



Industria y Comercio

SUPERINTENDENCIA

03-28249

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCION

21. **EXPEDIENTE No.**

03-28249

54. **TÍTULO** Compuesto alifático de anillo de 5 miembros que contiene nitrógeno

51. **CLASIFICACIÓN INTERNACIONAL** A61K 3/40

71. **SOLICITANTE** Tanabe Seiyaku Co., Ltd

DOMICILIO Osaka-shi, Osaka 541-8505, Japón

74. **APODERADO** Ramiro Castro Dague

22. **BOGOTÁ, D. C.,**

PETITORIO



.515

SUPERINDUSTRIA Y COMERCIO

Radicación : 03028249 00000000

Folios: 193

Fecha (A/D): 2003-04-03 16:44:33

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Tramite : 011 PCI-PAIENT 3/8 FASE NACI 411 PRESEHAL

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Industria y Comercio 028249 00
SUPERINTENDENCIA

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL

1

SOLICITUD DE:

☒ Patente de Invención.☐ Patente de Modelo de Utilidad.☒ Capítulo I.☐ Capítulo II.

2

SOLICITANTE
(71)Nombre: TANABE SEIYAKU CO., LTD.
Dirección: 2-10, Dosho-Machi 3-chome, Chuo-Ku,
Osaka-Shi, Osaka 541-8505, JAPON
Nacionalidad o Domicilio: JAPON
Lugar de Constitución: JAPON
Teléfono: Fax:
E-mail

IDENTIFICACION

C.C. ☐ NIT ☐C.E. ☐ Otro ☐

Cual _____

Número _____

3

REPRESENTANTE
O APODERADONombre: RAMIRO CASTRO DUQUE
Dirección: Cra. 7 No. 16-56 Piso 9
Teléfono: 380-2200 Fax: 380-2700
E-mail:

IDENTIFICACION

C.C. ☒ NIT ☐C.E. ☐ Otro ☐

Cual _____

Número 170.322 TP 1003

4

INVENTOR (ES)
(72)Nombre: Kosuke Yasuda, Hiroshi Morimoto, Saburo Kawanami, Masataka Hikota,
Takeshi Matsumoto, Kenji Arakawa
Dirección: 14-24, Fujimi 4-chome, Fukiage-machi, Kita-adachi-gun, Saitama 369-0121,
JP; 750-2-606, Onaricho 4-chome, Saitama-shi Saitama 331-0043, JP; 10-10, Negishi 2-
chome Saitama-shi, Saitama 336-0024, JP; 16-19, Kashiwacho 2-chome, Shiki-shi,
Saitama 353-0007 JP; 3-10-1203, Takasago 3-chome, Saitama-shi, Saitama 336-0011,
JP; 3-2-211, Segasaki 2-chome, Saitama-shi, Saitama 336-0909, Japón (Respectivam.)
Nacionalidad o Domicilio: Japón

5 PCT (86)

Solicitud Internacional No. PCT/JP01/08803 Fecha 05-10-2001

Publicación Internacional No. WO 02/30891 A1 Fecha 18-04-2002

15 Título (54): COMPUERTO ALIFATICO DE ANILLO DE 5 MIEMBROS QUE CONTIENE NITROGENO

7 Clasificación Internacional (51) A61K 31/40

8 Prioridad

SI ☒ NO ☐(33) País de
Origen

(32) Fecha

(31) Número de Solicitud

JP

06-10-2000

308528/2000

JP

12-10-2000

312562/2000

JP

30-03-2001

099251/2000

9 Comprobante de pago No. 03-15.280

Fecha 03-04-2003

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

10

ANEXOS

42

- ☒ Comprobante de pago de la tasa de presentación de la solicitud \$400 000
- ☐ Comprobante de pago por reconocimiento de prioridad
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica
- ☐ Poderes a favor del caso
- ☐ Documento de cese del inventor al solicitante o a su sucesor
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional (Resumen descriptivo reivindicaciones claims)
- ☐ Traducción de la solicitud internacional al castellano (Resumen descriptivo reivindicaciones claims)
- ☐ Copia del examen preliminar efectuado por la IPEA
- ☐ Traducción del examen preliminar efectuado por la IPEA
- ☐ De ser el caso copia del contrato de cesión
- ☐ De ser el caso documento que acredite la licencia o autorización de uso de conocimientos tecnológicos de las empresas extranjeras
- ☐ De ser el caso certificado de depósito del material biológico
- ☐ Acta final 12x12
- ☐ De ser el caso información sobre otras solicitudes de patente o títulos otorgados en el extranjero por el mismo titular o su sucesor relacionadas parcial o totalmente con la invención de esta solicitud
- ☐ Otros

11 FIRMACARACTERÍSTICA

12 Sobre la concesión de la patente,

NOMBRE DANIO CASEROL RUCHE

FIRMA

CC 170.322 del Regla TP 1033 del CSJ

Instrucciones para la presentación de los anexos ver reverso de esta página

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 15,280
FECHA : MARZO 3 DE 2003

SUPERINDUSTRIA Y COMERCIO
Radiacion : 03028249 00000000 Folio: 193
Fecha (AM): 2003-04-03 16:44:53
Tramite : 011 PCT-PATENT 378 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	2198734	03/03/2003	23,740,000.00

***** CONCEPTO *****

CANT. CONTABILITICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	400,000.00
	TOTAL :	\$ 400,000.00

SON: CUATROCIENTOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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

(12) 許協力条約に基づいて公開された国際出願

訂正版

(19) 世界知的所有権機関
国際事務局



(43) 国際公開日
2002 年 4 月 18 日 (18.04.2002)

PCT

(10) 国際公開番号
WO 02/30891 A1

(51) 国際特許分類⁷ C07D 207/16, 401/12, 403/12, 417/12, 409/14, 413/12, 491/048, 405/14, 405/12, 471/04, 495/04, 401/14, 409/12, 417/14, A61K 31/4439, 31/506, 31/501, 31/497, 31/5377, 31/428, 31/423, 31/498, 31/519, 31/401, 31/4709, 31/454, 31/4025, 31/427, 31/433, 31/55, 31/541, 31/437, 31/4725, 31/4365, 31/4035, 31/498, 31/41, 31/4155, C07D 277/06, 277/42, 277/82, A61P 43/00, 3/10

(21) 国際出願番号 PCT/JP01/08803

(22) 国際出願日 2001 年 10 月 5 日 (05 10 2001)

(25) 国際出願の言語 日本語

(26) 国際公開の言語 日本語

(30) 優先権データ
特願 2000-308528 2000 年 10 月 6 日 (06.10.2000) JP
特願 2000-312562 2000 年 10 月 12 日 (12.10.2000) JP
特願 2001-099251 2001 年 3 月 30 日 (30.03 2001) JP

(71) 出願人 (米国を除く全ての指定国について) 田辺製薬株式会社 (TANABE SEIYAKU CO., LTD.) [JP/JP], 〒541-8505 大阪府大阪市中央区道修町 3 丁目 2 番 10 号 Osaka (JP)

(72) 発明者; および

(75) 発明者/出願人 (米国についてのみ) 安田公助 (YASUDA, Kosuke) [JP/JP], 〒369-0121 埼玉県北足立郡牧上町富士見 4-14-24 Saitama (JP) 森本啓氏

(MORIMOTO, Hiroshi) [JP/JP], 〒331-0043 埼玉県さいたま市大成町 4-750-2-606 Saitama (JP). 河内三郎 (KAWANAMI, Saburo) [JP/JP], 〒336-0024 埼玉県さいたま市桜岸 2-10-10 Saitama (JP) 彦田匡敏 (HIKOTA, Masataka) [JP/JP], 〒353-0007 埼玉県志木市柏町 2 丁目 16 番 19 号 Saitama (JP) 松本 健 (MATSUMOTO, Takeshi) [JP/JP], 〒336-0011 埼玉県さいたま市高砂 3-3-10-1203 Saitama (JP). 荒川健司 (ARAKAWA, Kenji) [JP/JP], 〒336-0909 埼玉県さいたま市瀬ヶ崎 2-3-2-211 Saitama (JP)

(74) 代理人 弁理士 津国 豊 (TSUKUNI, Hajime), 〒105-0001 東京都港区虎ノ門 1 丁目 22 番 12 号 SVAX TSビル Tokyo (JP).

(81) 指定国 (国内) AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CO, CR, CU, CZ, DM, DZ, EC, EE, GD, GE, HR, HU, ID, IL, IN, IS, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PH, PL, RO, SG, SI, SK, TT, UA, US, UZ, VN, YU, ZA

(84) 指定国 (広域) ARIPO 特許 (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), ユーラシア 特許 (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), ヨーロッパ特許 (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI 特許 (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

添付公開書類

国際調査報告書

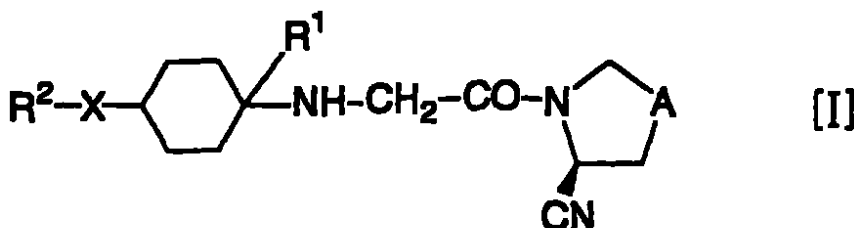
(48) この訂正版の公開日

2002 年 5 月 16 日

[続表]

(54) Title ALIPHATIC NITROGENOUS FIVE-MEMBERED RING COMPOUNDS

(54) 発明の名称 脂肪族含窒素五員環化合物



(57) Abstract Aliphatic nitrogenous five-membered ring compounds of the general formula [I] or pharmacologically acceptable salts thereof; a process for the preparation of the compounds or the salts, and pharmaceutical compositions containing the compounds or the salts as the active ingredient. [I] wherein A is CH₂- or S-, R¹ is hydrogen, lower alkyl, hydroxy-lower alkyl, or lower alkoxy-lower alkyl, X is N(R³)-, -O-, or CO-, R² is hydrogen or lower alkyl, and R³ is an optionally substituted cyclic group or optionally substituted amino

[続表有]

WO 02/30891 A1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP01/08803

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.⁷ C07D207/16, 401/12, 403/12, 417/12, 409/14, 413/12, 491/048, 405/14, 405/12, 471/04, 495/04, 401/14, 409/12, 417/14, A61K31/4439, 31/506, 31/501, 31/497, 31/5377, 31/428,

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int. Cl.⁷ C07D207/16, 401/12, 403/12, 417/12, 409/14, 413/12, 491/048, 405/14, 405/12, 471/04, 495/04, 401/14, 409/12, 417/14, A61K31/4439, 31/506, 31/501, 31/497, 31/5377, 31/428,

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

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

CA (STN), REGISTRY (STN), WPIDS (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6110949 A (Novartis AG), 29 August, 2000 (29.08.00), the whole document (Family: none)	1-19, 27-32
A	US 6011155 A (Novartis AG), 04 January, 2000 (04.01.00), the whole document & US 6124305 A	1-19, 27-32

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"T" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"Z" document member of the same patent family

Date of the actual completion of the international search
01 November, 2001 (01.11.01)

Date of mailing of the international search report
13 November, 2001 (13.11.01)

Name and mailing address of the ISA/
Japanese Patent Office

Authorized officer

Facsimile No.

Telephone No.

INTERNATIONAL SEARCH REPORT

International application No

PCT/JP01/08803

Continuation of A.

31/423, 31/498, 31/519, 31/401, 31/4709, 31/454, 31/4025, 31/427, 31/433, 31/55,
31/541, 31/437, 31/4725, 31/4365, 31/4035, 31/498, 31/41, 31/4155, C07K277/06, 277/42,
277/82, A61P43/00, 3/10,

Continuation of B

31/423, 31/498, 31/519, 31/401, 31/4709, 31/454, 31/4025, 31/427, 31/433, 31/55,
31/541, 31/437, 31/4725, 31/4365, 31/4035, 31/498, 31/41, 31/4155, C07K277/06, 277/42,
277/82

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP01/08803

6
X

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

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

1. ☒ Claims Nos. 20-26
because they relate to subject matter not required to be searched by this Authority, namely
Claims 20-26 relate to methods for treatment of the human body by therapy.
2. ☐ Claims Nos.
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically-
3. ☐ Claims Nos.
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

PATENT COOPERATION TREATY

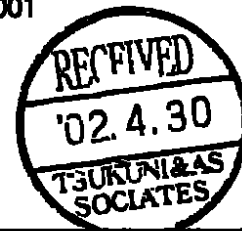
PCT

INFORMATION CONCERNING ELECTED
OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

From the INTERNATIONAL BUREAU

To

TSUKUNI, Hajime
SVAX TS Bldg
22-12, Toranomon 1-chome
Minato-ku, Tokyo 105-0001
JAPON

Date of mailing (day/month/year) 18 April 2002 (18 04 02)		
Applicant's or agent's file reference FP2471PCT		IMPORTANT INFORMATION
International application No. PCT/JP01/08803	International filing date (day/month/year) 05 October 2001 (05 10 01)	
Priority date (day/month/year) 06 October 2000 (06 10 00)		
Applicant TANABE SEIYAKU CO, LTD et al		

- 1 The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election

EP AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE,TR
National AU,BG,CA,CN,IL,KR,MN,NO,NZ,PL,RO,SK,US

- 2 The following Offices have waived the requirement for the notification of their election, the notification will be sent to them by the International Bureau only upon their request

AP GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZW
EA AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
OA BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG
National AE,AG,AL,BA,BB,BR,BZ,CO,CR,CU,CZ,DM,DZ,EC,EE,GD,GE,HR,HU,ID,IN,
IS,LC,LK,LR,LT,LV,MA,MG,MK,MX,PH,SG,SI,TT,UA,UZ,VN,YU,ZA

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 38(3)(b) and Rule 74.1)

Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide

The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer J Zahra
Facsimile No. (41 22) 740 14.35	Telephone No. (41-22) 338 83 38

PATENT COOPERATION TREATY

WO 02/30891
PCT/JP01/08803

B X

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From the INTERNATIONAL BUREAU

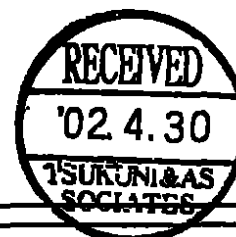
NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47 1(c), first sentence)

To

TSUKUNI, Hajime
SVAX TS Bldg
22-12, Toranomon 1-ch
Minato-ku, Tokyo 105-01
JAPON

164 up



Date of mailing (day/month/year) 18 April 2002 (18 04 02)		
Applicant's or agent's file reference FP2471PCT		IMPORTANT NOTICE
International application No. PCT/JP01/08803	International filing date (day/month/year) 05 October 2001 (05 10 01)	Priority date (day/month/year) 06 October 2000 (06 10 00)
Applicant TANABE SEIYAKU CO, LTD et al		

- 1 Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice
KR,US

In accordance with Rule 47 1(c), third sentence those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s)

- 2 The following designated Offices have waived the requirement for such a communication at this time

AE,AG,AL,AP,AU,BA,BB,BG,BR,BZ,CA,CN,CO,CR,CU,CZ,DM,DZ,EA,EC,EE,EP,GD,GE,HR,HU,ID,
IL,IN,IS,LC,LK,LR,LT,LV,MA,MG,MK,MN,MX,NO,NZ,OA,PH,PL,RO,SG,SI,SK,TT,UA,UZ,VN,YU,
ZA

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 48.1(a bis))

- 3 Enclosed with this notice is a copy of the international application as published by the International Bureau on
18 April 2002 (18.04.02) under No WO 02/30891

4. TIME LIMITS for filing a demand for international preliminary examination and for entry into national phase

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph be 30 MONTHS from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 18 months from the priority date, but also in respect of any designated Office, in the absence of filing of such demand where Article 22(1) as modified with effect from 1 April 2002 applies in respect of the designated Office For further details, see PCT Gazette No 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the PCT News letter, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20,21,30 or 31 months, or other time limit), Office by Office, refer to the PCT Gazette, the PCT Newsletter and the PCT Applicant's Guide Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>

For filing a demand for international preliminary examination, see the PCT Applicant's Guide, Volume I/A, Chapter IX Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II)

It is the applicant's sole responsibility to monitor all these limits.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer J Zahra
Facsimile No (41-22) 740 14 35	Telephone No (41 22) 338 91 11

PATENT COOPERATION TREATY

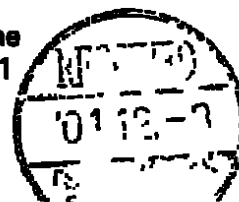
PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To

TSUKUNI, Hajime
SVAX TS Bldg
22-12, Toranomon 1-chome
Minato-ku, Tokyo 105-0001
JAPON

Date of mailing (day/month/year) 27 November 2001 (27 11 01)	
Applicant's or agent's file reference FP2471PCT	IMPORTANT NOTIFICATION
International application No PCT/JP01/08803	International filing date (day/month/year) 05 October 2001 (05 10 01)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 06 October 2000 (06 10 00)
Applicant TANABE SEIYAKU CO, LTD et al	

- 1 The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17 1(a) or (b).
- 2 This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
- 3 An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17 1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17 1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- 4 The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17 1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17 1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
06 Octo 2000 (06 10 00)	2000-308528	JP	23 Nove 2001 (23 11 01)
12 Octo 2000 (12 10 00)	2000-312562	JP	23 Nove 2001 (23 11 01)
30 Marc 2001 (30 03 01)	2001-099251	JP	23 Nove 2001 (23 11 01)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740 14.35	Authorized officer Somsak THIPHRAKESONE Telephone No. (41-22) 338 83.38
--	---

PATENT COOPERATION TREATY

PCT

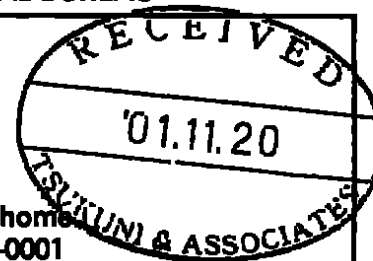
NOTIFICATION OF RECEIPT OF
RECORD COPY

(PCT Rule 24 2(a))

From the INTERNATIONAL BUREAU

To

TSUKUNI, Hajime
SVAX TS Bldg
22-12, Toranomon 1-chome
Minato-ku, Tokyo 105-0001
JAPON



Date of mailing (day/month/year) 09 November 2001 (09 11 01)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference FP2471PCT	International application No. PCT/JP01/08803

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below

Name(s) of the applicant(s) and State(s) for which they are applicants

TANABE SEIYAKU CO , LTD (for all designated States except US)
YASUDA, Kosuke et al (for US)

International filing date

05 October 2001 (05 10 01)

Priority date(s) claimed

06 October 2000 (06 10 00)

12 October 2000 (12 10 00)

30 March 2001 (30 03 01)

Date of receipt of the record copy
by the International Bureau

19 October 2001 (19 10 01)

List of designated Offices

AP GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZW

EA AM,AZ,BY,KG,KZ,MD,RU,TJ,TM

EP AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE,TR

OA BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG

National AE,AG,AL,AU,BA,BB,BG,BR,BZ,CA,CN,CO,CR,CU,CZ,DM,DZ,EC,EE,GD,GE,HR,HU,ID,
IL,IN,IS,KR,LC,LK,LR,LT,LV,MA,MG,MK,MN,MX,NO,NZ,PH,PL,RO,SG,SI,SK,TT,UA,US,UZ,VN,
YU,ZA

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740 14.35

Authorized officer

M. HONDA

Telephone No (41-22) 338.63.38

Continuation of Form PCT/IB/30.

NOTIFICATION OF RECEIPT OF RECORD COPY

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Date of mailing (day/month/year) 09 November 2001 (09 11 01)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference FP2471PCT	International application No. PCT/JP01/08803

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to

- ☒ time limits for entry into the national phase
- ☒ confirmation of precautionary designations
- ☒ requirements regarding priority documents

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated in the Notification of Receipt of Record Copy (Form PCT/IB/301) by paying national fees and furnishing translations, as prescribed by the applicable national laws

The time limit for performing these procedural acts is 20 MONTHS from the priority date or, for those designated States which the applicant elects in a demand for international preliminary examination or in a later election, 30 MONTHS from the priority date, provided that the election is made before the expiration of 18 months from the priority date. Some designated (or elected) Offices have fixed time limits which expire even later than 20 or 30 months from the priority date. In other Offices an extension of time or grace period, in some cases upon payment of an additional fee, is available.

In addition to these procedural acts, the applicant may also have to comply with other special requirements applicable in certain Offices. It is the applicant's responsibility to ensure that the necessary steps to enter the national phase are taken in a timely fashion. Most designated Offices do not issue reminders to applicants in connection with the entry into the national phase.

For detailed information about the procedural acts to be performed to enter the national phase before each designated Office, the applicable time limits and possible extensions of time or grace periods, and any other requirements, see the relevant Chapters of Volume II of the PCT Applicant's Guide. Information about the requirements for filing a demand for international preliminary examination is set out in Chapter IX of Volume I of the PCT Applicant's Guide.

GR and ES became bound by PCT Chapter II on 7 September 1986 and 8 September 1987, respectively, and may, therefore, be elected in a demand or a later election filed on or after 7 September 1986 and 8 September 1987, respectively, regardless of the filing date of the international application. (See second paragraph above.)

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

CONFIRMATION OF PRECAUTIONARY DESIGNATIONS

This notification lists only specific designations made under Rule 4.9(a) in the request. It is important to check that these designations are correct. Errors in designations can be corrected where precautionary designations have been made under Rule 4.9(b). The applicant is hereby reminded that any precautionary designations may be confirmed according to Rule 4.9(c) before the expiration of 15 months from the priority date. If it is not confirmed, it will automatically be regarded as withdrawn by the applicant. There will be no reminder and no invitation. Confirmation of a designation consists of the filing of a notice specifying the designated State concerned (with an indication of the kind of protection or treatment desired) and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled:

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 18 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 18-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 18-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity to furnish the priority document within a time limit which is reasonable under the circumstances.

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 18-month time limit is the filing date of the earliest application whose priority is claimed.

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特許協力条約に基づく国際出願
国際予備審査請求書

第 II 章

出願人は 次の国際出願が特許協力条約に従って国際予備審査の対象とされることを希望し、
優先資格のある全ての国を選択する。ただし 特許の表示がある場合を除く。



国際予備審査機関の名称		請求書の受理の日	
第 I 欄 出願人又は代理人の名称		出願人又は代理人の寄附記号 FP2471PCT	
国際出願番号	国際出願日 (日 月 年) 05 10 01	優先日 (最先のもの) (日 月 年) 06. 10 00	
発明の名称 脂肪族含窒素五員環化合物			
第 II 欄 出願人		電話番号	
氏名 (名称) 及びあて名 (姓・名の順に記載 法人は正式の完全な名称を記載、あて名は郵便番号及び国名も記載) 田辺製薬株式会社 TANABE SEIYAKU CO, LTD 〒541-8505 日本国大阪府大阪市中央区道修町3丁目2番10号 2-10, Dosho-machi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8505 JAPAN		ファクシミリ番号	
国名 (国名) 日本国 JAPAN		住所 (国名) 日本国 JAPAN	
氏名 (名称) 及びあて名 (姓・名の順に記載 法人は正式の完全な名称を記載、あて名は郵便番号及び国名も記載) 安田 公助 YASUDA Kosuke 〒369-0121 日本国埼玉県北足立郡吹上町富士見4-14-24 14-24, Fujimi 4-chome, Fukiage-machi, Kita-adachi-gun, Saitama 369-0121 JAPAN		加入電話番号	
国名 (国名) 日本国 JAPAN		住所 (国名) 日本国 JAPAN	
氏名 (名称) 及びあて名 (姓・名の順に記載 法人は正式の完全な名称を記載、あて名は郵便番号及び国名も記載) 森本 啓氏 MORIMOTO Hiroshi 〒331-0043 日本国埼玉県さいたま市大成町4-750-2-606 750-2-606, Onaricho 4-chome, Saitama-shi, Saitama 331-0043 JAPAN			
国名 (国名) 日本国 JAPAN		住所 (国名) 日本国 JAPAN	
☒ その他の出願人が記録されている。			

14

国籍出願番号

2

第11 州の代表者 又は代理人

この書面の記述を認用しないときは、この附紙を国領子館管掌官に寄附しないこと。

氏名（名称）及びあて名（姓・名の順に記載 法人は正式の完全な名称を記載 あて名は郵便番号及び国名も記載）

河南 三郎 KAWANAMI Saburo

〒336-0024 日本国埼玉県さいたま市根岸2-10-10

10-10, Negishi 2-chome, Saitama-shu, Saitama 336-0024 JAPAN

国名（国名）

日本国 JAPAN

住所（国名）

日本国 JAPAN

氏名（名称）及びあて名（姓・名の順に記載 法人は正式の完全な名称を記載 あて名は郵便番号及び国名も記載）

彦田 匡毅 HIKOTA Masataka

〒353-0007 日本国埼玉県志木市柏町2丁目16番19号

16-19, Kashiwacho 2-chome, Shiki-shi, Saitama 353-0007 JAPAN

国名（国名）

日本国 JAPAN

住所（国名）

日本国 JAPAN

氏名（名称）及びあて名（姓・名の順に記載 法人は正式の完全な名称を記載 あて名は郵便番号及び国名も記載）

松本 健 MATSUMOTO Takeshi

〒336-0011 日本国埼玉県さいたま市高砂3-3-10-1203

3-10-1203, Takasago 3-chome, Saitama-shi, Saitama 336-0011 JAPAN

国名（国名）

日本国 JAPAN

住所（国名）

日本国 JAPAN

氏名（名称）及びあて名（姓・名の順に記載 法人は正式の完全な名称を記載 あて名は郵便番号及び国名も記載）

荒川 健司 ARAKAWA Kenji

〒336-0909 日本国埼玉県さいたま市瀬ヶ崎2-3-2-211

3-2-211, Segasaki 2-chome, Saitama-shi, Saitama 336-0909 JAPAN

国名（国名）

日本国 JAPAN

住所（国名）

日本国 JAPAN

☐ その他の出願人が他の紙面に記載されている。

国式PC7/1PBA/401（総頁）（1998年7月 再版1999年1月）

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第III欄 代理人又は出願の代表者、通知のあて名

下記に記載された者は ☒ 代理人 又は ☐ 共通の代表者 として

- ☒ 既に選任された者であって 国際予備審査についても出願人を代理する者である。
- ☐ 今回新たに選任された者である。 先に選任されていた代理人又は共通の代表者は解任された。
- ☐ 既に選任された代理人又は共通の代表者に加えて 特に国際予備審査機関に対する手続のために、今回新たに選任された者である。

氏名 (名簿) 及びあて名 (姓 名の順に記載 法人は正式の完全な名簿を記載 あて名は郵便番号及び国名も記載)

7866 井理士 津 国 泰 TSUKUNI Hajime
〒105-0001 日本国東京都港区虎ノ門1丁目2番12号
SVAX TSビル
SVAX TS Bldg,
22-12, Toranomon 1-chome, Minato-ku, Tokyo 105-0001 JAPAN

電話番号
03-3502-7213

ファクシミリ番号
03-3502-7218

加入電話番号

☐ 通知のためのあて名 代理人又は共通の代表者が選任されておらず 上記枠内に特に通知が送付されるあて名を記載している場合は レ印を付す。

第IV欄 国際予備審査に対する基本事項

補正に関する記述 *

1 出願人は 次のものを基礎として国際予備審査を開始することを希望する。

- ☒ 出願時の国際出願を基礎とすること。
- ☐ 明細書に關して ☐ 出願時のものを基礎とすること。
- ☐ 特許協力条約第34条の規定に基づいてなされた補正を基礎とすること。
- ☐ 請求の範囲に關して ☐ 出願時のものを基礎とすること。
- ☐ 特許協力条約第19条の規定に基づいてなされた補正 (添付した説明書も含む) を基礎とすること。
- ☐ 特許協力条約第34条の規定に基づいてなされた補正を基礎とすること。
- ☐ 摘要に關して ☐ 出願時のものを基礎とすること。
- ☐ 特許協力条約第34条の規定に基づいてなされた補正を基礎とすること。

2 ☐ 出願人は 特許協力条約第19条の規定に基づく請求の範囲について行った補正を撤回し かつ、取り消されたものとみなして開始することを希望す。

3 ☐ 出願人は、国際予備審査の開始が係争目から入り凡経過まで懸念されることを希望する (ただし、国際予備審査機関が、特許協力条約第19条の規定に基づき付与した補正の幸しを受領し又は撤回補正を希望しない旨の出願人からの通知を受領した場合は除く (規則 89.1(d)))。 (この口は 特許協力条約第19条の規定に基づく撤回が終了していない場合にのみ レ印を付すことができる。)

*記入がない場合は、1) 補正がない又は国際予備審査機関が補正 (原本又は平し) を受領していないときは 出願時の国際出願を基礎に予備審査が開始され、2) 国際予備審査機関が 見解書又は予備審査報告書の作成開始前に補正 (原本又は平し) を受領したときは これらの補正を考慮して予備審査が開始又は続行される。

国際予備審査を行うための言語は、日本語.....であり。

- ☐ レ 国際出願の提出時の言語である。
- ☐ 国際審査のために提出した翻訳文の言語である。
- ☐ 国際出願の公開の言語である。
- ☐ 国際予備審査の目的のために提出した翻訳文の言語である。

第V欄 国の選択

出願人は 選択資格のある全ての指定国 (即ち 既に出願人によって指定されており かつ特許協力条約第2章に列載されている国) を選択する。

ただし 出願人は次の国の選択を希望しない。

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... 4 ...

第VI条 附合書類

この国際予備登録請求書には 国際予備登録のために 第IVに記載する書類による書類が添付されている。

国際予備登録機関記入欄

- 1 国際出版の請求文
- 2 特許協力条約第34条の規定に基づく修正書
- 3 特許協力条約第34条の規定に基づく修正書
- 4 特許協力条約第34条の規定に基づく修正書
- 5 書類
- 6 その他 (書類を具体的に記述する) :

枚
枚
枚
枚
枚
枚

受 領	未 受 領
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐

この国際予備登録請求書には さらに下記の書類が添付されている。

- 1 ☒ 手数料計算用紙
- 2 ☐ 別紙の記名押印された委任状
- 3 ☐ 包括委任状の写し
- 4 ☐ 記名押印 (署名) に関する説明書
- 5 ☐ 多国籍企業法 (MNC法) に関する説明書
- 6 ☐ その他 (書類を具体的に記述する)

第VII条 提出者の記名押印

本人の氏名 (名称) を記述し その次に押印する。

津 国 泰



国際予備登録機関記入欄

1 国際予備登録請求書の受理の受領の日

2 規則 80 1 (b) の規定による国際予備登録請求書の受理の日の訂正後の日付

3 ☐ 優先日から18月を経過後の国際予備登録請求書の受理。ただし、以下の4, 5の項目にはあてはまらない。 ☐ 出願人に通知した。

4 ☐ 規則 80 6 により延長が認められている優先日から18月の期間内の国際予備登録請求書の受理

5 ☐ 優先日から18月を経過後の国際予備登録請求書の受理であるが規則82により認められる。

国際事務局記入欄

国際予備登録請求書の国際予備登録機関からの受領の日

特許協力条約に基づく国際出願
願

出願人は、この国際出願が特許協力条約に従って処理されることを請求する。

国際出願番号

受理官庁記入欄

国際出願日

(受付印)

出願人又は代理人の登録記号
(特許する場合 最大12桁)

FP2471PCT

第I欄 発明の名称

脂肪族含窒素五員環化合物

第II欄 出願人

氏名(名称)及びあて名 (姓名の順に記載、法人は正式の完全な名称を記載、あて名は郵便番号及び国名も記載)

田辺製薬株式会社

TANABE SEIYAKU CO, LTD

〒541-8505 日本国大阪府大阪市中央区道修町3丁目2番10号

2-10, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8505 JAPAN

☐ この欄に記載した者は
発明者でもある。

電話番号

ファクシミリ番号

加入電信番号

国籍(国名)

日本国 JAPAN

住所(国名)

日本国 JAPAN

この欄に記載した者は、次の
指定国についての出願人である

☐

すべての指定国

☒

米國を除くすべての指定国

☐

米國のみ

☐

通記欄に記載した指定国

第III欄 その他の出願人又は発明者

氏名(名称)及びあて名 (姓名の順に記載、法人は正式の完全な名称を記載、あて名は郵便番号及び国名も記載)

安田 公助

YASUDA Kosuke

〒369-0121 日本国埼玉県北足立郡吹上町富士見4-14-24

14-24, Fujimi 4-chome, Fukiage-machi, Kita-adachi-gun, Saitama
369-0121 JAPAN

この欄に記載した者は
次に該当する

☐ 出願人のみである。

☒ 出願人及び発明者である。

☐ 発明者のみである。
(ここにレ印を付したときは
以下に記入しないこと)

国籍(国名)

日本国 JAPAN

住所(国名)

日本国 JAPAN

この欄に記載した者は、次の
指定国についての出願人である

☐

すべての指定国

☐

米國を除くすべての指定国

☒

米國のみ

☐

通記欄に記載した指定国

☒ その他の出願人又は発明者が通記欄に記載されている。

第IV欄 代理人又は共通の代表者、通知のあて名

次に記載された者は、国際機関において出願人のために行動する

☒

代理人

☐

共通の代表者

氏名(名称)及びあて名 (姓名の順に記載、法人は正式の完全な名称を記載、あて名は郵便番号及び国名も記載)

7866 井理士 津 国 肇 TSUKUNI Hajime

〒105-0001 日本国東京都港区虎ノ門1丁目22番12号

SVAX TS ビル

SVAX TS Bldg.

22-12, Toranomon 1-chome, Minato-ku, Tokyo 105-0001 JAPAN

電話番号

03-3502-7213

ファクシミリ番号

03-3502-7218

加入電信番号

☐ 通知のためのあて名 代理人又は共通の代表者が選任されておらず、上記枠内に特に通知が送付されるあて名を記載している場合は、レ印を付す。

第三欄の続		その他の出願人又は発明者	
この続表を使用しないときは、この用紙を願書に含めないこと。			
氏名(名称)及びあて名 (姓・名の順に記載。法人は正式の完全な名称を記載。あて名は郵便番号及び国名も記載)		この欄に記載した者は次に該当する	
森本 啓氏 MORIMOTO Hiroshi		☐ 出願人のみである。	
〒331-0043 日本国埼玉県さいたま市大成町4-750-2-606		☒ 出願人及び発明者である。	
750-2-606, Onaricho 4-chome, Saitama-shi, Saitama 331-0043 JAPAN		☐ 発明者のみである。 (ここに印を付したときは以下に記入しないこと)	
国籍(国名)	日本国 JAPAN	住所(国名)	日本国 JAPAN
この欄に記載した者は次の指定国についての出願人である ☐ すべての指定国 ☐ 米國を除くすべての指定国 ☒ 米國のみ ☐ 追加欄に記載した指定国			
氏名(名称)及びあて名 (姓・名の順に記載。法人は正式の完全な名称を記載。あて名は郵便番号及び国名も記載)		この欄に記載した者は次に該当する	
河南 三郎 KAWANAMI Saburo		☐ 出願人のみである。	
〒336-0024 日本国埼玉県さいたま市根岸2-10-10		☒ 出願人及び発明者である。	
10-10, Negishi 2-chome, Saitama-shi, Saitama 336-0024 JAPAN		☐ 発明者のみである。 (ここに印を付したときは以下に記入しないこと)	
国籍(国名)	日本国 JAPAN	住所(国名)	日本国 JAPAN
この欄に記載した者は次の指定国についての出願人である ☐ すべての指定国 ☐ 米國を除くすべての指定国 ☒ 米國のみ ☐ 追加欄に記載した指定国			
氏名(名称)及びあて名 (姓・名の順に記載。法人は正式の完全な名称を記載。あて名は郵便番号及び国名も記載)		この欄に記載した者は次に該当する	
彦田 匡毅 HIKOTA Masataka		☐ 出願人のみである。	
〒353-0007 日本国埼玉県志木市柏町2丁目16番19号		☒ 出願人及び発明者である。	
16-19, Kashiwacho 2-chome, Shiki-shi, Saitama 353-0007 JAPAN		☐ 発明者のみである。 (ここに印を付したときは以下に記入しないこと)	
国籍(国名)	日本国 JAPAN	住所(国名)	日本国 JAPAN
この欄に記載した者は次の指定国についての出願人である ☐ すべての指定国 ☐ 米國を除くすべての指定国 ☒ 米國のみ ☐ 追加欄に記載した指定国			
氏名(名称)及びあて名 (姓・名の順に記載。法人は正式の完全な名称を記載。あて名は郵便番号及び国名も記載)		この欄に記載した者は次に該当する	
松本 健 MATSUMOTO Takeshi		☐ 出願人のみである。	
〒336-0011 日本国埼玉県さいたま市高砂3-3-10-1203		☒ 出願人及び発明者である。	
3-10-1203, Takasago 3-chome, Saitama-shi, Saitama 336-0011 JAPAN		☐ 発明者のみである。 (ここに印を付したときは以下に記入しないこと)	
国籍(国名)	日本国 JAPAN	住所(国名)	日本国 JAPAN
この欄に記載した者は次の指定国についての出願人である ☐ すべての指定国 ☐ 米國を除くすべての指定国 ☒ 米國のみ ☐ 追加欄に記載した指定国			
氏名(名称)及びあて名 (姓・名の順に記載。法人は正式の完全な名称を記載。あて名は郵便番号及び国名も記載)		この欄に記載した者は次に該当する	
松本 健 MATSUMOTO Takeshi		☐ 出願人のみである。	
〒336-0011 日本国埼玉県さいたま市高砂3-3-10-1203		☒ 出願人及び発明者である。	
3-10-1203, Takasago 3-chome, Saitama-shi, Saitama 336-0011 JAPAN		☐ 発明者のみである。 (ここに印を付したときは以下に記入しないこと)	
国籍(国名)	日本国 JAPAN	住所(国名)	日本国 JAPAN
この欄に記載した者は次の指定国についての出願人である ☐ すべての指定国 ☐ 米國を除くすべての指定国 ☒ 米國のみ ☐ 追加欄に記載した指定国			
☒ その他の出願人又は発明者が他の続表に記載されている。			

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第Ⅲ欄の続		その他の出願人又は発明者	
この続欄を使用しないときは この用紙を願書に含めないこと。			
氏名 (名称) 及びあて名 (姓 名の順に記載 法人は正式の完全な名称を記載 あて名は郵便番号及び国名も記載) 荒川 健司 ARAKAWA Kenji 〒336-0909 日本国埼玉県さいたま市瀬ヶ崎2-3-2-211 3-2-211, Segasaki 2-chome, Saitama-shi, Saitama 336-0909 JAPAN		この欄に記載した者は 次に該当する ☐ 出願人のみである。 ☒ 出願人及び発明者である。 ☐ 発明者のみである。 (ここにレ印を付したときは 以下に記入しないこと)	
国籍 (国名)	日本国 JAPAN	住所 (国名)	日本国 JAPAN
この欄に記載した者は 次の 指定国についての出願人である ☐ すべての指定国 ☐ 米國を除くすべての指定国 ☒ 米國のみ ☐ 通定欄に記載した指定国			
氏名 (名称) 及びあて名 (姓 名の順に記載 法人は正式の完全な名称を記載 あて名は郵便番号及び国名も記載)		この欄に記載した者は 次に該当する ☐ 出願人のみである。 ☐ 出願人及び発明 である。 ☐ 発明者のみである。 (ここにレ印を付したときは 以下に記入しないこと)	
国籍 (国名)		住所 (国名)	
この欄に記載した者は 次の 指定国についての出願人である ☐ すべての指定国 ☐ 米國を除くすべての指定国 ☐ 米國のみ ☐ 通定欄に記載した指定国			
氏名 (名称) 及びあて名 (姓 名の順に記載 法人は正式の完全な名称を記載 あて名は郵便番号及び国名も記載)		この欄に記載した者は 次に該当する ☐ 出願人のみである。 ☐ 出願人及び発明者である。 ☐ 発明者のみである。 (ここにレ印を付したときは 以下に記入しないこと)	
国籍 (国名)		住所 (国名)	
この欄に記載した者は 次の 指定国についての出願人である ☐ すべての指定国 ☐ 米國を除くすべての指定国 ☐ 米國のみ ☐ 通定欄に記載した指定国			
氏名 (名称) 及びあて名 (姓 名の順に記載 法人は正式の完全な名称を記載 あて名は郵便番号及び国名も記載)		この欄に記載した者は 次に該当する ☐ 出願人のみである。 ☐ 出願人及び発明 である。 ☐ 発明者のみである。 (ここにレ印を付したときは 以下に記入しないこと)	
国籍 (国名)		住所 (国名)	
この欄に記載した者は 次の 指定国についての出願人である ☐ すべての指定国 ☐ 米國を除くすべての指定国 ☐ 米國のみ ☐ 通定欄に記載した指定国			
氏名 (名称) 及びあて名 (姓 名の順に記載 法人は正式の完全な名称を記載 あて名は郵便番号及び国名も記載)		この欄に記載した者は 次に該当する ☐ 出願人のみである。 ☐ 出願人及び発明 である。 ☐ 発明者のみである。 (ここにレ印を付したときは 以下に記入しないこと)	
国籍 (国名)		住所 (国名)	
この欄に記載した者は 次の 指定国についての出願人である ☐ すべての指定国 ☐ 米國を除くすべての指定国 ☐ 米國のみ ☐ 通定欄に記載した指定国			
☐ その他の出願人又は発明者が他の続欄に記載されている。			

20 X

第V欄 國の指定

規則4 9 (a) の規定に基づき次の指定を行う (前面する□にレ印を付すこと、少なくとも1つの□にレ印を付すこと)。

広域特許

- ☒ A P A R I P O 特許 G H ガーナ Ghana, G M ガンビア Gambia, K E ケニア Kenya, L S レノト Lesotho, M W マラウイ Malawi, M Z モザンビーク Mozambique, S D スーダン Sudan, S L シエラ レオネ Sierra Leone, S Z スワジランド Swaziland, T Z タンザニア United Republic of Tanzania, U G ウガンダ Uganda, Z W ジンバブエ Zimbabwe, 及びハラレプロトコルと特許協力条約の締約国である他の国
- ☒ E A ユーラシア特許 A M アルメニア Armenia, A Z アゼルバイジャン Azerbaijan, B Y ベラルーシ Belarus, K G キルギスタン Kyrgyzstan, K Z カザフスタン Kazakhstan, M D モルドヴァ Republic of Moldova, R U ロシア Russian Federation, T J タジキスタン Tajikistan, T M トルクメニスタン Turkmenistan, 及びユーラシア特許条約と特許協力条約の締約国である他の国
- ☒ E P ヨーロッパ特許 A T オーストリア Austria, B E ベルギー Belgium, C H and L I スイス及びリヒテンシュタイン Switzerland and Liechtenstein, C Y キプロス Cyprus, D E ドイツ Germany, D K デンマーク Denmark, E S スペイン Spain, F I フィンランド Finland, F R フランス France, G B 英国 United Kingdom, G R ギリシャ Greece, I E アイルランド Ireland, I T イタリア Italy, L U ルクセンブルグ Luxembourg, M C モナコ Monaco, N L オランダ Netherlands, P T ポルトガル Portugal, S E スウェーデン Sweden, T R トルコ Turkey, 及びヨーロッパ特許条約と特許協力条約の締約国である他の国
- ☒ O A O A P I 特許 B F ブルキナ ファソ Burkina Faso, B J ベナン Benin, C F 中央アフリカ Central African Republic, C G コンゴ Congo, C I コートジボアール Côte d'Ivoire, C M カメルーン Cameroon, G A ガボン Gabon, G N ギニア Guinea, G W ギニア ビサウ Guinea-Bissau, M L マリ Mali, M R モーリタニア Mauritania, N E ニジェール Niger, S N セネガル Senegal, T D チャード Chad, T G トーゴ Togo, 及びアフリカ知的財産権機構のメンバー国と特許協力条約の締約国である他の国 (他の種類の保護又は取り扱いを求める場合には点線の上に記載する)

国内特許 (他の種類の保護又は取り扱いを求める場合には点線の上に記載する)

- | | |
|---|---|
| ☒ A E アラブ首長国連邦 United Arab Emirates | ☒ L K スリ ランカ Sri Lanka |
| ☒ A G アンティグア・バーブーダ Antigua and Barbuda | ☒ L R リベリア Liberia |
| ☒ A L アルバニア Albania | ☐ L S レノト Lesotho |
| ☐ A M アルメニア Armenia | ☒ L T リトアニア Lithuania |
| ☐ A T オーストリア Austria | ☐ L U ルクセンブルグ Luxembourg |
| ☒ A U オーストラリア Australia | ☒ L V ラトヴィア Latvia |
| ☐ A Z アゼルバイジャン Azerbaijan | ☒ M A モロッコ Morocco |
| ☒ B A ボスニア・ヘルツェゴヴィナ Bosnia and Herzegovina | ☐ M D モルドヴァ Republic of Moldova |
| | ☒ M G マダガスカル Madagascar |
| ☒ B B バルバドス Barbados | ☒ M K マケドニア旧ユーゴスラヴィア共和国 The former Yugoslav Republic of Macedonia |
| ☒ B G ブルガリア Bulgaria | |
| ☒ B R ブラジル Brazil | ☒ M N モンゴル Mongolia |
| ☐ B Y ベラルーシ Belarus | ☐ M W マラウイ Malawi |
| ☒ B Z ベリーズ Belize | ☒ M X メキシコ Mexico |
| ☒ C A カナダ Canada | ☐ M Z モザンビーク Mozambique |
| ☐ C H and L I スイス及びリヒテンシュタイン Switzerland and Liechtenstein | ☒ N O ノルウェー Norway |
| ☒ C N 中国 China | ☒ N Z ニュー ジーランド New Zealand |
| ☒ C R コスタリカ Costa Rica | ☒ P L ポーランド Poland |
| ☒ C U キューバ Cuba | ☐ P T ポルトガル Portugal |
| ☒ C Z チェコ Czech Republic | ☒ R O ルーマニア Romania |
| ☐ D E ドイツ Germany | ☐ R U ロシア Russian Federation |
| ☐ D K デンマーク Denmark | ☐ S D スーダン Sudan |
| ☒ D M ドミニカ Dominica | ☐ S E スウェーデン Sweden |
| ☒ D Z アルジェリア Algeria | ☒ S G シンガポール Singapore |
| ☒ E E エストニア Estonia | ☒ S I スロヴェニア Slovenia |
| ☐ E S スペイン Spain | ☒ S K スロヴァキア Slovakia |
| ☐ F I フィンランド Finland | ☐ S L シエラ レオネ Sierra Leone |
| ☐ G B 英国 United Kingdom | ☐ T J タジキスタン Tajikistan |
| ☒ G D グレナダ Grenada | ☐ T M トルクメニスタン Turkmenistan |
| ☒ G E ジョージア Georgia | ☐ T R トルコ Turkey |
| ☐ G H ガーナ Ghana | ☒ T T トリニダード・トバゴ Trinidad and Tobago |
| ☐ G M ガンビア Gambia | ☐ T Z タンザニア United Republic of Tanzania |
| ☒ H R クロアチア Croatia | ☒ U A ウクライナ Ukraine |
| ☒ H U ハンガリー Hungary | ☐ U G ウガンダ Uganda |
| ☒ I D インドネシア Indonesia | ☒ U S 米国 United States of America |
| ☒ I L イスラエル Israel | |
| ☒ I N インド India | ☒ U Z ウズベキスタン Uzbekistan |
| ☒ I S アイスランド Iceland | ☒ V N ヴィエトナム Viet Nam |
| ☐ J P 日本 Japan | ☒ Y U ユーゴスラヴィア Yugoslavia |
| ☐ K E ケニア Kenya | ☒ Z A 南アフリカ共和国 South Africa |
| ☐ K G キルギスタン Kyrgyzstan | ☐ Z W ジンバブエ Zimbabwe |
| ☐ K P 北朝鮮 Democratic People's Republic of Korea | |
| ☒ K R 韓国 Republic of Korea | 下の□は、この様式の施行後に特許協力条約の締約国となった国を指定するためのものである。 |
| ☐ K Z カザフスタン Kazakhstan | ☒ C O コロンビア Republic of Colombia |
| ☒ L C セント ルシア Saint Lucia | ☒ E C エクアドル Republic of Ecuador |
| | ☒ P H フィリピン the Philippines |

指定の撤回の宣言 出願人は 上記の指定に加えて 規則4 9 (b) の規定に基づき 特許協力条約の下で認められる他の全ての国の指定を行う。但し、この宣言から除く旨の表示を通知にした国は 指定から除かれる。出願人は これらの通知される指定が撤回を条件としていること並びに優先日から15月が経過する前にその撤回がなされない指定は この期間の経過時に 出願人によって取り下げられたものとみなされることを宣言する。(指定の撤回は 指定を指定する通知の提出と指定手続費及び撤回手続費の納付とらなる。この撤回は 優先日から15月以内に受審官庁へ提出しなければならない。)

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第VI欄 優先権主張

☐ 他の優先権の主張（先の出願）が追記欄に記載されている

先の出願日 (日 月 年)	先の出願番号	先の出願		
		国内出願 国名	広域出願 *広域官庁名	国際出願 受理官庁名
(1) 06 10 00	特願 2000-308528	日本国 Japan		
(2) 12 10 00	特願 2000-312562	日本国 Japan		
(3) 30 03 '01	特願 2001-099251	日本国 Japan		

☒ 上記 () の番号の先の出願（ただし、本国際出願が提出される受理官庁に対して提出されたものに限る）のうち、次の () の番号のものについては、出願書類の送附原本を作成し、国際事務局へ送付することを、受理官庁（日本国特許庁の長官）に対して請求している

(1), (2), (3)

*先の出願が ARIPO の特許出願である場合には、その先の出願を行った工業所有権の保護のためのパリ条約同盟国の少なくとも 1ヶ国を追記欄に提示しなければならない（規則 4.10(b)(i)）。追記欄を参照。

第VII欄 国際調査機関

国際調査機関（ISA）の選択

ISA/J P

先の調査結果の利用請求、当該調査の照会（先の調査が 国際調査機関によって既に実施又は請求されている場合）

出願日 (日 月 年) 出願番号 国名 (又は広域官庁)

第VIII欄 照合欄：出願の言語

この国際出願の用紙の枚数は次のとおりである。

願書 - -	5 枚
明細書（配列表を除く） -	142 枚
請求の範囲	14 枚
要約書 - -	1 枚
図面 - -	0 枚
明細書の配列表 -	0 枚
合計	162 枚

この国際出願には、以下にチェックした書類が添付されている。

- | | |
|--|--|
| 1. ☒ 手数料計算用紙 | 5. ☐ 優先権主張（上記第VI欄の () の番号を記載する） |
| 2. ☒ 納付する手数料に相当する特許印紙を貼付した書面 | 6. ☐ 国際出願の翻訳文（翻訳に使用した言語名を記載する） |
| 3. ☒ 国際事務局の口座への振込みを証明する書面 | 7. ☐ 寄託した微生物又は他の生物材料に関する書面 |
| 4. ☐ 個別の記名押印された委任状 | 8. ☐ ステレオパッド又はアミノ酸配列表（フレキシブルディスク） |
| 5. ☐ 包括委任状の写し | 9. ☐ その他（書類名を詳細に記載する） |

要約書とともに提示する図面

本国際出願の使用言語 日本語

第IX欄 提出者の記名押印

本人の氏名（名称）を記載し、その次に押印する。

津 国 章



受理官庁記入欄

1 国際出願として提出された書類の実際の受理の日

2 図面

2 国際出願として提出された書類を補充する書面又は図面であって

☐ 受理された

その後期間内に受理されたものの実際の受理の日（訂正日）

☐ 不足図面がある

4 特許協力条約第 11 条 (2) に基づく必要な補充の期間内の受理の日

5 出願人により特定された
国際調査機関

ISA/J P

☐ 調査手数料未払いにつき 国際調査機関に
調査費用を過付していない。

国際事務局記入欄

記録原本の受理の日

様式 PCT/RO/101 (最終用紙) (1998 年 7 月 再版 2001 年 1 月)

22 21

SPECIFICATION

ALIPHATIC NITROGEN-CONTAINING 5-MEMBERED RING COMPOUND

5 TECHNICAL FIELD

The present invention relates to a novel aliphatic nitrogen-containing 5-membered ring compound having superior dipeptidylpeptidase IV (DPPIV) inhibitory action that is useful as a pharmaceutical.

