

Q.F.
Industria y Comercio
SUPERINTENDENCIA

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

SOLICITUD
PATENTE DE INVENCION

21. EXPEDIENTE No.

03-98005

54. TÍTULO

Amenas Cielens De N-Aroilo.

51. CLASIFICACIÓN INTERNACIONAL

71. SOLICITANTE

SMITHKLINE BEECHAM P.L.C

DOMICILIO

980 Great West Road, BENTFORD
MIDDLESEX TW8 9GS. INGLATERRA.

74. APODERADO

Carlos R. Ovarre.

22. BOGOTÁ, D. C.,

Nov. 5 - 2003.

SS

PETITORIO

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Industria y Comercio
SUPERINTENDENCIA

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SUPERINDUSTRIA Y COMERCIO

Radicación : 83098005 00000000

Folios: 275

Fecha (AMD): 2003-11-05 16:39:37

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Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONESFORMULARIO 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: SMITHKLINE BEECHAM P.L.C.

Dirección: 980 Great West Road Brentford Middlesex TW8 9GS
Inglaterra.

Nacionalidad o Domicilio:

Lugar de Constitución: BRITANICA.

Teléfono:

Fax:

E-Mail

IDENTIFICACION

C.C. ☐ NIT ☐C.E. ☐ Otro ☐

Cual _____

Número _____

③

REPRESENTANTE
O APODERADO

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Fax: 6386201

E-Mail: filings@olarteraisbock.com

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C.C. ☒ NIT ☐C.E. ☐ Otro ☐

Cual _____

Número 79.782.747 Bta TP 74.295

④

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(72)

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Dirección: VER PAGINA ADJUNTA.

Nacionalidad o Domicilio: VER PAGINA ADJUNTA.

⑤

PCT (85)

Solicitud Internacional No. PCT/GB02/02042

Fecha Mayo 2, 2002

Publicación Internacional No. WO 02/090355

Fecha Noviembre 14, 2002

⑥

Título (54)

AMINAS CICLICAS DE N-AROILLO.

⑦

Clasificación Internacional (51)

AGI K31/445

⑧

Prioridad

SI ☒ NO ☐

(33) País de Origen

VER PAGINA ADJUN.

(32) Fecha

VER PAGINA ADJUNTA.

(31) Número de Solicitud

VER PAGINA ADJUNTA.

⑨

Comprobante de pago No. 75,585; 80,211; 72,454.

Fecha 10-17-03; 11-05-03; 10-06-03.

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

10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- ☒ Poderes, si fuere el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- ☐ Traducción del examen preliminar internacional efectuado por la IPEA
- ☐ De ser el caso, copia del contrato de acceso
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12 x 12
- ☒ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional.
- ☒ Otros: BUSQUEDA INTERNACIONAL

11

FIGURA CARACTERISTICA

12

Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA: 
C.C. 74.782.747 de Btá T.P. 74.295

3

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PRIORIDADES SOLICITUD PCT No. PCT/GB02/ 02042

15/5

PAIS DE ORIGEN	FECHA	NUMERO DE SOLICITUD
GB	Mayo 5, 2001	0111189.7
GB	Mayo 5, 2001	0111184.8
GB	Septiembre 3, 2001	0110570.9
GB	Diciembre 19, 2001	0130392.4
GB	Diciembre 19, 2001	0130331.2

11/6

SUPERINDUSTRIA Y COMERCIO
Folios: 275
Radicacion : 03090005 00000000
Fecha (AMD): 2003-11-05 16:39:37
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 75,585
FECHA : OCTUBRE 17 DE 2003

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PASO
FREDERICK TORRES	DEVOLUCION TASA			586	17/10/2003	335,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		85 EXAMEN DE PATENTABILIDAD DE INVEN	335,000.00
		TOTAL :	335,000.00

CON: TRESCIENTOS TREINTA Y CINCO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

7/7 7

SUPERINDUSTRIA Y COMERCIO
Radicacion : 83898805 00000000 Folios: 275
Fecha (AMD): 2003-11-05 16:39:37
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 80,211
FECHA : NOVIEMBRE 5 DE 2003

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
FREDERICK TORRES	CONSIGNACION	BANCO POPULAR	050-00110-6	19921979	05/11/2003	1,310,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
50 50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	20 FOTOCOPIAS (CADA HOJA)	5,000.00
	TOTAL :	\$ 5,000.00

SON: CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

7/8
8

SUPERINDUSTRIA Y COMERCIO
Radicacion : 83898085 80000000 Folios: 275
Fecha (AMD): 2003-11-05 16:39:37
Tramite : 011 PCT-PATENT 379 FASE HACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 72,454
FECHA : OCTUBRE 6 DE 2003

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
FREDERICK TORRES	CONSIGNACION	BANCO POPULAR	050-00110-6	13988274	06/10/2003	4,950,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-00	PRORROGA DE TERMINOS	60,000.00
		31 PRORROGA DE TERMINOS	60,000.00
		TOTAL :	\$ 60,000.00

SON: SESENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

**APOSTILLA EN PODER DE REPRESENTACIÓN DE
SMITHKLINE BEECHAM P.L.C.**

PODER DE REPRESENTACION

Bilingüe inglés- español otorgado en Brentford, Middlesex, Inglaterra el 13 de agosto de 2003 y firmado por Peter John Giddings, Apoderado y Funcionario autorizado.

Certificado de Notario De Pinna en español certificando que Peter John Giddings es apoderado de Smithkline Beecham p.l.c. firmado por James Kerr Milligan

APOSTILLA

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

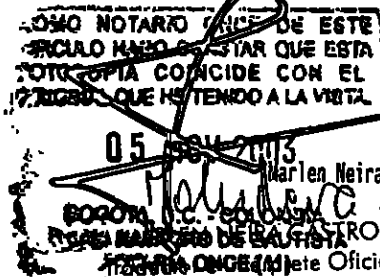
1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
- Este documento Público
2. ha sido firmado por James Kerr Milligan
3. Quien ejerce funciones de Notario público
4. Lleva el sello del Notario público

CERTIFICADO

5. En Londres
6. El 14 agosto 2003
7. Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la Mancomunidad
8. No. G229471
9. Gran Sello de la Oficina de Asuntos exteriores y de la Mancomunidad
10. Firma legible de J. Garbrah- Por el Secretario de Estado

Si el documento se usa en un país que no pertenece a la Convención de la Haya del 5 de octubre de 1961 debe pasar por la sección consular de la Misión que representa el país.

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 21 agosto-03.



Resolución No. 2117 del 7 Oct 1987

Yo, el infrascrito **JAMES KERR MILLIGAN**, Notario Público de la Ciudad de Londres, Inglaterra, por la Autoridad Real debidamente admitido y juramentado,

CERTIFICO:

QUE es auténtica la firma suscrita al pie del adjunto Poder, por ser del puño y letra del Señor Don **PETER JOHN GIDDINGS**, cuya identidad me consta, Apoderado de la Sociedad inglesa denominada "**SMITHKLINE BEECHAM p.l.c.**", Sociedad legalmente constituida y existente de acuerdo con las leyes de Inglaterra, e inscrita en la Oficina de Registro de Sociedades bajo el número **2337959**, con domicilio social en **980 Great West Road, Brentford, Middlesex TW8 9GS, Inglaterra;**

QUE el citado Señor Don **PETER JOHN GIDDINGS** está debida y suficientemente autorizado para firmar documentos de esta clase, en virtud del Poder otorgado en su favor por la referida Sociedad fechado el **30 de enero de 2003**, copia del cual he tenido a la vista;

Y QUE los objetos para los cuales se otorgó dicho Poder se encuentran dentro de los objetos o actividades de la citada Sociedad, de acuerdo con la Escritura Constitutiva y los Estatutos Sociales, los cuales he tenido a la vista.

Y PARA QUE CONSTE donde y como convenga y fuere necesario expido el presente Certificado que firmo y sello en Londres, el día de hoy trece de agosto del año dos mil tres.

COMO NOTARIO ENCE DE ESTE
CERTIFICADO MANDO QUE ESTA
FOTOCOPIA COINCIDE CON EL
ORIGINAL QUE HE TENIDO A LA VISTA

05 NOV 2003

JAMES KERR MILLIGAN, P.C. - COLOMBIA
Notario Público de Londres, Inglaterra

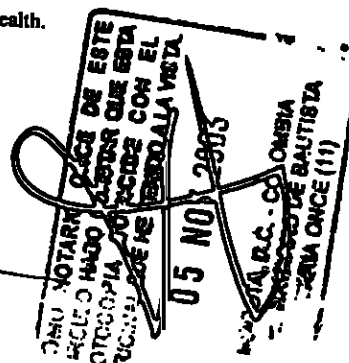
SCRIVENER
NOTARIES



APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord
This public document / Le présent acte public
2. Has been signed by **James Kerr Milligan**
a été signé par
3. Acting in the capacity of **Notary Public**
agissant en qualité de
4. Bears the seal/stamp of **The Said Notary Public**
est revêtu du sceau/timbre de
5. at London/à Londres
6. Certified/Attesté
the/le 14 August 2003
7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.
8. Number/sous No **G229471**
9. Stamp:
timbre:
10. Signature: **J. Garbrah**



For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961,
it should be presented to the consular section of the mission representing that country.

OLARTE RAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER - TORRE C
CALLE 100 No. 8A-55 Piso 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
Fax: +57-1 638-6201

www.olarteraisbeck.com

Power of Attorney

The undersigned,

domiciled in

980 Great West Road, Brentford, Middlesex TW8 9GS, GB
by means of these presents hereby grants to **Carlos R. Olarte, J. Ian Raisbeck and Ana María Frieri** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's Patents, Utility Models and Industrial Designs in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, appeals, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

Signature/Firma: _____


Peter John GIDDINGS as Attorney and Authorised

Date/Fecha: 13 August 2003

City/Country/Ciudad, País: Brentford, Middlesex, England

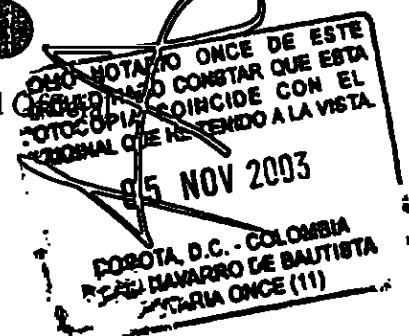
Poder

El suscrito,

SmithKline Beecham p.l.c.

domiciliado en

980 Great West Road, Brentford, Middlesex TW8 9GS, GB
por medio del presente otorga a **Carlos R. Olarte, J. Ian Raisbeck y Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de Patentes, Modelos de Utilidad y Diseños Industriales de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, apelaciones, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.



(19) World Intellectual Property Organization
International Bureau

PCT

(43) International Publication Date
14 November 2002 (14.11.2002)

PCT

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WO 02/090355 A1(51) International Patent Classification⁷: C07D 417/14,
A61K 31/445, C07D 413/12, 413/14, 401/12, A61K
31/505, C07D 471/04, A61K 31/5377, C07D 401/14,
498/04, 403/14, A61P 25/20, 9/10, 3/04.

(21) International Application Number: PCT/GB02/02042

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0121303.2	3 September 2001 (03.09.2001)	GB
0130392.4	19 December 2001 (19.12.2001)	GB
0130331.2	19 December 2001 (19.12.2001)	GB

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(72) Inventors; and

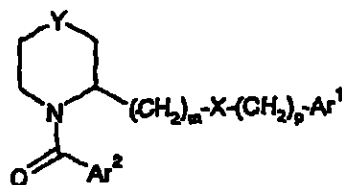
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lectual Property, GlaxoSmithKline, CN925.1, 980 Great West
Road, Brentford, Middlesex TW8 9GS (GB).(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CI, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VN, YU, ZA, ZM, ZW.(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
(BF, BJ, CH, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: N-AROYL CYCLIC AMINES



(1)

(57) Abstract: This invention relates to *N*-aryl
cyclic amine derivatives and their use as orexin
antagonists wherein: Y represents a bond, oxygen,
or a group (CH₂)_n, wherein n represents 1, 2 or 3;
m represents 1, 2, or 3; p represents 0 or 1; X is
NR, wherein R is H or (C₁₋₄)alkyl; Ar¹ is aryl, or
a mono or bicyclic heteroaryl group containing up
to 3 heteroatoms selected from N, O and S; any ofwhich may be optionally substituted; Ar² represents phenyl or a 5- or 6-membered heterocyclyl group containing up to 3 heteroatoms
selected from N, O and S, wherein the phenyl or heterocyclyl group is substituted by R¹ and further optional substituents; or Ar²
represents an optionally substituted bicyclic aromatic or bicyclic heteroaromatic group containing up to 3 heteroatoms selected from
N, O and S; R¹ represents hydrogen, optionally substituted (C₁₋₄)alkoxy, halo, cyano, optionally substituted (C₁₋₄)alkyl, optionally
substituted phenyl, or an optionally substituted 5- or 6- membered heterocyclyl group containing up to 4 heteroatoms selected from
N, O and S; when Ar¹ is aryl p is not 1; or a pharmaceutical acceptable salt thereof.

WO 02/090355 A1

N-AROYL CYCLIC AMINES

This invention relates to *N*-aroyl cyclic amine derivatives and their use as pharmaceuticals.

Many medically significant biological processes are mediated by proteins participating in signal transduction pathways that involve G-proteins and/or second messengers.

Polypeptides and polynucleotides encoding the human 7-transmembrane G-protein coupled neuropeptide receptor, orexin-1 (HFGAN72), have been identified and are disclosed in EP-A-875565, EP-A-875566 and WO 96/34877. Polypeptides and polynucleotides encoding a second human orexin receptor, orexin-2 (HFGANP), have been identified and are disclosed in EP-A-893498.

Polypeptides and polynucleotides encoding polypeptides which are ligands for the orexin-1 receptor, e.g. orexin-A (Lig72A) are disclosed in EP-A-849361.

Orexin receptors are found in the mammalian host and may be responsible for many biological functions, including pathologies including, but not limited to, depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis/disorder; depressive neurosis/disorder; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; sex disorder; sexual disorder; schizophrenia; manic depression; delirium; dementia; severe mental retardation and dyskinesias such as Huntington's disease and Gilles de la Tourette's syndrome; disturbed biological and circadian rhythms; feeding disorders, such as anorexia, bulimia, cachexia, and obesity; diabetes; appetite/taste disorders; vomiting/nausea; asthma; cancer; Parkinson's disease; Cushing's syndrome / disease; basophil adenoma; prolactinoma; hyperprolactinemia; hypopituitarism; hypophysis tumor / adenoma; hypothalamic diseases; Froehlich's syndrome; adrenohypophysis disease; hypophysis disease; hypophysis tumor / adenoma; pituitary growth hormone; adrenohypophysis hypofunction; adrenohypophysis hyperfunction; hypothalamic hypogonadism; Kallman's syndrome (anosmia, hyposmia); functional or psychogenic amenorrhea; hypopituitarism; hypothalamic hypothyroidism; hypothalamic-adrenal dysfunction; idiopathic hyperprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth hormone deficiency; dwarfism; gigantism; acromegaly; disturbed biological and circadian rhythms; and sleep disturbances associated with such diseases as neurological disorders, neuropathic pain and restless leg syndrome, heart and lung diseases; acute and congestive heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardial infarction; ischaemic or haemorrhagic stroke; subarachnoid haemorrhage; head injury such as sub-arachnoid haemorrhage associated with traumatic head injury; ulcers; allergies; benign prostatic hypertrophy; chronic renal failure; renal disease; impaired glucose tolerance; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain, such as hyperalgesia, causalgia and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndromes I and II; arthritic pain; sports injury pain; pain related to infection, e.g. HIV, post-polio syndrome, and post-herpetic neuralgia; phantom limb pain; labour pain; cancer pain; post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; nausea and vomiting; conditions associated with visceral pain

1744
14

including irritable bowel syndrome, migraine and angina; urinary bladder incontinence e.g. urge incontinence; tolerance to narcotics or withdrawal from narcotics; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; and neurodegenerative disorders, which includes nosological entities such as disinhibition-dementia-parkinsonism-amyotrophy complex; pallido-ponto-nigral degeneration, epilepsy, and seizure disorders.

Experiments have shown that central administration of the ligand orexin-A (described in more detail below) stimulated food intake in freely-feeding rats during a 4 hour time period. This increase was approximately four-fold over control rats receiving vehicle. These data suggest that orexin-A may be an endogenous regulator of appetite. Therefore, antagonists of its receptor may be useful in the treatment of obesity and diabetes, see *Cell*, 1998, 92, 573-585.

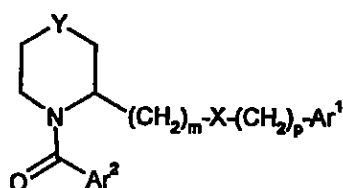
There is a significant incidence of obesity in westernised societies. According to WHO definitions a mean of 35% of subjects in 39 studies were overweight and a further 22% clinically obese. It has been estimated that 5.7% of all healthcare costs in the USA are a consequence of obesity. About 85% of Type 2 diabetics are obese, and diet and exercise are of value in all diabetics. The incidence of diagnosed diabetes in westernised countries is typically 5% and there are estimated to be an equal number undiagnosed. The incidence of both diseases is rising, demonstrating the inadequacy of current treatments which may be either ineffective or have toxicity risks including cardiovascular effects. Treatment of diabetes with sulfonylureas or insulin can cause hypoglycaemia, whilst metformin causes GI side-effects. No drug treatment for Type 2 diabetes has been shown to reduce the long-term complications of the disease. Insulin sensitisers will be useful for many diabetics, however they do not have an anti-obesity effect.

Rat sleep/EEG studies have also shown that central administration of orexin-A, an agonist of the orexin receptors, causes a dose-related increase in arousal, largely at the expense of a reduction in paradoxical sleep and slow wave sleep 2, when administered at the onset of the normal sleep period. Therefore antagonists of its receptor may be useful in the treatment of sleep disorders including insomnia.

The present invention provides *N*-aroyl cyclic amine derivatives which are non-peptide antagonists of human orexin receptors, in particular orexin-1 receptors. In particular, these compounds are of potential use in the treatment of obesity, including obesity observed in Type 2 (non-insulin-dependent) diabetes patients, and/or sleep disorders. Additionally these compounds are useful in the treatment of stroke, particularly ischemic or haemorrhagic stroke, and/or blocking the emetic response, i.e. useful in the treatment of nausea and vomiting.

International Patent Applications WO99/09024, WO99/58533, WO00/47577 and WO00/47580 disclose phenyl urea derivatives and WO00/47576 discloses quinolinyl cinnamide derivatives as orexin receptor antagonists. WO01/96302 discloses *N*-aroyl cyclic amine derivatives.

According to the invention there is provided a compound of formula (I):



(I)

wherein:

Y represents a bond, oxygen, or a group $(CH_2)_n$, wherein n represents 1, 2 or 3

m represents 1, 2, or 3;

p represents 0 or 1;

X is NR, wherein R is H or (C_{1-4}) alkyl;

Ar^1 is aryl, or a mono or bicyclic heteroaryl group containing up to 3 heteroatoms selected from N, O and S; any of which may be optionally substituted;

Ar^2 represents phenyl or a 5- or 6-membered heterocyclyl group containing up to 3 heteroatoms selected from N, O and S, wherein the phenyl or heterocyclyl group is substituted by R^1 and further optional substituents; or Ar^2 represents an optionally substituted bicyclic aromatic or bicyclic heteroaromatic group containing up to 3 heteroatoms selected from N, O and S;

R^1 represents hydrogen, optionally substituted (C_{1-4}) alkoxy, halo, cyano, optionally substituted (C_{1-6}) alkyl, optionally substituted phenyl, or an optionally substituted 5- or 6-membered heterocyclyl group containing up to 4 heteroatoms selected from N, O and S;

wherein when Y is a bond Ar^2 can not be 2-naphthyl;

when Ar^1 is aryl p is not 1;

or a pharmaceutically acceptable salt thereof.

X is preferably NH.

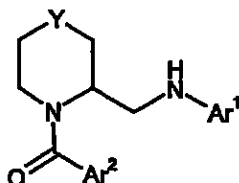
m is preferably 1.

p is preferably 0.

Even more preferably m is 1 when p is 0.

Preferably R is hydrogen.

Alternatively compounds of formula (I) are compounds of formula (Ia);



(Ia)

wherein:

Y represents a bond, oxygen, or a group $(CH_2)_n$, wherein n represents 1, 2 or 3

Ar^1 is a mono or bicyclic heteroaryl group containing up to 3 heteroatoms selected from N, O and S; any of which may be optionally substituted;

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Ar² represents phenyl or a 5- or 6-membered heterocyclyl group containing up to 3 heteroatoms selected from N, O and S, wherein the phenyl or heterocyclyl group is substituted by R¹ and further optional substituents; or Ar² represents an optionally substituted bicyclic aromatic or bicyclic heteroaromatic group containing up to 3 heteroatoms selected from N, O and S;

R¹ represents hydrogen, optionally substituted(C₁₋₄)alkoxy, halo, cyano, optionally substituted(C₁₋₆)alkyl, optionally substituted phenyl, or an optionally substituted 5- or 6-membered heterocyclyl group containing up to 4 heteroatoms selected from N, O and S; wherein when Y is a bond then Ar² can not be 2-naphthyl; or pharmaceutically acceptable salts thereof.

Preferably where Ar² represents phenyl or a 5- or 6-membered heterocyclyl group containing up to 3 heteroatoms selected from N, O and S, the R¹ group is situated adjacent to the point of attachment to the amide carbonyl.

Y is preferably a bond, oxygen or (CH₂)_n wherein n is 1 or 2.

Even more preferably Y is a bond, oxygen or (CH₂)_n wherein n is 1

Alternatively R¹ represents hydrogen, optionally substituted(C₁₋₄)alkoxy, halo, optionally substituted(C₁₋₆)alkyl, optionally substituted phenyl or an optionally substituted 5- or 6-membered heterocyclyl group containing up to 3 heteroatoms selected from N, O and S.

Alternatively R¹ represents optionally substituted(C₁₋₄)alkoxy, halo, optionally substituted(C₁₋₆)alkyl, optionally substituted phenyl or an optionally substituted 5- or 6-membered heterocyclyl group containing up to 3 heteroatoms selected from N, O and S.

Preferably R¹ is selected from trifluoromethoxy, methoxy, ethoxy, halo, cyano or an optionally substituted phenyl, pyridyl, pyrazolyl, pyrimidinyl, or oxadiazolyl group.

More preferably R¹ is selected from trifluoromethoxy, methoxy, ethoxy, halo, or an optionally substituted phenyl, pyridyl, pyrazolyl, pyrimidinyl, or oxadiazolyl group.

When Ar¹ is optionally substituted aryl it is preferably phenyl. Ar¹ may have up to 5, preferably 1, 2 or 3 optional substituents.

Examples of when Ar¹ is a mono or bicyclic heteroaryl are quinoxaliny, quinazolinyl, pyridopyrazinyl, benzoxazolyl, benzothiophenyl, benzimidazolyl, naphthyridinyl, pyridinyl, pyrimidinyl, or thiazolyl. Additionally Ar¹ can be selected from pyridazinyl, pyrazinyl, oxazolyl, triazolyl, imidazolyl, pyrazolyl, quinolinyl, benzofuranyl, indolyl, benzothiazolyl, oxazolyl[4,5-b]pyridinyl, pyridopyrimidinyl or isoquinolinyl. Furthermore Ar¹ can be furanyl or thienyl.

Preferably Ar¹ is benzoxazolyl, benzimidazolyl, quinoxaliny, quinazolinyl, pyrimidinyl, pyridinyl, naphthyridinyl. Additionally Ar¹ can be quinolinyl, pyridopyrimidine, thiazolyl, oxazolylpyridinyl, benzothiazolyl, isoquinolinyl or pyrazinyl.

More preferably Ar¹ is benzoxazolyl, benzimidazolyl, quinoxaliny, quinazolinyl, pyrimidinyl, pyridinyl, naphthyridinyl or oxazolyl[4,5-b]pyridinyl.

When Ar² is a 5- or 6-membered heterocyclyl group containing up to 3 heteroatoms selected from N, O and S, it may be furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazinyl, pyrimidinyl, isothiazolyl, isoxazolyl, pyrazinyl or pyrazolyl.

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When R^1 is a 5- or 6-membered heterocyclyl group containing up to 4 heteroatoms selected from N, O and S, it may be furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazinyl, pyrimidinyl, isothiazolyl, isoxazolyl, pyrazinyl or pyrazolyl. Additionally it can be tetrazolyl, piperazinyl, piperidinyl, morpholinyl or thiomorpholinyl.

Preferably when R^1 is a 5- or 6-membered heterocyclic ring containing up to 4 heteroatoms selected from N, O and S, it is furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazinyl, pyrimidinyl, isothiazolyl, isoxazolyl, pyrazinyl or pyrazolyl.

Preferably R^1 is a 5- or 6-membered heterocyclic ring it contains up to 3 heteroatoms selected from N, O and S.

When Ar^2 is an optionally substituted bicyclic aromatic or bicyclic heteroaromatic it is selected from benzofuryl, benzimidazolyl, quinoliny, quinoxaliny or naphthyl. Additionally it may be benzotriazolyl, benzothieryl, benzoxazolyl, naphthyridinyl, isoquinoliny or quinazoliny. Furthermore it can be indolyl, benzothiazolyl, or benzothiadiazolyl.

Preferably Ar^2 represents optionally substituted phenyl, pyridyl, thiazolyl, pyrazolyl, benzofuryl, naphthyl, triazolyl, quinoxaliny, quinoliny, isoquinoliny, benzimidazolyl, benzothieryl, benzotriazolyl, benzothiazolyl, indolyl or thienyl.

Alternatively Ar^2 represents optionally substituted phenyl, pyridyl, thiazolyl, pyrazolyl, benzofuryl, naphthyl or triazolyl. Preferably the triazolyl is 1,2,3-triazolyl.

More preferably Ar^2 represents optionally substituted thiazolyl, pyrazolyl or quinoliny.

Alternatively R^1 is selected from trifluoromethoxy, methoxy, halo, or an optionally substituted phenyl, pyridyl, pyrazolyl or oxadiazolyl group

Even more preferably R^1 represents a trifluoromethoxy group, methoxy group, iodo, or an optionally substituted phenyl, pyridyl, or oxadiazolyl group.

Optional substituents for the groups Ar^1 , Ar^2 , R and R^1 include halogen, hydroxy, oxo, cyano, nitro, (C_{1-4}) alkyl, (C_{1-4}) alkoxy, hydroxy (C_{1-4}) alkyl, hydroxy (C_{1-4}) alkoxy, halo (C_{1-4}) alkyl, halo (C_{1-4}) alkoxy, aryl (C_{1-4}) alkoxy, (C_{1-4}) alkylthio, hydroxy (C_{1-4}) alkyl, (C_{1-4}) alkoxy (C_{1-4}) alkyl, (C_{3-6}) cycloalkyl (C_{1-4}) alkoxy, (C_{1-4}) alkanoyl, (C_{1-4}) alkoxycarbonyl, (C_{1-4}) alkylsulfonyl, (C_{1-4}) alkylsulfonyloxy, (C_{1-4}) alkylsulfonyl (C_{1-4}) alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonyl (C_{1-4}) alkyl, (C_{1-4}) alkylsulfonamido, (C_{1-4}) alkylamido, (C_{1-4}) alkylsulfonamido (C_{1-4}) alkyl, (C_{1-4}) alkylamido (C_{1-4}) alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamido (C_{1-4}) alkyl, arylcarboxamido (C_{1-4}) alkyl, aroyl, aroyl (C_{1-4}) alkyl, or aryl (C_{1-4}) alkanoyl group; a group R^aR^bN- , $R^aOCO(CH_2)_r$, $R^aCON(R^b)(CH_2)_r$, $R^aR^bNCO(CH_2)_r$, $R^aR^bNSO_2(CH_2)_r$ or $R^aSO_2NR^b(CH_2)_r$, where each of R^a and R^b independently represents a hydrogen atom or a (C_{1-4}) alkyl group or where appropriate R^aR^b forms part of a (C_{3-6}) azacycloalkane or (C_{3-6}) (2-oxo)azacycloalkane ring and r represents zero or an integer from 1 to 4. Additional substituents are (C_{1-4}) acyl, aryl, aryl (C_{1-4}) alkyl, (C_{1-4}) alkylamino (C_{1-4}) alkyl, $R^aR^bN(CH_2)_n-$, $R^aR^bN(CH_2)_nO-$, wherein n represents an

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integer from 1 to 4. Additionally when the substituent is $R^aR^bN(CH_2)_n$ - or $R^aR^bN(CH_2)_nO$, R^a with at least one CH_2 of the $(CH_2)_n$ portion of the group form a (C_{3-6}) azacycloalkane and R^b represents hydrogen, a (C_{1-4}) alkyl group or with the nitrogen to which it is attached forms a second (C_{3-6}) azacycloalkane fused to the first (C_{3-6}) azacycloalkane.

5 Preferred optional substituents for Ar^2 are halogen, cyano, (C_{1-4}) alkyl. Additional preferred optional substituents are hydroxy (C_{1-4}) alkyl, (C_{1-4}) alkoxy (C_{1-4}) alkyl, $R^aR^bN(CH_2)_n$, R^aR^bN . Further optional substituents for Ar^2 can also be halogen, cyano, (C_{1-4}) alkyl, $R^aR^bN(CH_2)_nO$ or (C_{1-4}) alkoxy.

10 Preferred optional substituents for Ar^1 are halogen, cyano, (C_{1-4}) alkanoyl. Other preferred substituents are hydroxy (C_{1-4}) alkyl, (C_{1-4}) alkyl or CF_3 .

Preferred optional substituents for R^1 are halogen, (C_{1-4}) alkoxy (C_{1-4}) alkyl, R^aR^bN , $R^aR^bN(CH_2)_nO$ and $R^aR^bN(CH_2)_n$. Other preferred substituents are (C_{1-4}) alkoxy or (C_{1-4}) alkanoyl.

15 In the groups Ar^1 and Ar^2 , substituents positioned *ortho* to one another may be linked to form a ring.

Illustrative compounds of formula (I) are selected from:

Example	Compound Name
1	1-[2-(Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-(2-methyl-5-phenyl-thiazol-4-yl)-methanone.
2	1-[2-(Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-biphenyl-2-yl-methanone
3	1-[2-(Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
4	1-[2-(Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-(2-trifluoromethoxy-phenyl)-methanone
5	1-[2-(Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-naphthalen-1-yl-methanone
6	1-[2-(Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-(2-methoxy-phenyl)-methanone
7	1-[2-(Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-(2-iodo-phenyl)-methanone
8	1-[(S)-2-(Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-(2-trifluoromethoxy-phenyl)-methanone
9	1-[(S)-2-(Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
10	1-[(S)-2-(Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-biphenyl-2-yl-methanone
11	1-[(S)-2-(Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-(2-iodo-phenyl)-methanone
12	1-[2-Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-phenyl-methanone

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Example	Compound Name
13	1-{2-[(1H-Benzoimidazol-2-ylamino)-methyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
14	1-{2-[(1H-Benzoimidazol-2-ylamino)-methyl]-piperidin-1-yl}-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
15	1-[2-(Benzothiazol-2-ylaminomethyl)-piperidin-1-yl]-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
16	1-[2-(Benzothiazol-2-ylaminomethyl)-piperidin-1-yl]-1-(2-trifluoromethoxy-phenyl)-methanone
17	1-[2-(Benzothiazol-2-ylaminomethyl)-piperidin-1-yl]-1-biphenyl-2-yl-methanone
18	1-[2-(Benzothiazol-2-ylaminomethyl)-piperidin-1-yl]-1-(2-methyl-5-phenyl-thiazol-4-yl)-methanone
19	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(isoquinolin-1-ylaminomethyl)-piperidin-1-yl]-methanone
20	1-[2-(Isoquinolin-1-ylaminomethyl)-piperidin-1-yl]-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
21	1-[2-(Isoquinolin-1-ylaminomethyl)-piperidin-1-yl]-1-(2-trifluoromethoxy-phenyl)-methanone
22	1-(2-Iodo-phenyl)-1-[2-(isoquinolin-1-ylaminomethyl)-piperidin-1-yl]-methanone
23	1-[2-(Isoquinolin-1-ylaminomethyl)-piperidin-1-yl]-1-naphthalen-1-yl-methanone
24	1-[2-(Quinoxalin-2-ylaminomethyl)-piperidin-1-yl]-1-(2-trifluoromethoxy-phenyl)-methanone
25	1-[2-(Quinoxalin-2-ylaminomethyl)-piperidin-1-yl]-1-(3-trifluoromethoxy-phenyl)-methanone
26	1-(2-Iodo-phenyl)-1-[2-(quinoxalin-2-ylaminomethyl)-piperidin-1-yl]-methanone
27	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(quinoxalin-2-ylaminomethyl)-piperidin-1-yl]-methanone
28	1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-1-[2-(quinoxalin-2-ylaminomethyl)-piperidin-1-yl]-methanone
29	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[(R)-2-(quinazolin-2-ylaminomethyl)-piperidin-1-yl]-methanone
30	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[(S)-2-([1,5]naphthyridin-2-ylaminomethyl)-piperidin-1-yl]-methanone
31	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[(S)-2-([1,8]naphthyridin-2-ylaminomethyl)-piperidin-1-yl]-methanone
32	1-[(S)-2-(Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
33	1-[3-(Benzooxazol-2-ylaminomethyl)-morpholin-4-yl]-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

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Example	Compound Name
34	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(quinolin-2-ylaminomethyl)-piperidin-1-yl]-methanone
35	1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-1-[2-(quinolin-2-ylaminomethyl)-piperidin-1-yl]-methanone
36	1-[2-(Quinolin-2-ylaminomethyl)-piperidin-1-yl]-1-(2-trifluoromethoxy-phenyl)-methanone
37	1-[2-(Benzothiazol-2-ylaminomethyl)-piperidin-1-yl]-1-naphthalen-1-yl-methanone
38	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[(S)-2-(quinolin-2-ylaminomethyl)-piperidin-1-yl]-methanone
39	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(pyrimidin-2-ylaminomethyl)-piperidin-1-yl]-methanone
40	1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-1-[2-(pyrimidin-2-ylaminomethyl)-piperidin-1-yl]-methanone
41	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(pyrazin-2-ylaminomethyl)-piperidin-1-yl]-methanone
42	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[(S)-2-(quinazolin-4-ylaminomethyl)-piperidin-1-yl]-methanone
43	1-[5-(4-Fluoro-phenyl)-thiazol-4-yl]-1-[(S)-2-(quinazolin-4-ylaminomethyl)-piperidin-1-yl]-methanone
44	1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-1-[(S)-2-(quinazolin-4-ylaminomethyl)-piperidin-1-yl]-methanone
45	1-[4-(4-Fluoro-phenyl)-2-methyl-2H-pyrazol-3-yl]-1-[(S)-2-(quinazolin-4-ylaminomethyl)-piperidin-1-yl]-methanone
46	1-[4-(4-Fluoro-phenyl)-1H-pyrazol-3-yl]-1-[(S)-2-(quinazolin-4-ylaminomethyl)-piperidin-1-yl]-methanone
47	1-[5-(3-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[(S)-2-(quinazolin-4-ylaminomethyl)-piperidin-1-yl]-methanone
48	1-[5-(3-Fluoro-phenyl)-2-methyl-2H-[1,2,3]triazol-4-yl]-1-[(S)-2-(quinazolin-4-ylaminomethyl)-piperidin-1-yl]-methanone
49	1-Naphthalen-1-yl-1-[(S)-2-(quinazolin-4-ylaminomethyl)-piperidin-1-yl]-methanone
50	1-(5-Bromo-2-methoxy-phenyl)-1-[(S)-2-(quinazolin-4-ylaminomethyl)-piperidin-1-yl]-methanone
51	1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-1-[(S)-2-(quinazolin-4-ylaminomethyl)-piperidin-1-yl]-methanone
52	1-[(S)-2-(Quinazolin-4-ylaminomethyl)-piperidin-1-yl]-1-(2-trifluoromethoxy-phenyl)-methanone
53	1-[(S)-2-[(6,7-Difluoro-3-methyl-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
54	1-[(S)-2-[(6,7-Difluoro-3-methyl-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-thiazol-4-yl]-methanone

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Example	Compound Name
55	1-((S)-2-((6,7-Difluoro-3-methyl-quinoxalin-2-ylamino)-methyl)-piperidin-1-yl)-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
56	1-((S)-2-((6,7-Difluoro-3-methyl-quinoxalin-2-ylamino)-methyl)-piperidin-1-yl)-1-[4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-methanone
57	1-((S)-2-((6,7-Difluoro-3-methyl-quinoxalin-2-ylamino)-methyl)-piperidin-1-yl)-1-[2-(4-fluoro-phenyl)-5-methyl-2H-pyrazol-3-yl]-methanone
58	1-((S)-2-((6,7-Difluoro-3-methyl-quinoxalin-2-ylamino)-methyl)-piperidin-1-yl)-1-[4-(4-fluoro-phenyl)-2-methyl-2H-pyrazol-3-yl]-methanone
59	1-((S)-2-((6,7-Difluoro-3-methyl-quinoxalin-2-ylamino)-methyl)-piperidin-1-yl)-1-naphthalen-1-yl-methanone
60	1-((S)-2-((6,7-Difluoro-quinoxalin-2-ylamino)-methyl)-piperidin-1-yl)-1-quinolin-4-yl-methanone
61	1-((S)-2-((6,7-Difluoro-quinoxalin-2-ylamino)-methyl)-piperidin-1-yl)-1-[5-(4-fluoro-phenyl)-2-methyl-oxazol-4-yl]-methanone
62	1-((S)-2-((6,7-Difluoro-quinoxalin-2-ylamino)-methyl)-piperidin-1-yl)-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
63	1-((S)-2-((6,7-Difluoro-quinoxalin-2-ylamino)-methyl)-piperidin-1-yl)-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
64	1-((S)-2-((6,7-Difluoro-quinoxalin-2-ylamino)-methyl)-piperidin-1-yl)-1-(2-trifluoromethoxy-phenyl)-methanone
65	1-Biphenyl-2-yl-1-((S)-2-((6,7-difluoro-quinoxalin-2-ylamino)-methyl)-piperidin-1-yl)-methanone
66	1-(5-Bromo-2-methoxy-phenyl)-1-((S)-2-((6,7-difluoro-quinoxalin-2-ylamino)-methyl)-piperidin-1-yl)-methanone
67	1-((S)-2-((6,7-Difluoro-quinoxalin-2-ylamino)-methyl)-piperidin-1-yl)-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
68	1-((S)-2-((6,7-Difluoro-quinoxalin-2-ylamino)-methyl)-piperidin-1-yl)-1-[4-(4-fluoro-phenyl)-2-methyl-2H-pyrazol-3-yl]-methanone
69	1-((S)-2-((6,7-Difluoro-quinoxalin-2-ylamino)-methyl)-piperidin-1-yl)-1-[5-(4-fluoro-phenyl)-2-methyl-2H-[1,2,3]triazol-4-yl]-methanone
70	1-((S)-2-((6,7-Difluoro-quinoxalin-2-ylamino)-methyl)-piperidin-1-yl)-1-naphthalen-1-yl-methanone
71	1-((S)-2-((6,7-Difluoro-quinoxalin-2-ylamino)-methyl)-piperidin-1-yl)-1-[5-(4-fluoro-phenyl)-thiazol-4-yl]-methanone
72	1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-1-[(R)-2-(quinazolin-2-ylaminomethyl)-piperidin-1-yl]-methanone
73	1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-1-[2-(oxazol[4,5-b]pyridin-2-ylaminomethyl)-piperidin-1-yl]-methanone
74	1-[2-(Oxazol[4,5-b]pyridin-2-ylaminomethyl)-piperidin-1-yl]-1-(2-trifluoromethoxy-phenyl)-methanone
75	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(oxazol[4,5-b]pyridin-2-ylaminomethyl)-piperidin-1-yl]-methanone

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Example	Compound Name
76	1-(2-Iodo-phenyl)-1-[2-(oxazolo[4,5-b]pyridin-2-ylaminomethyl)-piperidin-1-yl]-methanone
77	1-{3-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-morpholin-4-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
78	1-{3-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-morpholin-4-yl}-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
79	1-{3-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-morpholin-4-yl}-1-[4-(4-fluoro-phenyl)-2-methyl-2H-pyrazol-3-yl]-methanone
80	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[(S)-2-(pyrido[2,3-b]pyrazin-2-ylaminomethyl)-piperidin-1-yl]-methanone
81	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[(S)-2-(pyrido[2,3-b]pyrazin-3-ylaminomethyl)-piperidin-1-yl]-methanone
82	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{2-[(4-phenyl-thiazol-2-ylamino)-methyl]-piperidin-1-yl}-methanone
93	1-{2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[4-(4-fluoro-phenyl)-2H-pyrazol-3-yl]-methanone
94	1-{2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
95	1-{2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[2-(4-fluoro-phenyl)-5-methyl-2H-pyrazol-3-yl]-methanone
96	1-{2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-2H-[1,2,3]triazol-4-yl]-methanone
97	2-(1-{2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl}-methanoyl)-benzonitrile
98	1-{2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-naphthalen-1-yl-methanone
99	1-(5-Bromo-2-methoxy-phenyl)-1-{2-[(6,7-difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl}-methanone
100	1-{2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
101	1-[(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
102	1-[(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl]-1-[5-(4-fluoro-phenyl)-thiazol-4-yl]-methanone
103	1-[(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl]-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
104	1-[(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl]-1-[4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-methanone
105	1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-1-[(S)-2-(oxazolo[4,5-b]pyridin-2-ylaminomethyl)-piperidin-1-yl]-methanone
106	1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-1-[(S)-2-[(methyl-oxazolo[4,5-b]pyridin-2-yl-amino)-methyl]-piperidin-1-yl]-methanone

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Example	Compound Name
83	1-((S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl)-1-quinoxalin-2-yl-methanone
84	1-((S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl)-1-quinolin-3-yl-methanone
85	1-((S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl)-1-isoquinolin-3-yl-methanone
86	1-((S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl)-1-(2-methoxy-pyridin-3-yl)-methanone
87	1-((S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl)-1-quinoxalin-6-yl-methanone
88	6-[[[(S)-1-{1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-nicotinonitrile
89	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-((S)-2-[(4-trifluoromethyl-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl)-methanone
90	1-(1H-Benzoimidazol-5-yl)-1-[(S)-2-(pyrido[2,3-b]pyrazin-2-ylaminomethyl)-piperidin-1-yl]-methanone Duplicate of Example 161
91	1-((S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl)-1-[2-dimethylamino-5-(4-fluoro-phenyl)-thiazol-4-yl]-methanone
92	1-((S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl)-1-[2-(3-dimethylamino-propoxy)-phenyl]-methanone
107	6-[[[(S)-1-{1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl)-methyl-amino]-nicotinonitrile
108	1-((S)-2-[[[(6,7-Difluoro-quinoxalin-2-yl)-methyl-amino]-methyl]-piperidin-1-yl)-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone

and pharmaceutically acceptable salts thereof.

