta solicitud es la necesidad de compuestos antimuscarínicos útiles para trastornos respiratorios tales como: obstrucción

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pulmonar crónica, bronquitis, hiperreactividad bronquial, asma, tos y rinitis; trastornos urológicos, gastrointestinales y cardiovasculares.

Para solucionar este problema técnico la solicitud en estudio proporciona nuevos agentes antimuscarínicos con alta afinidad por los receptores muscarínicos M3, con efecto potente y de larga duración.

Clasificación Internacional de Patentes (IPC.): C07D 453/02

3. De la solicitud de Patente

Reivindicaciones (*artículo 30 D 486*)

Una vez revisado el capítulo reivindicatorio esta dependencia encuentra:

Reivindicación 21: reivindicación que no se sabe de quien depende y si es independiente no se muestra la fórmula (V) que contiene los compuestos que se reivindican. Se requiere al solicitante eliminar dicha reivindicación ya que al haber eliminado los procesos que no eran nuevos, dejar esta reivindicación crea confusión.

4. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria 2/07/2002

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

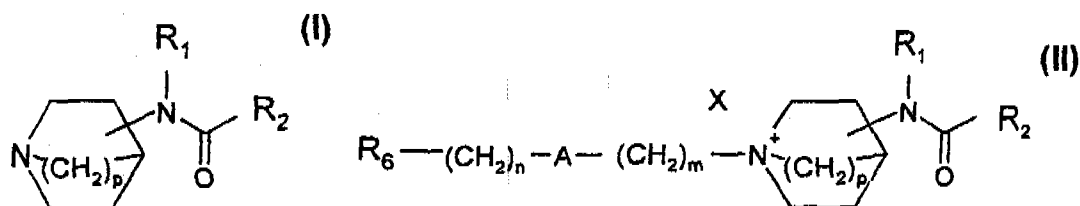
Nº	Documento	Título	Fecha de publicación*
D ₁	WO 01/04118	NOVEL QUINUCLIDINE DERIVATIVES AND MEDICINAL COMPOSITIONS CONTAINING THE SAME	2001/01/18
D ₂	EP0930298	FLUORINATED 1,4-DISUBSTITUTED PIPERIDINE DERIVATIVES	1999/07/21

5. Análisis de patentabilidad (artículo 14 D486)

Nivel inventivo (*artículo 18 D486*)

La presente Solicitud de Patente reivindica:

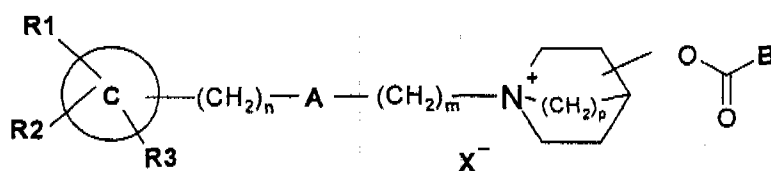
Reivindicaciones 1 - 20: Compuestos derivados de quinuclidina – amida de fórmula (I) y (II).



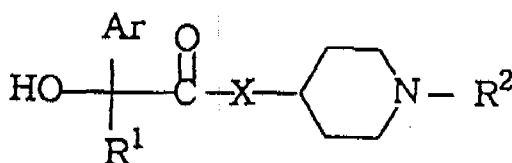
Reivindicación 22: composición farmacéutica que comprende un compuesto de las reivindicaciones 1 – 20 con un vehículo o diluyente.

Dichos compuestos están afectados por los siguientes documentos del Estado de la Técnica:

D1 enseña (ver folio 187) Compuestos de acuerdo a la formula (I) que muestran alta afinidad por los receptores muscarínicos M3.



D2 enseña (ver folio 239 a 253) nuevos derivados de piperidina fluorinados 1,4-disustituidos según la formula mostrada, con actividad antagonista selectiva para los receptores muscarínicos M3 con excelente actividad oral, duración de acción y farmacocinética y pocos efectos adversos.



La única **diferencia con D1** es que esta solicitud **posee un sustituyente adicional R1 con un N en vez de un O como en la anterioridad.**

El efecto técnico logrado por esta diferencia es actividad como antimuscarínico M3.

El Problema Técnico Objetivo se puede definir en como lograr **compuestos antimuscarínicos M3 alternativos a los previamente conocidos.**

Por lo tanto, la solicitud, tal como se reivindica es obvia, porque el experto medio en la materia enfrentado al problema de conseguir compuestos antimuscarínicos M3 y conociendo el estado de la técnica realizaría una **variación estructural en los compuestos de D1** cambiando un O por un N para llegar a los compuestos reivindicados sin obtener ventajas apreciables en cuanto a la actividad de los mismos definida por IC₅₀ para la solicitud (ejemplo 14 folio 225 IC₅₀ M₃ = 8,7 y ejemplo 32 folio 225 IC₅₀ M₃ = 7,9) con respecto a la anterioridad (compuesto 8 EXP 2004 128948