10

BACKGROUND ART

Dipeptidylpeptidase IV (DPPIV) is a kind of serine protease that specifically hydrolyzes a dipeptide of Xaa-Pro or Xaa-Ala (where Xaa may be any amino acid) from the N terminus of a polypeptide chain

There are various reports regarding the role of DPPIV (also called to as CD26) in the body and its relationship with diseases (Holst, et al., Diabetes, Vol. 47, pp. 1663-1670, 1998, Augustyns, et al., Current Medicinal Chemistry, Vol. 6, pp. 311-327, 1999; Meester, et al, Immunol Today, Vol 20, pp 367-375, 1999; and, Fleicher, et al, Immunol. Today, Vol. 15, pp 180-184, 1994)

GLP-1 (glucagon-like peptide 1) is a peptide hormone that mainly acts in the pancreas after being secreted from the lower small intestine after meals, and primarily has the function of amplifying glucose-induced insulin secretion. In addition, there are several reports suggesting that GLP-1 has an appetite-suppressing action. DPPIV hydrolyzes GLP-1, forming an inactive or antagonistic peptide

Substances that inhibit the enzyme activity of DPPIV enhance the insulin secretion response to oral glucose loading by enhancing the action of intrinsic GLP-1, thereby improving impaired glucose tolerance.

Consequently, DPPIV inhibitors are considered to be useful for the prophylaxis and treatment of diabetes

(particularly type 2 diabetes), etc Also, they are expected to be effective for the prophylaxis and treatment of other diseases induced or exacerbated by impaired glucose tolerance (including hyperglycemia (such as postprandial hyperglycemia), hyperinsulinemia, diabetes complications (such as renal disorder and neurological disorder), lipid metabolism disorder and obesity, etc)

Moreover, DPPIV inhibitors are also expected to be effective for the prophylaxis and treatment of diseases that are to be improved by enhancing the appetite-suppressing action of GLP-1 (including overeating and obesity, etc.).

Also, DPPIV (CD26) present on the surface of T cells is strongly upregulated following T cell activation, and plays an important role in the activation and proliferation of T cells. T cell activity is known to be suppressed when DPPIV (CD26) is blocked by antibodies or inhibitory substances. Also, there has been an interest in the correlation between this enzyme and the pathological state in collagen metabolism disorders and diseases associated with abnormal immunity. For example, the DPPIV (CD26) positive rate of peripheral blood T cells is elevated in rheumatoid patients, and high levels of DPPIV activity have been detected in the urine of nephritis patients. Moreover, DPPIV (CD26) is also thought to play an important role in the entry of HIV into lymphocytes.

Consequently, substances that inhibit DPPIV (CD26) are expected to demonstrate prophylactic and therapeutic effects against diseases including autoimmune diseases (such as arthritis and rheumatoid arthritis), osteoporosis, acquired immunodeficiency syndrome (AIDS) and rejections of transplanted organs and tissues.

On the other hand, as compounds having DPPIV inhibitory action, there are described 2-cyanopyrrolidine derivatives having DPPIV inhibitory action in International Patent Laid-Open Publications Nos. WO98/19998 and

24 *[Signature]*

WO00/34241

The present invention provides a novel aliphatic nitrogen-containing 5-membered ring compound having an excellent DPPIV inhibitory action.

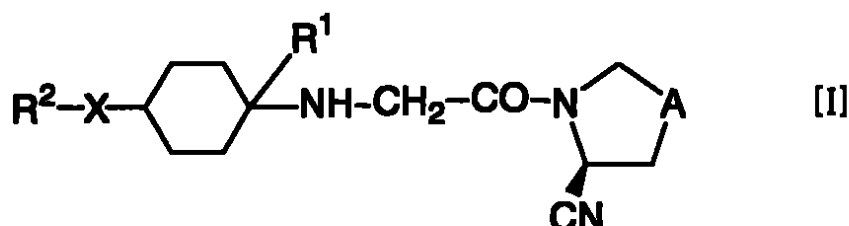
5

DISCLOSURE OF THE INVENTION

As a result of earnest research to solve the above problems, the present inventors found a novel aliphatic nitrogen-containing 5-membered ring compound having DPPIV
10 inhibitory action, thereby accomplished the present invention.

Namely, the present invention relates to an aliphatic nitrogen-containing 5-membered ring compound represented by the formula [I]:

15



wherein A represents -CH₂- or -S-,

R¹ represents hydrogen atom, a lower alkyl group, a
20 hydroxy lower alkyl group or a lower alkoxy lower alkyl group,

X represents -N(R³)-, -O- or -CO-, where R³ represents hydrogen atom or a lower alkyl group, and

R² represents (1) a cyclic group which may be
25 substituted, where the cyclic group portion is
(i) a monocyclic, bicyclic or tricyclic hydrocarbon group, or

(ii) a monocyclic, bicyclic or tricyclic heterocyclic group, or

30 (2) an amino group which may be substituted,
or a pharmaceutically acceptable salt thereof.

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BEST MODE FOR CARRYING OUT THE INVENTION

Although optical isomers based on an asymmetric carbon can be present in the objective compound [I] of the present invention, the present invention includes any of these optical isomers as well as mixtures thereof. In addition, although isomers (cis form or trans form) are also present based on the relative positions of substituents with respect to the standard plane of a cyclic group, the present invention also includes any of these isomers as well as mixtures thereof.

In the present invention, examples of a lower alkyl group, a lower alkylthio group, a lower alkylsulfonyl group, a lower alkoxy group and a lower alkylamino group include linear or branched groups having 1 to 6 carbon atoms, and particularly those having 1 to 4 carbon atoms. And, examples of a lower alkanoyl group and a lower alkanoylamino group include linear or branched groups having 2 to 7 carbon atoms, and particularly those having 2 to 5 carbon atoms. Examples of a lower cycloalkyl group and lower cycloalkenyl group include those having 3 to 8 carbon atoms, and particularly 3 to 6 carbon atoms. Examples of a lower alkylene group include linear or branched groups having 1 to 6 carbon atoms, and particularly 1 to 4 carbon atoms. Examples of a lower alkenyl group and lower alkenylene group include those having 2 to 7 carbon atoms, and particularly 2 to 5 carbon atoms. Further, examples of a halogen atom include fluorine, chlorine, bromine and iodine.

In the objective compound [I] of the present invention, examples of hydrogen atom or a lower alkyl group represented by R^3 include hydrogen atom, methyl group, etc. Among them, hydrogen atom is more preferred.

In the compound [I] of the present invention, examples of "hydrogen atom, a lower alkyl group, a hydroxy lower alkyl group or lower alkoxy lower alkyl group" represented by R^1 include hydrogen atom, methyl group, hydroxymethyl group and methoxymethyl group. Among them,

hydrogen atom is preferred

In the compound [I] of the present invention, a cyclic group portion of "a cyclic group which may be substituted" represented by R^1 includes

- 5 (i) a monocyclic, bicyclic or tricyclic hydrocarbon group and
(ii) a monocyclic, bicyclic or tricyclic heterocyclic group

Such monocyclic, bicyclic or tricyclic hydrocarbon groups include those having 3 to 15 carbon atoms, which may
10 be partially or completely saturated.

Monocyclic hydrocarbon groups include those having 3 to 7 carbon atoms, examples of which include phenyl group, cyclohexyl group, cyclopentyl group, cyclobutyl group, cyclopropyl group, etc.

15 Bicyclic hydrocarbon groups include those having 9 to 11 carbon atoms, examples of which include an indanyl group, an indenyl group, a naphthyl group, a tetrahydronaphthyl group and partially or completely saturated cyclic groups thereof, etc.

20 Tricyclic hydrocarbon groups include those having 12 to 15 carbon atoms, examples of which include a fluorenyl group, an anthryl group, a phenanthryl group and partially or completely saturated cyclic groups thereof, etc.

Monocyclic, bicyclic or tricyclic heterocyclic groups
25 include a monocyclic, bicyclic or tricyclic heterocyclic group containing 1 to 4 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, which may be partially or completely saturated.

Monocyclic heterocyclic groups include a heterocyclic
30 group containing 1 or 2 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom and comprising of a saturated or unsaturated 5- to 7-membered ring, examples of which include pyrrolidinyl group, an imidazolidinyl group, a pyrazolidinyl group, an oxolanyl group, a thiolanyl group,
35 a pyrrolinyl group, an imidazolinyl group, a pyrazolinyl group, a pyrrolyl group, an imidazolyl group, a pyrazolyl

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group, a triazolyl group, a tetrazolyl group, a furyl group, an oxazolyl group, an isoxazolyl group, an oxadiazolyl group, a thienyl group, a thiazolyl group, an isothiazolyl group, a thiadiazolyl group, a piperidyl group, a piperazinyl group, a morpholinyl group, a thiomorpholinyl group, a pyridyl group, a pyrimidinyl group, a pyrazinyl group, a pyridazinyl group, a pyranyl group, a tetrahydropyridyl group, a dihydropyridazinyl group, a perhydroazepinyl group, a perhydrothiazepinyl and partially or completely saturated cyclic groups thereof, etc.

Bicyclic heterocyclic groups include a heterocyclic group containing 1 to 3 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom and comprising two saturated or unsaturated 5- to 7-membered rings being fused, examples of which include an indolinyl group, an isoindolinyl group, an indolyl group, an indazolyl group, an isoindolyl group, a benzimidazolyl group, a benzothiazolyl group, a benzoxazolyl group, a benzodioxolanyl group, a benzothienyl group, a benzofuryl group, a thienopyridyl group, a thiazolopyridyl group, a pyrrolopyridyl group, a dihydropyrrolopyridyl group, a quinolyl group, an isoquinolyl group, a quinoxalinyl group, a quinazolinyl group, a phthalazinyl group, a cinnolinyl group, a chromanyl group, an isochromanyl group, a naphthyridinyl group and partially or completely saturated cyclic groups thereof, etc

Tricyclic heterocyclic groups include a heterocyclic group containing 1 to 4 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom and comprising three saturated or unsaturated 5- to 7-membered rings being fused, examples of which include a benzoxolanopyrimidyl group, a β -carbolinyl group, a carbazolyl group, a phenothiazinyl group, a phenoxazinyl group and partially or completely saturated cyclic groups thereof, etc

Among these cyclic groups (monocyclic, bicyclic or

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tricyclic hydrocarbon groups or monocyclic, bicyclic or tricyclic heterocyclic groups),

"(i) a monocyclic hydrocarbon group having 3 to 7 carbon atoms,

5 (ii) a bicyclic hydrocarbon groups having 9 to 11 carbon atoms,

(iii) a monocyclic heterocyclic group containing 1 or 2 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, or

10 (iv) a bicyclic heterocyclic group containing 1 to 3 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom and comprising two 5- to 7-membered rings being fused" is preferred, examples of which include

"phenyl group, cyclohexyl group, cyclopentyl group, cyclo-
15 butyl group, cyclopropyl group, an indanyl group, an indenyl group, a naphthyl group, tetrahydronaphthyl, a pyrrolidinyl group, an imidazolidinyl group, a pyrazolidinyl group, an oxolanyl group, a thiolanyl group, a pyrrolinyl group, an imidazolinyl group, a pyrazolinyl group, a
20 pyrrolyl group, an imidazolyl group, a pyrazolyl group, a triazolyl group, a tetrazolyl group, a furyl group, an oxazolyl group, an isoxazolyl group, an oxadiazolyl group, a thienyl group, a thiazolyl group, an isothiazolyl group, a thiadiazolyl group, a piperidyl group, a piperazinyl
25 group, a morpholinyl group, a thiomorpholinyl group, a pyridyl group, a pyrimidinyl group, a pyrazinyl group, a pyridazinyl group, a pyranyl group, a tetrahydropyridyl group, a dihydropyridazinyl group, a perhydroazepinyl group, a perhydrothiazepinyl group, an indolinyl group, an iso-
30 indolinyl group, an indolyl group, an indazolyl group, an isoindolyl group, a benzimidazolyl group, a benzothiazolyl group, a benzoxazolyl group, a benzodioxolanyl group, a benzothienyl group, a benzofuryl group, a thienopyridyl group, a thiazolopyridyl group, a pyrrolopyridyl group, a
35 dihydropyrrolopyridyl group, a quinolyl group, an iso-quinolyl group, a quinoxalinyl group, a quinazolinyl group,

29 

a phthalazinyl group, a cinnolinyl group, a chromanyl group, an isochromanyl group, a naphthyridinyl group and partially or completely saturated cyclic groups thereof, etc."

Among them, more preferred examples include:

5 "phenyl group, cyclohexyl group, a pyrrolidinyl group, a tetrazolyl group, a furyl group, a thienyl group, a thiazolyl group, a piperidyl group, a piperazinyl group, a morpholinyl group, a thiomorpholinyl group, a pyridyl group, a pyrimidinyl group, a pyrazinyl group, a pyridazinyl group,
10 a perhydroazepinyl group, an indolinyl group, an isoindolinyl group, a benzothienyl group, a thienopyridyl group, a pyrrolopyridyl group, a dihydropyrrolopyridyl group, a quinolyl group, an isoquinolyl group, a quinoxalinyl group and partially or completely saturated cyclic groups thereof,
15 etc.", and further preferred examples include

"a pyrrolidinyl group, a piperidyl group, a piperazinyl group, a morpholinyl group, a thiomorpholinyl group, a pyridyl group, a pyrimidinyl group, an indolinyl group, an isoindolinyl group, a pyrrolopyridyl group, a dihydro-
20 pyrrolopyridyl group and partially or completely saturated cyclic groups thereof, etc "

Among them, particularly preferred examples include

"1-pyrrolidinyl group, 1-piperidyl group, 1-piperazinyl group, 4-morpholinyl group, 4-thiomorpholinyl group, 2-
25 pyridyl group, 2-pyrimidinyl group, 2-isoindolinyl group, 1-indolinyl group, 2,3-dihydro-1H-pyrrolo[3,4-b]pyridin-2-yl group, etc ".

"A cyclic group (a monocyclic, bicyclic or tricyclic hydrocarbon group or a monocyclic, bicyclic or tricyclic
30 heterocyclic group) which may be substituted " represented by R¹ may be unsubstituted or have 1 to 3 substituents which are the same or different

Substituents in the cyclic group are not particularly limited, and examples of which include substituents

35 selected from the following "substituents of Group A"

Among them, "substituents of Group A'" are more preferred.

30 X
R

In the objective compound [I] of the present invention, "an amino group which may be substituted" represented by R^2 may be unsubstituted or may be an amino group having 1 or 2 substituents which are the same or different (a mono- or di-substituted amino group).

Substituents in the amino group are not particularly limited, and examples of which include substituents selected from the following "substituents of Group B". Among them, "substituents of Group B'" are more preferred.

"An amino group which may be substituted" represented by R^2 is preferably a substituted amino group (a mono- or di-substituted amino group), and more specifically "an amino group substituted by 1 or 2 substituents which are the same or different and selected from the group consisting of a lower alkyl group (methyl group, ethyl group, isopropyl group, butyl group, etc.), a lower cycloalkyl group, a lower alkoxy-substituted lower alkyl group, a pyrimidinyl group, a thiazolyl group and a thiadiazolyl group" is preferred. Among them,

"(i) an amino group di-substituted by substituents which are the same or different and selected from a lower alkyl group (methyl group, ethyl group, isopropyl group, butyl group, etc.), a lower cycloalkyl group and a lower alkoxy-substituted lower alkyl group, or

(ii) an amino group mono-substituted by a substituent selected from a pyrimidinyl group, a thiazolyl group and a thiadiazolyl group" is more preferred, and

"an amino group di-substituted by substituents which are the same or different and selected from a lower alkyl group (methyl group, ethyl group, isopropyl group, butyl group, etc.), a lower cycloalkyl group and a lower alkoxy-substituted lower alkyl group" is particularly preferred.

----Substituents of Group A:-----

As substituents of Group A, the following substituents are mentioned:

a halogen atom (Cl, F, Br, etc.), cyano group, nitro group,

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oxo group, hydroxy group, carboxy group, oxidyl group,
amino group, carbamoyl group, aminosulfonyl group, a lower
alkyl group, a lower alkoxy group; a lower alkanoyl group,
a lower alkoxycarbonyl group, a lower alkoxy-substituted
5 lower alkanoyl group; a lower alkoxycarbonyl-substituted
lower alkoxy group; a lower alkoxycarbonyl-substituted
lower alkoxycarbonyl group,
a lower alkylthio group,
a lower alkylsulfonyl group,
10 a di-lower alkylamino-substituted lower alkoxy group;
a di-lower alkylaminocarboxy group,
a lower alkyl group substituted by group(s) selected from
amino group, carbamoyl group, a halogen atom, hydroxy group,
carboxy group, a lower alkoxy group and a mono- or di-
15 substituted amino group
(substituents in the substituted amino group portion are
not particularly limited, and examples of which include
substituents of Group C mentioned below.),
a mono- or di-substituted amino group or a mono- or di-
20 substituted carbamoyl group
(substituents in the substituted amino group or substituted
carbamoyl group are not particularly limited, and examples
of which include substituents of Group C mentioned below),
a substituted or unsubstituted lower cycloalkyl group,
25 a substituted or unsubstituted lower cycloalkyl-CO-,
a substituted or unsubstituted lower cycloalkyl-lower alkyl
group,
a substituted or unsubstituted phenyl group,
a substituted or unsubstituted phenyl-O-,
30 a substituted or unsubstituted phenyl-CO-,
a substituted or unsubstituted phenyl-lower alkyl group,
a substituted or unsubstituted phenyl-O-lower alkyl group,
a substituted or unsubstituted phenylsulfonyl group,
a substituted or unsubstituted phenyl-lower alkoxy group,
35 a substituted or unsubstituted phenyl-lower alkoxycarbonyl
group,

a substituted or unsubstituted cycloalkenyl group (a cyclo-
butenyl group, etc.),
a substituted or unsubstituted bicyclic heterocyclic group,
a substituted or unsubstituted monocyclic 5- or 6-membered
5 heterocyclic group,
a substituted or unsubstituted monocyclic 5- or 6-membered
heterocyclic group-O-,
a substituted or unsubstituted monocyclic 5- or 6-membered
heterocyclic group-CO-,
10 a substituted or unsubstituted monocyclic 5- or 6-membered
heterocyclic group-CO-lower alkyl group, and
a substituted or unsubstituted monocyclic 5- or 6-membered
heterocyclic group-lower alkyl group
(substituents in the substituted lower cycloalkyl group
15 portion, substituted phenyl group portion, substituted
lower cycloalkenyl group portion, substituted bicyclic
heterocyclic group portion or substituted monocyclic 5- or
6-membered heterocyclic group portion are not particularly
limited, and examples of which include
20 a halogen atom (Cl, F, Br, etc), cyano group, nitro group,
oxo group and substituents in the substituents of Group C
mentioned below, etc.

Also, a monocyclic 5- or 6-membered heterocyclic
group portion includes a monocyclic 5- or 6-membered
25 heterocyclic group containing 1 or 2 hetero atoms selected
from nitrogen atom, oxygen atom and sulfur atom, and
specific examples include
a piperidyl group, a piperazinyl group, a morpholinyl group,
a pyridyl group, a pyrimidinyl group, a pyrazinyl group, a
30 pyridazinyl group, a pyrrolidinyl group, an imidazolidinyl
group, a pyrazolidinyl group, a pyrrolyl group, an imid-
azolyl group, a pyrazolyl group, a thiazolyl group, a
thiadiazolyl group, a thienyl group, etc.

Also, a bicyclic heterocyclic group portion includes
35 a bicyclic heterocyclic group containing 1 to 3 hetero
atoms selected from nitrogen atom, oxygen atom and sulfur

atom and comprising two 5- or 6-membered rings being fused, and examples of which include an isoindoliny1 group, an indoliny1 group, etc.)

5 ---Substituents group A' (particularly preferred substituents of Group A):-----

As more preferable substituents of Group A, the following substituents are mentioned.

a halogen atom (Cl, etc.), cyano group, nitro group; oxo group, carbamoyl group, a lower alkyl group, a lower alkoxy group; a lower alkanoyl group, a lower alkoxycarbonyl group; a lower alkoxy-substituted lower alkyl group, a mono- or di-substituted amino group (a lower cycloalkyl-carbonyl-substituted amino group, etc.), a mono- or di-substituted carbamoyl group (a phenyl-substituted carbamoyl group, etc),
15 a lower cycloalkyl-CO-,
a substituted or unsubstituted phenyl group (phenyl group, a halophenyl group, etc),
a substituted or unsubstituted phenyl-lower alkyl group (a phenyl-lower alkyl group, a halophenyl-lower alkyl group, etc),
20 a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group (a thienyl group, etc.),
a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group-O- (a pyrimidinyl group, a halo-pyrimidinyl group, etc.), and
25 a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group-CO- (a pyridylcarbonyl group, a thienyl-carbonyl group, etc.).
30 (In the above description, each monocyclic 5- or 6-membered heterocyclic group portion includes a monocyclic 5- or 6-membered heterocyclic group containing 1 or 2 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, and examples of which include a pyridyl group, a pyrimidinyl group, a thienyl group, etc)
35

-----Substituents of Group B.-----

As substituents of Group B, the following substituents are mentioned.

a lower alkyl group, a lower alkoxy-substituted lower alkyl
5 group, a lower alkoxycarbonyl-substituted lower alkyl
group, a hydroxy lower alkyl group, a carboxy lower alkyl
group,
a substituted or unsubstituted lower cycloalkyl group,
a substituted or unsubstituted lower cycloalkyl-lower alkyl
10 group,
a substituted or unsubstituted phenyl group,
a substituted or unsubstituted phenyl-lower alkyl group,
a substituted or unsubstituted bicyclic hydrocarbon group,
a substituted or unsubstituted monocyclic 5- or 6-membered
15 heterocyclic group,
a substituted or unsubstituted monocyclic 5- or 6-membered
heterocyclic group-lower alkyl group, and
a substituted or unsubstituted bicyclic heterocyclic group-
lower alkyl group
20 (substituents in the substituted lower cycloalkyl group
portion, substituted phenyl group portion, substituted
bicyclic hydrocarbon group portion, substituted monocyclic
5- or 6-membered heterocyclic group portion or substituted
bicyclic heterocyclic group portion are not particularly
25 limited, and examples of which include substituents in the
substituents of Group C mentioned below.

A bicyclic hydrocarbon group portion includes a bicyclic hydrocarbon group having 9 to 11 carbon atoms, and examples of which include an indanyl group, etc

30 Also, a monocyclic 5- or 6-membered heterocyclic
group portion includes a monocyclic 5- or 6-membered
heterocyclic group containing 1 or 2 hetero atoms selected
from nitrogen atom, oxygen atom and sulfur atom, and
examples of which include
35 a piperidyl group, a piperazinyl group, a morpholinyl group,
a pyridyl group, a pyrimidinyl group, a pyrazinyl group, a

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pyridazinyl group, a pyrrolidinyl group, an imidazolidinyl group, a pyrazolidinyl group, a pyrrolyl group, an imidazolyl group, a pyrazolyl group, a thiazolyl group, a thiadiazolyl group, a thienyl group, etc

5 Also, a bicyclic heterocyclic group portion includes a bicyclic heterocyclic group containing 1 to 3 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom and comprising two 5- or 6-membered rings being fused, and examples of which include a benzodioxolanyl group,
10 etc.).

-----Substituents of Group B' (more preferred substituents of Group B)-----

As more preferred substituents of Group B, the following substituents are mentioned:

15 a lower alkyl group (methyl group, ethyl group, isopropyl group, butyl group, etc.), a lower cycloalkyl group, a lower alkoxy-substituted lower alkyl group, a pyrimidinyl group, a thiazolyl group, a thiadiazolyl group.

As particularly preferred substituents of Group B,
20 the following substituents are exemplified

In case that R^2 is a di-substituted amino group, a lower alkyl group (methyl group, ethyl group, isopropyl group, butyl group, etc), a lower cycloalkyl group and a lower alkoxy-substituted lower alkyl group; and
25 in case that R^2 is a mono-substituted amino group, a pyrimidinyl group, a thiazolyl group and a thiadiazolyl group

-----Substituents of Group C:-----

As substituents of Group C, the following substituents are mentioned
30

a lower alkyl group; a hydroxy-lower alkyl group, a lower alkanoyl group, a lower cycloalkylcarbonyl group, a lower alkoxy group, a lower alkoxycarbonyl group; a lower alkyl-sulfonyl group, a di-lower alkyl-substituted carbamoyl
35 group, a di-lower alkylamino-substituted lower alkanoyl group; and

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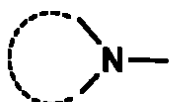
a substituted or unsubstituted phenyl group,
a substituted or unsubstituted phenyl-O-,
a substituted or unsubstituted phenyl-CO-,
a substituted or unsubstituted phenyl-lower alkanoyl group,
5 a substituted or unsubstituted phenyl-lower alkyl group,
a substituted or unsubstituted phenyl-lower alkoxy group,
a substituted or unsubstituted monocyclic 5- or 6-membered
heterocyclic group,
a substituted or unsubstituted monocyclic 5- or 6-membered
10 heterocyclic group-O- (a pyridyloxy group, etc.),
a substituted or unsubstituted monocyclic 5- or 6-membered
heterocyclic group-CO- (a pyridylcarbonyl group, etc.),
and
a substituted or unsubstituted monocyclic 5- or 6-membered
15 heterocyclic group-substituted amino group (a pyridylamino
group, etc)
(substituents in the substituted phenyl group portion or
substituted monocyclic 5- or 6-membered heterocyclic group
portion are not particularly limited, and examples of which
20 include
a halogen atom (Cl, F, Br, etc), cyano group, nitro group,
oxo group, a lower alkyl group, a lower alkoxy group, a
lower alkanoyl group, and a lower alkoxycarbonyl group, etc.
Also, a monocyclic 5- or 6-membered heterocyclic
25 group portion includes a monocyclic 5- or 6-membered
heterocyclic group containing 1 or 2 hetero atoms selected
from nitrogen atom, oxygen atom and sulfur atom, and
examples of which include
a piperidyl group, a piperazinyl group, a morpholinyl group,
30 a pyridyl group, a pyrimidinyl group, a pyrazinyl group, a
pyridazinyl group, a pyrrolidinyl group, an imidazolidinyl
group, a pyrazolidinyl group, a pyrrolyl group, an imid-
azolyl group, a pyrazolyl group, a thiazolyl group, a
thiadiazolyl group, a thienyl group, etc.)
35 In the objective compound [I] of the present
invention, as R² when X is -N(R³)- or -O-, a cyclic group

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which may be substituted may be mentioned as a preferred example.

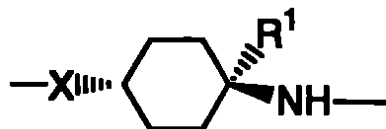
Also, in the objective compound [I] of the present invention, as R^2 when X is -CO-, there may be mentioned

- 5 (1) a monocyclic, bicyclic or tricyclic nitrogen-containing heterocyclic group which may be substituted or (2) an amino group which may be substituted, represented by the formula.



as preferred examples.

- 10 Also, in the objective compound [I] of the present invention, among the two kinds of cis-trans isomers based on a cyclohexyl ring in the structure [I] as a standard plane, a trans-isomeric compound is more preferred from the viewpoint of obtaining higher DPPIV inhibitory activity.
- 15 That is, among the objective compound [I] of the present invention, a compound having the following partial structure



- 20 or a pharmaceutically acceptable salt thereof is preferred.

In particular, for a compound in which the group X is -CO-, superiority of such trans isomer is remarkable

As one compound group of the compounds of the present invention, among the compounds [I], those in which R^2 is

- 25 (1) a cyclic group which may have 1 to 3 substituents which are the same or different and selected from the substituents of Group A, where the cyclic group portion is (i) a monocyclic, bicyclic or tricyclic hydrocarbon group, or (ii) a monocyclic, bicyclic or tricyclic heterocyclic group,
- 30 or
- (2) an amino group having 1 or 2 substituents which are the same or different and selected from the substituents of

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Group B can be mentioned. (Compound Group 1)

Also, as other compound groups, among the compounds [I] or the above-mentioned Compound Group 1, the compounds in which R^2 is

- 5 (1) a cyclic group which may be substituted, where the cyclic group portion is selected from the following (i) to (iv) -
- "(i) a monocyclic hydrocarbon group having 3 to 7 carbon atoms,
- 10 (ii) a bicyclic hydrocarbon groups having 9 to 11 carbon atoms,
- (iii) a monocyclic heterocyclic group containing 1 or 2 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, and
- 15 (iv) a bicyclic heterocyclic group containing 1 to 3 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom and comprising two 5- to 7-membered rings being fused, or
- (2) a substituted amino group,
- 20 can be mentioned (Compound Group 2).

Also, among the above-mentioned Compound Group 2, the compounds in which R^2 is

- (1) a cyclic group which may be substituted wherein the cyclic group portion is a group selected from
- 25 phenyl group, cyclohexyl group, cyclopentyl group, cyclobutyl group, cyclopropyl group, an indanyl group, an indenyl group, a naphthyl group, tetrahydronaphthyl, a pyrrolidinyl group, an imidazolidinyl group, a pyrazolidinyl group, an oxolanyl group, a thiolanyl group, a pyrrolinyl group,
- 30 an imidazoliny group, a pyrazolinyl group, a pyrrolyl group, an imidazolyl group, a pyrazolyl group, a triazolyl group, a tetrazolyl group, a furyl group, an oxazolyl group, an isoxazolyl group, an oxadiazolyl group, a thienyl group, a thiazolyl group, an isothiazolyl group,
- 35 a thiadiazolyl group, a piperidyl group, a piperazinyl group, a morpholinyl group, a thiomorpholinyl group, a

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pyridyl group, a pyrimidinyl group, a pyrazinyl group, a
pyridazinyl group, a pyranyl group, a tetrahydropyridyl
group, a dihydropyridazinyl group, a perhydroazepinyl group,
a perhydrothiazepinyl group, an indolinyl group, an iso-
5 indolinyl group, an indolyl group, an indazolyl group, an
isoindolyl group, a benzimidazolyl group, a benzothiazolyl
group, a benzoxazolyl group, a benzodioxolanyl group, a
benzothienyl group, a benzofuryl group, a thienopyridyl
group, a thiazolopyridyl group, a pyrrolopyridyl group, a
10 dihydropyrrolopyridyl group, a quinolyl group, an iso-
quinolyl group, a quinoxalinyl group, a quinazolinyl group,
a phthalazinyl group, a cinnolinyl group, a chromanyl group,
an isochromanyl group, a naphthyridinyl group and partially
or completely saturated cyclic groups thereof; or

15 (2) a substituted amino group can be mentioned (Compound
Group 3)

Also, in Compound Group 3, as more preferred compound
group, the compounds in which R^1 is

(1) a cyclic group which may be substituted, where the
20 cyclic group portion is a group selected from the group
consisting of phenyl group, cyclohexyl group, a pyrrolidin-
yl group, a tetrazolyl group, a furyl group, a thienyl
group, a thiazolyl group, a piperidyl group, a piperazinyl
group, a morpholinyl group, a thiomorpholinyl group, a
25 pyridyl group, a pyrimidinyl group, a pyrazinyl group, a
pyridazinyl group, a perhydroazepinyl group, an indolinyl
group, an isoindolinyl group, a benzothienyl group, a
thienopyridyl group, a pyrrolopyridyl group, a dihydro-
pyrrolopyridyl group, a quinolyl group, an isoquinolyl
30 group, a quinoxalinyl group and partially or completely
saturated cyclic groups thereof, or

(2) a substituted amino group can be mentioned (Compound
Group 4).

Also, in Compound Group 4, as more preferred compound
35 group, the compounds in which R^1 is

(1) a cyclic group which may be substituted wherein the

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cyclic group portion is a group selected from a pyrrolidinyl group, a piperidyl group, a piperazinyl group, a morpholinyl group, a thiomorpholinyl group, a pyridyl group, a pyrimidinyl group, an indolinyl group, an isoindolinyl group, a pyrrolopyridyl group, a dihydro-pyrrolopyridyl group and partially or completely saturated cyclic groups thereof, or

(2) a substituted amino group can be mentioned (Compound Group 5)

10 Also, among the compounds [I], as another more preferred compound group, the compounds in which R^2 is

(1) a cyclic group which may have 1 to 3 substituents, which are the same or different, selected from the substituents of Group A', where the cyclic group portion is

15 selected from the group consisting of

a pyrrolidinyl group, a piperidyl group, a piperazinyl group, a morpholinyl group, a thiomorpholinyl group, a pyridyl group, a pyrimidinyl group, an indolinyl group, an isoindolinyl group, a pyrrolopyridyl group, a dihydro-

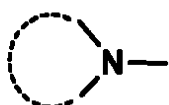
20 pyrrolopyridyl group and partially or completely saturated cyclic groups thereof, or

(2) an amino group substituted by 1 or 2 substituents, which are the same or different, selected from the substituents of Group B' can be mentioned (Compound Group 6)

25 Also, among the compounds [I], or among each of the above-mentioned Compound Groups 1, 2, 3, 4, 5 and 6, a compound group in which, when X is $-N(R^3)-$ or $-O-$, R^2 is a cyclic group which may be substituted can be mentioned. (Compound Group 7)

30 Also, among the compounds [I], or among each of the above-mentioned Compound Groups 1, 2, 3, 4, 5 and 6, a group of compounds in which, when X is $-CO-$, R^2 is (1) a monocyclic, bicyclic or tricyclic nitrogen-containing heterocyclic group which may be substituted or (2) an amino
35 group which may be substituted, represented by the formula:

21



can be mentioned. (Compound Group 8)

Also, among the compounds [I] or the above-mentioned Compound Groups 1, 2, 3, 4, 5, 6, 7 or 8, as more preferred compound groups,

a compound group in which X is -CO- or -O- and A is -CH₂-,

a compound group in which X is -CO- or -O-, A is -CH₂- and R¹ is hydrogen atom,

a compound group in which X is -CO-, A is -CH₂- and R¹ is hydrogen atom;

a compound group in which X is -CO-, A is -CH₂-, R¹ is hydrogen atom and R² is a cyclic group which may be substituted,

a compound group in which X is -CO-, A is -CH₂-, R¹ is hydrogen atom and R² is a substituted amino group,

a compound group in which X is -CO- or -O- and A is -S-,

a group of compounds in which X is -CO- or -O-, A is -S- and R¹ is hydrogen atom;

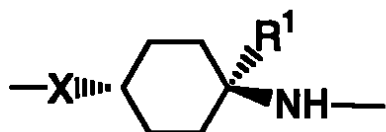
a compound group in which X is -CO-, A is -S- and R¹ is hydrogen atom,

a compound group in which X is -CO-, A is -S-, R¹ is hydrogen atom and R² is a cyclic group which may be substituted;

a compound group in which X is -CO-, A is -S-, R¹ is hydrogen atom and R² is a substituted amino group, etc. may be

mentioned.

Also, in each of the above-mentioned compound groups, as a more preferred compound group, a compound group having the following partial structure.



can be mentioned.

Also, among the compounds [I], the following compounds can be mentioned as examples of preferred compounds;

42 

- (S) - 2 - cyano - 1 - [trans - 4 - (5 - nitro - 2 - pyridylamino) - cyclohexylamino] acetylpyrrolidine,
- (S) - 2 - cyano - 1 - [trans - 4 - (5 - cyano - 2 - pyridyloxy) - cyclohexylamino] acetylpyrrolidine,
- 5 (S) - 2 - cyano - 1 - [trans - 4 - (dimethylaminocarbonyl) - cyclohexylamino] acetylpyrrolidine,
- (S) - 2 - cyano - 1 - [trans - 4 - (morpholinocarbonyl) cyclohexylamino] acetylpyrrolidine,
- (S) - 2 - cyano - 1 - [trans - 4 - (5 - bromo - 2 - pyrimidinyloxy) - cyclohexylamino] acetylpyrrolidine;
- 10 (S) - 2 - cyano - 1 - [trans - 4 - (5 - pyrimidinylaminocarbonyl) - cyclohexylamino] acetylpyrrolidine;
- (S) - 2 - cyano - 1 - [trans - 4 - (N - ethyl - N - methoxyethylamino - carbonyl) cyclohexylamino] acetylpyrrolidine,
- 15 (S) - 2 - cyano - 1 - [trans - 4 - (N - ethyl - N - isopropylamino - carbonyl) cyclohexylamino] acetylpyrrolidine,
- (S) - 2 - cyano - 1 - [trans - 4 - (N - methyl - N - butylamino - carbonyl) cyclohexylamino] acetylpyrrolidine;
- (S) - 2 - cyano - 1 - [trans - 4 - [(S) - 2 - methoxymethylpyrrolidin - 1 - ylcarbonyl] cyclohexylamino] acetylpyrrolidine,
- 20 (S) - 2 - cyano - 1 - [trans - 4 - (3 - carbamoylpiperidinocarbonyl) cyclohexylamino] acetylpyrrolidine,
- (S) - 2 - cyano - 1 - [trans - 4 - (3 - nitro - 2 - pyridylamino) cyclohexylamino] acetylpyrrolidine;
- 25 (S) - 2 - cyano - 1 - [trans - 4 - (4 - acetylpiperazin - 1 - ylcarbonyl) cyclohexylamino] acetylpyrrolidine;
- (S) - 2 - cyano - 1 - [trans - 4 - (2 - isoindolinylcarbonyl) cyclohexylamino] acetylpyrrolidine,
- (S) - 2 - cyano - 1 - [trans - 4 - [4 - (3 - pyridylcarbonyl) piperazin - 1 - ylcarbonyl] cyclohexylamino] acetylpyrrolidine,
- 30 (S) - 2 - cyano - 1 - [trans - 4 - [4 - (3 - thenoyl) piperazin - 1 - ylcarbonyl] cyclohexylamino] acetylpyrrolidine;
- (S) - 2 - cyano - 1 - [trans - 4 - [4 - (4 - chlorophenyl) piperazin - 1 - ylcarbonyl] cyclohexylamino] acetylpyrrolidine,
- 35 (S) - 2 - cyano - 1 - [trans - 4 - (cis - 2, 6 - dimethylmorpholino - carbonyl) cyclohexylamino] acetylpyrrolidine,

43

(S) - 2 - cyano - 1 - [trans - 4 - (5 - nitro - 2 - isoindoliny -
carbonyl) cyclohexylamino] acetylpyrrolidine,

(S) - 2 - cyano - 1 - [trans - 4 - (piperidinocarbonyl) cyclo -
hexylamino] acetylpyrrolidine,

5 (S) - 2 - cyano - 1 - [trans - 4 - (4 - carbamoylpiperidinocarbon -
yl) cyclohexylamino] acetylpyrrolidine;

(S) - 2 - cyano - 1 - [trans - 4 - (1 - pyrrolidinylcarbonyl) -
cyclohexylamino] acetylpyrrolidine,

10 (S) - 2 - cyano - 1 - [trans - 4 - (4 - cyclopropylcarbonyl -
piperazin - 1 - ylcarbonyl) cyclohexylamino] acetylpyrrolidine,

(S) - 2 - cyano - 1 - [trans - 4 - (4 - propionylpiperazin - 1 - yl -
carbonyl) cyclohexylamino] acetylpyrrolidine,

(S) - 2 - cyano - 1 - [trans - 4 - (1 - indoliny carbonyl) cyclo -
hexylamino] acetylpyrrolidine,

15 (S) - 2 - cyano - 1 - [trans - 4 - (2, 3 - dihydro - 1H - pyrrolo [3, 4 -
b] pyridin - 2 - ylcarbonyl) cyclohexylamino] acetylpyrrolidine,

(S) - 2 - cyano - 1 - [trans - 4 - [4 - (2 - pyrimidinyloxy) -
piperidinocarbonyl] cyclohexylamino] acetylpyrrolidine,

20 (S) - 2 - cyano - 1 - [trans - 4 - [4 - (5 - bromo - 2 - pyrimidinyloxy) -
piperidinocarbonyl] cyclohexylamino] acetylpyrrolidine;

(S) - 2 - cyano - 1 - [trans - 4 - (cis - 3, 5 - dimethyl - 4 - benzyl -
piperazin - 1 - ylcarbonyl) cyclohexylamino] acetylpyrrolidine;

(S) - 2 - cyano - 1 - [trans - 4 - (4 - cyclohexylcarbonylamino -
piperidinocarbonyl) cyclohexylamino] acetylpyrrolidine,

25 (S) - 2 - cyano - 1 - [trans - 4 - [4 - (N - phenylcarbamoyl) -
piperazin - 1 - ylcarbonyl] cyclohexylamino] acetylpyrrolidine;

(S) - 2 - cyano - 1 - [trans - 4 - (4 - ethoxycarbonylpiperazin - 1 -
ylcarbonyl) cyclohexylamino] acetylpyrrolidine,

30 (S) - 2 - cyano - 1 - [trans - 4 - [4 - (2 - thienyl) piperidino -
carbonyl] cyclohexylamino] acetylpyrrolidine,

(S) - 2 - cyano - 1 - [trans - 4 - (1, 1 - dioxoperhydro - 1, 4 - thia -
zin - 4 - ylcarbonyl) cyclohexylamino] acetylpyrrolidine,

(R) - 4 - cyano - 3 - [trans - 4 - (5 - nitro - 2 - pyridylamino) cyclo -
hexylamino] acetylthiazolidine,

35 (R) - 4 - cyano - 3 - [trans - 4 - (5 - cyano - 2 - pyridyloxy) cyclo -
hexylamino] acetylthiazolidine,

44 

(R)-4-cyano-3-[trans-4-(dimethylaminocarbonyl)cyclohexylamino]acetylthiazolidine,

(R)-4-cyano-3-[trans-4-(2-isoindolinylylcarbonyl)cyclohexylamino]acetylthiazolidine;

5 (R)-4-cyano-3-[trans-4-(morpholinocarbonyl)cyclohexylamino]acetylthiazolidine, and

(R)-4-cyano-3-[trans-4-(pyrrolidinylcarbonyl)cyclohexylamino]acetylthiazolidine.

The objective compound [I] or a pharmaceutically
10 acceptable salt thereof of the present invention has superior inhibitory action on the enzyme activity of DPPIV. They have superior inhibitory action especially on human DPPIV. In addition, they also exhibit high selectivity with respect to DPPIV (namely, type IV dipeptidylpeptidase)
15 in various serine proteases (e.g., plasmin, thrombin, prolylendopeptidase, trypsin and dipeptidylpeptidase II).

Also, the objective compound [I] or a pharmaceutically acceptable salt thereof of the present invention improves insulin secretion response to oral glucose loading
20 by means of its DPPIV inhibitory action.

Thus, the objective compound [I] or a pharmaceutically acceptable salt thereof of the present invention is useful as prophylactic or therapeutic agents for diseases relating to DPPIV (diseases mediated by DPPIV), that is,
25 diseases which is expected to be alleviated by inhibiting DPPIV enzyme activity.

Examples of such diseases include diabetes (e.g., type 1 diabetes and type 2 diabetes), hyperglycemia (such as postprandial hyperglycemia), hyperinsulinemia, diabetes
30 complications (such as renal disorder and neurological disorder), obesity, overeating, lipid metabolism disorder (such as hyperlipemia including hypertriglyceridemia and others), autoimmune diseases (such as arthritis and rheumatoid arthritis), osteoporosis, acquired immunodeficiency syndrome (AIDS) and rejection of transplanted organs
35 and tissues.

45 ~~40~~

The objective compound [I] or a pharmaceutically acceptable salt thereof of the present invention is particularly useful as a prophylactic or therapeutic agent of diabetes (and particularly type 2 diabetes).

5 Also, the compound of the present invention has low toxicity, and thus, has a high degree of safety when used as a pharmaceutical compound. Also, it also demonstrates superior pharmacokinetic characteristics [including bio-availability, in vitro metabolic stability (stability in
10 human liver homogenates), P450 inhibitory action, protein binding capabilities, etc.].

The DPPIV inhibitory action of the compound of the present invention as well as its pharmaceutical efficacy (including anti-hyperglycemia effect and the effect of
15 improving insulin secretion response to glucose loading) based on that action can be confirmed by known methods or methods equivalent to those methods (WO98/19998, WO00/34241, Holst, et al., Diabetes, Vol 47, pp. 1663-1670, 1998; Augustyns, et al., Current Medicinal Chemistry, Vol
20 6, pp. 311-327, 1999, Meester, et al., Immunol Today, Vol 20, pp. 367-375, 1999; and, Fleicher, et al., Immunol. Today, Vol 15, pp 180-184, 1994).

The objective compound [I] of the present invention can be used for a pharmaceutical use either in a free form
25 or in a form of a pharmaceutically acceptable salt. Examples of the pharmaceutically acceptable salt of the compound [I] include an inorganic acid salt such as hydrochloride, sulfate, phosphate or hydrobromide, and an organic acid salt such as acetate, fumarate, oxalate,
30 citrate, methanesulfonate, benzenesulfonate, tosylate or maleate, etc. In addition, in case that a compound has a substituent(s) such as carboxyl group, a salt with a base (for example, an alkali metal salt such as a sodium salt, a potassium salt, etc , or an alkaline earth metal salt such
35 as a calcium salt and the like) may be mentioned.

The objective compound [I] or a pharmaceutically

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acceptable salt thereof of the present invention includes its internal salt, an adduct, a solvate and a hydrate.

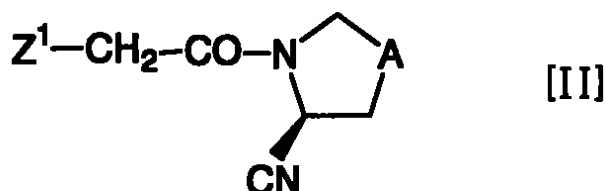
The objective compound [I] or a pharmaceutically acceptable salt thereof of the present invention can be administered orally or parenterally and used as commonly used pharmaceutical preparations such as a tablet, granule, capsule, powder, injection solution and inhalant. For example, the compound of the present invention can be used with an excipient or a diluent acceptable for general pharmaceuticals such as a binder, disintegrator, extender, filler and lubricant, to form a preparation according to the usual method.

The administration dose of the objective compound [I] or a pharmaceutically acceptable salt thereof of the present invention may vary depending on the administration method, age, weight and condition of a patient, and it is generally about 0.01 to 300 mg/kg, particularly preferably about 0.1 to 30 mg/kg per day.