Additional compounds of formula (I) are selected from:

Example	Compound Name
109	1-((S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl)-1-(4-fluoro-benzofuran-2-yl)-methanone
110	2-[[[(S)-1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-nicotinonitrile
111	2-[[[(S)-1-{1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanoyl}-piperidin-2-ylmethyl)-amino]-nicotinonitrile
112	2-[[[(S)-1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-isonicotinonitrile
113	1-Benzo[b]thiophen-2-yl-1-((S)-2-[(6,7-difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl)-methanone
114	1-(1H-Benzoimidazol-5-yl)-1-((S)-2-[(6,7-difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl)-methanone

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Example	Compound Name
115	1-(1H-Benzotriazol-5-yl)-1-[(S)-2-[(6,7-difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl]-methanone
116	1-Benzothiazol-6-yl-1-[(S)-2-[(6,7-difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl]-methanone
117	1-(3,4-Dichloro-phenyl)-1-[(S)-2-[(6,7-difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl]-methanone
118	1-[(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl]-1-(3,4-dimethoxy-phenyl)-methanone
121	1-Isoquinolin-3-yl-1-[(S)-2-(pyrido[2,3-b]pyrazin-2-ylaminomethyl)-piperidin-1-yl]-methanone
122	1-(1H-Indol-5-yl)-1-[(S)-2-(pyrido[2,3-b]pyrazin-2-ylaminomethyl)-piperidin-1-yl]-methanone
123	1-[(S)-2-(Pyrido[2,3-b]pyrazin-2-ylaminomethyl)-piperidin-1-yl]-1-quinolin-4-yl-methanone
124	1-[(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl]-1-[4-(4-fluoro-phenyl)-1-(2-methoxy-ethyl)-1H-pyrazol-3-yl]-methanone
125	1-[(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl]-1-(2,4-dimethyl-thiazol-5-yl)-methanone
126	1-[(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-1-methyl-1H-[1,2,3]triazol-4-yl]-methanone
127	6-[[[(S)-1-(1-[4-(4-Fluoro-phenyl)-1-(2-methoxy-ethyl)-1H-pyrazol-3-yl]-methanoyl)-piperidin-2-ylmethyl]-amino]-nicotinonitrile
128	1-[(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
129	1-[(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl]-1-[4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-methanone
130	1-[(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2H-[1,2,3]triazol-4-yl]-methanone
131	1-[(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl]-1-quinolin-2-yl-methanone
132	1-[(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-1-methyl-1H-[1,2,3]triazol-4-yl]-methanone
133	1-[(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-hydroxymethyl-thiazol-4-yl]-methanone
134	1-[(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl]-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
135	1-[(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl]-1-quinolin-8-yl-methanone
136	2-[[[(S)-1-(1H-Benzoimidazol-5-yl-methanoyl)-piperidin-2-ylmethyl]-amino]-6,7-difluoro-quinoline-3-carbonitrile
137	6,7-Difluoro-2-[[[(S)-1-(1-isoquinolin-3-yl-methanoyl)-piperidin-2-ylmethyl]-amino]-quinoline-3-carbonitrile

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Example	Compound Name
138	6,7-Difluoro-2-[[[(S)-1-{1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-quinoline-3-carbonitrile
139	6,7-Difluoro-2-[[[(S)-1-(1-naphthalen-2-yl-methanoyl)-piperidin-2-ylmethyl]-amino]-quinoline-3-carbonitrile
140	6,7-Difluoro-2-[[[(S)-1-{1-[4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-quinoline-3-carbonitrile
141	6,7-Difluoro-2-[[[(S)-1-(1-1H-indol-6-yl-methanoyl)-piperidin-2-ylmethyl]-amino]-quinoline-3-carbonitrile
142	2-[[[(S)-1-(1-Benzothiazol-6-yl-methanoyl)-piperidin-2-ylmethyl]-amino]-6,7-difluoro-quinoline-3-carbonitrile
143	1-[(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl]-1-naphthalen-2-yl-methanone
144	1-[(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl]-1-(6-fluoro-benzofuran-2-yl)-methanone
145	1-[(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl]-1-(5-fluoro-benzofuran-2-yl)-methanone
146	1-[(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl]-1-(7-fluoro-benzofuran-2-yl)-methanone
147	1-(5,7-Difluoro-benzofuran-2-yl)-1-[(S)-2-[(6,7-difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl]-methanone
148	2-[[[(S)-1-{1-[4-(4-Fluoro-phenyl)-1H-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-nicotinonitrile
149	2-[[[(S)-1-{1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-nicotinonitrile
150	2-[[[(S)-1-{1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-isonicotinonitrile
151	1-[(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl]-1-{2-[3-(3-dimethylamino-propoxy)-phenyl]-thiophen-3-yl}-methanone
152	1-{2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-{2-[3-(3-dimethylamino-propoxy)-phenyl]-thiophen-3-yl}-methanone
153	1-{2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-1-quinolin-8-yl-methanone
154	1-[(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl]-1-(1-methyl-1H-indol-2-yl)-methanone
155	1-[(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl]-1-(1H-indol-6-yl)-methanone
156	1-Benzo[1,2,3]thiadiazol-5-yl-1-[(S)-2-[(6,7-difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl]-methanone
157	3-(1-[(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl]-methanoyl)-benzoic acid methyl ester
158	1-[(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl]-1-[1-(2-dimethylamino-ethyl)-4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-methanone

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Example	Compound Name
159	1-((S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl)-1-[1-(2-dimethylamino-ethyl)-4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-methanone
160	1-[4-(4-Fluoro-phenyl)-1-(2-methoxy-ethyl)-1H-pyrazol-3-yl]-1-[(S)-2-(pyrido[2,3-b]pyrazin-2-ylaminomethyl)-piperidin-1-yl]-methanone
162	1-(1H-Benzoimidazol-5-yl)-1-((S)-2-[(5-bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl)-methanone
163	1-Benzofuran-2-yl-1-((S)-2-[(5-bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl)-methanone
164	1-((S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl)-1-(2-methoxy-phenyl)-methanone
165	1-((S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl)-1-quinolin-4-yl-methanone
166	1-((S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl)-1-[3-(3-dimethylamino-propoxy)-phenyl]-methanone
170	1-((S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl)-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
119	1-((S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl)-1-[1-ethyl-4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-methanone
120	1-((S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl)-1-[5-(4-fluoro-phenyl)-2H-[1,2,3]triazol-4-yl]-methanone
167	1-((S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl)-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
168	1-((S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl)-1-[5-(2-fluoro-phenyl)-thiazol-4-yl]-methanone
169	1-((S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl)-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
171	1-{2-[[((S)-1-{1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl]-piperidin-2-ylmethyl)-amino]-pyrimidin-5-yl]}-ethanone
172	1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-1-((S)-2-[[5-(1-hydroxy-ethyl)-pyrimidin-2-ylamino]-methyl]-piperidin-1-yl)-methanone
173	2-[[((S)-1-{1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl]-piperidin-2-ylmethyl)-amino]-pyrimidine-5-carbonitrile
174	3-(1-((S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl)-methanoyl)-N-methyl-benzamide

and pharmaceutically acceptable salts thereof.

Further compounds of formula (I) are selected from:

Example	Compound Name
175	1-((S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl)-1-phenyl-methanone

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Example	Compound Name
176	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-hydroxymethyl-thiazol-4-yl]-methanone
177	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-methanone
178	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-quinolin-8-yl-methanone
179	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-(2-ethoxy-phenyl)-methanone
180	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-(2-methyl-5-phenyl-thiazol-4-yl)-methanone
181	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-{5-[3-(3-dimethylamino-propoxy)-phenyl]-2-methyl-thiazol-4-yl}-methanone
182	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-(2-propoxy-phenyl)-methanone
183	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-(2-isopropoxy-phenyl)-methanone
184	1-(2-Benzoyloxy-phenyl)-1-{(S)-2-[(5-bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-methanone
185	1-[3-(1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl)-methanoyl)-4-ethoxy-phenyl]-ethanone
186	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-(2-ethoxy-6-methoxy-phenyl)-methanone
187	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-(2-ethoxy-6-methyl-phenyl)-methanone
188	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-(2-ethoxy-naphthalen-1-yl)-methanone
189	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(2-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
190	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(3-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
191	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(2-fluoro-phenyl)-thiazol-4-yl]-methanone
192	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-(5-phenyl-thiazol-4-yl)-methanone

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Example	Compound Name
193	1-{{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-(2-methyl-4-phenyl-thiazol-5-yl)-methanone
194	1-{{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
195	1-{{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
196	1-{{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-chloro-phenyl)-2-methyl-thiazol-4-yl]-methanone
197	1-{{(S)-2-[(5-Bromo-pyridin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
198	1-{{(S)-2-[(5-Bromo-pyridin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
199	1-[3-(Benzooxazol-2-ylaminomethyl)-morpholin-4-yl]-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
200	1-{3-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-morpholin-4-yl}-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
201	1-{{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(3-fluoro-phenyl)-thiazol-4-yl]-methanone
202	1-{{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-methoxy-phenyl)-2-methyl-thiazol-4-yl]-methanone
203	3,5-Difluoro-4-[[[(S)-1-{1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-benzonitrile
204	3,5-Difluoro-4-[[[(S)-1-{1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl]-piperidin-2-ylmethyl)-amino]-benzonitrile
205	3,5-Difluoro-4-[[[(S)-1-{1-[4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-methanoyl]-piperidin-2-ylmethyl)-amino]-benzonitrile
206	3,5-Difluoro-4-[[[(S)-1-{1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanoyl]-piperidin-2-ylmethyl)-amino]-benzonitrile
207	4-[[[(S)-1-(1-Benzofuran-7-yl-methanoyl)-piperidin-2-ylmethyl)-amino]-3,5-difluoro-benzonitrile
208	3,5-Difluoro-4-[[[(S)-1-{1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl]-pyrrolidin-2-ylmethyl)-amino]-benzonitrile
209	1-{{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[2-dimethylamino-5-(4-fluoro-phenyl)-thiazol-4-yl]-methanone
210	1-(2-Amino-5-phenyl-thiazol-4-yl)-1-{{(S)-2-[(5-bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-methanone

Example	Compound Name
211	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(3-methoxy-phenyl)-2-methyl-thiazol-4-yl]-methanone
212	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[2-(4-fluoro-phenyl)-thiophen-3-yl]-methanone
213	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-(2-pyridin-2-yl-phenyl)-methanone
214	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[4-fluoro-2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
215	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[2-(4-methoxy-phenyl)-thiophen-3-yl]-methanone
216	1-{(S)-2-[(5-Ethyl-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
217	1-{(S)-2-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl}-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
218	1-{(S)-2-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl}-pyrrolidin-1-yl}-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
219	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methoxy-thiazol-4-yl]-methanone
220	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-fluoro-2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
221	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-(2-phenyl-thiophen-3-yl)-methanone
222	2'-{1-[(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl]-methanoyl}-biphenyl-4-carbonitrile
223	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[2-(3-methoxy-phenyl)-thiophen-3-yl]-methanone
224	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-(2-pyrazol-1-yl-phenyl)-methanone
225	1-{2-[(S)-1-{1-[5-(4-Chloro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-pyrrolidin-2-ylmethyl)-amino]-pyrimidin-5-yl}-methanone
226	1-{(S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
227	1-{(S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
228	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[(S)-2-[(5-methyl-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl]-methanone
229	6-[(S)-1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]methanoyl}-pyrrolidin-2-ylmethyl)-amino]-nicotinonitrile
230	5-(1-{2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-methanoyl)-4H-benzo[1,4]oxazin-3-one
231	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-[4-(4-fluoro-phenyl)-1-(2-piperidin-1-yl-ethyl)-1H-pyrazol-3-yl]-methanone

Example	Compound Name
232	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[1-(2-dimethylamino-ethyl)-4-(4-fluoro-phenyl)-1 <i>H</i> -pyrazol-3-yl]-methanone
233	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[2-ethyl-5-(4-fluoro-phenyl)-thiazol-4-yl]-methanone
234	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{(S)-2-[(6-methyl-2-methylsulfanyl-pyrimidin-4-ylamino)-methyl]-pyrrolidin-1-yl}-methanone
235	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{(S)-2-[(2-methylsulfanyl-pyrimidin-4-ylamino)-methyl]-pyrrolidin-1-yl}-methanone
236	1-{(S)-2-[(Dimethyl-trifluoromethyl-pyrimidin-4-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
237	1-{(S)-2-[(2,6-Dimethyl-pyrimidin-4-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
238	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{(S)-2-[(6-trifluoromethyl-pyrimidin-4-ylamino)-methyl]-pyrrolidin-1-yl}-methanone
239	1-(3-[[[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl]-morpholin-4-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
240	1-(3-[[[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl]-morpholin-4-yl]-1-[2-(4-fluoro-phenyl)-thiophen-3-yl]-methanone
241	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-(4-ethyl-quinolin-8-yl)-methanone
242	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-isoquinolin-1-yl-methanone
243	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-(2-methyl-quinolin-5-yl)-methanone
244	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-(3-methyl-quinolin-4-yl)-methanone
245	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-(2,3-dichloro-phenyl)-methanone
246	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-(7-chloro-3-methyl-quinolin-8-yl)-methanone
247	1-[5-(4-Chloro-phenyl)-2-methyl-thiazol-4-yl]-1-{(S)-2-[(5-chloro-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-methanone
248	1-{2-[[[(S)-1-{1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanoyl}-pyrrolidin-2-ylmethyl)-amino]-pyrimidin-5-yl]-ethanone
249	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{(S)-2-[(5-trifluoromethyl-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-methanone
250	1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-(4-ethyl-quinolin-8-yl)-methanone
251	1-{(S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[2-dimethylamino-5-(4-fluoro-phenyl)-thiazol-4-yl]-methanone
252	1-{(S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-(2-pyridin-2-yl-phenyl)-methanone

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Example	Compound Name
253	1-((S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl)-1-[2-ethyl-5-(4-fluoro-phenyl)-thiazol-4-yl]-methanone
254	1-Biphenyl-2-yl-1-((S)-2-[(5-chloro-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl)-methanone
255	1-((S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl)-1-(2,3-dichloro-phenyl)-methanone
256	1-{5-[3-(4-Chloro-butoxy)-phenyl]-2-methyl-thiazol-4-yl}-1-((S)-2-[(5-chloro-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl)-methanone
257	1-((S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl)-1-[2-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
258	1-((S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl)-1-[2-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
259	1-{3-[(5-Bromo-pyridin-2-ylamino)-methyl]-morpholin-4-yl}-1-[2-(4-fluoro-phenyl)-thiophen-3-yl]-methanone
260	1-((S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl)-1-[2,4-dimethyl-quinolin-8-yl]-methanone
261	1-((S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl)-1-(2-phenyl-quinolin-4-yl)-methanone
262	1-((S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl)-1-(2-methyl-quinolin-4-yl)-methanone
263	1-((S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl)-1-(6-bromo-quinolin-4-yl)-methanone
264	1-((S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl)-1-(2-methyl-quinolin-8-yl)-methanone
265	1-((S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl)-1-(8-bromo-quinolin-4-yl)-methanone
266	1-((S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl)-1-[1-(3-dimethylamino-propyl)-4-(4-fluorophenyl)-1H-pyrazol-3-yl]-methanone
267	1-((S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl)-1-[1-(2-dimethylamino-ethyl)-4-(4-fluorophenyl)-1H-pyrazol-3-yl]-methanone
268	1-((S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl)-1-[4-(4-fluoro-phenyl)-1-(2-piperidine-1-yl-ethyl)-1H-pyrazol-3-yl]-methanone
269	1-((S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl)-1-[4-(4-fluoro-phenyl)-1-(3-piperidine-1-yl-propyl)-1H-pyrazol-3-yl]-methanone
270	1-((S)-2-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl)-piperidin-1-yl)-1-isoquinolin-1-yl-methanone
271	1-((S)-2-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl)-piperidin-1-yl)-1-(2,3-dichloro-phenyl)-methanone
272	1-((S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl)-1-[2-dimethylaminomethyl-5-(4-fluoro-phenyl)-thiazol-4-yl]-methanone
273	1-((S)-2-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl)-piperidin-1-yl)-1-(3-methyl-quinolin-4-yl)-methanone

Example	Compound Name
274	1-((S)-2-[[5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl]-piperidin-1-yl)-1-(2-methyl-quinolin-5-yl)-methanone
275	1-((S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl)-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

and pharmaceutically acceptable salts thereof.

Preferred compounds of formula (I) are selected from:

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Example	Compound Name
1	1-[2-(Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-(2-methyl-5-phenyl-thiazol-4-yl)-methanone
32	1-[(S)-2-(Benzooxazol-2-ylaminomethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
93	1-{2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[4-(4-fluoro-phenyl)-2H-pyrazol-3-yl]-methanone
105	1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-1-[(R)-2-(oxazol[4,5-b]pyridin-2-ylaminomethyl)-piperidin-1-yl]-methanone
106	1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-1-[(R)-2-[(methyl-oxazol[4,5-b]pyridin-2-yl-amino)-methyl]-piperidin-1-yl]-methanone
107	6-[[[(S)-1-{1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl]-piperidin-2-ylmethyl)-methyl-amino]-nicotinonitrile
108	1-((S)-2-[[[(6,7-Difluoro-quinoxalin-2-yl)-methyl-amino]-methyl]-piperidin-1-yl]-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
171	1-[2-[[[(S)-1-{1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl]-piperidin-2-ylmethyl)-amino]-pyrimidin-5-yl]-ethanone
172	1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-1-((S)-2-[[5-(1-hydroxy-ethyl)-pyrimidin-2-ylamino]-methyl]-piperidin-1-yl)-methanone
173	2-[[[(S)-1-{1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl]-piperidin-2-ylmethyl)-amino]-pyrimidine-5-carbonitrile
174	3-(1-[(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl]-methanoyl)-N-methyl-benzamide
194	1-((S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl)-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
195	1-[(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl]-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
196	1-[(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl]-1-[5-(4-chloro-phenyl)-2-methyl-thiazol-4-yl]-methanone

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Example	Compound Name
197	1-{(S)-2-[(5-Bromo-pyridin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
198	1-{(S)-2-[(5-Bromo-pyridin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
200	1-{3-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-morpholin-4-yl}-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
203	3,5-Difluoro-4-[[{(S)-1-{1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-ylmethyl)-amino]-benzonitrile
208	3,5-Difluoro-4-[[{(S)-1-{1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-pyrrolidin-2-ylmethyl)-amino]-benzonitrile
216	1-{(S)-2-[(5-Ethyl-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
217	1-((S)-2-[[{(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl}-pyrrolidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
218	1-((S)-2-[[{(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl}-pyrrolidin-1-yl]-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
225	1-[2-[[{(S)-1-{1-[5-(4-Chloro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-pyrrolidin-2-ylmethyl)-amino]-pyrimidin-5-yl]-ethanone
226	1-{(S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
227	1-{(S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
228	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{(S)-2-[(5-methyl-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-methanone
229	6-[[{(S)-1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanyol}-pyrrolidin-2-ylmethyl)-amino]-nicotinonitrile
234	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{(S)-2-[(6-methyl-2-methylsulfanyl-pyrimidin-4-ylamino)-methyl]-pyrrolidin-1-yl}-methanone
235	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{(S)-2-[(2-methylsulfanyl-pyrimidin-4-ylamino)-methyl]-pyrrolidin-1-yl}-methanone
239	1-(3-[[{(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl}-morpholin-4-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
240	1-(3-[[{(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl}-morpholin-4-yl]-1-[2-(4-fluoro-phenyl)-thiophen-3-yl]-methanone
249	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{(S)-2-[(5-trifluoromethyl-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl}-methanone

and pharmaceutically acceptable salts thereof.

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When a halogen atom is present in the compound of formula (I) it may be fluorine, chlorine, bromine or iodine.

When the compound of formula (I) contains an alkyl group, whether alone or forming part of a larger group, e.g. alkoxy or alkylthio, the alkyl group may be straight chain, branched or cyclic, or combinations thereof, it is preferably methyl or ethyl.

When used herein the term aryl means a 5- to 6- membered aromatic ring for example phenyl, or a 7 to 12 membered bicyclic ring system where at least one of the rings is aromatic for example naphthyl.

It will be appreciated that compounds of formula (I) may exist as *R* or *S* enantiomers. The present invention includes within its scope all such isomers, including mixtures. Where additional chiral centres are present in compounds of formula (I), the present invention includes within its scope all possible diastereoisomers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

It will be understood that the invention includes pharmaceutically acceptable derivatives of compounds of formula (I) and that these are included within the scope of the invention.

Particular compounds according to the invention include those mentioned in the examples and their pharmaceutically acceptable derivatives.

As used herein "pharmaceutically acceptable derivative" includes any pharmaceutically acceptable salt, ester or salt of such ester of a compound of formula (I) which, upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof.

It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulphuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Other salts e.g. oxalates, may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention. Also included within the scope of the invention are solvates and hydrates of compounds of formula (I).

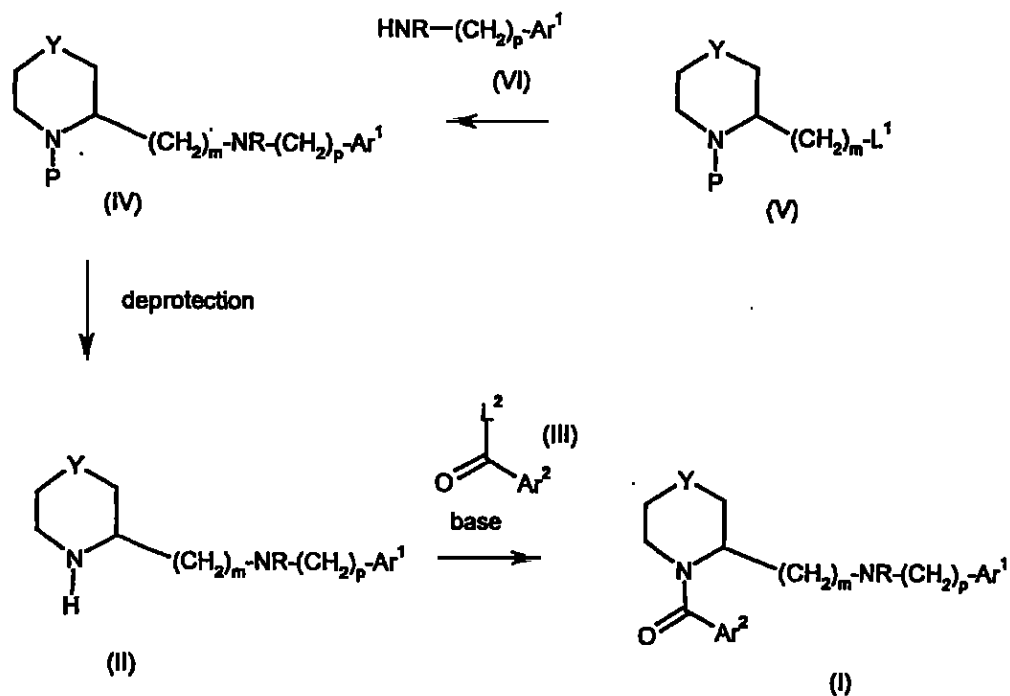
Certain of the compounds of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions.

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According to a further feature of the invention there is provided a process for the preparation of compounds of formula (I) and derivatives thereof. The following schemes detail some synthetic routes to compounds of the invention.

5 Scheme 1a



10 wherein Ar^1 , Ar^2 , Y, m, p and R are as defined for formula (I), L^1 and L^2 are leaving groups, and P is a protecting group.

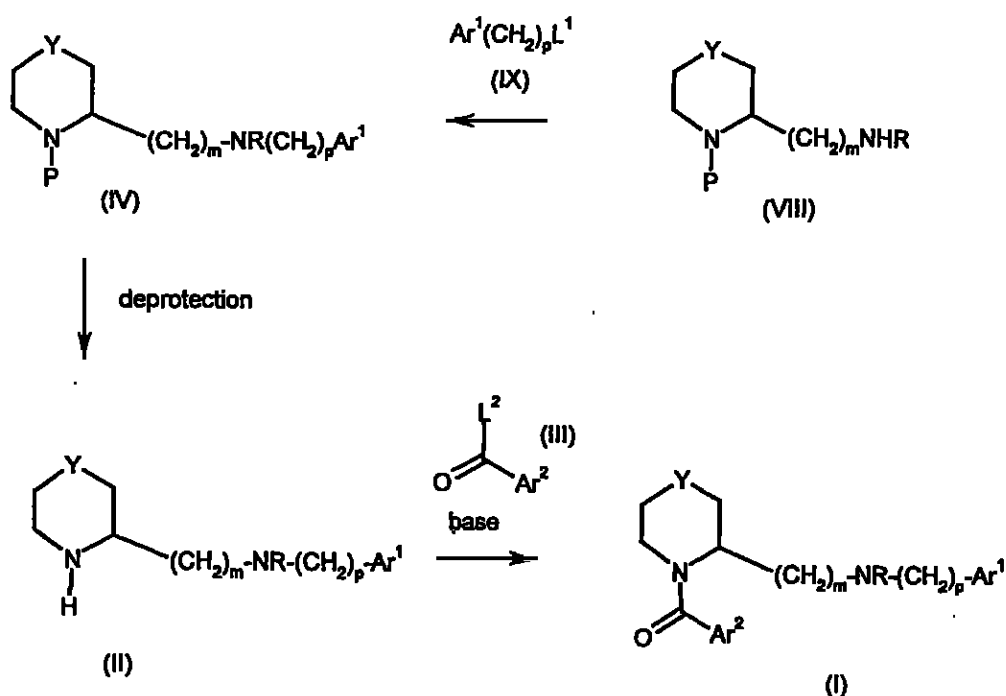
Examples of suitable leaving groups L^1 include halogen, hydroxy, OSO_2Me , $OSO_2(4-tolyl)$. The reaction of (V) with (VI) preferably proceeds in an inert solvent such as N,N-dimethylformamide in the presence of a base such as triethylamine, sodium hydride or potassium t-butoxide.

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Scheme 1b

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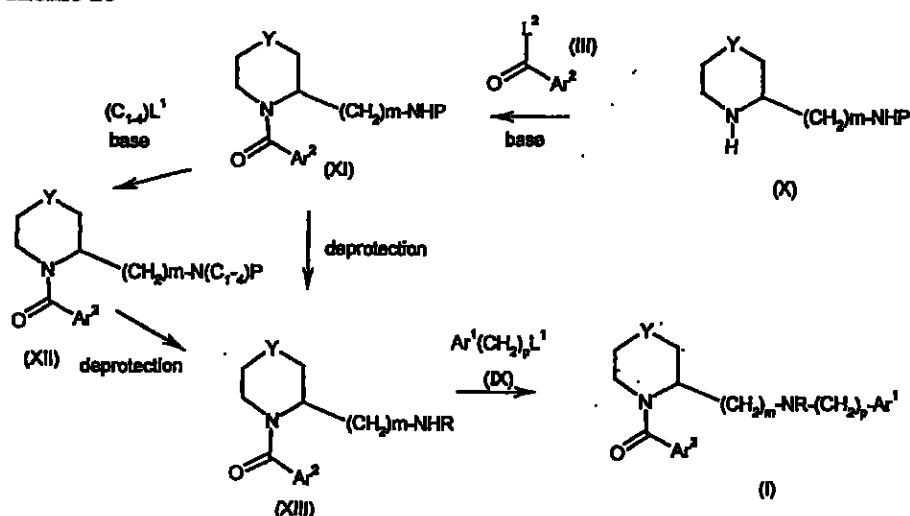
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Reaction of (VIII) with (IX) proceeds in an inert solvent such as dimethylformamide or xylene in the presence of a base such as potassium carbonate or diisopropylethylamine, preferably at elevated temperatures.

5 Alternatively where m is 1 and p is 0 or 1 compounds may be prepared as shown in scheme 1c.

Scheme 1c



10 Reaction of (XI) with an alkylating agent $(\text{C}_{1-4})\text{L}^1$ proceeds in the presence of a base such as sodium hydride in an inert solvent such as dimethylformamide.

Examples of suitable leaving groups L^2 include halogen, hydroxy, $\text{OC}(=\text{O})\text{alkyl}$ and $\text{OC}(=\text{O})\text{O-alkyl}$. The transformation (II) to (I) may be carried out in an inert solvent such as dichloromethane, in the presence of a base such as triethylamine. Alternatively this step

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may be carried out when L^2 represents hydroxy, in which case reaction with (II) takes place in an inert solvent such as dichloromethane in the presence of a diimide reagent such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, and an activator such as 1-hydroxybenzotriazole.

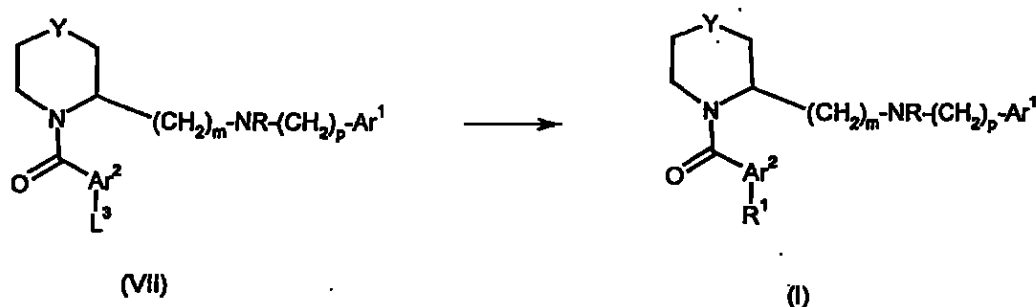
5 Examples of protecting groups P include *t*-butoxycarbonyl, trifluoroacetyl, optionally substituted benzyl and benzyloxycarbonyl. Deprotection conditions are respectively, acid (e.g. trifluoroacetic acid in dichloromethane), base (e.g. sodium hydroxide in a solvent such as aqueous methanol) and catalytic hydrogenolysis in an inert solvent (e.g. using palladium on charcoal in a lower alcohol or ethyl acetate).

10 Compounds of formula (V), (VI) and (IX) are known in the literature or can be prepared by known methods. Compounds (VIII) can be prepared by known methods.

Within the schemes above there is scope for functional group interconversion; for example in compound (V), conversion of one value of L^1 to another value of L^1 ; or in compounds (IV) conversion of protecting group P for another protecting group P, or
15 conversion of one compound of formula (I) to another of formula (I) by interconversion of substituents.

When R^1 is an aromatic group, the substituent R^1 may be introduced at the final stage as illustrated in Scheme 2 by reaction of a compound of formula (VII) where L^3 represents a leaving group such as halogen (preferably bromo or iodo) or
20 trifluoromethylsulfonyloxy, and all other variables are as previously defined, with a reagent R^1M , where M is the residue of an organometallic species e.g. $B(OH)_2$ or trialkylstannyl. Such a process may be carried out in an inert solvent such as 1,2-dimethoxyethane or 1,4-dioxan, in the presence of a transition metal catalyst such as $Pd(PPh_3)_4$.

25 Scheme 2



Wherein Y, Ar^2 , m, p, Ar^1 , R, R^1 and Y are as defined for compounds of formula (I).
30 L^3 is a leaving group.

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, e.g. 5 to 1000, preferably 10 to 100 compounds of formula (I). Compound libraries may be prepared by a combinatorial 'split and mix' approach or by
multiple parallel synthesis using either solution phase or solid phase chemistry, by
35 procedures known to those skilled in the art.

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Thus according to a further aspect of the invention there is provided a compound library comprising at least 2 compounds of formula (I), or pharmaceutically acceptable derivatives thereof.

5 Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

The compounds of formula (I) and their pharmaceutically acceptable derivatives are useful for the treatment of diseases or disorders where an antagonist of a human Orexin receptor is required such as obesity and diabetes; prolactinoma; hypoprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth hormone
10 deficiency; Cushing's syndrome/disease; hypothalamic-adrenal dysfunction; dwarfism; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; sleep disturbances associated with diseases such as neurological disorders, neuropathic pain and restless leg syndrome; heart and lung diseases; depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis/disorder; depressive neurosis/disorder; anxiety
15 neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; sex disorder; sexual disorder; schizophrenia; manic depression; delirium; dementia; bulimia and hypopituitarism. Additionally the compounds of formula (I) and pharmaceutically acceptable derivatives are useful for the treatment of stroke, particularly ischemic or haemorrhagic and/or in blocking an emetic response i.e. nausea and
20 vomiting.

The compounds of formula (I) and their pharmaceutically acceptable derivatives are particularly useful for the treatment of obesity, including obesity associated with Type 2 diabetes, and sleep disorders. Additionally the compounds of formula (I) and
25 pharmaceutically acceptable derivatives are useful for the treatment of stroke, particularly ischemic or haemorrhagic and/or in blocking an emetic response i.e. nausea and vomiting.

Other diseases or disorders which may be treated in accordance with the invention include disturbed biological and circadian rhythms; adrenohypophysis disease; hypophysis disease; hypophysis tumor / adenoma; adrenohypophysis hypofunction; functional or psychogenic amenorrhea; adrenohypophysis hyperfunction; migraine; hyperalgesia; pain;
30 enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndromes I and II; arthritic pain; sports injury pain; pain related to infection e.g. HIV, post-polio syndrome and post-herpetic neuralgia; phantom limb pain; labour pain; cancer pain; post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; and
35 tolerance to narcotics or withdrawal from narcotics.

The invention also provides a method of treating or preventing diseases or disorders where an antagonist of a human Orexin receptor is required, which comprises administering to a subject in need thereof an effective amount of a compound of formula (I), or a
40 pharmaceutically acceptable derivative thereof.

The invention also provides a compound of formula (I), or a pharmaceutically acceptable derivative thereof, for use in the treatment or prophylaxis of diseases or disorders where an antagonist of a human Orexin receptor is required.

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The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for the treatment or prophylaxis of diseases or disorders where an antagonist of a human Orexin receptor is required.

- 5 For use in therapy the compounds of the invention are usually administered as a pharmaceutical composition. The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier.

- 10 The compounds of formula (I) and their pharmaceutically acceptable derivatives may be administered by any convenient method, e.g. by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration, and the pharmaceutical compositions adapted accordingly.

- 15 The compounds of formula (I) and their pharmaceutically acceptable derivatives which are active when given orally can be formulated as liquids or solids, e.g. as syrups, suspensions, emulsions, tablets, capsules or lozenges.

A liquid formulation will generally consist of a suspension or solution of the active ingredient in a suitable liquid carrier(s) e.g. an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring and/or colouring agent.

- 20 A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations, such as magnesium stearate, starch, lactose, sucrose and cellulose.

- 25 A composition in the form of a capsule can be prepared using routine encapsulation procedures, e.g. pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), e.g. aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

- 30 Typical parenteral compositions consist of a solution or suspension of the active ingredient in a sterile aqueous carrier or parenterally acceptable oil, e.g. polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

- 35 Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active ingredient in a pharmaceutically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a disposable dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a
40 compressed gas e.g. air, or an organic propellant such as a fluorochlorohydrocarbon or hydrofluorocarbon. Aerosol dosage forms can also take the form of pump-atomisers.

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Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles where the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

5 Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Compositions suitable for transdermal administration include ointments, gels and patches.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

10 The dose of the compound of formula (I), or a pharmaceutically acceptable derivative thereof, used in the treatment or prophylaxis of the abovementioned disorders or diseases will vary in the usual way with the particular disorder or disease being treated, the weight of the subject and other similar factors. However, as a general rule, suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 500 mg. Unit doses may be administered more than once a day for example two or three times a day, so that the total daily dosage is in the range of about 0.01 to 100 mg/kg; and such therapy may extend for a number of weeks or months. In the case of pharmaceutically acceptable derivatives the above figures are calculated as the parent compound of formula (I).

No toxicological effects are indicated/expected when a compound of formula (I) is administered in the above mentioned dosage range.

20 Human Orexin-A has the amino acid sequence:

pyroGlu Pro Leu Pro Asp Cys Cys Arg Gln Lys Thr Cys Ser Cys Arg Leu

1 5 10 15

Tyr Glu Leu Leu His Gly Ala Gly Asn His Ala Ala Gly Ile Leu Thr

20 25 30

25 Leu-NH₂

Orexin-A can be employed in screening procedures for compounds which inhibit the ligand's activation of the orexin-1 receptor.

In general, such screening procedures involve providing appropriate cells which express the orexin-1 receptor on their surface. Such cells include cells from mammals, yeast, *Drosophila* or *E. coli*. In particular, a polynucleotide encoding the orexin-1 receptor is used to transfect cells to express the receptor. The expressed receptor is then contacted with a test compound and an orexin-1 receptor ligand to observe inhibition of a functional response. One such screening procedure involves the use of melanophores which are transfected to express the orexin-1 receptor, as described in WO 92/01810.

35 Another screening procedure involves introducing RNA encoding the orexin-1 receptor into *Xenopus* oocytes to transiently express the receptor. The receptor oocytes are then contacted with a receptor ligand and a test compound, followed by detection of inhibition of a signal in the case of screening for compounds which are thought to inhibit activation of the receptor by the ligand.

40 Another method involves screening for compounds which inhibit activation of the receptor by determining inhibition of binding of a labelled orexin-1 receptor ligand to cells which have the receptor on their surface. This method involves transfecting a eukaryotic cell with DNA encoding the orexin-1 receptor such that the cell expresses the receptor on its

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surface and contacting the cell or cell membrane preparation with a compound in the presence of a labelled form of an orexin-1 receptor ligand. The ligand may contain a radioactive label. The amount of labelled ligand bound to the receptors is measured, e.g. by measuring radioactivity.

- 5 Yet another screening technique involves the use of FLIPR equipment for high throughput screening of test compounds that inhibit mobilisation of intracellular calcium ions, or other ions, by affecting the interaction of an orexin-1 receptor ligand with the orexin-1 receptor.

- 10 All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

- 15 The following Examples illustrate the preparation of pharmacologically active compounds of the invention. The Descriptions D1-D105 illustrate the preparation of intermediates to compounds of the invention.

In the Examples ¹H NMR's were measured at 250MHz in CDCl₃ unless otherwise stated.

- 20 **Description 1: (S) 2-Aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester**
a) 2,2,2-Trifluoro-N-[(S)-1-((R)-2-hydroxy-1-phenyl-ethyl)-piperidin-2-ylmethyl]-acetamide
(R)-2-[(S)-2-Aminomethyl-piperidin-1-yl]-2-phenyl-ethanol (20.0g) (Froelich, Olivier; Desos, Patrice; Bonin, Martine; Quirion, Jean-Charles; Husson, Henri-Philippe; Zhu, Jieping, J. Org. Chem. 1996, 61, 6700) and triethylamine (13.0ml) were dissolved in
25 dichloromethane (500ml), cooled to 0°C and trifluoroacetic anhydride (12.66ml) added dropwise. The mixture was warmed to room temperature and stirred overnight. The organic phase was washed with water, separated, dried and solvent removed at reduced pressure. The residue was column chromatographed [silica gel, 0 – 10% (9:1 methanol/ammonia) in dichloromethane eluant] to give the title compound (28.0g) as a
30 yellow oil.
Mass Spectrum (API⁺): Found 331 (MH⁺). C₁₆H₂₁F₃N₂O₂ requires 330.
[α]_D -55°@ 28° 1% in chloroform
b) 2,2,2-Trifluoro-N-(S)-1-piperidin-2-ylmethyl-acetamide
2,2,2-Trifluoro-N-[(S)-1-((R)-2-hydroxy-1-phenyl-ethyl)-piperidin-2-ylmethyl]-acetamide
35 (28.0g) was dissolved in ethanol (200ml) containing Pearlmans catalyst (2.0g) and shaken under a hydrogen atmosphere (50psi) at 50°C for 3 hours. The reaction mixture was filtered and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, 0 – 10% (9:1 methanol/ammonia) in dichloromethane eluant) to give the title compound (14.18g) as a colourless oil.
40 Mass Spectrum (API⁺): Found 211 (MH⁺). C₈H₁₃F₃N₂O requires 210.
[α]_D +18°@ 28° 1% in chloroform
¹H NMR δ: (d⁶-DMSO) 1.07 (1H, m), 1.32 (2H, m), 1.35 – 1.60 (2H, m), 1.72 (1H, m), 2.54 (1H, t), 2.70 (1H, m), 3.00 (1H, d), 3.17 (3H, m), 9.30 (1H, br. s.)

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c) (S)-2-[(2,2,2-Trifluoro-ethanoylamino)-methyl]-piperidine-1-carboxylic acid *tert* butyl ester

2,2,2-Trifluoro-N-(S)-1-piperidin-2-ylmethyl-acetamide (14.18g) was dissolved in dichloromethane (250ml) and treated with di-*tert*-butyl dicarbonate (14.95g). The mixture was stirred for 16h, washed with water, 2N hydrochloric acid and saturated brine, dried and solvent removed at reduced pressure to give the title compound (18.3g)

Mass Spectrum (API⁺): Found 311 (MH⁺). C₁₃H₂₁F₃N₂O₃ requires 310.