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$IC_{50} M_3 = 4.8$; compuesto 18 $IC_{50} M_3 = 6.6$, compuesto 20 $IC_{50} M_3 = 6.8$; compuesto 36 $IC_{50} M_3 = 2.7$; compuesto 39 $IC_{50} M_3 = 3.8$; compuesto 44 $IC_{50} M_3 = 4.4$; compuesto 8 $IC_{50} M_3 = 4.8$; compuesto 53 $IC_{50} M_3 = 5.6$; compuesto 77 $IC_{50} M_3 = 3.1$; compuesto 78 $IC_{50} M_3 = 5$; compuesto 89 $IC_{50} M_3 = 5.4$); y teniendo en cuenta que incluso **D₂ enseñaba también** compuestos con actividad antimuscarínica en donde ya se predecía que al ser los esteres y las amidas isómeros, puede un ester ser reemplazado por una amida como actividad rutinaria de laboratorio, sin perder la actividad antimuscarínica, de esta forma haría una combinación de las enseñanzas de ambos documentos llegando a lo reivindicado sin lograr superar tampoco los niveles de actividad o potencia.

En conclusión, no se considera que la presente solicitud merezca reconocimiento de nivel inventivo.

6. Conclusión:

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

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D ₁	WO 01/04118	1 - 22	NIVEL INVENTIVO
D ₂	EP 0930298	1 - 22	NIVEL INVENTIVO

7. Respuesta a los argumentos del solicitante:

1. El solicitante anexa las estructuras químicas de los compuestos individuales particulares de formula (I) que se desean proteger, adjunta la tabla con datos IC_{50} de algunos ejemplos representativos, elimina reivindicaciones de usos y de procedimiento por no ser nuevas.
2. Dice el solicitante que el termino "sales farmacéuticamente aceptables" esta claramente descrito y limitado en la memoria descriptiva en donde es evidente a cuales compuestos se refieren dichas sales.

Se admite como válido el argumento del solicitante para incluir dicho término.

3. Dice el solicitante que D₁ se refiere a derivados de éster de quinuclidina a diferencia de los compuestos de la presente solicitud que son derivados de amidas quinuclidinas. No hay indicaciones en D₁ que sugieran la modificación del grupo éster por el grupo amida. Es conocido que cualquier modificación puede cambiar drásticamente las propiedades de una molécula dada por esto partiendo de D₁ no se hubiera esperado que los compuestos fueran activos frente a los receptores muscarínicos M₃. El examinador no tuvo en cuenta que no se trata de un cambio de un Oxígeno por un R1 con un N, sino una modificación estructural significativa de grupos funcionales y por lo tanto de un compuesto que tiene una estructura inesperada. Mas aún estos compuestos sorprendentemente han demostrado ser antagonistas muscarínicos M₃ muy potentes y con efecto de larga duración, como se demuestra en la tabla adjunta, por lo tanto se debe tener en cuenta que antes del desarrollo de la presente invención no era obvio que con una modificación estructural tan importante las quinuclidinas fueran activas frente a los receptores

muscarínicos M₃ e incluso presentaran mejoras sustanciales en términos de potencia y duración del efecto.

Se remite al solicitante al actual análisis de nivel inventivo en donde el documento D₂ a diferencia del documento D₁, sí sugiere hacer el intercambio de un éster por una amida ya que se consideran isómeros, de esta forma un experto en la materia consideraría de forma obvia hacer este intercambio obteniendo los derivados de amidas quinuclidinas de la presente solicitud que de hecho presentan la misma o incluso menor actividad o potencia con respecto a los derivados de éster de quinuclidina de la anterioridad. De esta forma comparando los datos adjuntados no se muestran ventajas con respecto a la actividad medida como IC₅₀, por lo tanto no se considera que presenten 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 60 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 numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha
12 FEB. 2010

CONCEPTO TÉCNICO No. 25	EXAMINADOR TÉCNICO Código No. 202087
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EXAMEN TECNICO DE FONDO

N° Radicación	04128948	Fecha de presentación	27/12/2004
N° Solicitud Internacional	PCT/EP2003/006708	Fecha Solicitud Internacional	15/01/2004
N° Prioridad	P 200201539	Fecha de Prioridad	2/07/2002

Palabras clave

CLASIFICACIONES INTERNACIONALES DE BUSQUEDA

A61K31/439; A61K45/00; A61P1/00; A61P11/00; A61P13/00; A61P25/02; C07D453/02; C07D487/08; A61K31/439; A61K45/00; A61P1/00; A61P11/00; A61P13/00; A61P25/00; C07D453/00; C07D487/00

DOCUMENTOS CORRESPONDIENTES EN OTROS PAISES

US2006167042	CA2492535		
MXPA04012271	AU2003242757		
ES2204295			
EP1519933			
CN1678610			

Patente Original WO 2004/005285

BASES DE DATOS CONSULTADAS

EPOLINE
ESPACENET

INFORMES DE EXAMENES EN OTRAS OFICINAS

Oficina	Fecha	Rev. afectadas

ANTERIORIDADES ENCONTRADAS

Documento	Relevancia	Rev. afectadas
WO 01/04118	Particular (x)	1 - 20, 22, 24 21, 23

LITERATURA NO PATENTES

Documento	Relevancia	Rev. afectadas

Observaciones

Fecha del examen 12/03/2008