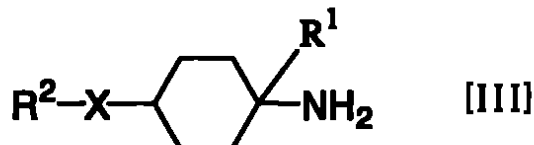
The objective compound [I] of the present invention can be prepared according to the following (Process A) and (Process B), but it is not limited to these processes.

(Process A)

The objective compound [I] of the present invention can be prepared by reacting a compound represented by the formula [II]:



wherein Z^1 represents a reactive residue and A has the same meaning as defined above, with a compound represented by the formula [III].



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wherein R^1 , R^2 and X have the same meanings as defined above,

or a salt thereof, and optionally, by making the product into a pharmaceutically acceptable salt

5 As examples of the salt of the compound [III], a salt with an inorganic acid such as hydrochloride and sulfate, or a salt with an inorganic base such as an alkali metal salt and an alkaline earth metal salt can be used.

10 As the reactive residue of Z^1 , commonly used reactive residues such as a halogen atom, a lower alkylsulfonyloxy group and an arylsulfonyloxy group can be used, among which the halogen atom is particularly preferred.

The reaction of the compound [II] with the compound [III] or the salt thereof can be carried out in a suitable solvent or without solvent in the presence or absence of an acid acceptor

15 As the solvent, any solvents may be suitable as long as it does not adversely affect to the reaction, and, for example, acetonitrile, methanol, ethanol, isopropyl alcohol, propyl alcohol, acetone, dimethylformamide, dimethyl
20 sulfoxide, tetrahydrofuran, ether, dioxane, ethyl acetate, toluene, methylene chloride, dichloroethane, chloroform or a mixed solvent of these solvents can be suitably used.

25 This reaction suitably proceeds at 0 to 120°C, particularly at room temperature to 80°C

30 As the acid acceptor, an inorganic base (for example, alkali metal hydride such as sodium hydride, alkali metal carbonate such as sodium carbonate and potassium carbonate, alkali metal alkoxide such as sodium methoxide, alkali metal such as sodium, and alkali metal hydroxide such as sodium hydroxide and potassium hydroxide, etc.) or an organic base (for example, triethylamine, diisopropyl-ethylamine, N-methylmorpholine, pyridine, dimethylaniline, dimethylaminopyridine, etc.) can be suitably used.

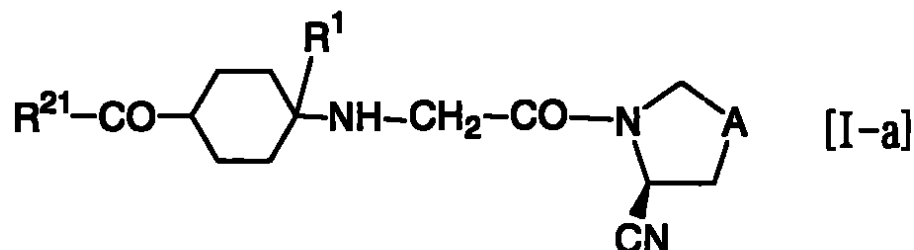
35 (Process B)

In addition, among the objective compound [I] of the

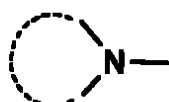
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present invention,

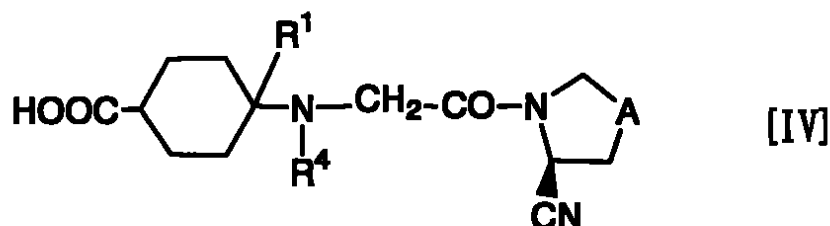
the compound represented by the formula [I-a]



5 wherein R^{21} represents (1) a monocyclic, bicyclic or tricyclic nitrogen-containing heterocyclic group which may be substituted or (2) an amino group which may be substituted, and represented by the formula



10 and R^1 and A have the same meanings as defined above, can be prepared by reacting a compound represented by the formula [IV]:

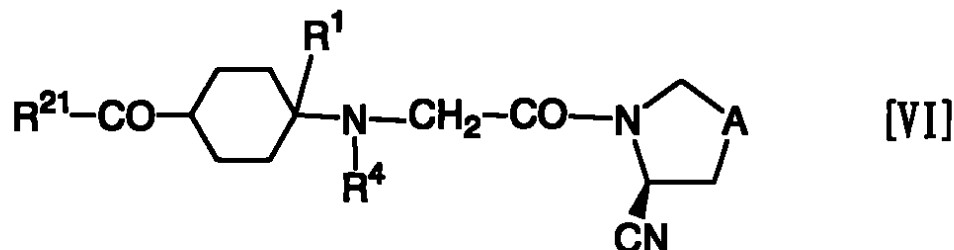


15 wherein R^4 represents a protective group for an amino group, and R^1 and A have the same meanings as defined above,

or a salt thereof with the compound represented by the formula [V]:



20 or a salt thereof to obtain a compound represented by the formula [VI]:



49 

wherein R^1 , R^4 , R^{21} and A have the same meanings as defined above,

or a salt thereof, and by removing the protective group for the amino group (R^4) from the product, and optionally, by
5 making the product into a pharmaceutically acceptable salt

As examples of salts of the compounds [IV] to [VI], a salt with an inorganic acid such as hydrochloride and sulfate, or a salt with an inorganic base such as an alkali metal salt and an alkaline earth metal salt can be used

10 As the protective group for the amino group of R^4 , any of the commonly used protective groups for the amino group such as t-butoxycarbonyl group, benzyloxycarbonyl group, trifluoroacetyl group, chloroacetyl group, 9-fluorenylmethyloxycarbonyl group, etc. can be suitably used

15 The reaction of the compound [IV] or a salt thereof with the compound [V] or a salt thereof can be carried out in a suitable solvent or without solvent in the presence or absence of a condensing agent.

As the solvent, any solvents may be suitable as long
20 as it does not adversely affect to the reaction, and, for example, acetonitrile, methanol, ethanol, isopropyl alcohol, propyl alcohol, acetone, dimethylformamide, tetrahydrofuran, ether, dioxane, ethyl acetate, toluene, methylene chloride, dichloroethane, chloroform or a mixed solvent of these
25 solvents can be suitably used.

This reaction suitably proceeds at 0 to 120°C, particularly at room temperature to 80°C

For the condensing agent, O-benzotriazol-1-yl-N,N,N',N'-tetramethyluroniumhexafluorophosphate, DCC
30 (dicyclohexylcarbodiimide), EDC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide), chloroformates (for example, ethyl chloroformate and isobutyl chloroformate) and carbonyldiimidazole can be suitably used.

Also, for promoting the reaction, additives such as
35 base (sodium carbonate, sodium hydrogencarbonate, triethylamine, pyridine, 4-dimethylaminopyridine, diisopropyl-

ethylamine, 1,8-diazabicyclo[5 4 0]undec-7-ene, etc.), 1-hydroxybenzotriazole, 1-hydroxysuccinimide, etc can be added to the above condensing agents

5 The subsequent removal of the protective group (R^4) for the amino group of the compound [VI] can be carried out according to the conventional method, and it can be carried out, for example, in a suitable solvent or without solvent by an acid treatment, base treatment or catalytic reduction

10 As the solvent, any solvents may be suitable as long as it does not adversely affect to the reaction, and, for example, methanol, ethanol, isopropyl alcohol, propyl alcohol, dioxane, methylene chloride, chloroform, dichloroethane, ether, tetrahydrofuran, ethyl acetate, toluene or a mixed solvent of these solvents can be suitably used.

15 This reaction suitably proceeds at -78 to 80°C , particularly at 0°C to room temperature

As the acid, an inorganic acid such as hydrochloric acid, sulfuric acid, etc , and an organic acid such as acetic acid, trifluoroacetic acid, methanesulfonic acid, p-toluenesulfonic acid, etc can be suitably used

20

As the base, an inorganic base (for example, alkali metal hydride such as sodium hydride, etc , alkali metal carbonate such as sodium carbonate, potassium carbonate, etc , alkali metal alkoxide such as sodium methoxide, etc ,
25 alkali metal such as sodium, etc , and alkali metal hydroxide such as sodium hydroxide, potassium hydroxide, etc.) or an organic base (for example, triethylamine, diisopropylethylamine, morpholine, N-methylmorpholine, pyridine, piperidine, dimethylaniline, dimethylamino-pyridine, etc.) can be suitably used.

30

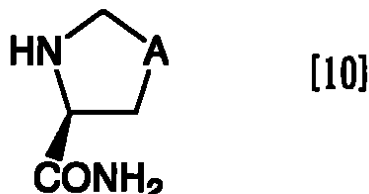
The catalytic reduction can be carried out by suitably using palladium-carbon, palladium hydroxide-carbon, platinum oxide or Raney nickel under hydrogen atmosphere.

The starting material [II] of the present invention
35 can be prepared, for example, according to the method described in International Patent Publications Nos WO

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98/19998, WO 00/34241, Reference Examples (Reference Example 1 or 2) mentioned below and the like

For example, the compound [II] can be obtained by reacting a compound represented by the formula [10]:



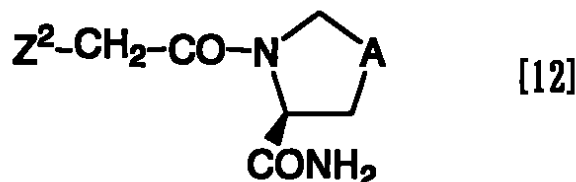
5

wherein A has the same meaning as defined above, with a compound represented by the formula [11]:



wherein Z^2 and Z^1 represent reactive residues which may be the same or different, in the presence of an acid acceptor (for example, triethylamine) to obtain a compound represented by the formula [12]:

10



15

wherein Z^2 and A have the same meanings as defined above,

and treating the product with a dehydrating agent (for example, phosphorous oxychloride, trifluoroacetic anhydride, etc) according to the conventional method.

20

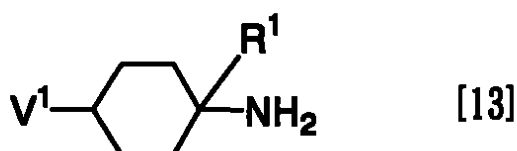
As the reactive residue of Z^2 or Z^1 , the same reactive residue commonly used as in the above Z^1 can be suitably used.

25

The starting material [III] can be prepared, for example, by the same method as described in Reference Examples (Reference Examples 3 to 14) mentioned below

For example, the compound [III] in which X is $-\text{N}(\text{R}^3)-$ or $-\text{O}-$ can be prepared by reacting a compound represented by the formula [13].

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wherein V^1 represents $-\text{NH}(\text{R}^3)-$ or hydroxy group, and R^1 and R^3 have the same meanings as defined above, an amino group-protected material thereof or a salt thereof with a compound represented by the formula [14]:

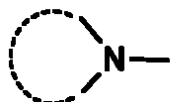


wherein Z^4 represents a reactive residue and R^2 has the same meaning as defined above, in the presence or absence of an acid acceptor (for example, an organic base such as triethylamine, diisopropylethylamine, etc., and an inorganic base such as sodium hydride, potassium carbonate, etc.), and, if necessary, by removing the protective group for the amino group according to the conventional method.

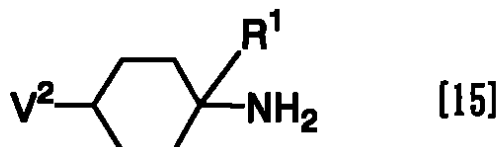
As the protective group for the amino group, any of the same protective groups commonly used as in the above R^4 can be suitably used.

As the reactive residue of Z^4 , the same reactive residues commonly used as in the above Z^1 can be suitably used.

For example, the compound [III] in which X is $-\text{CO}-$ and R^2 is a group represented by the formula:



can be produced by reacting a compound represented by the formula [15]:



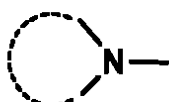
wherein V^2 represents $-\text{COOH}$ and R^1 has the same meaning as defined above,

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an amino group-protected material thereof or a salt thereof with a compound represented by the formula [16]

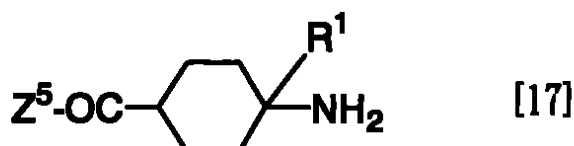


5 wherein R^{22} represents (1) a monocyclic, bicyclic or tricyclic nitrogen-containing heterocyclic group which may be substituted or (2) an amino group which may be substituted, represented by the formula.



10 and forms a cyclic or straight amine together with hydrogen atom, or a salt thereof, in the presence of a condensing agent (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, etc.) and, if necessary, by removing the protective group for the amino group according to the conventional method

15 Or else, the compound [III] in which X is -CO- can be obtained by reacting a compound represented by the formula [17]:



20 wherein Z^5 represents a reactive residue and R^1 has the same meaning as defined above, an amino group-protected material thereof or a salt thereof with a compound represented by the formula [18]:



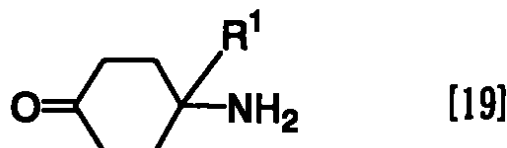
25 wherein R^5 represents a lower alkyl group and R^3 has the same meaning as defined above, in the presence of a palladium catalyst (for example, dichlorobis(triphenylphosphine)palladium, etc.)

30 As the protective group for the amino group, any of the same protective groups commonly used as in the above R^4 can be suitably used Also, as the reactive residue of Z^5 , the same reactive residues commonly used as in the

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above Z^1 can be suitably used.

Or else, the compound [III] in which X is $-N(R^3)-$ can be prepared by reacting the compound represented by the formula [19]



5

wherein R^1 has the same meaning as defined above, an amino group-protected material thereof or a salt thereof with the compound represented by the formula [20]



10 wherein V^3 represents $-N(R^3)H$ and R^2 has the same meaning as defined above, in the presence of a reducing agent (sodium triacetoxyborohydride, etc) and, if necessary, by removing the protective group for the amino group according to the conventional method.

15

As the protective group for the amino group, any of the same protective groups commonly used as in the above R^4 can be suitably used.

20 The starting materials [10] to [20] can be prepared according to known methods or in the same manner as described in Reference Examples mentioned below.

In order to obtain a trans form of the starting material [III] taking a cyclohexane ring as a standard plane, each trans form of the starting cyclohexane compounds (the compounds [13], [15], [17], etc.) may be used.

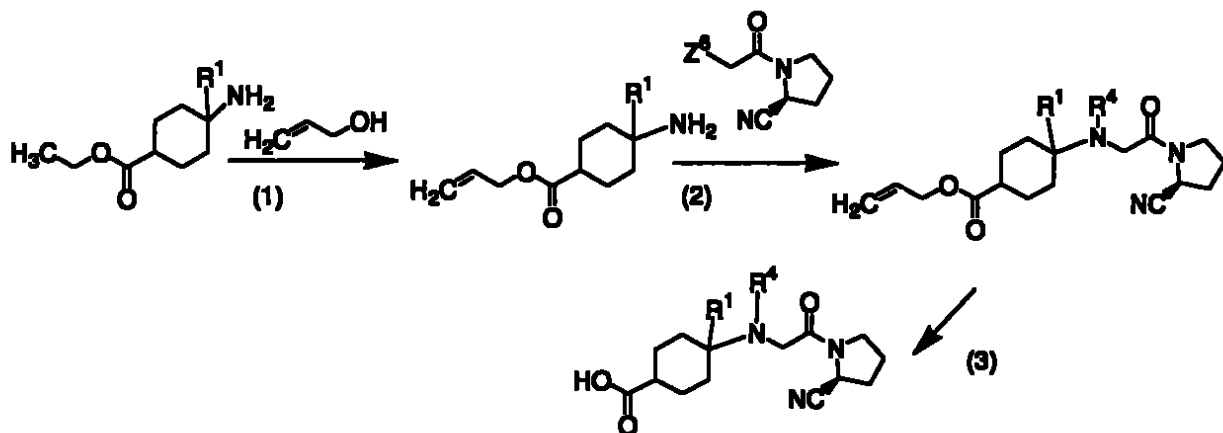
25

Also, the starting material [IV] can be prepared, for example, in the same manner as in the process described in Example (Example 3-1, (1) to (3)) mentioned below or in accordance with these processes, as shown in the following figure. (In the figure, Z^6 represents a reactive residue, R^4 represents a protective group for an amino group and other symbols have the same meanings as defined above.)

30

SS ~~10~~

As the reactive residue of Z^6 , the same reactive residues commonly used as in the above Z^1 can be suitably used.



[Compound IV]

5 The compound [I] of the present invention or its starting material prepared according to the above is isolated in a free form or as a salt thereof, and purified. The salt can be prepared by subjecting to the salt-forming treatment conventionally used

10 Isolation and purification can be carried out by applying the usual chemical operations such as extraction, concentration, crystallization, filtration, recrystallization, various kinds of chromatographies and the like

15 In the compound of the present invention, optical isomers such as racemic isomers, optically active isomers, diastereomers, etc. can be present alone or as mixtures thereof. A stereochemically pure isomer can be derived by using a stereochemically pure starting material or by separating an optical isomer according to the general separation process for racemic resolution. Also, diastereomeric mixtures can be separated according to the conventional method, for example, fractional crystallization or by chromatography.

25 EXAMPLES

The present invention will be described in detail by referring to the following Examples but these Examples do

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not intend to limit the present invention.

Example 1a-1

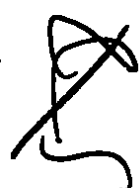
A acetonitrile-methanol solution containing 100 mg of (S)-1-bromoacetyl-2-cyanopyrrolidine (Reference Example 1 mentioned below) and 327 mg of N-(5-nitro-2-pyridyl)-trans-1,4-cyclohexanediamine (Reference Example 3-1 mentioned below) was stirred at room temperature for 15 hours. Water was added to the reaction mixture and the mixture was extracted with chloroform. After the extract was dried over sodium sulfate, the solvent was removed under reduced pressure. The residue was purified by diol column chromatography (solvent 0 to 10% methanol-chloroform) to obtain an oily product. The oily product was dissolved in 0.5 ml of ethyl acetate-0.5 ml of chloroform, and then, 1.0 ml of 2N hydrochloric acid-ether and 2 ml of ether were successively added thereto. Precipitates were collected by filtration and washed with ether to obtain (S)-2-cyano-1-[trans-4-(5-nitro-2-pyridylamino)cyclohexylamino]acetylpyrrolidine dihydrochloride (Example 1a-1 in Table 1a).

Examples 1a-2 to 1d-152

Using (S)-1-bromoacetyl-2-cyanopyrrolidine and corresponding starting materials, they were treated in the same manner as in Example 1a-1, compounds of Tables 1a to 1d shown below (Examples 1a-2 to 1a-89, 1b-1 to 1b-71, 1c-1 to 1c-52 and 1d-1 to 152) were obtained. Incidentally, the corresponding starting materials were obtained by the similar method as described in Reference Examples mentioned below, by known methods or by a method in combination of these methods.

Provided that the compound of Example 1d-77 was obtained by using trans-4-(1-piperazinylcarbonyl)cyclohexylamine as a starting material.

Also, the compound of Example 1c-39 (namely, (S)-2-cyano-1-[trans-4-[(N-carboxymethyl-N-methylamino)carbonyl]-cyclohexylamino]acetylpyrrolidine hydrochloride) was obtained by treating the compound of Example 1c-38 (namely,

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(S)-2-cyano-1-[trans-4-[(N-tert-butoxycarbonylmethyl-N-methylamino)carbonyl]cyclohexylamino]acetylpyrrolidine) with trifluoroacetic acid, followed by treating with hydrochloric acid

5 Also, the compound of the Example 1d-14 (namely, (S)-2-cyano-1-[trans-4-(1-piperazinylcarbonyl)cyclohexylamino]-acetylpyrrolidine·dihydrochloride) was obtained by treating a free form of the compound of Example 1d-70 ((S)-2-cyano-1-[trans-4-(4-benzyloxycarbonyl-1-piperazinylcarbonyl)cyclohexylamino]acetylpyrrolidine) with trimethylsilyl iodide.

Examples 2-1 and 2-2

(1) A mixture of 600 mg of 4-tert-butoxycarbonylamino-4-methylcyclohexanone (the compound of Reference Example 6-1, 15 (3)), 783 mg of sodium triacetoxyborohydride, 343 mg of 3-cyanoaniline, 159 mg of acetic acid and 6 ml of dichloroethane was stirred at room temperature for 16 hours. The mixture was diluted with an aqueous saturated sodium hydrogencarbonate solution and then extracted with chloroform 20 The extract was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (solvent: hexane-ethyl acetate (4:1) to (1:1)) to obtain 304 mg of N-tert-butoxycarbonyl-1-methyl-c-4-(3-cyano-phenylamino)-r-1-cyclohexylamine and 292 mg of N-tert-butoxycarbonyl-1-methyl-t-4-(3-cyano-phenylamino)-r-1-cyclohexylamine. 25 (2) 243 mg of N-tert-butoxycarbonyl-1-methyl-c-4-(3-cyano-phenylamino)-r-1-cyclohexylamine obtained in the above (1) was stirred in a mixture of 2 ml of 4N hydrochloric acid/ 30 dioxane and 2 ml of ethanol at room temperature for 15 hours

After the reaction mixture was concentrated, to the residue were added 320 mg of (S)-1-bromoacetyl-2-cyanopyrrolidine, 0.6 ml of triethylamine, 3.5 ml of acetonitrile and 1 ml of methanol and the mixture was stirred at 35 room temperature for 15 hours. The mixture was diluted

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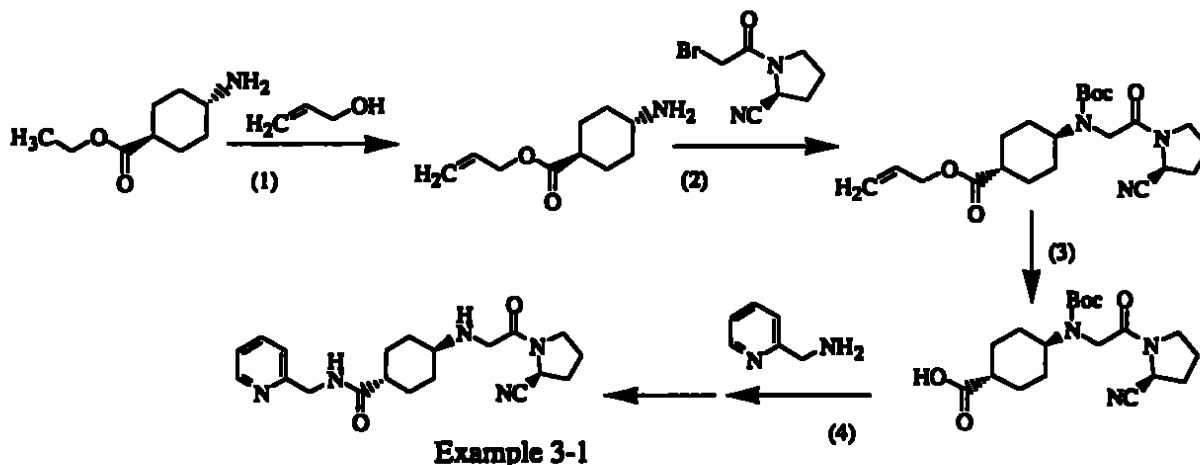
with an aqueous saturated sodium hydrogencarbonate solution and extracted with chloroform. The extract was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (solvent: chloroform-methanol (50 1)) to obtain 154 mg of the compound, which was then treated with hydrochloric acid to yield (S)-2-cyano-1-[1-methyl-c-4-(3-cyano-phenylamino)-r-1-cyclohexylamino]acetylpyrrolidine·dihydrochloride (Table 2: Example 2-1)

(3) Using N-tert-butoxycarbonyl-1-methyl-t-4-(3-cyano-phenylamino)-r-1-cyclohexylamine obtained in the above (1), it was treated in the same manner as in (2), (S)-2-cyano-1-[1-methyl-c-4-(3-cyano-phenylamino)-r-1-cyclohexylamino]-acetylpyrrolidine·dihydrochloride (Example 2-2 in Table 2) was obtained.

Examples 2-3 to 2-8

Using corresponding starting materials, they were treated in the same manner as in Examples 2-1 to 2-2, compounds of Examples 2-3 to 2-8 shown in Table 2 were obtained.

Example 3-1



(1) In water was dissolved 5.0 g of trans-4-ethoxycarbonyl-cyclohexylamine·dihydrochloride, and after the solution was made basic by adding potassium carbonate, the solution was extracted with chloroform. The extract was washed with brine, dried over anhydrous sodium sulfate, and the solvent

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was removed under reduced pressure. A mixture of the residue, 5.1 g of p-toluensulfonic acid monohydrate and 50 ml of allyl alcohol was refluxed for 48 hours. The reaction mixture was concentrated, and then, diluted with
5 chloroform. The chloroform solution was washed with an aqueous potassium carbonate solution, water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel
10 flash column chromatography (solvent: chloroform-methanol-aqueous ammonia (500:10:1)) to obtain 3.29 g of trans-4-(2-propenyloxycarbonyl)cyclohexylamine
(2) A mixture of 507 mg of the compound obtained in the above (1), 400 mg of (S)-1-bromoacetyl-2-cyanopyrrolidine, 714 mg of N,N-diisopropylethylamine and 4 ml of aceto-
15 nitrile was stirred at 50°C for 12 hours. After cooling to room temperature, 476 mg of N,N-diisopropylethylamine, followed by 4 ml of acetonitrile solution containing 803 mg of di-tert-butylidicarbonate were added to the reaction mixture, and the mixture was stirred at room temperature
20 for 3 hours. After the reaction mixture was concentrated, the concentrate was diluted with ethyl acetate. The ethyl acetate solution was washed with an aqueous 10% citric acid solution, water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The
25 residue was purified by silica gel flash chromatography (solvent: chloroform-methanol (100:1)) to obtain 658 mg of (S)-2-cyano-1-[N-tert-butoxycarbonyl-trans-4-(2-propenyl-oxycarbonyl)cyclohexylamino]acetylpyrrolidine.
(3) A mixture of 600 mg of the compound obtained in the
30 above (2), 165 mg of tetrakis(triphenylphosphine)palladium, 271 mg of ammonium formate and 6 ml of dioxane was stirred at 50°C for 1 hour. After cooling, the reaction mixture was poured into water and extracted with chloroform. The extract was washed with brine, dried over anhydrous sodium
35 sulfate, and then, the solvent was removed under reduced pressure. The residue was purified by silica gel flash

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chromatography (solvent: chloroform-methanol (50 1)) to obtain 394 mg of (S)-2-cyano-1-(N-tert-butoxycarbonyl-trans-4-carboxycyclohexylamino)acetylpyrrolidine

(4) A solution of 2 ml N,N-dimethylformamide containing 150
5 mg of the compound obtained in the above (3), 64 mg of 2-aminomethylpyridine, 114 mg of 1-ethyl-3-(3-dimethylamino-propyl)-carbodiimide and 80 mg of 1-hydroxybenzotriazole was stirred at room temperature for 24 hours. An aqueous saturated sodium hydrogencarbonate solution was added to
10 the reaction mixture and the mixture was extracted with chloroform. The extract was washed with brine and dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residue was dissolved in 3 ml of acetonitrile, and 1 ml of an acetonitrile solution of
15 118 mg of trimethylsilyl iodide was added dropwise to the solution under ice-cooling, and the mixture was stirred at room temperature for 30 minutes. To the reaction mixture were added methanol and water, and after stirring for a while, the mixture was neutralized with an aqueous
20 saturated sodium hydrogencarbonate solution, and then, extracted with chloroform. The extract was washed with an aqueous saturated sodium hydrogencarbonate solution, water and brine, dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure. The
25 residue was purified by diol chromatography (solvent chloroform) to obtain an oily product. The oily product was dissolved in 1 ml of ethyl acetate, and then, 0.5 ml of 1N hydrochloric acid-ether followed by 2 ml of ether were added thereto, and precipitates were washed with ether to
30 obtain 106 mg of (S)-2-cyano-1-[trans-4-(2-pyridylmethylaminocarbonyl)cyclohexylamino]acetylpyrrolidine dihydrochloride (Example 3-1 in Table 3)

Examples 3-2 to 3-12

35 The compounds of Examples 3-2 to 3-12 in Table 3 were obtained in the same manner as in Example 3-1 (4), using

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(S)-2-cyano-1-(N-tert-butoxycarbonyl-trans-4-carboxycyclohexylamino)acetylpyrrolidine (the compound of the above Example 3-1 (3)) and the corresponding starting materials Examples 4-1 to 4-32

- 5 A solution of 2 ml of acetonitrile-1 ml of methanol containing 100 mg of (R)-3-chloroacetyl-4-cyanothiazolidine (the compound of Reference Example 2 mentioned below) and 372 mg of N-(5-nitro-2-pyridyl)-trans-1,4-cyclohexane-diamine was stirred at room temperature for 15 hours.
- 10 Water was added to the reaction mixture and the mixture was extracted with chloroform. After the extract was dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure. The residue was purified by diol column chromatography (solvent: 0 to 5% methanol-chloro-
- 15 form) to obtain an oily product. The oily product was dissolved in 0.5 ml of ethyl acetate-0.5 ml of chloroform, and 1.0 ml of 2N hydrochloric acid-ether was added thereto, followed by 2 ml of ether. Precipitates were collected by filtration and washed with ether to obtain 173 mg of (R)-4-
- 20 cyano-3-[trans-4-(5-nitro-2-pyridylamino)cyclohexylamino]-acetylthiazolidine dihydrochloride (Example 4-1 in Table 4).

Also, the compounds of Examples 4-2 to 4-32 in Table 4 were obtained in the same manner as mentioned above, using the corresponding starting materials

25 Reference Example 1

According to the process described in the literature (WO 98/19998), (S)-1-bromoacetyl-2-cyanopyrrolidine was obtained by reacting L-prolineamide (commercially available product) and bromoacetyl bromide, followed by dehydration.

30 Reference Example 2

- L-thioprolinaamide hydrochloride was synthesized according to the process described in the literature (Ashworth et. al, Bioorg Med. Chem. Lett, Vol 6, pp 2745-2748, 1996). 2 36 ml of chloroacetyl chloride was
- 35 added to a solution of 150 ml of dichloromethane containing 5.00 g of L-thioprolinaamide hydrochloride thus obtained

and 8.67 ml of triethylamine under ice-cooling, and the mixture was stirred at the same temperature for 1 hour. To the reaction mixture was added a dichloromethane solution containing 4.8 ml of pyridine and 8.4 ml of trifluoroacetic anhydride, and the mixture was further stirred at room temperature for 1 hour. The reaction mixture was washed with an aqueous 10% HCl solution and water, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure, and subsequently, the residue was crystallized from ether to obtain 4.82 g of (R)-3-chloro-acetyl-4-cyanothiazolidine as yellow-brownish crystals. Reference Examples 3-1 to 3-40

A solution of 5-nitro-2-chloropyridine (2.50 g) and trans-1,4-cyclohexanediamine (5.40 g) in ethanol (15 ml)-tetrahydrofuran (10 ml) was stirred at room temperature for 5 days. The precipitates were removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (solvent: chloroform-methanol-concentrated aqueous ammonia (20:4:1)) and crystallized from ethyl acetate to obtain N-(5-nitro-2-pyridyl)-trans-1,4-cyclohexanediamine (Reference Example 3-1 in Table 5).

Also, the compounds of Examples 3-2 to 3-40 in Table 5 were obtained in the same manner as mentioned above, using the corresponding starting materials. Reference Examples 3-41 to 3-44

A N,N-dimethylacetamide (30 ml) solution containing 4-nitrofluorobenzene (1.69 g) and trans-1,4-cyclohexanediamine (4.1 g) was stirred at 144°C for 3 days. After cooling, an aqueous saturated potassium carbonate solution was added to the reaction solution, and the reaction mixture was extracted with ethyl acetate. The extract was dried over anhydrous potassium carbonate, and then, the solvent was removed under reduced pressure. The residue was purified by silica gel flash column chromatography (solvent: chloroform-methanol-ammonia (90:10:1)), and the

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solvent was removed to obtain trans-N-(4-nitrophenyl)-1,4-cyclohexanediamine (Reference Example 3-41 in Table 5) (2.31 g).

Also, the compounds of Examples 3-42 to 3-44 in Table 5 were obtained in the same manner as mentioned above, using the corresponding starting materials.

Reference Examples 3-45 to 3-47

25 mL of an ethanol solution containing 1.23 g of N-tert-butoxycarbonyl-trans-1,4-cyclohexanediamine, 1.0 g of 2-chloro-3-nitro-pyridine 1-oxide and 700 mg of dimethylaminopyridine was refluxed under argon atmosphere for 2 hours.

After cooling, the reaction solution was concentrated under reduced pressure, the residue was dissolved in chloroform, washed with water, dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure. The obtained residue was purified by silica gel flash column chromatography (solvent chloroform-methanol (30:1)) to obtain red powder. The resulting compound was dissolved in 5mL of trifluoroacetic acid and the solution was stirred at room temperature for 3 hours. After the solvent was removed under reduced pressure, the residue was purified by silica gel flash column chromatography (solvent: aqueous ammonia-saturated chloroform-methanol (10:1)) to obtain 110 mg of N-(3-nitropyridine-1-oxid-2-yl)-trans-1,4-cyclohexanediamine (Reference Example 3-45 in Table 5).

Also, the compounds of Examples 3-46 to 3-47 in Table 5 were obtained in the same manner as mentioned above, using corresponding starting materials.

Reference Examples 3-48 to 3-49

In the mixed solvent of 5 ml of ethanol and 4 ml of tetrahydrofuran were dissolved 168 mg of N-tert-butoxycarbonyl-trans-4-[(6-chloro-3-pyridazinyl)amino]cyclohexylamine (Reference Example 3-46) and 0.5 ml of triethylamine. To the solution was added 50 mg of 10% palladium carbon and the mixture was stirred under hydrogen atmosphere with

normal pressure at room temperature for 1 day. After the catalyst was removed by filtration, the solvent was removed, and the residue was stirred in 2 ml of trifluoroacetic acid for 3 hours. The solvent was removed, an aqueous 10% sodium hydroxide solution was added to the residue, the mixture was extracted with chloroform and dried over anhydrous sodium sulfate. Subsequently, the solvent was removed under reduced pressure to obtain 61 mg of trans-4-(pyridazin-3-ylamino)cyclohexylamine (Reference Example 3-48 in Table 5)

Also, the compound of Example 3-49 in Table 5 was obtained by treating the corresponding starting material (Reference Example 3-47) in the same manner as mentioned above.

Reference Examples 3-50 to 3-58

Also, the compounds of Examples 3-50 to 3-58 in Table 5 were obtained in the same manner as in Reference Example 9-50 or Reference Example 9-55.

Reference Example 3-59

Ethyl 4-chloro-2-phenyl-5-pyrimidinecarboxylate and N-tert-butoxycarbonyl-trans-1,4-cyclohexanediamine were reacted in ethanol in the presence of dimethylaminopyridine in the same manner as in Reference Example 3-49 to obtain N-tert-butoxycarbonyl-trans-4-(5-ethoxycarbonyl-2-phenyl-4-pyrimidinylamino)cyclohexylamine

The compound was treated in the same manner as in Reference Example 9-56 (1) and (2) to obtain trans-4-(5-morpholinocarbonyl-2-phenyl-4-pyrimidinylamino)cyclohexylamine (Reference 3-59 in Table 5).

Reference Example 4

(1) To 150 ml of a tetrahydrofuran suspension containing 10 g of trans-4-aminocyclohexanol was added 15ml of triethylamine, 50 ml of a tetrahydrofuran solution containing 2-chloro-5-nitropyridine was further added thereto under ice-cooling, and then, the mixture was stirred at room temperature for 18 hours. Water was added to the reaction mixture

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and the mixture was extracted with chloroform. The extract was washed with brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel flash column chromatography (solvent: ethyl acetate-hexane (2:1)) to obtain 8.52 g of trans-4-(5-nitro-2-pyridylamino)cyclohexanol.

(2) To 10 ml of a dichloromethane solution containing 1.0 g of the compound obtained in the above (1) was added 1.8 ml of triethylamine, 0.65 ml of methanesulfonyl chloride was

further added thereto under ice-cooling, and the mixture was stirred for 1 hour. An aqueous saturated sodium bicarbonate solution was added to the reaction mixture and the mixture was extracted with chloroform. The extract was washed with water and brine, dried over anhydrous sodium

sulfate, and then, the solvent was removed under reduced pressure. 1.37 g of sodium azide was added to a solution of the residue dissolved in 10 ml of dimethylformamide and the mixture was stirred at 50°C for 3 days. After cooling, an aqueous saturated sodium bicarbonate solution was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was washed with water and brine, dried over sodium sulfate, and then, the solvent was removed under reduced pressure. The residue was purified by silica gel flash column chromatography (solvent: ethyl acetate-hexane (1:5)) to obtain 758 mg of cis-4-azide-N-(5-nitro-2-pyridyl)cyclohexylamine.

(3) A solution comprising 10 ml of tetrahydrofuran-1 ml of water, containing 640 mg of the compound obtained in the above (2) and 704 mg of triphenylphosphine was stirred at room temperature for 2 days. The reaction mixture was concentrated, and the residue was purified by silica gel flash column chromatography (solvent: ethyl acetate-methanol (10:1)) to obtain 531 mg of N-(5-nitro-2-pyridyl)-cis-1,4-cyclohexanediamine (the compound of Reference

Example 4 in Table 5)

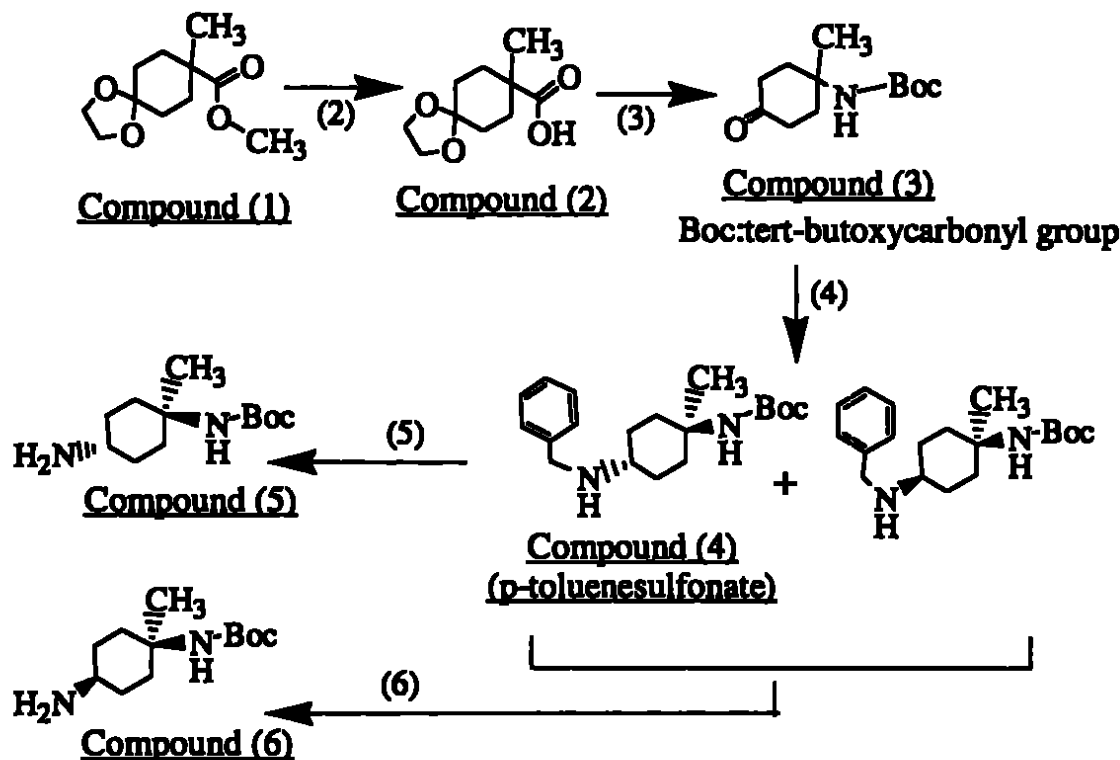
Reference Examples 5-1 to 5-6

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- (1) In 600 mL of dimethylformamide were suspended 60.0 g of trans-4-tert-butoxycarbonylaminocyclohexyl methanesulfonate and 20.1 g of sodium azide and the suspension was stirred at 90°C for 6 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with water and brine, dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure to obtain 47.9 g of cis-4-azide-N-(tert-butoxycarbonyl)cyclohexylamine.
- (2) In 8 mL of tetrahydrofuran were suspended 500 mg of the compound obtained in the above (1) and 100 mg of palladium-carbon (wet) and the suspension was vigorously stirred under hydrogen atmosphere at room temperature for 1.5 hours. During the course, hydrogen in the system was replaced twice. The insolubles were removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (solvent: chloroform-methanol (20:1), followed by chloroform-methanol-aqueous ammonia (100:10:1)) to obtain 395 mg of N-tert-butoxycarbonyl-cis-1,4-cyclohexanediamine.
- (3) A suspension comprising 10 mL of 2-propanol, 2.0 g of the compound obtained in the above (2), 1.63 g of 2-chloro-3-nitropyridine and 1.95 mL of diisopropylethylamine was stirred at 80°C for 1 day. After the reaction mixture was concentrated under reduced pressure, water was added thereto and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (solvent: chloroform, followed by chloroform-ethyl acetate (7:1)). To a suspension of the resultant compound in ethanol was added hydrochloric acid-dioxane, the mixture was stirred at room temperature for 18 hours, and the precipitates were collected by filtration to obtain 2.15 g of N-(3-nitro-2-pyridyl)-cis-1,4-cyclohexanediamine dihydrochloride (Reference Example 5-1 in Table 5).

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Also, the compounds of Reference Examples 5-2 to 5-6 in Table 5 were obtained in the same manner as mentioned above, using the corresponding starting materials Reference Example 6-1



(1) According to the process described in the literature (JP83-118577), methyl 1,4-dioxaspiro[4.5]decan-8-carboxylate was reacted with methyl iodide in the presence of LDA (lithium diisopropylamide) to obtain methyl 8-methyl-1,4-dioxaspiro[4.5]decan-8-carboxylate (the compound (1) of the above figure).

(The starting materials were synthesized according to the process described in the literature by Rosemund et al. (Chem. Ber., 1975, Vol. 108, pp. 1871-1895) and the literature by Black et al. (Synthesis, 1981, p. 829))

(2) A mixture of 3.80 g of the compound obtained in the above (1), 3.55 g of sodium hydroxide, 16 mL of methanol and 25 mL of water was refluxed for 2 hours. The reaction mixture was ice-cooled, adjusted its pH to 5 by 2N hydrochloric acid and an aqueous 10% citric acid solution, and extracted with ethyl acetate. The extract was washed with

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water and brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to obtain 3.46 g of 8-methyl-1,4-dioxaspiro[4.5]decan-8-carboxylic acid (the compound (2) of the above figure)

5 (3) A mixture comprising 16.19 g of the compound obtained in the above (2), 24.51 g of diphenylphosphoryl azide, 9.00 g of triethylamine and 160 mL of toluene was refluxed for 2.5 hours. The reaction mixture was ice-cooled, washed with an aqueous saturated sodium hydrogencarbonate solution,
10 water and brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. To a solution of the resulting compound in 100 mL of dimethylacetamide was gradually added 9.55 g of potassium tert-butoxide under ice-cooling, and the mixture was stirred at
15 room temperature for 1 hour. The reaction mixture was poured into ice-water, and the precipitated crystals were collected by filtration, washed with water and dried. To a solution of the resulting compound in 100 mL of tetrahydrofuran was added 100 mL of an aqueous solution containing
20 30.87 g of p-toluenesulfonic acid hydrate, and the mixture was stirred at room temperature for 16 hours. The mixture was diluted with an aqueous saturated sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with water and brine, dried over anhydr-
25 ous sodium sulfate, and the solvent was removed under reduced pressure to obtain 10.41 g of 4-tert-butoxycarbonylamino-4-methylcyclohexanone (the compound (3) of the above figure).

(4) A mixture comprising 10.41 g of the compound obtained
30 in the above (3), 11.01 g of sodium triacetoxymethylborohydride, 5.10 mL of benzylamine and 150 mL of methylene chloride was stirred at room temperature for 16 hours. The mixture was diluted with an aqueous saturated sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was
35 washed with water and brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure.

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To a solution of the resulting compound in 15 mL of methanol was added 3.32 g of p-toluenesulfonic acid hydrate, followed by 160 mL of ether. The precipitates were collected by filtration, washed with ether and dried to obtain 7.49 g of N-benzyl-t-4-tert-butoxycarbonylamino-4-methyl-r-1-cyclohexylamine p-toluenesulfonate (the compound (4) of the above figure).

(5) A mixture comprising 16.63 g of the compound obtained in the above (4), 5.0 g of 10% palladium-carbon and 400 mL of methanol was stirred under hydrogen atmosphere (1 atm) for 24 hours. 10% palladium-carbon was removed by filtration and the filtrate was concentrated. The resulting residue was dissolved in a mixture of 50 mL of an aqueous 10% sodium hydroxide solution and 300 mL of ether, the ether layer was washed with water and brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to obtain 6.87 g of t-4-tert-butoxycarbonylamino-4-methyl-r-1-cyclohexylamine (the compound (5) of the above figure).

(6) The filtrate in the step of the above (4) was treated with an aqueous sodium hydroxide solution and extracted with chloroform. The extract was washed with water and brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was applied to NH-silica gel column chromatography (solvent: hexane-ethyl acetate (30:1 to 3:1) to obtain N-benzyl-c-4-tert-butoxycarbonylamino-4-methyl-r-1-cyclohexylamine. Then, this compound was treated in the same manner as described in the above (5) to obtain c-4-tert-butoxycarbonylamino-4-methyl-r-1-cyclohexylamine (the compound (6) of the above figure).

Reference Example 6-2

In the same manner as in Reference Example 6-1 (1) to (5) or (6) except for using benzyloxymethyl chloride instead of methyl iodide in the step of Reference Example 6-1 (1), t-4-tert-butoxycarbonylamino-4-hydroxymethyl-r-1-

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cyclohexylamine or c-4-tert-butoxycarbonylamino-4-hydroxymethyl-r-1-cyclohexylamine was obtained.

Also, in the same manner as in Reference Example 6-1 (1) to (5) or (6) except for using methoxymethyl chloride instead of methyl iodide in the step of Reference Example 6-1 (1), t-4-tert-butoxycarbonylamino-4-methoxymethyl-r-1-cyclohexylamine or c-4-tert-butoxycarbonylamino-4-methoxymethyl-r-1-cyclohexylamine was obtained.

Reference Examples 7-1 to 7-18

10 A mixture comprising 1 70 g of t-4-tert-butoxycarbonylamino-4-methyl-r-1-cyclohexylamine (the compound obtained in the above Reference Example 6-1 (5)), 2.04 g of 2-chloropyrimidine, 3 24 mL of diisopropylethylamine and 13 mL of 2-propanol was refluxed for 12 hours. After cooling, 15 the reaction mixture was diluted with water and extracted with ethyl acetate. The extract was washed with water and brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (solvent ethyl 20 acetate-hexane (30:70 to 50:50)). The resulting compound was dissolved in 4 mL of dioxane, 10 mL of 4N hydrochloric acid-dioxane was added thereto, and the mixture was stirred for 8 hours. The reaction mixture was diluted with ether and the precipitated crystals were collected by filtration 25 and washed with ether. The resulting crystals were dissolved in water, which was saturated with potassium carbonate, subsequently extracted with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to obtain 587 mg 30 of 1-methyl-t-4-(2-pyrimidinylamino)-r-1-cyclohexylamine (Reference Example 7-1 in Table 5).

Also, the compounds of Reference Examples 7-2 to 7-5 in Table 5 were obtained in the same manner as mentioned above, using the corresponding starting materials.

35 Also, the compounds of Reference Examples 7-6 to 7-9 in Table 5 were obtained in the same manner as mentioned

above, using c-4-tert-butoxycarbonylamino-4-methyl-r-1-cyclohexylamine (the compound obtained in the above Reference Example 6-1, (6)) and the corresponding starting materials.

5 Also, the compounds of Reference Examples 7-10 to 7-18 in Table 5 were obtained in the same manner as mentioned above, using t- or c-4-tert-butoxycarbonylamino-4-hydroxymethyl-r-1-cyclohexylamine (Reference Example 6-2) and the corresponding starting materials.