[α]_D²⁰ -94° @ 28° 1% in chloroform

¹H NMR δ: (d⁶-DMSO) 1.27 (1H, m), 1.36, 1.47 (9H, s), 1.49 – 1.58 (5H, m), 2.88 (1H, m), 3.22 (1H, m), 3.49 (1H, m), 3.84 (1H, m), 4.34 (1H, m) and 9.42 (1H, br. s.).

d) (S) 2-Aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester

(S)-2-[(2,2,2-Trifluoro-ethanoylamino)-methyl]-piperidine-1-carboxylic acid *tert* butyl ester (18.2g) was dissolved in methanol (500ml) and treated with potassium carbonate (16.1g). After stirring for 16h solvent was removed at reduced pressure and the residue partitioned between dichloromethane/water. The organic phase was separated, washed with brine, dried and solvent removed at reduced pressure. the residue was column chromatographed (silica gel, 0 – 10% (9:1 methanol/ammonia) in dichloromethane eluant) to give the title compound (8.82g) of description 1.

Mass Spectrum (API⁺): Found 215 (MH⁺). C₁₁H₂₂N₂O₂ requires 214.

[α]_D²⁰ -32.2° @ 28° 1% in chloroform

¹H NMR δ: 1.44 (2H, m), 1.50 (9H, s), 2.64 – 2.80 (2H, m), 2.94 (1H, dd), 3.99 (1H, m) and 4.15 (1H, m).

Description 2: (RS) 2-(Benzoxazol-2-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester

(RS) 2-Aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester (0.21g) and 2-chlorobenzoxazole (0.153g) and triethylamine (0.1g) were combined in tetrahydrofuran (10ml) and stirred at room temperature for 4 hours. The mixture was partitioned between ethyl acetate and water, the organic phase dried and solvent removed at reduced pressure to give the title compound (0.36g) as an oil that solidified on standing.

Mass Spectrum (API⁺): Found 332 (MH⁺). C₁₈H₂₃N₃O₃ requires 331.

Description 3: (RS) Benzoxazol-2-yl-piperidin-2-ylmethyl-amine

The compound of description 2 (0.36g) was stirred in trifluoroacetic acid (10ml) containing water (1 drop) for 3 hours. Solvent was removed at reduced pressure and the residue column chromatographed (silica gel, 0 – 10% (9:1 methanol/ammonia) in dichloromethane eluant) to give the title compound (0.23g).

Mass Spectrum (API⁺): Found 232 (MH⁺). C₁₃H₁₇N₃O requires 231.

Description 4: (R)-2-[(S)-2-(Benzoxazol-2-ylaminomethyl)-piperidin-1-yl]-2-phenyl-ethanol

A mixture of (R)-2-[(S)-2-Aminomethyl-piperidin-1-yl]-2-phenyl-ethanol (1.0g) (Froelich, Olivier; Desos, Patrice; Bonin, Martine; Quirion, Jean-Charles; Husson, Henri-Philippe;

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Zhu, Jieping. J. Org. Chem. 1996, 61, 6700) and 2-chlorobenzoxazole (0.66g) were combined in tetrahydrofuran (40ml) containing triethylamine (0.43g) and stirred at room temperature for 1 hours. The mixture was partitioned between ethyl acetate and water, the organic phase separated, dried and solvent removed at reduced pressure. the residue was column chromatographed (silica gel, 30% pentane in ethyl acetate – ethyl acetate) to give the title compound (1.1g).

¹H NMR δ: 1.59 – 1.71 (4H, m), 1.91 (1H, t), 2.73 (1H, m), 2.95 (1H, m), 3.71 (2H, m), 4.0 (1H, m), 4.10 (1H, m), 4.26 (1H, m), 5.7 (1H, m), 7.03 (1H, m), 7.17 (1H, m), 7.23 – 7.26 (3H, m) and 7.32 – 7.40 (4H, m). Mass Spectrum (AP⁺): Found 352 (MH⁺). C₂₁H₂₃N₃O₂ requires 351.

Description 5: Benzoxazol-2-yl-(S)-1-piperidin-2-ylmethyl-amine

The compound of description 4 (1.15g) in ethanol (60 ml) containing Pearlman's catalyst (0.23g) was shaken under an atmosphere of hydrogen (50psi) for 24 hours. Additional Pearlman's catalyst was added and shaking under hydrogen at 50psi continued for a further 12 hours. The reaction was filtered through kieselguhr, the filtrate evaporated at reduced pressure and the residue column chromatographed (silica gel, ethyl acetate – ethyl acetate/methanol 1:1 eluant) to give the title compound (0.49g) as an oil.

¹H NMR δ: 1.16 – 1.85 (7H, m), 2.64 (1H, m), 2.85 – 2.99 (1H, m), 3.11 (1H, m), 3.31 (1H, m), 3.55 (1H, m), 7.00 (1H, dd), 7.12 (1H, m), 7.20 (1H, d) and 7.30 (1H, m). Mass Spectrum (AP⁺): Found 232 (MH⁺). C₁₃H₁₇N₃O requires 231.

Description 6: (RS)-Benzoxazol-2-yl-(4-benzyl-morpholin-3-ylmethyl)-amine

From (4-benzyl-morpholin-3-yl)-methylamine (1g) (Morie, Toshiya; Kato, Shiro; Harada, Hiroshi; Yoshida, Naoyuki; Fujiwara, Iwao; Matsumoto, Jun-ichi., Chem. Pharm. Bull. 1995, 43, 1137-47) and 2-chlorobenzoxazole (0.78g), the title compound (0.77g) was prepared according to the method of D4.

¹H NMR δ: 2.33 (1H, m), 2.73 – 2.80 (2H, m), 3.33 (1H, d), 3.51 – 3.90 (6H, m), 4.10 (1H, d), 5.58 (1H, s), 7.04 (1H, m), 7.17 (1H, m) and 7.24 – 7.39 (7H, m). Mass Spectrum (AP⁺): Found 324 (MH⁺). C₁₉H₂₁N₃O₂ requires 323.

Description 7: (RS)-Benzoxazol-2-yl-morpholin-3-ylmethyl-amine

From the compound of D6 (0.77g) the title compound (0.55g) was prepared according to the method of D5.

¹H NMR δ: 2.93 – 3.23 (2H, m), 3.46 – 4.03 (7H, m), 6.95 – 7.23 (4H, m). Mass Spectrum (AP⁺): Found 234 (MH⁺). C₁₂H₁₅N₃O₂ requires 233.

Description 8: (RS) 2-(1H-Benzoimidazol-2-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester

(RS)-2-Aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester (0.25g) and 2-chlorobenzimidazole (0.15g) were combined and warmed to 100°C for 48 hours. After cooling to room temperature the mixture was column chromatographed (silica gel, ethyl acetate/pentane 1:4 – ethyl acetate/pentane 1:1 eluant) to give the title compound (0.1g).

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¹H NMR δ: 1.47 (9H, m), 1.65 – 1.81 (7H, m), 2.85 (1H, t), 3.47 (2H, m), 3.91 (1H, d), 4.32 (1H, s), 5.78 (1H, s), 7.04 (3H, m) and 7.29 (1H, s).

Mass Spectrum (API⁺): Found 331 (MH⁺). C₁₈H₂₆N₄O₂ requires 330.

5 **Description 9: (RS)-(1*H*-Benzoimidazol-2-yl)-piperidin-2-ylmethyl-amine dihydrochloride.**

The compound of D8 (0.39g) was stirred in a mixture of 4M HCl in dioxan/methanol (1:1) for 4 hours. Solvent was removed at reduced pressure to give the title compound (0.28g) as a foam.

10 Mass Spectrum (API⁺): Found 231 (MH⁺). C₁₃H₁₈N₄ requires 230.

Description 10: (RS) 2-(Quinolin-2-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester

15 The title compound (0.1g) was prepared from (RS) 2-aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester (0.5ml) and 2-chloroquinoline (0.5g) according to the procedure of D8. Mass Spectrum (API⁺): Found 342 (MH⁺). C₂₀H₂₇N₃O₂ requires 341.

Description 11: (RS)-Piperidin-2-ylmethyl-quinolin-2-yl-amine

20 The title compound (0.29g) was prepared from the compound of D10 according to the method of D9. After removal of solvent the residue was dissolved in dichloromethane, washed with saturated sodium hydrogen carbonate, the organic phase separated, dried and solvent removed at reduced pressure to give the title compound.

25 ¹H NMR δ: 1.20 – 1.96 (6H, m), 2.64 (1H, m), 2.85 (1H, m), 3.10 (1H, m), 3.35 (1H, m), 3.60 (1H, m), 5.17 (1H, m), 6.66 (1H, d), 7.19 (1H, dt), 7.48 – 7.58 (2H, m), 7.66 (1H, d) and 7.78 (1H, d).

Mass Spectrum (API⁺): Found 242 (MH⁺). C₁₅H₁₉N₃ requires 241.

Description 12: (RS)-2-(Benzothiazol-2-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester

30 The title compound (1.2g) after column chromatography (silica gel, 5% diethyl ether/hexane – diethyl ether eluant) was prepared from (RS) 2-aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester (2.0g) and 2-chlorobenzothiazole (1.58g) according to the method of D2. Mass Spectrum (API⁺): Found 348 (MH⁺). C₁₈H₂₅N₃O₂S requires 347.

35 **Description 13: (RS)-Benzothiazol-2-yl-piperidin-2-ylmethyl-amine**

The compound of D12 (1.2g) was dissolved in methanol (60ml) and treated with 4N HCl in dioxan (12 ml). the mixture was stirred for 4h, added to water containing sodium hydrogen carbonate and extracted with ethyl acetate (x 3). The combined organic phase was dried and solvent removed at reduced pressure to give the title compound (0.70g).

40 Mass Spectrum (API⁺): Found 348 (MH⁺). C₁₃H₁₇N₃S requires 347.

Description 14: 2-(RS)-(Isoquinolin-1-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester

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The title compound (0.76g) was prepared from (RS) 2-aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester (1.6ml) and 1-chloroisoquinoline (0.8g) according to the method used for the preparation of the compound of D8.

Mass Spectrum (API⁺): Found 342 (MH⁺). C₂₀H₂₇N₃O₂ requires 341.

5

Description 15: Isoquinolin-1-yl-piperidin-2-ylmethyl-amine

The title compound (0.39g) was prepared according to the method of description 13 from the compound of D14 (0.75g).

Mass Spectrum (API⁺): Found 242 (MH⁺). C₁₅H₁₉N₃ requires 241.

10

Description 16: (S) 2-(Quinolin-2-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester

The title compound (0.11g) was prepared from (S) 2-aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester (1.23g) and 2-chloroquinoline (1g) according to the procedure of D8.

Mass Spectrum (API⁺): Found 342 (MH⁺). C₂₀H₂₇N₃O₂ requires 341.

15

Description 17: (S)-Piperidin-2-ylmethyl-quinolin-2-yl-amine

The compound of D16 (0.11g) was dissolved in dichloromethane (10ml) and trifluoroacetic acid (1ml) added. The mixture was stirred for 4h, poured into ice containing potassium carbonate and extracted with 10% methanol/dichloromethane (x 3). The combined organic extracts were dried and solvent removed at reduced pressure to give the title compound (0.05g).

20

Mass Spectrum (API⁺): Found 242 (MH⁺). C₁₅H₁₉N₃ requires 241.

Description 18: (RS) 2-(Quinoxalin-2-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester

The title compound (0.73g) was prepared from (RS) 2-aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester (1ml) and 2-chloroquinoxaline (0.5g) according to the procedure of D8.

Mass Spectrum (API⁺): Found 343 (MH⁺). C₁₉H₂₆N₄O₂ requires 342

30

Description 19: (RS)-Piperidin-2-ylmethyl-quinoxalin-2-yl-amine

The title compound (0.36g) was prepared from the compound of D18 (0.71g) according to the method of D17.

Mass Spectrum (API⁺): Found 243 (MH⁺). C₁₄H₁₈N₄ requires 242.

35

Description 20: (RS) 2-(Pyrimidin-2-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester

A mixture of (RS) 2-aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester (1.28g) and 2-chloropyrimidine was heated at 100°C for 48 hours. After cooling to room temperature the mixture was column chromatographed (silica gel, 0 – 10% (9:1 methanol/ammonia) in dichloromethane eluant) to give the title compound (0.42g) as an oil.

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Mass Spectrum (API⁺): Found 293 (MH⁺). C₁₅H₂₄N₄O₂ requires 292.

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46**Description 21: (RS)-Piperidin-2-ylmethyl-pyrimidin-2-yl-amine**

The title compound (0.350g) was prepared from the compound of D20 (0.4g) according to the method of D17.

Mass Spectrum (API⁺): Found 193 (MH⁺). C₁₀H₁₆N₄ requires 192.

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Description 22: (RS) 2-(Pyrazin-2-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester

The title compound (0.18g) was prepared from (RS) 2-aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester (0.54g) and 2-chloropyrazine according to the method of D20.

10 Mass Spectrum (API⁺): Found 293 (MH⁺). C₁₅H₂₄N₄O₂ requires 292.

Description 23: (RS)-Piperidin-2-ylmethyl-pyrazin-2-yl-amine

The title compound (0.18g) was prepared from the compound of D22 (0.08g) according to the method of D17.

15 Mass Spectrum (API⁺): Found 193 (MH⁺). C₁₀H₁₆N₄ requires 192.

Description 24: (S)-2-(Quinazolin-4-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester

20 (S)-2-Aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (1.0g), 4-chloroquinoxaline (0.768g) and diisopropylethylamine (0.816ml) were dissolved in tetrahydrofuran (75ml) and heated to reflux for 6 hours under an atmosphere of argon. After cooling, the reaction solution was partitioned between ethyl acetate and water. The organic layer was washed with saturated sodium hydrogen carbonate solution, saturated brine, dried and evaporated. The residue was chromatographed over silica gel, eluting with a gradient of 50 to 100% ethyl acetate in hexane. The title compound was obtained as a white foam (1.44g).
25 ¹H NMR δ: 1.40 (3H, s), 2.90 (1H, dt), 3.35-3.50 (1H, br.), 3.9-4.05 (1H, br.), 4.15-4.3 (1H, br.), 4.68-4.82 (1H, br.), 6.9-7.2 (1H, br.), 7.40 (1H, t), 7.65-7.85 (3H, m), 8.65 (1H, s).

Description 25: (S)-2-(Quinazolin-4-ylaminomethyl)-piperidine

30 (S)-2-(Quinazolin-4-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester (1.2g) was dissolved in trifluoroacetic acid (60ml) and stirred at room temperature for 2 hours. The solution was then evaporated and the residue chromatographed over silica gel, eluting with 0 to 10% (9:1 methanol – concentrated ammonia solution) in dichloromethane. The title compound was obtained as a white foam (0.84g), MH⁺ 243.

35

Description 26: (S)-2-[(6,7-Difluoro-3-methylquinoxalin-2-ylamino)methyl]-piperidine-1-carboxylic acid *tert* buty ester

40 (S)-2-Aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (1.14g), and 2-chloro-6,7-difluoro-3-methylquinoxaline *Teng et al PCT Int. Appl (2000), WO00/42026A1 20000720* (1.14g) were dissolved in DMF (2ml) and heated to 90°C for 3 days under an atmosphere of argon. After cooling, the reaction solution was partitioned between ethyl acetate and water. The organic layer was washed with water, saturated brine, dried and evaporated. The

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residue was chromatographed over silica gel, eluting with a gradient of 10 to 50% ethyl acetate in hexane. The title compound was obtained as a pink foam (0.524g), MH^+ 393.

- 5 **Description 27:** (S)-2-[(6,7-Difluoro-3-methylquinoxalin-2-ylamino)methyl]-piperidine (S)-2-[(6,7-Difluoro-3-methylquinoxalin-2-ylamino)methyl]-piperidine-1-carboxylic acid *tert* butyl ester (0.524g) was dissolved in trifluoroacetic acid (15ml) and stirred at room temperature for 3 hours. The solution was then evaporated and the residue chromatographed over silica gel, eluting with 0 to 10% (9:1 methanol – concentrated ammonia solution) in dichloromethane. The title compound was obtained as a white solid
10 (0.289g), MH^+ 293.

- Description 28:** (S)-2-[(6,7-Difluoroquinoxalin-2-ylamino)methyl]-piperidine-1-carboxylic acid *tert* butyl ester
(S)-2-Aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (0.607g), and 2-chloro-6,7-difluoroquinoxaline *McQuaid et. al. J. Med. Chem. (1992), 35(18), 3319-24* (0.569g)
15 were dissolved in dimethylformamide (1ml) and heated to 90 °C for 5 days under an atmosphere of argon. After cooling, the reaction solution was partitioned between ethyl acetate and water. The organic layer was washed with water, saturated brine, dried and evaporated. The residue was chromatographed over silica gel, eluting with a gradient of 10 to 50% ethyl acetate in hexane. The title compound was obtained as a pale yellow solid
20 (0.460g), MH^+ 379.

- Description 29:** (S)-2-[(6,7-Difluoroquinoxalin-2-ylamino)methyl]-piperidine (S)-2-[(6,7-Difluoroquinoxalin-2-ylamino)methyl]-piperidine-1-carboxylic acid *tert* butyl ester (0.460g) was dissolved in trifluoroacetic acid (10ml) and stirred at room temperature for 3 hours. The solution was then evaporated and the residue chromatographed over silica gel, eluting with 0 to 10% (9:1 methanol – concentrated ammonia solution) in dichloromethane. The title compound was obtained as a pale yellow foam (0.286g), MH^+ 279.
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- Description 30:** (R,S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidine-1-carboxylic acid *tert* butyl ester
(R,S)-2-Aminomethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (3.0g) and 2-chloro-6,7-difluoroquinoxaline (3.0g) were combined in xylene (20ml) containing
35 diisopropylethylamine (3ml) and heated at 130°C for 24 hours. Solvent was removed at reduced pressure and the residue column chromatographed (silica gel, diethyl ether:petroleum ether 1:1) to give the title compound (3.4g)
Mass Spectrum (API^+): Found 365 (MH^+). $C_{18}H_{22}F_2N_4O_2$ requires 364.

- Description 31:** (R,S)-2-[(6,7-Difluoroquinoxalin-2-ylamino)methyl]-pyrrolidine The compound of D30 (3.4g) was dissolved in dichloromethane (100ml) and treated with trifluoroacetic acid (15ml). After 3h additional trifluoroacetic acid (40ml) and dichloromethane (100ml) was added. The mixture was stirred for 48h, poured into excess
40

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48

- aqueous sodium hydrogen carbonate, the organic phase separated, dried and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, 5% (9:1 methanol/ammonia)/ dichloromethane to give the title compound (0.9g) Mass Spectrum (API⁺): Found 265 (MH⁺). C₁₃H₁₄F₂N₄ requires 264. ¹H NMR δ: 1.56 (1H, m), 1.72 – 1.93 (3H, m), 2.96 (2H, m), 3.28 (1H, m), 3.49 (1H, m), 3.64 (1H, m), 7.39 (1H, dd), 7.59 (1H, dd) and 8.16 (1H, s).

Description 32: (S)-2-(quinazolin-2-ylamino)methyl-piperidine-1-carboxylic acid *tert* butyl ester

- The title compound (0.6g) was prepared from (S)-2-aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (0.68g) and 2-chloroquinazoline (0.53g) according to the method of D30.
Mass Spectrum (API⁺): Found 343 (MH⁺). C₁₉H₂₆N₄O₂ requires 342.

Description 33: (S)-1-Piperidin-2-ylmethyl-quinazolin-2-yl-amine

- The title compound (0.384g) was prepared from the compound of D32 (0.6g) according to the method of D31
Mass Spectrum (API⁺): Found 243 (MH⁺). C₁₄H₁₈N₄ requires 242.
¹H NMR δ: 1.18 – 1.65 (6H, m), 2.66 (1H, m), 3.08 – 3.23 (2H, m), 3.50 (1H, m), 3.69 (1H, m), 6.16 (1H, br. s), 7.20 (1H, t), 7.54 – 7.69 (3H, m) and 8.91 (1H, s).

Description 34: (S)-2-([1,5]Naphthyridin-2-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester

- The title compound (0.48g) was prepared from (S)-2-aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (0.59g) and 2-chloro-1,5-naphthyridine *Rapoport, et al J. Org. Chem. (1971), 36(3), 450-4* (0.40g) according to the method of D30.
Mass Spectrum (API⁺): Found 343 (MH⁺). C₁₉H₂₆N₄O₂ requires 342.

Description 35: [1,5]Naphthyridin-2-yl-(S)-1-piperidin-2-ylmethyl-amine

- The title compound (0.30g) was prepared from the compound of D34 (0.48g) according to the method of D31.
Mass Spectrum (API⁺): Found 243 (MH⁺). C₁₄H₁₈N₄ requires 242.
¹H NMR δ: 1.25 – 1.88 (6H, m), 2.68 (1H, m), 2.98 (1H, m), 3.16 (1H, m), 3.37 – 3.50 (1H, m), 3.66 (1H, m), 6.85 (1H, d), 7.41 (1H, dd), 7.95 (1H, t) and 8.58 (1H, m).

Description 36: (S)-2-(1,8-Naphthyridin-2-ylamino)methyl-piperidine-1-carboxylic acid *tert* butyl ester

- The title compound (0.28g) was prepared from (S)-2-aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (0.35g) and 2-chloro-1,8-naphthyridine (0.19g) according to the method of D30.
Mass Spectrum (API⁺): Found 343 (MH⁺). C₁₉H₂₆N₄O₂ requires 342.

Description 37: [1,8]Naphthyridin-2-yl-(S)-1-piperidin-2-ylmethyl-amine

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The title compound (0.11g) was prepared from the compound of D36 (0.28g) according to the method of D31.

Mass Spectrum (API⁺): Found 243 (MH⁺). C₁₄H₁₈N₄ requires 242.

5 **Description 38: (RS) 2-(4-Azabenzoxazol-2-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester**

The title compound (0.7g) was prepared from (RS)-2-aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (0.64g) and 2-methylthio-4-azabenzoxazole *Chu-Moyeret al J. Org. Chem. (1995), 60(17), 5721-5.* (0.5g) according to the method of D30.

10 Mass Spectrum (API⁺): Found 333 (MH⁺). C₁₇H₂₄N₄O₃ requires 332.

Description 39: (RS)-Oxazolo[4,5-b]pyridin-2-yl-piperidin-2-ylmethyl-amine

The title compound (0.55g) was prepared from the compound of D38 (0.7g) according to the method of D31.

15 Mass Spectrum (API⁺): Found 233 (MH⁺). C₁₂H₁₆N₄O requires 232.

Description 40: ((S)-1-{1-[2-(3-Methyl-[1,2,4]-oxadiazol-5-yl)-phenyl]-methanoyl}-piperidin-2-ylmethyl)-carbamic acid *tert* butyl ester

20 A mixture of (S)-1-piperidin-2-ylmethyl-carbamic acid *tert* butyl ester (2.0g) and 2-(3-methyl-[1,2,4]oxadiazol-5-yl)-benzoic acid (1.9) in dimethylformamide (10ml containing diisopropylethylamine (2.4ml) was treated with [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] (3.55g) and stirred at 90°C for 16 hours. Solvent was removed at reduced pressure and the residue column chromatographed (silica gel, diethyl ether eluant) to give the title compound (3.4g).

25 Mass Spectrum (API⁺): Found 401 (MH⁺). C₂₁H₂₈N₄O₄ requires 400.

Description 41: 1-((S)-2-Aminomethyl-piperidin-1-yl)-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

30 The title compound (0.53g) was prepared from the compound of D40 according to the method of D13.

Mass Spectrum (API⁺): Found 301 (MH⁺). C₁₆H₂₀N₄O₂ requires 300.

Description 42: Methyl-((S)-1-{1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanoyl}-piperidin-2-ylmethyl)-carbamic acid dimethyl-ethyl ester

35 ((S)-1-{1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanoyl}-piperidin-2-ylmethyl)-carbamic acid *tert* butyl ester (0.4g) in tetrahydrofuran (5ml) was treated with sodium hydride (0.1g). After evolution of hydrogen had ceased iodomethane (0.1ml) was added and the reaction stirred for 16 hours. The reaction was quenched with ice/water, extracted with diethyl ether (x 3), the combined organic extracts dried and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, diethyl ether) to give the title compound (0.2g).

40 Mass Spectrum (API⁺): Found 415 (MH⁺). C₂₂H₃₀N₄O₄ requires 414.

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50**Description 43: 1-[(R)-2-Methylaminomethyl-piperidin-1-yl]-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone**

The title compound (0.15g) was prepared from the compound of D42 according to the method of D13.

- 5 Mass Spectrum (API⁺): Found 315 (MH⁺). C₁₁H₁₂N₄ requires 314.

Description 44: (S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidine-1-carboxylic acid *tert* butyl ester

- 10 The title compound (0.53g) was prepared from (S)-2-aminomethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.5g) and 2-chloro-6,7-difluoroquinoxaline (0.5g) according to the method of D30.

Mass Spectrum (API⁺): Found 365 (MH⁺). C₁₈H₂₂F₂N₄O₂ requires 364.

Description 45: (S)-2-[(6,7-Difluoroquinoxalin-2-ylamino)methyl]-pyrrolidine

- 15 The title compound (0.38g) was prepared from the compound of D44 (0.53g) according to the method of D31.

Mass Spectrum (API⁺): Found 265 (MH⁺). C₁₃H₁₄F₂N₄ requires 264.

Description 46: (RS)-3-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-morpholine-4-carboxylic acid *tert* butyl ester

- 20 The title compound (0.58g) was prepared from 2-aminomethylmorpholine-4-carboxylic acid *tert*-butyl ester (0.82g) and 2-chloro-6,7-difluoroquinoxaline (0.76g) according to the method of D30.

Mass Spectrum (API⁺): Found 381 (MH⁺). C₁₈H₂₂F₂N₄O₃ requires 380.

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Description 47: (6,7-Difluoro-quinoxalin-2-yl)-morpholin-3-ylmethyl-amine

- 30 The compound of D46 (0.58g) was dissolved in trifluoroacetic acid and stirred for 3 hours. Solvent was removed at reduced pressure and the residue partitioned between aqueous sodium hydrogen carbonate and ethyl acetate. The organic phase was separated dried, solvent removed at reduced pressure and the residue column chromatographed (silica gel, 0 – 10% (9:1 methanol/ammonia) in dichloromethane, eluant) to give the title compound (0.327g).

Mass Spectrum (API⁺): Found 281 (MH⁺). C₁₃H₁₄F₂N₄O requires 280.

- 35 **Description 48: 2-(Pyrido[2,3-*b*]pyrazin-2-ylaminomethyl)-piperidine-1-carboxylic acid *tert*-butyl ester and 2-(Pyrido[2,3-*b*]-pyrazin-3-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester**

- 40 A mixture of (S)-2-aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester (1.0g) and a 2:1 mixture of 2-chloro-pyrido[2,3-*b*]pyrazine and 3-chloro-pyrido[2,3-*b*]pyrazine (0.8g) was combined and warmed to 90°C for 18 hours. The mixture was diluted with ethyl acetate, washed with aqueous sodium hydrogen carbonate and water, the organic phase dried and solvent was removed at reduced pressure. The residue was column chromatographed (silica gel, dichloromethane 0 to 6% ethanol in dichloromethane, 1%

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51**Description 43: 1-[(R)-2-Methylaminomethyl-piperidin-1-yl]-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone**

The title compound (0.15g) was prepared from the compound of D42 according to the method of D13.

- 5 Mass Spectrum (API⁺): Found 315 (MH⁺). C₁₁H₁₂N₄ requires 314.

Description 44: (S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidine-1-carboxylic acid *tert* butyl ester

- 10 The title compound (0.53g) was prepared from (S)-2-aminomethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.5g) and 2-chloro-6,7-difluoroquinoxaline (0.5g) according to the method of D30.

Mass Spectrum (API⁺): Found 365 (MH⁺). C₁₈H₂₂F₂N₄O₂ requires 364.

Description 45: (S)-2-[(6,7-Difluoroquinoxalin-2-ylamino)methyl]-pyrrolidine

- 15 The title compound (0.38g) was prepared from the compound of D44 (0.53g) according to the method of D31.

Mass Spectrum (API⁺): Found 265 (MH⁺). C₁₃H₁₄F₂N₄ requires 264.

Description 46: (RS)-3-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-morpholine-4-carboxylic acid *tert* butyl ester

- 20 The title compound (0.58g) was prepared from 2-aminomethylmorpholine-4-carboxylic acid *tert*-butyl ester (0.82g) and 2-chloro-6,7-difluoroquinoxaline (0.76g) according to the method of D30.

Mass Spectrum (API⁺): Found 381 (MH⁺). C₁₈H₂₂F₂N₄O₃ requires 380.

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Description 47: (6,7-Difluoro-quinoxalin-2-yl)-morpholin-3-ylmethyl-amine

- 30 The compound of D46 (0.58g) was dissolved in trifluoroacetic acid and stirred for 3 hours. Solvent was removed at reduced pressure and the residue partitioned between aqueous sodium hydrogen carbonate and ethyl acetate. The organic phase was separated dried, solvent removed at reduced pressure and the residue column chromatographed (silica gel, 0 – 10% (9:1 methanol/ammonia) in dichloromethane, eluant) to give the title compound (0.327g).

Mass Spectrum (API⁺): Found 281 (MH⁺). C₁₃H₁₄F₂N₄O requires 280.

- 35 **Description 48: 2-(Pyrido[2,3-*b*]pyrazin-2-ylaminomethyl)-piperidine-1-carboxylic acid *tert*-butyl ester and 2-(Pyrido[2,3-*b*]pyrazin-3-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester**

- 40 A mixture of (S)-2-aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester (1.0g) and a 2:1 mixture of 2-chloro-pyrido[2,3-*b*]pyrazine and 3-chloro-pyrido[2,3-*b*]pyrazine (0.8g) was combined and warmed to 90°C for 18 hours. The mixture was diluted with ethyl acetate, washed with aqueous sodium hydrogen carbonate and water, the organic phase dried and solvent was removed at reduced pressure. The residue was column chromatographed (silica gel, dichloromethane 0 to 6% ethanol in dichloromethane, 1%

X52
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- increments) to give as the faster running component 2-(pyrido[2,3-*b*]pyrazin-2-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester (0.48g). mass spectrum (API⁺): Found 344 (MH⁺). C₁₇H₂₅N₅O₂ requires 343 and 2-(pyrido[2,3-*b*]pyrazin-3-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester (0.3g) mass spectrum (API⁺):
- 5 Found 344 (MH⁺). C₁₇H₂₅N₅O₂ requires 343.

Description 49: Piperidin-2-ylmethyl-pyrido[2,3-*b*]pyrazin-2-yl-amine trifluoroacetate salt

- 10 2-(Pyrido[2,3-*b*]pyrazin-2-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester (0.48g) was dissolved in dichloromethane (3ml), cooled (ice bath) and treated with trifluoroacetic acid (2ml). The mixture was stirred for 3 hours at room temperature, solvent removed at reduced pressure and the residue co-evaporated with toluene to give the title compound (0.45g).

Mass spectrum (API⁺): Found 244 (MH⁺). C₁₃H₁₇N₅ requires 243.

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Description 50: Piperidin-2-ylmethyl-pyrido[2,3-*b*]pyrazin-3-yl-amine trifluoroacetate salt

- 20 The title compound (0.3g) was prepared from 2-(pyrido[2,3-*b*]pyrazin-3-ylaminomethyl)-piperidine-1-carboxylic acid *tert* butyl ester (0.3g) according to the method of description 49

Mass spectrum (API⁺): Found 244 (MH⁺). C₁₃H₁₇N₅ requires 243.

- 25 **Description 51: 2-Thioureidomethyl-piperidine-1-carboxylic acid *tert* butyl ester**
Benzoyl chloride (1.2ml) was added dropwise to sodium thiocyanate (0.90g) in acetone (50ml). When the addition was complete the mixture was refluxed for 15 minutes, cooled to room temperature and (RS) 2-aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester (2.0g) in acetone (5ml) added. The mixture was refluxed for 2 hours, cooled to room temperature and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, 0 – 10% (9:1 methanol/ammonia) in dichloromethane eluant) to give the title product (1.95g).

Mass spectrum (API⁺): Found 274 (MH⁺). C₁₂H₂₃N₃O₂S requires 273.

- 35 **Description 52: 2-[(4-Phenyl-thiazol-2-ylamino)-methyl]-piperidine-1-carboxylic acid *tert* butyl ester**

- The compound of description 51 (1.95g) was dissolved in ethanol (100ml) containing triethylamine (0.99ml). Phenacyl bromide (1.42g) was added and the mixture stirred for 16 hours. Solvent was removed at reduced pressure and the residue partitioned between ethyl acetate and water. The organic phase was separated and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, dichloromethane eluant) to give the title compound (2.42g).

Mass spectrum (API⁺): Found 274 (MH⁺). C₂₀H₂₇N₃O₂S requires 273.

Description 53: (4-Phenyl-thiazol-2-yl)-piperidin-2-ylmethyl-amine

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The title compound (1.55g) was prepared from the compound of D52 (2.42g) according to the method of D47.

Mass spectrum (API⁺): Found 174 (MH⁺). C₁₃H₁₉N₃O₂S requires 173.

5 **Description 54: 2-[(5-Cyano-pyridin-2-ylamino)-methyl]-piperidine-1-carboxylic acid *tert* butyl ester.**

The title compound (1.54g) was prepared from (S)-2-aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (2.0g) and 2-chloro-5-cyanopyridine (1.29g) in the presence of diisopropylethylamine (1.21g) according to the method of D28.

10 Mass spectrum (API⁺): Found 317 (MH⁺). C₁₇H₂₄N₄O₂ requires 316.

Description 55: 6-[(Piperidin-2-ylmethyl)-amino]-nicotinonitrile

The title compound (1.56g) was prepared from the compound of D54 (1.53g) and trifluoroacetic acid according to the method of D29.

15 Mass spectrum (API⁺): Found 217 (MH⁺). C₁₂H₁₆N₄ requires 216.

Description 56: 2-[(4-Trifluoromethyl-pyrimidin-2-ylamino)-methyl]-piperidine-1-carboxylic acid *tert* butyl ester

20 The title compound (0.298g) was prepared from (S)-2-aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (1.0g) and 2-chloro-4-trifluoropyrimidine (0.85g) according to the method of D28.

Mass spectrum (API⁺): Found 361 (MH⁺). C₁₆H₂₃F₃N₄O₂ requires 360.

Description 57: Piperidin-2-ylmethyl-(4-trifluoromethyl-pyrimidin-2-yl)-amine.

25 The title compound (0.25g) was prepared from the compound of D56 (0.29g) and trifluoroacetic acid according to the method of D29.

Mass spectrum (API⁺): Found 261 (MH⁺). C₁₁H₁₅F₃N₄ requires 260.

30 **Description 58: ((S)-1-[1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl]-piperidin-2-ylmethyl)-carbamic acid *tert* butyl ester**

The title compound (3.96g) was prepared from (S)-1-piperidin-2-ylmethyl-carbamic acid *tert* butyl ester (2.14g) and 4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl carboxylic acid (2.20g) according to the method of D40.

Mass spectrum (API⁺): Found 417 (MH⁺). C₂₂H₂₉FN₄O₃ requires 416:

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Description 59: ((S)-1-[1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl]-piperidin-2-ylmethyl)-methyl-carbamic acid dimethyl-ethyl ester.

The title compound (2.0g) was prepared from the compound of description 58 (3.85g) according to the method of D42.

40 Mass spectrum (API⁺): Found 431 (MH⁺). C₂₃H₃₁FN₄O₃ requires 430

Description 60: 1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-1-((S)-2-methylaminomethyl-piperidin-1-yl)-methanone

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The title compound (0.15g) was prepared for the compound of D59 (0.50g) according to the method of D29.

5 **Description 61: (S)-2-[(3-Cyano-pyridin-2-ylamino)-methyl]-piperidine-1-carboxylic acid *tert* butyl ester**

The title compound (0.66g) was prepared from (S)-2-aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (1.55g) and 2-chloro-3-cyanopyridine (1.0g) according to the method of D28.

Mass spectrum (API⁺): Found 317 (MH⁺). C₁₇H₂₄N₄O₂ requires 316

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Description 62: 2-[(S)-1-Piperidin-2-ylmethyl-amino]-nicotinonitrile

The title compound (0.53g) was prepared from the compound of D61 (0.663g) and trifluoroacetic acid according to the method of D29.

Mass spectrum (API⁺): Found 217 (MH⁺). C₁₂H₁₆N₄ requires 216

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Description 63: (S)-2-[(4-Cyano-pyridin-2-ylamino)-methyl]-piperidine-1-carboxylic acid *tert* butyl ester

The title compound (0.24g) was prepared from (S)-2-aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (1.14g) and 2-chloro-4-cyanopyridine (0.74g) according to the method of D28.

20

Mass spectrum (API⁺): Found 317 (MH⁺). C₁₇H₂₄N₄O₂ requires 316

Description 64: 4-Cyano-2-[(S)-1-Piperidin-2-ylmethyl-amino]-pyridine

The title compound (0.17g) was prepared from the compound of D63 (0.243g) and trifluoroacetic acid according to the method of D29.

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Mass spectrum (API⁺): Found 217 (MH⁺). C₁₂H₁₆N₄ requires 216

Description 65: (S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidine-1-carboxylic acid *tert* butyl carbonate.

30 (S)-2-Aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester (1g), 5-bromo-2-chloropyrimidine (0.9g) were combined in xylene (20ml) containing potassium carbonate (1.29g) and diisopropylethylamine (2.43g) and warmed to reflux for 48h. The mixture was cooled to room temperature, filtered and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, pentane – 25% ethyl acetate/pentane). The
35 appropriate fractions were collected, solvent removed at reduced pressure to give the title compound (1.43g) as a colourless gum

Mass spectrum (API⁺): Found 272 (MH⁺ - *tert* BOC). C₁₀H₁₄N₄Br requires 371

Description 66: (S) (5-Bromo-pyrimidin-2-yl)-piperidin-2-ylmethyl-amine

40 The title compound (1.40g) was prepared from the compound of D65 (2.1 g) according to the method of D9.

Mass spectrum (API⁺): Found 272 (MH⁺). C₁₀H₁₄N₄Br requires 271.

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SS

Description 67: (S) 2-[(3-Cyano-6,7-difluoro-quinolin-2-ylamino)-methyl]-piperidine-1-carboxylic acid *tert* butyl ester.

- (S)-2-Aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (1.1g) and 2-chloro-3-cyano-5,6-difluoroquinoline (1.12g) according to the method of D28 were combined in xylene (15ml) containing potassium carbonate (4.0g) and diisopropylethylamine (4ml) and boiled for 20 hours. The reaction mixture was cooled to room temperature, filtered and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, dichloromethane eluant) to give after combining appropriate fractions the title compound (1.8g).
- 10 Mass spectrum (API⁺): Found 403 (MH⁺). C₂₁H₂₄F₂N₄O₂ requires 402

Description 68: (S) 6,7-Difluoro-2-[(piperidin-2-ylmethyl)-amino]-quinoline-3-carbonitrile

- The title compound (1.40g) was prepared from the compound of D67 (1.8g) according to the method of D9.
- 15 Mass spectrum (API⁺): Found 303 (MH⁺). C₁₆H₁₆F₂N₄ requires 302

Description 69: (S) 2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-carboxylic acid *tert* butyl carbonate.

- (S)-2-Aminomethyl-pyrrolidine-1-carboxylic acid *tert* butyl ester (2g), 5-bromo-2-chloropyrimidine (1.93g) were combined in xylene (40ml) containing potassium carbonate (2.76g) and diisopropylethylamine (5.23ml) and warmed to reflux for 20h. The mixture was cooled to room temperature, filtered and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, pentane - 25% ethyl acetate/pentane). The appropriate fractions were collected, solvent removed at reduced pressure to give the title compound (1.78g) as a colourless gum
- 20
25
Mass spectrum (API⁺): Found 257 (MH⁺ - *tert* BOC). C₁₄H₂₁BrN₄O₂ requires 357

Description 70: (S) (5-Bromo-pyrimidin-2-yl)-pyrrolidin-2-ylmethyl-amine

- The title compound (1.40g) was prepared from the compound of D69 (1.78 g) according to the method of D9.
- 30
Mass spectrum (API⁺): Found 258 (MH⁺). C₉H₁₂N₄Br requires 257.

Description 71: 3-(1-[(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl]-methanoyl)-benzoic acid

- 3-(1-[(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl]-methanoyl)-benzoic acid methyl ester (0.5g) was dissolved in methanol (15ml) and treated with 1M sodium hydroxide (1.7ml). The reaction mixture was stirred for 12 h, additional 1M sodium hydroxide (1.7ml) added and stirring continued for a further 24h. The reaction mixture was diluted with water and washed with ethyl acetate. The aqueous phase was acidified with 2M hydrochloric acid and extracted with ethyl acetate (x 3). the combined organic phase was dried (MgSO₄), filtered and solvent removed at reduced pressure to give the title compound (0.463g) as a yellow solid.
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Mass spectrum (API⁺): Found 427 (MH⁺). C₂₂H₂₀F₂N₄O₃ requires 426.

Description 72: 1,1,1-Trifluoromethanesulphonic acid, 5-bromo-pyridin-2-yl ester

To a solution of 5-bromo-2-pyridone (3g) in dichloromethane (60ml) and pyridine (60ml) at 0°C under argon was added dropwise trifluoromethane sulphonic anhydride (5.4g). The resulting mixture was warmed to ambient temperature and after 20h was evaporated and the residue chromatographed on silica gel eluting with ethyl acetate to afford the title product (3.5g) as a yellow oil. ¹H NMR δ: 7.10 (1H, d, J = 8 Hz), 8.00 (1H, dd, 2.4 and 8 Hz), 8.46 (1H, d, J = 2.4 Hz).

Description 73: (S)-2-[(5-Bromopyridin-2-ylamino)-methyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

The title product (0.22g) was obtained from (S)-2-aminomethyl-pyrrolidine-1-carboxylic acid *tert* butyl ester (1g) and the compound of D72 (1.7g) according to the method of D69.

Mass Spectrum (Electrospray LC/MS), API⁺: Found 356 (MH⁺). C₁₅H₂₂⁷⁹BrN₃O₂ requires 355.

Description 74: (5-Bromo-pyridin-2-yl)-(S)-1-pyrrolidin-2-ylmethylamine

To a solution of the compound from D73 (0.49g) in dichloromethane (40ml) at ambient temperature was added trifluoroacetic acid (5ml). After 48h, the reaction mixture was evaporated and partitioned between chloroform and 1M sodium hydroxide. The aqueous layer was extracted with chloroform and the combined organic extracts dried and evaporated to afford the title compound (0.33g) as an orange oil. ¹H NMR δ: 1.44 - 1.48 (1H, m), 1.71 - 1.81 (3H, m), 2.05 (1H, br s), 2.93 (2H, m), 3.09 - 3.13 (1H, m), 3.35 - 3.41 (2H, m), 4.99 (1H, br s), 6.32 (1H, d, J = 9 Hz), 7.43 (1H, dd, J = 3 and 9 Hz), 8.08 (1H, d, J = 3 Hz).

Description 75: N-(4-Benzyl-morpholin-3-ylmethyl)-2,2,2-trifluoroacetamide

To (4-benzyl-morpholin-3-yl)-methylamine (7.34g) in dichloromethane (240ml) was added triethylamine (5.83ml), followed by dropwise addition of trifluoroacetic anhydride (8.23g) over 25 min at 0°C under argon. The reaction mixture was allowed to reach ambient temperature and after stirring for 18h, was diluted in dichloromethane and washed with saturated aqueous sodium hydrogencarbonate. The organic phase was separated, dried and evaporated to afford a brown gum that was purified on silica gel, eluting with ethyl acetate-pentane mixtures to afford the title product (5.17g) as an orange gum. Mass Spectrum (API⁺): Found 303 (MH⁺). C₁₄H₁₇F₃N₂O₂ requires 302.

Description 76: 2,2,2-Trifluoro-N-morpholin-3-ylmethyl acetamide

To the compound from D75 (1.62g) in methanol (40ml) was added palladium black (0.45g) and formic acid (10 drops) and the mixture stirred at ambient temperature for 16h. Further palladium black (0.225g) and formic acid (10 drops) were added and after 1h, the reaction mixture was filtered through kieselguhr and the filtrate evaporated to an orange gum. Re-

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evaporation from dichloromethane provided the title compound (1.4g) as a pink solid. Mass Spectrum (API⁺): Found 213 (MH⁺). C₇H₁₁F₃N₂O₂ requires 212.

5 **Description 77: 3-[(2,2,2-Trifluoro-ethanoylamino)-methyl]-morpholine-4-carboxylic acid *tert*-butyl ester**

A mixture of the compound from D76 (1.75g), triethylamine (2.25ml) and di-*tert*-butyl dicarbonate (3.59g) in dichloromethane (75ml) was stirred at ambient temperature for 18h. The reaction mixture was diluted with dichloromethane and washed successively with 2M hydrochloric acid, water and brine, dried and evaporated to a gum. Chromatography on silica gel eluting with ethyl acetate-pentane mixtures afforded the title compound (1.70g) as a pale yellow solid. Mass Spectrum (API⁺): Found 213 (MH⁺-Boc)⁺. C₁₂H₁₉F₃N₂O₄ requires 312.

15 **Description 78: 3-Aminomethyl-morpholine-4-carboxylic acid *tert*-butyl ester**

A mixture of the compound from D77 (1.7g) and potassium carbonate (3.77g) in methanol (80 ml) and water (27 ml) was stirred at ambient temperature for 4h and then heated at 50°C for a further 2h. The reaction mixture was concentrated to remove methanol, diluted with water and extracted with ethyl acetate (x3) and dichloromethane (x4). The combined extracts were dried and evaporated to afford the title product (0.97g) as a yellow gum. Mass Spectrum (API⁺): Found 116 (MH⁺-Boc)⁺. C₁₀H₂₀N₂O₃ requires 216.

25 **Description 79: 3-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-morpholine-4-carboxylic acid *tert*-butyl ester**

The title compound (1.19g) was obtained from the compound of D78 (0.97g) and 5-bromo-2-chloropyrimidine (0.87g) according to the method of D30. Mass spectrum (API⁺): Found 273 (MH⁺-Boc). C₁₄H₂₁⁷⁹BrN₄O₃ requires 372.

30 **Description 80: (5-Bromo-pyrimidin-2-yl)-morpholin-3-ylmethyl amine**

To the compound of D79 (1.15g) in dichloromethane (45 ml) at 0°C was added trifluoroacetic acid (5 ml) and the reaction mixture then stirred at ambient temperature for 2h. The resulting solution was poured onto ice and saturated aqueous potassium carbonate solution, and then extracted with dichloromethane (x2). The organic extracts were dried and evaporated to afford the title product (0.85g) as an off white solid. Mass Spectrum (API⁺): Found 273 (MH⁺). C₉H₁₃⁷⁹BrN₄O requires 272.

35 **Description 81: (S)-2-[(4-Cyano-2,6-difluoro-phenylamino)-methyl]-piperidine-1-carboxylic acid *tert*-butyl ester**

(S)-2-Aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (1.36g) and 3,4,5-trifluorobenzonitrile (1.00g) were heated under argon in xylene (10 ml) containing diisopropylethylamine (3.3 ml) for 16h. The reaction mixture was cooled and partitioned between ethyl acetate and water. The organic phase was washed with brine, dried and evaporated to give a solid which was triturated with pentane-ether to afford the title product (0.16 g) as an off white powder. Chromatography of the mother liquors on silica gel eluting

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with ethyl acetate-pentane mixtures afforded further title product (0.92 g). Mass Spectrum (AP⁺): Found 252 (MH⁺-Boc). C₁₈H₂₃F₂N₃O₂ requires 351.

- Description 82: 3,5-Difluoro-4-(((S)-1-piperidin-2-ylmethyl)-amino)-benzonitrile**
5 Trifluoroacetic acid (3 ml) was added to a solution of D81 (1.05 g) in dichloromethane (27 ml) at 0 °C. The reaction was allowed to reach ambient temperature, stirred for 4 h and then poured into saturated aqueous potassium carbonate. The aqueous phase was extracted with dichloromethane and the combined extracts dried and evaporated to afford the title compound (0.59g) as an off white solid. Mass Spectrum (AP⁺): Found 252 (MH⁺).
10 C₁₃H₁₅F₂N₃ requires 251.

- Description 83: (S)-2-[(4-Cyano-2,6-difluoro-phenylamino)-methyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester**
The title compound (0.295g) was obtained from (S)-2-aminomethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.402g) and 3,4,5-trifluorobenzonitrile (0.314g) using a
15 similar procedure to that described in Description 81. Mass Spectrum (AP⁺): Found 238 (MH⁺-Boc) C₁₇H₂₁F₂N₃O₂ requires 337.

- Description 84: 3,5-Difluoro-4-(((S)-1-pyrrolidin-2-ylmethyl)-amino)-benzonitrile**
20 The title compound (0.19g) was obtained from the compound of D83 (0.28g) using a similar procedure to that described in Description 82.

- Description 85: (S)-2-[(5-Ethyl-pyrimidin-2-ylamino)-methyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester**
25 The title compound (0.10g) was obtained from (S)-2-aminomethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.75g) and 2-chloro-5-ethyl pyrimidine (0.53g) using a similar procedure to that described in description 81. Mass Spectrum (Electrospray LC/MS): Found 307 (MH⁺). C₁₆H₂₆N₄O₂ requires 306.

- Description 86: (5-Ethyl-pyrimidin-2-yl)-(S)-1-pyrrolidin-2-ylmethylamine**
30 The title compound (0.07g) was obtained from the compound of D85 (0.10g) using the method of D9. Mass Spectrum (Electrospray LC/MS): Found 207 (MH⁺). C₁₁H₁₈N₄ requires 206.

- Description 87: (S)-2-[(2,2,2-Trifluoro-ethanoylamino)-methyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester**
35 To a solution of (S)-2-aminomethyl pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.3g) in dichloromethane (50 ml) containing triethylamine (1.4 ml) was added trifluoroacetic anhydride (1.6g) dropwise under argon. After 16h at ambient temperature the reaction
40 mixture was diluted with dichloromethane and washed with brine. The aqueous layer was extracted with dichloromethane and the combined extracts dried and evaporated. Chromatography of the residue on silica gel eluting with pentane-ethyl acetate mixtures afforded the title compound (1.43g) as an orange oil. ¹H NMR δ: 1.30 - 1.50 (1H, m), 1.47

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(9H, s), 1.60 - 1.75 (1H, m), 1.80 - 1.95 (2H, m), 2.00 - 2.10 (1H, m), 3.22 - 3.30 (1H, m), 3.30 - 3.55 (3H, m), 9.03 (1H, br s).

5 **Description 88: (S)-2-[[Methyl-(2,2,2-trifluoro-ethanoyl)-amino]-methyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester**

Sodium hydride (0.23g, 60 % dispersion in oil) was added to a solution of the compound of D87 (1.4g) in dimethylformamide (30 ml) under argon. After 1h, iodomethane (0.32 ml) was added and the reaction mixture stirred for a further 16h before being partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined extracts washed with brine, dried and evaporated to give the title compound
10 (1.6g) as an orange oil. Mass Spectrum (API⁺): Found 311 (MH⁺). C₁₃H₂₁F₃N₂O₃ requires 310.

15 **Description 89: (S)-2-Methylaminomethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester**

A mixture of the compound of D88 (1.47g) and 1M potassium carbonate (20 ml) in methanol (50 ml) was stirred at ambient temperature for 20 h. After removal of the methanol *in vacuo*, the residue was partitioned between chloroform and water. The aqueous layer was extracted with chloroform and the combined extracts dried and evaporated to
20 afford the title product (0.82g) as an orange oil.

Description 90: (S)-2-[[5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

The title product (0.85g) was obtained from the compound of D89 (0.82g) and 5-bromo-2-chloro pyrimidine (0.77g) in a similar manner to that described in the procedure of description 81. Mass Spectrum (API⁺): Found 371 (MH⁺). C₁₅H₂₃⁷⁹BrN₄O₂ requires 370.

Description 91: (5-Bromo-pyrimidin-2-yl)-methyl-(S)-1-pyrrolidin-2-yl)methylamine

A solution of the compound from D90 (0.82g) in dichloromethane (50 ml) and trifluoroacetic acid (10 ml) was stirred at ambient temperature for 20 h. evaporated and partitioned between ethyl acetate and 1M sodium hydroxide. The organic phase was separated, dried and evaporated to afford the title product as an orange oil (0.54g). Mass Spectrum (API⁺): Found 271 (MH⁺). C₁₀H₁₅⁷⁹BrN₄ requires 270.

35 **Description 92: (S)-2-[(5-Acetyl-pyrimidin-2-ylamino)-methyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester**

The title compound (0.57g) was prepared from the compound of D69 (1.06g) (1-ethoxyvinyl)tributyl tin (1.2 ml) and tetrakis (triphenylphosphine)palladium (0) (0.172g) according to the method of Example 171. Mass Spectrum (API⁺): Found 321 (MH⁺).
40 C₁₆H₂₄N₄O₃ requires 320.

Description 93: 1-{2-[[((S)-1-Pyrrolidin-2-ylmethyl)-amino]-pyrimidin-5-yl}-ethanone trifluoroacetate

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To a solution of the compound of D92 (0.57g) in dichloromethane (18ml) at 0°C was added trifluoroacetic acid (2ml) dropwise. The reaction mixture was stirred at ambient temperature for 2h, and evaporated to afford the title compound as a yellow gum (1.13g). Mass Spectrum (API⁺): Found 221 (MH⁺). C₁₁H₁₆N₄O requires 220.

5

Description 94: (S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

(S)-2-Aminomethyl pyrrolidine-1-carboxylic acid *tert*-butyl ester (3.38g), 2,5-dichloropyrimidine (2.50g), potassium carbonate (4.67g) and diisopropylethylamine (8.79ml) were heated in xylene (60 ml) at 100°C for 3.75h. The cooled reaction mixture was filtered and the filtrate evaporated to a gum which was chromatographed on silica gel, eluting with ethyl acetate-pentane fractions, to afford the title compound as a pale yellow solid (2.55g). Mass Spectrum (API⁺): Found 213 (MH⁺-^tBoc). C₁₄H₂₁³⁵ClN₄O₂ requires 312.

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Description 95: (5-Chloro-pyrimidin-2-yl)-(S)-1-pyrrolidin-2-ylmethylamine

The compound of D94 (2.5g) was dissolved in dichloromethane (63 ml), cooled to 0°C and trifluoroacetic acid (7 ml) added dropwise. The reaction mixture was stirred at ambient temperature for 2h, recooled to 0°C and further trifluoroacetic acid (3 ml) added. After 2h at ambient temperature the mixture was carefully poured into ice-saturated potassium carbonate and the organic layer separated. The aqueous phase was extracted with dichloromethane (x4) and the combined extracts dried and evaporated to afford the title product (1.74g) as an orange solid. Mass Spectrum (Electrospray LC/MS): Found 213 (MH⁺). C₉H₁₃³³ClN₄ requires 212.

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Description 96: (S)-2-[(5-Cyano-pyridin-2-ylamino)-methyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

(S)-2-Aminomethyl pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.3g), 6-chloronicotinonitrile (0.21g), potassium carbonate (0.41g) and diisopropylethylamine (0.78 ml) were heated in xylene at 130°C for 26h, cooled and the mixture filtered through kieselguhr. The filtrate was evaporated and the residue chromatographed on silica gel, eluting with ethyl acetate-hexane mixtures to afford the title compound (0.2g). Mass Spectrum (API⁺): Found 303 (MH⁺). C₁₆H₂₂N₄O₂ requires 302.

Description 97: 6-[(S)-1-Pyrrolidin-2-ylmethyl]-amino]-nicotinonitrile

A solution of the compound of D96 (0.2g) in dichloromethane (20 ml) and trifluoroacetic acid (2.5 ml) was stirred at ambient temperature for 2h., evaporated and partitioned between dichloromethane and 1M sodium hydroxide. The aqueous phase was extracted with dichloromethane and the combined extracts dried and evaporated to afford the title compound as a gum (0.137g). Mass Spectrum (Electrospray LC/MS): Found 203 (MH⁺). C₁₁H₁₄N₄ requires 202.

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61**Description 98: 1,1,1-Trifluoromethanesulfonic acid 6-methyl-2-methylsulfanyl-pyrimidin-4-yl ester**

To a solution of 6-methyl-2-methylsulfanyl-pyrimidin-4-ol (1 g) in dichloromethane (40 ml) containing triethylamine (1.35 ml) at 0°C under argon was added trifluoromethanesulphonic anhydride (1.46 ml) dropwise. The resulting solution was allowed to reach ambient temperature and stirred for 16h. before being partitioned between dichloromethane and saturated aqueous sodium hydrogen carbonate solution. The organic phase was washed with brine, dried and evaporated and the residue chromatographed on silica gel, eluting with ethyl acetate-pentane mixtures, to afford the title compound (0.8g). ¹H NMR δ: 2.53 (3H, s), 2.55 (3H, s), 6.63 (1H, s).

Description 99: 2,2,2-Trifluoro-N-(S)-1-pyrrolidin-2-ylmethyl-acetamide

The title compound (2.31g) was obtained from the compound of D87 (5.5g) using the method of D97. ¹H NMR δ: 1.30 - 1.50 (1H, m), 1.70 - 1.95 (3H, m), 2.20 (1H, br s), 2.85 - 2.90 (1H, m), 2.94 - 2.97 (1H, m), 3.07 - 3.12 (1H, m), 3.37 - 3.39 (1H, m), 3.44 - 3.48 (1H, m), 7.15 (1H, br s).

Description 100: 2,2,2-Trifluoro-N-((S)-1-{1-[5-(4-fluorophenyl)-2-methyl-thiazol-4-yl]-methanoyl}-pyrrolidin-2-ylmethyl)-acetamide

The title compound (3.84g) was obtained from the compound of D99 (2.31g) and 5-(4-fluorophenyl)-2-methyl-thiazole-4-carboxylic acid (3.08g) using the method of Example 229. Mass Spectrum (Electrospray LC/MS): Found 416 (MH⁺). C₁₈H₁₇F₄N₃O₂S requires 415.

Description 101: 1-((S)-2-Aminomethyl-pyrrolidin-1-yl)-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

The title compound (2.45g) was obtained from the compound of D100 (3.84g) using a similar procedure to that described in D78. Mass Spectrum (Electrospray LC/MS): Found 320 (MH⁺). C₁₆H₁₈FN₃OS requires 319.

Description 102: 3-[(2,2,2-Trifluoro-ethanoylamino)-methyl]-morpholine-4-carboxylic acid *tert*-butyl ester

The title compound (0.56g) was obtained from the compound of D77 (0.55g) and iodomethane (0.12 ml) using a method similar to that of Description 88. Mass Spectrum (API⁺): Found 227 (MH⁺-^tBoc). C₁₃H₂₁F₃N₂O₄ requires 326.

Description 103: 3-Methylaminomethyl-morpholine-4-carboxylic acid *tert*-butyl ester

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The title compound (0.29g) was obtained from the compound of D102 (0.56g) using the method of Description 89.

5 **Description 104: 3-[[[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl]-morpholine-4-carboxylic acid *tert*-butyl ester**

The title compound (0.3g) was obtained from the compound of D103 (0.29g) and 5-bromo-2-chloropyrimidine (0.26g) using the method of Description 81. Mass Spectrum (Electrospray LC/MS): Found 287 (MH^+ -^tBoc). $C_{15}H_{23}^{79}BrN_4O_3$ requires 386.

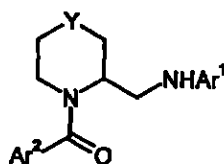
10 **Description 105: (5-Bromo-pyrimidin-2-yl)-methyl-morpholin-3-ylmethyl-amine**

The title compound (0.19g) was obtained from the compound of D104 (0.3g) according to the method of Description 91. Mass Spectrum (API^+): Found 287 (MH^+). $C_{10}H_{15}^{79}BrN_4O$ requires 286.

15 **Example 1: 1-[2-(Benzoxazol-2-ylaminomethyl)-piperidin-1-yl]-1-(2-methyl-5-phenyl-thiazol-4-yl)-methanone**

20 The amine of D3 (0.11g), triethylamine (0.05g) and 2-methyl-5-phenyl-thiazole-4-carbonyl chloride (0.12g) were combined in dichloromethane (5ml) and shaken for 16 hours. The organic phase was washed with water, filtered through a Whatman phase-separation filter tube, solvent removed at reduced pressure to give after column chromatography (silica gel, 0 – 10% (9:1 methanol/ammonia) in dichloromethane eluant) the title compound (0.13g). Mass Spectrum (API^+): Found 433 (MH^+). $C_{24}H_{24}N_4O_2S$ requires 432.

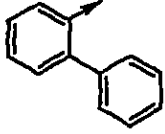
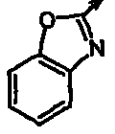
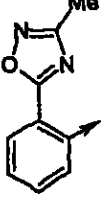
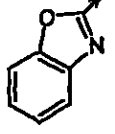
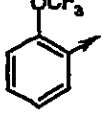
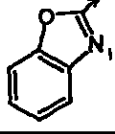
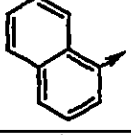
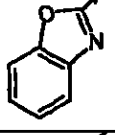
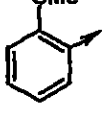
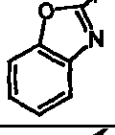
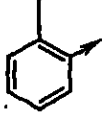
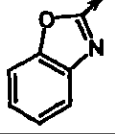
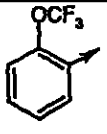
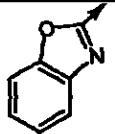
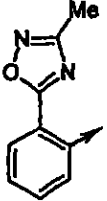
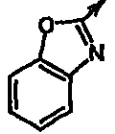
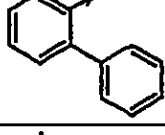
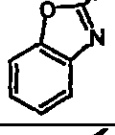
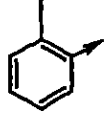
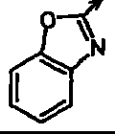
25 The compounds of the Examples below were prepared from the appropriate amine and acid chloride using a similar procedure to that described in Example, 1.



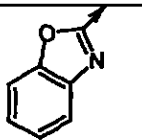
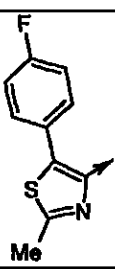
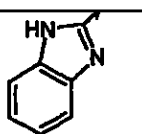
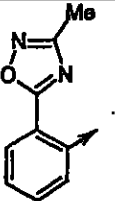
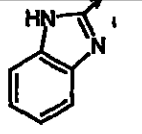
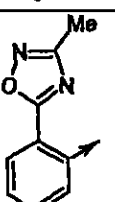
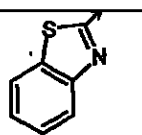
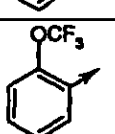
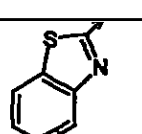
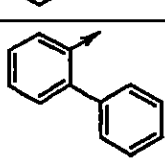
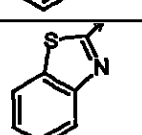
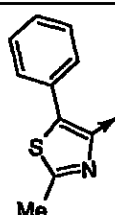
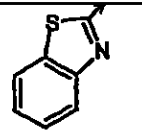
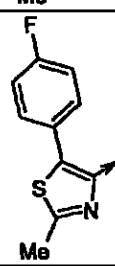
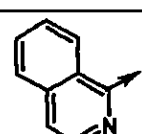
30

Example	Amine	Y	Ar ²	Ar ¹	Mass Spectrum (Electrospray LC/MS) API^+
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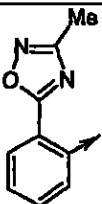
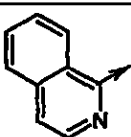
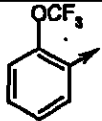
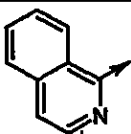
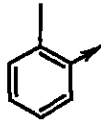
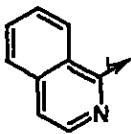
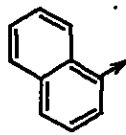
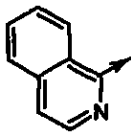
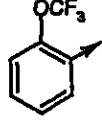
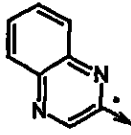
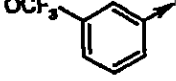
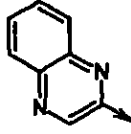
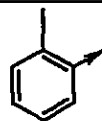
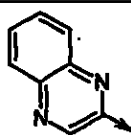
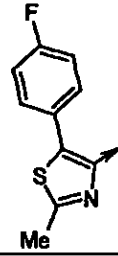
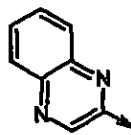
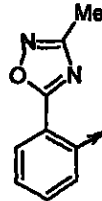
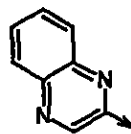
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2	D3	CH ₂			Found 412 (MH ⁺). C ₂₆ H ₂₅ N ₃ O ₂ requires 411
3	D3	CH ₂			Found 418 (MH ⁺). C ₂₃ H ₂₃ N ₅ O ₃ requires 417
4	D3	CH ₂			Found 420 (MH ⁺). C ₂₁ H ₂₀ F ₃ N ₃ O ₃ requires 419
5	D3	CH ₂			Found 386 (MH ⁺). C ₂₄ H ₂₃ N ₃ O ₂ requires 385
6	D3	CH ₂			Found 366 (MH ⁺). C ₂₁ H ₂₃ N ₃ O ₃ requires 365
7	D3	CH ₂			Found 462 (MH ⁺). C ₂₀ H ₂₀ IN ₃ O ₂ requires 461
8	D5	CH ₂			Found 420 (MH ⁺). C ₂₁ H ₂₀ F ₃ N ₃ O ₃ requires 419
9	D5	CH ₂			Found 418 (MH ⁺). C ₂₃ H ₂₃ N ₅ O ₃ requires 417
10	D5	CH ₂			Found 412 (MH ⁺). C ₂₆ H ₂₅ N ₃ O ₂ requires 411
11	D5	CH ₂			Found 462 (MH ⁺). C ₂₀ H ₂₀ IN ₃ O ₂ requires 461

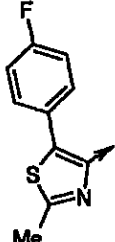
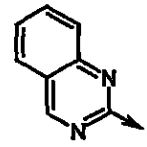
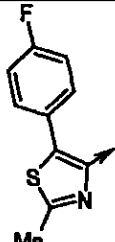
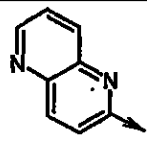
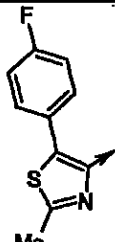
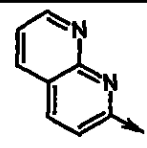
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12	D3	CH ₂	Ph		Found 336 (MH ⁺). C ₂₀ H ₂₁ N ₃ O ₂ requires 335
13	D9	CH ₂			Found 450 (MH ⁺). C ₂₄ H ₂₄ FN ₃ OS requires 449
14	D9	CH ₂			Found 417 (MH ⁺). C ₂₃ H ₂₄ N ₆ O ₂ requires 416
15	D13	CH ₂			Found 434 (MH ⁺). C ₂₃ H ₂₃ N ₅ O ₂ S requires 433
16	D13	CH ₂			Found 436 (MH ⁺). C ₂₁ H ₂₀ F ₃ N ₃ O ₂ S requires 435
17	D13	CH ₂			Found 428 (MH ⁺). C ₂₆ H ₂₅ N ₃ OS requires 427
18	D13	CH ₂			Found 449 (MH ⁺). C ₂₄ H ₂₄ N ₄ OS ₂ requires 448
19	D15	CH ₂			Found 461 (MH ⁺). C ₂₆ H ₂₅ FN ₄ OS requires 460

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20	D15	CH ₂			Found 428 (MH ⁺). C ₂₅ H ₂₅ N ₅ O ₂ requires 427
21	D15	CH ₂			Found 430 (MH ⁺). C ₂₃ H ₂₂ F ₃ N ₅ O ₂ requires 429
22	D15	CH ₂			Found 472 (MH ⁺). C ₂₂ H ₂₂ IN ₃ O requires 471
23	D15	CH ₂			Found 396 (MH ⁺). C ₂₆ H ₂₅ N ₃ O requires 395
24	D19	CH ₂			Found 431 (MH ⁺). C ₂₂ H ₂₁ F ₃ N ₄ O ₂ requires 430
25	D19	CH ₂			Found 431 (MH ⁺). C ₂₂ H ₂₁ F ₃ N ₄ O ₂ requires 430
26	D19	CH ₂			Found 473 (MH ⁺). C ₂₁ H ₂₁ IN ₄ O requires 472
27	D19	CH ₂			Found 462 (MH ⁺). C ₂₅ H ₂₄ FN ₅ OS requires 461
28	D19	CH ₂			Found 429 (MH ⁺). C ₂₄ H ₂₄ N ₆ O ₂ requires 428

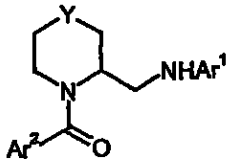
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29	D33	CH ₂			Found 462 (MH ⁺). C ₂₅ H ₂₄ FN ₅ OS requires 461
30	D35	CH ₂			Found 462 (MH ⁺). C ₂₅ H ₂₄ FN ₅ OS requires 461
31	D37	CH ₂			Found 462 (MH ⁺). C ₂₅ H ₂₄ FN ₅ OS requires 461

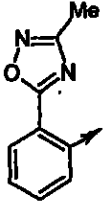
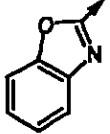
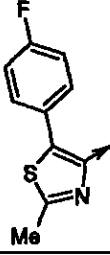
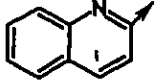
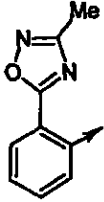
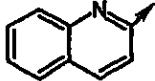
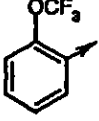
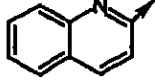
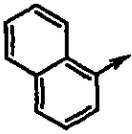
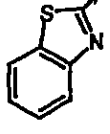
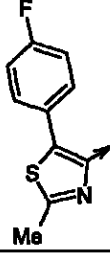
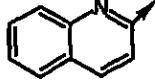
Example 32: 1-[(S)-2-(Benzoxazol-2-ylaminomethyl)-piperidin-1-yl]-1-[5-(4-fluorophenyl)-2-methyl-thiazol-4-yl]-methanone

- 5 A mixture of amine D5 (0.05g), 2-methyl-5-phenyl-thiazole-4-carboxylic acid (0.026g) and diisopropylethylamine (0.06ml) in dimethylformamide (5ml) was treated with [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] (0.042g) and the mixture stirred for 48 hours. The mixture was diluted with ethyl acetate, washed with
- 10 sodium hydrogen carbonate and water, dried, solvent removed at reduced pressure and the residue column chromatographed (silica gel, dichloromethane – 1% methanol/dichloromethane) to give the title compound (0.05g).
- Mass Spectrum (AP⁺): Found 451 (MH⁺). C₂₄H₂₃FN₄O₂S requires 450.

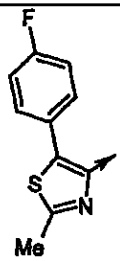
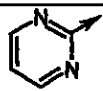
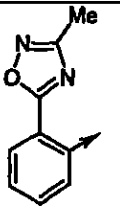
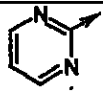
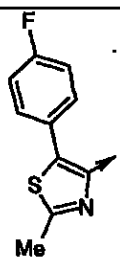
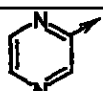
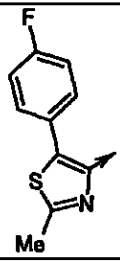
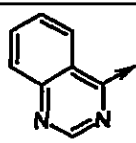
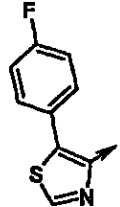
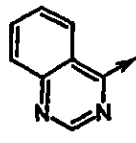
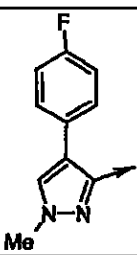
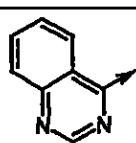
- 15 The compounds of the Examples below were prepared from the appropriate amine and acid using similar procedures to that described in Example 32.



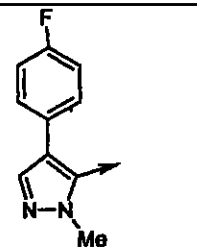
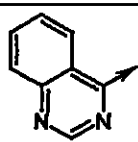
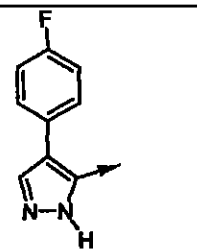
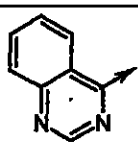
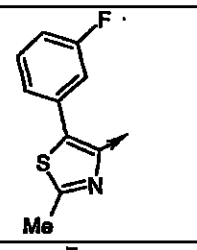
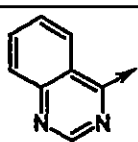
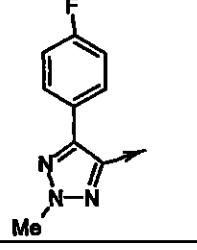
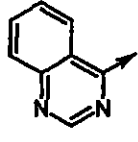
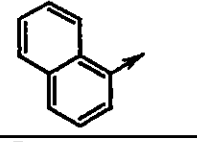
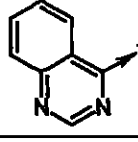
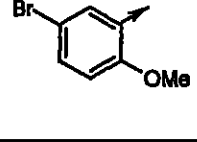
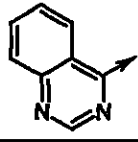
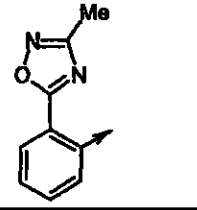
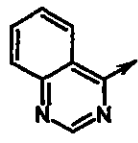
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Example	Amine	Y	Ar ²	Ar ¹	Mass Spectrum (Electrospray LC/MS), API ⁺
33	D7	O			Found 420 (MH ⁺). C ₂₂ H ₂₁ N ₅ O ₄ requires 419
34	D11	CH ₂			Found 461 (MH ⁺). C ₂₆ H ₂₅ FN ₄ OS requires 460
35	D11	CH ₂			Found 428 (MH ⁺). C ₂₅ H ₂₅ N ₅ O ₂ requires 427 Prepared as the HCl salt
36	D11	CH ₂			Found 430 (MH ⁺). C ₂₃ H ₂₂ F ₃ N ₃ O ₂ requires 429 Prepared as the HCl salt
37	D13	CH ₂			Found 402 (MH ⁺). C ₂₄ H ₂₃ N ₃ OS requires 401
38	D17	CH ₂			Found 461 (MH ⁺). C ₂₆ H ₂₅ FN ₄ OS requires 460

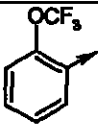
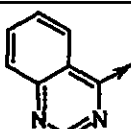
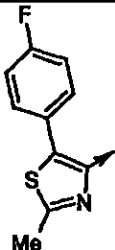
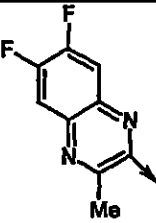
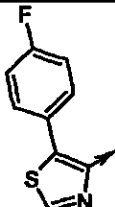
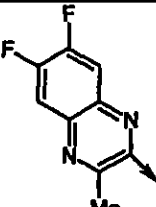
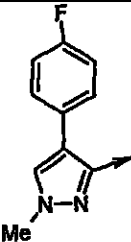
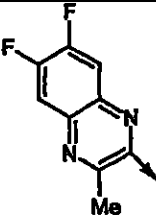
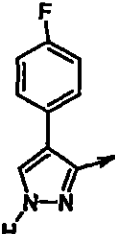
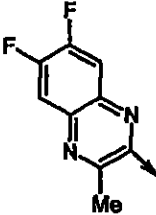
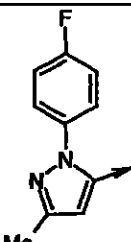
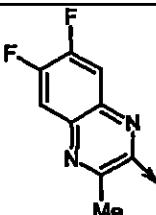
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39	D21	CH ₂			Found 412 (MH ⁺). C ₂₁ H ₂₂ FN ₃ OS requires 411
40	D21	CH ₂			Found 379 (MH ⁺). C ₂₀ H ₂₂ N ₆ O ₂ requires 378
41	D23	CH ₂			Found 412 (MH ⁺). C ₂₁ H ₂₂ FN ₃ OS requires 411
42	D25	CH ₂			Found 462 (MH ⁺). C ₂₅ H ₂₄ FN ₃ OS requires 461
43	D25	CH ₂			Found 448 (MH ⁺). C ₂₄ H ₂₂ FN ₃ OS requires 447
44	D25	CH ₂			Found 445 (MH ⁺). C ₂₅ H ₂₅ FN ₆ O requires 444

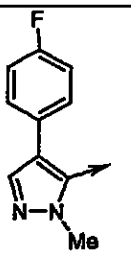
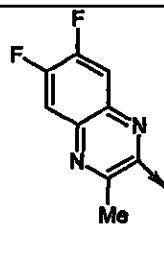
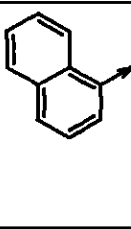
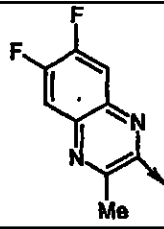
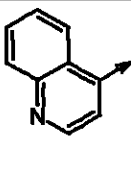
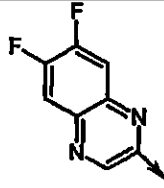
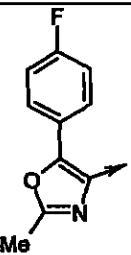
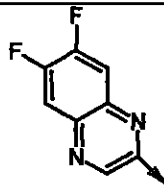
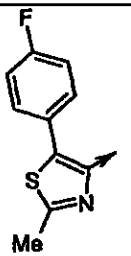
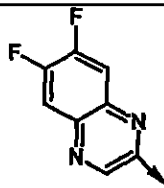
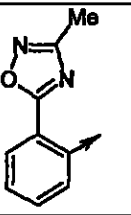
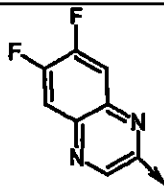
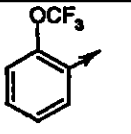
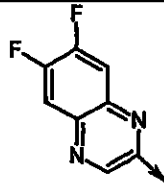
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45	D25	CH ₂			Found 445 (MH ⁺). C ₂₅ H ₂₃ FN ₂ O requires 444
46	D25	CH ₂			Found 431 (MH ⁺). C ₂₄ H ₂₃ FN ₂ O requires 430
47	D25	CH ₂			Found 462 (MH ⁺). C ₂₅ H ₂₄ FN ₃ OS requires 461
48	D25	CH ₂			Found 446 (MH ⁺). C ₂₄ H ₂₄ FN ₃ O requires 445
49	D25	CH ₂			Found 397 (MH ⁺). C ₂₅ H ₂₄ N ₄ O requires 396
50	D25	CH ₂			Found 456 (MH ⁺). C ₂₂ H ₂₃ ⁷⁹ BrN ₄ O ₂ requires 455.
51	D25	CH ₂			Found 429 (MH ⁺). C ₂₄ H ₂₄ N ₆ O ₂ requires 428

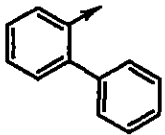
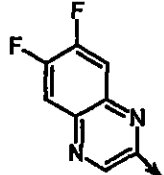
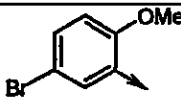
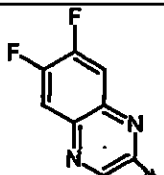
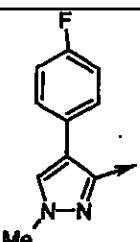
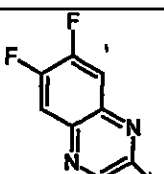
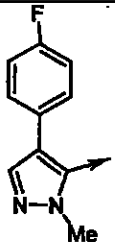
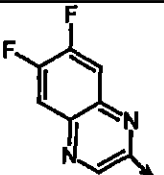
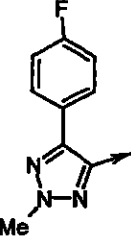
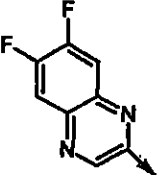
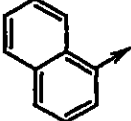
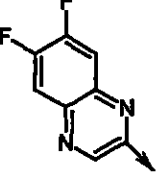
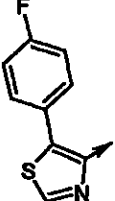
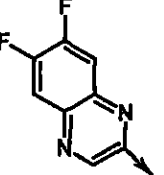
1770
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52	D25	CH ₂			Found 431 (MH ⁺). C ₂₂ H ₂₁ F ₃ N ₄ O ₂ requires 430
53	D27	CH ₂			Found 512 (MH ⁺). C ₂₆ H ₂₄ F ₃ N ₅ OS requires 511
54	D27	CH ₂			Found 498 (MH ⁺). C ₂₅ H ₂₂ F ₃ N ₅ OS requires 497
55	D27	CH ₂			Found 495 (MH ⁺). C ₂₆ H ₂₅ F ₃ N ₆ O requires 494
56	D27	CH ₂			Found 481 (MH ⁺). C ₂₅ H ₂₃ F ₃ N ₆ O requires 480
57	D27	CH ₂			Found 495 (MH ⁺). C ₂₆ H ₂₅ F ₃ N ₆ O requires 494

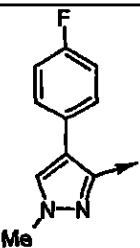
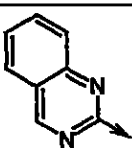
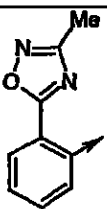
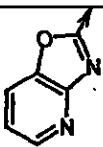
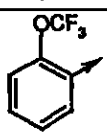
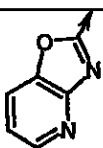
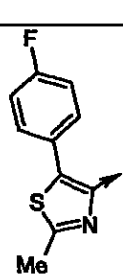
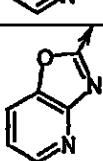
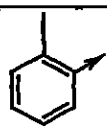
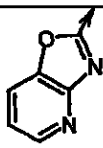
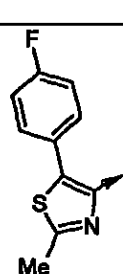
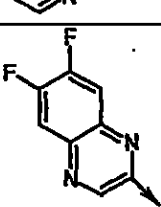
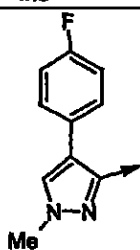
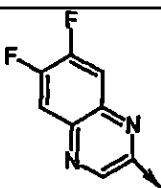
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58	D27	CH ₂			Found 495 (MH ⁺). C ₂₆ H ₂₅ F ₃ N ₆ O requires 494
59	D27	CH ₂			Found 447 (MH ⁺). C ₂₆ H ₂₄ F ₂ N ₄ O requires 446
60	D29	CH ₂			Found 434 (MH ⁺). C ₂₄ H ₂₁ F ₂ N ₅ O requires 433
61	D29	CH ₂			Found 482 (MH ⁺). C ₂₅ H ₂₂ F ₃ N ₅ O ₂ requires 481
62	D29	CH ₂			Found 498 (MH ⁺). C ₂₅ H ₂₂ F ₃ N ₅ OS requires 497
63	D29	CH ₂			Found 465 (MH ⁺). C ₂₄ H ₂₂ F ₂ N ₆ O ₂ requires 464
64	D29	CH ₂			Found 467 (MH ⁺). C ₂₂ H ₁₉ F ₅ N ₄ O ₂ requires 466