10 Reference Examples 7-19 to 7-23

4-tert-Butoxycarbonylamino-4-methylcyclohexanone (the compound (3) of Reference Example 6-1) and the corresponding starting materials (an amine compounds) were reacted in the presence of sodium triacetoxymethylborohydride at room temperature for 16 hours under stirring, and then, an acid treatment of the reaction mixture was carried out to remove a protective group (t-butoxycarbonyl group), to obtain the compounds of Reference Examples 7-19 to 7-23 in Table 5. Reference Examples 8-1 to 8-4

20 (1) To 160 ml of a methylene chloride solution containing 16.93 g of 4-(tert-butoxycarbonylamino)cyclohexanone and 10 55 ml of N-methylbenzylamine was added 19.08 g of sodium triacetoxymethylborohydride under ice-cooling, and the mixture was stirred at room temperature for 14 hours. The reaction mixture was diluted with an aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The extract was washed with water and brine, dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure. The resulting residue was suspended in hexane and collected by filtration. This mother liquor was concentrated, and the residue was purified by NH-silica gel chromatography (solvent hexane-ethyl acetate (97:3 to 83:17)), and the residue was further suspended in hexane and collected by filtration, whereby it was combined with the product previously obtained by filtration to give 13.55 g of N'-benzyl-N-tert-butoxycarbonyl-N'-methyl-trans-1,4-

cyclohexanediamine

A suspension of 13.53 g of this compound and 2.00 g of palladium hydroxide-carbon suspended in methanol was subjected to catalytic hydrogenation under normal pressure at room temperature over 5 hours. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to obtain 9.93 g of N-tert-butoxycarbonyl-N'-methyl-trans-1,4-cyclohexanediamine.

(2) The compound obtained in the above (1) and the corresponding starting materials (chloride) were used and reacted under reflux in 2-propanol in the presence of diisopropylethylamine for 12 hours as in Reference Example 7-1, and the resulting compound was subjected to acid treatment with hydrochloric acid, and then, neutralized with potassium carbonate to obtain the compounds of Reference Examples 8-1 to 8-4 in Table 5

Reference Examples 9-1 to 9-45

2.04 g of 60 % sodium hydride was gradually added to 150 ml of a tetrahydrofuran solution containing 10.0 g of trans-4-(tert-butoxycarbonylamino)cyclohexanol and 7.35 g of 2-chloro-5-nitropyridine, and 30 mL of dimethylsulfoxide was further added thereto, and then, the mixture was stirred at room temperature for 1 day. The reaction mixture was poured into water and extracted with chloroform. The extract was washed with water and brine, dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure. The residue was applied to silica gel column chromatography (solvent: chloroform alone to chloroform-ethyl acetate (20:1)). The obtained powder crystals were suspended in ethyl acetate-hexane mixed solution and collected by filtration to obtain 12.20 g of trans-1-tert-butoxycarbonylamino-4-(5-nitro-2-pyridyloxy)-cyclohexane. To 10 ml of an ethanol suspension containing 800 mg of this compound was added 2 ml of 2N hydrochloric acid-dioxane solution, and the mixture was stirred at room temperature for 18 hours. The precipitates were collected

by filtration to obtain 568 mg of trans-4-(5-nitro-2-pyridyloxy)cyclohexylamine hydrochloride (Reference Example 9-1 in Table 6)

Also, the compounds of Reference Examples 9-2 to 9-45 in Table 6 were obtained in the same manner as mentioned above, using the corresponding starting materials.

Reference Examples 9-46 to 9-47

60% sodium hydride was added to 10 ml of a tetrahydrofuran suspension containing 1.00 g of trans-4-amino-cyclohexanol hydrochloride and the mixture was refluxed for 1 hour. After cooling to room temperature, 2-chloropyrimidine was slowly added thereto and the mixture was stirred at room temperature for 6 hours. The reaction mixture was poured into ice-cold water and extracted with chloroform. The extract was washed with brine and dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure. The residue was purified by NH-silica gel column chromatography (solvent, ethyl acetate-hexane (1:4) to chloroform alone) to obtain 788 mg of trans-4-(2-pyrimidinylloxy)cyclohexylamine (Reference Example 9-46 in Table 6).

Also, the compound of Examples 9-47 in Table 6 was obtained in the same manner as mentioned above, using the corresponding starting materials.

Reference Example 9-48

In the same manner as in Reference Example 9-1, trans-1-tert-butoxycarbonylamino-4-(3-nitro-2-pyridyloxy)-cyclohexane was obtained. Subsequently, a suspension of 3.35 g of this compound in 30 ml of ethanol was stirred at 50°C, and 155 mg of palladium-carbon (dry) and then 1.6 ml of hydrazine monohydrate were added thereto. After the mixture was stirred for 10 minutes, 185 mg of the remaining palladium-carbon was added thereto and the mixture was refluxed for 40 minutes. After the reaction mixture was cooled to room temperature, the insolubles were removed by filtration and the filtrate was concentrated under reduced

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pressure. The resulting residue was crystallized from ethanol-water (1 1) and the crystals were collected by filtration to obtain 2.58 g of trans-1-tert-butoxycarbonyl-amino-4-(3-amino-2-pyridyloxy)cyclohexane.

5 Then, hydrochloric acid-dioxane was added to an ethanol solution of this compound to subject to acid treatment to obtain trans-4-(3-amino-2-pyridyloxy)cyclohexylamine hydrochloride (Reference Example 9-48 in Table 6).
Reference Example 9-49

10 In the same manner as in Reference Example 9-1 by using trans-4-(tert-butoxycarbonylamino)cyclohexanol and the corresponding starting materials, trans-4-(5-ethoxycarbonyl-2-methylthiopyrimidin-4-yloxy)cyclohexylamine hydrochloride was obtained.

15 The hydrochloride compound was made into an aqueous solution, and the solution was treated with potassium carbonate and extracted with chloroform to obtain its free form (Reference Example 9-49).
Reference Examples 9-50 to 9-54

20 In 50 mL of chloroform was dissolved 2.75 g of N-tert-butoxycarbonyl-trans-4-(5-ethoxycarbonyl-2-methylthiopyrimidin-4-yloxy)cyclohexylamine (a compound of Reference Example 9-49 prior to deprotection (hydrochloric acid-dioxane treatment)), 1.73 g of 75%-m-chloroperbenzoic acid
25 was added to the solution, and the mixture was stirred at room temperature for 30 minutes. Then, 1.14 g of dimethylamine hydrochloride and 2.79 mL of triethylamine were added thereto and the mixture was further stirred for 5 hours.
An aqueous saturated sodium hydrogencarbonate solution was
30 added to the reaction mixture, and the mixture was stirred. Then, the chloroform layer was collected by separation, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by silica gel flash chromatography (solvent: hexane-chloro-
35 form (50:50 to 100:0)) to obtain 2.74 g of N-tert-butoxycarbonyl-trans-4-[5-ethoxycarbonyl-2-(dimethylamino)-

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pyrimidin-4-yloxy]cyclohexylamine.

This compound was deprotected by treating with hydrochloric acid-dioxane, and subsequently neutralized with potassium carbonate to obtain trans-4-[5-ethoxycarbonyl-2-(dimethylamino)pyrimidin-4-yloxy]cyclohexylamine (Reference Example 9-50 in Table 6)

Also, the compounds of Reference Examples 9-51 to 9-54 in Table 6 were obtained in the same manner as mentioned above.

10 Reference Examples 9-55 to 9-57

(1) In 15 mL of ethanol was dissolved 2.675 g of N-tert-butoxycarbonyl-trans-4-[5-ethoxycarbonyl-2-(dimethylamino)pyrimidin-4-yloxy]cyclohexylamine (the compound of Reference Example 9-50 prior to deprotection treatment), 3.27 mL of an aqueous 3N-sodium hydroxide solution was added thereto at room temperature, and the mixture was stirred overnight. The reaction mixture was diluted with water, and then, citric acid was added thereto until the solution became neutral. The precipitated crystals were collected by filtration, washed with water and dried under reduced pressure to obtain 2.015 g of N-tert-butoxycarbonyl-trans-4-[5-carboxy-2-(dimethylamino)pyrimidin-4-yloxy]cyclohexylamine.

(2) The compound obtained in the above (1) was used as a starting material and reacted with a starting amine compound in the same manner as in Reference Example 11-1. The resulting compound (hydrochloride) was made into an aqueous solution, and the solution was treated with potassium carbonate and extracted with chloroform to obtain a free form.

Thus, the compounds of Reference Examples 9-55 to 9-57 in Table 6 were obtained.

Reference Examples 9-58 to 9-64

(1) 0.494 ml of DMSO was slowly added dropwise to 10 ml of a methylene chloride solution containing 0.526 ml of oxalyl chloride under argon gas atmosphere at -78°C. After 15

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minutes from the completion of the addition, 30 ml of a methylene chloride suspension containing trans-4-tert-butoxycarbonylamino-cyclohexanol in was added dropwise, and further 30 minutes later, 2 52 ml of triethylamine was added thereto and the mixture was stirred at -78°C for 30 minutes and at 0°C for 15 minutes. An aqueous sodium bicarbonate solution was added to the reaction mixture and the mixture was extracted with chloroform. The extract was dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure. The resulting residue was suspended in a hexane-isopropyl ether mixed solvent and collected by filtration to obtain 0.903 g of 4-(tert-butoxycarbonylamino)cyclohexanone

(2) To 350 ml of a toluene solution containing 33.05 g of the compound obtained in the above (1) was added dropwise 313 ml of 1.0 M diisobutyl aluminum hydride-toluene solution at -78°C, and the mixture was stirred at the same temperature for 4 hours. After an excessive reagent was decomposed by adding 33 ml of methanol dropwise to the mixture, 100 ml of water was added thereto, and the mixture was stirred for 1 hour. The precipitated insolubles were removed by filtration. The organic layer of the filtrate was separated and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, the resulting residue was suspended in chloroform-isopropyl ether mixed solvent under heating and the insolubles were removed by filtration. The filtrate was concentrated, and then, the same operation was performed with isopropyl ether. The resulting filtrate was concentrated and the residue was purified by silica gel flash column chromatography (solvent: ethyl acetate-hexane (1:2 to 1:1)), and the obtained colorless crystals were further suspended in hexane-isopropyl ether mixed solvent under heating and subjected to filtration at 0°C to obtain 6.95 g of cis-4-tert-butoxycarbonylamino-cyclohexanol.

(3) The compounds of Reference Examples 9-58 to 9-64 in

Table 6 were obtained in the same manner as in Reference Example 9-1, using the above-obtained cis-4-tert-butoxycarbonylamino-cyclohexanol and the corresponding starting materials.

5 Reference Example 10-1

(1) A mixture comprising 9.13 g of 4-tert-butoxycarbonylamino-4-methylcyclohexanone, 3.05 g of sodium borohydride and 100 mL of isopropyl alcohol was stirred at room temperature for 1 hour. Under ice-cooling, the reaction mixture was diluted with an aqueous saturated ammonium chloride solution and extracted with ethyl acetate. The resulting extract was washed with water and brine, dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure to obtain 9.20 g of a mixture of t-4-tert-butoxycarbonylamino-4-methyl-r-1-cyclohexanol and c-4-tert-butoxycarbonylamino-4-methyl-r-1-cyclohexanol.

(2) A mixture comprising 9.20 g of the compound obtained in the above (1), 8.26 g of p-methoxybenzoic acid chloride, 5.93 g of dimethylaminopyridine and 100 mL of methylene chloride was refluxed for 20 hours. After cooling, the reaction mixture was washed with an aqueous saturated sodium hydrogencarbonate solution, an aqueous 10% citric acid solution, water and brine, dried over anhydrous sodium sulfate, and then, the solvent was removed. The residue was crystallized from n-hexane to obtain 0.68 g of c-4-tert-butoxycarbonylamino-4-methyl-O-(4-methoxyphenyl-carbonyl)-r-1-cyclohexanol (cis compound).

Also, the residue was purified by silica gel column chromatography [solvent ethyl acetate/n-hexane (1/10)] to obtain 3.50 g of a mixture (1.5) of the above compound (cis compound) and t-4-tert-butoxycarbonylamino-4-methyl-O-(4-methoxyphenylcarbonyl)-r-1-cyclohexanol (trans compound).

(3) A mixture comprising 10.68 g of the cis compound obtained in the above (2), 6.10 g of sodium hydroxide, 150 mL of methanol and 120 mL of water was heated at external

temperature of 75°C for 1 hour After cooling the reaction mixture, the solvent was removed under reduced pressure and extracted with ethyl acetate The extract was washed with an aqueous saturated sodium hydrogencarbonate solution, water and brine, dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure to obtain 6.61 g of c-4-tert-butoxycarbonylamino-4-methyl-r-1-cyclohexanol.

(4) In the same manner as in the above (3) by using 3.50 g of the mixture (1 5) of cis form and trans form obtained in the above (2), 1.77 g of t-4-tert-butoxycarbonylamino-4-methyl-r-1-cyclohexanol was obtained

Reference Examples 10-2 to 10-8

The compounds of Reference Examples 10-2 and 10-3 in Table 6 were obtained in the same manner as in Reference Example 9-1 by using t-4-tert-butoxycarbonylamino-4-methyl-r-1-cyclohexanol (Reference Example 10-1 (4)) and the corresponding starting materials. Also, the compounds of Reference Examples 10-4 to 10-8 in Table 6 were obtained in the same manner as mentioned above by using c-4-tert-butoxycarbonylamino-4-methyl-r-1-cyclohexanol (Reference Example 10-1 (3)) and the corresponding starting materials. Reference Examples 11-1 to 11-38 and 12-1 to 12-96

A mixture comprising 500 mg of trans-4-(tert-butoxycarbonylamino)cyclohexanecarboxylic acid, 250 mg of N-methyl-benzylamine, 434 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 306 mg of 1-hydroxybenzotriazol and 5 ml of N,N-dimethylformamide was stirred at room temperature for 15 hours. The reaction mixture was made basic by adding an aqueous sodium hydrogencarbonate solution, and extracted with ethyl acetate The extract was washed with water and brine, dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure to obtain 691 mg of N-benzyl-trans-4-tert-butoxycarbonylamino-N-methylcyclohexanecarboxamide A mixture comprising 670 mg of this compound, 5 mL of 4N-

hydrochloric acid-dioxane and 5 ml of dioxane was stirred at room temperature for 12 hours. The reaction mixture was concentrated to obtain 585 mg of trans-4-amino-N-benzyl-N-methylcyclohexanecarboxamide hydrochloride (Reference

5 Example 11-1 in Table 7)

Also, the compounds of Reference Examples of 11-2 to 11-38 and 12-1 to 12-96 in Table 7 and Table 8 mentioned below were obtained in the same manner as mentioned above by using the corresponding starting amine compounds

10 (straight chain amine compounds or cyclic secondary amine compounds such as a piperidine compound, a piperazine compound, etc.) (Provided that in case of free compounds, they can be obtained by saturating an aqueous solution of a hydrochloride salt compound with potassium carbonate, and
15 after extracting the solution with chloroform, drying the extract over sodium sulfate and removing the solvent under reduced pressure.)

(As the starting amine compounds (a piperidine compound, a piperazine compound, etc.), those synthesized by the
20 methods of Reference Examples 15-1 to 15-11 mentioned below, or known methods or combined methods thereof were used.)
Reference Example 12-97

(1) A mixture comprising 4.5 g of trans-4-(tert-butoxycarbonylamino)cyclohexanecarboxylic acid, 2.29 g of
25 thiomorpholine, 3.90 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, 2.74 g of 1-hydroxybenzotriazole and 30 ml of N,N-dimethylformamide was stirred at room temperature for 4 hours.

The reaction mixture was made basic by adding an
30 aqueous sodium hydrogencarbonate solution, and extracted with ethyl acetate. The extract was washed with water and brine, dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure. The residue was suspended in diisopropyl ether and precipitates were
35 collected by filtration to obtain N-tert-butoxycarbonyl-trans-4-(4-thiomorpholinylcarbonyl)cyclohexylamine

(2) To 50 ml of a chloroform solution containing 5.4 g of the compound obtained in the above (1) was added 8.9 g of 75%-m-chloroperbenzoic acid under ice-cooling, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was made basic by adding an aqueous sodium hydrogencarbonate solution, and extracted with ethyl acetate. The extract was washed with water and brine, dried over sodium sulfate, and then, the solvent was removed under reduced pressure. The residue was suspended in diisopropyl ether, and precipitates were collected by filtration.

Then, this compound was suspended in 25 mL of dioxane, 4N hydrochloric acid-dioxane solution (25 mL) was added thereto, and the mixture was stirred for 16 hours. Ether was added to the reaction mixture and precipitates were collected by filtration and dissolved in water. The solution was made basic by adding potassium carbonate, and extracted with chloroform. After the extract was dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure. The residue was suspended in diisopropyl ether and precipitates were collected by filtration to obtain trans-4-(1,1-dioxo-4-thiomorpholinyl-carbonyl)cyclohexylamine (Reference Example 12-97 in Table 8).

Reference Examples 13-1 to 13-7

To 50 ml of a methylene chloride suspension containing 5.07 g of trans-4-(benzyloxycarbonylamino)cyclohexanecarboxylic acid were added 4.0 ml of thionyl chloride and 0.3 ml of N,N-dimethylformamide and the mixture was stirred at room temperature for 1 hour.

The reaction mixture was concentrated under reduced pressure and 500 mg of the residual solid was added to 8 ml of an ice-cold methylene chloride solution containing 207 mg of 2-aminopyrimidine and 0.4 ml of triethylamine. After stirring at room temperature for 2 hours, water was added to the reaction mixture and the mixture was extracted with

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chloroform The extract was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (solvent chloroform-methanol (50 1)) to obtain 240 mg of N-benzyloxycarbonyl-trans-4-
5 [(pyrimidin-2-ylamino)carbonyl]cyclohexylamine.

This compound was applied to deprotection treatment to obtain trans-4-[(pyrimidin-2-ylamino)carbonyl]cyclohexylamine (Reference Example 13-1 in Table 8).

Also, the compounds of Reference Examples 13-2 to 13-
10 7 in Table 8 were obtained in the same manner as mentioned above by using the corresponding starting materials instead of 2-aminopyrimidine

The deprotection was carried out as mentioned below by using hydrogen bromide-acetic acid. That is, the
15 compound was stirred in 3 ml of 30% hydrogen bromide-acetic acid solution at 50°C for 4 hours 30 ml of diisopropyl ether was added to the reaction mixture and precipitates were collected by filtration to obtain a hydrobromide of the deprotected compound. This hydrobromide was made into
20 a solution and the solution was saturated with potassium carbonate and extracted with chloroform to obtain a free form.

Provided that the deprotection of the compound of Reference Example 13-2 was carried out by using palladium-carbon as mentioned below. That is, to a methanol-tetra-
25 hydrofuran suspension of the compound were added 10% palladium-carbon catalyst and ammonium formate, and the mixture was refluxed. The insolubles were removed by filtration and the filtrate was concentrated under reduced
30 pressure.

Reference Examples 13-8 to 13-16

Under argon atmosphere, a mixture comprising 1.0 g trans-4-(benzyloxycarbonylamino)cyclohexanecarbonyl chloride, 1.92 g of tributylphenyltin, 61 mg of dichlorobis-
35 (triphenylphosphine)palladium and 10 mL of dioxane was stirred at 110°C for 12 hours. After cooling, the reaction

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mixture was concentrated by a centrifugal concentrator, and then, the residue was dissolved in tetrahydrofuran and evaporated to dryness with 5 g of silica gel. The resulting residue was purified by silica gel flash chromatography (solvent: ethyl acetate-hexane (1 2) to (1:1) to obtain 883 mg of N-benzyloxycarbonyl-trans-4-benzoylcyclohexylamine.

870 mg of this compound was stirred with 1.0 g of trimethylsilyl iodide and 5 mL of chloroform under argon atmosphere at room temperature for 2 hours. Disappearance of the starting material was confirmed by TLC, 0.17 mL of methanol and 5 mL of diethyl ether were added to the reaction mixture and the mixture was stirred at room temperature for 3 days. The resulting precipitates were collected by filtration, washed with anhydrous diethyl ether, and dried to obtain 830 mg of trans-4-benzoylcyclohexylamine (Reference Example 13-8 in Table 8).

Also, the compounds of Reference Examples 13-9 to 13-16 in Table 8 were obtained in the same manner as mentioned above.

Reference Example 13-17

(1) trans-4-Methoxycarbonylcyclohexane-1-carbonyl chloride was obtained from 5 g of trans-4-methoxycarbonylcyclohexane-1-carboxylic acid and oxalyl chloride. 7.58 g of morpholine was added dropwise to 50 mL of a methylene chloride solution thereof under ice-cooling, and the mixture was stirred for 2 hours. The reaction mixture was poured into an aqueous 10% citric acid solution, extracted with chloroform, dried over anhydrous magnesium sulfate, and then, the solvent was removed under reduced pressure. The residue was purified by silica gel flash column chromatography (solvent: ethyl acetate-hexane (1 1) to ethyl acetate-chloroform (1:1)) and crystallized from hexane to obtain 6.49 g of trans-1-methoxycarbonyl-4-(morpholinocarbonyl)-cyclohexane.

(2) Under argon atmosphere, 10 mL of a tetrahydrofuran solution containing 2.0 g of the compound obtained in the

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above (1) was added dropwise to 40 mL of a hexane-tetrahydrofuran (3 5) solution containing LDA (lithium diisopropylamide) (0 024 mol) prepared at the time of using at -78°C and the temperature of the mixture was elevated to
5 -30°C over 2 hours, while stirring. The reaction mixture was cooled again to -78°C, reacted with 1.46 mL of methyl iodide, and allowed to stand to 0°C, and then, water was added thereto and the mixture was extracted with ethyl acetate. The extract was successively washed with an
10 aqueous 10% citric acid solution, water and brine, dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure. The residue was purified by silica gel flash column chromatography (solvent ethyl acetate-hexane (1:2) to (1 1)) to obtain 1.47 g of isomeric
15 mixture of 1-methoxycarbonyl-1-methyl-4-(morpholinocarbonyl)cyclohexane. This mixture was stirred in a mixture comprising 158 mg of sodium hydroxide, 1 mL of ethanol and 1 mL of water at room temperature for 12 hours. The reaction mixture was extracted with diethyl ether, the
20 extract was washed with water, dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure. The residue was recrystallized from a mixed solvent comprising diethyl ether-hexane to obtain 592 mg of single isomer of 1-methoxycarbonyl-1-methyl-4-(morpholine-carbonyl)cyclohexane
25 (3) 546 mg of the compound (single isomer) obtained in the above (2) was stirred in a mixture comprising 251 mg of sodium hydroxide, 5 mL of methanol and 10 mL of water at 110°C for 2 hours. After cooling, pH of the reaction
30 mixture was adjusted to 3 by 10% hydrochloric acid, extracted three times with chloroform, the extract was dried over anhydrous magnesium sulfate, and then, the solvent was removed under reduced pressure. 5 mL of a toluene solution containing 479 mg of the resulting
35 compound (carboxylic acid), 550 mg of diphenylphosphoryl azide and 216 mg of benzyl alcohol was stirred under

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heating for 12 hours After cooling, an aqueous 10% citric acid solution was added to the reaction mixture, and the toluene layer was separated, washed with brine and dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure The resulting residue was purified by silica gel flash chromatography (solvent. ethyl acetate-hexane (1:2)) to (1.1) to obtain 387 mg of N-benzyloxycarbonyl-1-methyl-4-(morpholinocarbonyl)cyclohexylamine.

10 This compound was deprotected by treating with trimethylsilyl iodide to obtain 1-methyl-4-(morpholinocarbonyl)cyclohexylamine (Reference Example 13-17 in Table 8). Reference Examples 13-18 to 13-21

15 N-tert-butoxycarbonyl-trans-4-(1-piperazinylcarbonyl)cyclohexylamine was obtained by treating trans-4-(tert-butoxycarbonylamino)cyclohexanecarboxylic acid and piperazine in the same manner as in the above-mentioned Reference Example 11-1.

20 Methyl chlorocarbonate was added dropwise to a mixture comprising 400 mg of this compound, 260 mg of triethylamine and 8 mL of methylene chloride under ice-cooling, and the mixture was stirred at room temperature overnight The reaction mixture was successively washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure The resulting residue was suspended in diisopropyl ether and precipitates were collected by filtration to obtain 410 mg N-tert-butoxycarbonyl-trans-4-(4-methoxycarbonyl-1-piperazinylcarbonyl)cyclohexylamine.

30 This compound was deprotected under acidic conditions according to the conventional method and the acidic mixture was returned to basic to obtain trans-4-(4-methoxycarbonyl-1-piperazinylcarbonyl)cyclohexylamine (Reference Example 13-18 of Table 8).

35 Also, the compounds of Reference Examples 13-19 to 13-21 in Table 8 were obtained in the same manner as

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mentioned above

Reference Example 13-22

A mixture comprising 623 mg of N-tert-butoxycarbonyl-trans-4-(piperazinocarbonyl)cyclohexylamine, 340 mg of 3,4-diethoxy-3-cyclobuten-1,2-dione and 5 ml of ethanol was stirred at room temperature for 2.5 days. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (solvent: chloroform-methanol (50 1)) and subsequently triturated with ether

This compound was deprotected by treating with hydrochloric acid-dioxane to obtain trans-4-[4-(4-ethoxy-1,2-dioxo-3-cyclobuten-3-yl)piperazinylcarbonyl]cyclohexylamine (Reference Example 13-22 in Table 8)

Reference Example 13-23

(1) A mixture comprising 1101 mg of N-benzyloxycarbonylpiperazine, 1131 mg of 3,4-dibutoxy-3-cyclobutene-1,2-dione and 5 ml of ethanol was stirred at room temperature for 25 hours. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (solvent: chloroform-ethyl acetate (19.1)) to obtain 1570 mg of 1-benzyloxycarbonyl-4-(4-butoxy-1,2-dioxo-3-cyclobuten-3-yl)-piperazine

This compound was deprotected by treating with palladium-carbon in the presence of 3 ml of 10% hydrochloric acid under hydrogen atmosphere to obtain 4-(4-butoxy-1,2-dioxo-3-cyclobuten-3-yl)-piperazine.

(2) The compound obtained in the above (1) was reacted with trans-(4-benzyloxycarbonylamino)cyclohexanecarbonyl chloride in methylene chloride in the presence of triethylamine to obtain N-benzyloxycarbonyl-trans-4-[4-(4-butoxy-1,2-dioxo-3-cyclobuten-3-yl)piperazinocarbonyl]cyclohexylamine.

(3) The compound obtained in the above (2) and dimethylamine hydrochloride were reacted in ethanol in the presence of triethylamine to obtain N-benzyloxycarbonyl-trans-4-[4-(4-dimethylamino-1,2-dioxo-3-cyclobuten-3-yl)piperazinyl-

carbonyl]cyclohexylamine. This compound was deprotected by treating with trimethylsilyl iodide to obtain trans-4-[4-(4-dimethylamino-1,2-dioxo-3-cyclobuten-3-yl)piperazinyl-carbonyl]cyclohexylamine (Reference Example 13-23 in Table 8)

Reference Example 13-24

0 15 ml of triethylamine and 0.07 ml of methane-sulfonyl chloride were added to 10 ml of a tetrahydrofuran-methylene chloride suspension containing 0.31 g of N-
10 benzyloxycarbonyl-trans-4-[(5-hydroxymethyl-2-isoindolin-yl)carbonyl]cyclohexylamine under ice-cooling, and the mixture was stirred under ice-cooling for 1 hour. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. After the extract was dried
15 over sodium sulfate, the solvent was removed under reduced pressure. To the residue were added 5 ml of dimethyl-formamide and 0.25 ml of morpholine, and the mixture was stirred at room temperature overnight. Water was added to the reaction mixture and the mixture was extracted with
20 ethyl acetate. After the extract was dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (solvent: chloroform-methanol = 100:1). This compound was treated with palladium-carbon under hydrogen
25 atmosphere to obtain trans-4-[(5-morpholinomethyl-2-isoindolinyl)carbonyl]cyclohexylamine (Reference Example 13-24 in Table 8)

Reference Examples 13-25 to 13-29

(1) 20 g of manganese dioxide was added to 120 ml of a
30 chloroform solution containing 4.0 g of N-benzyloxycarbonyl-trans-4-[(5-hydroxymethyl-2-isoindolinyl)carbonyl]cyclohexylamine, and the mixture was stirred at room temperature for 4 hours. Manganese dioxide was removed by filtration through Celite and the solvent was removed under reduced
35 pressure. The residue was suspended in hexane-ethyl acetate and the crystals were collected by filtration to obtain

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N-benzyloxycarbonyl-trans-4-[(5-formyl-2-isoindoliny1)-
carbonyl]cyclohexylamine

(2) To an aqueous solution containing 3.35 g of silver
nitrate were added 2.75 g of the compound obtained in the
5 above (1) and 110 ml of ethanol under ice-cooling, and then,
an aqueous solution containing 2.61 g of potassium hydrox-
ide was added dropwise thereto. The mixture was stirred
under ice-cooling for 1 hour and separated by filtration
through Celite, and then, the solvent was removed under
10 reduced pressure. To the residue was added 50 ml of an
aqueous 1N hydrochloric acid solution and the mixture was
extracted with chloroform. After the extract was dried
over anhydrous sodium sulfate, the solvent was removed
under reduced pressure. The residue was suspended in
15 hexane-ether and the crystals were collected by filtration
to obtain N-benzyloxycarbonyl-trans-4-[(5-carboxy-2-iso-
indoliny1)carbonyl]cyclohexylamine.

(3) The compound obtained in the above (2) was used and
condensed with a starting amine compound in the same manner
20 as in Reference Example 11-1, and subsequently treated with
palladium-carbon under hydrogen atmosphere to obtain trans-
4-[(5-dimethylaminocarbonyl-2-isoindoliny1)carbonyl]cyclo-
hexylamine (Reference 13-25 in Table 8).

Also, the compounds of Reference Examples 13-26 to
25 13-29 in Table 8 were obtained in the same manner as
mentioned above.

Reference Examples 13-30 to 13-33

(1) 2.6 g of tert-butylcarbamate, 3.5 ml of triethyl-
silane and 1.15 ml of trifluoroacetic acid were added to 25
30 ml of an acetonitrile suspension containing 3.0 g of N-
benzyloxycarbonyl-trans-4-[(5-formyl-2-isoindoliny1)carbon-
yl]cyclohexylamine (the compound obtained in Reference
Example 13-25 (1)), and the mixture was stirred at room
temperature overnight. Water was added to the reaction
35 mixture and the mixture was extracted with chloroform.
After the extract was dried over anhydrous sodium sulfate,

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the solvent was removed under reduced pressure The residue was suspended in hexane-ethyl acetate and the crystals were collected by filtration to obtain N-benzyloxycarbonyl-trans-4-[(5-tert-butoxycarbonylaminomethyl-2-isoindoliny-
5 yl)carbonyl]cyclohexylamine.

(2) The compound obtained in the above (1) was treated with palladium-carbon under hydrogen atmosphere to obtain trans-4-[(5-tert-butoxycarbonylaminomethyl-2-isoindoliny-
10 yl)carbonyl]cyclohexylamine (Reference Example 13-30 in Table 8)

(3) The compound obtained in the above (1) was treated with 4N hydrochloric acid-dioxane to obtain N-benzyloxycarbonyl-trans-4-[(5-aminomethyl-2-isoindoliny-
15 yl)carbonyl]cyclohexylamine hydrochloride.

(4) 0.25 ml of cyclopropanecarbonyl chloride was added to 5
15 ml of a methylene chloride-pyridine solution containing 0.5 g of the compound (hydrochloride) obtained in the above (3), and the mixture was stirred at room temperature for 4 hours Diluted aqueous hydrochloric acid solution was added to the reaction mixture and the mixture was extracted with chloro-
20 form After the extract was dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure The residue was purified by silica gel chromatography (solvent, chloroform-methanol = 50/1) to obtain crystals This compound was treated with palladium-carbon under
25 hydrogen atmosphere to obtain trans-4-[(5-cyclopropyl-carbonylaminomethyl-2-isoindoliny-
yl)carbonyl]cyclohexylamine (Reference Example 13-31 in Table 8)

Also, the compounds of Reference Examples 13-32 to 13-33 in Table 8 were obtained in the same manner as
30 mentioned above

Reference Example 13-34

(1) 0.08 g of hydroxylamine hydrochloride and 0.09 g of sodium formate were added to 3 ml of a formic acid solution containing 0.3 g of N-benzyloxycarbonyl-trans-4-[(5-formyl-
35 2-isoindoliny-
yl)carbonyl]cyclohexylamine (the compound obtained in Reference Example 13-25 (1)), and the mixture

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was refluxed for 3 hours. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. After the extract was dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure. The residue was purified by NH silica gel chromatography (solvent chloroform-ethyl acetate = 50 1), and the resulting compound was treated with trimethylsilyl iodide to obtain trans-4-[(5-cyano-2-isoindolyl)carbonyl]cyclohexylamine hydroiodide (Reference Example 13-34 in Table 8).

10 Reference Examples 13-35 to 13-46

(1) 17 33 g of stannous chloride was added to a hydrated ethanol (120 ml of ethanol + 12 ml of water) suspension containing 6.08 g of N-benzyloxycarbonyl-trans-4-[(6-nitro-1-indolyl)carbonyl]cyclohexylamine (the compound obtained in the same manner as in Reference Example 13-1 before deprotection), and the mixture was refluxed under argon atmosphere for 4.5 hours. An aqueous 10% sodium hydroxide solution was added to the reaction mixture to adjust pH of the mixture to pH 9 to 10, the mixture was diluted with 300 ml of chloroform and dried over anhydrous magnesium sulfate, and then, the insolubles were removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (solvent: chloroform-ethyl acetate (2:1)) to obtain 4.72 g of N-benzyloxycarbonyl-trans-4-[(6-amino-1-indolyl)carbonyl]cyclohexylamine

(2) 0.12 ml of pyridine and 0.104 ml of acetic anhydride were added to 10 ml of a methylene chloride solution containing 396 mg of the compound obtained in the above (1), and the mixture was stirred for 5 hours. 5% hydrochloric acid was added to the reaction mixture and the mixture was extracted with chloroform. The extracted layer was successively washed with water and an aqueous saturated sodium bicarbonate solution and dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure. The residue was purified by silica gel column

90 X

chromatography (solvent chloroform-ethyl acetate (1 1))

This compound was deprotected by treating with palladium-carbon to obtain trans-4-[(6-acetylamino-1-indoliny)carbonyl]cyclohexylamine (Reference Example 13-35 in Table 8)

Also, the compounds of Reference Examples 13-36 to 13-37 in Table 8 were obtained in the same manner as mentioned above.

(3) 0.085 ml of methanesulfonyl chloride was added to 10 ml of a pyridine solution containing 400 mg of the compound obtained in the above (1) at room temperature, and the mixture was stirred for 5 hours. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in chloroform, washed successively with 5% hydrochloric acid, water and an aqueous saturated sodium bicarbonate solution and dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (solvent chloroform-ethyl acetate (2.1))

This compound was deprotected by treating with palladium-carbon to obtain trans-4-[(6-methylsulfonylamino-1-indoliny)carbonyl]cyclohexylamine (Reference Example 13-38 in Table 8)

(4) 15 ml of N,N-dimethylformamide solution containing 403 mg of the compound obtained in the above (1), 169 mg of N,N-dimethylglycine hydrochloride, 243 mg of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride, 173 mg of 1-hydroxybenzotriazole and 0.181 ml of triethylamine in was stirred at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in ethyl acetate, successively washed with an aqueous saturated sodium bicarbonate solution, water and brine, dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (solvent: chloroform-methanol (50:1)).

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This compound was deprotected by treating with palladium-carbon to obtain trans-4-[[6-(dimethylamino)-methylcarbonyl-1-indoliny]carbonyl]cyclohexylamine (Reference Example 13-39 in Table 8)

5 (5) 0.8 ml of an aqueous 37% formalin solution and 635 mg of sodium triacetoxyborohydride were added to 10 ml of an acetonitrile suspension containing 402 mg of the compound obtained in the above (1) at room temperature, and the mixture was stirred for 15 hours. The reaction mixture
10 was diluted with water and extracted with ethyl acetate. The extracted layer was washed with water and brine in order, dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (solvent
15 chloroform-ethyl acetate (2:1)).

This compound was deprotected by treating with palladium-carbon to obtain trans-4-[(6-dimethylamino-1-indoliny]carbonyl]cyclohexylamine (Reference Example 13-40 in Table 8)

20 (6) The compounds of Reference Examples 13-41 to 13-46 were obtained in the same manner as in the above (1) to (5) except for using N-benzyloxycarbonyl-trans-4-[(5-nitro-1-indoliny]carbonyl]cyclohexylamine (the compound obtained in the same manner as in Reference Example 13-1) as a
25 starting material.

Reference Examples 13-47 to 13-52

451 mg of potassium carbonate and 238 mg of 2-(dimethylamino)ethyl chloride hydrochloride were added to 5 ml of a N,N-dimethylformamide solution containing 400 mg of N-
30 benzyloxycarbonyl-trans-4-[(5-hydroxy-1-indoliny]carbonyl]cyclohexylamine (the compound obtained in the same manner as in Reference Example 13-1), and the mixture was stirred at 50°C for 19 hours. The reaction mixture was concentrated under reduced pressure, and a solution of the
35 residue in chloroform was washed with water, dried over sodium sulfate, and then, the solvent was removed under

92 ~~24~~

reduced pressure The residue was purified by silica gel column chromatography (solvent: chloroform-methanol (30:1)).

100 mg of 10% palladium-carbon catalyst and 920 mg of ammonium formate were added to 10 ml of methanol-10 ml of tetrahydrofuran suspension containing this compound, and the mixture was refluxed for 17 hours. The insolubles were removed by filtration, and the filtrate was concentrated under reduced pressure to obtain 281 mg of trans-4-{{5-(2-dimethylaminoethyl)oxy-1-indoliny]carbonyl}cyclohexylamine (Reference Example 13-47 in Table 8).

Also, the compounds of Reference Examples 13-48 to 13-52 in Table 8 were obtained in the same manner as mentioned above

Reference Examples 14-1 to 14-16

15 A mixture comprising 400 mg of cis-4-(tert-butoxy-carbonylamino)cyclohexanecarboxylic acid, 216 mg of 4-hydroxypiperidine, 244 mg of 1-hydroxybenzotriazole, 686 mg of O-benzotriazol-1-yl-N,N,N',N'-tetramethyluroniumhexa-fluorophosphate, 398 µl of N-methylmorpholine and 11 ml of N,N-dimethylformamide was stirred at room temperature for 14 hours Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was washed with an aqueous 10% citric acid solution, water and brine, dried over anhydrous sodium sulfate, and then, the solvent was removed under reduced pressure The resulting residue was dissolved in 5 ml of dioxane, then, 6 ml of 4N hydrochloric acid-dioxane was added thereto, and the mixture was stirred at room temperature for 12 hours The reaction mixture was concentrated, methanol was added to the residue and the mixture was concentrated under reduced pressure Next, ether was added to the residue, and the mixture was concentrated under reduced pressure to obtain cis-4-(4-hydroxypiperidinocarbonyl)cyclohexylamine·hydrochloride (Reference Example 14-1 in Table 8)

35 Also, the compounds of Examples 14-2 to 14-16 in Table 8 were obtained in the same manner as mentioned above,

using the corresponding starting materials. (Provided that in case of free compounds, they can be obtained by saturating an aqueous solution of a hydrochloride salt compound with potassium carbonate, and after extracting the solution with chloroform, drying the extract over anhydrous sodium sulfate and removing the solvent under reduced pressure)

Reference Example 15-1

To a dimethylformamide (7 ml) solution containing N-(tert-butoxycarbonyl)piperazine (10 g) were added potassium carbonate (742 mg) and then butyl iodide (1.09 g), and the mixture was stirred at room temperature for 15 hours to undergo reaction, thereby obtaining N-tert-butoxycarbonyl-N-butylpiperazine. This compound was acid-treated with hydrochloric acid to obtain N-butylpiperazine-dihydrochloride

Also, N-isopropylpiperazine-dihydrochloride was obtained in the same manner as mentioned above

Reference Example 15-2

Dimethylamine hydrochloride (430 mg) was added to a methylene chloride (10 ml) solution containing 4-(tert-butoxycarbonyl)piperidone (10 g), and under ice-cooling, triethylamine (0.84 ml) and triacetoxyborohydride (1.17 g) were further added thereto, and the mixture was stirred at room temperature for 3 hours to undergo reaction, thereby obtaining N-tert-butoxycarbonyl-4-dimethylaminopiperidine. This compound was acid-treated with hydrochloric acid to obtain 4-(dimethylamino)piperidine-dihydrochloride.

Reference Example 15-3

Sodium triacetoxyborohydride (10.51 g) was added to a methylene chloride (50 ml) solution containing N-formylpiperazine (5.08 g) and cyclohexanecarboxyaldehyde (7.50 g) under ice-cooling, and the mixture was stirred at room temperature for 18 hours to undergo reaction, thereby obtaining 1-formyl-4-cyclohexylmethylpiperazine, which was then acid-treated with hydrochloric acid to obtain 1-(cyclohexylmethyl)piperazine-hydrochloride.

Reference Example 15-4

60% Sodium hydride (0 232 g) was gradually added to a tetrahydrofuran (4.5 ml) solution containing 1-tert-butoxycarbonyl-4-hydroxypiperidine (0 900 g) and 2-chloropyrimidine (0 666 g), and 2 hours later, dimethyl sulfoxide (1 0 ml) was added thereto, and the mixture was stirred at room temperature for 1 day to undergo reaction, thereby obtaining 1-tert-butoxycarbonyl-4-(2-pyrimidinylloxy)piperidine. This compound was acid-treated with hydrochloric acid to obtain 4-(2-pyrimidinylloxy)piperidine·hydrochloride

Also, the following compounds were obtained in the same manner as mentioned above

4-(5-Cyano-2-pyridylloxy)piperidine·hydrochloride

4-(5-Bromo-2-pyrimidinylloxy)piperidine·hydrochloride

4-(p-Nitrophenoxy)piperidine·hydrochloride

Reference Example 15-5

A mixture comprising N-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (700 mg), morpholine (319 μ L), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (702 mg), 1-hydroxybenzotriazole (495 mg) and N,N-dimethylformamide (9 ml) was stirred at room temperature for 16 hours to undergo reaction, and the resulting compound was acid-treated with hydrochloric acid to obtain 4-(morpholinocarbonyl)piperidine·hydrochloride

Also, the following compounds were obtained in the same manner as mentioned above

4-(Diethylaminocarbonyl)piperidine·hydrochloride

4-(N-methyl-N-benzylaminocarbonyl)piperidine·hydrochloride

4-(p-Chlorophenylaminocarbonyl)piperidine hydrochloride

Reference Example 15-6

A mixture comprising 4-amino-1-(tert-butoxycarbonyl)-piperidine (700 mg), benzoic acid (512 mg), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (804 mg), 1-hydroxybenzotriazole (567 mg) and N,N-dimethylformamide (10 ml) was stirred at room temperature for 16 hours to undergo reaction, and the resulting compound was acid-treated with

95 ~~10~~

hydrochloric acid to obtain 4-(benzoylamino)piperidine·hydrochloride

Also, the following compounds were obtained in the same manner as mentioned above

- 5 4-(2-Pyridylcarbonylamino)piperidine hydrochloride
4-(Cyclohexylcarbonylamino)piperidine·hydrochloride
Reference Example 15-7

An acetonitrile (7 ml) solution containing N-(tert-butoxycarbonyl)piperazine (700 mg), N-methyl-N-phenyl-carbamoyl chloride (700 mg) and triethylamine (1.05 mL) was
10 stirred at room temperature for 15 hours to undergo reaction, and the resulting compound was acid-treated with hydrochloric acid to obtain 1-(N-methyl-N-phenylamino-carbonyl)piperazine·hydrochloride

15 Reference Example 15-8

Methanesulfonyl chloride (3.65 ml) was added to a methylene chloride (50 ml) solution containing N-formyl-piperazine (5.08 g) and triethylamine (6.85 ml) under ice-cooling, and the mixture was stirred at room temperature
20 for 18 hours to undergo reaction, thereby obtaining 1-formyl-4-methanesulfonylpiperazine. This compound was acid-treated with hydrochloric acid to obtain 1-methanesulfonylpiperazine·hydrochloride. Also, 1-(phenylsulfonyl)piperazine·hydrochloride was obtained in the same manner
25 as mentioned above by using the corresponding starting material

Reference Example 15-9

0.84 ml of triethylamine and 0.37 ml of methanesulfonyl chloride were added to 10 ml of a tetrahydrofuran
30 solution containing 0.99 g of 2-tert-butoxycarbonyl-5-(hydroxymethyl)isoindoline under ice-cooling, and the mixture was stirred under ice-cooling for 1 hour. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. After the extract was dried
35 over sodium sulfate, the solvent was removed under reduced pressure. To the residue were added 20 ml of ethanol and

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1 0.2 ml of diisopropylethylamine, and the mixture was
refluxed for 30 minutes. The reaction mixture was concen-
trated under reduced pressure, and ethyl acetate and an
aqueous 5% hydrochloric acid solution were added to the
5 residue, followed by the extraction. After the extract was
dried over sodium sulfate, the solvent was removed under
reduced pressure. The residue was purified by silica gel
chromatography (solvent hexane-ethyl acetate = 4:1) to
obtain an oily product. This oily product was dissolved in
10 5 ml of dioxane, then, 8 ml of 4N hydrochloric acid-dioxane
was added thereto, and the mixture was stirred at room tem-
perature. The precipitates precipitated by addition of 20
ml of ether were collected by filtration and washed with
ether to obtain 5-(ethoxymethyl)isoindoline·hydrochloride.

15 Also, the following compounds were obtained in the
same manner as mentioned above

5-(Methoxymethyl)isoindoline·hydrochloride

5-(Isopropylloxymethyl)isoindoline·hydrochloride

Reference Example 15-10

20 0.85 ml of triethylamine and 0.35 ml of methyl
chloroformate were added to 8 ml of a methylene chloride
solution containing 0.72 g of 5-amino-2-tert-butoxycarbon-
ylisoindoline, and the mixture was stirred at room tempera-
ture for 5 hours. Water was added to the reaction mixture
25 and the mixture was extracted with ethyl acetate. After
the extract was dried over anhydrous sodium sulfate, the
solvent was removed under reduced pressure. The residue
was purified by silica gel chromatography (solvent chloro-
form-ethyl acetate = 2:1) to obtain an oil. This oil was
30 dissolved in 5 ml of dioxane, then, 8 ml of 4N hydrochloric
acid-dioxane was added thereto, and the mixture was stirred
at room temperature. The precipitates precipitated by
addition of 20 ml of ether were collected by filtration and
washed with ether to obtain 5-(methoxycarbonylamino)iso-
35 indoline hydrochloride

Also, the following compounds were obtained in the

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same manner as mentioned above.

5-(Acetylamino)isoindoline hydrochloride

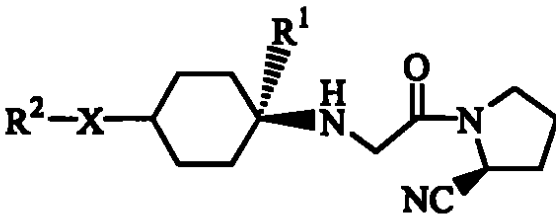
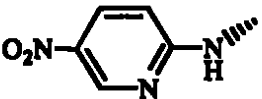
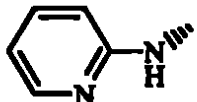
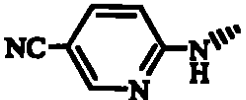
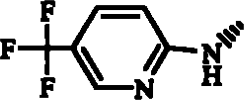
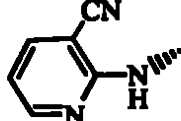
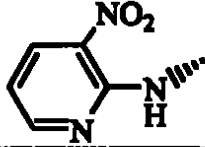
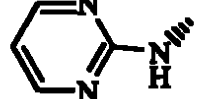
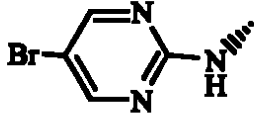
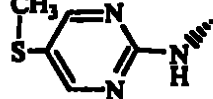
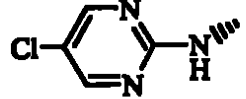
Reference Example 15-11

2-tert-Butoxycarbonyl-5-aminoisoindoline (the compound obtained in the same manner as in WO 00/23428) and dimethylglycine were used as starting materials and reacted in the same manner as in Reference Example 11-1 to obtain 5-(dimethylaminomethylcarbonylamino)isoindoline.

In the following Table 1a to Table 1d and Table 2 to Table 8, chemical structures and physical properties of the compounds of the above Examples and Reference Examples are shown. (In Tables, "Me" represents a methyl group Also, in Tables, MS'APCI (m/z) represents mass spectrometric value (atmospheric pressure chemical ionization mass spectrum).)