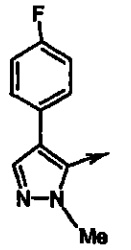
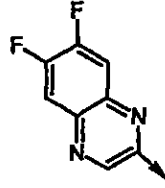
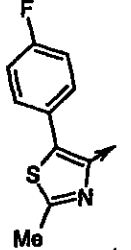
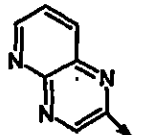
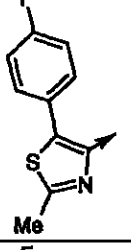
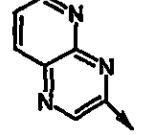
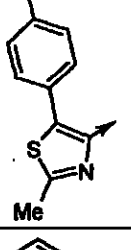
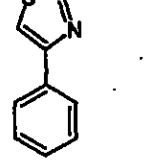
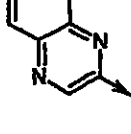
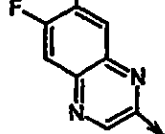
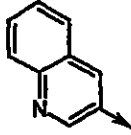
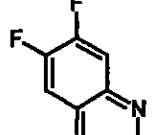
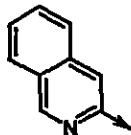
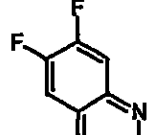
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65	D29	CH ₂			Found 459 (MH ⁺). C ₂₇ H ₂₄ F ₂ N ₄ O requires 458
66	D29	CH ₂			Found 491 (MH ⁺). C ₂₂ H ₂₁ ⁷⁹ BrF ₂ N ₄ O ₂ requires 490
67	D29	CH ₂			Found 481 (MH ⁺). C ₂₅ H ₂₃ F ₃ N ₆ O requires 480
68	D29	CH ₂			Found 481 (MH ⁺). C ₂₅ H ₂₃ F ₃ N ₆ O requires 480
69	D29	CH ₂			Found 482 (MH ⁺). C ₂₄ H ₂₂ F ₃ N ₇ O requires 481
70	D29	CH ₂			Found 433 (MH ⁺). C ₂₅ H ₂₂ F ₂ N ₄ O requires 432
71	D29	CH ₂			Found 484 (MH ⁺). C ₂₄ H ₂₀ F ₃ N ₅ OS requires 483

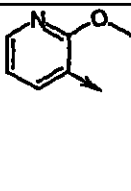
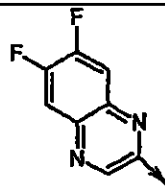
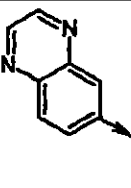
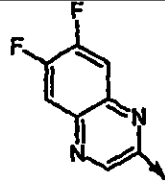
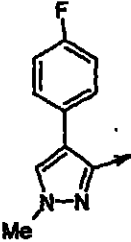
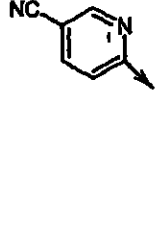
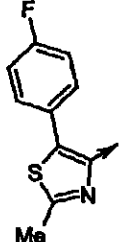
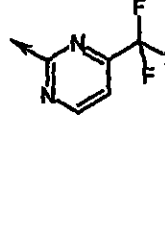
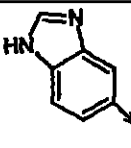
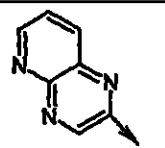
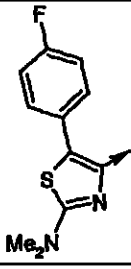
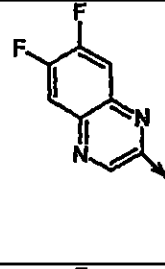
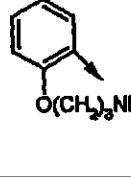
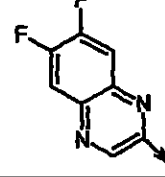
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23

72	D33	CH ₂			Found 445 (MH ⁺). C ₂₅ H ₂₅ FN ₆ O requires 444
73	D39	CH ₂			Found 419 (MH ⁺). C ₂₂ H ₂₂ N ₆ O ₃ requires 418
74	D39	CH ₂			Found 421 (MH ⁺). C ₂₀ H ₁₉ F ₃ N ₄ O ₃ requires 420
75	D39	CH ₂			Found 452 (MH ⁺). C ₂₃ H ₂₂ FN ₅ O ₂ S requires 451
76	D39	CH ₂			Found 463 (MH ⁺). C ₁₉ H ₁₉ IN ₄ O ₂ requires 462
77	D47	O			Found 500 (MH ⁺). C ₂₄ H ₂₀ F ₃ N ₅ O ₂ S requires 499
78	D47	O			Found 483 (MH ⁺). C ₂₄ H ₂₁ F ₃ N ₆ O ₂ requires 482

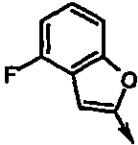
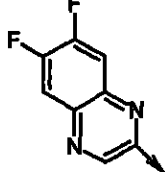
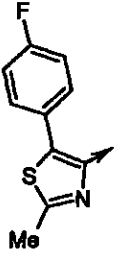
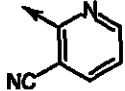
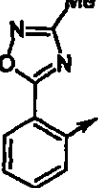
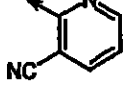
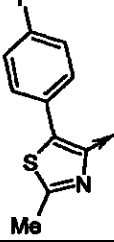
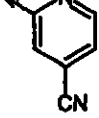
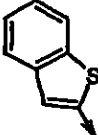
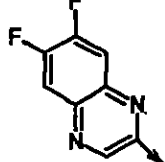
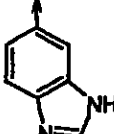
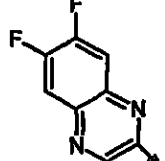
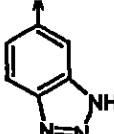
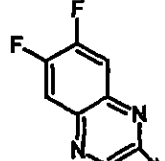
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79	D47	O			Found 483 (MH ⁺). C ₂₄ H ₂₁ F ₃ N ₆ O ₂ requires 482
80	D49	CH ₂			Found 463 (MH ⁺). C ₂₄ H ₂₃ FN ₆ OS requires 462
81	D50	CH ₂			Found 463 (MH ⁺). C ₂₄ H ₂₃ FN ₆ OS requires 462
82	D53	CH ₂			Found 493 (MH ⁺). C ₂₆ H ₂₅ FN ₄ OS ₂ requires 492
83	D29	CH ₂			Found 435 (MH ⁺). C ₂₃ H ₂₀ F ₂ N ₆ O requires 434
84	D29	CH ₂			Found 434 (MH ⁺). C ₂₄ H ₂₁ F ₂ N ₅ O requires 433
85	D29	CH ₂			Found 434 (MH ⁺). C ₂₄ H ₂₁ F ₂ N ₅ O requires 433

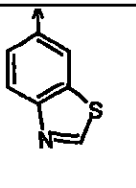
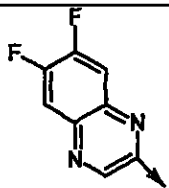
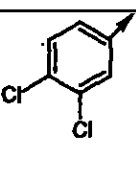
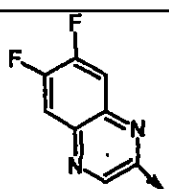
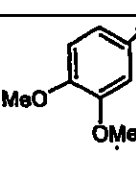
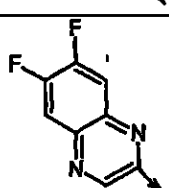
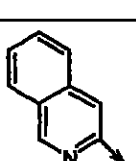
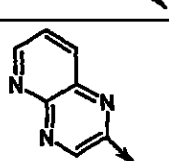
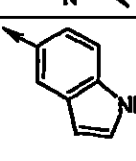
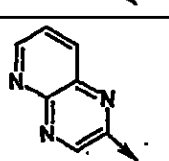
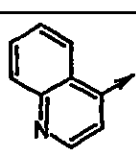
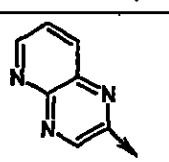
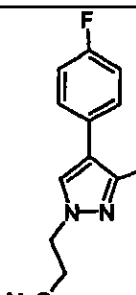
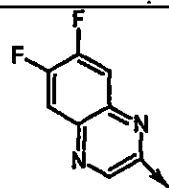
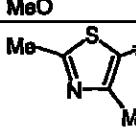
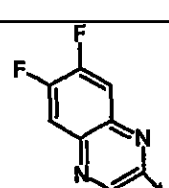
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86	D29	CH ₂			Found 414 (MH ⁺). C ₂₁ H ₂₁ F ₂ N ₅ O ₂ requires 413
87	D29	CH ₂			Found 435 (MH ⁺). C ₂₃ H ₂₀ F ₂ N ₆ O requires 434
88	D55	CH ₂			Found 419 (MH ⁺). C ₂₃ H ₂₃ FN ₆ O requires 418
89	D57	CH ₂			Found 480 (MH ⁺). C ₂₂ H ₂₁ F ₄ N ₅ OS requires 479
90	D49	CH ₂			Found 388(MH ⁺). C ₂₁ H ₂₁ N ₇ O requires 387
91	D29	CH ₂			Found 527 (MH ⁺). C ₂₆ H ₂₅ F ₃ N ₆ OS requires 526
92	D29	CH ₂			Found 484 (MH ⁺). C ₂₆ H ₃₁ F ₂ N ₅ O ₂ requires 483

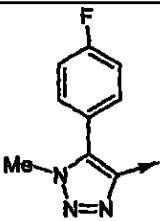
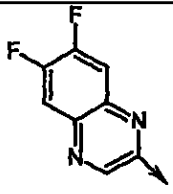
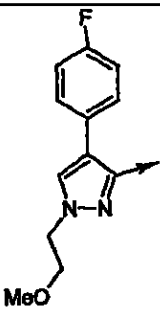
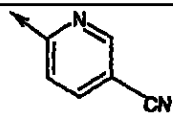
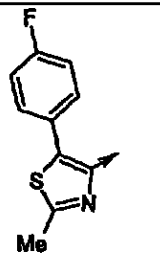
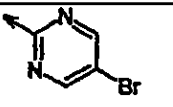
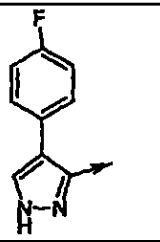
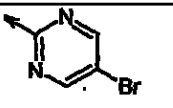
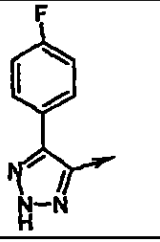
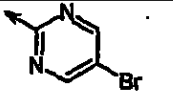
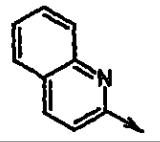
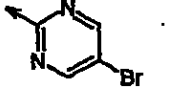
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109	D29	CH ₂			Found 441 (MH ⁺). C ₂₃ H ₁₉ F ₃ N ₄ O ₂ requires 440
110	D62	CH ₂			Found 436 (MH ⁺). C ₂₃ H ₂₂ FN ₃ OS requires 435
111	D62	CH ₂			Found 403 (MH ⁺). C ₂₂ H ₂₂ N ₆ O ₂ requires 402
112	D64	CH ₂			Found 436 (MH ⁺). C ₂₃ H ₂₂ FN ₃ OS requires 435
113	D29	CH ₂			Found 439 (MH ⁺). C ₂₃ H ₂₀ F ₂ N ₄ OS requires 438
114	D29	CH ₂			Found 423 (MH ⁺). C ₂₂ H ₂₀ F ₂ N ₆ O requires 422
115	D29	CH ₂			Found 424 (MH ⁺). C ₂₁ H ₁₉ F ₂ N ₇ O requires 423

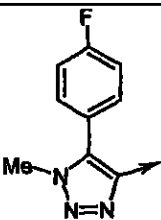
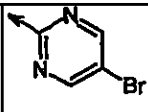
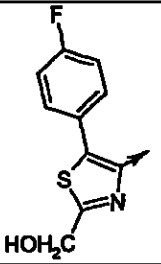
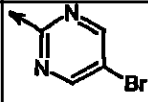
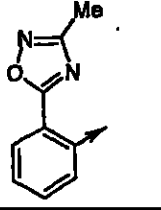
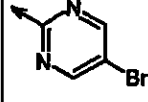
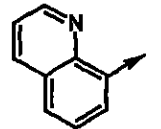
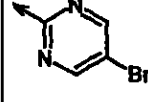
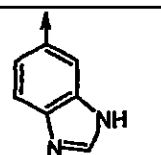
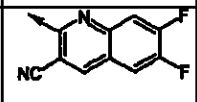
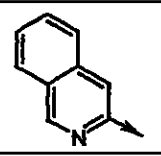
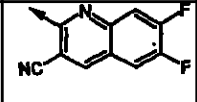
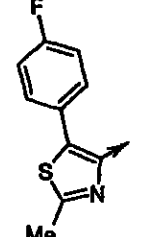
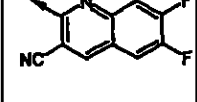
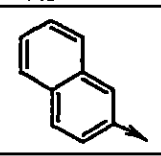
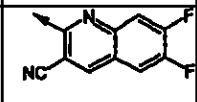
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116	D29	CH ₂			Found 440 (MH ⁺). C ₂₂ H ₁₉ F ₂ N ₅ OS requires 439
117	D29	CH ₂			Found 452 (MH ⁺). C ₂₁ H ₁₈ Cl ₂ F ₂ N ₄ O requires 451
118	D29	CH ₂			Found 443 (MH ⁺). C ₂₃ H ₂₄ F ₂ N ₄ O ₃ requires 442
121	D49	CH ₂			Found 399 (MH ⁺). C ₂₃ H ₂₂ N ₆ O requires 398
122	D49	CH ₂			Found 387 (MH ⁺). C ₂₂ H ₂₂ N ₆ O requires 386
123	D49	CH ₂			Found 399 (MH ⁺). C ₂₃ H ₂₂ N ₆ O requires 398
124	D29	CH ₂			Found 525 (MH ⁺). C ₂₇ H ₂₇ F ₃ N ₆ O ₂ requires 524
125	D29	CH ₂			Found 418 (MH ⁺). C ₂₀ H ₂₁ F ₂ N ₅ OS requires 417

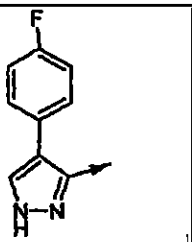
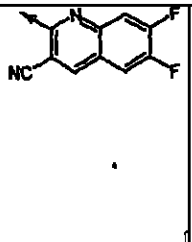
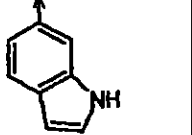
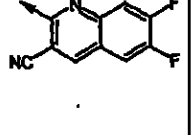
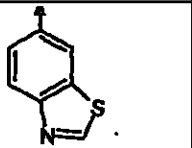
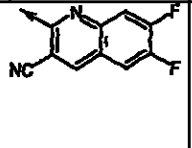
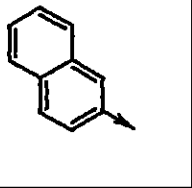
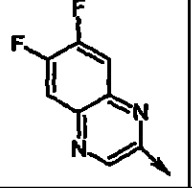
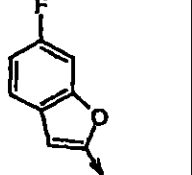
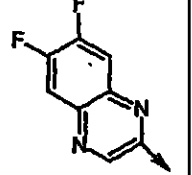
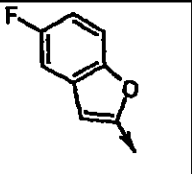
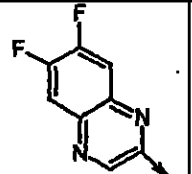
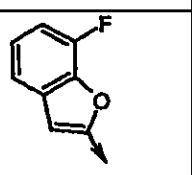
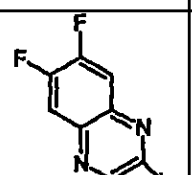
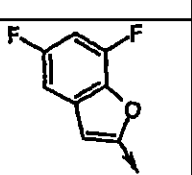
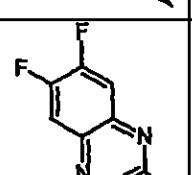
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126	D29	CH ₂			Found 482 (MH ⁺). C ₂₄ H ₂₂ F ₃ N ₇ O requires 481
127	D55	CH ₂			Found 463 (MH ⁺). C ₂₅ H ₂₇ FN ₆ O ₂ requires 462
128	D66	CH ₂			Found 490 (MH ⁺). C ₂₁ H ₂₁ ⁷⁹ BrFN ₅ OS requires 489
129	D66	CH ₂			Found 459 (MH ⁺). C ₂₀ H ₂₀ ⁷⁹ BrFN ₆ O requires 458
130	D66	CH ₂			Found 460 (MH ⁺). C ₁₉ H ₁₉ BrFN ₇ O requires 459
131	D66	CH ₂			Found 426 (MH ⁺). C ₂₀ H ₂₀ ⁷⁹ BrN ₅ O requires 425

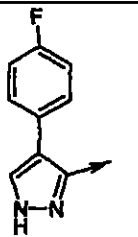
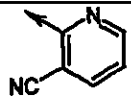
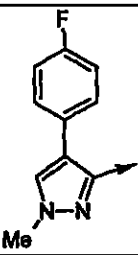
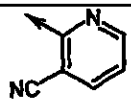
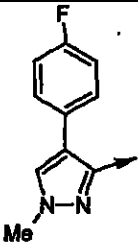
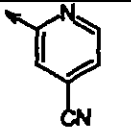
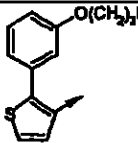
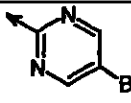
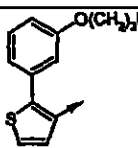
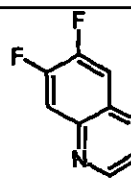
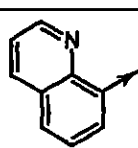
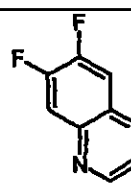
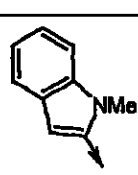
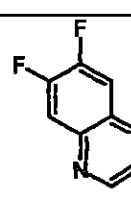
179
79

132	D66	CH ₂			Found 474 (MH ⁺). C ₂₀ H ₂₁ ⁷⁹ BrFN ₇ O requires 473
133	D66	CH ₂			Found 506 (MH ⁺). C ₂₁ H ₂₁ ⁷⁹ BrFN ₃ O ₂ S requires 505
134	D66	CH ₂			Found 457 (MH ⁺). C ₂₀ H ₂₁ ⁷⁹ BrN ₆ O ₂ requires 456
135	D66	CH ₂			Found 426 (MH ⁺). C ₂₀ H ₂₀ ⁷⁹ BrN ₃ O requires 425
136	D68	CH ₂			Found 447 (MH ⁺). C ₂₄ H ₂₀ F ₂ N ₆ O requires 446
137	D68	CH ₂			Found 458 (MH ⁺). C ₂₆ H ₂₁ F ₂ N ₅ O requires 457
138	D68	CH ₂			Found 522 (MH ⁺). C ₂₇ H ₂₂ F ₃ N ₅ OS requires 521
139	D68	CH ₂			Found 457 (MH ⁺). C ₂₇ H ₂₂ F ₂ N ₄ O requires 456

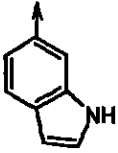
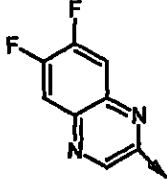
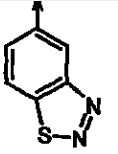
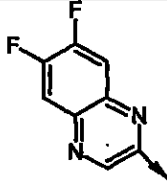
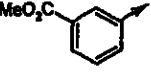
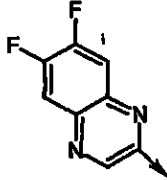
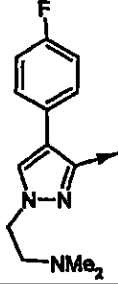
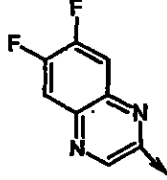
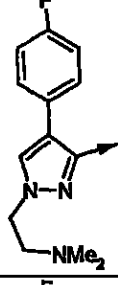
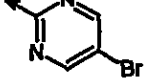
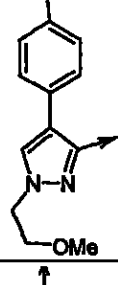
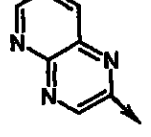
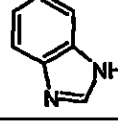
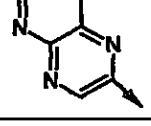
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140	D68	CH ₂			Found 491 (MH ⁺). C ₂₆ H ₂₁ F ₃ N ₆ O requires 490
141	D68	CH ₂			Found 446 (MH ⁺). C ₂₅ H ₂₁ F ₂ N ₅ O requires 445
142	D68	CH ₂			Found 464 (MH ⁺). C ₂₄ H ₁₉ F ₂ N ₅ OS requires 463
143	D29	CH ₂			Found 433 (MH ⁺). C ₂₅ H ₂₂ F ₂ N ₄ O requires 432
144	D29	CH ₂			Found 441 (MH ⁺). C ₂₃ H ₁₉ F ₃ N ₄ O ₂ requires 440
145	D29	CH ₂			Found 441 (MH ⁺). C ₂₃ H ₁₉ F ₃ N ₄ O ₂ requires 440
146	D29	CH ₂			Found 441 (MH ⁺). C ₂₃ H ₁₉ F ₃ N ₄ O ₂ requires 440
147	D29	CH ₂			Found 459 (MH ⁺). C ₂₃ H ₁₈ F ₄ N ₄ O ₂ requires 458

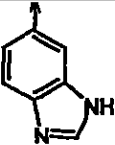
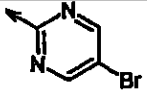
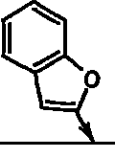
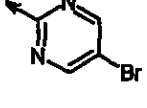
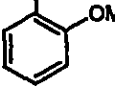
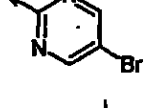
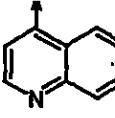
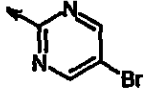
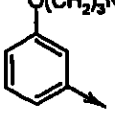
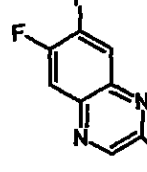
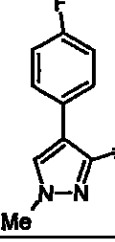
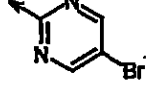
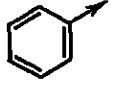
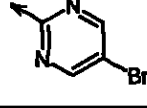
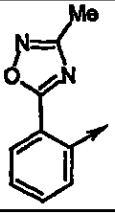
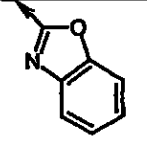
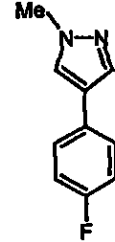
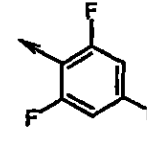
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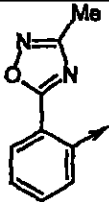
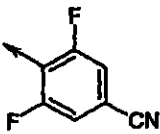
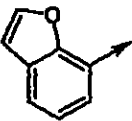
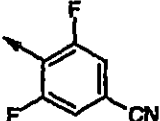
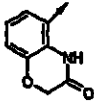
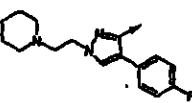
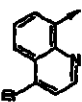
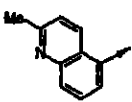
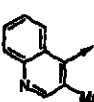
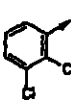
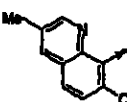
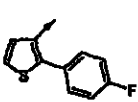
148	D62	CH ₂			Found 405 (MH ⁺). C ₂₂ H ₂₁ FN ₆ O requires 404
149	D62	CH ₂			Found 419 (MH ⁺). C ₂₃ H ₂₃ FN ₆ O requires 418
150	D64	CH ₂			Found 419 (MH ⁺). C ₂₃ H ₂₃ FN ₆ O requires 418
151	D66	CH ₂			Found 558 (MH ⁺). C ₂₆ H ₃₂ ⁷⁹ BrN ₅ O ₂ S requires 557
152	D29	CH ₂			Found 566 (MH ⁺). C ₃₀ H ₃₃ F ₂ N ₅ O ₂ S requires 565
153	D29	CH ₂			Found 427 (MH ⁺). C ₂₀ H ₂₀ BrN ₅ O requires 426
154	D29	CH ₂			Found 436 (MH ⁺). C ₂₄ H ₂₃ F ₂ N ₅ O requires 435

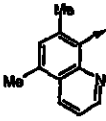
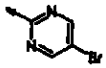
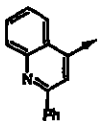
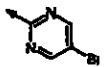
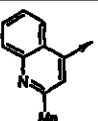
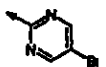
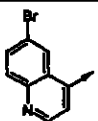
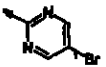
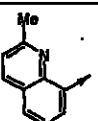
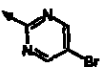
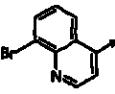
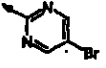
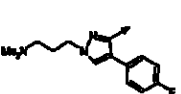
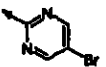
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155	D29	CH ₂			Found 422 (MH ⁺). C ₂₃ H ₂₁ F ₂ N ₃ O requires 421
156	D29	CH ₂			Found 441 (MH ⁺). C ₂₁ H ₁₈ F ₂ N ₆ OS requires 440
157	D29	CH ₂			Found 441 (MH ⁺). C ₂₃ H ₂₂ F ₂ N ₄ O ₃ requires 440
158	D29	CH ₂			Found 538 (MH ⁺). C ₂₈ H ₃₀ F ₃ N ₇ O requires 537
159	D66	CH ₂			Found 530 (MH ⁺). C ₂₄ H ₂₉ ⁷⁹ BrFN ₇ O requires 529
160	D49	CH ₂			Found 490 (MH ⁺). C ₂₆ H ₂₈ FN ₇ O ₂ requires 489
161	D49	CH ₂			Found 388 (MH ⁺). C ₂₁ H ₂₁ N ₇ O requires 387

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162	D66	CH ₂			Found 415 (MH ⁺) C ₁₈ H ₁₉ ⁷⁹ BrN ₆ O requires 414
163	D66	CH ₂			Found 415 (MH ⁺). C ₁₉ H ₁₉ ⁷⁹ BrN ₄ O ₂ requires 414
164	D66	CH ₂			Found (MH ⁺) 405 C ₁₈ H ₂₁ ⁷⁹ BrN ₄ O ₂ requires 404
165	D66	CH ₂			Found 426 (MH ⁺) C ₂₀ H ₂₀ ⁷⁹ BrN ₅ O requires 425
166	D29	CH ₂			Found 484 (MH ⁺). C ₂₆ H ₃₁ F ₂ N ₅ O ₂ requires 483
170	D66	CH ₂			Found 473 (MH ⁺). C ₂₁ H ₂₂ ⁷⁹ BrFN ₆ O requires 472
175	D66	CH ₂			Found 375 (MH ⁺) C ₁₇ H ₁₉ ⁷⁹ BrN ₄ O requires 374.
199	D7	O			Found 420 (MH ⁺) C ₂₂ H ₂₁ N ₅ O ₄ requires 419.
204	D82	CH ₂			Found 454 (MH ⁺). C ₂₄ H ₂₂ F ₃ N ₅ O requires 453

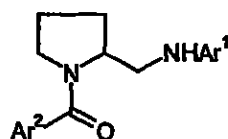
206	D82	CH ₂			Found 438 (MH ⁺). C ₂₃ H ₂₁ F ₂ N ₃ O ₂ requires 437.
207	D82	CH ₂			Found 396 (MH ⁺). C ₂₂ H ₁₉ F ₂ N ₃ O ₂ requires 395.
230	D66	CH ₂			Found 446 (MH ⁺). C ₁₉ H ₂₀ ⁷⁹ BrN ₅ O ₃ requires 445.
231	D66	CH ₂			Found 570 (MH ⁺). C ₂₇ H ₃₃ ⁷⁹ BrFN ₇ O requires 569.
241	D66	CH ₂			Found 454 (MH ⁺). C ₂₂ H ₂₄ ⁷⁹ BrN ₅ O requires 453.
242	D66	CH ₂			Found 448 (MNa ⁺). C ₂₀ H ₂₀ ⁷⁹ BrN ₅ O requires 425.
243	D66	CH ₂			Found 440 (MH ⁺). C ₂₁ H ₂₂ ⁷⁹ BrN ₅ O requires 439.
244	D66	CH ₂			Found 440 (MH ⁺). C ₂₁ H ₂₂ ⁷⁹ BrN ₅ O requires 439.
245	D66	CH ₂			Found 443 (MH ⁺). C ₁₇ H ₁₇ ⁷⁹ Br ³⁵ Cl ₂ N ₄ O requires 442.
246	D66	CH ₂			Found 474 (MH ⁺). C ₂₁ H ₂₁ ⁷⁹ Br ³⁵ ClN ₅ O requires 473.
259	D80	O			Found 476 (MH ⁺). C ₂₁ H ₁₉ ⁷⁹ BrFN ₃ O ₂ S requires 475.

260	D66	CH ₂			Found 454 (MH ⁺). C ₂₂ H ₂₄ ⁷⁹ BrN ₅ O requires 453.
261	D66	CH ₂			Found 502 (MH ⁺). C ₂₆ H ₂₄ ⁷⁹ BrN ₅ O requires 501.
262	D66	CH ₂			Found 440 (MH ⁺). C ₂₁ H ₂₂ ⁷⁹ BrN ₅ O requires 439.
263	D66	CH ₂			Found 504 (MH ⁺). C ₂₀ H ₁₉ ⁷⁹ Br ₂ N ₅ O requires 503.
264	D66	CH ₂			Found 440 (MH ⁺). C ₂₁ H ₂₂ ⁷⁹ BrN ₅ O requires 439.
265	D66	CH ₂			Found 504 (MH ⁺). C ₂₀ H ₁₉ ⁷⁹ Br ₂ N ₅ O requires 503.
266	D66	CH ₂			Found 544 (MH ⁺). C ₂₅ H ₃₁ ⁷⁹ BrFN ₇ O requires 543.

Example 93: 1-[2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-pyrrolidin-1-yl]-1-[4-(4-fluoro-phenyl)-2-H-pyrazol-3-yl]-methanone

- 5 The amine of D31 (0.085g) in dimethylformamide (3ml) was treated with 4-(4-fluoro-phenyl)-2H-pyrazole-3-carboxylic acid (0.125g), diisopropylethylamine (0.07ml) and [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] (0.11g). the mixture was shaken for 48 hours. Solvent was removed at reduced pressure and the residue extracted with dichloromethane. The filtrate was evaporated under reduced pressure and the residue column chromatographed (silica gel, 3% methanol/diethyl ether) to give the title compound (0.1g).
- 10

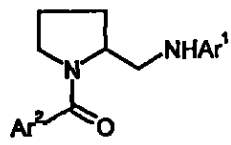
Mass Spectrum (AP⁺): Found 453 (MH⁺). C₂₃H₁₉F₃N₆O requires 452.



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residue column chromatographed (silica gel, 3% methanol/diethyl ether) to give the title compound (0.1g).

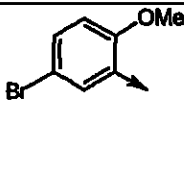
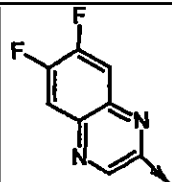
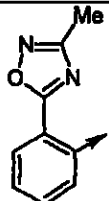
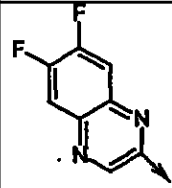
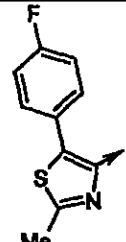
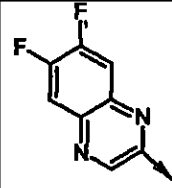
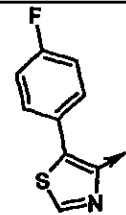
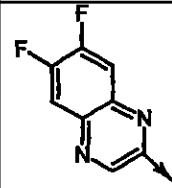
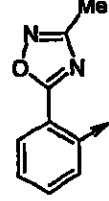
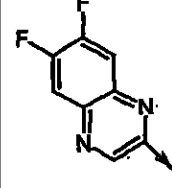
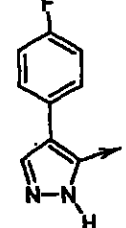
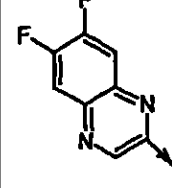
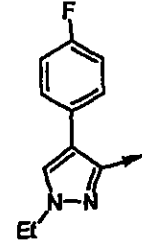
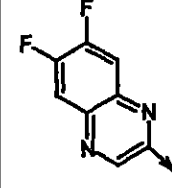
Mass Spectrum (AP⁺): Found 453 (MH⁺). C₂₃H₁₉F₃N₆O requires 452.



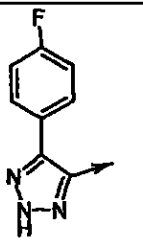
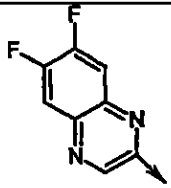
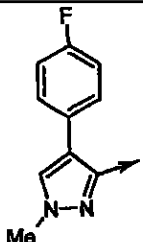
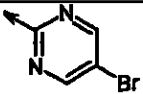
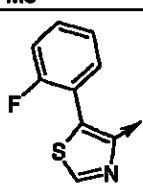
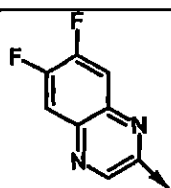
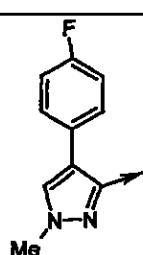
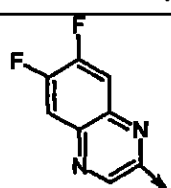
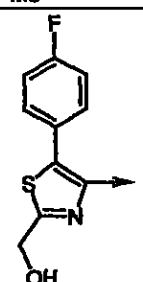
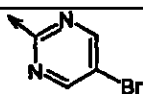
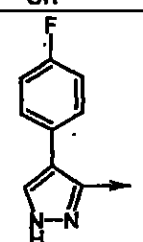
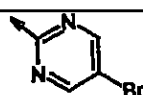
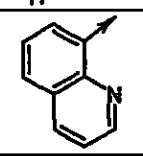
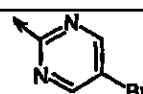
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Example	Amine	Ar ²	Ar ¹	Mass Spectrum (Electrospray LC/MS), AP ⁺
94	D31			Found 484 (MH ⁺). C ₂₄ H ₂₀ F ₃ N ₅ OS requires 483
95	D31			Found 467 (MH ⁺). C ₂₄ H ₂₁ F ₃ N ₆ O requires 466
96	D31			Found 468 (MH ⁺). C ₂₃ H ₂₀ F ₃ N ₇ O requires 467
97	D31			Found 394 (MH ⁺). C ₂₁ H ₁₇ F ₂ N ₃ O requires 393
98	D31			Found 419 (MH ⁺). C ₂₄ H ₂₀ F ₂ N ₄ O requires 418

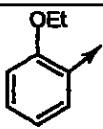
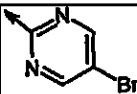
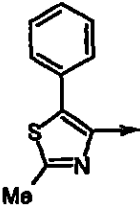
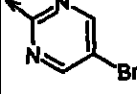
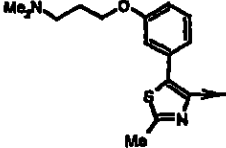
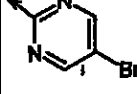
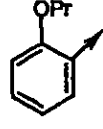
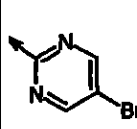
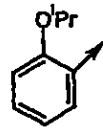
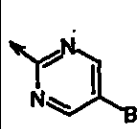
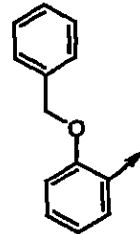
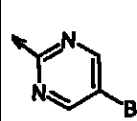
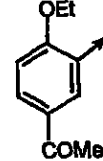
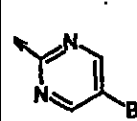
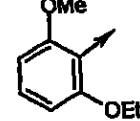
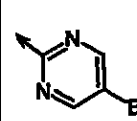
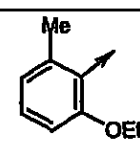
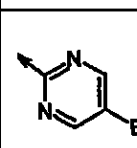
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99	D31			Found 478 (MH ⁺). C ₂₁ H ₁₉ BrF ₂ N ₄ O ₂ requires 477
100	D31			Found 451 (MH ⁺). C ₂₃ H ₂₀ F ₂ N ₆ O ₂ requires 450
101	D45			Found 484 (MH ⁺). C ₂₄ H ₂₀ F ₃ N ₅ OS requires 483
102	D45			Found 470 (MH ⁺). C ₂₃ H ₁₈ F ₃ N ₅ OS requires 469
103	D45			Found 451 (MH ⁺). C ₂₃ H ₂₀ F ₂ N ₆ O ₂ requires 450
104	D45			Found 453 (MH ⁺). C ₂₃ H ₁₉ F ₃ N ₆ O requires 452
119	D45			Found 481 (MH ⁺). C ₂₅ H ₂₃ F ₃ N ₆ O requires 480

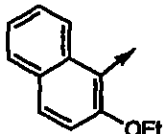
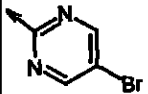
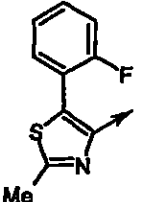
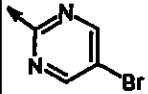
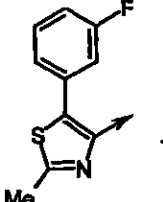
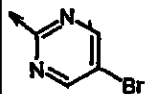
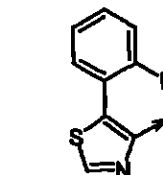
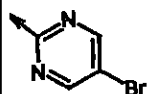
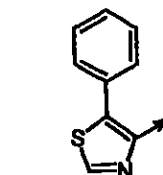
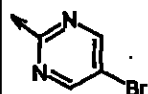
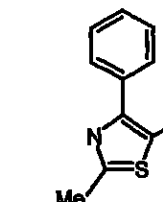
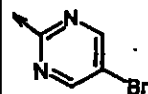
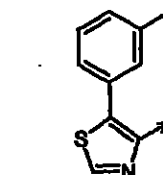
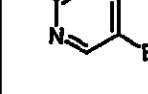
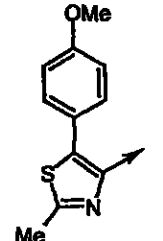
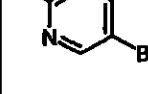
88

120	D45			Found 454 (MH ⁺). C ₂₂ H ₁₈ F ₃ N ₇ O requires 453
167	D70			Found 459 (MH ⁺). C ₂₀ H ₂₀ ⁷⁹ BrFN ₆ O requires 458
168	D45			Found 470 (MH ⁺). C ₂₃ H ₁₈ F ₃ N ₅ OS requires 469
169	D45			Found 467 (MH ⁺). C ₂₄ H ₂₁ F ₃ N ₆ O requires 466
176	D70			Found 514 (MNa ⁺). C ₂₀ H ₁₉ ⁷⁹ BrFN ₅ O ₂ S requires 491.
177	D70			Found 445 (MH ⁺). C ₁₉ H ₁₈ ⁷⁹ BrFN ₆ O requires 444.
178	D70			Found 434 (MNa ⁺). C ₁₉ H ₁₈ ⁷⁹ BrN ₅ O requires 411.

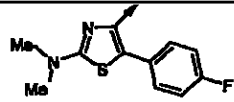
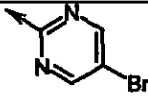
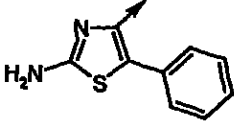
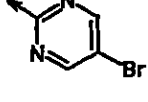
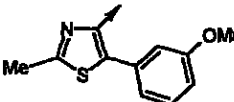
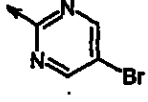
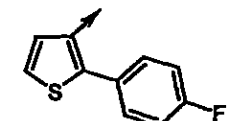
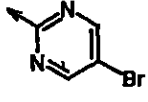
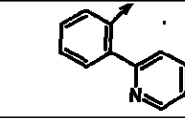
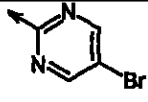
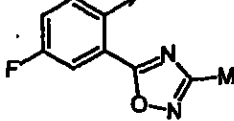
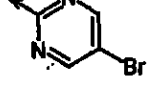
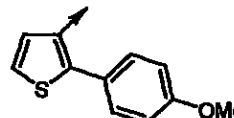
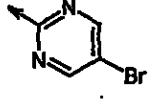
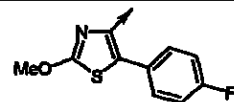
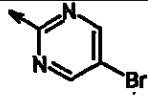
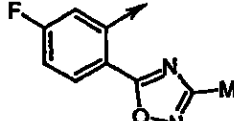
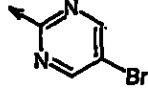
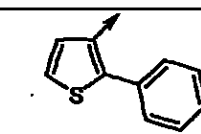
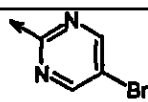
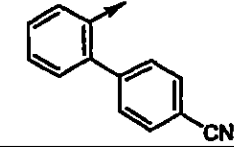
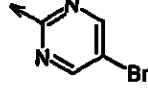
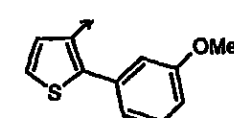
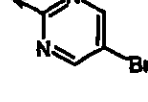
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179	D70			Found 405 (MH ⁺). C ₁₈ H ₂₁ ⁷⁹ BrN ₄ O ₂ requires 404.
180	D70			Found 458 (MH ⁺). C ₂₀ H ₂₀ ⁷⁹ BrN ₅ OS requires 457.
181	D70			Found 559 (MH ⁺). C ₂₃ H ₃₁ ⁷⁹ BrN ₆ O ₂ S requires 558.
182	D70			Found 419 (MH ⁺). C ₁₉ H ₂₃ ⁷⁹ BrN ₄ O ₂ requires 418.
183	D70			Found 419 (MH ⁺). C ₁₉ H ₂₃ ⁷⁹ BrN ₄ O ₂ requires 418.
184	D70			Found 467 (MH ⁺). C ₂₃ H ₂₃ ⁷⁹ BrN ₄ O ₂ requires 466.
185	D70			Found 447 (MH ⁺). C ₂₀ H ₂₃ ⁷⁹ BrN ₄ O ₃ requires 446.
186	D70			Found 435 (MH ⁺). C ₁₉ H ₂₃ ⁷⁹ BrN ₄ O ₃ requires 434.
187	D70			Found 419 (MH ⁺). C ₁₉ H ₂₃ ⁷⁹ BrN ₄ O ₂ requires 418

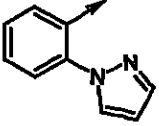
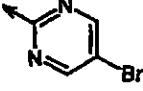
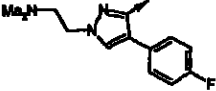
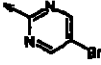
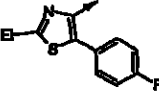
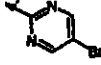
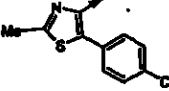
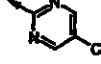
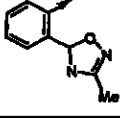
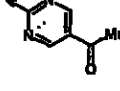
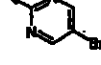
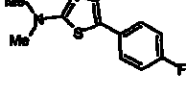
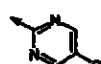
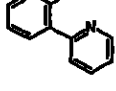
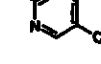
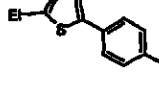
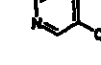
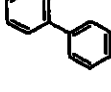
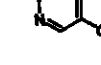
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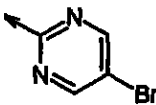
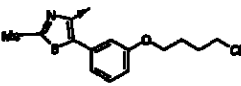
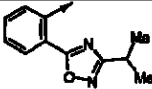
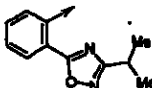
188	D70			Found 455 (MH ⁺). C ₂₂ H ₂₃ ⁷⁹ BrN ₄ O ₂ requires 454.
189	D70			Found 476 (MH ⁺). C ₂₀ H ₁₉ ⁷⁹ BrFN ₅ OS requires 475.
190	D70			Found 476 (MH ⁺). C ₂₀ H ₁₉ ⁷⁹ BrFN ₅ OS requires 475.
191	D70			Found 462 (MH ⁺). C ₁₉ H ₁₇ ⁷⁹ BrFN ₅ OS requires 461.
192	D70			Found 444 (MH ⁺). C ₁₉ H ₁₈ ⁷⁹ BrN ₃ OS requires 443.
193	D70			Found 458 (MH ⁺). C ₂₀ H ₂₀ ⁷⁹ BrN ₅ OS requires 457.
201	D70			Found 462 (MH ⁺). C ₂₀ H ₁₇ ⁷⁹ BrFN ₅ OS requires 461.
202	D70			Found 488 (MH ⁺). C ₂₁ H ₂₂ ⁷⁹ BrN ₅ O ₂ S requires 487.