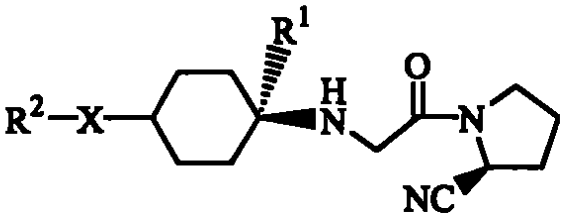
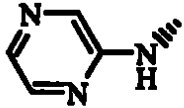
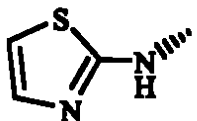
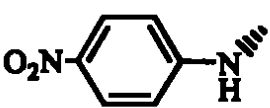
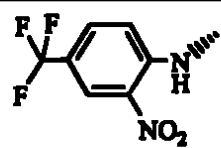
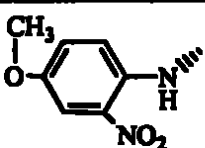
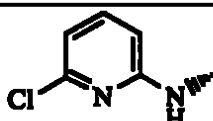
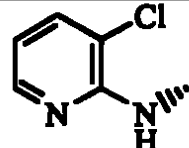
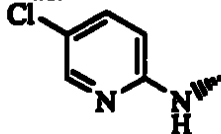
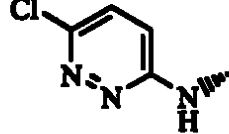
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Table 1a

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1a-1		H	2HCl	Colorless powder MS APCI (m/z): 373 [M+H] ⁺
1a-2		H	2HCl	Brownish powder MS APCI (m/z): 328 [M+H] ⁺
1a-3		H	HCl	Colorless powder MS APCI (m/z): 353 [M+H] ⁺
1a-4		H	2HCl	Colorless powder MS APCI (m/z): 396 [M+H] ⁺
1a-5		H	2HCl	Colorless powder MS APCI (m/z): 353 [M+H] ⁺
1a-6		H	2HCl	Yellowish powder MS APCI (m/z): 373 [M+H] ⁺
1a-7		H	2HCl	Colorless powder MS APCI (m/z): 329 [M+H] ⁺
1a-8		H	2HCl	Colorless powder MS APCI (m/z): 407, 409 [M+H] ⁺
1a-9		H	2HCl	Pale yellowish powder MS APCI (m/z): 375 [M+H] ⁺
1a-10		H	2HCl	Colorless powder MS APCI (m/z): 363 [M+H] ⁺

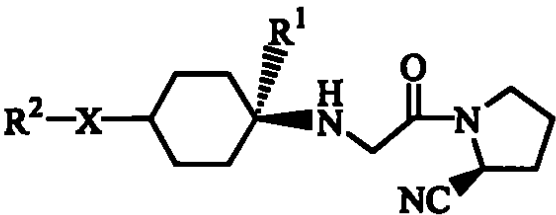
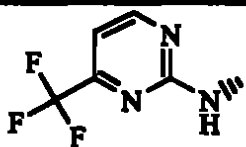
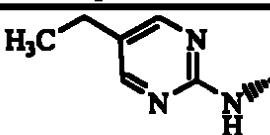
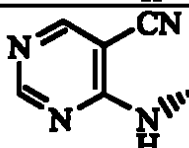
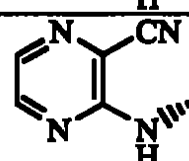
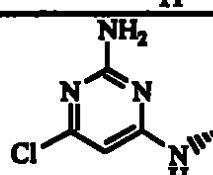
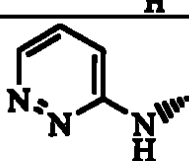
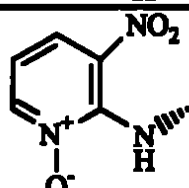
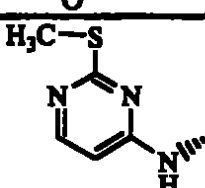
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Table 1a (continued)

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1a-11		H	2HCl	Colorless powder MS APCI (m/z): 329 [M+H] ⁺
1a-12		H	HCl	Pale brownish powder MS APCI (m/z): 334 [M+H] ⁺
1a-13		H	HCl	Colorless powder MS APCI (m/z): 372 [M+H]
1a-14		H	HCl	Colorless powder MS APCI (m/z): 440 [M+H]
1a-15		H	HCl	Colorless powder MS APCI (m/z): 402 [M+H]
1a-16		H	2HCl	Purified powder MS APCI (m/z): 364, 362
1a-17		H	2HCl	Purified powder MS APCI (m/z): 364, 362
1a-18		H	2HCl	Purified powder MS APCI (m/z): 364, 362
1a-19		H	2HCl	Purified powder MS APCI (m/z): 365, 363

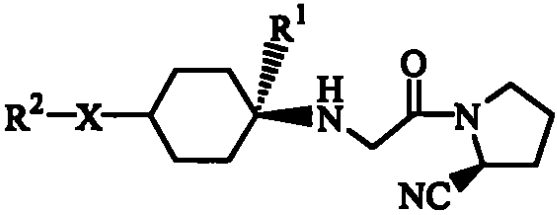
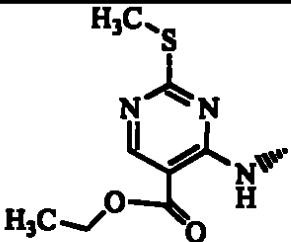
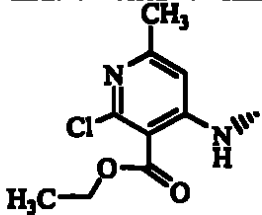
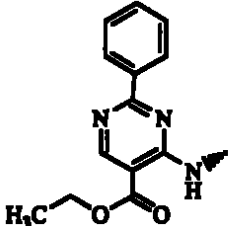
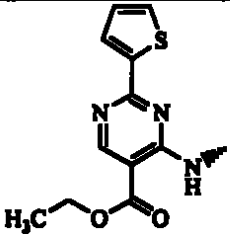
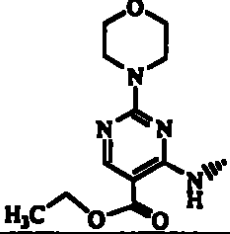
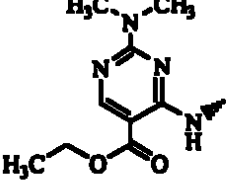
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Table 1a (continued)

				
Example No	R²-X-	R¹	Salt	Physical properties, etc.
1a-20		H	2HCl	Purified powder MS APCI (m/z) : 397
1a-21		H	2HCl	Purified powder MS APCI (m/z) : 357
1a-22		H	2HCl	Purified powder MS APCI (m/z) : 354
1a-23		H	2HCl	Purified powder MS APCI (m/z) : 354
1a-24		H	2HCl	Colorless powder MS APCI (m/z) : 378 [M+H] +
1a-25		H	2HCl	Purified powder MS APCI (m/z) : 329
1a-26		H	HCl	Brownish powder MS APCI (m/z) 389 [M+H]
1a-27		H	2HCl	Colorless powder MS APCI (m/z) : 375 [M+H] +

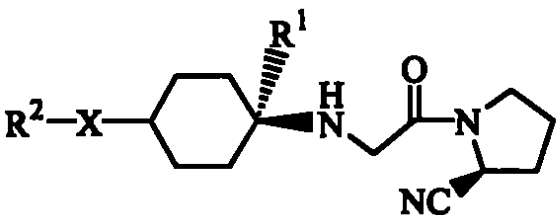
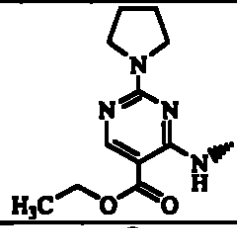
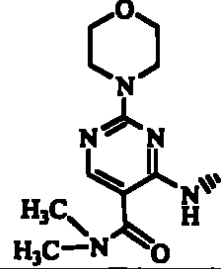
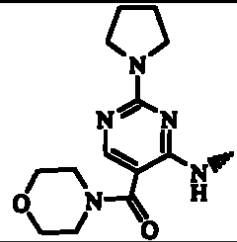
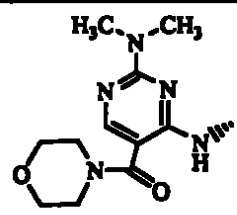
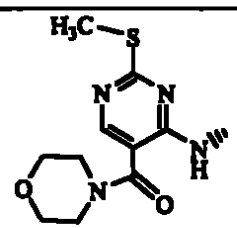
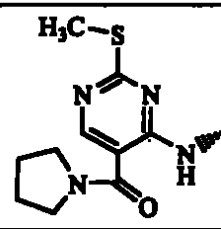
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Table 1a (continued)

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc
1a-28		H	2HCl	Colorless powder MS APCI (m/z) : 447 [M+H] ⁺
1a-29		H	2HCl	Colorless powder MS APCI (m/z) : 448 [M+H] ⁺
1a-30		H	2HCl	Colorless powder MS APCI (m/z) : 477 [M+H] ⁺
1a-31		H	2HCl	Colorless powder MS APCI (m/z) : 483 [M+H] ⁺
1a-32		H	2HCl	Colorless powder MS APCI (m/z) : 486 [M+H] ⁺
1a-33		H	2HCl	Colorless powder MS APCI (m/z) : 444 [M+H] ⁺

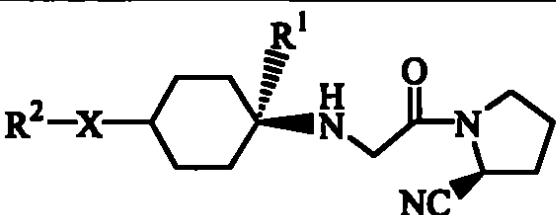
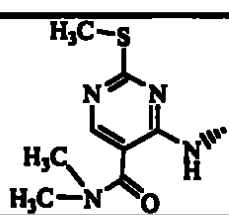
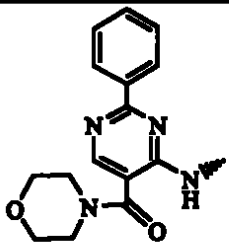
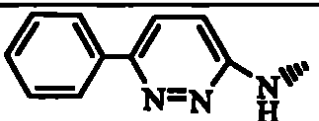
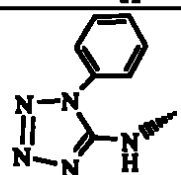
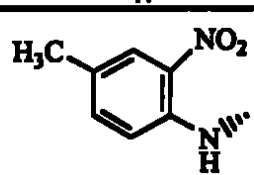
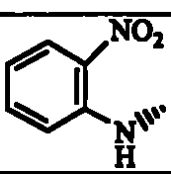
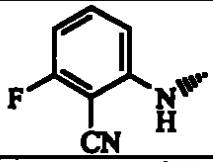
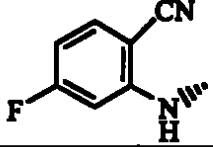
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Table 1a (continued)

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc
1a-34		H	2HCl	Colorless powder MS APCI (m/z) : 470 [M+H] ⁺
1a-35		H	2HCl	Colorless powder MS APCI (m/z) : 485 [M+H] ⁺
1a-36		H	2HCl	Colorless powder MS APCI (m/z) : 511 [M+H] ⁺
1a-37		H	2HCl	Colorless powder MS APCI (m/z) : 485 [M+H] ⁺
1a-38		H	2HCl	Colorless powder MS APCI (m/z) : 488 [M+H] ⁺
1a-39		H	2HCl	Colorless powder MS APCI (m/z) : 472 [M+H] ⁺

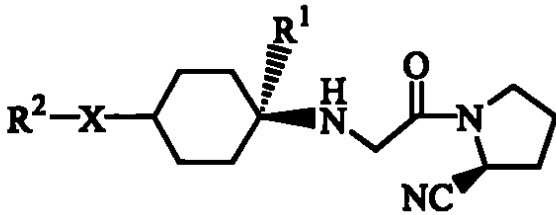
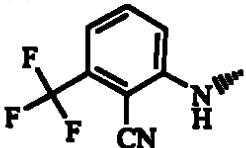
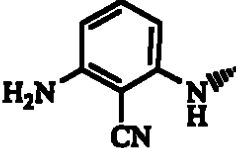
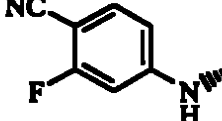
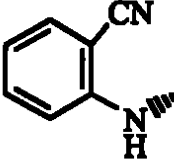
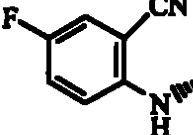
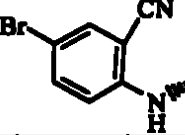
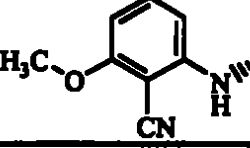
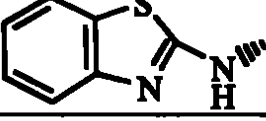
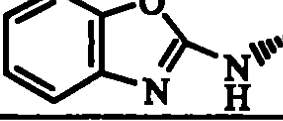
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Table 1a (Continued)

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1a-40		H	2HCl	Colorless powder MS APCI (m/z) : 446 [M+H] ⁺
1a-41		H	2HCl	Colorless powder MS APCI (m/z) : 518 [M+H] ⁺
1a-42		H	2HCl	Purified powder MS APCI (m/z) : 405
1a-43		H	2HCl	Colorless powder MS APCI (m/z) : 395 [M+H] ⁺
1a-44		H	2HCl	Purified powder MS APCI (m/z) : 386
1a-45		H	2HCl	Purified powder MS APCI (m/z) : 372
1a-46		H	2HCl	Purified powder MS APCI (m/z) : 370
1a-47		H	2HCl	Purified powder MS APCI (m/z) : 370

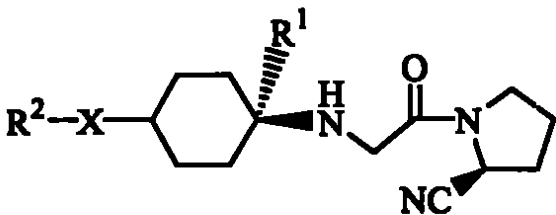
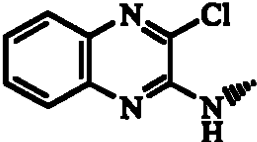
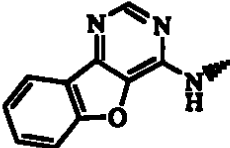
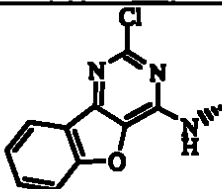
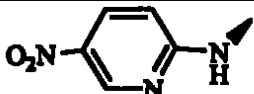
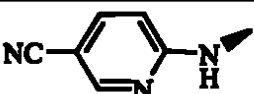
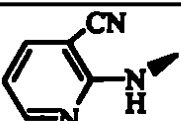
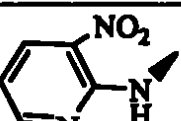
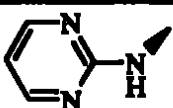
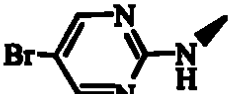
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Table 1a (Continued)

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1a-48		H	2HCl	Purified powder MS APCI (m/z) : 420
1a-49		H	3HCl	Purified powder MS APCI (m/z) : 367
1a-50		H	2HCl	Purified powder MS APCI (m/z) : 370
1a-51		H	2HCl	Colorless powder MS APCI (m/z) : 352 [M+H]
1a-52		H	2HCl	Colorless powder MS APCI (m/z) : 370 [M+H]
1a-53		H	2HCl	Colorless powder MS APCI (m/z) : 432, 430 [M+H]
1a-54		H	2HCl	Colorless powder MS APCI (m/z) : 382 [M+H]
1a-55		H	2HCl	Colorless powder MS APCI (m/z) : 384 [M+H] +
1a-56		H	2HCl	Colorless powder MS APCI (m/z) : 368 [M+H] +

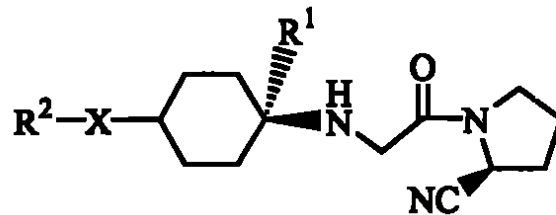
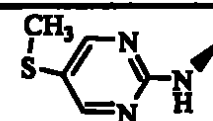
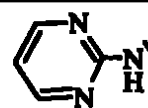
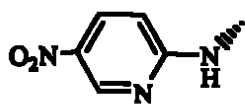
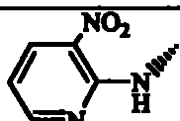
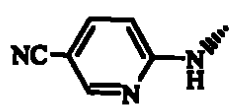
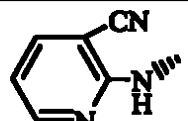
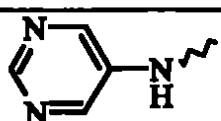
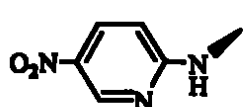
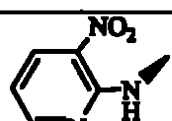
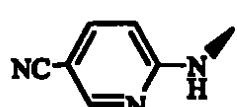
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Table 1a (continued)

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1a-57		H	2HCl	Colorless powder MS APCI (m/z) : 413 [M+H] ⁺
1a-58		H	2HCl	Colorless powder MS APCI (m/z) : 419 [M+H] ⁺
1a-59		H	2HCl	Colorless powder MS APCI (m/z) : 453 [M+H] ⁺
1a-60		H	2HCl	Colorless powder MS APCI (m/z) : 373 [M+H] ⁺
1a-61		H	2HCl	Colorless powder MS APCI (m/z) : 353 [M+H] ⁺
1a-62		H	2HCl	Pale yellowish powder MS APCI (m/z) : 353 [M+H] ⁺
1a-63		H	2HCl	Pale brownish powder MS APCI (m/z) : 373 [M+H] ⁺
1a-64		H	2HCl	Colorless powder MS APCI (m/z) : 329 [M+H] ⁺
1a-65		H	2HCl	Pale yellowish powder MS APCI (m/z) : 409 [M+H] ⁺

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Table 1a (Continued)

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc
1a-66		H	2HCl	Pale yellowish powder MS APCI (m/z): 375 [M+H] ⁺
1a-67		Me	2HCl	Colorless powder MS APCI (m/z): 343 [M+H] ⁺
1a-68		Me	2HCl	Pale yellowish powder MS APCI (m/z): 387 [M+H] ⁺
1a-69		Me	2HCl	Yellowish powder MS APCI (m/z): 387 [M+H] ⁺
1a-70		Me	2HCl	Colorless powder MS APCI (m/z): 367 [M+H] ⁺
1a-71		Me	2HCl	Colorless powder MS APCI (m/z): 367 [M+H] ⁺
1a-72		Me	2HCl	Brownish powder MS APCI (m/z): 343 [M+H] ⁺
1a-73		Me	2HCl	Pale yellowish powder MS APCI (m/z): 387 [M+H] ⁺
1a-74		Me	2HCl	Yellowish powder MS APCI (m/z): 387 [M+H] ⁺
1a-75		Me	2HCl	Colorless powder MS APCI (m/z): 367 [M+H] ⁺

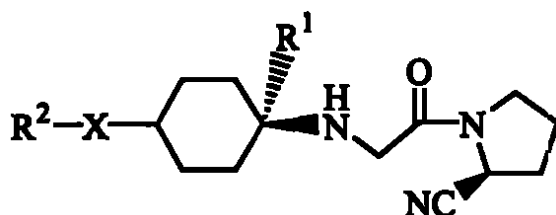
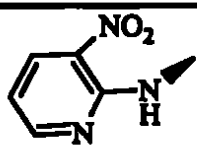
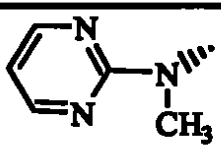
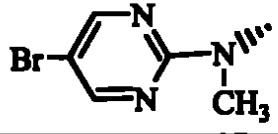
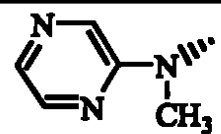
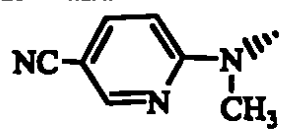
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Table 1a (Continued)

Example No.	R ² -X-	R ¹	Salt	Physical properties, etc
1a-76		Me	2HCl	Colorless powder MS APCI (m/z) : 367 [M+H] ⁺
1a-77		CH ₂ OH	2HCl	Pale yellowish powder MS APCI (m/z) : 405 [M+H] ⁺
1a-78		CH ₂ OH	2HCl	Pale yellowish powder MS APCI (m/z) : 403 [M+H] ⁺
1a-79		CH ₂ OH	2HCl	Colorless powder MS APCI (m/z) : 383 [M+H] ⁺
1a-80		CH ₂ OH	2HCl	Pale yellowish powder MS APCI (m/z) : 403 [M+H] ⁺
1a-81		CH ₂ OH	2HCl	Colorless powder MS APCI (m/z) : 383 [M+H] ⁺
1a-82		CH ₂ OH	2HCl	Colorless powder MS APCI (m/z) : 383 [M+H] ⁺
1a-83		CH ₂ OH	2HCl	Pale yellowish powder MS APCI (m/z) : 383 [M+H] ⁺
1a-84		CH ₂ OH	2HCl	Pale yellowish powder MS APCI (m/z) : 403 [M+H] ⁺

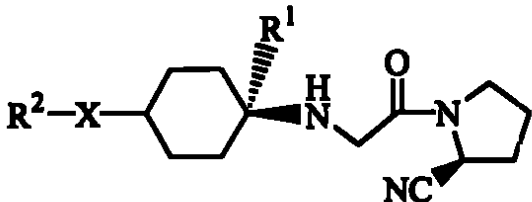
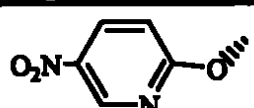
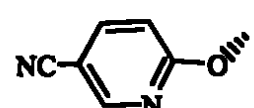
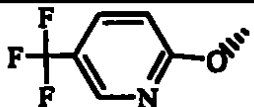
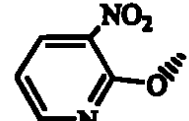
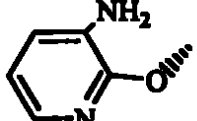
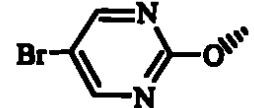
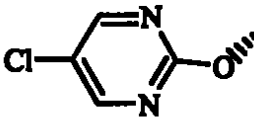
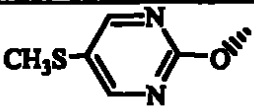
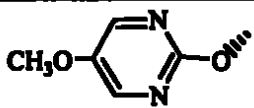
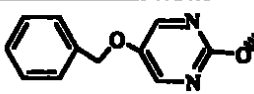
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Table 1a (Continued)

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1a-85		CH ₂ OH	2HCl	Pale yellowish powder MS APCI (m/z) : 403 [M+H] ⁺
1a-86		H	2HCl	Purified powder MS APCI (m/z) : 343 [M+H] ⁺
1a-87		H	2HCl	Purified powder MS APCI (m/z) : 421 [M+H] ⁺
1a-88		H	2HCl	Purified powder MS APCI (m/z) : 343 [M+H] ⁺
1a-89		H	2HCl	Purified powder MS APCI (m/z) : 367 [M+H] ⁺

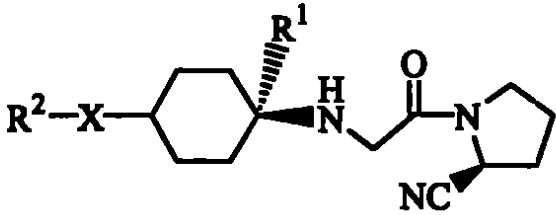
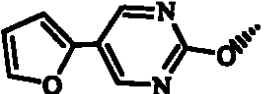
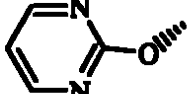
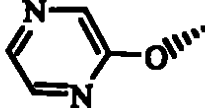
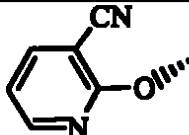
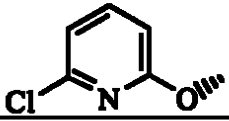
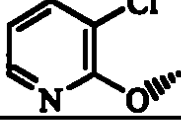
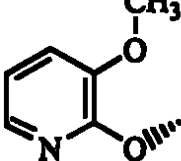
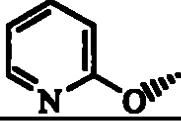
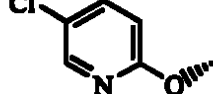
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Table 1b

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1b-1		H	HCl	Colorless powder MS APCI (m/z) : 374 [M+H] ⁺
1b-2		H	HCl	Colorless crystal Gradually decomposed around at melting point: 233°C MS APCI (m/z) : 354 [M+H] ⁺
1b-3		H	HCl	Colorless powder MS APCI (m/z) : 397 [M+H] ⁺
1b-4		H	HCl	Pale yellowish powder MS APCI (m/z) : 374 [M+H] ⁺
1b-5		H	2HCl	Colorless powder MS APCI (m/z) : 344 [M+H] ⁺
1b-6		H	HCl	Colorless powder MS APCI (m/z) : 410 [M+H] ⁺
1b-7		H	HCl	Colorless powder MS APCI (m/z) : 364 [M+H] ⁺
			Free form	Colorless crystal Melting point: 129-130°C (decomposed)
1b-8		H	HCl	Pale yellowish powder MS APCI (m/z) : 376 [M+H] ⁺
1b-9		H	HCl	Colorless MS APCI (m/z) : 360 [M+H] ⁺
1b-10		H	HCl	Colorless powder MS APCI (m/z) : 436 [M+H] ⁺

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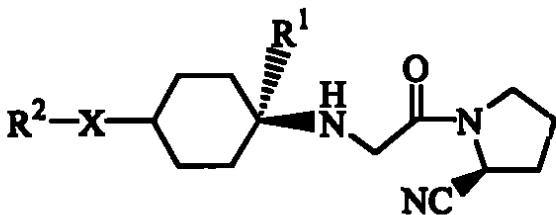
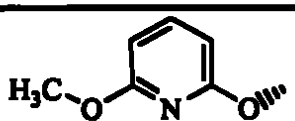
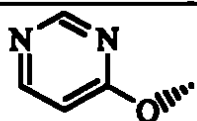
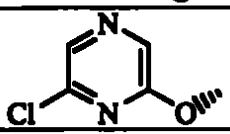
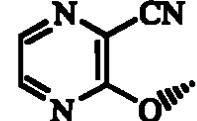
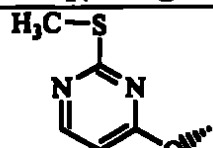
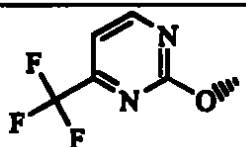
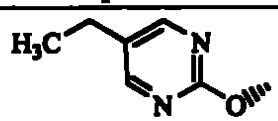
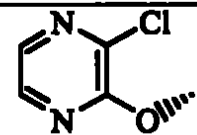
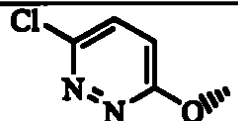
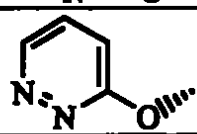
Table 1b (Continued)

				
Example No	R ² -X-	R ¹	Salt	Physical properties, etc.
1b-11		H	HCl	Colorless powder MS APCI (m/z) : 396 [M+H] ⁺
1b-12		H	HCl	Colorless powder MS APCI (m/z) : 330 [M+H] ⁺
1b-13		H	HCl	Pale yellowish powder MS APCI (m/z) : 373 [M+H] ⁺
1b-14		H	HCl	Purified powder MS APCI (m/z) : 330 [M+H] ⁺
1b-15		H	HCl	Purified powder MS APCI (m/z) : 354 [M+H] ⁺
1b-16		H	2HCl	Purified powder MS APCI (m/z) : 365, 363
1b-17		H	2HCl	Purified powder MS APCI (m/z) : 365, 363
1b-18		H	2HCl	Purified powder MS APCI (m/z) : 359
1b-19		H	2HCl	Purified powder MS APCI (m/z) : 329
1b-20		H	2HCl	Purified powder MS APCI (m/z) : 365, 363

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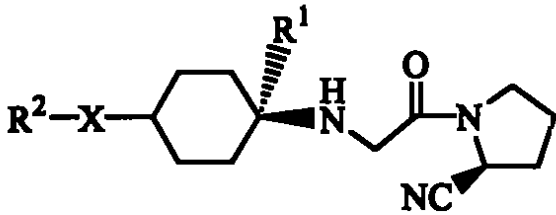
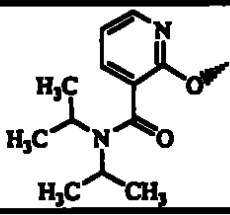
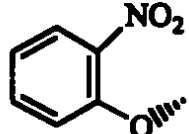
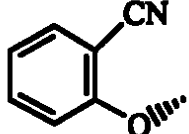
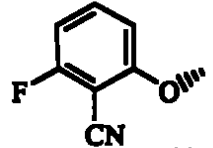
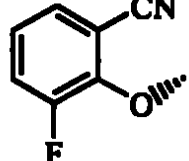
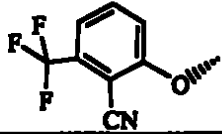
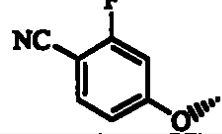
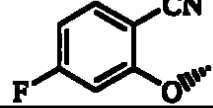
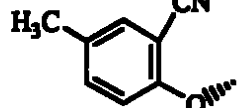
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Table 1b (Continued)

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1b-21		H	2HCl	Purified powder MS APCI (m/z) : 359
1b-22		H	HCl	Colorless powder MS APCI (m/z) : 330 [M+H] ⁺
1b-23		H	HCl	Purified powder MS APCI (m/z) : 366, 364
1b-24		H	HCl	Purified powder MS APCI (m/z) : 355
1b-25		H	HCl	Colorless powder MS APCI (m/z) : 376 [M+H] ⁺
1b-26		H	HCl	Purified powder MS APCI (m/z) : 398
1b-27		H	HCl	Purified powder MS APCI (m/z) : 358
1b-28		H	HCl	Purified powder MS APCI (m/z) : 366, 364
1b-29		H	HCl	Purified powder MS APCI (m/z) : 366, 364
1b-30		H	HCl	Purified powder MS APCI (m/z) : 330

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Table 1b (Continued)

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1b-31		H	2HCl	Purified powder MS APCI (m/z) : 456
1b-32		H	HCl	Purified powder MS APCI (m/z) : 373
1b-33		H	HCl	Colorless powder MS APCI (m/z) : 353 [M+H]
1b-34		H	HCl	Colorless powder MS APCI (m/z) : 371 [M+H] ⁺
1b-35		H	HCl	Colorless powder MS APCI (m/z) : 371 [M+H] ⁺
1b-36		H	HCl	Colorless powder MS APCI (m/z) : 421 [M+H] ⁺
1b-37		H	HCl	Colorless powder MS APCI (m/z) : 371 [M+H] ⁺
1b-38		H	HCl	Colorless powder MS APCI (m/z) : 371 [M+H] ⁺
1b-39		H	HCl	Colorless powder MS APCI (m/z) : 367 [M+H]

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Table 1b (Continued)

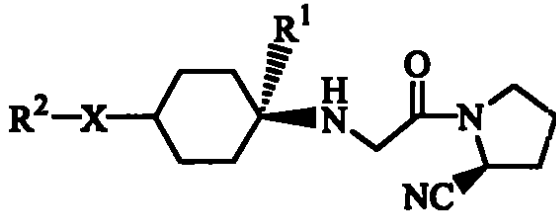
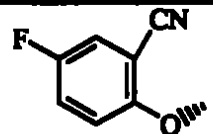
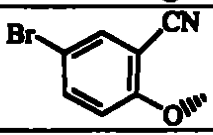
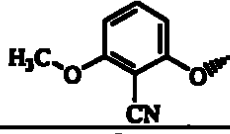
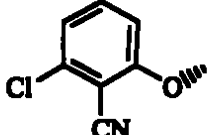
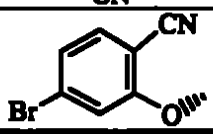
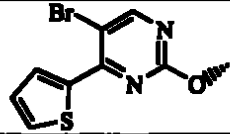
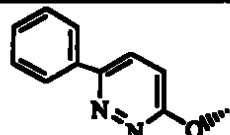
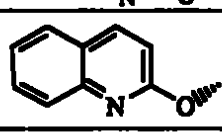
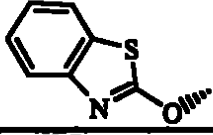
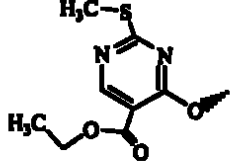
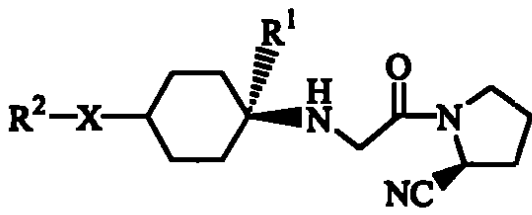
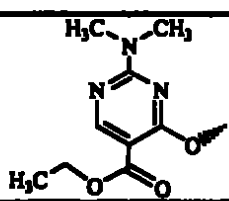
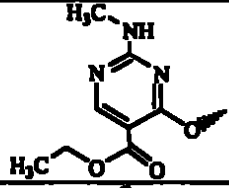
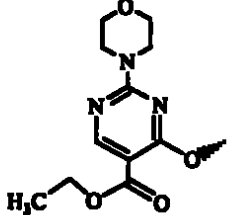
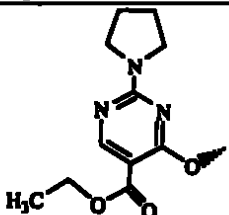
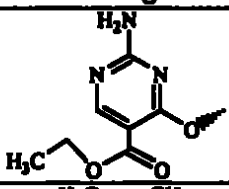
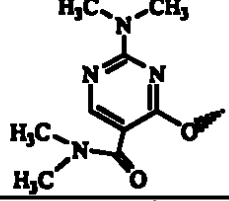
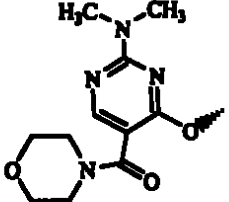
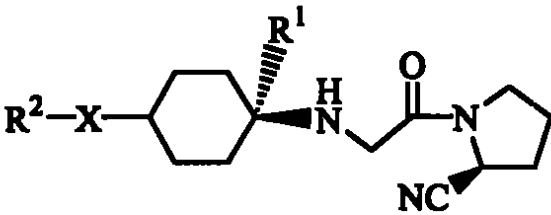
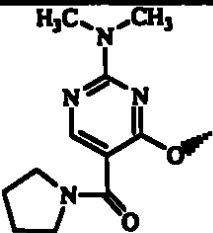
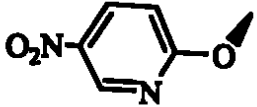
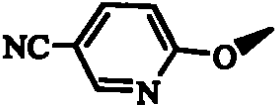
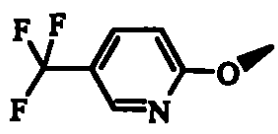
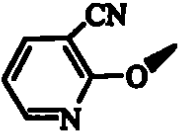
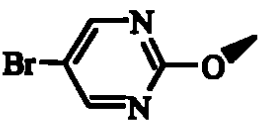
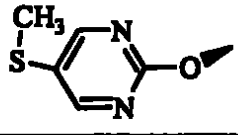
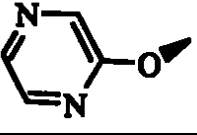
				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1b-40		H	HCl	Pale brownish powder MS APCI (m/z) : 371 [M+H]
1b-41		H	HCl	Colorless powder MS APCI (m/z) : 433, 431 [M+H]
1b-42		H	HCl	Colorless powder MS APCI (m/z) : 383 [M+H]
1b-43		H	HCl	Colorless powder MS APCI (m/z) : 387 [M+H]
1b-44		H	HCl	Colorless powder MS APCI (m/z) : 433, 431 [M+H]
1b-45		H	HCl	Purified powder MS APCI (m/z) : 492, 490
1b-46		H	HCl	Purified powder MS APCI (m/z) : 406
1b-47		H	HCl	Purified powder MS APCI (m/z) : 379
1b-48		H	HCl	Colorless powder MS APCI (m/z) : 385 [M+H] +
1b-49		H	HCl	Purified powder MS APCI (m/z) : 448

Table 1b (Continued)

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1b-50		H	2HCl	Purified powder MS APCI (m/z) : 445
1b-51		H	2HCl	Purified powder MS APCI (m/z) : 431
1b-52		H	2HCl	Purified powder MS APCI (m/z) : 487
1b-53		H	2HCl	Purified powder MS APCI (m/z) : 471
1b-54		H	2HCl	Purified powder MS APCI (m/z) : 417
1b-55		H	2HCl	Purified powder MS APCI (m/z) : 444
1b-56		H	2HCl	Purified powder MS APCI (m/z) : 486

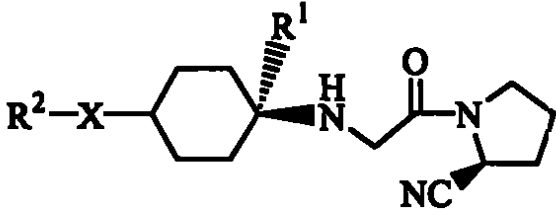
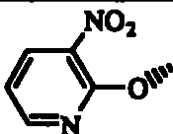
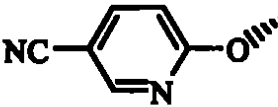
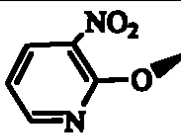
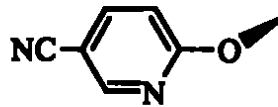
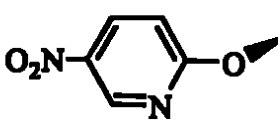
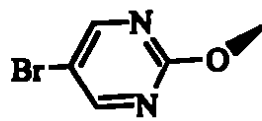
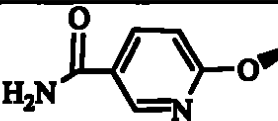
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Table 1b (Continued)

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1b-57		H	2HCl	Purified powder MS APCI (m/z) : 470
1b-58		H	HCl	Colorless powder MS APCI (m/z) : 374 [M+H] ⁺
1b-59		H	HCl	Colorless powder MS APCI (m/z) : 354 [M+H] ⁺
1b-60		H	HCl	Colorless powder MS APCI (m/z) : 397 [M+H] ⁺
1b-61		H	HCl	Colorless powder MS APCI (m/z) : 354 [M+H] ⁺
1b-62		H	HCl	Colorless powder MS APCI (m/z) : 408 [M+H] ⁺
1b-63		H	HCl	Yellowish powder MS APCI (m/z) : 376 [M+H] ⁺
1b-64		H	HCl	Colorless powder MS APCI (m/z) : 330 [M+H] ⁺

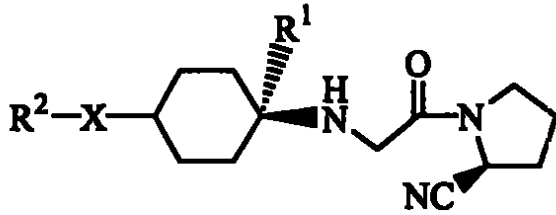
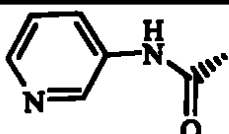
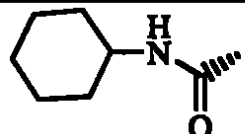
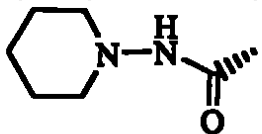
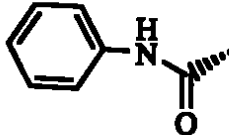
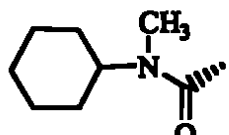
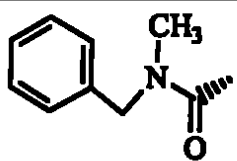
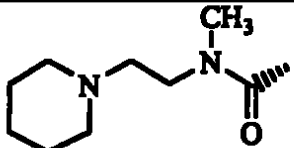
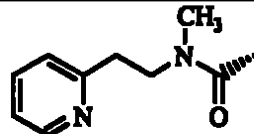
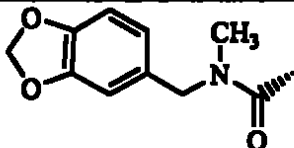
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Table 1b (Continued)

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1b-65		Me	HCl	Purified powder MS APCI (m/z) : 388 [M+H] ⁺
1b-66		Me	HCl	Purified powder MS APCI (m/z) : 368 [M+H] ⁺
1b-67		Me	HCl	Purified powder MS APCI (m/z) : 388 [M+H] ⁺
1b-68		Me	HCl	Purified powder MS APCI (m/z) : 368 [M+H] ⁺
1b-69		Me	HCl	Purified powder MS APCI (m/z) : 388 [M+H] ⁺
1b-70		Me	HCl	Purified powder MS APCI (m/z) : 424 [M+H] ⁺
1b-71		Me	HCl	Purified powder MS APCI (m/z) : 386 [M+H] ⁺

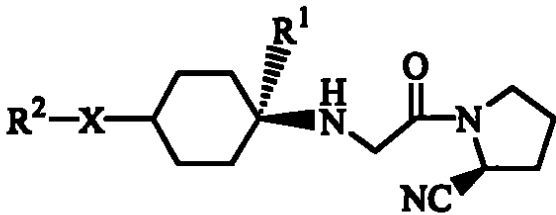
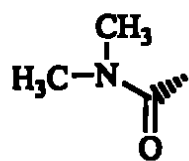
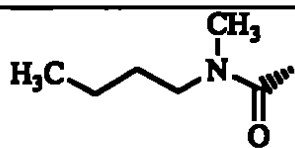
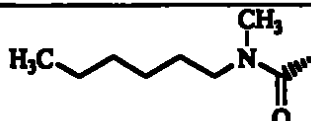
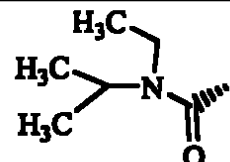
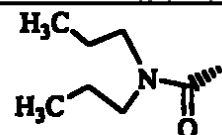
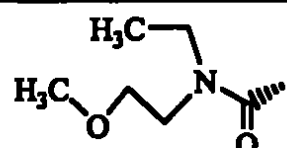
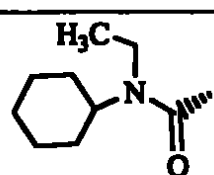
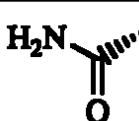
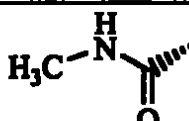
117 ~~118~~

Table 1c

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1c-1		H	2HCl	Colorless powder MS APCI (m/z) : 356 [M+H] ⁺
1c-2		H	HCl	Colorless powder MS APCI (m/z) : 361 [M+H]
1c-3		H	HCl	Purified powder MS APCI (m/z) : 362
1c-4		H	HCl	Colorless powder MS APCI (m/z) : 355 [M+H] ⁺
1c-5		H	HCl	Colorless powder MS APCI (m/z) : 375 [M+H]
1c-6		H	HCl	Colorless powder MS APCI (m/z) : 383 [M+H] ⁺
1c-7		H	2HCl	Purified powder MS APCI (m/z) : 404
1c-8		H	2HCl	Colorless powder MS APCI (m/z) : 398 [M+H]
1c-9		H	HCl	Purified powder MS APCI (m/z) : 427

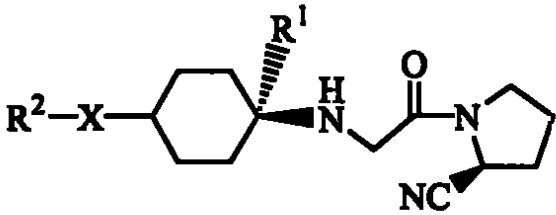
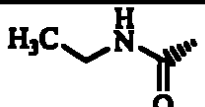
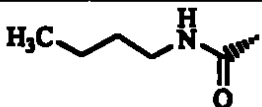
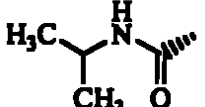
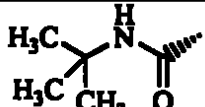
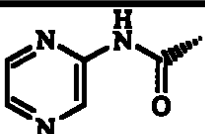
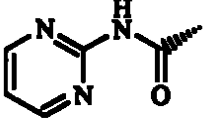
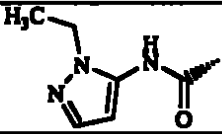
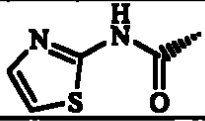
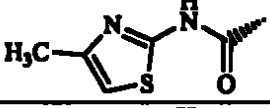
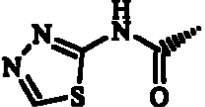
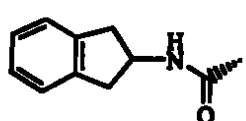
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Table 1c (Continued)

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1c-10		H	HCl	Colorless crystal Melting point: 211°C (decomposed) MS APCI (m/z): 307 [M+H]
1c-11		H	HCl	Purified powder MS APCI (m/z): 349
1c-12		H	HCl	Colorless powder MS APCI (m/z): 377 [M+H] ⁺
1c-13		H	HCl	Purified powder MS APCI (m/z): 349
1c-14		H	HCl	Colorless powder MS APCI (m/z): 363 [M+H] ⁺
1c-15		H	HCl	Purified powder MS APCI (m/z): 365
1c-16		H	HCl	Colorless powder MS APCI (m/z): 389 [M+H] ⁺
1c-17		H	HCl	Pale brownish purified resin state MS APCI (m/z): 279 [M+H] ⁺
1c-18		H	HCl	Purified powder MS APCI (m/z): 293 [M+H] ⁺

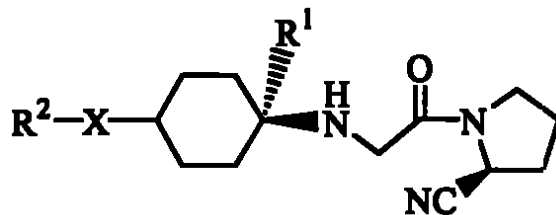
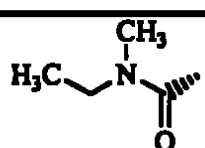
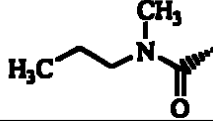
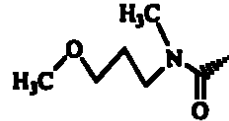
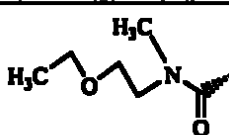
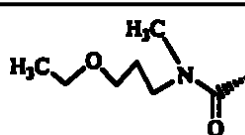
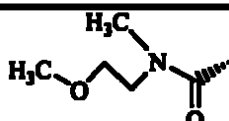
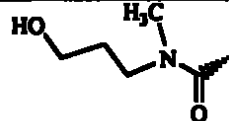
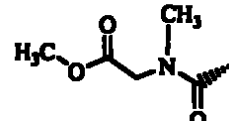
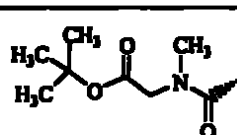
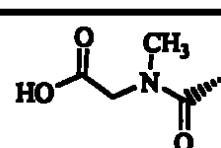
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Table 1c (Continued)

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1c-19		H	HCl	Purified powder MS APCI (m/z) : 307 [M+H] ⁺
1c-20		H	HCl	Purified powder MS APCI (m/z) : 335 [M+H] ⁺
1c-21		H	HCl	Purified powder MS APCI (m/z) : 321 [M+H] ⁺
1c-22		H	HCl	Purified powder MS APCI (m/z) : 335 [M+H] ⁺
1c-23		H	HCl	Colorless powder MS APCI (m/z) : 357 [M+H] ⁺
1c-24		H	HCl	Colorless powder MS APCI (m/z) : 357 [M+H] ⁺
1c-25		H	HCl	Colorless powder MS APCI (m/z) : 373 [M+H] ⁺
1c-26		H	HCl	Colorless powder MS APCI (m/z) : 362 [M+H] ⁺
1c-27		H	HCl	Colorless powder MS APCI (m/z) : 376 [M+H] ⁺
1c-28		H	HCl	Pale brownish powder MS APCI (m/z) : 363 [M+H] ⁺
1c-29		H	HCl	Colorless purified powder MS APCI (m/z) : 395 [M+H] ⁺

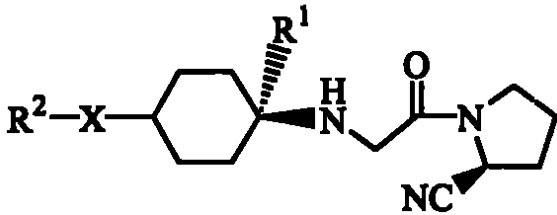
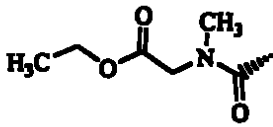
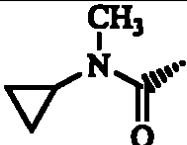
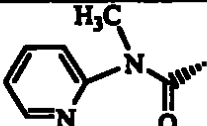
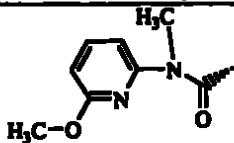
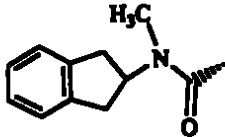
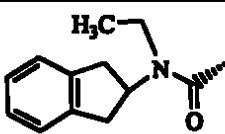
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Table 1c (Continued)

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1c-30		H	HCl	Purified powder MS APCI (m/z) : 321 [M+H] ⁺
1c-31		H	HCl	Purified powder MS APCI (m/z) : 335 [M+H] ⁺
1c-32		H	HCl	Brownish purified resin state MS APCI (m/z) : 365 [M+H] ⁺
1c-33		H	HCl	Pale brownish purified powder MS APCI (m/z) : 365 [M+H] ⁺
1c-34		H	HCl	Pale brownish purified resin state MS APCI (m/z) : 379 [M+H] ⁺
1c-35		H	HCl	Purified powder MS APCI (m/z) : 351
1c-36		H	HCl	Purified powder MS APCI (m/z) : 351
1c-37		H	HCl	Colorless purified powder MS APCI (m/z) : 365 [M+H] ⁺
1c-38		H	HCl	Colorless purified powder MS APCI (m/z) : 407 [M+H] ⁺
1c-39		H	HCl	Colorless purified powder MS APCI (m/z) : 351 [M+H] ⁺