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209	D70			Found 505 (MH ⁺). C ₂₁ H ₂₂ ⁷⁹ BrFN ₆ OS requires 504
210	D70			Found 459 (MH ⁺). C ₁₉ H ₁₉ ⁷⁹ BrN ₆ OS requires 458.
211	D70			Found 488 (MH ⁺). C ₂₁ H ₂₂ ⁷⁹ BrN ₅ O ₂ S requires 487.
212	D70			Found 461 (MH ⁺). C ₂₀ H ₁₈ ⁷⁹ BrFN ₄ OS requires 460.
213	D70			Found 460(MNa ⁺). C ₂₁ H ₂₀ ⁷⁹ BrN ₅ O requires 437.
214	D70			Found 461 (MH ⁺). C ₁₉ H ₁₈ ⁷⁹ BrFN ₆ O ₂ requires 460.
215	D70			Found 473 (MH ⁺). C ₂₁ H ₂₁ ⁷⁹ BrN ₄ O ₂ requires 472.
219	D70			Found 492 (MH ⁺). C ₂₀ H ₁₉ ⁷⁹ BrFN ₅ O ₂ S requires 491.
220	D70			Found 461 (MH ⁺). C ₁₉ H ₁₈ ⁷⁹ BrFN ₆ O ₂ requires 460.
221	D70			Found 443 (MH ⁺). C ₂₀ H ₁₉ ⁷⁹ BrN ₄ OS requires 442.
222	D70			Found 462 (MH ⁺). C ₂₃ H ₂₀ ⁷⁹ BrN ₅ O requires 461.
223	D70			Found 473 (MH ⁺). C ₂₁ H ₂₁ ⁷⁹ BrN ₄ O ₂ S requires 472.

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224	D70			Found 449 (MNa ⁺). C ₁₉ H ₁₉ ⁷⁹ BrN ₆ O requires 426.
232	D70			Found 516 (MH ⁺). C ₂₃ H ₂₇ ⁷⁹ BrFN ₇ O requires 515.
233	D70			Found 490 (MH ⁺). C ₂₁ H ₂₁ ⁷⁹ BrFN ₅ OS requires 489.
247	D95			Found 448 (MH ⁺). C ₂₀ H ₁₉ ³⁵ Cl ₂ N ₅ OS requires 447.
248	D93			Found 407 (MH ⁺). C ₂₁ H ₂₂ N ₆ O ₃ requires 406.
250	D70			Found 440 (MH ⁺). C ₂₁ H ₂₂ ⁷⁹ BrN ₅ O requires 439.
251	D95			Found 461 (MH ⁺). C ₂₁ H ₂₂ ³⁵ ClFN ₆ OS requires 460.
252	D95			Found 416 (MNa ⁺). C ₂₁ H ₂₀ ³⁵ ClN ₅ O requires 393.
253	D95			Found 468 (MNa ⁺). C ₂₁ H ₂₁ ³⁵ ClFN ₅ OS requires 445.
254	D95			Found 393 (MH ⁺). C ₂₂ H ₂₁ ³⁵ ClN ₄ O requires 392.

255	D70			Found 429 (MH ⁺). C ₁₆ H ₁₅ ⁷⁹ Br ³⁵ Cl ₂ N ₄ O requires 428.
256	D95			Found 520 (MH ⁺). C ₂₄ H ₂₇ ³⁵ Cl ₂ N ₅ O ₂ S requires 519.
257	D95			Found 427 (MH ⁺). C ₂₁ H ₂₃ ³⁵ ClN ₆ O ₂ requires 426.
258	D70			Found 471 (MH ⁺). C ₂₁ H ₂₃ ⁷⁹ BrN ₆ O ₂ requires 470.

Example 105: 1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-1-[(S)-2-(oxazolo[4,5-b]]pyridin-2-ylaminomethyl)-piperidin-1-yl]-methanone

5 The compound of D41 (0.51g) and 2-methylsulfanyl-oxazolo[4,5-b]pyridine (0.25g) were combined and heated under argon at 90°C for 18 hours. The mixture was column chromatographed (5% methanol, diethyl ether eluant) to give the title compound (0.26g).
Mass Spectrum (AP⁺): Found 419 (MH⁺). C₂₂H₂₂N₆O₃ requires 418.

Example 106: 1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-1-[(R)-2-[(methyl-oxazolo[4,5-b]pyridin-2-yl-amino)-methyl]piperidin-1-yl]-methanone

10 The title compound (0.015g) was prepared from the compound of D43 (0.15g) according to the method of Example 105.
Mass Spectrum (AP⁺): Found 433 (MH⁺). C₂₃H₂₄N₆O₃ requires 432.

Example 107: 6-[[[(S)-1-[1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl]-piperidin-2-ylmethyl]-methyl-amino]-nicotinonitrile

15 The title compound (0.078g) was prepared from the compound of D60 (0.45g) and 2-chloro-5-cyanopyridine (0.189g) according to the method of D26.
Mass Spectrum (AP⁺): Found 433 (MH⁺). C₂₄H₂₅FN₆O requires 432.

Example 108: 1-[(S)-2-[[[(6,7-Difluoro-quinoxalin-2-yl)-methyl-amino]-methyl]-piperidin-1-yl]-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone

20 The title compound (0.031g) was prepared from the compound of D60 (0.15g) and 2-chloro-6,7-difluoroquinoxaline (0.091g) according to the method of D26.
Mass Spectrum (AP⁺): Found 495 (MH⁺). C₂₆H₂₅F₃N₆O requires 494.

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Example 171: 1-{2-[(S)-1-{1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl]-amino}-pyrimidin-5-yl}-ethanone

A mixture of 1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone (0.5g) and 1-ethoxyvinyltributyltin (0.42ml) tetrakis(triphenylphosphine)palladium[0] (0.06g) was boiled in dioxane (8ml) for 16h. 2N Hydrochloric acid was added, the mixture stirred for 90 min, water was added and the mixture extracted (x3) with ethyl acetate. The combined ethyl acetate extracts were dried, solvent removed at reduced pressure and the residue column chromatographed (silica gel, ethyl acetate → 2% methanol ethyl acetate to give the title compound (0.3g) as a yellow foam.

Mass Spectrum (API⁺): Found 437 (MH⁺). C₂₃H₂₅FN₆O₂ requires 436.

Example 172: 1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-1-[(S)-2-[(5-(1-hydroxy-ethyl)-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl]-methanone

1-{2-[(S)-1-{1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl]-amino}-pyrimidin-5-yl}-ethanone (0.2g) was dissolved in methanol (20ml) and sodium borohydride (0.4g) added. The reaction was stirred overnight, water was added and stirring continued for 30min. The reaction mixture was extracted with ethyl acetate (x3), the organic extracts combined, dried (MgSO₄) and solvent removed at reduced pressure to give the title compound as a colourless foam.

Mass Spectrum (API⁺): Found 439 (MH⁺). C₂₃H₂₇FN₆O₂ requires 438.

Example 173: 2-[(S)-1-{1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl}-piperidin-2-ylmethyl]-amino]-pyrimidine-5-carbonitrile

1-{(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidin-1-yl}-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone (0.35g) in N-methylpyrrolidinone (10ml) containing copper(I)cyanide (0.13g) was heated to reflux for 5h. The reaction mixture was diluted with water, filtered (Kieselguhr) and the filtrate extracted with ethyl acetate. The ethyl acetate phase was washed with water and brine, dried (MgSO₄), filtered and solvent removed at reduced pressure. The residue was column chromatographed (silica gel; ethyl acetate: pentane 1:1 → ethyl acetate eluant), the appropriate fractions combined and solvent removed at reduced pressure to give the title compound (0.019g).

Mass Spectrum (API⁺): Found 420 (MH⁺). C₂₂H₂₂FN₇O requires 419.

Example 174: 3-(1-{(S)-2-[(6,7-Difluoro-quinoxalin-2-ylamino)-methyl]-piperidin-1-yl}-methanoyl)-N-methyl-benzamide

The compound of description 71 (0.10g) was dissolved in dimethylformamide (5ml) containing HATU (0.095g) and diisopropylethylamine (0.131ul) and stirred for 30 min. Methylamine (1M in tetrahydrofuran, 0.125ml) was added and stirring continued for 16h. The reaction mixture was diluted with diethyl ether, washed with water (x3), saturated brine and dried (MgSO₄). Solvent was removed at reduced pressure and the residue column chromatographed (silica gel; ethyl acetate → 10% methanol:ethyl acetate to give the title compound (0.018g).

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Mass Spectrum (API⁺): Found 440 (MH⁺). C₂₃H₂₃F₂N₅O₂ requires 439.

Example 194: 1-[(S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

- 5 A mixture of the amine of D70 (0.070g), 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (0.065g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (0.042g) and 1-hydroxybenzotriazole hydrate (0.037g) in dimethylformamide (2ml) was stirred at ambient temperature for 18h, evaporated *in vacuo* and the residue partitioned between ethyl acetate and water. The organic layer was dried (Na₂SO₄), evaporated and the residue chromatographed on silica gel eluting with a 30% - 100% ethyl acetate in pentane gradient to afford the title product (0.083g) as a white solid. Mass Spectrum (Electrospray LC/MS), API⁺: Found 476 (MH⁺). C₂₀H₁₉⁷⁹BrFN₅OS requires 475.
- 10

- Example 195: 1-[(S)-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl]-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone** The title compound (0.053g) was obtained from the amine of D70 (0.070g) and 2-(3-methyl-[1,2,4]oxadiazol-5-yl)-benzoic acid (0.056g) using the method of Example 194. Mass Spectrum (Electrospray LC/MS) : Found 443 (MH⁺). C₁₉H₁₉⁷⁹BrN₆O₂ requires 442.
- 15

- Example 196: 1-[(S)-2-[5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl]-1-[5-(4-chloro-phenyl)-2-methyl-thiazol-4-yl]-methanone**
The title compound (0.078g) was obtained from the amine of D70 (0.077g) and 5-(4-chloro-phenyl)-2-methyl-thiazole-4-carboxylic acid (0.076g) according to the method of Example 32. Mass spectrum (Electrospray LC/MS), API⁺: Found 492 (MH⁺). C₂₀H₁₉⁷⁹Br³⁵ClN₅O₂ requires 491.
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- Example 197: 1-[(S)-2-[(5-Bromo-pyridin-2-ylamino)-methyl]-pyrrolidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone**
The title compound (0.135g) was obtained from the amine of D74 (0.11g) and 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (0.12g) according to the method of Example 32. Mass Spectrum API⁺: Found 475 (MH⁺). C₂₁H₂₀⁷⁹BrFN₄OS requires 474.
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- Example 198: 1-[(S)-2-[(5-Bromo-pyridin-2-ylamino)-methyl]-pyrrolidin-1-yl]-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone**
The title compound (0.10g) was obtained from the amine of D74 (0.11g) and 4-(4-fluoro-phenyl)-1-methyl-1H-pyrazole-3-carboxylic acid (0.12g) according to the method of Example 32. Mass Spectrum API⁺: Found 458 (MH⁺). C₂₁H₂₁⁷⁹BrFN₅O requires 457.
- 35

- Example 200: 1-[3-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-morpholin-4-yl]-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone**
The title compound (0.393g) was obtained from the compound of D80 (0.3g) and 4-(4-fluorophenyl)-1-methyl-1H-pyrazole-3-carboxylic acid (0.242g) according to the method of Example 32. Mass Spectrum (API⁺): Found 475 (MH⁺). C₂₀H₂₀⁷⁹BrFN₆O₂ requires 474.
- 40

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Example 203: 3,5-Difluoro-4-(((S)-1-{1-[5-(4-fluorophenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-ylmethyl)-amino)-benzonitrile

The title compound (0.090g) was obtained from the compound of D82 (0.073g) and 5-(4-fluorophenyl)-2-methyl-thiazole-4-carboxylic acid (0.069g) according to the method of Example 32. Mass Spectrum (Electrospray LC/MS): Found 471. $C_{24}H_{21}F_3N_4OS$ requires 470.

Example 208: 3,5-Difluoro-4-(((S)-1-{1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-pyrrolidin-2-ylmethyl)-amino)-benzonitrile

The title compound (0.09g) was obtained from the compound of D84 and 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (0.095g) according to the method of Example 32. Mass Spectrum (Electrospray LC/MS): Found 457 (MH^+). $C_{23}H_{19}F_3N_4OS$ requires 456.

Example 216: 1-((S)-2-[(5-Ethyl-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl)-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

The title compound (0.05g) was obtained from the compound of D86 (0.07g) and 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (0.068g) according to the method of Example 32. Mass Spectrum (Electrospray LC/MS): Found 426 (MH^+). $C_{22}H_{24}FN_3OS$ requires 425.

Example 217: 1-((S)-2-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl)-pyrrolidin-1-yl)-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

The title compound (0.1g) was obtained from the compound of D91 (0.275g) and 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (0.285g) according to the method of Example 32. Mass Spectrum (Electrospray LC/MS): Found 490 (MH^+). $C_{21}H_{21}^{79}BrFN_3OS$ requires 489.

Example 218: 1-((S)-2-[(5-Bromo-pyrimidin-2-yl)-methyl-amino]-methyl)-pyrrolidin-1-yl)-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone

The title compound (0.02g) was obtained from the compound of D91 (0.275g) and 4-(4-fluoro-phenyl)-1-methyl-1H-pyrazole-3-carboxylic acid (0.260g) according to the method of Example 32. Mass Spectrum (Electrospray LC/MS): Found 473 (MH^+). $C_{21}H_{22}^{79}BrFN_6O$ requires 472.

Example 225: 1-{2-[[((S)-1-{1-[5-(4-Chloro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-pyrrolidin-2-ylmethyl)-amino]-pyrimidin-5-yl]-ethanone

The title product (0.04g) was obtained from the compound of D93 (0.133g) and 5-(4-chloro-phenyl)-2-methyl-thiazole-4-carboxylic acid (0.076g) using a similar procedure to that described in Example 32. Mass Spectrum (Electrospray LC/MS): Found 456 (MH^+). $C_{22}H_{22}^{35}ClN_5O_2S$ requires 455.

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Example 226: 1-((S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl)-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

- The title product (0.095g) was obtained from the amine of D95 (0.064g) and 5-(4-fluorophenyl)-2-methyl-thiazole-4-carboxylic acid (0.071g) using the method of Example 32. Mass Spectrum (Electrospray LC/MS): Found 432 (MH^+). $C_{20}H_{19}^{35}ClFN_5OS$ requires 431.

Example 227: 1-((S)-2-[(5-Chloro-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl)-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

- The title compound (0.052g) was obtained from the amine of D95 (0.064g) and 2-(3-methyl-[1,2,4]oxadiazol-5-yl)-benzoic acid (0.061g) according to the method of Example 32. Mass Spectrum (Electrospray LC/MS): Found 399 (MH^+). $C_{19}H_{19}^{35}ClN_6O_2$ requires 398.

- Example 228: 1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-((S)-2-[(5-methyl-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl)-methanone**

- To the compound of Example 194 (0.36g) in dimethylformamide was added lithium chloride (0.096g), tetramethyl tin (0.126 ml) and dichlorobis(triphenylphosphine) palladium (0) (0.035g) and the resulting mixture heated at 100°C under argon for 18h. The reaction was then evaporated, diluted with dichloromethane, filtered and the filtrate washed with water, dried and evaporated. Chromatography of the residue on silica gel, eluting with methanol-dichloromethane mixtures, afforded the title product (0.2g) as a yellow amorphous solid. Mass Spectrum (AP^+): Found 412 (MH^+). $C_{21}H_{22}FN_5OS$ requires 411.

- Example 229: 6-(((S)-1-[1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl]-pyrrolidin-2-ylmethyl)-amino)-nicotinonitrile**

- A mixture of the amine of D97 (0.134g), 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (0.172g), EDC (0.139g) and 1-hydroxybenzotriazole (0.01g) in dichloromethane (8 ml) was stirred at ambient temperature for 7 days. The reaction was washed with saturated aqueous sodium bicarbonate solution, dried and evaporated. Chromatography of the residue on silica gel, eluting with ethyl acetate - hexane mixtures afforded the title product (0.196g). Mass Spectrum (Electrospray LC/MS): Found 422 (MH^+). $C_{22}H_{20}FN_5OS$ requires 421.

- Example 234: 1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-((S)-2-[(6-methyl-2-methylsulfanyl-pyrimidin-4-ylamino)-methyl]-pyrrolidin-1-yl)-methanone**

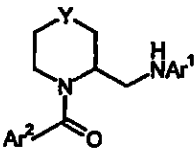
- The title product (0.095g) was obtained from the amine of D101 (0.15g) and the compound of D98 (0.14g) using a similar method to that described in D69. Mass Spectrum (Electrospray LC/MS): Found 458 (MH^+). $C_{22}H_{24}FN_5OS_2$ requires 457.

- Example 235: 1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-((S)-2-[(2-methylsulfanyl-pyrimidin-4-ylamino)-methyl]-pyrrolidin-1-yl)-methanone**

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The title compound (0.05g) was obtained from the amine of D101 (0.15g) and 4-chloro-2-methylsulfanyl-pyrimidine (0.076g) using a similar method to that described in D69. Mass Spectrum (Electrospray LC/MS): Found 444 (MH⁺). C₂₁H₂₂FN₅OS₂ requires 443.

- 5 The following compounds were prepared using methods similar to that described in Examples 234 and 235.



Example	Amine	Y	Ar ²	Ar ¹	Mass spectrum (Electrospray LC/MS), API ⁺
236	D101	Bond			Found 494 (MH ⁺). C ₂₃ H ₂₃ F ₄ N ₅ OS requires 493.
237	D101	Bond			Found 426 (MH ⁺). C ₂₂ H ₂₄ FN ₅ OS requires 425.
238	D101	Bond			Found 466 (MH ⁺). C ₂₁ H ₁₉ F ₄ N ₅ OS requires 465.

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Example 239: 1-(3-(((5-Bromo-pyrimidin-2-yl)-methyl-amino)-methyl)-morpholin-4-yl)-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone The title compound (0.056g) was obtained from the compound of D105 (0.095g) and 5-(4-fluorophenyl)-2-methyl-thiazole-4-carboxylic acid (0.10g) according to the method of Example 32. Mass Spectrum (Electrospray LC/MS): Found 506 (MH⁺). C₂₁H₂₁⁷⁹BrFN₅O₂S requires 505.

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Example 240: 1-(3-(((5-Bromo-pyrimidin-2-yl)-methyl-amino)-methyl)-morpholin-4-yl)-1-[2-(4-fluoro-phenyl)-thiophen-3-yl]-methanone To the compound of D105 (0.095g) in dichloromethane (8ml) containing triethylamine (0.06ml) was added 2-(4-fluorophenyl)-thiophene-3-carbonyl chloride (0.084g). After 72h at ambient temperature the reaction mixture was washed with brine, dried and evaporated; the residue was chromatographed on silica gel, eluting with ethyl acetate-pentane mixtures to afford the title product (0.093g). Mass Spectrum (Electrospray LC/MS): Found 491 (MH⁺). C₂₁H₂₀⁷⁹BrFN₄O₂S requires 490.

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Example 249: 1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-((S)-2-[(5-trifluoromethyl-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl)-methanone

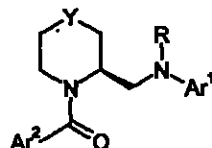
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Example 249: 1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[(S)-2-[(5-trifluoromethyl-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-yl]-methanone

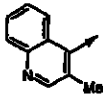
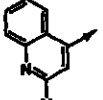
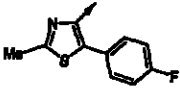
To the compound from Example 194 (0.36g) in dimethylformamide (5ml) was added potassium trifluoroacetate (0.23g), copper iodide (0.3g) and toluene (5ml) and the resulting mixture heated at reflux under Dean-Stark conditions for 3h, before refluxing for a further 20h. The reaction mixture was cooled, poured into water/ether and filtered through kieselguhr. The aqueous layer from the filtrate was extracted with ether, and the combined ether extracts washed with water, dried and evaporated. The aqueous was re-extracted with dichloromethane and the extract evaporated. The combined extracts were chromatographed on silica gel, eluting with methanol-dichloromethane mixtures, to afford the title product (0.001g). Mass Spectrum (Electrospray LC/MS): Found 466 (MH⁺). C₂₁H₁₉F₄N₅OS requires 465.

The compounds in the table below were prepared using methods described above

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Example	X	R	Ar ²	Ar ¹	Mass Spectrum (Electrospray LC/MS), API ⁺
267	CH ₂	H			Found 486 (MH ⁺). C ₂₄ H ₂₉ ³⁵ ClFN ₇ O requires 485.
268	CH ₂	H			Found 526 (MH ⁺). C ₂₇ H ₃₃ ³⁵ ClFN ₇ O requires 525.
269	CH ₂	H			Found 540 (MH ⁺). C ₂₈ H ₃₅ ³⁵ ClFN ₇ O requires 539.
270	CH ₂	Me			Found 440 (MH ⁺). C ₂₁ H ₂₂ ⁷⁹ BrN ₅ O requires 439.
271	CH ₂	Me			Found 457 (MH ⁺). C ₁₈ H ₁₉ ⁷⁹ Br ³⁵ Cl ₂ N ₄ O requires 456.
272	CH ₂	H			Found 489 (MH ⁺). C ₂₃ H ₂₆ ³⁵ ClFN ₆ OS requires 488.

273	CH ₂	Me			Found 454 (MH ⁺). C ₂₂ H ₂₄ ⁷⁹ BrN ₅ O requires 453.
274	CH ₂	Me			Found: 454 (MH ⁺). C ₂₂ H ₂₄ ⁷⁹ BrN ₅ O requires 453.
275	CH ₂	H			Found 446 (MH ⁺). C ₂₁ H ₂₁ ³⁵ ClFN ₅ OS requires 445.

It is understood that the present invention covers all combinations of particular and preferred groups described herein above.

Determination of Orexin-1 Receptor Antagonist Activity

The orexin-1 receptor antagonist activity of the compounds of formula (I) was determined in accordance with the following experimental method.

Experimental Method

CHO-DG44 cells expressing the human orexin-1 receptor were grown in cell medium (MEM medium with Earl's salts) containing 2 mM L-Glutamine, 0.4 mg/mL G418 Sulphate from GIBCO BRL and 10% heat inactivated fetal calf serum from Gibco BRL. The cells were seeded at 20,000 cells/100 μ l/well into 96-well black clear bottom sterile plates from Costar which had been pre-coated with 10 μ g/well of poly-L-lysine from SIGMA. The seeded plates were incubated overnight at 37C in 5% CO₂.

Agonists were prepared as 1 mM stocks in water:DMSO (1:1). EC50 values (the concentration required to produce 50% maximal response) were estimated using 11x half log unit dilutions (Biomek 2000, Beckman) in Tyrode's buffer containing probenecid (10 mM HEPES with 145mM NaCl, 10mM glucose, 2.5 mM KCl, 1.5 mM CaCl₂, 1.2 mM MgCl₂ and 2.5mM probenecid; pH7.4). Antagonists were prepared as 10 mM stocks in DMSO (100%). Antagonist IC50 values (the concentration of compound needed to inhibit 50% of the agonist response) were determined against 3.0 nM human-orexin-A using 11x half log unit dilutions in Tyrode's buffer containing 10% DMSO and probenecid.

On the day of assay 50 μ l of cell medium containing probenecid (Sigma) and Fluo3AM (Texas Fluorescence Laboratories) was added (Quadra, Tomtec) to each well to give final concentrations of 2.5 mM and 4 μ M, respectively. The 96-well plates were incubated for 60 min at 37C in 5% CO₂. The loading solution containing dye was then aspirated and cells were washed with 4x150 μ l Tyrode's buffer containing probenecid and 0.1% gelatin (Denley Cell Wash). The volume of buffer left in each well was 125 μ l. Antagonist or buffer (25 μ l) was added (Quadra) the cell plates gently shaken and incubated at 37C in 5% CO₂ for 30 minutes. Cell plates were then transferred to the Fluorescent

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Imaging Plate Reader (FLIPR, Molecular Devices) instrument. Prior to drug addition a single image of the cell plate was taken (signal test), to evaluate dye loading consistency. The run protocol used 60 images taken at 1 second intervals followed by a further 24 images at 5 second intervals. Agonists were added (by the FLIPR) after 20 seconds (during continuous reading). From each well, peak fluorescence was determined over the whole assay period and the mean of readings 1-19 inclusive was subtracted from this figure. The peak increase in fluorescence was plotted against compound concentration and iteratively curve fitted using a four parameter logistic fit (as described by Bowen and Jerman, *TIPS*, 1995, 16, 413-417) to generate a concentration effect value. Antagonist K_b values were calculated using the equation:

$$K_b = IC_{50} / (1 + (3/EC_{50}))$$

where EC_{50} was the potency of human orexin-A determined in the assay (in nM terms) and IC_{50} is expressed in molar terms.

Compounds of Examples tested according to this method had pK_b values in the range 6.7 – 9.7 at the human cloned orexin-1 receptor.

The orexin-2 receptor antagonist activity of the compounds of formula (I) was determined in accordance with the following experimental method.

20 Experimental Method

CHO-DG44 cells expressing the human orexin-2 receptor were grown in cell medium (MEM medium with Earl's salts) containing 2 mM L-Glutamine, 0.4 mg/mL G418 Sulphate from GIBCO BRL and 10% heat inactivated fetal calf serum from Gibco BRL. The cells were seeded at 20,000 cells/100 μ l/well into 96-well black clear bottom sterile plates from Costar which had been pre-coated with 10 μ g/well of poly-L-lysine from SIGMA. The seeded plates were incubated overnight at 37C in 5% CO_2 .

Agonists were prepared as 1 mM stocks in water:DMSO (1:1). EC_{50} values (the concentration required to produce 50% maximal response) were estimated using 11x half log unit dilutions (Biomek 2000, Beckman) in Tyrode's buffer containing probenecid (10 mM HEPES with 145mM NaCl, 10mM glucose, 2.5 mM KCl, 1.5 mM $CaCl_2$, 1.2 mM $MgCl_2$ and 2.5mM probenecid; pH7.4). Antagonists were prepared as 10 mM stocks in DMSO (100%). Antagonist IC_{50} values (the concentration of compound needed to inhibit 50% of the agonist response) were determined against 10.0 nM human orexin-A using 11x half log unit dilutions in Tyrode's buffer containing 10% DMSO and probenecid.

On the day of assay 50 μ l of cell medium containing probenecid (Sigma) and Fluo3AM (Texas Fluorescence Laboratories) was added (Quadra, Tomtec) to each well to give final concentrations of 2.5 mM and 4 μ M, respectively. The 96-well plates were incubated for 60 min at 37C in 5% CO_2 . The loading solution containing dye was then aspirated and cells were washed with 4x150 μ l Tyrode's buffer containing probenecid and 0.1% gelatin (Denley Cell Wash). The volume of buffer left in each well was 125 μ l. Antagonist or buffer (25 μ l) was added (Quadra) the cell plates gently shaken and incubated at 37C in 5% CO_2 for 30 min. Cell plates were then transferred to the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices) instrument. Prior to drug addition a single image

for
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of the cell plate was taken (signal test), to evaluate dye loading consistency. The run protocol used 60 images taken at 1 second intervals followed by a further 24 images at 5 second intervals. Agonists were added (by the FLIPR) after 20 sec (during continuous reading). From each well, peak fluorescence was determined over the whole assay period and the mean of readings 1-19 inclusive was subtracted from this figure. The peak increase in fluorescence was plotted against compound concentration and iteratively curve fitted using a four parameter logistic fit (as described by Bowen and Jerman, *TIPS*, 1995, 16, 413-417) to generate a concentration effect value. Antagonist Kb values were calculated using the equation:

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$$K_b = IC_{50} / (1 + (3/EC_{50}))$$

where EC50 was the potency of human orexin-A determined in the assay (in nM terms) and IC50 is expressed in molar terms.

Compounds of Examples tested according to this method had pKb values in the range <6.3 - 9.1 at the human cloned orexin-2 receptor.

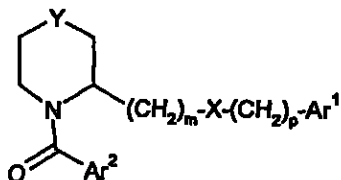
15 The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of
20 example and without limitation the following claims:

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CLAIMS

1. A compound of formula (I):



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(I)

wherein:

Y represents a bond, oxygen, or a group $(\text{CH}_2)_n$, wherein n represents 1, 2 or 3
m represents 1, 2, or 3;

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p represents 0 or 1;

X is NR, wherein R is H or (C_{1-4}) alkyl;

Ar^1 is aryl, or a mono or bicyclic heteroaryl group containing up to 3 heteroatoms selected from N, O and S; any of which may be optionally substituted;

Ar^2 represents phenyl or a 5- or 6-membered heterocyclyl group containing up to 3 heteroatoms selected from N, O and S, wherein the phenyl or heterocyclyl group is substituted by R^1 and further optional substituents; or Ar^2 represents an optionally substituted bicyclic aromatic or bicyclic heteroaromatic group containing up to 3 heteroatoms selected from N, O and S;

R^1 represents hydrogen, optionally substituted (C_{1-4}) alkoxy, halo, cyano, optionally substituted (C_{1-6}) alkyl, optionally substituted phenyl, or an optionally substituted 5- or 6-membered heterocyclyl group containing up to 4 heteroatoms selected from N, O and S;

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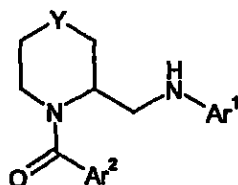
wherein when Y is a bond Ar^2 can not be 2-naphthyl;

when Ar^1 is aryl p is not 1;

or a pharmaceutically acceptable salt thereof.

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2. A compound of formula (Ia);



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(Ia)

wherein:

Y represents a bond, oxygen, or a group $(\text{CH}_2)_n$, wherein n represents 1, 2 or 3

Ar^1 is a mono or bicyclic heteroaryl group containing up to 3 heteroatoms selected from N, O and S; any of which may be optionally substituted;

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- Ar² represents phenyl or a 5- or 6-membered heterocyclyl group containing up to 3 heteroatoms selected from N, O and S, wherein the phenyl or heterocyclyl group is substituted by R¹ and further optional substituents; or Ar² represents an optionally substituted bicyclic aromatic or bicyclic heteroaromatic group containing up to 3 heteroatoms selected from N, O and S;
- R¹ represents hydrogen, optionally substituted(C₁₋₄)alkoxy, halo, cyano, optionally substituted(C₁₋₆)alkyl, optionally substituted phenyl, or an optionally substituted 5- or 6-membered heterocyclyl group containing up to 4 heteroatoms selected from N, O and S; wherein when Y is a bond then Ar² can not be 2-naphthyl; or a pharmaceutically acceptable salt thereof.
3. A compound according to claim 1 or 2 wherein Y is a bond, oxygen or (CH₂)_n where n is 1 or 2.
4. A compound according to any preceding claim wherein Ar² represents an optionally substituted phenyl, pyridyl, thiazolyl, pyrazolyl, benzofuryl, naphthyl, triazolyl, quinoxaliny, quinoliny, isoquinoliny, benzimidazolyl, benzothienyl, benzotriazolyl, benzothiazolyl, indolyl or thienyl.
5. A compound according to any preceding claim wherein Ar¹ represents an optionally substituted is benzoxazolyl, benzimidazolyl, quinoxaliny, quinazoliny, pyrimidinyl, pyridiny, naphthyridiny, quinoliny, pyridopyrimidine, thiazolyl, oxazolylpyridiny, benzothiazolyl, isoquinoliny or pyraziny.
6. A compound according to any preceding claim wherein R¹ is selected from trifluoromethoxy, methoxy, ethoxy, halo, cyano or an optionally substituted phenyl, pyridyl, pyrazolyl, pyrimidinyl, or oxadiazolyl group.
7. A compound of formula (I) as defined in any one of Examples 1 to 275, or a pharmaceutically acceptable salt of any one thereof.
8. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
9. A method of treating or preventing diseases or disorders where an antagonist of a human orexin receptor is required, which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) as defined in any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof.

AMINAS CÍCLICAS DE N- AROILO

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Este invento se relaciona con derivados de aminas cíclicas de N- aroilo y su uso como farmacéuticos.

Muchos procesos biológicos médicamente significativos están mediados por las proteínas que participan en las rutas de transducción de señales que involucran proteínas- G y/o segundos mensajeros.

Se han identificado los polipéptidos y polinucleótidos que codifican el receptor neuropeptídico acoplado a proteína- G de transmembrana- 7 humana, orexina- 1 (HFGAN72), y se divulgan en EP- A- 875565, EP- A- 875566 y WO 96/34877. Se han identificado los polipéptidos y polinucleótidos que codifican un segundo receptor de orexina humana, orexina- 2 (HFGANP), y se divulgan en EP- A- 893- 498.

Los polipéptidos y polinucleótidos que codifican polipéptidos los cuales son ligandos para el receptor de orexina- 1, ej., orexina- A (Lig72A) son divulgados en EP- A- 849361.

Los receptores de la orexina son encontrados en el hospedero mamífero y pueden ser responsables de muchas funciones biológicas, incluyendo patologías que incluyen, pero no están limitadas a, depresión; ansiedad; adicciones; trastorno compulsivo obsesivo; neurosis/trastorno afectivo; neurosis/trastorno depresivo; neurosis de ansiedad; trastorno distímico; trastorno de conducta; trastorno de ánimo; disfunción sexual; disfunción psicosexual; trastorno sexual; esquizofrenia; enfermedad maníaco depresiva; delirio; demencia; retardo mental severo y discinesias tales como enfermedad de Huntington y síndrome de Gilles de la Tourett; ritmos biológicos y circadianos alterados; trastornos de alimentación, tales como anorexia, bulimia, cachexia, y obesidad; diabetes; trastornos de apetito/gusto; vómito/náuseas; asma; cáncer; enfermedad de Parkinson; síndrome/ enfermedad de Cushing; adenoma de basófilos; prolactinoma; hiperprolactinemia; hipopituitarismo; tumor/adenoma de la hipofisis; enfermedades hipotalámicas; síndrome de Froehlich; enfermedad de la adenohipofisis; enfermedad de la hipofisis; tumor/adenoma de

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- la hipófisis; hormona de crecimiento pituitario; hipofunción de la adenohipófisis; hiperfunción de la adenohipófisis; hipogonadismo hipotalámico; síndrome de Kallman (anosmia, hiposmia); amenorrea funcional o psicogénica; hipopituitarismo; hipotiroidismo hipotalámico; disfunción hipotalámica- adrenal; hiperprolactinemia idiopática; trastornos
- 5 hipotalámicos de deficiencia de hormonas de crecimiento; deficiencia de hormonas de crecimiento idiopáticas; enanismo; gigantismo; acromegalia; ritmos biológicos y circadianos alterados; y alteraciones de sueño asociadas con enfermedades tales como trastornos neurológicos, dolor neuropático y síndrome de Ekbom (de piernas inquietas), enfermedades cardíacas y pulmonares; falla cardíaca aguda y congestiva; hipotensión;
- 10 hipertensión; retención urinaria; osteoporosis; angina de pecho; infarto del miocardio; apoplejía isquémica o hemorrágica; hemorragia subaracnoidea; lesión cefálica tal como hemorragia subaracnoidea asociada con lesión cefálica traumática; úlceras; alergias; hipertrofia prostática benigna; falla renal crónica; enfermedad renal; tolerancia deteriorada a la glucosa; migraña; hiperalgesia, causalgia y alodinia; dolor agudo; dolor por
- 15 quemaduras; dolor facial atípico; dolor neuropático; dolor de espalda; síndromes I y II de dolor regional complejo; dolor artrítico; dolor por lesiones deportivas; dolor relacionado con infección; ej., VIH, síndrome post- polio, y neuralgia post- herpética; dolor de extremidad fantasma; y dolor de trabajo de parto; dolor por cáncer; dolor post- quimioterapéutico; dolor post- apoplejía; dolor post- operativo; neuralgia; vómito y náusea;
- 20 condiciones asociadas con dolor visceral incluyendo síndrome de intestino irritable, migraña y angina; incontinencia de vejiga urinaria e.j., incontinencia de urgencia; tolerancia a narcóticos o abstinencia a narcóticos; trastornos del sueño; apnea del sueño; narcolepsia; insomnio, parasomnio; síndrome de intervalo del jet; y trastornos neurodegenerativos, los cuales incluyen entidades nosológicas tales como complejo de desinhibición- demencia-
- 25 parkinsonismo- amiotrofia; degeneración palido- ponto- nigral, epilepsia, y trastornos por ataques apopléjicos.

Los experimentos han demostrado que la administración central del ligando de la orexina- A (descrito con mayor detalle a continuación) estimuló la absorción de alimento en ratas con alimentación libre durante un periodo de tiempo de 4 horas. Este aumento fue

30 aproximadamente cuatro veces mayor con respecto a las ratas de control que recibieron el

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vehículo. Estos datos indican que la orexina- A puede ser un regulador endógeno del apetito. Por lo tanto, los antagonistas de su receptor pueden ser útiles en el tratamiento de la obesidad y la diabetes, ver *Cell*, 1998, 92, 573- 585.

Existe una incidencia significativa de obesidad en las sociedades occidentales.

- 5 Según las definiciones WHO un promedio de 35% de los sujetos en 39 estudios tuvieron sobrepeso y un 22% adicional fueron clínicamente obesos. Se ha estimado que 5.7% de todos los costos de salud en Estados Unidos son consecuencia de la obesidad.

Aproximadamente 85% de los diateticos tipo 2 son obesos, y la dieta y el ejercicio son de valor en todos los diabéticos. La incidencia de diabetes diagnosticada en países

- 10 occidentales es típicamente 5% y se estima que hay un número igual no diagnosticado. La incidencia de ambas enfermedades está creciendo, demostrando la insuficiencia de los actuales tratamientos los cuales pueden ser ineficaces o tener riesgos de toxicidad que incluyen efectos cardiovasculares. El tratamiento de la diabetes con sulfonilureas o insulina puede producir hipoglicemia, mientras que la metformina produce efectos secundarios del
- 15 tracto GI. No se ha mostrado ningún tratamiento farmacológico para la diabetes tipo 2, que reduzca las complicaciones a largo plazo de la enfermedad. Los sensibilizadores de insulina serán útiles para muchos diabéticos, sin embargo estos no tienen un efecto anti- obesidad.

Estudios de sueño/EEG en ratas también han mostrado que la administración central de la orexina- A, un agonista de los receptores de la orexina, produce un aumento en

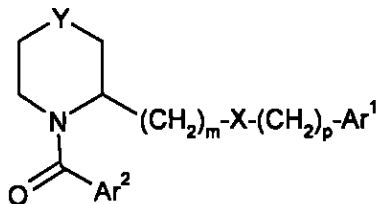
20 excitación relacionado con la dosis, mayormente a expensas de una reducción en sueño paradójico y sueño NREM 2, cuando se administra al comienzo del periodo de sueño normal. Por lo tanto los antagonistas de su receptor pueden ser útiles en el tratamiento de transtornos de sueño incluyendo insomnio.

- 25 El presente invento proporciona derivados de aminos cíclicas de N- aroilo los cuales son antagonistas no peptídicos de receptores de la orexina humana, en particular receptores de la orexina- 1. En particular, estos compuestos son de uso potencial en el tratamiento de la obesidad, incluyendo obesidad observada en pacientes con diabetes tipo 2 (no insulino dependiente) y/o trastornos del sueño. Adicionalmente estos compuestos son útiles en el tratamiento de la apoplejía, particularmente apoplejía isquémica o hemorrágica, y/o que
- 30 bloquean la respuesta emética, es decir, son útiles en el tratamiento de nauseas y vomito.

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Las solicitudes de patentes internacionales WO99/09024, WO99/58533, WO00/47577 y WO00/47580 divulgan derivados de urea de fenilo y la WO00/47576 divulga derivados de cinamida de quinolinilo como antagonistas de los receptores de la orexina. WO01/96302 divulga derivados de aminas cíclicas de N- aroilo.

5 Según el invento se proporciona un compuesto de la fórmula (I):



en donde:

10 Y representa un enlace, oxígeno, o un grupo $(CH_2)_n$, en donde n representa 1, 2 o 3
m representa 1, 2, o 3;

p representa 0 o 1;

X es NR, en donde R es H o C1- 4alquilo;

15 Ar^1 es arilo, o un grupo heteroarilo mono o bicíclico que contiene hasta 3 heteroátomos seleccionados de N, O y S; cualquiera de los cuales puede ser opcionalmente substituido;

20 Ar^2 representa fenilo o un grupo heterociclilo de 5 o 6 miembros que contiene hasta 3 heteroátomos seleccionados de N, O y S, en donde el grupo fenilo o heterociclilo es substituido por R^1 y substituyentes opcionales adicionales; o Ar^2 representa un grupo bicíclico aromático o bicíclico heteroaromático opcionalmente substituido que contiene hasta 3 heteroátomos seleccionados de N, O y S;

R^1 representa hidrógeno, C1- 4alcoxilo opcionalmente substituido, halo, ciano, C1- 6alquilo opcionalmente substituido, fenilo opcionalmente substituido, o un grupo fenilo heterociclilo de 5 o 6 miembros opcionalmente substituido que contiene hasta 4 heteroátomos seleccionados de N, O y S;

25 en donde cuando Y es un enlace, Ar^2 no puede ser 2- naftilo;
cuando Ar^1 es arilo p no es 1;
o una sal farmacéuticamente aceptable del mismo.

X es preferiblemente NH.

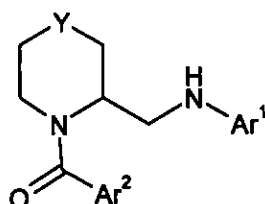
m es preferiblemente 1.

p es preferiblemente 0.

Aún más preferiblemente m es 1 cuando p es 0.

5 Preferiblemente R es hidrógeno.

Alternativamente los compuestos de la fórmula (I) son compuestos de la fórmula (Ia);



10 en donde;

Y representa un enlace, oxígeno, o un grupo $(CH_2)_n$, en donde n representa 1, 2 o 3

Ar^1 es un grupo heteroarilo mono o bicíclico que contiene hasta 3 heteroátomos seleccionados de N, O y S; cualquiera de los cuales puede ser opcionalmente sustituido;

15 Ar^2 representa fenilo o un grupo heterociclilo de 5 o 6 miembros que contiene hasta 3 heteroátomos seleccionados de N, O, y S, en donde el grupo fenilo o heterociclilo es sustituido por R^1 y sustituyentes opcionales adicionales; o Ar^2 representa un grupo bicíclico aromático o bicíclico heteroaromático opcionalmente sustituido que contiene hasta 3 heteroátomos seleccionados de N, O y S;

20 R^1 representa hidrógeno, C1-4alcoxilo opcionalmente sustituido, halo, ciano, C1-6alquilo opcionalmente sustituido, fenilo opcionalmente sustituido, o un grupo fenilo heterociclilo de 5 o 6 miembros opcionalmente sustituido que contiene hasta 4 heteroátomos seleccionados de N, O y S;

25 en donde cuando Y es un enlace entonces Ar^2 no puede ser 2-naftilo; o sales farmacéuticamente aceptables del mismo.

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Preferiblemente donde Ar^2 representa fenilo o un grupo heterociclilo de 5 o 6 miembros que contiene hasta 3 heteroátomos seleccionados de N, O y S, el grupo R^1 está situado adyacente al punto de unión a la carbonilo amida.

Y es preferiblemente un enlace, oxígeno o $(CH_2)_n$ en donde n es 1 o 2.

5 Aún más preferiblemente Y es un enlace, oxígeno o $(CH_2)_n$ en donde n es 1.

Alternativamente R^1 representa hidrógeno, C1- 4alcoxilo opcionalmente substituido, halo, C1- 6alquilo opcionalmente substituido, fenilo opcionalmente substituido, o un grupo fenilo heterociclilo de 5 o 6 miembros opcionalmente substituido que contiene hasta 4 heteroátomos seleccionados de N, O y S;

10 Alternativamente R^1 representa C1- 4alcoxilo opcionalmente substituido, halo, C1- 6alquilo opcionalmente substituido, fenilo opcionalmente substituido, o un grupo fenilo heterociclilo de 5 o 6 miembros opcionalmente substituido que contiene hasta 3 heteroátomos seleccionados de N, O y S;

15 Preferiblemente R^1 es seleccionado de trifluorometoxilo, metoxilo, etoxilo, halo, ciano o un grupo fenilo, piridilo, pirazolilo, pirimidinilo, u oxadiazolilo opcionalmente substituido.

Mas preferiblemente R^1 es seleccionado de trifluorometoxilo, metoxilo, etoxilo, halo, o un grupo fenilo, piridilo, pirazolilo, pirimidinilo, u oxadiazolilo opcionalmente substituido.

20 Cuando Ar^1 es arilo opcionalmente substituido éste preferiblemente es fenilo. Ar^1 puede tener hasta 5, preferiblemente 1, 2 o 3 substituyentes opcionales.

25 Ejemplos de cuando Ar^1 es heteroarilo mono o bicíclico son quinoxalinilo, quinazolinilo, piridopirazinilo, benzoxazolilo, benzotiofenilo, benzimidazolilo, naftiridinilo, piridinilo, pirimidinilo, o tiazolilo. Adicionalmente Ar^1 puede ser seleccionado de piridazinilo, pirazinilo, oxaxolilo, triazolilo, imidazolilo, pirazolilo, quinolinilo, benzofuranilo, indolilo, benzotiazolilo, oxazolilo[4,5- b]piridiilo, piridopirimidinilo o isoquinolinilo. Además Ar^1 puede ser furanilo o tienilo.

30 Preferiblemente Ar^1 es benzoxazolilo, benzimidazolilo, quinoxalinilo, quinazolinilo, pirimidinilo, piridinilo, naftiridinilo. Adicionalmente Ar^1 puede ser quinolinilo, piridopirimidina, tiazolilo, oxazolilpiridinilo, benzotiazolilo, isoquinolinilo o pirazinilo.

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Más preferiblemente Ar¹ es benzoxazolilo, benzimidazolilo, quinoxalinilo, quinazolinilo, pirimidinilo, piridinilo, naftiridinilo o oxazolil[4,5- b]piridinilo.

Cuando Ar² es un grupo heterociclilo de 5 o 6 miembros que contiene hasta 3 heteroátomos seleccionados de N, O y S, éste puede ser furanilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, oxadiazolilo, tiadiazolilo, piridilo, triazolilo, triazinilo, piridazinilo, pirimidinilo, isotiazolilo, isoxazolilo, pirazinilo o pirazolilo.

Cuando R¹ es un grupo heterociclilo de 5 o 6 miembros que contiene hasta 4 heteroátomos seleccionados de N, O y S, éste puede ser furanilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, oxadiazolilo, tiadiazolilo, piridilo, triazolilo, triazinilo, triazinilo, piridazinilo, pirimidinilo, isotiazolilo, isoxazolilo, pirazinilo o pirazolilo. Adicionalmente éste puede ser tetrazoilo, piperazinilo, piperidinilo, morfolinilo o tiomorfolinilo.

Preferiblemente cuando R¹ es un anillo heterocíclico de 5 o 6 miembros que contiene hasta 4 heteroátomos seleccionados de N, O y S, éste es furanilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, oxadiazolilo, tiadiazolilo, piridilo, triazolilo, triazinilo, piridazinilo, pirimidinilo, isotiazolilo, isoxazolilo, pirazinilo o pirazolilo.

Preferiblemente R¹ es un anillo heterocíclico de 5 o 6 miembros que contiene hasta 3 heteroátomos seleccionados de N, O y S.

Cuando Ar² es un grupo aromático bicíclico o heteroaromático bicíclico opcionalmente sustituido, éste es seleccionado de benzofurilo, benzimidazolilo, quinolinilo, quinoxalinilo o naftilo. Adicionalmente éste puede ser benzotriazolilo, benzotienilo, benzoxazolilo, naftiridinilo, isoquinolinilo o quinazolinilo. Además éste puede ser indolilo, benzotiazolilo, o benzotiadiazolilo.

Preferiblemente Ar² representa fenilo, piridilo, tiazolilo, pirazolilo, benzofurilo, naftilo, triazolilo, quinoxalinilo, quinolinilo, isoquinolinilo, benzimidazolilo, benzotienilo, benzotriazolilo, benzotiazolilo, indolilo o tienilo opcionalmente sustituido.

Alternativamente Ar² representa tienilo, piridilo, tiazolilo, pirazolilo, benzofurilo, naftilo o triazolilo opcionalmente sustituido. Preferiblemente el triazolilo es 1,2,3-triazolilo.

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Más preferiblemente Ar^2 representa tiazolilo, pirazolilo o quinolinilo opcionalmente sustituido.

Alternativamente R^1 es seleccionado de trifluorometoxilo, metoxilo, halo, o un grupo tienilo, piridilo, pirazolilo o oxadiazolilo opcionalmente sustituido.

- 5 Aún más preferiblemente R^1 representa un grupo trifluorometoxilo, metoxilo, yodo, o un grupo tienilo, piridinilo, o oxadiazolilo opcionalmente sustituido.

- Substituyentes opcionales para los grupos Ar^1 , Ar^2 , R y R^1 incluyen el grupo halogeno, hidroxilo, oxo, ciano, nitro, C1- 4alquilo, C1- 4alcoxilo, hidroxilo- C1- C4alquilo, hidroxilo- C1- C4alcoxilo, haloC1- 4alquilo, halo- C1- 4alcoxilo, arilo- C1- 4alcoxilo, C1- 4alquiltio, hidroxilo- C1- 4alquilo, C1- 4alcoxilo- C1- 4alquilo, C3- 6cicloalquilo- C1- 4alcoxilo, C1- 4alcanoilo, C1- 4alcoxycarbonilo, C1- 4alquilsulfonilo, C1- 4alquilsulfoniloxilo, C1- 4alquilsulfonilo- C1- 4alquilo, arilsulfonilo, arilsulfoniloxilo, arilsulfonilo- C1- 4alquilo, C1- 4alquilsulfonamido, C1- 4alquilamido, C1- 4alquilsulfonamido- C1- 4alquilo, C1- 4alquilamido- C1- 4alquilo, arilsulfonamido, arilcarboxamido, arilsulfonamido- C1- 4alquilo, arilcarboxamido- C1- 4alquilo, aroilo, aroilo- c1- 4alquilo, o arilo- C1- 4alcanoilo; un grupo R^aR^bN- , $R^aOCO(CH_2)_r$, $R^aCON(R^a)(CH_2)_r$, $R^aR^bNCO(CH_2)_r$, $R^aR^bNSO_2(CH_2)_r$ o $R^aSO_2NR^b(CH_2)_r$ donde cada R^a y R^b independientemente representa un átomo de hidrógeno o un grupo C1- 4alquilo o donde R^aR^b forma parte de un anillo de C3- 6azacicloalcano o C3- 6- 2- oxo- azacicloalcano y r representa cero o un entero entre 1 y 4. Substituyentes adicionales son C1- 4acilo, arilo, arilo- C1- 4alquilo, C1- 4aquilamino- C1- 4alquilo, $R^aR^bN(CH_2)_n-$, $R^aR^bN(CH_2)_nO-$, donde n representa un entero entre 1 y 4. Adicionalmente cuando el substituyente es $R^aR^bN(CH_2)_n-$ o $R^aR^bN(CH_2)_nO$, R^a con al menos un CH_2 de la porción $(CH_2)_n$ del grupo forma un C3- 6azacicloalcano y R^b representa hidrógeno, un grupo c1- 4- alquilo o con el nitrógeno al cual está unido forma un segundo C3- 6- azacicloalcano fusionado al primer C3- 6azacicloalcano.
- 10
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Sustituyentes opcionales preferidos para Ar^2 son halogeno, ciano, C1- 4alquilo. Sustituyentes opcionales preferidos adicionales son hidroxilo- C1- 4alquilo, C1- 4alcoxilo- C1- 4alquilo, $R^aR^bN(CH_2)_n$, $R^aR^bN(CH_2)_nO$ o C1- 4alcoxilo.

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Sustituyentes opcionales preferidos para Ar¹ son halogeno, ciano, C1- 4alcanoilo. Otros sustituyentes preferidos son hidroxilo- C1- 4alquilo, C1- 4alquilo o CF₃.

Sustituyentes opcionales preferidos para R¹ son halogeno, C1- 4alcoxilo- C1- 4alquilo, R^aR^bN, R^aR^bN(CH₂)_nO y R^aR^bN(CH₂)_n. Otros substituyentes preferidos son C1- 4alcoxilo o C1- 4alcanoilo.

En los grupos Ar¹ y Ar², los substituyentes que se encuentran colocados en posición orto entre sí pueden ser enlazados para formar un anillo.

Compuestos ilustrativos de la fórmula (I) son seleccionados de:

Tabla

10

Ejemplo	Nombre del Compuesto
1	1- [2- (Benzooxazol- 2- ilaminometil)- piperidin- 1- il]- 1- (2- metil- 5- fenil)- tiazol- 4- il)- metanona.
2	1- [2- (Benzooxazol- 2- ilaminometil)- piperidin- 1- il]- 1- bifenil- 2- il)- metanona
3	1- [2- (Benzooxazol- 2- ilaminometil)- piperidin- 1- il]- 1- [2- (3- metil- [1,2,4]oxadiazol- 5- il-)- fenil]- metanona
4	1- [2- (Benzooxazol- 2- ilaminometil)- piperidin- 1- il]- 1- (2- trifluorometoxi- fenil)- metanona
5	1- [2- (Benzooxazol- 2- ilaminometil)- piperidin- 1- il]- 1- naftalen- 1- il)- metanona
6	1- [2- (Benzooxazol- 2- ilaminometil)- piperidin- 1- il]- 1- (2- metoxi- fenil)- metanona
7	1- [2- (Benzooxazol- 2- ilaminometil)- piperidin- 1- il]- 1- (2- yodo- fenil)- metanona
8	1- [(S)- 2- (Benzooxazol- 2- ilaminometil)- piperidin- 1- il]- 1- (2- trifluorometoxi- fenil)- metanona
9	1- [(S)- 2- (Benzooxazol- 2- ilaminometil)- piperidin- 1- il]- 1- [2- (3- metil- [1,2,4]oxadiazol- 5- il)- fenil]- metanona

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10	1- [(S)- 2- (Benzooxazol- 2- ilaminometil)- piperidin- 1- il]- 1- bifenil- 2- il- metanona
11	1- [(S)- 2- (Benzooxazol- 2- ilaminometil)- piperidin- 1- il]- 1- (2- yodo- fenil)- metanona
12	1- [2- Benzooxazol- 2- ilaminometil)- piperidin- 1- il]- 1- fenil)- metanona.
13	1- {2- [(1H- Benzoimidazol- 2- ilamino)- metil]- piperidin- 1- il}- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona
14	1- {2- [(1H- Benzoimidazol- 2- ilamino)- metil]- piperidin- 1- il}- 1- [2- (3- metil- [1,2,4]oxadiazol- 5- il)- fenil]- metanona
15	1- [2- (Benzotiazol- 2- ilaminometil)- piperidin- 1- il]- 1- [2- (3- metil- [1,2,4]oxadiazol- 5- il)- fenil]- metanona
16	1- [2- (Benzotiazol- 2- ilaminometil)- piperidin- 1- il]- 1- (2- trifluorometoksi- fenil)- metanona
17	1- [2- (Benzotiazol- 2- ilaminometil)- piperidin- 1- il]- 1- bifenil- 2- il- metanona
18	1- [2- (Benzotiazol- 2- ilaminometil)- piperidin- 1- il]- 1- (2- metil- 5- fenil- tiazol- 4- il)- metanona
19	1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- 1- [2- (isoquinolin- 1- ilaminometil)- piperidin- 1- il]- metanona
20	1- [2- (Isoquinolin- 1- ilaminometil)- piperidin- 1- il]- 1- [2- (3- metil- [1,2,4]oxadiazol- 5- il)- fenil]- metanona
21	1- [2- (Isoquinolin- 1- ilaminometil)- piperidin- 1- il]- 1- (2- trifluorometoksi- fenil)- metanona
22	1- (2- Yodo- fenil)- 1- [2- (isoquinolin- 1- ilaminometil)- piperidin- 1- il]- metanona
23	1- [2- (Isoquinolin- 1- ilaminometil)- piperidin- 1- il]- 1- naftalen- 1- il- metanona
24	1- [2- (Quinoxalin- 2- ilaminometil)- piperidin- 1- il]- 1- (2-

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	trifluorometoxi- fenil)- metanona
25	1- [2- (Quinoxalin- 2- ilaminometil)- piperidin- 1- il]- 1- (3- trifluorometoxi- fenil)- metanona
26	1- (2- Yodo- fenil)- 1- [2- (quinoxalin- 2- ilaminometil)- piperidin- 1- il]- metanona
27	1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- 1- [2- (quinoxalin- 2- ilaminometil)- piperidin- 1- il]- metanona
28	1- [2- (3- Metil- [1,2,4]oxadiazol- 5- il)- fenil]- 1- [2- (quinoxalin- 2- ilaminometil)- piperidin- 1- il]- metanona
29	1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- 1- [(R)- 2- (quinazolin- 2- ilaminometil)- piperidin- 1- il]- metanona
30	1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- 1- [(S)- 2- ([1,5]naftiridin- 2- ilaminometil)- piperidin- 1- il]- metanona
31	1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- 1- [(S)- 2- ([1,8]naftiridin- 2- ilaminometil)- piperidin- 1- il]- metanona
32	1- [(S)- 2- (Benzooxazol- 2- ilaminometil)- piperidin- 1- il]- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona
33	1- [3- (Benzooxazol- 2- ilaminometil)- morfolin- 4- il]- 1- [2- (3- metil- [1,2,4]oxadiazol- 5- il)- fenil]- metanona
34	1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- 1- [2- (quinolin- 2- ilaminometil)- piperidin- 1- il]- metanona
35	1- [2- (3- Metil- [1,2,4]oxadiazol- 5- il)- fenil]- 1- [2- (quinolin- 2- ilaminometil)- piperidin- 1- il]- metanona
36	1- [2- (Quinolin- 2- ilaminometil)- piperidin- 1- il]- 1- (2- trifluorometoxi- fenil)- metanona
37	1- [2- (Benzotiazol- 2- ilaminometil)- piperidin- 1- il]- 1- naftalen- 1- il- metanona
38	1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- 1- [(S)- 2- (quinolin- 2- ilaminometil)- piperidin- 1- il]- metanona

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39	1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- 1- [2- (pirimidin- 2- ilaminometil)- piperidin- 1- il]- metanona
40	1- [2- (3- Metil- [1,2,4]oxadiazol- 5- il)- fenil]- 1- [2- (pirimidin- 2- ilaminometil)- piperidin- 1- il]- metanona
41	1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- 1- [2- (pirazin- 2- ilaminometil)- piperidin- 1- il]- metanona
42	1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- 1- [(S)- 2- (quinazolin- 4- ilaminometil)- piperidin- 1- il]- metanona
43	1- [5- (4- Fluoro- fenil)- tiazol- 4- il]- 1- [(S)- 2- (quinazolin- 4- ilaminometil)- piperidin- 1- il]- metanona
44	1- [4- (4- Fluoro- fenil)- 2- metil- 1H- pirazol- 3- il]- 1- [(S)- 2- (quinazolin- 4- ilaminometil)- piperidin- 1- il]- metanona
45	1- [4- (4- Fluoro- fenil)- 2- metil- 2H- pirazol- 3- il]- 1- [(S)- 2- (quinazolin- 4- ilaminometil)- piperidin- 1- il]- metanona
46	1- [4- (4- Fluoro- fenil)- 1H- pirazol- 3- il]- 1- [(S)- 2- (quinazolin- 4- ilaminometil)- piperidin- 1- il]- metanona
47	1- [5- (3- Fluoro- fenil)- 2- metil- tiazol- 4- il]- 1- [(S)- 2- (quinazolin- 4- ilaminometil)- piperidin- 1- il]- metanona
48	1- [5- (3- Fluoro- fenil)- 2- metil- 2H- [1,2,3]triazol- 4- il]- 1- [(S)- 2- (quinazolin- 4- ilaminometil)- piperidin- 1- il]- metanona
49	1- Naftalen- 1- il- 1- [(S)- 2- (quinazolin- 4- ilaminometil)- piperidin- 1- il]- metanona
50	1- (5- Bromo- 2- metoxi- fenil)- 1- [(S)- 2- (quinazolin- 4- ilaminometil)- piperidin- 1- il]- metanona
51	1- [2- (3- Metil- [1,2,4]oxadiazol- 5- il)- fenil]- 1- [(S)- 2- (quinazolin- 4- ilaminometil)- piperidin- 1- il]- metanona
52	1- [(S)- 2- (Quinazolin- 4- ilaminometil)- piperidin- 1- il]- 1- (2- trifluorometoxi- fenil)- metanona
53	1- {(S)- 2- [(6,7- Difluoro- 3- metil- quinoxalin- 2- ilamino)- metil]-

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	piperidin- 1- il}- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona
54	1- {(S)- 2- [(6,7- Difluoro- 3- metil- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [5- (4- fluoro- fenil)- tiazol- 4- il]- metanona
55	1- {(S)- 2- [(6,7- Difluoro- 3- metil- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [4- (4- fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanona
56	1- {(S)- 2- [(6,7- Difluoro- 3- metil- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [4- (4- fluoro- fenil)- 1H- pirazol- 3- il]- metanona
57	1- {(S)- 2- [(6,7- Difluoro- 3- metil- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [2- (4- fluoro- fenil)- 5- metil- 2H- pirazol- 3- il]- metanona
58	1- {(S)- 2- [(6,7- Difluoro- 3- metil- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [4- (4- fluoro- fenil)- 2- metil- 2H- pirazol- 3- il]- metanona
59	1- {(S)- 2- [(6,7- Difluoro- 3- metil- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- naftalen- 1- il- metanona
60	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- quinolin- 4- il- metanona
61	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [5- (4- fluoro- fenil)- 2- metil- oxazol- 4- il]- metanona
62	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona
63	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [2- (3- metil- [1,2,4]oxadiazol- 5- il)- fenil]- metanona
64	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- (2- trifluorometoxi- fenil)- metanona
65	1- Bifenil- 2- il- 1- {(S)- 2- [(6,7- difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- metanona
66	1- (5- Bromo- 2- metoxi- fenil)- 1- (S)- 2- [(6,7- difluoro- quinoxalin- 2-

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	ilamino)- metil]- piperidin- 1- il}- metanona
67	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [4- (4- fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanona
68	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [4- (4- fluoro- fenil)- 2- metil- 2H- pirazol- 3- il]- metanona
69	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [5- (4- fluoro- fenil)- 2- metil- 2H- [1,2,3]triazol- 4- il]- metanona
70	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- naftalen- 1- il- metanona
71	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [5- (4- fluoro- fenil)- tiazol- 4- il]- metanona
72	1- [4- (4- Fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- 1- [(R)- 2- (quinazolin- 2- ilaminometil)- piperidin- 1- il]- metanona
73	1- [2- (3- Metil- [1,2,4]oxadiazol- 5- il)- fenil]- 1- [2- (oxazolo[4,5- b]piridin- 2- ilaminometil)- piperidin- 1- il]- metanona
74	1- [2- (Oxazolo[4,5- b]piridin- 2- ilaminometil)- piperidin- 1- il]- 1- (2- trifluorometoxi- fenil)- metanona
75	1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- 1- [2- (oxazolo[4,5,b]piridin- 2- ilaminometil)- piperidin- 1- il]- metanona
76	1- (2- Yodo- fenil)- 1- [2- (oxazolo[4,5,b]piridin- 2- ilaminometil)- piperidin- 1- il]- metanona
77	1- {3- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- morfolin- 4- il}- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona
78	1- {3- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- morfolin- 4- il}- 1- [4- (4- fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanona
79	1- {3- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- morfolin- 4- il}- 1- [4- (4- fluoro- fenil)- 2- metil- 2H- pirazol- 3- il]- metanona
80	1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- 1- [(S)- 2- (pirido[2,3,b]pirazin- 2- ilaminometil)- piperidin- 1- il]- metanona

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81	1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- 1- [(S)- 2- (pirido[2,3,b]pirazin- 3- ilaminometil)- piperidin- 1- il]- metanona
82	1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- 1- {2- [(4- fenil- tiazol- 2- ilamino)- metil]- piperidin- 1- il}- metanona
93	1- {2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [4- (4- fluoro- fenil)- 2H- pirazol- 3- il]- metanona
94	1- {2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona
95	1- {2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [2- (4- fluoro- fenil)- 5- metil- 2H- pirazol- 3- il]- metanona
96	1- {2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [5- (4- fluoro- fenil)- 2- metil- 2H- [1,2,3]triazol- 4- il]- metanona
97	2- (1- {2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- pirrolidin- 1- il}- metanoil)- benzonitrilo
98	1- {2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- naftalen- 1- il- metanona
99	1- (5- Bromo- 2- metoxi- fenil)- 1- {2- [(6,7- difluoro- quinoxalin- 2- ilamino)- metil]- pirrolidin- 1- il}- metanona
100	1- {2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [2- (3- metil- [1,2,4]oxadiazol- 5- il)- fenil]- metanona
101	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona
102	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [5- (4- fluoro- fenil)- tiazol- 4- il]- metanona
103	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [2- (3- metil- [1,2,4]oxadiazol- 5- il)- fenil]- metanona
104	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [4- (4- fluoro- fenil)- 1H- pirazol- 3- il]- metanona
105	1- [2- (3- Metil- [1,2,4]oxadiazol- 5- il)- fenil]- 1- [(S)- 2- (oxazolo[4,5-

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	b]piridin- 2- ilaminometil)- piperidin- 1- il]- metanona
106	1- [2- (3- Metil- [1,2,4]oxadiazol- 5- il)- fenil]- 1- {(S)- 2- [(metil-oxazolo[4,5- b]piridin- 2- il- amino)- metil]- piperidin- 1- il}- metanona
83	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- quinoxalin- 2- il- metanona
84	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- quinolin- 3- il- metanona
85	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- isoquinolin- 3- il- metanona
86	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- (2- metoxi- piridin- 3- il)- metanona
87	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- quinoxalin- 6- il- metanona
88	6- [((S)- 1- {1- [4- Fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanoil}- piperidin- 2- ilmetil)- amino]- nicotinonitrilo
89	1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- 1- {(S)- 2- [(4- trifluorometil- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- metanona
90	1- (1H- Benzoimidazol- 5- il)- 1- [(S)- 2- (pirido[2,3,b]pirazin- 2- ilaminometil)- piperidin- 1- il]- metanona Duplicado del Ejemplo 161
91	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [2- dimetilamino- 5- (4- fluoro- fenil)- tiazol- 4- il]- metanona
92	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [2- (3- dimetilamino- propoxi)- fenil]- metanona
107	6- [((S)- 1- {1- [4- (4- Fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanoil}- piperidin- 2- ilmetil)- metil- amino]- nicotinonitrilo
108	1- ((S)- 2- {[(6,7- Difluoro- quinoxalin- 2- il)- metil- amino]- metil}- piperidin- 1- il)- 1- [4- (4- fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanona

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Y sales farmacéuticamente aceptables de los mismos.

Los compuestos adicionales de la fórmula I son seleccionados a partir de:

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Ejemplo	Nombre del Compuesto
109	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- (4- fluoro- benzofuran- 2- il)- metanona
110	2- [((S)- 1- {1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- metanoil}- piperidin- 2- ilmetil)- amino]- nicotinonitrilo
111	2- [((S)- 1- {1- [2- (3- Metil- [1,2,4]oxadiazol- 5- il)- fenil]- metanoil}- piperidin- 2- ilmetil)- amino]- nicotinonitrilo
112	2- [((S)- 1- {1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- metanoil}- piperidin- 2- ilmetil)- amino]- isonicotinonitrilo
113	1- Benzo[b]tiofen- 2- il- 1- {(S)- 2- [(6,7- difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- metanona
114	1- (1H- Benzoimidazol- 5- il)- 1- {(S)- 2- [6,7- difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- metanona
115	1- (1H- Benzotriazol- 5- il)- 1- {(S)- 2- [(6,7- difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- metanona
116	1- Benzotriazol- 6- il- 1- {(S)- 2- [(6,7- difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- metanona
117	1- (3,4- Dicloro- fenil)- 1- {(S)- 2- [(6,7- difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- metanona
118	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- (3,4- dimetoxi- fenil)- metanona
121	1- Isoquinolin- 3- il- 1- [(S)- 2- (pirido[2,3- b]pirazin- 2- ilaminometil)- piperidin- 1- il]- metanona
122	1- (1H- Indol- 5- il)- 1- [(S)- 2- (pirido[(2,3- b]pirazin- 2- ilaminometil)-

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	piperidin- 1- il}- metanona
124	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [4- (4- fluoro- fenil)- 1- (2- metoxi- etil)- 1H- pirazol- 3- il]- metanona
125	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- (2,4- dimetil- tiazol- 5- il)- metanona
126	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [5- (4- fluoro- fenil)- 1- metil- 1H- [1,2,3]triazol- 4- il]- metanona
127	6- [((S)- 1- {1- [4- (4- Fluoro- fenil)- 1- (2- metoxi- etil)- 1H- pirazol- 3- il]- metanoil)- piperidin- 2- ilmetil]- amino]- nicotinonitrilo
128	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona
129	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [4- (4- fluoro- fenil)- 1H- pirazol- 3- il]- metanona
130	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [5- (4- fluoro- fenil)- 2H- [1,2,3]triazol- 4- il]- metanona
131	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- quinolin- 2- il- metanona
132	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [5- (4- fluoro- fenil)- 1- metil- 1H- [1,2,3]triazol- 4- il]- metanona
133	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [5- (4- fluoro- fenil)- 2- idroximetil- tiazol- 4- il]- metanona
134	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [2- (3- metil- [1,2,4]oxadiazol- 5- il)- fenil]- metanona
135	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- quinolin- 8- il- metanona
136	2- {[(S)- 1- (1- 1H- Benzoimidazol- 5- il- metanoil)- piperidin- 2- ilmetil]- amino}- 6,7- difluoro- quinolina- 3- carbonitrilo
137	6,7- Difluoro- 2- {[(S)- 1- (1- isoquinolin- 3- il- metanoil)- piperidin- 2-

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	ilmetil]- amino}- quinolina- 3- carbonitrilo
138	6,7- Difluoro- 2- [((S)- 1- {1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanoi}- piperidin- 2- ilmetil)- amino]- quinolina- 3- carbonitrilo
139	6,7- Difluoro- 2{[(S)- 1- naftalen- 2- il- metanoil)- piperidin- 2- ilmetil]- amino}- quinolina- 3- carbonitrilo
140	6,7- Difluoro- 2{[(S)- 1- {1- [4- fluoro- fenil)- 1H- pirazol- 3- il]- metanoil}- piperidin- 2- ilmetil)- amino]- quinolina- 3- carbonitrilo
141	6,7- Difluoro- 2{[(S)- 1- (1- 1H- indol- 6- il- metanoil)- piperidin- 2- ilmetil]- amino}- quinolina- 3- carbonitrilo
142	2- {[(S)- 1- (1- 1H- Benzotiazol- 6- il- metanoil)- piperidin- 2- ilmetil]- amino}- 6,7- difluoro- quinolina- 3- carbonitrilo
143	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- naftalen- 2- il- metanona
144	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- (6- fluoro- benzofuran- 2- il)- metanona
145	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- (5- fluoro- benzofuran- 2- il)- metanona
146	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- (7- fluoro- benzofuran- 2- il)- metanona
147	1- (5- 7- Difluoro- benzofuran- 2- il)- 1- {(S)- 2- [(6,7- difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- metanona
148	2- [((S)- 1- {1- [4- (4- Fluoro- fenil)- 1H- pirazol- 3- il]- metanoil}- piperidin- 2- ilmetil)- amino]- nicotinonitrilo
149	2- [((S)- 1- {1- [4- (4- Fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanoil}- piperidin- 2- ilmetil)- amino]- nicotinonitrilo
150	2- [((S)- 1- {1- [4- (4- Fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanoil}- piperidin- 2- ilmetil)- amino]- isonicotinonitrilo
151	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- {2- [3- (3- dimetilamino- propoxi)- fenil]- tiofen- 3- il}- metanona

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152	1- {2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- {2- [3- (3- dimetilamino- propoxi)- fenil]- tiofen- 3- il}- metanona
153	1- {2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- quinolin- 8- il- metanona
154	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- (1- metil- 1H- indol- 2- il)- metanona
155	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- (1H- indol- 6- il)- metanona
156	1- Benzol[1,2,3]tiadiazol- 5- il- 1- {(S)- 2- [(6,7- difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- metanona
157	Ester metilico del acido benzoico 3- (1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- metanoil)
158	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [1- (2- dimetilamino- etil)- 4- (4- fluoro- fenil)- 1H- pirazol- 3- il]- metanona
159	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [1- (2- dimetilamino- etil)- 4- (fluoro- fenil)- 1H- pirazol- 3- il]- metanona
160	1- [4- (4- Fluoro- fenil)- 1- (2- metoxi- etil)- 1H- pirazol- 3- il]- 1- [(S)- 2- (pirido[2,3,b]pirazin- 2- ilaminometil)- piperidin- 1- il]- metanona
162	1- (1H- Benzoimidazol- 5- il)- 1- {(S)- 2- [(5- bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- metanona
163	1- Benzofuran- 2- il- 1- {(S)- 2- [(5- bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- metanona
164	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- (2- metoxi- fenil)- metanona
165	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- quinolin- 4- il- metanona
166	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [3- (3- dimetilamino- propoxi)- fenil]- metanona

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170	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [4- (4- (fluoro- fenil)- 1- metil- 1H- pirazol- 3- il)- metanona
119	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [1- etil- 4- (4- fluoro- fenil)- 1H- pirazol- 3- il]- metanona
120	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [5- (4- fluoro- fenil)- 2H- [1,2,3]triazol- 4- il]- metanona
167	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [4- (4- fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanona
168	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [5- (2- fluoro- fenil)- tiazol- 4- il]- metanona
169	1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [4- (4- fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanona
171	1- {2- [((S)- 1- {1- [4- (4- Fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanoil}- piperidin- 2- ilmetil)- amino]- pirimidin- 5- il}- etanona
172	1- [4- (4- Fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- 1- ((S)- 2- {[5- (1- hidroxi- etil)- pirimidin- 2- ilamino]- metil}- piperidin- 1- il)- metanona
173	2- [((S)- 1- {1- [4- (4- Fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanoil}- piperidin- 2- ilmetil)- amino]- pirimidina- 5- carbonitrilo
174	3- (1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il)- metanoil)- N- metil- benzamida

Y sales farmacéuticamente aceptables de los mismos.

Los compuestos adicionales de la fórmula (I) son seleccionados a partir de:

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Ejemplo	Nombre del Compuesto
175	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- fenil- metanona
176	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1-

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	[5- (4- fluoro- fenil)- 2- hidroximetil- tiazol- 4- il]- metanona
177	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [4- (4- fluoro- fenil)- 1H- pirazol- 3- il]- metanona
178	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- quinolin- 8- il- metanona
179	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- (2- etoxi- fenil)- metanona
180	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- (2- metil- 5- fenil- tiazol- 4- il)- metanona
181	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- {5- [3- (3- dimetilamino- propoxi)- fenil]- 2- metil- tiazol- 4- il}- metanona
182	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- (2- propoxi- fenil)- metanona
183	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- (2- isopropoxi- fenil)- metanona
184	1- (2- Benziloxi- fenil)- 1- {(S)- 2- [(5- bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- metanona
185	1- [3- (1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- metanoil)- 4- etoxi- fenil]- etanona
186	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- (2- etoxi- 6- metoxi- fenil)- metanona
187	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- (2- etoxi- 6- metil- fenil)- metanona
188	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- (2- etoxi- naftalen- 1- il)- metanona
189	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [5- (2- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona
190	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1-

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	[5- (3- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona
191	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [5- (2- fluoro- fenil)- tiazol- 4- il]- metanona
192	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- (5- fenil- tiazol- 4- il)- metanona
193	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- (2- metil- 4- fenil- tiazol- 5- il)- metanona
194	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona
195	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [2- (3- metil- [1,2,4]oxadiazol- 5- il)- fenil]- metanona
196	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [5- (4- cloro- fenil)- 2- metil- tiazol- 4- il]- metanona
197	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona
198	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [4- (4- fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanona
199	1- [3- (Benzooxazol- 2- ilaminometil)- morfolin- 4- il]- 1- [2- (3- metil- [1,2,4]oxadiazol- 5- il)- fenil]- metanona
200	1- {3- [(5- Bromo- pirimidin- 2- ilamino)- metil]- morfolin- 4- il}- 1- [4- (4- fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanona
201	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [5- (3- fluoro- fenil)- tiazol- 4- il]- metanona
202	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [5- (4- metoxi- fenil)- 2- metil- tiazol- 4- il]- metanona
203	3,5- Difluoro- 4- [((S)- 1- {1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanoil}- piperidin- 2- ilmetil)- amino]- benzonitrilo
204	3,5- Difluoro- 4- [((S)- 1- {1- [4- (4- fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanoil}- piperidin- 2- ilmetil)- amino]- benzonitrilo

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205	3,5- Difluoro- 4- [((S)- 1- {1- [4- (4- fluoro- fenil)- 1 <i>H</i> - pirazol- 3- il]- metanoil}- piperidin- 2- ilmetil)- amino]- benzonitrilo
206	3,5- Difluoro- 4- [((S)- 1- {1- [2- (3- metil- [1,2,4]oxadiazol- 5- il)- fenil]- metanoil}- piperidin- 2- ilmetil)- amino]- benzonitrilo
207	4- {[(S)- 1- (1- Benzofuran- 7- il- metanoil)- piperidin- 2- ilmetil]- amina}- 3,5- difluoro- benzonitrilo
208	3,5- Difluoro- 4- [((S)- 1- {1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanoil}- pirrolidin- 2- ilmetil)- amino]- benzonitrilo
209	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [2- dimetilamino- 5- (4- fluoro- fenil)- tiazol- 4- il]- metanona
210	1- (2- Amino- 5- fenil- tiazol- 4- il)- 1- {(S)- 2- [(5- bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- metanona
211	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [5- (3- metoxi- fenil)- 2- metil- tiazol- 4- il]- metanona
212	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [2- (4- fluoro- fenil)- tiofen- 3- il]- metanona
213	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- (2- piridin- 2- il- fenil)- metanona
214	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [4- fluoro- 2- (3- metil- [1,2,4]oxadiazol- 5- il)- fenil]- metanona
215	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [2- (4- metoxi- fenil)- tiofen- 3- il]- metanona
216	1- {(S)- 2- [(5- Etil- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona
217	1- ((S)- 2- {[(5- Bromo- pirimidin- 2- il)- metil- amino]- metil}- pirrolidin- 1- il}- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona
218	1- ((S)- 2- {[(5- Bromo- pirimidin- 2- il)- metil- amino]- metil}- pirrolidin- 1- il)- 1- [4- (4- fluoro- fenil)- 1- metil- 1 <i>H</i> - pirazol- 3- il]- metanona
219	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1-

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	[5- (4- fluoro- fenil)- 2- metoxi- tiazol- 4- il]- metanona
220	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [5- fluoro- 2- (3- metil- [1,2,4]oxadiazol- 5- il)- fenil]- metanona
221	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- (2- fenil- tiofen- 3- il)- metanona
222	2'- (1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- metanoil)- bifenil- 4- carbonitrilo
223	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [2- (3- metoxi- fenil)- tiofen- 3- il]- metanona
224	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- (2- pirazol- 1- il- fenil)- metanona
225	1- {2- [((S)- 1- {1- [5- (4- Cloro- fenil)- 2- metil- tiazol- 4- il]- metanoil)- pirrolidin- 2- ilmetil)- amino]- pirimidin- 5- il}- etanona
226	1- {(S)- 2- [(5- Cloro- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona
227	1- {(S)- 2- [(5- Cloro- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [2- (3- metil- [1,2,4]oxadiazol- 5- il)- fenil]- metanona
228	1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- 1- {(S)- 2- [(5- metil- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- metanona
229	6- [((S)- 1- {1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]metanoil)- pirrolidin- 2- ilmetil)- amino]- nicotinonitrilo
230	5- (1- {2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- metanoil)- 4 <i>H</i> - benzo[1,4]oxazin- 3- ona
231	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [4- (4- fluoro- fenil)- 1- (2- piperidin- 1- il- etil)- 1 <i>H</i> - pirazol- 3- il]- metanona
232	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [1- (2- dimetilamino- etil)- 4- (4- fluoro- fenil)- 1 <i>H</i> - pirazol- 3- il]- metanona

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233	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [2- etil- 5- (4- fluoro- fenil)- tiazol- 4- il]- metanona
234	1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- 1- {(S)- 2- [(6- metil- 2- metilsulfanil- pirimidin- 4- ilamino)- metil]- pirrolidin- 1- il}- metanona
235	1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- 1- {(S)- 2- [(2- metilsulfanil- pirimidin- 4- ilamino)- metil]- pirrolidin- 1- il}- metanona
236	1- {(S)- 2- [Dimetil- trifluorometil- pirimidin- 4- ilamino)- metil]- pirrolidin- 1- il}- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona
237	1- {(S)- 2- [Dimetil- pirimidin- 4- ilamino)- metil]- pirrolidin- 1- il}- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona
238	1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- 1- {(S)- 2- [(6- trifluorometil- pirimidin- 4- ilamino)- metil]- pirrolidin- 1- il}- metanona
239	1- (3- {[5- Bromo- pirimidin- 2- il)- metil- amino]- metil}- morfolin- 4- il)- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona
240	1- (3- {[5- Bromo- pirimidin- 2- il)- metil- amino]- metil}- morfolin- 4- il)- 1- [2- (4- fluoro- fenil)- tiofen- 3- il]- metanona
241	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- (4- etil- quinolin- 8- il)- metanona
242	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- isoquinolin- 1- il- metanona
243	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- (2- metil- quinolin- 5- il)- metanona
244	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- (3- metil- quinolin- 4- il)- metanona
245	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- (2,3- dicloro- fenil)- metanona
246	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- (7- cloro- 3- metil- quinolin- 8- il)- metanona
247	1- [5- (4- Cloro- fenil)- 2- metil- tiazol- 4- il]- 1- {(S)- 2- [(5- cloro-

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	pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- metanona
248	1- {2- [((S)- 1- {1- [2- (3- Metil- [1,2,4]oxadiazol- 5- il)- fenil]- metanoil)- pirrolidin- 2- ilmetil)- amino]- pirimidin- 5- il}- etanona
249	1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- 1- {(S)- 2- [(5- trifluorometil- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- metanona
250	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- (4- etil- quinolin- 8- il)- metanona
251	1- {(S)- 2- [(5- Cloro- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [2- dimetilamino- 5- (4- fluoro- fenil)- tiazol- 4- il]- metanona
252	1- {(S)- 2- [(5- Cloro- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- (2- piridin- 2- il- fenil)- metanona
253	1- {(S)- 2- [(5- Cloro- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [2- etil- 5- (4- fluoro- fenil)- tiazol- 4- il]- metanona
254	1- Bifenil- 2- il- 1- {(S)- 2- [(5- cloro- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- metanona
255	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- (2,3- dicloro- fenil)- metanona
256	1- {5- [3- (4- Cloro- butoxi)- fenil]- 2- metil- tiazol- 4- il}- 1- {(S)- 2- [(5- cloro- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- metanona
257	1- {(S)- 2- [(5- Cloro- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [2- (3- isopropil- [1,2,4]oxadiazol- 5- il)- fenil]- metanona
258	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [2- (3- isopropil- [1,2,4]oxadiazol- 5- il)- fenil]- metanona
259	1- {3- [(5- Bromo- piridin- 2- ilamino)- metil]- morfolin- 4- il}- 1- [2- (4- fluoro- fenil)- tiofen- 3- il]- metanona
260	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [2,4- dimetil- quinolin- 8- il)- metanona
261	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- (2- fenil- quinolin- 4- il)- metanona

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262	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- (2- metil- quinolin- 4- il)- metanona
263	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- (6- bromo- quinolin- 4- il)- metanona
264	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- (2- metil- quinolin- 8- il)- metanona
265	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- (8- bromo- quinolin- 4- il)- metanona
266	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [1- (3- dimetilamino- propil)- 4- (4- fluorofenil)- 1H- pirazol- 3- il)- metanona
267	1- {(S)- 2- [(5- Cloro- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [1- (2- dimetilamino- etil)- 4- (4- fluorofenil)- 1H- pirazol- 3- il)- metanona
268	1- {(S)- 2- [(5- Cloro- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [4- (4- fluoro- fenil)- 1- (2- piperidina- 1- il- etil)- 1H- pirazol- 3- il)- metanona
269	1- {(S)- 2- [(5- Cloro- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [4- (4- fluoro- fenil)- 1- (3- piperidina- 1- il- propil)- 1H- pirazol- 3- il)- metanona
270	1- ((S)- 2- {[(5- Bromo- pirimidin- 2- il)- metil- amino]- metil}- piperidin- 1- il)- 1- isoquinolin- 1- il- metanona
271	1- ((S)- 2- {[(5- Bromo- pirimidin- 2- il)- metil- amino]- metil}- piperidin- 1- il)- 1- (2,3- dicloro- fenil)- metanona
272	1- {(S)- 2- [(5- Cloro- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [2- dimetilaminometil- 5- (4- fluoro- fenil)- tiazol- 4- il]- metanona
273	1- ((S)- 2- {[(5- Bromo- pirimidin- 2- il)- metil- amino]- metil}- piperidin- 1- il)- 1- (3- metil- quinolin- 4- il)- metanona
274	1- ((S)- 2- {[(5- Bromo- pirimidin- 2- il)- metil- amino]- metil}- piperidin-

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	1- il}- 1- (2- metil- quinolin- 5- il)- metanona
275	1- {(S)- 2- [(5- Cloro- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona

Y sales farmacéuticamente aceptables de los mismos.