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22
1

Table 1c (Continued)

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1c-40		H	HCl	Colorless purified powder MS APCI (m/z) : 379 [M+H] ⁺
1c-41		H	HCl	Colorless purified powder MS APCI (m/z) : 333 [M+H] ⁺
1c-42		H	2HCl	Purified powder MS APCI (m/z) : 370 [M+H] ⁺
1c-43		H	2HCl	Purified powder MS APCI (m/z) : 400 [M+H] ⁺
1c-44		H	HCl	Colorless purified powder MS APCI (m/z) : 409 [M+H] ⁺
1c-45		H	HCl	Colorless purified powder MS APCI (m/z) : 423 [M+H] ⁺

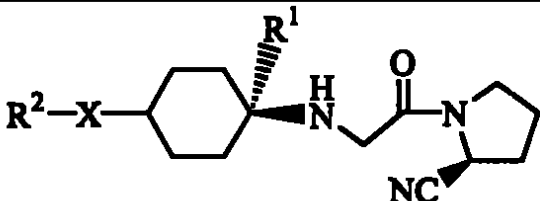
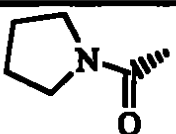
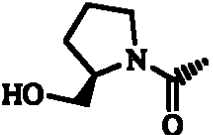
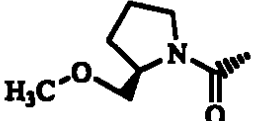
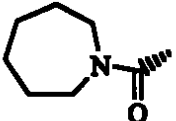
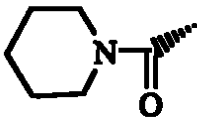
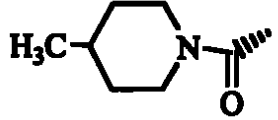
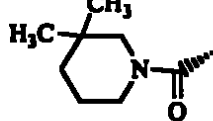
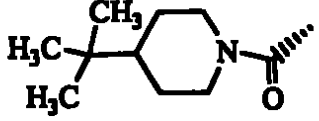
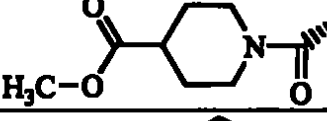
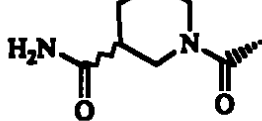
122 29
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Table 1c (Continued)

Example No.	R²-X-	R¹	Salt	Physical properties, etc.
1c-46		H	HCl	Purified powder MS APCI (m/z) : 307 [M+H] ⁺
1c-47		H	HCl	Colorless powder MS APCI (m/z) : 335 [M+H] ⁺
1c-48		H	HCl	Purified powder MS APCI (m/z) : 479 [M+H] ⁺
1c-49		H	HCl	Purified powder MS APCI (m/z) : 498 [M+H] ⁺
1c-50		H	HCl	Purified powder MS APCI (m/z) : 492 [M+H] ⁺
1c-51		H	2HCl	Purified powder MS APCI (m/z) : 492 [M+H] ⁺
1c-52		H	2HCl	Colorless powder MS APCI (m/z) : 452 [M+H] ⁺

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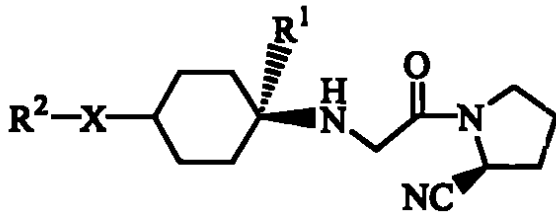
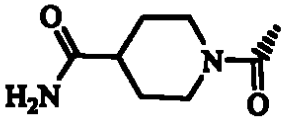
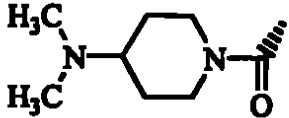
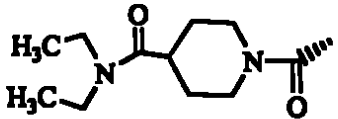
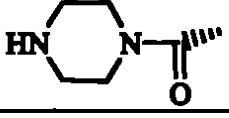
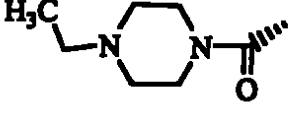
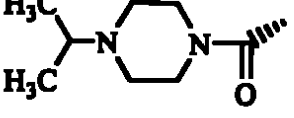
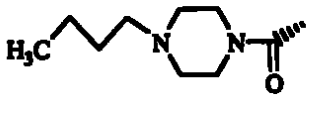
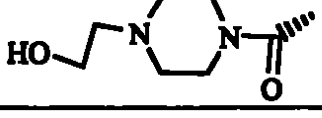
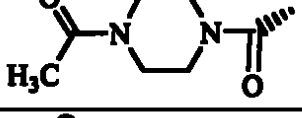
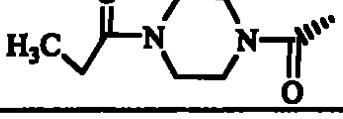
Table 1d

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1d-1		H	HCl	Colorless powder MS APCI (m/z): 333 [M+H] ⁺
1d-2		H	HCl	Purified powder MS APCI (m/z): 363
1d-3		H	HCl	Purified powder MS APCI (m/z): 377
1d-4		H	HCl	Colorless powder MS APCI (m/z): 361 [M+H] ⁺
1d-5		H	HCl	Colorless powder MS APCI (m/z): 347 [M+H] ⁺
1d-6		H	HCl	Colorless powder MS APCI (m/z): 361 [M+H] ⁺
1d-7		H	HCl	Colorless powder MS APCI (m/z): 375 [M+H] ⁺
1d-8		H	HCl	Purified powder MS APCI (m/z): 403 [M+H] ⁺
1d-9		H	HCl	Purified powder MS APCI (m/z): 405 [M+H] ⁺
1d-10		H	Free form	Purified powder MS APCI (m/z): 390

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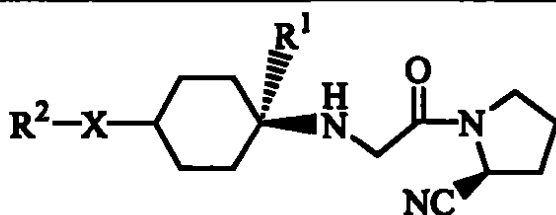
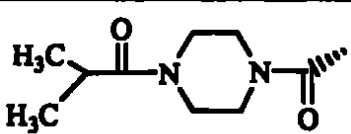
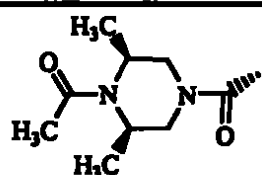
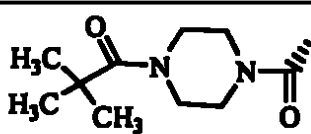
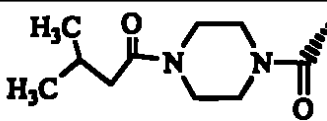
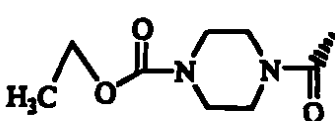
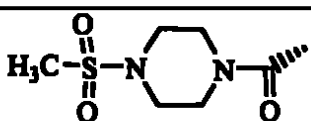
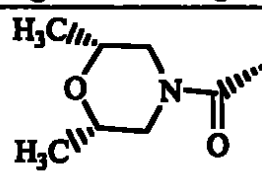
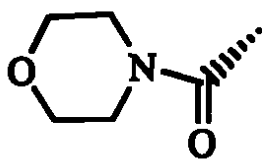
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Table 1d (Continued)

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1d-11		H	HCl	Colorless powder MS APCI (m/z) : 390 [M+H] ⁺
1d-12		H	2HCl	Colorless powder MS APCI (m/z) : 390 [M+H] ⁺
1d-13		H	HCl	Purified powder MS APCI (m/z) : 446 [M+H] ⁺
1d-14		H	2HCl	Colorless powder MS APCI (m/z) : 348 [M+H] ⁺
1d-15		H	2HCl	Purified powder MS APCI (m/z) : 376
1d-16		H	2HCl	Colorless powder MS APCI (m/z) : 390 [M+H] ⁺
1d-17		H	2HCl	Colorless powder MS APCI (m/z) : 404 [M+H] ⁺
1d-18		H	2HCl	Colorless powder MS APCI (m/z) : 392 [M+H] ⁺
1d-19		H	HCl	Colorless powder MS APCI (m/z) : 390 [M+H] ⁺
1d-20		H	HCl	Purified powder MS APCI (m/z) : 404

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77

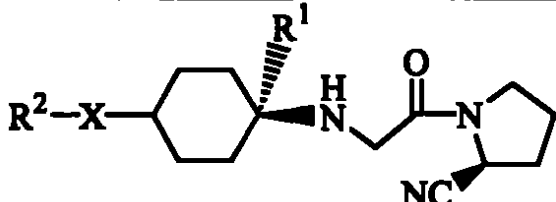
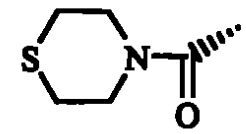
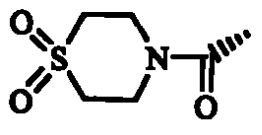
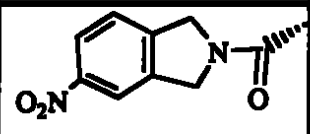
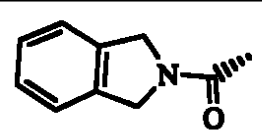
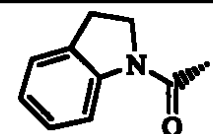
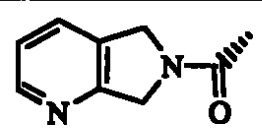
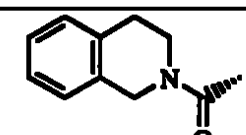
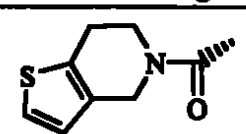
Table 1d (Continued)

				
Example No	R ² -X-	R ¹	Salt	Physical properties, etc.
1d-21		H	HCl	Purified powder MS APCI (m/z) : 418
1d-22		H	HCl	Colorless powder
1d-23		H	HCl	Purified powder MS APCI (m/z) : 432
1d-24		H	HCl	Purified powder MS APCI (m/z) : 432
1d-25		H	HCl	Colorless crystal Gradually decomposed at around Melting point: 198°C MS APCI (m/z) : 420 [M+H] ⁺
1d-26		H	HCl	Purified powder MS APCI (m/z) : 426 [M+H] ⁺
1d-27		H	HCl	Colorless crystal Melting point: 207-211°C MS APCI (m/z) : 377 [M+H] ⁺
1d-28		H	HCl	Colorless crystal Melting point: 219°C (decomposed) MS APCI (m/z) : 349 [M+H] ⁺
			Methane sulfonic acid	Colorless crystal Melting point: 217-218°C (decomposed)

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Table 1d (Continued)

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc
1d-29		H	HCl	Colorless powder MS APCI (m/z): 365 [M+H] ⁺
1d-30		H	HCl	Colorless powder MS APCI (m/z): 397 [M+H] ⁺
1d-31		H	HCl	Pale brownish powder MS APCI (m/z): 426 [M+H] ⁺
1d-32		H	HCl	Colorless crystal Melting point: 198-200°C (decomposed) MS APCI (m/z): 381 [M+H] ⁺
1d-33		H	HCl	Pale yellowish powder MS APCI (m/z): 381 [M+H] ⁺
1d-34		H	2HCl	Colorless crystal Melting point: >300°C MS APCI (m/z): 382 [M+H] ⁺
1d-35		H	HCl	Purified powder MS APCI (m/z): 395
1d-36		H	HCl	Purified powder MS APCI (m/z): 401

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Table 1d (Continued)

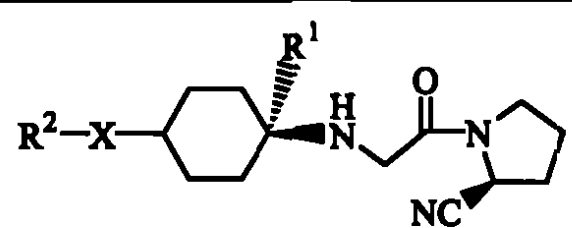
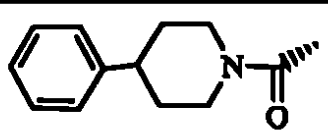
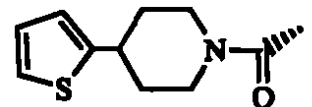
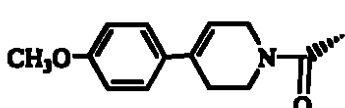
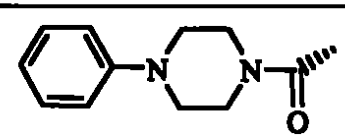
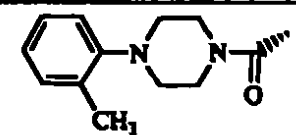
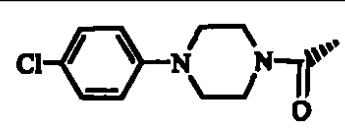
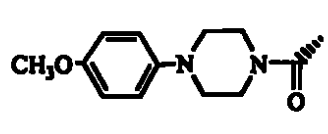
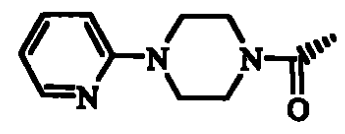
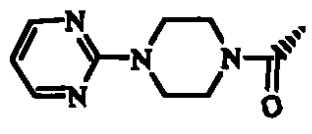
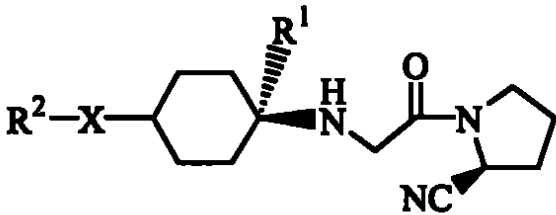
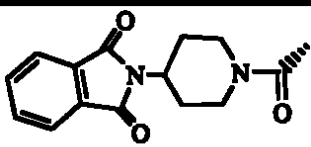
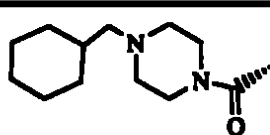
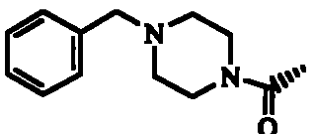
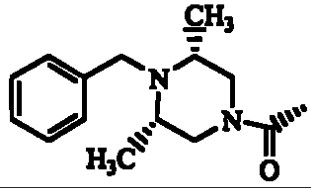
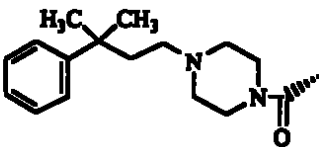
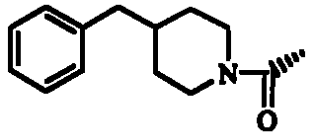
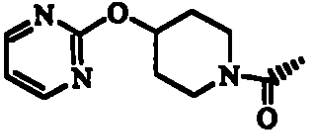
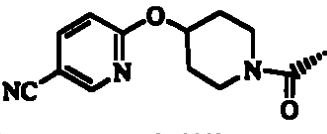
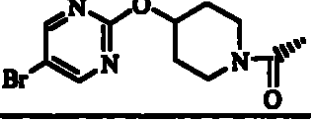
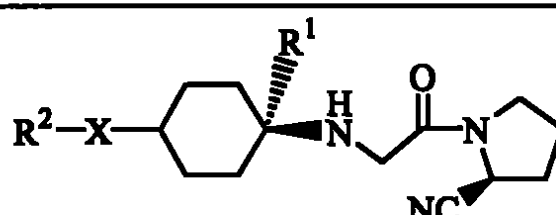
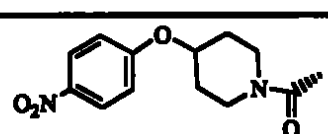
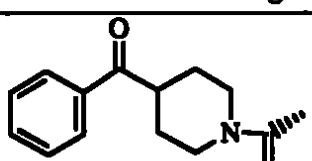
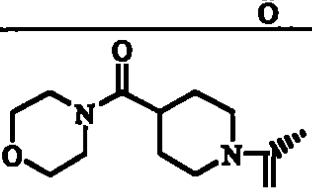
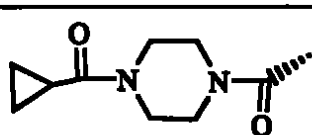
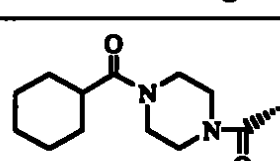
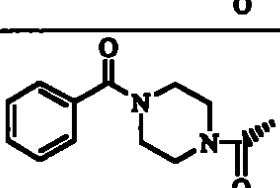
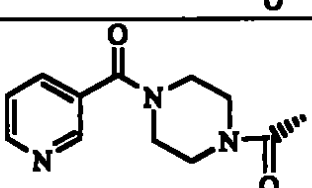
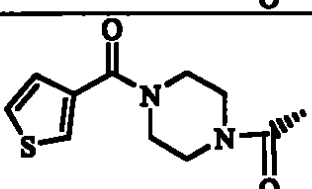
				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1d-37		H	HCl	Purified powder MS APCI (m/z) : 423
1d-38		H	HCl	Colorless powder MS APCI (m/z) : 429 [M+H] ⁺
1d-39		H	HCl	Colorless powder MS APCI (m/z) : 451 [M+H] ⁺
1d-40		H	HCl	Purified powder MS APCI (m/z) : 424
1d-41		H	2HCl	Colorless powder MS APCI (m/z) : 438 [M+H]
1d-42		H	2HCl	Colorless powder MS APCI (m/z) : 458 [M+H]
1d-43		H	2HCl	Purified powder MS APCI (m/z) : 454
1d-44		H	2HCl	Purified powder MS APCI (m/z) : 425
1d-45		H	2HCl	Colorless powder MS APCI (m/z) : 426 [M+H] ⁺

Table 1d (Continued)

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1d-46		H	HCl	Colorless powder MS APCI (m/z) : 492 [M+H] ⁺
1d-47		H	2HCl	Purified powder MS APCI (m/z) : 444 [M+H] ⁺
1d-48		H	2HCl	Purified powder MS APCI (m/z) : 438
1d-49		H	2HCl	Colorless powder MS APCI (m/z) : 466 [M+H]
1d-50		H	2HCl	Purified powder MS APCI (m/z) : 494
1d-51		H	HCl	Purified powder MS APCI (m/z) : 437
1d-52		H	Maleic acid	Purified powder Melting point: 180-183°C
1d-53		H	HCl	Purified powder MS APCI (m/z) : 465
1d-54		H	HCl	Purified powder MS APCI (m/z) : 521, 519

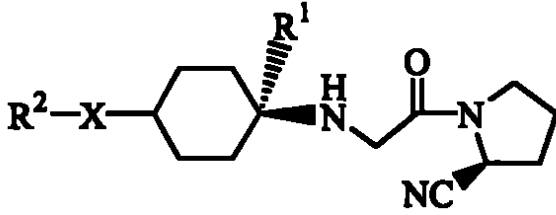
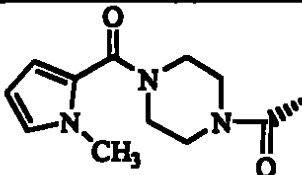
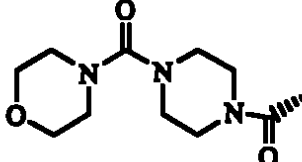
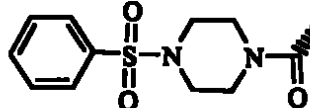
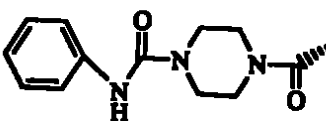
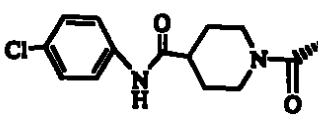
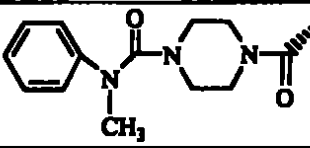
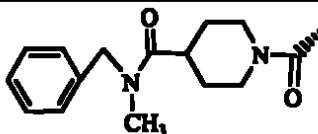
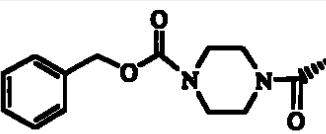
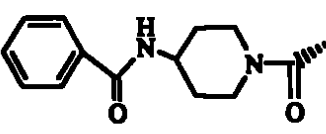
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Table 1d (Continued)

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1d-55		H	HCl	Purified powder MS APCI (m/z): 484
1d-56		H	HCl	Purified powder MS APCI (m/z): 451
1d-57		H	HCl	Purified powder MS APCI (m/z): 460 [M+H] ⁺
1d-58		H	HCl	Purified powder MS APCI (m/z): 416
1d-59		H	HCl	Purified powder MS APCI (m/z): 458
1d-60		H	HCl	Colorless powder MS APCI (m/z): 452 [M+H] ⁺
1d-61		H	2HCl	Colorless powder MS APCI (m/z): 453 [M+H] ⁺
1d-62		H	HCl	Colorless powder MS APCI (m/z): 458 [M+H] ⁺

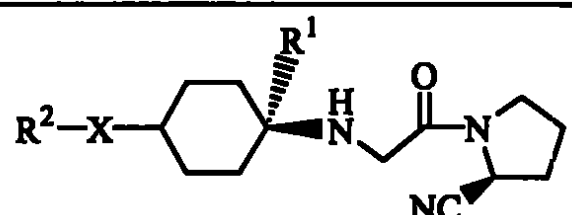
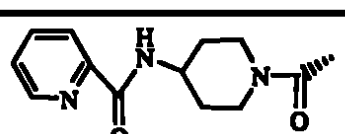
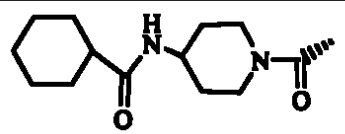
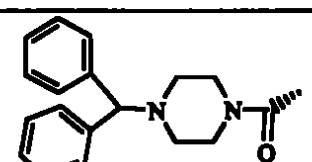
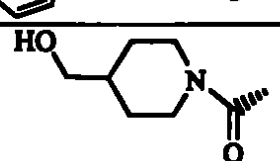
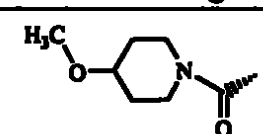
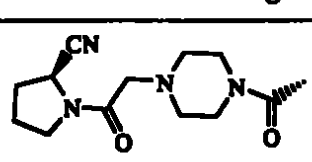
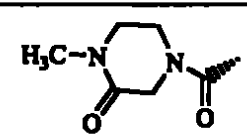
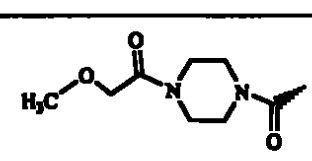
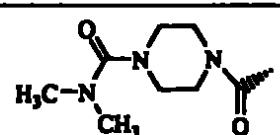
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Table 1d (Continued)

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1d-63		H	HCl	Colorless powder MS APCI (m/z): 455 [M+H]
1d-64		H	HCl	Colorless powder MS APCI (m/z): 461 [M+H] ⁺
1d-65		H	HCl	Purified powder MS APCI (m/z): 488 [M+H] ⁺
1d-66		H	HCl	Colorless powder MS APCI (m/z): 467 [M+H] ⁺
1d-67		H	HCl	Purified powder MS APCI (m/z): 500 [M+H] ⁺
1d-68		H	HCl	Colorless powder MS APCI (m/z): 481 [M+H] ⁺
1d-69		H	HCl	Purified powder MS APCI (m/z): 494 [M+H] ⁺
1d-70		H	HCl	Colorless powder MS APCI (m/z): 482 [M+H] ⁺
1d-71		H	HCl	Purified powder MS APCI (m/z): 466 [M+H] ⁺

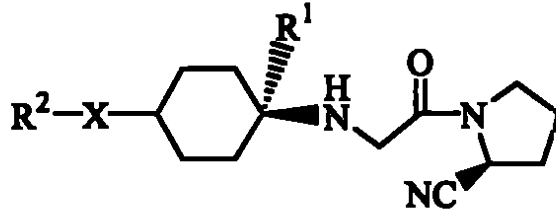
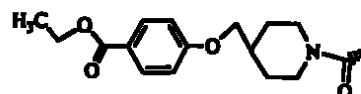
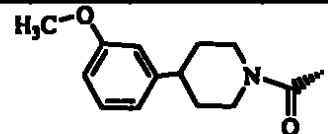
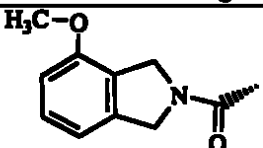
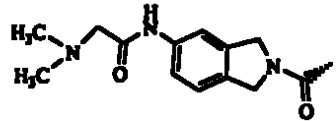
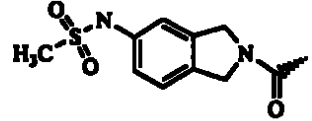
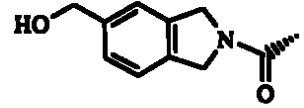
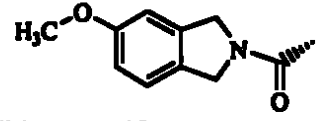
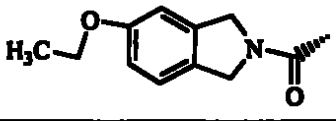
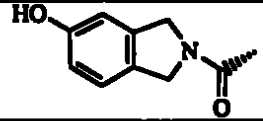
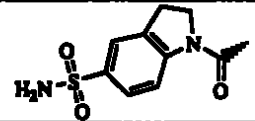
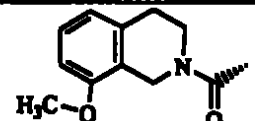
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Table 1d (Continued)

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1d-72		H	2HCl	Purified powder MS APCI (m/z) : 467 [M+H] ⁺
1d-73		H	HCl	Purified powder MS APCI (m/z) : 472 [M+H] ⁺
1d-74		H	2HCl	Purified powder MS APCI (m/z) : 514 [M+H] ⁺
1d-75		H	HCl	Purified powder MS APCI (m/z) : 377
1d-76		H	HCl	Purified powder MS APCI (m/z) : 377
1d-77		H	2HCl	Colorless powder MS APCI (m/z) : 484 [M+H] ⁺
1d-78		H	HCl	Purified powder MS APCI (m/z) : 376
1d-79		H	HCl	Pale yellowish powder MS APCI (m/z) : 420 [M+H] ⁺
1d-80		H	HCl	Colorless powder MS APCI (m/z) : 419 [M+H] ⁺

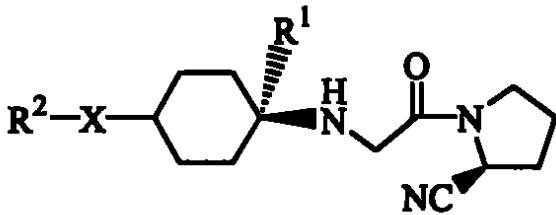
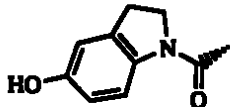
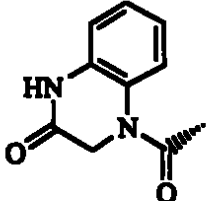
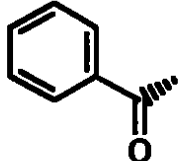
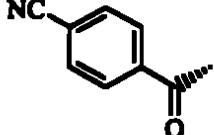
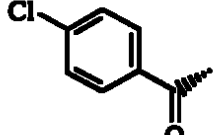
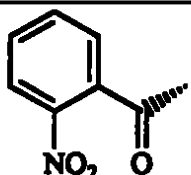
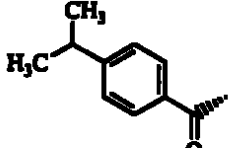
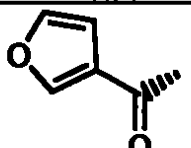
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Table 1d (Continued)

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1d-81		H	HCl	Colorless purified powder MS APCI (m/z) : 524 [M+H] ⁺
1d-82		H	HCl	Colorless purified powder MS APCI (m/z) : 453 [M+H] ⁺
1d-83		H	HCl	Colorless powder MS APCI (m/z) : 411 [M+H] ⁺
1d-84		H	2HCl	Colorless purified powder MS APCI (m/z) : 481 [M+H] ⁺
1d-85		H	HCl	Colorless purified powder MS APCI (m/z) : 474 [M+H] ⁺
1d-86		H	HCl	Purified powder MS APCI (m/z) : 411 [M+H] ⁺
1d-87		H	HCl	Colorless purified powder MS APCI (m/z) : 411 [M+H] ⁺
1d-88		H	HCl	Colorless purified powder MS APCI (m/z) : 425 [M+H] ⁺
1d-89		H	HCl	Colorless powder MS APCI (m/z) : 397 [M+H] ⁺
1d-90		H	Free form	Colorless solid MS APCI (m/z) : 460 [M+H] ⁺
1d-91		H	HCl	Colorless powder MS APCI (m/z) : 425 [M+H] ⁺

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Table 1d (Continued)

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1d-92		H	HCl	Colorless powder MS APCI (m/z) : 397 [M+H]
1d-93		H	HCl	Purified powder MS APCI (m/z) : 410
1d-94		H	HCl	Purified powder MS APCI (m/z) : 340 [M+H]
1d-95		H	HCl	Purified powder MS APCI (m/z) : 365 [M+H]
1d-96		H	HCl	Colorless powder MS APCI (m/z) : 374 [M+H]
1d-97		H	HCl	Yellowish powder MS APCI (m/z) : 385 [M+H]
1d-98		H	HCl	Colorless powder MS APCI (m/z) : 382 [M+H]
1d-99		H	HCl	Purified powder MS APCI (m/z) : 330 [M+H]

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Table 1d (Continued)

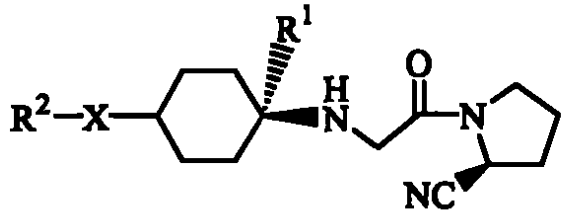
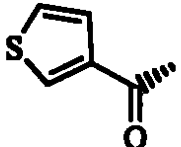
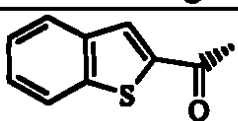
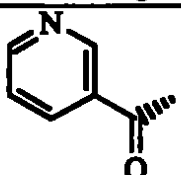
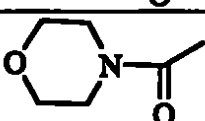
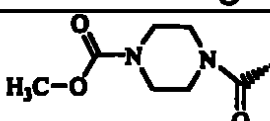
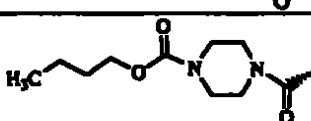
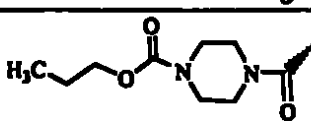
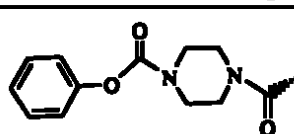
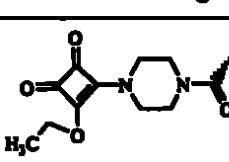
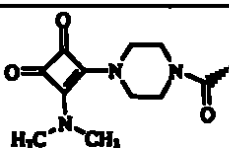
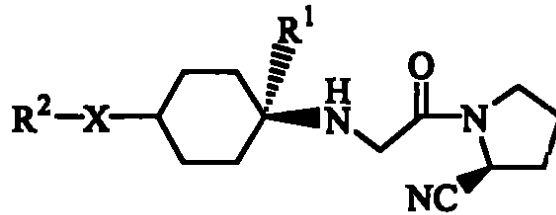
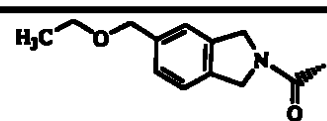
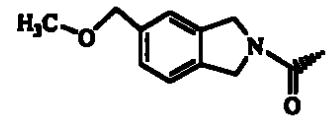
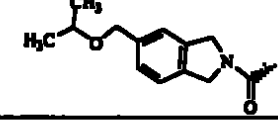
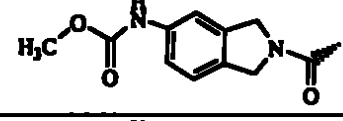
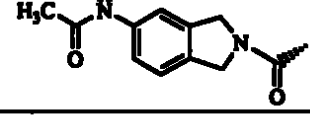
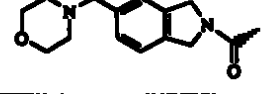
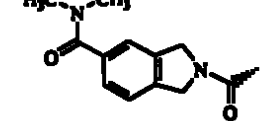
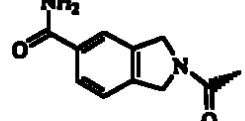
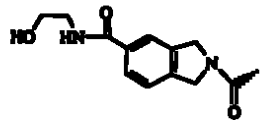
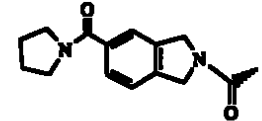
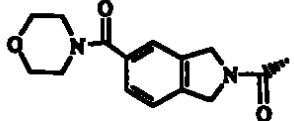
				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1d-100		H	HCl	Purified powder MS APCI (m/z) : 346 [M+H]
1d-101		H	HCl	Colorless powder MS APCI (m/z) : 396 [M+H]
1d-102		H	2HCl	Colorless powder MS APCI (m/z) : 341 [M+H]
1d-103		Me	HCl	Purified powder MS APCI (m/z) : 363 [M+H]
1d-104		H	HCl	Colorless powder MS APCI (m/z) : 406 [M+H]
1d-105		H	HCl	Colorless powder MS APCI (m/z) : 448 [M+H]
1d-106		H	HCl	Colorless powder MS APCI (m/z) : 434 [M+H]
1d-107		H	HCl	Colorless powder MS APCI (m/z) : 468 [M+H]
1d-108		H	HCl	Pale yellowish powder MS APCI (m/z) : 472 [M+H]
1d-109		H	HCl	Pale yellowish powder MS APCI (m/z) : 471 [M+H]

Table 1d (Continued)

				
Example No.	R²-X-	R¹	Salt	Physical properties, etc.
1d-110		H	HCl	Purified powder MS APCI (m/z) : 439 [M+H]⁺
1d-111		H	HCl	Colorless purified powder MS APCI (m/z) : 425 [M+H]⁺
1d-112		H	HCl	Purified powder MS APCI (m/z) : 453 [M+H]⁺
1d-113		H	HCl	Colorless purified powder MS APCI (m/z) : 454 [M+H]⁺
1d-114		H	HCl	Colorless purified powder MS APCI (m/z) : 438 [M+H]⁺
1d-115		H	2HCl	Purified powder MS APCI (m/z) : 480 [M+H]⁺
1d-116		H	HCl	Colorless purified powder MS APCI (m/z) : 452 [M+H]⁺
1d-117		H	HCl	Colorless purified powder MS APCI (m/z) : 424 [M+H]⁺
1d-118		H	HCl	Colorless purified powder MS APCI (m/z) : 468 [M+H]⁺
1d-119		H	HCl	Colorless purified powder MS APCI (m/z) : 478 [M+H]⁺
1d-120		H	HCl	Colorless purified powder MS APCI (m/z) : 494 [M+H]⁺

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Table 1d (Continued)

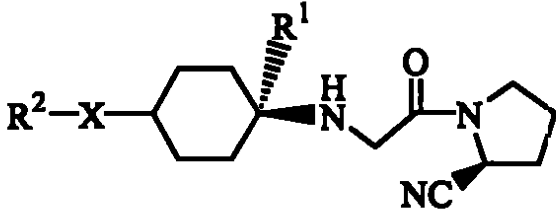
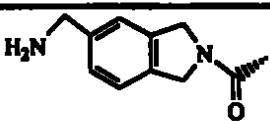
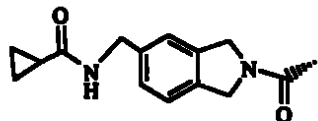
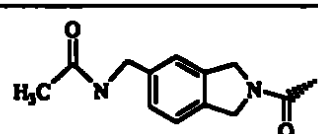
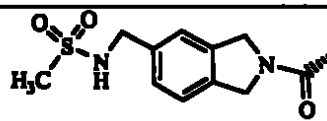
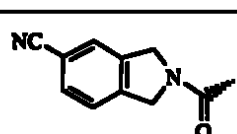
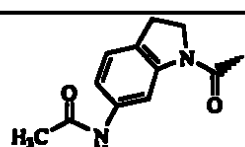
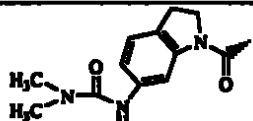
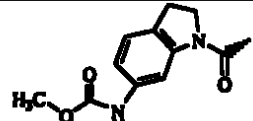
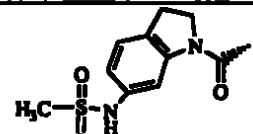
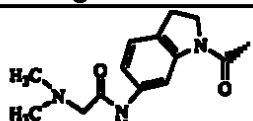
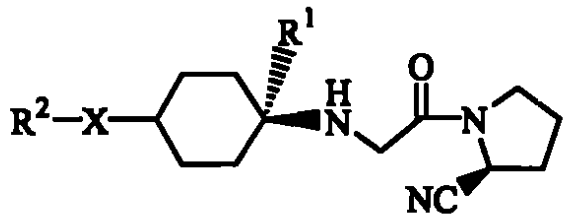
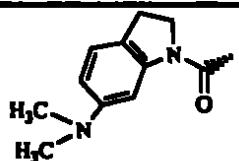
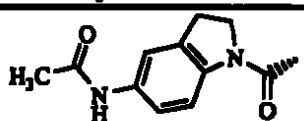
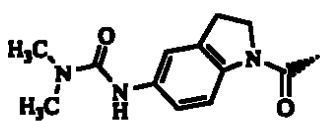
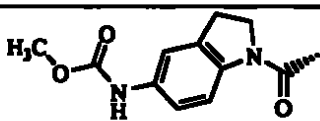
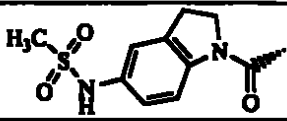
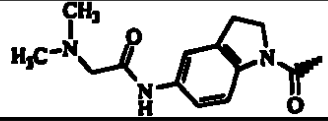
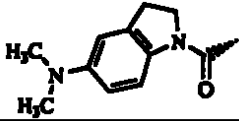
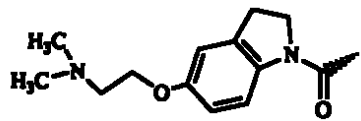
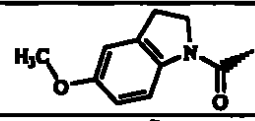
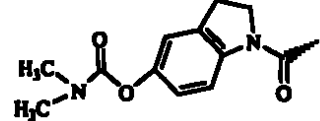
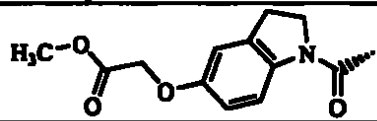
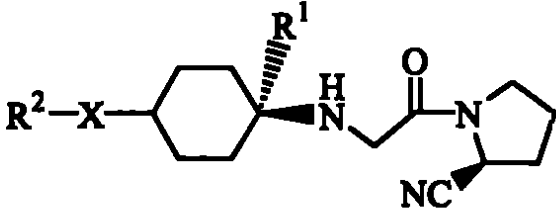
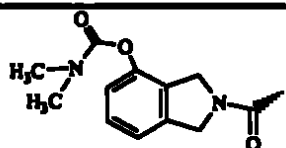
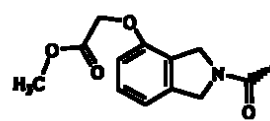
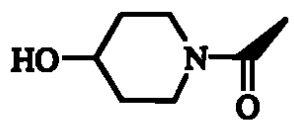
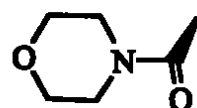
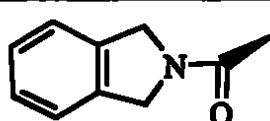
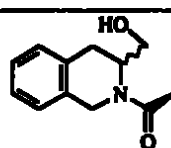
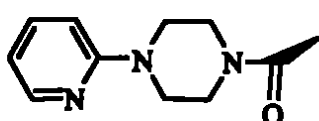
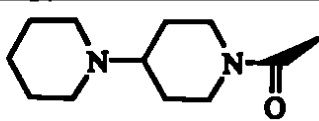
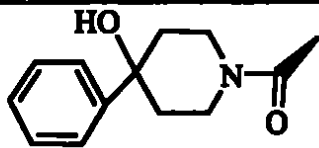
				
Example No	R ² -X-	R ¹	Salt	Physical properties, etc.
1d-121		H	2HCl	Colorless purified powder MS APCI (m/z): 410
1d-122		H	HCl	Colorless purified powder MS APCI (m/z): 478 [M+H] ⁺
1d-123		H	HCl	Colorless purified powder MS APCI (m/z): 452 [M+H] ⁺
1d-124		H	HCl	Colorless purified powder MS APCI (m/z): 488 [M+H] ⁺
1d-125		H	HCl	Colorless purified powder MS APCI (m/z): 406 [M+H] ⁺
1d-126		H	HCl	Colorless powder MS APCI (m/z): 438 [M+H] ⁺
1d-127		H	HCl	Colorless powder MS APCI (m/z): 467 [M+H] ⁺
1d-128		H	HCl	Colorless powder MS APCI (m/z): 454 [M+H] ⁺
1d-129		H	HCl	Colorless powder MS APCI (m/z): 474 [M+H] ⁺
1d-130		H	2HCl	Colorless powder MS APCI (m/z): 481 [M+H] ⁺

Table 1d (Continued)

				
Example No	R ² -X-	R ¹	Salt	Physical properties, etc.
1d-131		H	2HCl	Colorless powder MS APCI (m/z) : 424 [M+H]
1d-132		H	HCl	Colorless powder MS APCI (m/z) : 438 [M+H]
1d-133		H	HCl	Yellow brownish powder MS APCI (m/z) : 467 [M+H]
1d-134		H	HCl	Colorless powder MS APCI (m/z) : 454 [M+H]
1d-135		H	HCl	Colorless powder MS APCI (m/z) : 474 [M+H]
1d-136		H	2HCl	Pale brownish powder MS APCI (m/z) : 481 [M+H]
1d-137		H	2HCl	Colorless powder MS APCI (m/z) : 424 [M-H]
1d-138		H	2HCl	Pale yellowish powder MS APCI (m/z) : 468 [M+H] +
1d-139		H	HCl	Colorless powder MS APCI (m/z) : 411 [M+H] +
1d-140		H	HCl	Colorless powder MS APCI (m/z) : 468 [M+H] +
1d-141		H	HCl	Colorless powder MS APCI (m/z) : 469 [M+H]

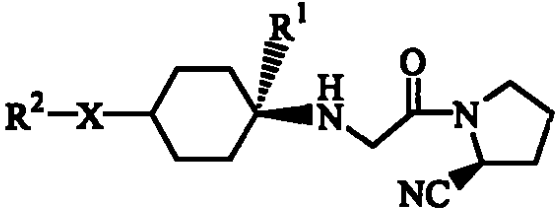
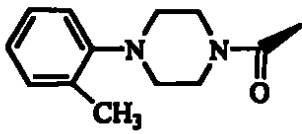
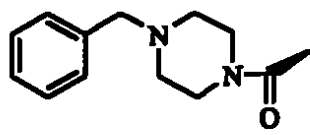
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26

Table 1d (Continued)

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
1d-142		H	HCl	Colorless powder MS APCI (m/z) : 468 [M+H] ⁺
1d-143		H	HCl	Colorless powder MS APCI (m/z) : 469 [M+H] ⁺
1d-144		H	HCl	Purified powder MS APCI (m/z) : 363 [M+H] ⁺
1d-145		H	HCl	Colorless powder MS APCI (m/z) : 349 [M+H] ⁺
1d-146		H	HCl	Purified powder MS APCI (m/z) : 381 [M+H] ⁺
1d-147		H	HCl	Colorless powder MS APCI (m/z) : 425 [M+H] ⁺
1d-148		H	2HCl	Colorless powder MS APCI (m/z) : 425 [M+H] ⁺
1d-149		H	2HCl	Colorless resin state MS APCI (m/z) : 430 [M+H] ⁺
1d-150		H	HCl	Colorless powder MS APCI (m/z) : 439 [M+H] ⁺

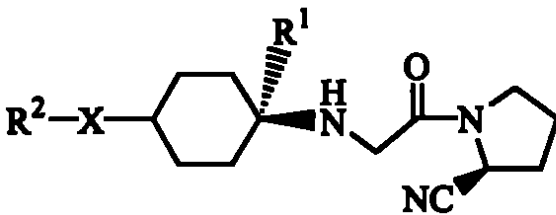
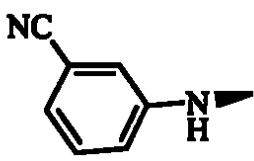
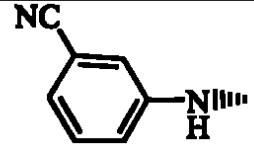
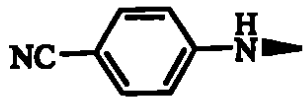
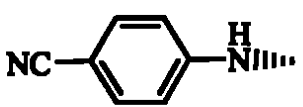
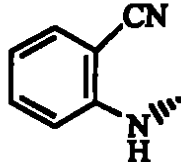
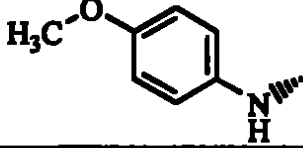
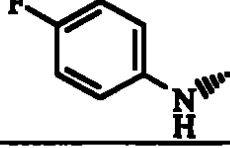
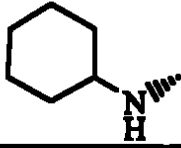
139 ~~139~~

Table 1d (Continued)

				
Example No.	R²-X-	R¹	Salt	Physical properties, etc.
1d-151		H	2HCl	Purified powder MS APCI (m/z) : 438 [M+H] ⁺
1d-152		H	2HCl	Colorless powder MS APCI (m/z) : 438 [M+H] ⁺

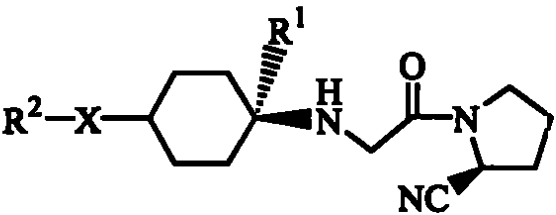
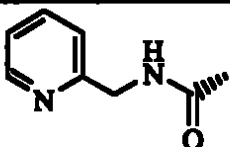
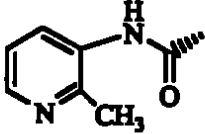
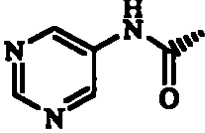
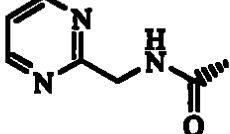
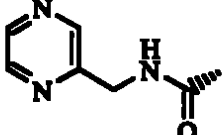
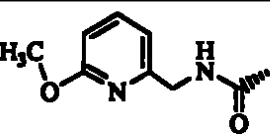
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Table 2

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
2-1		Me	2HCl	Purified powder MS APCI (m/z) : 366
2-2		Me	2HCl	Purified powder MS APCI (m/z) : 366
2-3		Me	2HCl	Purified powder MS APCI (m/z) . 366
2-4		Me	2HCl	Purified powder MS APCI (m/z) . 366
2-5		Me	2HCl	Purified powder MS APCI (m/z) : 366
2-6		Me	2HCl	Purified powder MS APCI (m/z) : 371
2-7		Me	2HCl	Purified powder MS APCI (m/z) : 359
2-8		Me	2HCl	Purified powder MS APCI (m/z) : 347

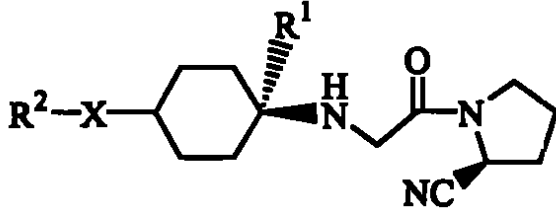
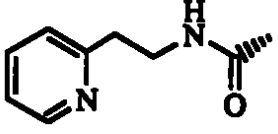
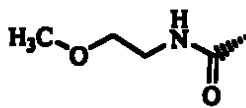
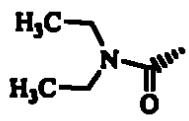
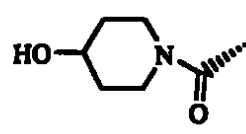
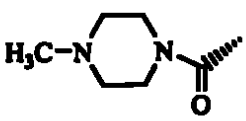
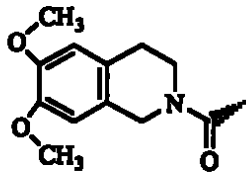
141

Table 3

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
3-1		H	2HCl	Colorless powder MS APCI (m/z): 370 [M+H] ⁺
3-2		H	2HCl	Colorless powder MS APCI (m/z): 370 [M+H] ⁺
3-3		H	2HCl	Colorless powder MS APCI (m/z): 357 [M+H] ⁺
3-4		H	2HCl	Resin state MS APCI (m/z): 371 [M+H] ⁺
3-5		H	2HCl	Resin state MS APCI (m/z): 371 [M+H] ⁺
3-6		H	2HCl	Resin state MS APCI (m/z): 400 [M+H] ⁺

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Table 3 (Continued)

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
3-7		H	2HCl	Resin state MS APCI (m/z): 384 [M+H] ⁺
3-8		H	HCl	Colorless powder MS APCI (m/z): 337 [M+H] ⁺
3-9		H	HCl	Colorless powder MS APCI (m/z): 335 [M+H] ⁺
3-10		H	HCl	Pale yellowish powder MS APCI (m/z): 363 [M+H] ⁺
3-11		H	2HCl	Colorless powder MS APCI (m/z): 362 [M+H] ⁺
3-12		H	HCl	Colorless powder MS APCI (m/z): 455 [M+H] ⁺

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Table 4

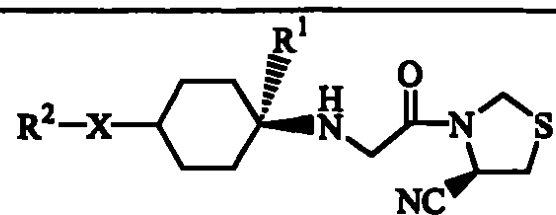
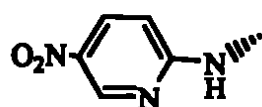
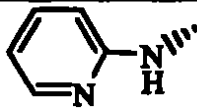
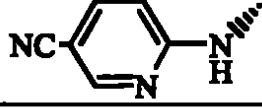
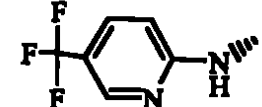
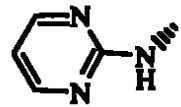
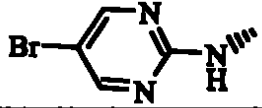
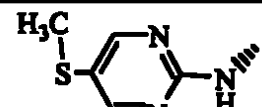
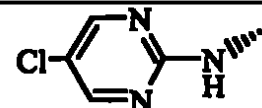
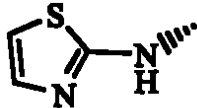
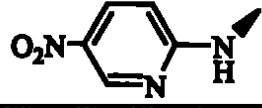
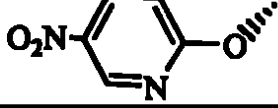
				
Example No.	R²-X-	R¹	Salt	Physical properties, etc.
4-1		H	2HCl	Pale yellowish powder MS APCI (m/z) : 391 [M+H]⁺
4-2		H	2HCl	Colorless powder MS APCI (m/z) : 346 [M+H]⁺
4-3		H	2HCl	Pale yellowish powder MS APCI (m/z) : 371 [M+H]⁺
4-4		H	2HCl	Colorless powder MS APCI (m/z) : 414 [M+H]⁺
4-5		H	HCl	Colorless powder Melting point: >300°C MS APCI (m/z) : 347 [M+H]⁺
4-6		H	2HCl	Colorless powder MS APCI (m/z) : 425 427 [M+H]⁺
4-7		H	2HCl	Colorless powder MS APCI (m/z) : 393 [M+H]⁺
4-8		H	2HCl	Colorless powder MS APCI (m/z) : 381
4-9		H	2HCl	Colorless powder MS APCI (m/z) : 352 [M+H]⁺
4-10		H	2HCl	Pale yellowish powder MS APCI (m/z) : 391 [M+H]⁺
4-11		H	HCl	Colorless powder MS APCI (m/z) : 392 [M+H]⁺

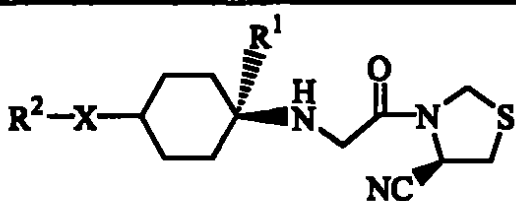
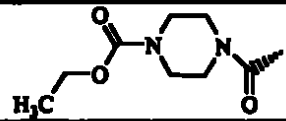
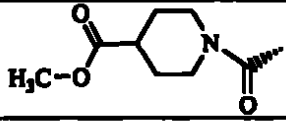
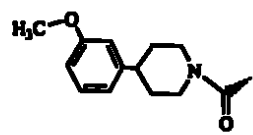
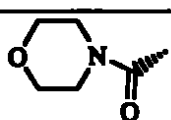
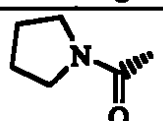
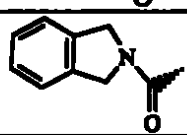
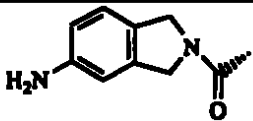
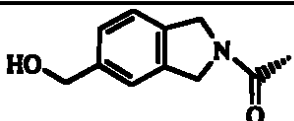
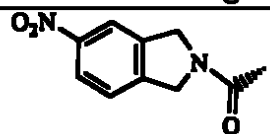
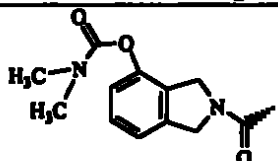


Table 4 (Continued)

Example No.	R²-X-	R¹	Salt	Physical properties, etc.
4-12		H	HCl	Colorless powder MS APCI (m/z) : 372 [M+H]⁺
4-13		H	HCl	Colorless powder MS APCI (m/z) : 426 [M+H]⁺
4-14		H	HCl	Colorless powder MS APCI (m/z) : 382 [M+H]⁺
4-15		H	HCl	Colorless powder MS APCI (m/z) : 394 [M+H]⁺
4-16		H	HCl	Colorless powder Melting point: 80°C- (Decomposed) MS APCI (m/z) : 348 [M+H]⁺
4-17		H	HCl	Colorless powder MS APCI (m/z) : 414 [M+H]⁺
4-18		H	HCl	Pale yellowish powder MS APCI (m/z) : 391 [M+H]⁺
4-19		H	2HCl	Colorless powder MS APCI (m/z) : 374 [M+H]⁺
4-20		H	HCl	Colorless purified powder MS APCI (m/z) : 297 [M+H]⁺
4-21		H	HCl	Purified powder MS APCI (m/z) : 325 [M+H]⁺
4-22		H	HCl	Colorless purified powder MS APCI (m/z) : 397 [M+H]⁺

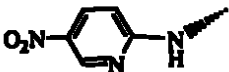
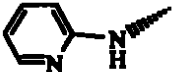
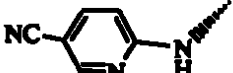
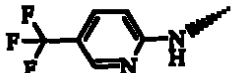
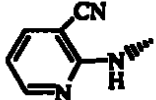
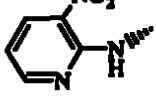
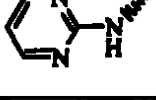
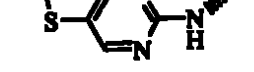
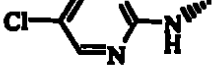
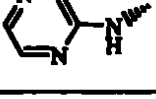
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Table 4 (Continued)

				
Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
4-23		H	HCl	Colorless powder MS APCI (m/z) : 438 [M+H] ⁺
4-24		H	HCl	Colorless powder MS APCI (m/z) : 423 [M+H] ⁺
4-25		H	HCl	Colorless. purified powder MS APCI (m/z) : 471 [M+H] ⁺
4-26		H	HCl	Colorless powder MS APCI (m/z) : 367 [M+H] ⁺
4-27		H	HCl	Colorless powder MS APCI (m/z) : 351 [M+H] ⁺
4-28		H	HCl	Colorless powder MS APCI (m/z) : 399 [M+H] ⁺
4-29		H	2HCl	Colorless powder MS APCI (m/z) : 414 [M+H] ⁺
4-30		H	HCl	Colorless powder MS APCI (m/z) : 429 [M+H] ⁺
4-31		H	HCl	Colorless powder MS APCI (m/z) : 444 [M+H] ⁺
4-32		H	HCl	Colorless powder MS APCI (m/z) : 486 [M+H] ⁺

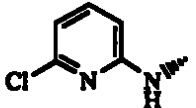
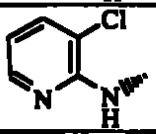
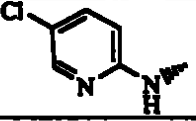
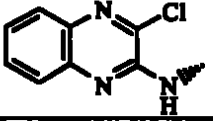
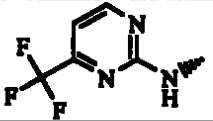
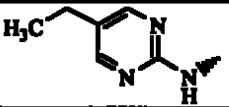
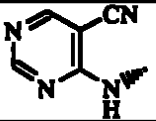
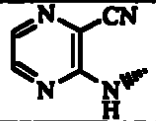
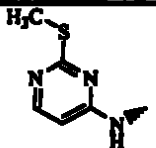
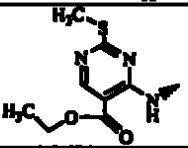
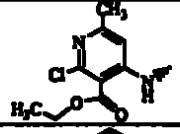
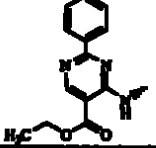
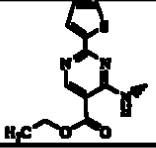
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Table 5

$\text{R}^2\text{-X}-\text{C}_6\text{H}_{10}-\text{NH}_2$				
Reference Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
3-1		H	Free form	Yellowish crystal Melting point: 156-158°C
3-2		H	Free form	Pale brownish crystal Melting point: 110-122°C
3-3		H	Free form	Colorless crystal Melting point: 152-154°C
3-4		H	Free form	Pale brownish crystal Melting point: 77-80°C
3-5		H	Free form	Pale yellowish needle-like crystal Melting point: 107-108°C
3-6		H	Free form	Yellowish needle-like crystal Melting point: 84°C-
3-7		H	Free form	Colorless crystal Melting point: 128-129°C
3-8		H	Free form	Colorless crystal Melting point: 140-141°C
3-9		H	Free form	Pale yellowish crystal Melting point: 116-118°C
3-10		H	2HCl	Colorless crystal Melting point: >300°C
3-11		H	Free form	Pale yellowish needle-like crystal Melting point: 92-94°C
3-12		H	Free form	Brownish crystal Melting point: 120-123°C

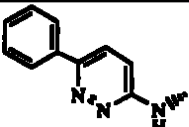
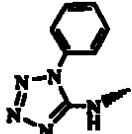
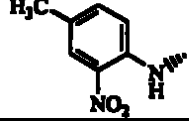
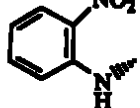
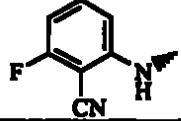
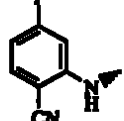
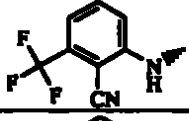
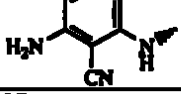
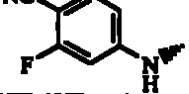
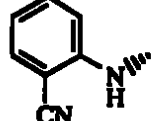
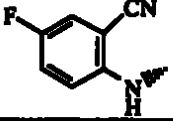
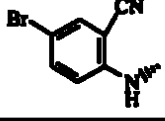
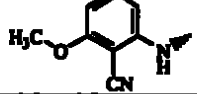
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Table 5 (Continued)

Reference Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
3-13		H	Free form	Powder MS APCI (m/z) : 228, 226
3-14		H	Free form	Oil MS APCI (m/z) : 228, 226
3-15		H	Free form	Oil MS APCI (m/z) : 228, 226
3-16		H	Free form	Oil
3-17		H	Free form	Powder MS APCI (m/z) : 261
3-18		H	Free form	Oil MS APCI (m/z) : 221
3-19		H	Free form	Powder MS APCI (m/z) : 218
3-20		H	Free form	Powder MS APCI (m/z) : 218
3-21		H	Free form	Yellowish oil MS APCI (m/z) : 239 [M+H] ⁺
3-22		H	Free form	Yellowish foam MS APCI (m/z) : 311 [M+H] ⁺
3-23		H	Free form	Yellowish oil MS APCI (m/z) : 312 [M+H] ⁺
3-24		H	Free form	Colorless oil
3-25		H	Free form	Colorless oil

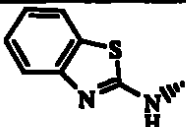
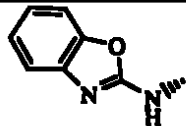
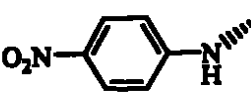
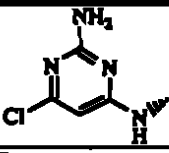
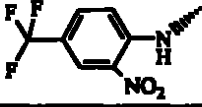
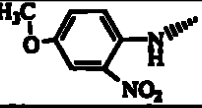
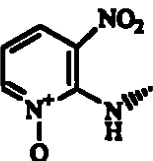
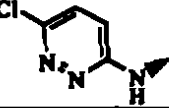
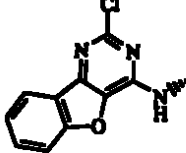
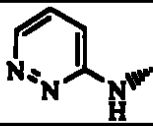
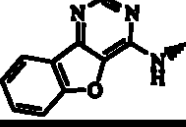
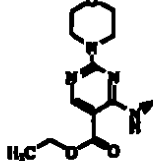
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Table 5 (Continued)

Reference Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
3-26		H	Free form	Powder MS APCI (m/z) : 269
3-27		H	Free form	Yellowish oil MS APCI (m/z) : 259 [M+H] ⁺
3-28		H	Free form	Oil MS APCI (m/z) : 250
3-29		H	Free form	Powder MS APCI (m/z) : 236
3-30		H	Free form	Powder MS APCI (m/z) : 234
3-31		H	Free form	Oil MS APCI (m/z) : 234
3-32		H	Free form	Powder MS APCI (m/z) : 284
3-33		H	Free form	Powder MS APCI (m/z) : 231
3-34		H	Free form	Powder MS APCI (m/z) : 234
3-35		H	Free form	Pale brownish crystal Melting point: 99-102°C MS APCI (m/z) : 216 [M+H] ⁺
3-36		H	Free form	Yellowish resin MS APCI (m/z) : 234 [M+H] ⁺
3-37		H	Free form	Pale reddish brownish powder MS APCI (m/z) : 296, 294 [M+H] ⁺
3-38		H	Free form	Pale reddish brownish powder MS APCI (m/z) : 246 [M+H] ⁺

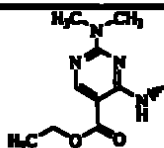
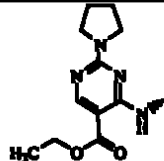
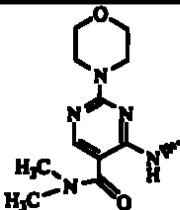
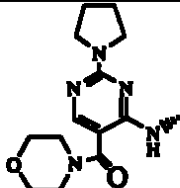
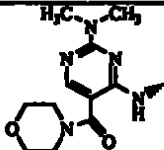
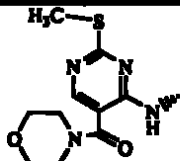
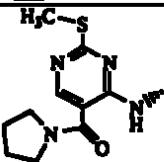
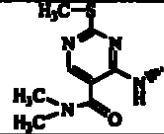
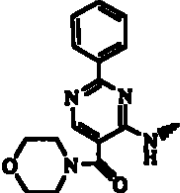
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Table 5 (Continued)

Reference Example No	R ¹ -X-Y-	R ²	Salt	Physical properties, etc.
3-39		H	Free form	Oil
3-40		H	Free form	Oil
3-41		H	Free form	Yellowish crystal Melting point. 135-136.5°C
3-42		H	Free form	Yellowish powder MS APCI (m/z) : 242 [M+H] ⁺
3-43		H	Free form	Yellowish crystal Melting point: 81.5-83.5°C
3-44		H	Free form	Reddish liquid MS APCI (m/z) : 266 [M+H]
3-45		H	Free form	Dark reddish powder MS APCI (m/z) : 253 [M+H]
3-46		H	Free form	Powder MS APCI (m/z) : 229, 227
3-47		H	Free form	Oil
3-48		H	Free form	Powder MS APCI (m/z) : 193
3-49		H	Free form	Oil
3-50		H	Free form	Colorless oil

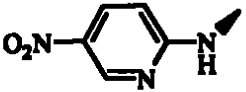
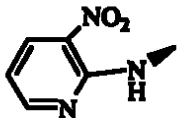
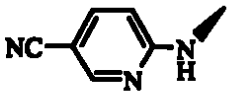
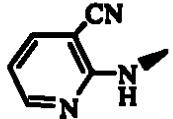
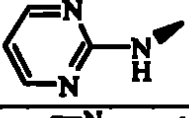
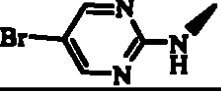
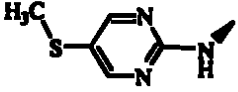
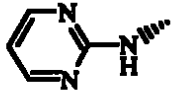
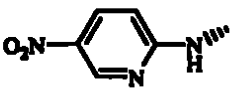
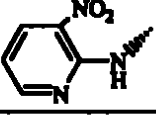
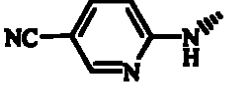
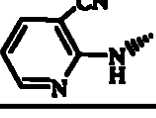
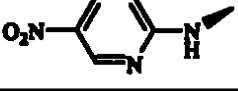
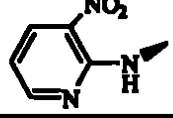
150
X
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Table 5 (Continued)

Reference Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
3-51		H	Free form	Colorless oil
3-52		H	Free form	Colorless oil
3-53		H	Free form	Yellowish oil
3-54		H	Free form	Colorless oil
3-55		H	Free form	Colorless oil
3-56		H	Free form	Yellowish oil
3-57		H	Free form	Colorless foam
3-58		H	Free form	Colorless oil
3-59		H	Free form	Colorless oil

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151

Table 5 (Continued)

Reference Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
4		H	Free form	Pale yellowish solid Melting point: 153-155°C
5-1		H	2HCl	Yellowish crystal Melting point: 219-222°C
5-2		H	2HCl	Colorless powder MS APCI(m/z): 217 [M+H] ⁺
5-3		H	2HCl	Colorless crystal Melting point: 215-218°C
5-4		H	2HCl	Colorless crystal Melting point: 245-250°C
5-5		H	2HCl	Colorless crystal Melting point: 303°C
5-6		H	2HCl	Yellowish crystal Melting point: 234-237°C
7-1		Me	Free form	Colorless crystal Melting point: 121-123°C
7-2		Me	Free form	Yellowish crystal Melting point: 164-166°C
7-3		Me	Free form	Yellowish crystal Melting point: 40-43°C
7-4		Me	Free form	Pale yellowish crystal Melting point: 147-148°C
7-5		Me	Free form	Colorless crystal Melting point: 111-112°C
7-6		Me	Free form	Pale brownish crystal Melting point: 121-124°C
7-7		Me	Free form	Yellowish crystal Melting point: 58-59°C

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X3

Table 5 (Continued)

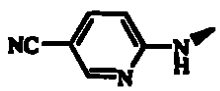
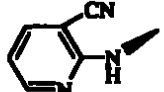
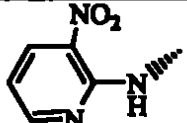
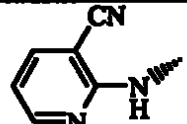
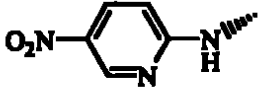
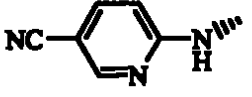
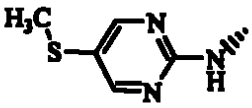
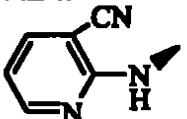
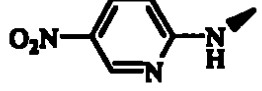
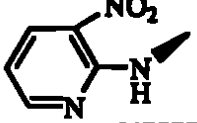
Reference Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
7-8		Me	Free form	Colorless crystal Melting point: 182-184°C
7-9		Me	Free form	Pale brownish crystal Melting point 76-79°C
7-10		CH ₂ OH	2HCl	Pale yellowish solid MS APCI (m/z) : 267 [M+H] ⁺
7-11		CH ₂ OH	2HCl	Colorless solid MS APCI (m/z) : 247 [M+H] ⁺
7-12		CH ₂ OH	2HCl	Yellowish powder MS APCI (m/z) . 267 [M+H] ⁺
7-13		CH ₂ OH	Free form	Colorless oil MS APCI (m/z) : 247 [M+H] ⁺
7-14		CH ₂ OH	2HCl	Pale yellowish solid MS APCI (m/z) : 269 [M+H] ⁺
7-15		CH ₂ OH	2HCl	Colorless powder MS APCI (m/z) : 247 [M+H] ⁺
7-16		CH ₂ OH	2HCl	Colorless solid MS APCI (m/z) : 247 [M+H] ⁺
7-17		CH ₂ OH	2HCl	Yellowish powder MS APCI (m/z) : 267 [M+H] ⁺
7-18		CH ₂ OH	2HCl	Pale yellowish solid MS APCI (m/z) : 267 [M+H] ⁺

Table 5 (Continued)

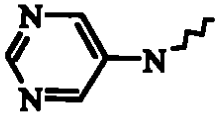
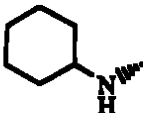
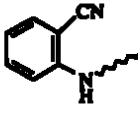
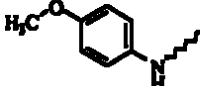
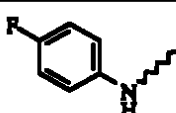
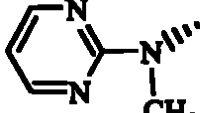
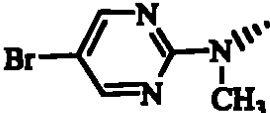
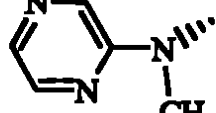
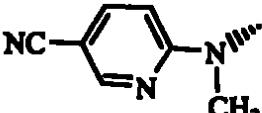
Reference Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
7-19		Me	2HCl	Colorless resin state MS APCI (m/z): 207 [M+H] ⁺
7-20		Me	Free form	Powder MS APCI (m/z): 311
7-21		Me		
7-22		Me		
7-23		Me		
8-1		H	Free form	Colorless resin MS APCI (m/z): 207 [M+H] ⁺
8-2		H	Free form	Colorless crystal Melting point: 109-112°C
8-3		H	Free form	Pale brownish resin MS APCI (m/z): 207 [M+H] ⁺
8-4		H	Free form	Colorless crystal Melting point: 85-87°C



Table 6

$\text{R}^2\text{-X}-\text{C}_6\text{H}_{10}-\text{CH}(\text{R}^1)\text{NH}_2$				
Reference Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
9-1		H	HCl	Colorless crystal Melting point: 271°C
9-2		H	HCl	Colorless crystal Melting point: 289°C
9-3		H	HCl	Colorless crystal Melting point: 253-254°C
9-4		H	HCl	Pale yellowish crystal Melting point: 230°C
9-5		H	Free form	Colorless crystal Melting point: 70-72°C
9-6		H	Free form	Colorless crystal Melting point: 58-59°C
9-7		H	HCl	Colorless crystal Melting point: 284°C (decomposed)
9-8		H	HCl	Colorless crystal Melting point: 279-280°C (decomposed)
9-9		H	HCl	Colorless crystal Melting point: 275°C (decomposed)
9-10		H	HCl	Colorless crystal Melting point: 275-276°C (decomposed)
9-11		H	HCl	Colorless crystal Melting point: 194°C
9-12		H	Free form	Pale yellowish crystal Melting point: 222-223°C

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Table 6 (Continued)

Reference Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
9-13		H	Free form	Crystal Melting point: 91-94°C MS APCI (m/z) : 229, 227
9-14		H	Free form	Powder MS APCI (m/z) : 229, 227
9-15		H	Free form	Powder MS APCI (m/z) : 223
9-16		H	Free form	Powder MS APCI (m/z) : 193
9-17		H	Free form	Powder MS APCI (m/z) : 229, 227
9-18		H		
9-19		H	Free form	Oil
9-20		H		
9-21		H		
9-22		H	Free form	Colorless powder MS APCI (m/z) : 240 (M+H) ⁺
9-23		H		
9-24		H	Free form	Powder MS APCI (m/z) : 222
9-25		H	Free form	Oil
9-26		H	Free form	Powder MS APCI (m/z) : 262, 260
9-27		H	Free form	Powder MS APCI (m/z) : 194

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Table 6 (Continued)

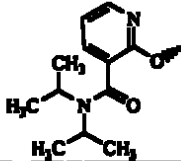
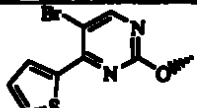
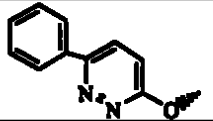
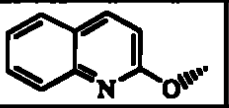
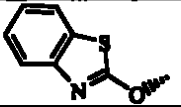
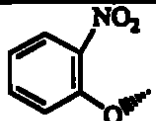
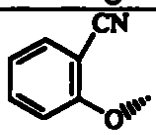
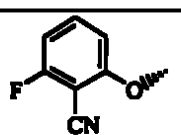
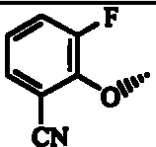
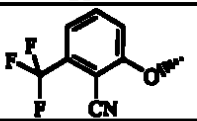
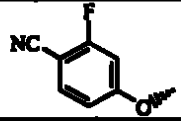
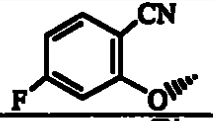
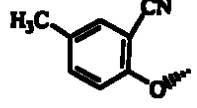
Reference Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
9-28		H	Free form	Oil MS APCI (m/z) : 320
9-29		H	Free form	Powder MS APCI (m/z) : 356, 354
9-30		H	Free form	Powder MS APCI (m/z) : 270
9-31		H	Free form	Powder MS APCI (m/z) : 243
9-32		H	Free form	Oil
9-33		H	Free form	Powder MS APCI (m/z) : 237
9-34		H	HCl	Colorless crystal Melting point: 215-218°C MS APCI (m/z) : 217 [M+H]
9-35		H	Free form	Yellowish oil
9-36		H	Free form	Yellowish oil
9-37		H	Free form	Yellowish oil
9-38		H	Free form	Colorless oil
9-39		H	Free form	Colorless oil
9-40		H	HCl	Colorless crystal Melting point: 253-254°C MS APCI (m/z) : 231 [M+H]

Table 6 (Continued)

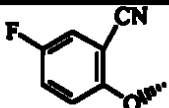
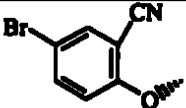
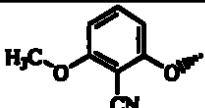
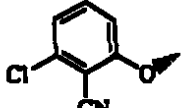
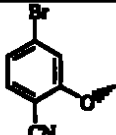
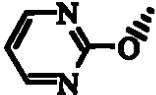
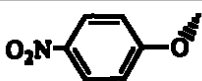
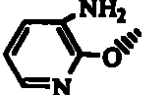
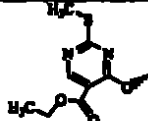
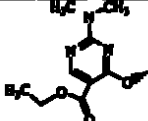
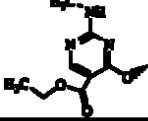
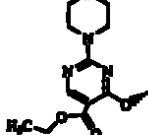
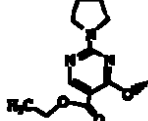
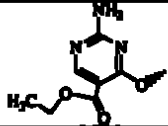
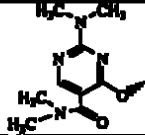
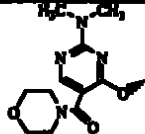
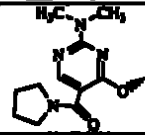
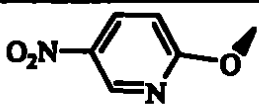
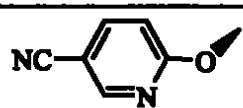
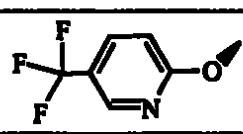
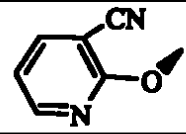
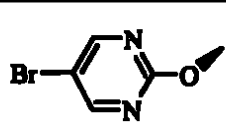
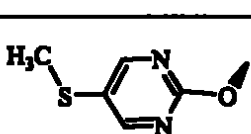
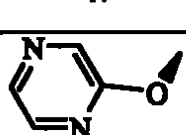
Reference Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
9-41		H	HCl	Pale green melting point: 270-285°C MS APCI (m/z): 235 [M+H]
9-42		H	HCl	Colorless crystal melting point: 283-284°C MS APCI (m/z): 297, 295 [M+H]
9-43		H	HCl	Colorless crystal melting point: 246-247°C MS APCI (m/z): 247 [M+H]
9-44		H	HCl	Colorless crystal melting point: 285-294°C MS APCI (m/z): 251 [M+H]
9-45		H	HCl	Colorless crystal melting point: >300°C MS APCI (m/z): 297, 295 [M+H]
9-46		H	Free form	Pale brownish semi-solid MS APCI (m/z): 194 [M+H] IR (cm ⁻¹): 3351
9-47		H	HCl	Yellow brownish crystal melting point: 238-240°C
9-48		H	HCl	Pale brownish crystal melting point: 180°C (decomposed)
9-49		H	Free form	
9-50		H	Free form	
9-51		H	Free form	
9-52		H	Free form	
9-53		H	Free form	

Table 6 (Continued)

Reference Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
9-54		H	Free form	
9-55		H	Free form	
9-56		H	Free form	
9-57		H	Free form	
9-58		H	HCl	Pale brownish powder MS APCI (m/z): 238 [M+H] ⁺
9-59		H	HCl	Colorless powder MS APCI (m/z): 218 [M+H] ⁺
9-60		H	HCl	Colorless crystal melting point: 234-235°C (decomposed)
9-61		H	HCl	Colorless crystal melting point: 126°C
9-62		H	HCl	Pale yellowish crystal melting point: 206-207°C (decomposed)
9-63		H	HCl	Pale yellowish crystal melting point: 148-150°C (decomposed)
9-64		H	HCl	Colorless crystal melting point: 189-191°C (decomposed)

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Table 6 (Continued)

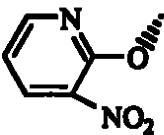
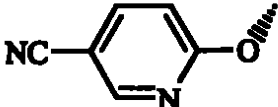
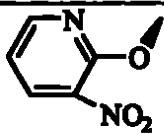
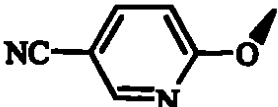
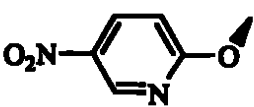
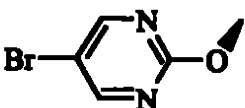
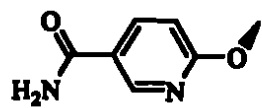
Reference Example No	R ² -X-	R ¹	Salt	Physical properties, etc.
10-2		Me	Free form	Colorless liquid MS APCI (m/z): 252 [M+H] ⁺
10-3		Me	Free form	Colorless crystal Melting point: 73-76°C
10-4		Me	Free form	Colorless liquid MS APCI (m/z): 252 [M+H] ⁺
10-5		Me	Free form	Colorless crystal Melting point: 88-89°C
10-6		Me	Free form	Colorless crystal Melting point: 90-94°C
10-7		Me	Free form	Colorless crystal Melting point: 97-100°C
10-8		Me	Free form	Colorless crystal Melting point: 150-154°C

Table 7

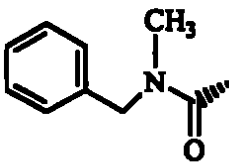
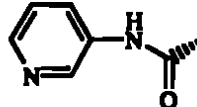
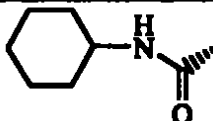
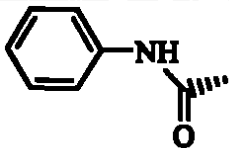
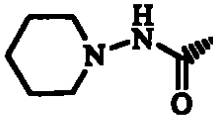
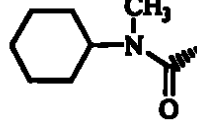
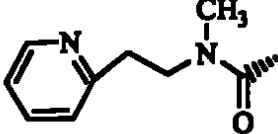
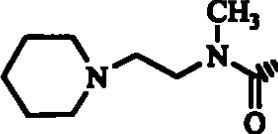
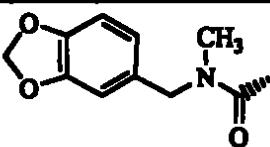
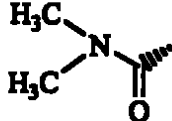
$\text{R}^2\text{-X}-\text{C}_6\text{H}_{10}-\text{NH}_2$				
Reference Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
11-1		H	HCl	Colorless solid Melting point 150-153°C MS APCI (m/z) : 247 [M+H] ⁺
11-2		H	2HCl	Colorless crystal Melting point 294-295°C
11-3		H	Free form	Colorless crystal Melting point: 185.5-186°C
11-4		H	HCl	Colorless solid Melting point: >300°C MS APCI (m/z) : 219 [M+H] ⁺
11-5		H	Free form	Colorless solid Melting point: 163-166°C
11-6		H	Free form	Colorless liquid MS APCI (m/z) : 239 [M+H]
11-7		H	Free form	Colorless liquid MS APCI (m/z) : 262 [M+H]
11-8		H	Free form	Colorless liquid
11-9		H	Free form	Colorless liquid
11-10		H	Free form	Liquid MS APCI (m/z) : 171 [M+H]

Table 7 (Continued)

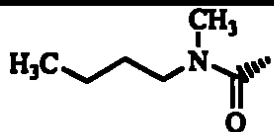
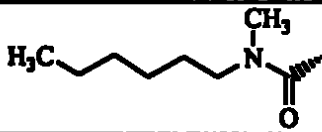
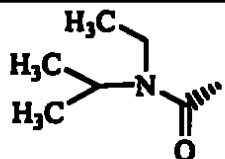
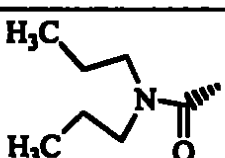
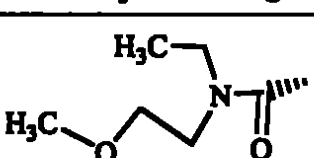
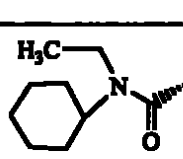
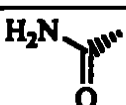
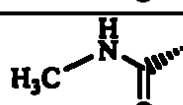
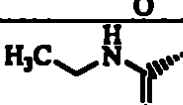
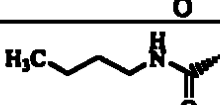
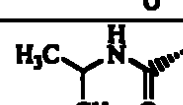
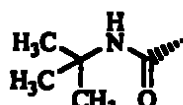
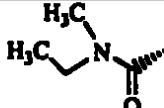
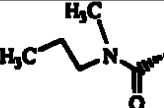
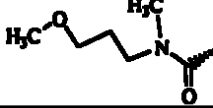
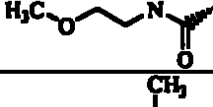
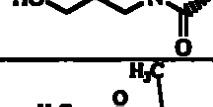
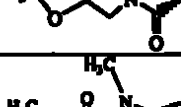
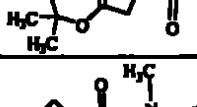
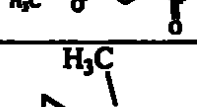
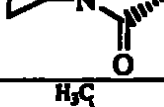
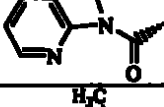
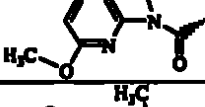
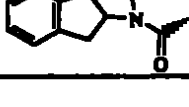
Reference Example No	R ² -X-	R ¹	Salt	Physical properties, etc.
11-11		H	Free form	Pale yellowish oil MS APCI (m/z): 213
11-12		H	Free form	Colorless oil MS APCI (m/z): 241 [M+H] ⁺
11-13		H	Free form	Pale yellowish oil MS APCI (m/z): 213
11-14		H	HCl	Colorless liquid MS APCI (m/z): 227 [M+H] ⁺
11-15		H	Free form	Pale yellowish oil MS APCI (m/z): 229
11-16		H	Free form	Colorless oil MS APCI (m/z): 253 [M+H] ⁺
11-17		H	HI	Colorless powder MS APCI (m/z): 143 [M+H] ⁺
11-18		H	Free form	Colorless crystal MS APCI (m/z): 157
11-19		H	Free form	Colorless crystal MS APCI (m/z): 171
11-20		H	Free form	Colorless crystal MS APCI (m/z): 199
11-21		H	Free form	Colorless crystal MS APCI (m/z): 185
11-22		H	Free form	Colorless crystal Meltingpoint: 142°C (Decomposed) MS APCI (m/z): 199 [M+H] ⁺

Table 7 (Continued)

Reference Example No.	R ² -X-	R ¹	Salt	Physical properties, etc
11-23		H	Free form	Colorless oil MS APCI (m/z) : 185
11-24		H	Free form	Colorless oil MS APCI (m/z) : 199
11-25		H	Free form	Colorless resin MS APCI (m/z) : 229 [M+H] ⁺
11-26		H	Free form	Colorless resin MS APCI (m/z) : 229 [M+H] ⁺
11-27		H	Free form	Colorless resin MS APCI (m/z) : 243 [M+H] ⁺
11-28		H	Free form	Colorless oil MS APCI (m/z) : 215
11-29		H	Free form	Colorless oil MS APCI (m/z) : 215
11-30		H	Free form	Colorless resin MS APCI (m/z) : 229 [M+H] ⁺
11-31		H	Free form	Colorless resin MS APCI (m/z) : 271 [M+H] ⁺
11-32		H	Free form	Colorless resin MS APCI (m/z) : 243 [M+H] ⁺
11-33		H	Free form	Colorless resin MS APCI (m/z) : 197 [M+H] ⁺
11-34		H	Free form	Pale brownish resin
11-35		H	Free form	Pale brownish resin
11-36		H	Free form	Pale brownish resin

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Table 7 (Continued)

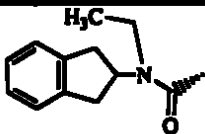
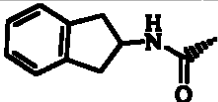
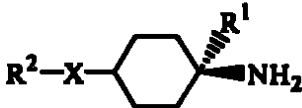
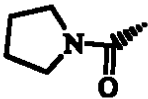
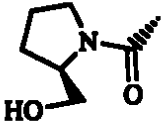
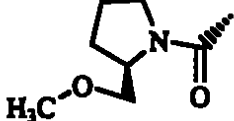
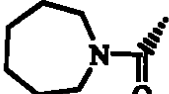
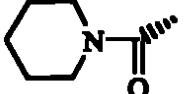
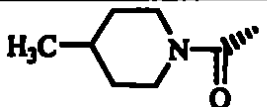
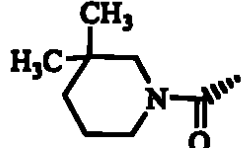
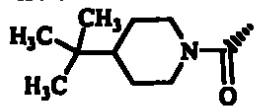
Reference Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
11-37		H	Free form	Pale brownish resin
11-38		H	Free form	Pale brownish resin

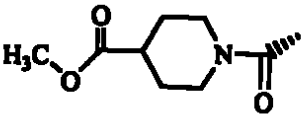
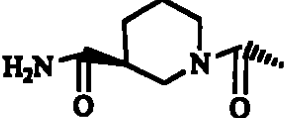
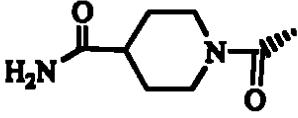
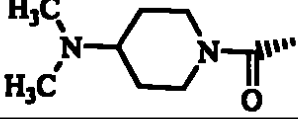
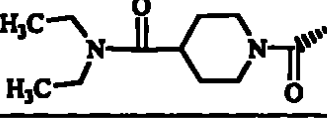
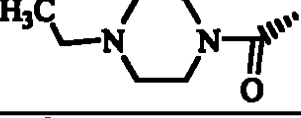
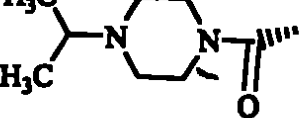
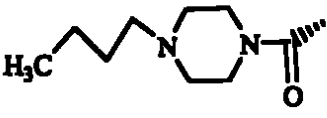
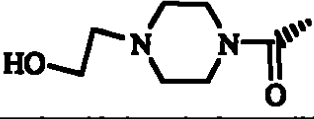
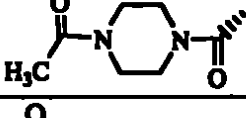
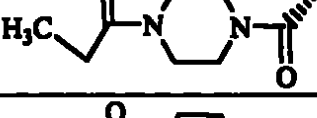
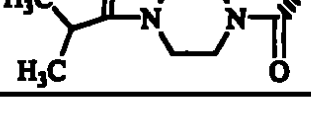
Table 8

				
Reference Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
12-1		H	Free form	Colorless oil MS APCI (m/z): 197 [M+H] ⁺
12-2		H	Free form	Colorless liquid
12-3		H	Free form	Pale yellowish oil MS APCI (m/z): 241
12-4		H	Free form	Colorless oil MS APCI (m/z): 225 [M+H] ⁺
12-5		H	Free form	Colorless oil MS APCI (m/z): 211 [M+H] ⁺
12-6		H	Free form	Colorless oil MS APCI (m/z): 225 [M+H] ⁺
12-7		H	Free form	Colorless oil MS APCI (m/z): 239 [M+H] ⁺
12-8		H	Free form	Colorless liquid MS APCI (m/z): 267 [M+H] ⁺

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Table 8 (Continued)

Reference Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
12-9		H	Free form	Colorless liquid MS APCI (m/z) : 269 [M+H] ⁺
12-10		H	Free form	Colorless oil MS APCI (m/z) : 254
12-11		H	HCl	Colorless oil MS APCI (m/z) : 254 [M+H] ⁺
12-12		H	2HCl	Colorless powder MS APCI (m/z) : 254 [M+H] ⁺
12-13		H	HCl	Colorless resin MS APCI (m/z) : 310 [M+H] ⁺
12-14		H	Free form	Colorless solid MS APCI (m/z) : 240
12-15		H	2HCl	Colorless powder MS APCI (m/z) : 254 [M+H] ⁺
12-16		H	2HCl	Colorless powder MS APCI (m/z) : 268 [M+H] ⁺
12-17		H	2HCl	Colorless powder MS APCI (m/z) : 256 [M+H] ⁺
12-18		H	Free form	Colorless powder MS APCI (m/z) : 254 [M+H] ⁺
12-19		H	Free form	Colorless solid Melting point: 93-96°C
12-20		H	Free form	Colorless solid Melting point: 242-245°C

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Table 8 (Continued)

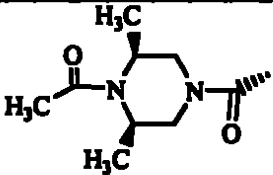
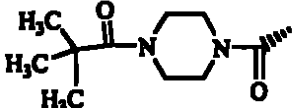
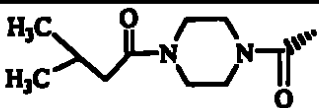
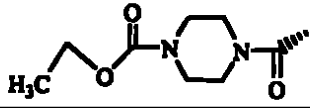
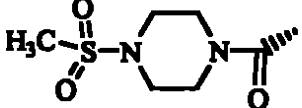
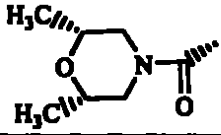
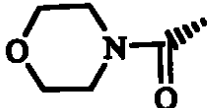
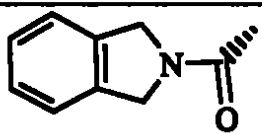
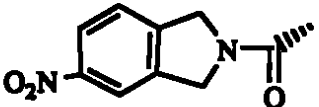
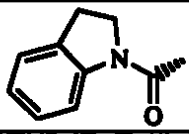
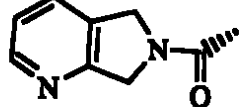
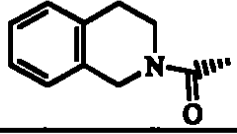
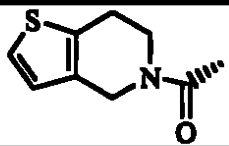
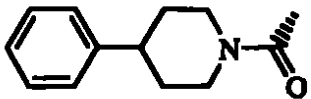
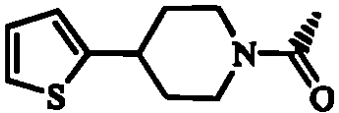
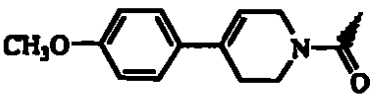
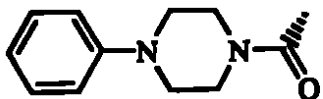
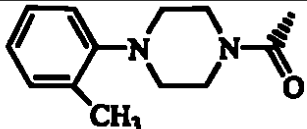
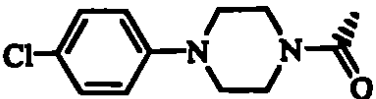
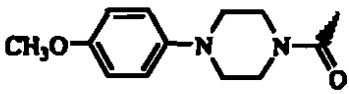
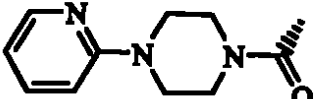
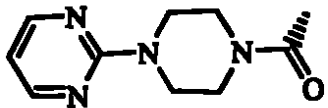
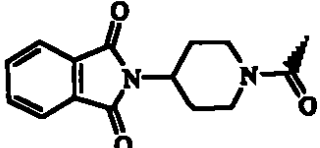
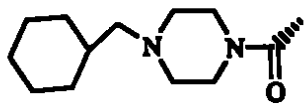
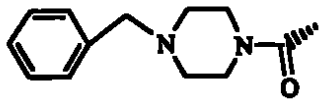
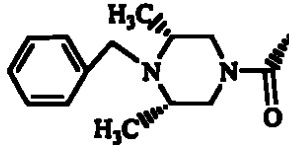
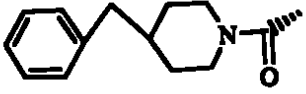
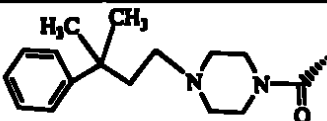
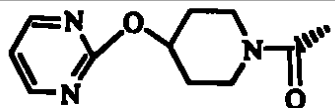
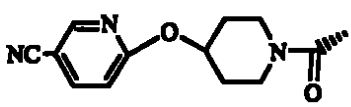
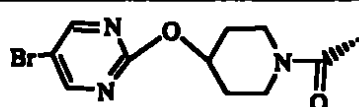
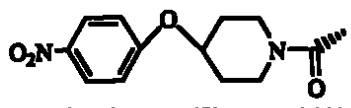
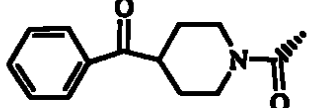
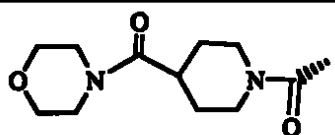
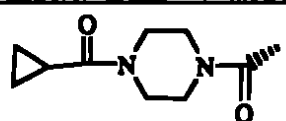
Reference Example No	R ² -X-	R ¹	Salt	Physical properties, etc.
12-21		H	Free form	Colorless liquid MS APCI (m/z): 282 [M+H]
12-22		H	Free form	Colorless solid Melting point: 173-176°C
12-23		H	Free form	Colorless solid Melting point: 135-137°C
12-24		H	Free form	Colorless crystal Melting point: 90-92°C
12-25		H	Free form	Colorless crystal Melting point: 152-153°C
12-26		H	Free form	Colorless liquid MS APCI (m/z): 241 [M+H]
12-27		H	Free form	Colorless crystal Melting point: 75-80°C
12-28		H	Free form	Colorless crystal Melting point: 170-173°C
12-29		H	Free form	Colorless oil MS APCI (m/z): 290 [M+H] ⁺
12-30		H	HCl	Pale brownish solid Melting point: 230-233°C
12-31		H	2HCl	Pale yellowish solid MS APCI (m/z): 246[M+H] ⁺
12-32		H	Free form	Colorless solid Melting point: 150-155°C

Table 8 (Continued)

Reference Example No	R ² -X-	R ¹	Salt	Physical properties, etc.
12-33		H	Free form	Colorless solid Melting point: 55-69°C
12-34		H	Free form	Colorless solid Melting point: 166-170°C
12-35		H	Free form	Colorless oil MS APCI (m/z): 293 [M+H] ⁺
12-36		H	Free form	Colorless powder MS APCI (m/z): 315 [M+H] ⁺
12-37		H	Free form	Colorless solid Melting point: 135-189°C
12-38		H	Free form	Colorless liquid MS APCI (m/z) 302 [M+H] ⁺
12-39		H	Free form	Colorless crystal Melting point: 131-132°C
12-40		H	Free form	Colorless solid Melting point: 81-83°C
12-41		H	Free form	Colorless solid Melting point: 185-189°C
12-42		H	2HCl	Colorless powder MS APCI (m/z): 290 [M+H] ⁺
12-43		H	HCl	Colorless solid MS APCI (m/z): 356 [M+H] ⁺

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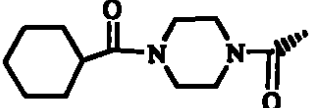
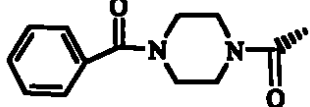
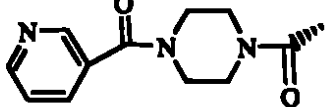
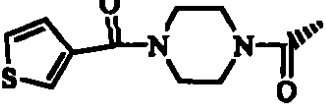
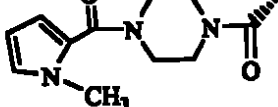
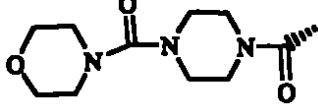
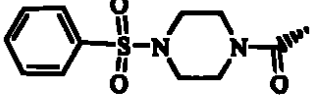
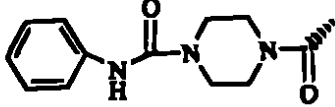
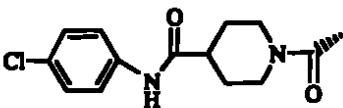
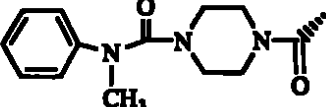
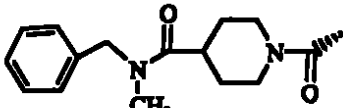
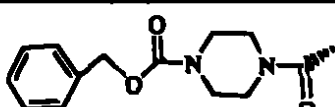
Table 8 (Continued)

Reference Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
12-44		H	Free form	Colorless crystal Melting point: 59-60°C
12-45		H	Free form	Colorless liquid MS APCI(m/z): 302
12-46		H	Free form	Colorless liquid MS APCI(m/z): 330 [M+H]
12-47		H	Free form	Colorless powder MS APCI(m/z): 301
12-48		H	Free form	Colorless liquid MS APCI(m/z): 358
12-49		H	Free form	Colorless crystal Melting point: 120-121°C
12-50		H	Free form	Pale yellowish crystal Melting point: 119-120°C
12-51		H	Free form	Colorless crystal Melting point: 144-145°C
12-52		H	Free form	Yellowish crystal Melting point: 140-141°C
12-53		H	Free form	Colorless crystal Melting point: 110-111°C
12-54		H	HCl	Colorless crystal Melting point: 97-°C MS APCI(m/z): 324 [M+H] ⁺
12-55		H	Free form	Colorless solid Melting point: 245-248°C

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Table 8 (Continued)

Reference Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
12-56		H	Free form	Colorless solid Melting point: 202-205°C
12-57		H	Free form	Colorless crystal Melting point: 150-153°C
12-58		H	Free form	Colorless liquid MS APCI (m/z): 317 [M+H]
12-59		H	Free form	Colorless crystal Melting point: 158-162°C
12-60		H	Free form	Colorless liquid MS APCI (m/z): 319 [M+H]
12-61		H	HCl	Colorless powder MS APCI (m/z): 325 [M+H] ⁺
12-62		H	Free form	Colorless crystal Melting point: 148-150°C
12-63		H	Free form	Colorless powder MS APCI (m/z): 331 [M+H] ⁺
12-64		H	Free form	Colorless resin MS APCI (m/z): 364 [M+H] ⁺
12-65		H	Free form	Colorless oil MS APCI (m/z): 345 [M+H] ⁺
12-66		H	Free form	Colorless oil MS APCI (m/z): 358 [M+H] ⁺
12-67		H	Free form	Colorless crystal Melting point: 70°C

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Table 8 (Continued)

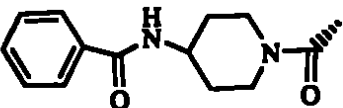
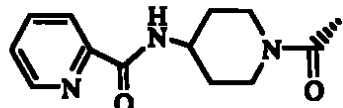
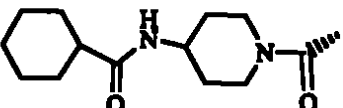
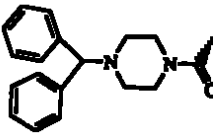
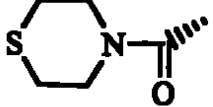
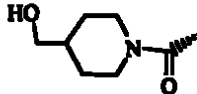
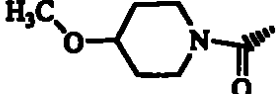
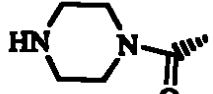
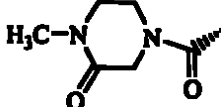
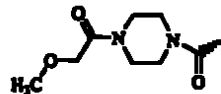
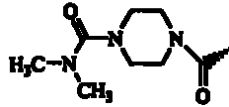
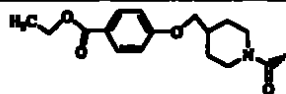
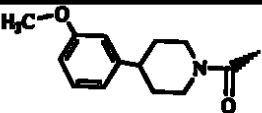
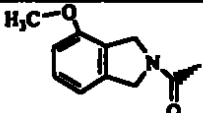
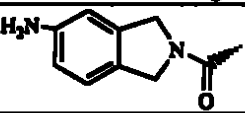
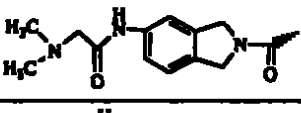
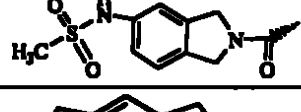
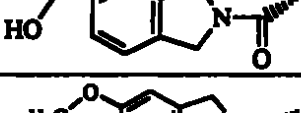
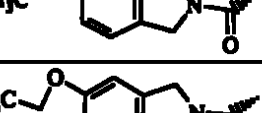
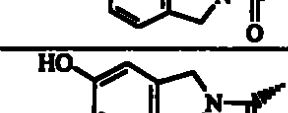
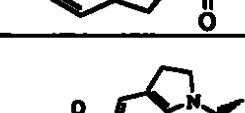
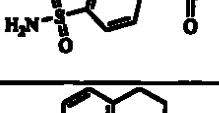
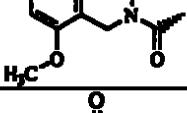
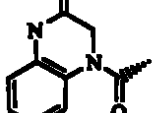
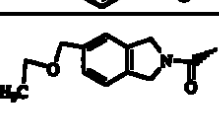
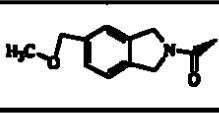
$\text{R}^2\text{-X}-\text{C}_6\text{H}_{10}-\text{C}(\text{R}^1)(\text{NH}_2)$				
Reference Example No	R ² -X-	R ¹	Salt	Physical properties, etc.
12-68		H	Free form	Colorless crystal Melting point: 188-190°C
12-69		H	2HCl	Colorless crystal Melting point: 180°C (Decomposed) MS APCI (m/z): 331 [M+H] ⁺
12-70		H	Free form	Slightly brownish crystal Melting point: 214-216°C
12-71		H	Free form	Colorless liquid MS APCI (m/z): 378 [M+H] ⁺
12-72		H	HCl	Colorless powder MS APCI (m/z): 229 [M+H] ⁺
12-73		H	Free form	Colorless oil MS APCI (m/z): 241
12-74		H	Free form	Colorless crystal MS APCI (m/z): 241
12-75		H	Free form	
12-76		H	Free form	Colorless oil MS APCI (m/z): 240
12-77		H	Free form	Colorless powder MS APCI (m/z): 284 [M+H] ⁺
12-78		H	Free form	Pale yellowish crystal Melting point: 99-104°C MS APCI (m/z): 283 [M+H] ⁺
12-79		H	Free form	Colorless resin MS APCI (m/z): 389 [M+H] ⁺

Table 8 (Continued)

Reference Example No	R ² -X-	R ¹	Salt	Physical properties, etc.
12-80		H	Free form	Colorless resin MS APCI (m/z): 317 [M+H] ⁺
12-81		H	Free form	Colorless powder MS APCI (m/z): 275 [M+H] ⁺
12-82		H	Free form	Colorless foam
12-83		H	Free form	Pale brownish resin
12-84		H	Free form	Pale brownish resin
12-85		H	Free form	Pale brownish resin
12-86		H	Free form	Colorless powder MS APCI (m/z): 275 [M+H] ⁺
12-87		H	Free form	Colorless powder MS APCI (m/z): 289 [M+H] ⁺
12-88		H	HCl	Colorless solid MS APCI (m/z): 261 [M+H] ⁺
12-89		H	HCl	Colorless solid Melting point: 277-279°C MS APCI (m/z): 324 [M+H] ⁺
12-90		H	HCl	Colorless solid MS APCI (m/z): 289 [M+H] ⁺
12-91		H	Free form	Colorless crystal MS APCI (m/z): 274
12-92		H	Free form	Pale brownish resin
12-93		H	Free form	Pale brownish resin

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Table 8 (Continued)

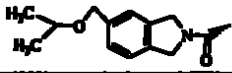
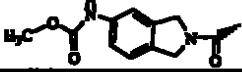
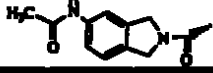
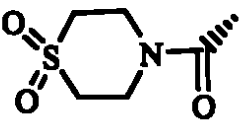
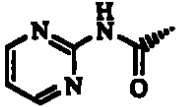
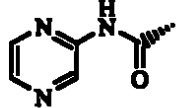
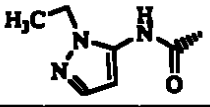
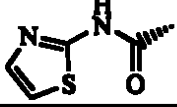
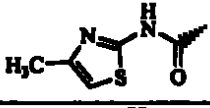
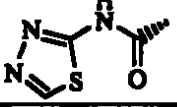
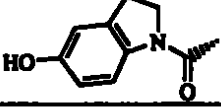
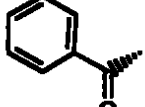
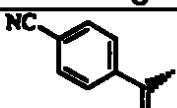
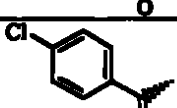
Reference Example No	R ² -X-	R ¹	Salt	Physical properties, etc.
12-94		H	Free form	Pale brownish resin
12-95		H	Free form	Pale brownish resin
12-96		H	Free form	Pale brownish resin
12-97		H	Free form	Colorless crystal Melting point: 152-153°C
13-1		H	Free form	Brownish oil MS APCI(m/z): 221 [M+H] ⁺
13-2		H	Free form	Pale yellowish powder MS APCI(m/z): 221 [M+H] ⁺
13-3		H	Free form	Pale yellowish oil MS APCI(m/z): 237 [M+H] ⁺
13-4		H	Free form	Brownish powder MS APCI(m/z): 226 [M+H] ⁺
13-5		H	Free form	Brownish oil MS APCI(m/z): 240 [M+H] ⁺
13-6		H	Free form	Brownish oil MS APCI(m/z): 227 [M+H] ⁺
13-7		H	HBr	Pale brownish powder MS APCI(m/z): 261 [M+H] ⁺
13-8		H	HI	Yellowish powder MS APCI(m/z): 204 [M+H]
13-9		H	HI	Yellowish powder MS APCI(m/z): 229 [M+H]
13-10		H	HI	Yellowish powder MS APCI(m/z): 238 [M+H]

Table 8 (Continued)

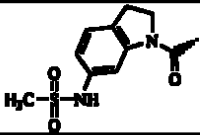
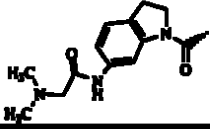
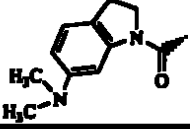
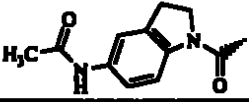
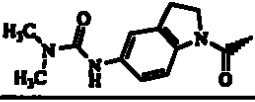
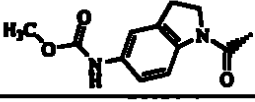
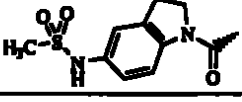
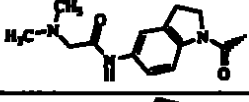
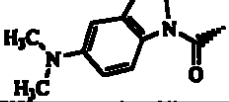
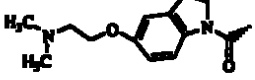
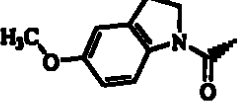
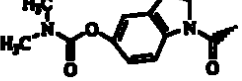
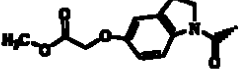
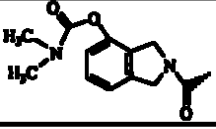
Reference Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
13-11		H	Free form	Yellowish powder MS APCI (m/z): 249 [M+H]
13-12		H	Free form	Yellowish powder MS APCI (m/z): 246 [M+H]
13-13		H	HI	Yellowish powder MS APCI (m/z): 194 [M+H]
13-14		H	HI	Yellowish powder MS APCI (m/z): 210 [M+H]
13-15		H	HI	Yellowish powder MS APCI (m/z): 260 [M+H]
13-16		H	2HI	Yellowish powder MS APCI (m/z): 205 [M+H]
13-17		Me	HI	Yellowish powder MS APCI (m/z): 227 [M+H]
13-18		H	Free form	Colorless semi-solid MS APCI (m/z): 270 [M+H]
13-19		H	Free form	Colorless semi-solid MS APCI (m/z): 312 [M+H]
13-20		H	Free form	Colorless resin MS APCI (m/z): 298 [M+H]
13-21		H	Free form	Colorless oil MS APCI (m/z): 332 [M+H]
13-22		H	HCl	Colorless powder Melting point: >300°C MS APCI (m/z): 336 [M+H]
13-23		H	HI	Brownish powder

Table 8 (Continued)

Reference Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
13-24		H	Free form	Pale brownish resin
13-25		H	Free form	Pale brownish resin
13-26		H	Free form	Pale brownish resin
13-27		H	Free form	Pale brownish resin
13-28		H	Free form	Pale brownish resin
13-29		H	Free form	Pale brownish resin
13-30		H	Free form	Pale brownish resin
13-31		H	Free form	Colorless powder MS APCI(m/z): 342 [M+H] ⁺
13-32		H	HI	Colorless powder MS APCI(m/z): 315 [M+H] ⁺
13-33		H	HI	Colorless powder MS APCI(m/z): 352 [M+H] ⁺
13-34		H	HI	Pale brownish powder
13-35		H	Free form	Brownish oil
13-36		H	Free form	Brownish oil
13-37		H	Free form	Brownish oil

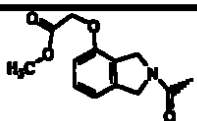
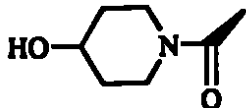
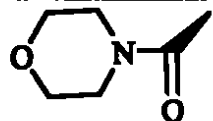
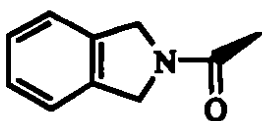
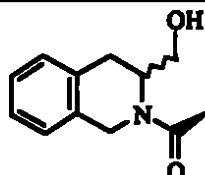
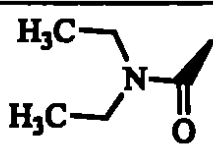
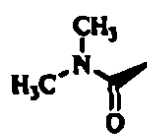
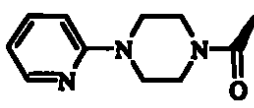
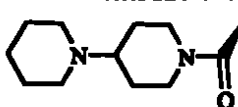
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Table 8 (Continued)

Reference Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
13-38		H	Free form	Brownish oil
13-39		H	Free form	Brownish oil
13-40		H	Free form	Brownish oil
13-41		H	Free form	
13-42		H	HI	Brownish powder
13-43		H	Free form	
13-44		H	Free form	
13-45		H	HI	Brownish powder
13-46		H	Free form	
13-47		H	Free form	Colorless crystal Melting point: 199-202°C MS APCI (m/z): 332 [M+H] ⁺
13-48		H	Free form	Pale brownish powder MS APCI (m/z): 275 [M+H] ⁺
13-49		H	Free form	Colorless powder MS APCI (m/z): 332 [M+H] ⁺
13-50		H	Free form	Colorless powder
13-51		H	Free form	Colorless powder MS APCI (m/z): 332 [M+H] ⁺

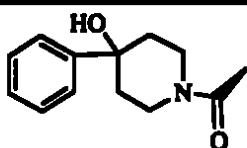
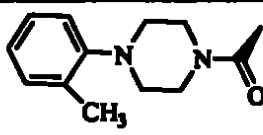
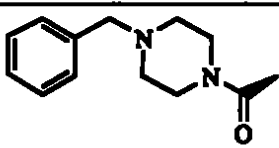
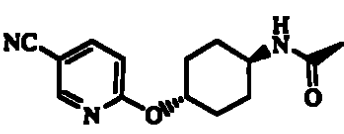
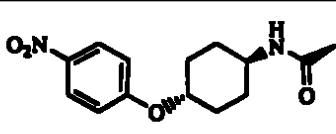
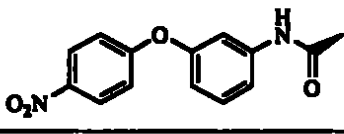
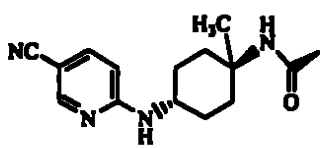
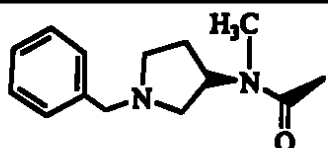
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Table 8 (Continued)

Reference Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
13-52		H	Free form	Colorless powder MS APCI (m/z): 333 [M+H] ⁺
14-1		H	HCl	Colorless resin MS APCI (m/z): 227 [M+H] ⁺
14-2		H	HCl	Colorless powder MS APCI (m/z): 213 [M+H] ⁺
14-3		H	Free form	Pale reddish crystal Melting point: 144-145°C
14-4		H	Free form	Colorless oil MS APCI (m/z): 289 [M+H] ⁺
14-5		H	HCl	Colorless powder MS APCI (m/z): 199 [M+H] ⁺
14-6		H	Free form	Pale yellowish oil MS APCI (m/z): 171 [M+H] ⁺
14-7		H	Free form	Colorless oil MS APCI (m/z): 289 [M+H] ⁺
14-8		H	2HCl	Brownish powder MS APCI (m/z): 294 [M+H] ⁺

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Table 8 (Continued)

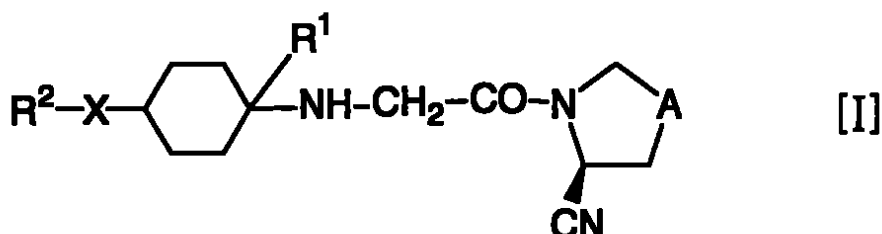
Reference Example No.	R ² -X-	R ¹	Salt	Physical properties, etc.
14-9		H	Free form	Colorless powder MS APCI (m/z) : 303 [M+H] ⁺
14-10		H	Free form	Colorless oil MS APCI (m/z) : 302 [M+H] ⁺
14-11		H	Free form	Colorless oil MS APCI (m/z)
14-12		H	Free form	Colorless crystal Melting point: 188-193°C
14-13		H	Free form	Pale yellowish crystal Melting point: 194-196°C
14-14		H	Free form	Slightly yellowish resin MS APCI (m/z) : 356 [M+H] ⁺
14-15		H	Free form	Slightly yellowish resin MS APCI (m/z) : 356 [M+H] ⁺
14-16		H	Free form	Brownish oil MS APCI (m/z) : 316 [M+H] ⁺

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CLAIMS

1. An aliphatic nitrogen-containing 5-membered ring compound represented by the formula [I]

5



wherein A represents -CH₂- or -S-,

R¹ represents hydrogen atom, a lower alkyl group, a hydroxy lower alkyl group or a lower alkoxy lower alkyl group,

10

X represents -N(R³)-, -O- or -CO-, where R³ represents hydrogen atom or a lower alkyl group, and

R² represents (1) a cyclic group which may be substituted, where the cyclic group portion is

15

(i) a monocyclic, bicyclic or tricyclic hydrocarbon group, or

(ii) a monocyclic, bicyclic or tricyclic heterocyclic group, or

(2) an amino group which may be substituted,

20

or a pharmaceutically acceptable salt thereof

2 The compound according to Claim 1, wherein R² is

(1) a cyclic group which may have 1 to 3 substituents which are the same or different and selected from the substi-

25

tuents of Group A mentioned below, where the cyclic group portion is (i) a monocyclic, bicyclic or tricyclic hydrocarbon group, or (ii) a monocyclic, bicyclic or tricyclic heterocyclic group, or

(2) an amino group which may have 1 or 2 substituents which

30

are the same or different and selected from the substituents of Group B mentioned below.

Substituents of Group A:

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- a halogen atom, cyano group; nitro group, oxo group;
hydroxy group, carboxy group, oxidyl group; amino group,
carbamoyl group, aminosulfonyl group; a lower alkyl group,
a lower alkoxy group, a lower alkanoyl group; a lower
5 alkoxycarbonyl group; a lower alkoxy-substituted lower
alkanoyl group,
a lower alkoxycarbonyl-substituted lower alkoxy group;
a lower alkoxycarbonyl-substituted lower alkoxycarbonyl
group;
10 a lower alkylthio group;
a lower alkylsulfonyl group;
a di-lower alkylamino-substituted lower alkoxy group;
a di-lower alkylaminocarboxy group,
a lower alkyl group substituted by group(s) selected from
15 amino group, carbamoyl group, a halogen atom, hydroxy group,
carboxy group, a lower alkoxy group and mono- or di-
substituted amino group;
a mono- or di-substituted amino group;
a mono- or di-substituted carbamoyl group,
20 a substituted or unsubstituted lower cycloalkyl group;
a substituted or unsubstituted lower cycloalkyl-CO-;
a substituted or unsubstituted lower cycloalkyl-lower alkyl
group;
a substituted or unsubstituted phenyl group;
25 a substituted or unsubstituted phenyl-O-;
a substituted or unsubstituted phenyl-CO-;
a substituted or unsubstituted phenyl-lower alkyl group;;
a substituted or unsubstituted phenyl-O-lower alkyl group;
a substituted or unsubstituted phenylsulfonyl group,
30 a substituted or unsubstituted phenyl-lower alkoxy group;
a substituted or unsubstituted phenyl-lower alkoxycarbonyl
group;
a substituted or unsubstituted lower cycloalkenyl group;
a substituted or unsubstituted bicyclic heterocyclic group;
35 a substituted or unsubstituted monocyclic 5- or 6-membered
heterocyclic group;

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a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group-O-,

a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group-CO-;

5 a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group-CO-lower alkyl group, and

a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group-lower alkyl group

Substituents of Group B

10 a lower alkyl group, a lower alkoxy-substituted lower alkyl group, a lower alkoxycarbonyl-substituted lower alkyl group; a hydroxy lower alkyl group, a carboxy lower alkyl group,

a substituted or unsubstituted lower cycloalkyl group;

15 a substituted or unsubstituted lower cycloalkyl-lower alkyl group,

a substituted or unsubstituted phenyl group;

a substituted or unsubstituted phenyl-lower alkyl group,,

a substituted or unsubstituted bicyclic hydrocarbon group,

20 a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group;

a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group-lower alkyl group, and

a substituted or unsubstituted bicyclic heterocyclic group-

25 lower alkyl group.

3 The compound according to Claim 2, wherein when the "substituent selected from the substituents of Group A" is a mono- or di-substituted amino lower alkyl group, a mono-
30 or di-substituted amino group or a mono- or di-substituted carbamoyl group, then the substituent has substituent(s) selected from the substituents of Group C mentioned below, when the "substituent selected from the substituents of Group A" is a substituted lower cycloalkyl group, a substi-
35 tuted lower cycloalkyl-CO-, a substituted lower cycloalkyl-lower alkyl group, a substituted phenyl group, a substi-

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tuted phenyl-O-, a substituted phenyl-CO-, a substituted phenyl-lower alkyl group, a substituted phenyl-O-lower alkyl group, a substituted phenylsulfonyl group, a substituted phenyl-lower alkoxy group, a substituted phenyl-lower alkoxy carbonyl group, a substituted lower cycloalkenyl group, a substituted bicyclic heterocyclic group, a substituted monocyclic 5- or 6-membered heterocyclic group, a substituted monocyclic 5- or 6-membered heterocyclic group-O-, a substituted monocyclic 5- or 6-membered heterocyclic group-CO-, a substituted monocyclic 5- or 6-membered heterocyclic group-CO-lower alkyl group or a substituted monocyclic 5- or 6-membered heterocyclic group-lower alkyl group, then the substituent has substituent(s) selected from a halogen atom, cyano group, nitro group, oxo group and the substituents of Group C mentioned below, and when the "substituent selected from the substituents of Group B" is a substituted lower cycloalkyl group, a substituted lower cycloalkyl-lower alkyl group, a substituted phenyl group, a substituted phenyl-lower alkyl group, a substituted bicyclic hydrocarbon group, a substituted monocyclic 5- or 6-membered heterocyclic group, a substituted monocyclic 5- or 6-membered heterocyclic group-lower alkyl group or a substituted bicyclic heterocyclic group-lower alkyl group, then the substituent has substituent(s) selected from the substituents of Group C mentioned below

Substituents of Group C

a lower alkyl group; a hydroxy-lower alkyl group, a lower alkanoyl group, a lower cycloalkylcarbonyl group; a lower alkoxy group, a lower alkoxy carbonyl group; a lower alkyl-sulfonyl group; a di-lower alkyl-substituted carbamoyl group; a di-lower alkylamino-substituted lower alkanoyl group,
a substituted or unsubstituted phenyl group,
a substituted or unsubstituted phenyl-O-,
a substituted or unsubstituted phenyl-CO-,
a substituted or unsubstituted phenyl-lower alkanoyl group;

a substituted or unsubstituted phenyl-lower alkyl group,
a substituted or unsubstituted phenyl-lower alkoxy group,
a substituted or unsubstituted monocyclic 5- or 6-membered
heterocyclic group,

- 5 a substituted or unsubstituted monocyclic 5- or 6-membered
heterocyclic group-O-;
a substituted or unsubstituted monocyclic 5- or 6-membered
heterocyclic group-CO-; and
a substituted or unsubstituted monocyclic 5- or 6-membered
10 heterocyclic group-substituted amino group;
(in the substituents of Group C, a substituent in the
substituted phenyl group portion or the substituted
monocyclic 5- or 6-membered heterocyclic group portion is
selected from a halogen atom, cyano group, nitro group, oxo
15 group, a lower alkyl group, a lower alkoxy group, a lower
alkanoyl group and a lower alkoxycarbonyl group).

4. The compound according to any one of Claims 1 to 3,
wherein R² is

- 20 (1) a cyclic group which may be substituted, where the
cyclic group portion is a group selected from the following
(i) to (iv)
(i) a monocyclic hydrocarbon group having 3 to 7 carbon
atoms,
25 (ii) a bicyclic hydrocarbon group having 9 to 11 carbon
atoms,
(iii) a monocyclic heterocyclic group containing 1 or 2
hetero atoms selected from nitrogen atom, oxygen atom and
sulfur atom, and
30 (iv) a bicyclic heterocyclic group containing 1 to 3 hetero
atoms selected from nitrogen atom, oxygen atom and sulfur
atom and comprising two 5- to 7-membered rings being fused,
or
(2) a substituted amino group.

35

5. The compound according to Claim 4, wherein R² is

(1) a cyclic group which may be substituted, where the cyclic group portion is a group selected from phenyl group, cyclohexyl group, cyclopentyl group, cyclobutyl group, cyclopropyl group, an indanyl group, an indenyl group, a naphthyl group, tetrahydronaphthyl, a pyrrolidinyl group, an imidazolidinyl group, a pyrazolidinyl group, an oxolanyl group, a thiolanyl group, a pyrrolinyl group, an imidazolinyl group, a pyrazolinyl group, a pyrrolyl group, an imidazolyl group, a pyrazolyl group, a triazolyl group, a tetrazolyl group, a furyl group, an oxazolyl group, an isoxazolyl group, an oxadiazolyl group, a thienyl group, a thiazolyl group, an isothiazolyl group, a thiadiazolyl group, a piperidyl group, a piperazinyl group, a morpholinyl group, a thiomorpholinyl group, a pyridyl group, a pyrimidinyl group, a pyrazinyl group, a pyridazinyl group, a pyranyl group, a tetrahydropyridyl group, a dihydropyridazinyl group, a perhydroazepinyl group, a perhydrothiazepinyl group, an indolinyl group, an isoindolinyl group, an indolyl group, an indazolyl group, an isoindolyl group, a benzimidazolyl group, a benzothiazolyl group, a benzoxazolyl group, a benzodioxolanyl group, a benzothienyl group, a benzofuryl group, a thienopyridyl group, a thiazolopyridyl group, a pyrrolopyridyl group, a dihydropyrrolopyridyl group, a quinolyl group, an isoquinolyl group, a quinoxalinyl group, a quinazolinyl group, a phthalazinyl group, a cinnolinyl group, a chromanyl group, an isochromanyl group, a naphthyridinyl group and partially or completely saturated cyclic groups thereof, or

(2) a substituted amino group.

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6. The compound according to Claim 5, wherein R² is

(1) a cyclic group which may be substituted, where the cyclic group portion is a group selected from the group consisting of phenyl group, cyclohexyl group, a pyrrolidinyl group, a tetrazolyl group, a furyl group, a thienyl group, a thiazolyl group, a piperidyl group, a piperazinyl

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group, a morpholinyl group, a thiomorpholinyl group, a pyridyl group, a pyrimidinyl group, a pyrazinyl group, a pyridazinyl group, a perhydroazepinyl group, an indolinyl group, an isoindolinyl group, a benzothienyl group, a

5 thienopyridyl group, a pyrrolopyridyl group, a dihydro-pyrrolopyridyl group, a quinolyl group, an isoquinolyl group, a quinoxalinyl group and partially or completely saturated cyclic groups thereof; or

(2) a substituted amino group.

10

7. The compound according to Claim 6, wherein R^2 is

(1) a cyclic group which may be substituted, where the cyclic group portion is a group selected from the group consisting of

15 a pyrrolidinyl group, a piperidyl group, a piperazinyl group, a morpholinyl group, a thiomorpholinyl group, a pyridyl group, a pyrimidinyl group, an indolinyl group, an isoindolinyl group, a pyrrolopyridyl group, a dihydro-pyrrolopyridyl group and partially or completely saturated

20 cyclic groups thereof; or

(2) a substituted amino group.

8. The compound according to any one of Claims 1 to 3, wherein R^2 is

25 (1) a cyclic group which may have 1 to 3 substituents which are the same or different and selected from the substituents of Group A' mentioned below, where the cyclic group portion is selected from the group consisting of

30 a pyrrolidinyl group, a piperidyl group, a piperazinyl group, a morpholinyl group, a thiomorpholinyl group, a pyridyl group, a pyrimidinyl group, an indolinyl group, an isoindolinyl group, a pyrrolopyridyl group, a dihydro-pyrrolopyridyl group and partially or completely saturated cyclic groups thereof, or

35 (2) an amino group substituted by 1 or 2 substituents which are the same or different and selected from the substitu-

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ents of Group B' mentioned below

Substituents of Group A':

- a halogen atom, cyano group, nitro group, oxo group, carbamoyl group, a lower alkyl group, a lower alkoxy group, a lower alkanoyl group, a lower alkoxycarbonyl group, a lower alkoxy-substituted lower alkyl group, a mono- or di-substituted amino group, a mono- or di-substituted carbamoyl group, a lower cycloalkyl-CO-,
- 10 a substituted or unsubstituted phenyl group, a substituted or unsubstituted phenyl-lower alkyl group, a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group, a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group-O-, and
- 15 a substituted or unsubstituted monocyclic 5- or 6-membered heterocyclic group-CO-.

Substituents of Group B'

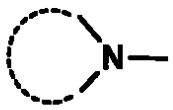
- a lower alkyl group, a lower cycloalkyl group, a lower alkoxy-substituted lower alkyl group, a pyrimidinyl group, a thiazolyl group and a thiadiazolyl group.
- 20

9. The compound according to any one of Claims 1 to 8, wherein X is -N(R³)- or -O-, and R² is a cyclic group which may be substituted.

25

10 The compound according to any one of Claims 1 to 8, wherein X is -CO-, and R² is (1) a monocyclic, bicyclic or tricyclic nitrogen-containing heterocyclic group which may be substituted or (2) an amino group which may be substituted, and represented by the formula.

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11. The compound according to any one of Claims 1 to 8,

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wherein X is -CO- or -O-, and A is -CH₂-

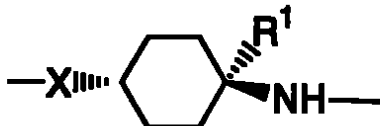
12 The compound according to any one of Claims 1 to 8,
wherein X is -CO- or -O-, A is -CH₂-, and R¹ is hydrogen
5 atom

13. The compound according to any one of Claims 1 to 8,
wherein X is -CO-, A is -CH₂-, and R¹ is hydrogen atom.

10 14. The compound according to any one of Claims 1 to 8,
wherein X is -CO-, A is -CH₂-, R¹ is hydrogen atom, and R²
is a cyclic group which may be substituted

15 15. The compound according to any one of Claims 1 to 8,
wherein X is -CO-, A is -CH₂-, R¹ is hydrogen atom, and R²
is a substituted amino group

16 The compound according to any one of Claims 1 to 15
which has a partial structure shown below.



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17 A compound selected from the group consisting of.

(S)-2-cyano-1-[trans-4-(5-nitro-2-pyridylamino)-
cyclohexylamino]acetylpyrrolidine,

25 (S)-2-cyano-1-[trans-4-(5-cyano-2-pyridyloxy)cyclo-
hexylamino]acetylpyrrolidine,

(S)-2-cyano-1-[trans-4-(dimethylaminocarbonyl)cyclo-
hexylamino]acetylpyrrolidine,

30 (S)-2-cyano-1-[trans-4-(morpholinocarbonyl)cyclo-
hexylamino]acetylpyrrolidine,

(S)-2-cyano-1-[trans-4-(5-bromo-2-pyrimidinylloxy)-
cyclohexylamino]acetylpyrrolidine,

(S)-2-cyano-1-[trans-4-(5-pyrimidinylaminocarbonyl)-
cyclohexylamino]acetylpyrrolidine;

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(S)-2-cyano-1-[trans-4-(N-ethyl-N-methoxyethylamino-carbonyl)cyclohexylamino]acetylpyrrolidine,

(S)-2-cyano-1-[trans-4-(N-ethyl-N-isopropylamino-carbonyl)cyclohexylamino]acetylpyrrolidine;

5 (S)-2-cyano-1-[trans-4-(N-methyl-N-butylamino-carbonyl)cyclohexylamino]acetylpyrrolidine;

(S)-2-cyano-1-[trans-4-[(S)-2-methoxymethylpyrrolidin-1-ylcarbonyl]cyclohexylamino]acetylpyrrolidine;

10 (S)-2-cyano-1-[trans-4-(3-carbamoylpiperidino-carbonyl)cyclohexylamino]acetylpyrrolidine;

(S)-2-cyano-1-[trans-4-(3-nitro-2-pyridylamino)-cyclohexylamino]acetylpyrrolidine,

(S)-2-cyano-1-[trans-4-(4-acetylpiperazin-1-yl-carbonyl)cyclohexylamino]acetylpyrrolidine,

15 (S)-2-cyano-1-[trans-4-(2-isoindolinylcarbonyl)-cyclohexylamino]acetylpyrrolidine;

(S)-2-cyano-1-[trans-4-[4-(3-pyridylcarbonyl)-piperazin-1-ylcarbonyl]cyclohexylamino]acetylpyrrolidine;

20 (S)-2-cyano-1-[trans-4-[4-(3-thenoyl)piperazin-1-yl-carbonyl]cyclohexylamino]acetylpyrrolidine,

(S)-2-cyano-1-[trans-4-[4-(4-chlorophenyl)piperazin-1-ylcarbonyl]cyclohexylamino]acetylpyrrolidine;

(S)-2-cyano-1-[trans-4-(cis-2,6-dimethylmorpholino-carbonyl)cyclohexylamino]acetylpyrrolidine,

25 (S)-2-cyano-1-[trans-4-(5-nitro-2-isoindolinyl-carbonyl)cyclohexylamino]acetylpyrrolidine,

(S)-2-cyano-1-[trans-4-(piperidinocarbonyl)cyclohexylamino]acetylpyrrolidine,

30 (S)-2-cyano-1-[trans-4-(4-carbamoylpiperidino-carbonyl)cyclohexylamino]acetylpyrrolidine,

(S)-2-cyano-1-[trans-4-(1-pyrrolidinylcarbonyl)-cyclohexylamino]acetylpyrrolidine,

(S)-2-cyano-1-[trans-4-(4-cyclopropylcarbonyl-piperazin-1-ylcarbonyl)cyclohexylamino]acetylpyrrolidine,

35 (S)-2-cyano-1-[trans-4-(4-propionylpiperazin-1-yl-carbonyl)cyclohexylamino]acetylpyrrolidine;

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(S) - 2-cyano-1- [trans-4- (1-indolinylcarbonyl) cyclohexylamino] acetylpyrrolidine;

(S) - 2-cyano-1- [trans-4- (2,3-dihydro-1H-pyrrolo[3,4-b]pyridin-2-ylcarbonyl) cyclohexylamino] acetylpyrrolidine,

5 (S) - 2-cyano-1- [trans-4- [4- (2-pyrimidinyl) - piperidinocarbonyl] cyclohexylamino] acetylpyrrolidine,

(S) - 2-cyano-1- [trans-4- [4- (5-bromo-2-pyrimidinyl) - piperidinocarbonyl] cyclohexylamino] acetylpyrrolidine,

10 (S) - 2-cyano-1- [trans-4- (cis-3,5-dimethyl-4-benzylpiperazin-1-ylcarbonyl) cyclohexylamino] acetylpyrrolidine,

(S) - 2-cyano-1- [trans-4- (4-cyclohexylcarbonylamino-piperidinocarbonyl) cyclohexylamino] acetylpyrrolidine,

(S) - 2-cyano-1- [trans-4- [4- (N-phenylcarbamoyl) - piperazin-1-ylcarbonyl] cyclohexylamino] acetylpyrrolidine,

15 (S) - 2-cyano-1- [trans-4- (4-ethoxycarbonylpiperazin-1-ylcarbonyl) cyclohexylamino] acetylpyrrolidine;

(S) - 2-cyano-1- [trans-4- [4- (2-thienyl) piperidinocarbonyl] cyclohexylamino] acetylpyrrolidine,

20 (S) - 2-cyano-1- [trans-4- (1,1-dioxoperhydro-1,4-thiazin-4-ylcarbonyl) cyclohexylamino] acetylpyrrolidine,

(R) - 4-cyano-3- [trans-4- (5-nitro-2-pyridylamino) - cyclohexylamino] acetylthiazolidine,

(R) - 4-cyano-3- [trans-4- (5-cyano-2-pyridyl) cyclohexylamino] acetylthiazolidine,

25 (R) - 4-cyano-3- [trans-4- (dimethylaminocarbonyl) cyclohexylamino] acetylthiazolidine,

(R) - 4-cyano-3- [trans-4- (2-isoindolinylcarbonyl) cyclohexylamino] acetylthiazolidine,

30 (R) - 4-cyano-3- [trans-4- (morpholinocarbonyl) cyclohexylamino] acetylthiazolidine, and

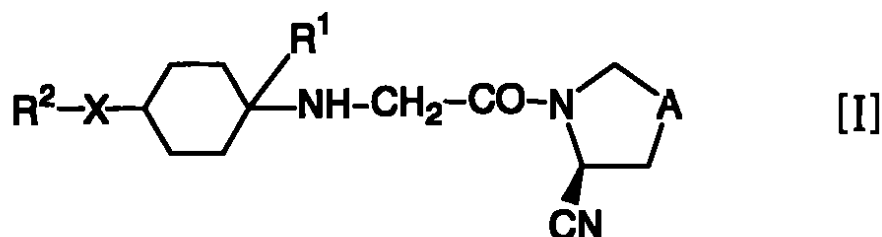
(R) - 4-cyano-3- [trans-4- (pyrrolidinylcarbonyl) cyclohexylamino] acetylthiazolidine,

or a pharmaceutically acceptable salt thereof

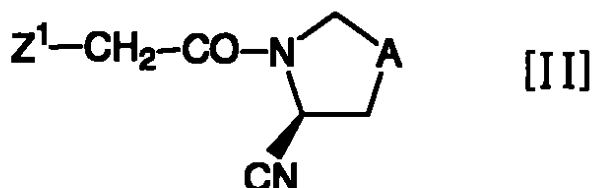
35 18 A method for preparing an aliphatic nitrogen-containing 5-membered ring compound represented by the

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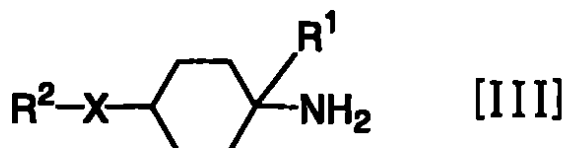
formula [I].



wherein A represents -CH₂- or -S-,
R¹ represents hydrogen atom, a lower alkyl group, a
5 hydroxy lower alkyl group or a lower alkoxy lower
alkyl group,
X represents -N(R³)-, -O- or -CO-, where R³ repre-
sents hydrogen atom or a lower alkyl group, and
R² represents (1) a cyclic group which may be
10 substituted, where the cyclic group portion
represents
(1) a monocyclic, bicyclic or tricyclic hydrocarbon
group, or
(ii) a monocyclic, bicyclic or tricyclic
15 heterocyclic group, or
(2) an amino group which may be substituted,
or a pharmaceutically acceptable salt thereof, which
comprises reacting a compound represented by the formula
[II].



20 wherein A has the same meaning as defined above and
Z¹ represents a reactive residue,
with a compound represented by the formula [III]:



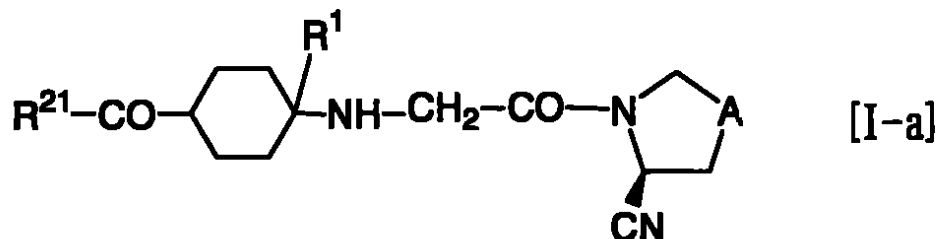
25 wherein R¹, X and R² has the same meaning as defined
above,

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or a salt thereof, and optionally making the product into a pharmaceutically acceptable salt thereof

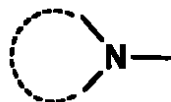
19. A method for preparing an aliphatic nitrogen-containing 5-membered ring compound represented by the formula [I-a]



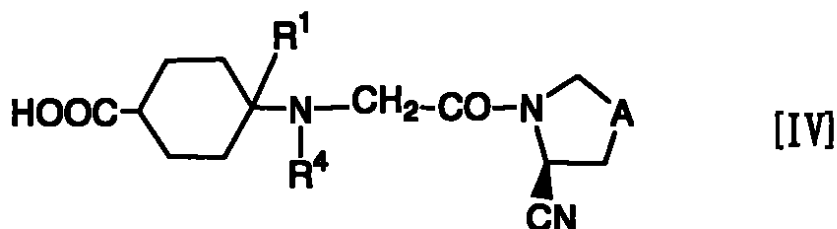
wherein A represents -CH₂- or -S-,

R¹ represents hydrogen atom, a lower alkyl group, a hydroxy lower alkyl group or a lower alkoxy lower alkyl group, and

R²¹ represents (1) a monocyclic, bicyclic or tricyclic nitrogen-containing heterocyclic group, which may be substituted or (2) an amino group which may be substituted, and represented by the formula:



or a pharmaceutically acceptable salt thereof, which comprises reacting a compound represented by the formula [IV]:



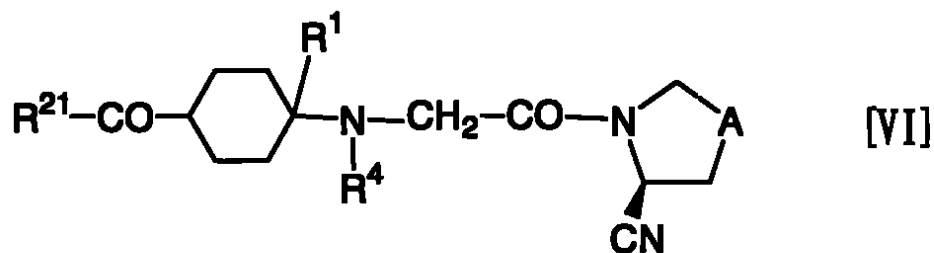
wherein A and R¹ have the same meanings as defined above and R⁴ represents a protective group for an amino group,

or a salt thereof with the compound represented by the formula [V]:



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wherein R^{21} has the same meaning as defined above,
or a salt thereof to obtain a compound represented by the
formula [VI]



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wherein R^1 , R^4 , R^{21} and A have the same meanings as
defined above,

or a salt thereof, and subsequently removing the protective
group for an amino group R^4 , and optionally making the
10 product into a pharmaceutically acceptable salt thereof.

15

20. A method for inhibiting dipeptidylpeptidase IV
activity by using the compound according to any one of
Claims 1 to 17.

15

21. A method for treatment or prophylaxis of a disease,
which comprises administering to a patient an effective
dose of the compound according to any one of Claims 1 to 17.

20

22 The method for treatment or prophylaxis of a disease
according to Claim 21, wherein the disease is expected to
be alleviated by inhibiting dipeptidylpeptidase IV activity

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23 The method for treatment or prophylaxis of a disease
according to Claim 21, wherein the disease is diabetes.

24 The method for treatment or prophylaxis of a disease
according to Claim 21, wherein the disease is type 2
diabetes.

30

25 Use of the compound according to any one of Claims 1
to 17 as an inhibitor of dipeptidylpeptidase IV.

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26. Use of the compound according to any one of Claims 1 to 17 as a pharmaceutically effective ingredient of a medicine.

5 27 Use of the compound according to any one of Claims 1 to 17 for the preparation of a medicine.

28 The use according to Claim 26 or 27, wherein the medicine is for the treatment or prophylaxis of a disease
10 that is expected to be improved by inhibiting dipeptidyl-peptidase IV activity.

29 The use according to Claim 26 or 27, wherein the medicine is for the treatment or prophylaxis of diabetes.
15

30 The use according to Claim 26 or 27, wherein the medicine is for the treatment or prophylaxis of type 2 diabetes.

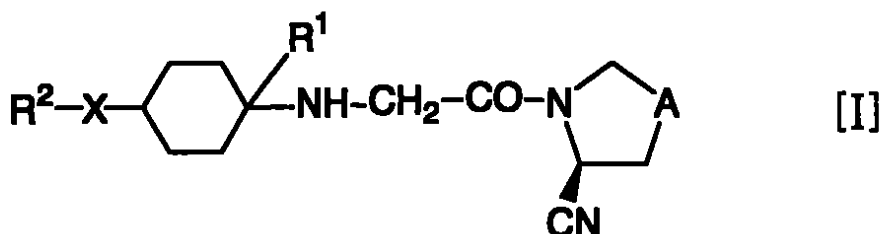
20 31 A pharmaceutical composition comprising the compound according to any one of Claims 1 to 17 as an effective ingredient.

32. The pharmaceutical composition according to Claim 31
25 wherein the pharmaceutical composition is a dipeptidyl-peptidase IV inhibitor.

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ABSTRACT

The present invention is to provide an aliphatic nitrogen-containing 5-membered ring compound represented by the formula [I]



wherein A represents -CH₂- or -S-,
R¹ represents hydrogen atom, a lower alkyl group, a hydroxy lower alkyl group or a lower alkoxy lower alkyl group,
X represents -N(R³)-, -O- or -CO-, where R³ represents hydrogen atom or a lower alkyl group, and
R² represents (1) a cyclic group which may be substituted, or (2) an amino group which may be substituted,
or a pharmaceutically acceptable salt thereof, a method for preparing the above-mentioned compound and a pharmaceutical composition comprising the above-mentioned compound as an effective ingredient.

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL

TRAMITE

		USUARIO	RADICADOR
PATENTE DE INVENCION	MODELO DE UTILIDAD	()	(x)
- Indicación de que se solicita la concesión de una patente		()	(y)
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.		()	(x)
- Descripción de la invención.		()	()
- Dibujos de ser estos pertinentes		()	(x)
- Comprobante de Pago de las tasas establecidas			
COMPLETA (x)	INCOMPLETA ()	()	()
DISEÑO INDUSTRIAL ()			
- Indicación de que se solicita el registro de Diseño Industrial		()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.		()	()
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño		()	()
- Comprobante de pago de las tasas establecidas		()	()
COMPLETA ()	INCOMPLETA	()	()
ESQUEMA DE TRAZADO ()			
- Indicación de que solicita el registro de un Esquema de trazado.		()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud.		()	()
- Representación gráfica del esquema de trazado		()	()
- Comprobante de pago de las tasas establecidas.		()	()
COMPLETA ()	INCOMPLETA	()	()

Firma Responsable:

Eduar Novillo

Fecha:

03-04-2003