Los compuestos preferidos de la fórmula I son seleccionados a partir de:

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Ejemplo	Nombre del Compuesto
1	1- [2- (Benzooxazol- 2- ilaminometil)- piperidin- 1- il]- 1- (2- metil- 5- fenil- tiazol- 4- il)- metanona
32	1- [(S)- 2- (Benzooxazol- 2- ilaminometil)- piperidin- 1- il]- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona
93	1- {2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [4- (4- fluoro- fenil)- 2H- pirazol- 3- il]- metanona
105	1- [2- (3- Metil- [1,2,4]oxadiazol- 5- il)- fenil]- 1- [(R)- 2- (oxazolo[4,5- b]piridin- 2- ilaminometil)- piperidin- 1- il]- metanona
106	1- [2- (3- Metil- [1,2,4]oxadiazol- 5- il)- fenil]- 1- {(R)- 2- [(metil- oxazolo[4,5- b]piridin- 2- il- amino)- metil]- piperidin- 1- il}- metanona
107	6- [((S)- 1- {1- [4- (4- Fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanoil}- piperidin- 2- ilmetil)- metil- amino]- nicotinonitrilo
108	1- ((S)- 2- {[(6,7- Difluoro- quinoxalin- 2- il)- metil- amino]- metil}- piperidin- 1- il)- 1- [4- (4- fluoro- fenil)- 1- metil- 1H- pirazol- 3il]- metanona
171	1- {2- [((S)- 1- {1- [4- (4- Fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanoil}- piperidin- 2- ilmetil)- amino]- pirimidin- 5- il}- etanona
172	1- [4- (4- Fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- 1- ((S)- 2- {[5- (1- hidroxi- etil)- pirimidin- 2- ilamino]- metil}- piperidin- 1- il)- metanona
173	2- [((S)- 1- {1- [4- (4- Fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]-

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	metanoil}- piperidin- 2- ilmetil)- amino]- pirimidina- 5- carbonitrilo
174	3- (1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- metanoil)- N- metil- benzamida
194	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona
195	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [2- (3- metil- [1,2,4]oxadiazol- 5- il)- fenil]- metanona
196	1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [5- (4- cloro- fenil)- 2- metil- tiazol- 4- il]- metanona
197	1- {(S)- 2- [(5- Bromo- piridin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona
198	1- {(S)- 2- [(5- Bromo- piridin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [4- (4- fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanona
200	1- {3- [(5- Bromo- pirimidin- 2- ilamino)- metil]- morfolin- 4- il}- 1- [4- (4- fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanona
203	3,5- Difluoro- 4- [((S)- 1- {1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanoil}- piperidin- 2- ilmetil)- amino]- benzonitrilo
208	3,5- Difluoro- 4- [((S)- 1- {1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanoil}- pirrolidin- 2- ilmetil)- amino]- benzonitrilo
216	1- {(S)- 2- [(5- Etil- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona
217	1- ((S)- 2- {[5- Bromo- pirimidin- 2- il)- metil- amino]- metil}- pirrolidin- 1- il)- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona
218	1- ((S)- 2- {[5- Bromo- pirimidin- 2- il)- metil- amino]- metil}- pirrolidin- 1- il)- 1- [4- (4- fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanona
225	1- {2- [((S)- 1- {1- [5- (4- Cloro- fenil)- 2- metil- tiazol- 4- il]- metanoil}- pirrolidin- 2- ilmetil)- amino]- pirimidin- 5- il}- etanona
226	1- {(S)- 2- [(5- Cloro- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona

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227	1- {(S)- 2- [(5- Cloro- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [2- (3- metil- [1,2,4]oxadiazol- 5- il)- fenil]- metanona
228	1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- 1- {(S)- 2- [(5- metil- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- metanona
229	6- [((S)- 1- {1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- metanoil}- pirrolidin- 2- ilmetil)- amino]- nicotinonitrilo
234	1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- 1- {(S)- 2- [(6- metil- 2- metilsulfanil- pirimidin- 4- ilamino)- metil]- pirrolidin- 1- il}- metanona
235	1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- 1- {(S)- 2- [(2- metilsulfanil- pirimidin- 4- ilamino)- metil]- pirrolidin- 1- il}- metanona
239	1- (3- {[5- Bromo- pirimidin- 2- il)- metil- amino]- metil}- morfolin- 4- il)- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona
240	1- (3- {[5- Bromo- pirimidin- 2- il)- metil- amino]- metil}- morfolin- 4- il)- 1- [2- (4- fluoro- fenil)- tiofen- 3- il]- metanona
249	1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- 1- {(S)- 2- [(5- trifluorometil- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- metanona

Cuando un átomo de halógeno está presente en el compuesto la fórmula (I) éste puede ser fluor, cloro, bromo o yodo.

Cuando el compuesto la fórmula (I) contiene un grupo alquilo, sólo o formando parte de un grupo mayor, ej., alcoxilo o alquiltio, el grupo alquilo puede ser lineal, ramificado o cíclico, o combinaciones de los mismos, éste preferiblemente es metilo o etilo.

Cuando se utiliza en la presente el término arilo significa un grupo aromático de 5 o 6 miembros por ejemplo fenilo, o un sistema bicíclico de 7 a 12 miembros donde al menos uno de los anillos es aromático por ejemplo naftilo.

Se apreciará que los compuestos de la fórmula (I) pueden existir como enantiómeros. El presente invento incluye dentro de su alcance todos estos isómeros, incluyendo mezclas. Donde se presentan centros quirales adicionales en los compuestos de la fórmula (I), el presente invento incluye dentro de su alcance todos los diastereoisómeros posibles, incluyendo mezclas de los mismos. Las diferentes formas isoméricas pueden ser

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separadas o resueltas entre sí por métodos convencionales, o cualquier isómero dado puede ser obtenido mediante métodos sintéticos convencionales o mediante síntesis estereoespecíficas o asimétricas.

5 Se entenderá que el invento incluye derivados farmacéuticamente aceptables de los compuestos de la fórmula (I) y que estos están incluidos dentro del alcance del invento.

Compuestos particulares según el invento incluyen aquellos mencionados en los ejemplos y sus derivados farmacéuticamente aceptables.

10 Como se utiliza en la presente "derivado farmacéuticamente aceptable" incluye cualquier sal farmacéuticamente aceptable, éster o sal de tal éster de un compuesto la fórmula (I) el cual, al administrar al receptor es capaz de proporcionar (directa o indirectamente) un compuesto la fórmula (I) o un metabolito activo o residuo del mismo.

Se apreciará que para utilizar en medicina las sales de los compuestos de la fórmula (I) deben ser farmacéuticamente aceptables. Sales farmacéuticamente aceptables apropiadas serán manifiestas para aquellos con experiencia en el estado la técnica e incluyen sales de 15 adición ácida formadas con ácidos inorgánicos ej., ácido clorhídrico, hidrobromico, sulfúrico, nítrico o fosfórico; y ácidos orgánicos ej., ácido succínico, maleico, acético, fumárico, cítrico, tartárico, benzoico, p- toluensulfónico, metanosulfónico o naftalensulfónico. Otras sales ej., oxalatos, pueden ser utilizadas, por ejemplo en la separación de los compuestos de la fórmula (I) y están incluidas dentro del alcance del 20 presente invento. También incluidos dentro del alcance del presente invento están los solvatos e hidratos de compuestos de la fórmula (I).

Ciertos compuestos de la fórmula (I) pueden formar sales de adición ácida con uno o más equivalentes del ácido. El presente invento incluye dentro de su alcance todas las formas estoiquiométricas y no estoiquiométricas posibles.

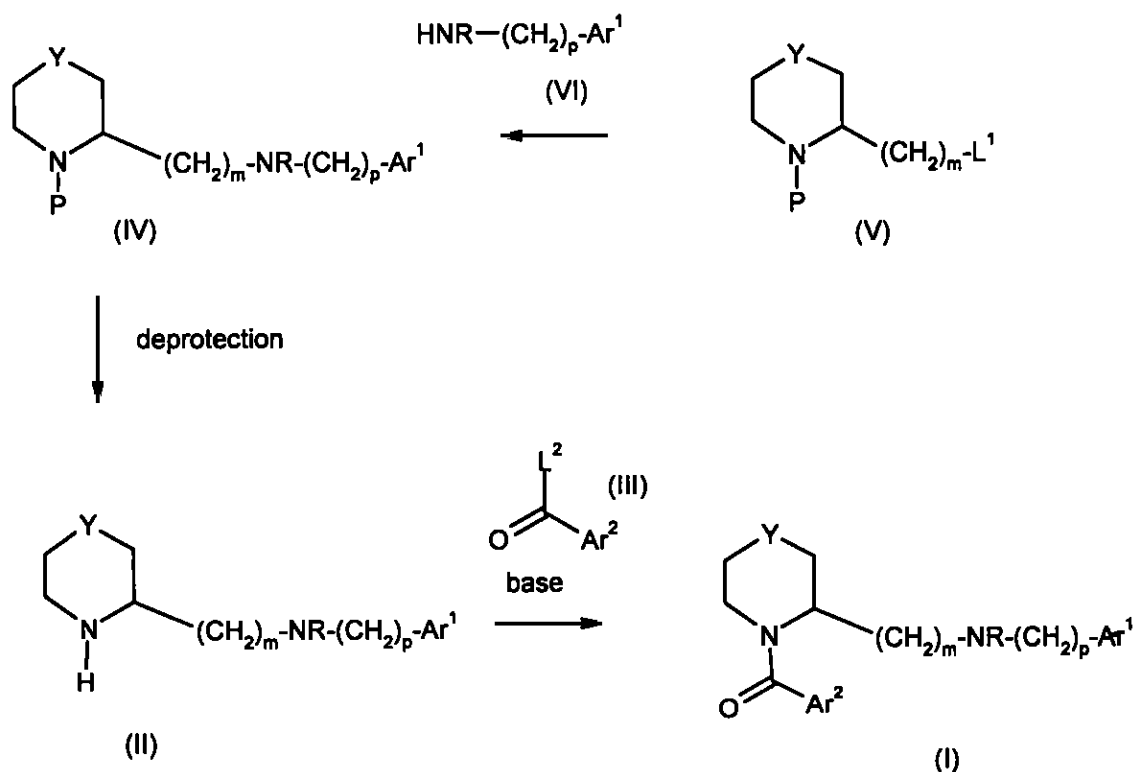
25 Puesto que los compuestos de la fórmula (I) están diseñados para utilizar en composiciones farmacéuticas, fácilmente se entenderá que estos son cada uno preferiblemente proporcionados en forma sustancialmente pura, por ejemplo al menos 60% de pureza, más apropiadamente 75% de pureza y preferiblemente al menos 85%, especialmente 98% de pureza (los porcentajes están basados en el peso). Se pueden utilizar

preparaciones impuras de los compuestos para preparar las formas más puras utilizadas en las composiciones farmacéuticas.

Según una característica adicional del invento se proporciona un proceso para la preparación de compuestos de la fórmula (I) y derivados de los mismos. Los siguientes

5 esquemas detallan alguna rutas sintéticas para los compuestos del invento.

Esquema 1a

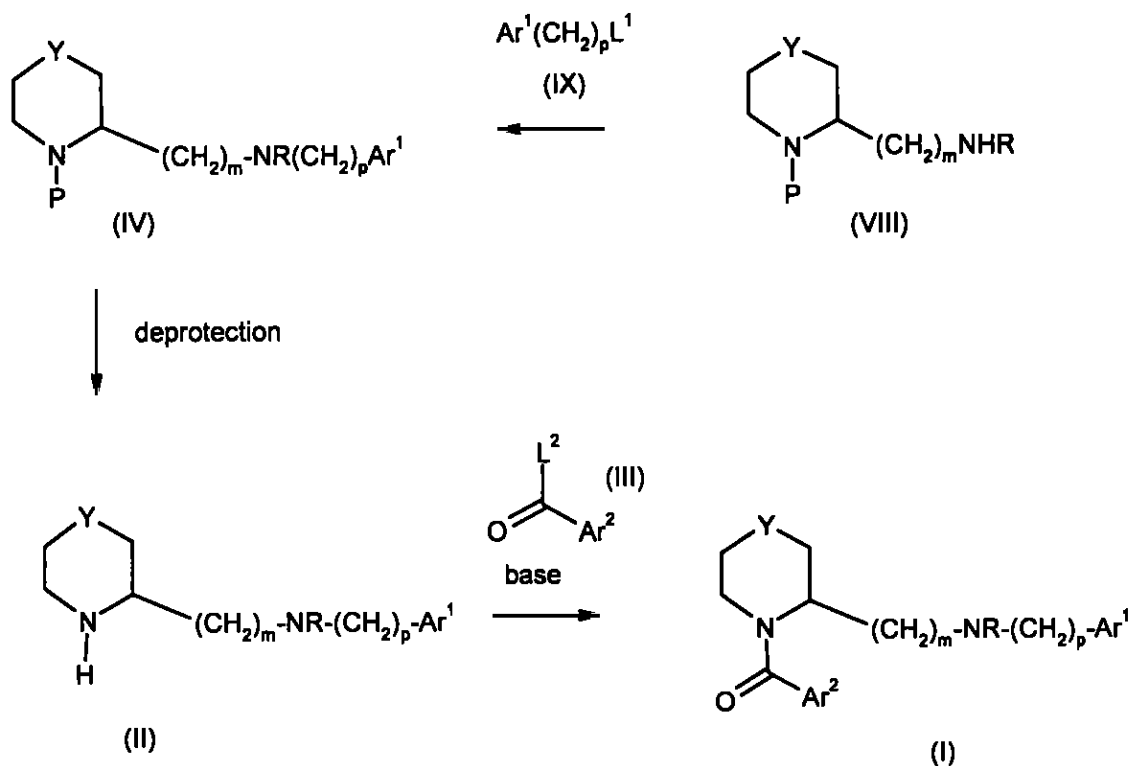


Donde Ar^1 , Ar^2 , Y, m, p y R son tal como se definieron para la fórmula (I), L^1 y L^2 son grupos salientes, y P es un grupo protector.

Ejemplos de grupos salientes apropiados L^1 incluyen halógeno, hidroxilo, OSO_2Me , $\text{OSO}_2(4\text{-tolilo})$. La reacción de (V) con (VI) preferiblemente se lleva a cabo en un solvente inerte tal como N,N- dimetilformamida en presencia de una base tal como trietilamida, hidruro de sodio o t- butoxido de potasio.

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Esquema 1b

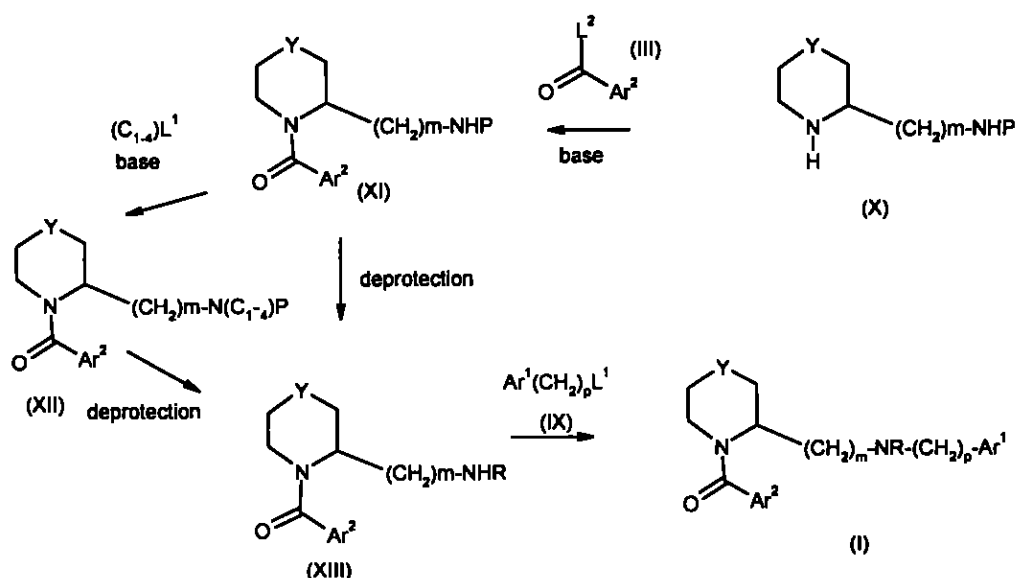


5 La reacción de (VIII) con (IX) se lleva a cabo en un solvente inerte tal como dimetilformamida o xileno en presencia de una base tal como carbonato de potasio o diisopropiletilamina, preferiblemente a temperaturas elevadas.

Alternativamente donde m es 1 y p es 0 o 1, los compuestos se pueden preparar tal como se muestra en el esquema 1c.

Esquema 1c

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La reacción de (XI) con un agente de alquilación $(C_{1-4})L^1$ se lleva a cabo en presencia de una base tal como hidruro de sodio en un solvente inerte tal como dimetilformamida.

Ejemplos de grupos salientes apropiados L^2 incluyen halógeno, hidroxilo, $OC(=O)$ alquilo y $OC(=O)O^-$ alquilo. La transformación (II) a (I) puede ser realizada en un solvente inerte tal como diclorometano, en presencia de una base tal como trietilamina. Alternativamente este paso puede ser realizado cuando L^2 representa hidroxilo, en cuyo caso la reacción con (II) tiene lugar en un solvente inerte tal como diclorometano en presencia de un reactivo de diimida tal como hidrocloreuro de 1- etil- 3- (3- dimetilaminopropil)carbodiimida, y un activador tal como 1- hidroxibenzotriazol.

Ejemplos de grupos protectores P incluyen *t*- butiloxicarbonilo, trifluoroacetilo, bencilo y benciloxicarbonilo opcionalmente substituido. Las condiciones de desprotección son respectivamente, ácido (ej., ácido trifluoroacético en diclorometano), base (ej., hidroxido de sodio en un solvato tal como metanol acuoso) e hidrógenolisis catalítica en un solvente inerte (ej., utilizando paladio o carbón de leña en un alcohol inferior o acetato de etilo).

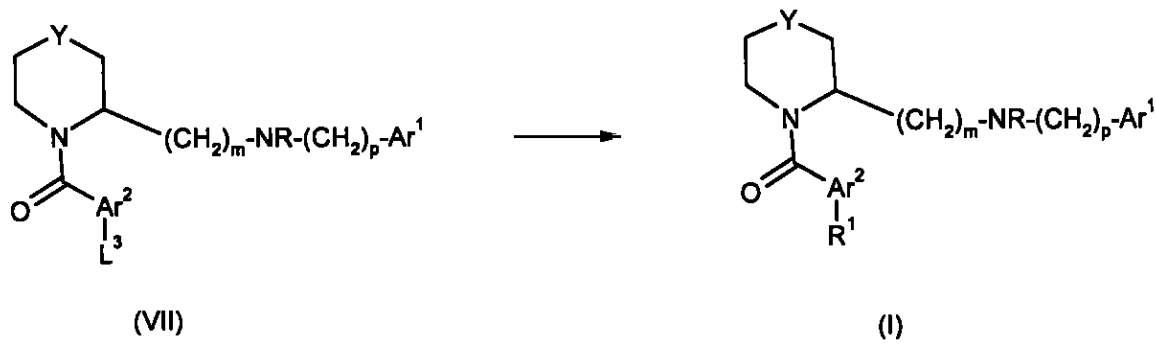
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Los compuestos de la fórmula (V), (VI) y (IX) son conocidos en la literatura o se pueden preparar mediante métodos conocidos. Los compuestos (VIII) se pueden preparar mediante métodos conocidos.

Dentro de los esquemas anteriores existe alcance para interconversión de grupos funcionales; por ejemplo al compuesto (V), la conversión de un valor de L^1 a otro valor de L^1 ; o en compuestos (IV) la conversión del grupo protector P por otro grupo protector P, o la conversión de un compuesto de la fórmula (I) a otro de la fórmula (I) mediante interconversión de substitutos.

Cuando R^1 es un grupo aromático, el substituyente R^1 puede ser introducido en la etapa final tal como se ilustró en el Esquema 2 mediante la reacción de un compuesto de la fórmula (VII) donde L^3 representa un grupo saliente tal como halógeno (preferiblemente bromo o yodo) o trifluorometilsulfoniloxilo, y todas las demás variables son tal como se definieron previamente, con un reactivo R^1M , donde M es el residuo de una especie organometálica ej., $B(OH)_2$ o trialquilestanilo. Tal proceso puede ser llevado a cabo en un solvente inerte tal como 1,2- dimetoxietano o 1,4- dioxano, en la presencia de un catalizador metálico de transición tal como $Pd(PPh_3)_4$.

Esquema 2



En donde Y, Ar^2 , m, p, Ar^1 , R, R^1 y Y son tal como se definió para los compuestos de la fórmula (I). L^3 es un grupo saliente.

Los compuestos de la fórmula (I) se pueden preparar de manera única o como librerías de compuestos que comprenden al menos 2, ej., 5 a 100 compuestos de la fórmula (I). Las librerías de compuestos se pueden preparar mediante un enfoque “división y

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mezcla” combinatorio o mediante síntesis paralela múltiple utilizando química de fase de solución o fase sólida, mediante procedimientos conocidos en el estado de la técnica.

Por lo tanto según un aspecto adicional del invento se proporcionó una librería de compuestos que comprende al menos 2 compuestos de la fórmula (I), o derivados

5 farmacéuticamente aceptables de los mismos.

Las sales farmacéuticamente aceptables se pueden preparar de manera convencional mediante la reacción con el ácido apropiado o derivado ácido.

Los compuestos de la fórmula (I) y sus derivados farmacéuticamente aceptables son útiles para el tratamiento de enfermedades o trastornos tales como obesidad y diabetes

10 donde se requiere un antagonista de un receptor de la orexina humana; prolactinoma; hipoprolactinemia; trastornos hipotalámicos de deficiencia de hormonas de crecimiento; deficiencia de hormonas de crecimiento idiopáticas; síndrome /enfermedad de cushing; disfunción hipotalámica/adrenal; enanismo; trastornos del sueño; apnea del sueño; narcolepsia; insomnio; parasomnio; síndrome de retraso de jet; alteraciones de sueño
15 asociadas con enfermedades tales como trastornos neurológicos, dolor neuropático y síndrome de Ekbom; enfermedades cardíacas y pulmonares; depresión; ansiedad; adicciones; trastorno compulsivo obsesivo; neurosis/trastorno afectivo; neurosis/trastorno depresivo; neurosis de ansiedad; transtorno distímico; trastorno de conducta; trastorno de animo; disfunción sexual; disfunción psicosexual; trastorno sexual; esquizofrenia;
20 enfermedad maniaco depresiva; delirio; demencia; bulimia e hipopituitarismo.

Adicionalmente los compuestos de la fórmula (I) y los derivados farmacéuticamente aceptables son útiles para el tratamiento de apoplejía, particularmente isquémica o hemorrágica y/o para bloquear una respuesta emética es decir nauseas y vomito.

Los compuestos la fórmula (I) y sus derivados farmacéuticamente aceptables son
25 particularmente útiles para el tratamiento de obesidad, incluyendo obesidad asociada con diabetes tipo 2, y trastornos de sueño. Adicionalmente los compuestos la fórmula (I) y derivados farmacéuticamente aceptables son útiles para el tratamiento de apoplejía, particularmente isquémica o hemorrágica y/o para bloquear una respuesta emética es decir nauseas y vomito.

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Otras enfermedades o trastornos que pueden ser tratados según el invento incluyen ritmos biológicos y circadianos alterados; enfermedad de la adenohipofisis; enfermedad de la hipofisis; tumor/adenoma de la hipofisis; hipofunción de la adenohipofisis; amenorrea funcional o psicogénica; hiperfunción de la adenohipofisis; migraña; hiperalgesia; dolor; 5 sensibilidad aumentada o exagerada al dolor tal como hiperalgesia, causalgia y alodinia; dolor agudo; dolor por quemaduras; dolor facial atípico; dolor neuropático; dolor de espalda; síndromes I y II de dolor regional complejo; dolor artrítico; dolor por lesiones deportivas; dolor relacionado con infección; ej., VIH, síndrome post- polio, y neuralgia post- herpética; dolor de extremidad fantasma; y dolor de trabajo de parto; dolor de cáncer; 10 dolor post- quimioterapéutico; dolor post- apoplejía; dolor post- operativo; neuralgia; y tolerancia a narcóticos o abstinencia a narcóticos.

El invento también proporciona un método para tratar o prevenir enfermedades o trastornos donde se requiere un antagonista de un receptor de la orexina humana, el cual comprende la administración a un sujeto en necesidad del mismo de una cantidad efectiva 15 de un compuesto de la fórmula (I), o un derivado farmacéuticamente aceptable del mismo.

El invento también proporciona un compuesto de la fórmula (I), o un derivado farmacéuticamente aceptable del mismo, para utilizar en el tratamiento o profilaxis de enfermedades o trastornos donde se requiere un antagonista de un receptor de la orexina humana.

El invento también proporciona el uso de un compuesto la fórmula (I), o un derivado farmacéuticamente aceptable del mismo, en la fabricación de medicamentos para el tratamiento o profilaxis de enfermedades o trastornos donde se requiere un antagonista 20 de un receptor de la orexina humana.

Para utilizar en terapia los compuestos del invento usualmente son administrados 25 como una composición farmacéutica. El invento también proporciona una composición farmacéutica que comprende un compuesto de la fórmula (I), o derivados farmacéuticamente aceptables del mismo, y un vehículo farmacéuticamente aceptable.

Los compuestos de la fórmula (I) y sus derivados farmacéuticamente aceptables pueden ser administrados mediante cualquier método conveniente, ej., administración oral,

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parenteral, bucal, sublingual, nasal, rectal o transdermal, y las composiciones farmacéuticas adaptadas en consecuencia.

Los compuestos de la fórmula (I) y sus derivados farmacéuticamente aceptables los cuales son activos cuando se administran de manera oral se pueden formular como líquidos o sólidos, ej. como jarabes, suspensiones, emulsiones, tabletas, cápsulas o pastillas.

Una formulación líquida generalmente constará de una suspensión o solución del ingrediente activo en un vehículo líquido apropiado ej. un solvente acuoso tal como agua, etanol o glicerina, o un solvente no acuoso, tal como glicol de polietileno o un aceite. La formulación también puede contener un agente de suspensión, preservativo, agente

saborizante y/o colorante.

Una composición en forma de tableta se puede preparar utilizando cualquier vehículo farmacéuticamente apropiado comúnmente utilizado para preparar formulaciones sólidas, tal como estearato de magnesio, almidón, lactosa, sacarosa y celulosa.

Una composición en la forma de una cápsula se puede preparar utilizando procedimientos de encapsulación comunes, ej. pellets que contienen el ingrediente activo se pueden preparar utilizando vehículos estándares y luego se llenan formando cápsulas de gelatina dura; alternatively una dispersión o suspensión se pueden preparar utilizando cualquier vehículo farmacéuticamente apropiado, ej., gomas acuosas, celulosas, silicatos o aceites y la dispersión o suspensión luego llenada en una cápsula de gelatina suave.

Composiciones parenterales típicas constan de una solución o suspensión del ingrediente activo en un vehículo acuoso estéril y aceite parenteralmente aceptable, ej. glicol de polietileno, polivinilpirrolidona, lecitina, aceite de cacahuete o aceite de ajonjolí. Alternativamente, la solución se puede liofilizar y luego reconstituir con un solvente apropiado inmediatamente antes de la administración.

Composiciones para administración nasal se pueden convenientemente formular como aerosoles, gotas, geles y polvos. Las formulaciones en aerosol típicamente comprenden una solución o suspensión fina del ingrediente activo en un solvente acuoso o no acuoso farmacéuticamente aceptable y son usualmente presentadas en cantidades de dosis únicas o de múltiples dosis en forma estéril en un recipiente sellado el cual puede tomar la forma de un cartucho o repuesto para utilizar con un dispositivo de atomización.

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Alternativamente el recipiente sellado puede ser un dispositivo de dispensación desechable tal como un inhalador nasal de dosis única o un dispensador de aerosol equipado con una válvula medidora. Donde la forma de dosificación comprende un dispensador de aerosol, éste contendrá un propulsor el cual puede ser un gas comprimido, ej., aire, o propulsor orgánico tal como un fluoroclorohidrocarburo o hidrofluorocarbono. Las formas de dosificación de aerosol también pueden tomar la forma de atomizadores de bomba.

Las composiciones adecuadas para administración bucal o sublingual incluyen tabletas y pastillas donde el ingrediente activo es formulado con un vehículo tal como azúcar y acacia, tragacanto, o gelatina y glicerina.

Las composiciones para administración rectal están convenientemente en la forma de supositorios que contienen una base supositoria convencional tal como manteca de cacao.

Las composiciones apropiadas para administración transdermal incluyen ungüentos, geles y parches.

Preferiblemente la composición está en la forma de dosis unitaria tal como una tableta, cápsula o ampolla.

La dosis del compuesto de la fórmula (I), o un derivado farmacéuticamente aceptable del mismo, utilizado en el tratamiento o profilaxis de los trastornos anteriormente mencionados o enfermedades variará en la forma usual con el trastorno o enfermedad particular tratado, el peso del sujeto y otros factores similares. Sin embargo, como regla general, las dosis unitarias apropiadas pueden estar entre 0.05 y 1000 mg, más apropiadamente entre 0.05 y 500 mg. Las dosis unitarias se pueden administrar más de una vez al día por ejemplo dos o tres veces al día, de manera que la dosis diaria total esté en el rango entre 0.01 y 100 mg/kg aproximadamente; y tal terapia se puede extender durante varias semanas o meses. En el caso de derivados farmacéuticamente aceptables, las anteriores cifras son calculadas como el compuesto precursor de la fórmula (I).

No se indicaron/esperaron efectos toxicológicos cuando un compuesto de la fórmula (I) es administrado en el rango de dosificación anteriormente mencionado.

Orexina- A humana tiene la secuencia aminoacida:

PyroGlu Pro Leu Pro Asp Cys Cys Arg Gln Lys Thr Cys Ser Cys Arg Leu

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1 5 10 15
Tyr Glu Leu Leu His Gly Ala Gly Asn His Ala Ala Gly Ile Leu Thr
20 25 30
Leu- NH₂

5 La orexina- A se puede emplear en procedimientos de clasificación para compuestos que inhiben la activación del ligando del receptor de la orexina- 1.

En general, tales procedimientos de clasificación involucran el suministro de células apropiadas las cuales expresan el receptor de la orexina- 1 sobre su superficie. Tales células incluyen células de mamíferos, levadura, Drosophila o *E. Coli*. En particular, un
10 polinucleotido que codifica el receptor de la orexina- 1 es utilizado para transfectar células para así expresar el receptor. El receptor expresado es luego colocado en contacto con un compuesto de prueba y un ligando del receptor de orexina- 1 para observar inhibición de una respuesta funcional. Tal procedimiento de clasificación involucra el uso de melanoforos los cuales son transfectados para expresar el receptor de la orexina- 1, tal
15 como se describió en WO 92/01810.

Otro procedimiento de clasificación trata sobre la introducción de ARN, que codifica el receptor de la orexina- 1, en oocitos *Xenopus* para expresar temporalmente el receptor. Los oocitos receptores son luego colocados en contacto con un ligando receptor y un compuesto de prueba, seguido por la detección de inhibición de una señal en el caso de
20 clasificación para compuestos que se considera inhiben la activación del receptor por el ligando.

Otro método trata sobre la clasificación para compuestos que inhiben la activación del receptor al determinar la inhibición de unión de un ligando de receptor de la orexina- 1 rotulado a las células que tienen el receptor sobre su superficie. Este método lleva a cabo
25 una transfección de una célula eucariótica con ADN que codifica el receptor de la orexina- 1 de tal manera que la célula expresa el receptor sobre su superficie y pone en contacto la célula o preparación de membrana celular con un compuesto en la presencia de una forma rotulada de un ligando del receptor de la orexina- 1. El ligando puede contener un rotulo radioactivo. La cantidad de ligando rotulado unido a los receptores es medida, ej., mediante
30 radioactividad.

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Aún otra técnica de clasificación involucra el uso de equipo FLIPR para clasificación de alto rendimiento de compuestos de prueba que inhiben la movilización de iones de calcio intracelular, u otros iones, al afectar la interacción de un ligando del receptor de la orexina- 1 con el receptor de la orexina- 1.

5 Todas las publicaciones, incluyendo pero sin limitar a patentes y solicitudes de patentes, citadas en esta especificación son incorporadas en la presente como referencia.

Los siguientes ejemplos ilustran la preparación de compuestos farmacológicamente activos del invento. Las descripciones D1- D105 ilustran la preparación de intermedios a compuestos del invento.

10 En los ejemplos ¹H NMR's fueron medidos a 250MHz en CDCl₃ a menos que se declare lo contrario.

Descripción 1: Ester tert butílico del ácido (S) 2- aminometil- piperidina- 1- carboxílico

15 **a) 2,2,2- trifluoro- N- [(S)- 1- ((R)- 2- hidroxí- 1- fenil—etil)- piperidin- 2- ilmetil]- acetamida**

(R)- 2- [(S)- 2- aminometil- piperidin- 1- il)- 2- fenil- etanol (20.0g) (Froelich, Oliver; Desos, Patrice; Bonin, Matine; Quirion, Jean- Charles; Husson, Henri- Philippe; Zhu, Jieping., J. Org. Chem, 1996, 61, 6700) y trietilamina (13.0ml) fueron disueltos en
20 diclorometano (500ml), enfriados a 0°C y se agregó anhídrido trifluoroacético (12.66ml) por goteo. La mezcla fue calentada a temperatura ambiente y agitada durante la noche. La fase orgánica fue lavada con agua, separada, y el solvente removido a presión reducida. El
residuo fue cromatografiado en columna (Gel sílice, 0 – 10%(9:1 metanol/amoniaco) en eluyente de diclorometano) para proporcionar el compuesto del título (28.0g) como un
25 aceite amarillo.

Espectro de masa: (API⁺): encontrado 331 (MH⁺). C₁₆ H₂₁F₃N₂O₂ requiere 330.

[α]_D - 55° @ 28° 1% en cloroformo

b) 2,2,2- trifluoro- N- (S)- 1- piperidin- 2- ilmetil- acetamida

2,2,2- trifluoro- N- [(S)- 1- ((R)- 2- hidroxí- 1- fenil- etil)- piperidin- 2- ilmetil]- acetamida
30 (28.0g) fue disuelta en etanol (200ml) que contenía catalizador Pearlman's (2.0g) y agitando

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bajo una atmósfera de hidrógeno (50psi) a 50°C durante 3 horas. La mezcla de reacción fue filtrada y el solvente fue removido a presión reducida. El residuo fue cromatograficado en columna (gel de sílice, 0 – 10%(9:1 metanol/amoniaco) en eluyente de diclorometano) para proporcionar el compuesto del titulo (14.18g) como un aceite incoloro.

5 Espectro de masa (API⁺): encontrado 211(MH⁺). C₈H₁₃F₃N₂O requiere 210.

[α]_D + 10° @ 28° 1% en cloroformo

¹H NMR δ (d⁶- DMSO) 1.07 (1H, m), 1.32(2H, m), 1.35 – 1.60 (2H, m), 1.72 (1H, m), 2.54 (1H, t), 2.70 (1H, m), 3.00(1H, d), 3.17 (3H, m), 9.30 (1H, br; s.)



10 **c) Ester tert butílico del ácido (S)- 2- [(2,2,2- Trifluoro- etanoilamino)- metil]- piperidina- 1- carboxílico**

2,2,2- trifluoro- N- (S)- 1- piperidin- 2- ilmetil- acetamida (14.18mg) fue disuelta en diclorometano (250ml) y tratada con dicarbonato di- tert- butílico (14.95g). La mezcla fue agitada durante 16h, lavada con agua, ácido 2N hidroclico y saturada con salmuera,

15 secada y el solvente removido a presión reducida para proporcionar el compuesto del titulo (18.3g)

Espectro de masa: (API⁺): C₁₃H₂₁F₃N₂O₃ requiere 310.

[α]_D - 94° @28°1% en cloroformo

¹H NMR δ (d⁶- DMSO) 1.27 (1H, m), 1.36, 1.47(9H, s), 1.49- 1.58 (5H, m), 2.88 (1H, m),
20 3.22 (1H, m), 3.49 (1H, m), 3.84(1H, m), 4.34 (3H, m) y 9.42 (1H, br. s.)



d)Ester tert butílico del ácido (S) 2- aminometil- piperidina- 1- carboxílico

Ester tert butílico del ácido (S)- 2- [(2,2,2- Trifluoro- etanoilamino)- metil]- piperidina- 1- carboxílico (18.2g) fue disuelto en metanol (500ml) y tratado con carbonato de potasio

25 (16.1g). Después de agitar durante 16h el solvente fue removido a presión reducida y el residuo fue particionado entre diclorometano/agua. La fase orgánica fue separada, lavada con salmuera, secada y el solvente fue removido a presión reducida. El residuo fue

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cromatografado en columna (Gel de Sílice, 0 – 10% (9:1 metanol/amoniaco) en eluyente de diclorometano) para proporcionar el compuesto del título (8.82g) de la descripción 1.

Espectro de masa: (API⁺): encontrado 215 (MH⁺). C₁₁H₂₂N₂O₂ requiere 214.

5 [α]_D - 32.2° @ 28° 1% en cloroformo

¹H NMR δ: 1.44 (2H, m), 1.50 (9H, s), 2.64- 2.80 (2H, m),
2.94 (1H, dd), 3.99 (1H, m) y 4.15 (1H, m).

Descripción 2: Ester tert butílico del ácido (RS) 2- (Benzoxazol- 2- ilaminometil)- piperidina- 1- carboxílico

10 Ester tert butílico del ácido (RS) 2- Aminometil- piperidina- 1- carboxílico (0.21g) y 2- clorobenzoxazol 80.153g) y trietilamino (0.1g) fueron combinados en tetrahidrofurano (10ml) y agitados a temperatura ambiente durante 4 horas. La mezcla fue particionada entre acetato etílico y agua, la fase orgánica fue secada y el solvente fue removido a presión
15 reducida para proporcionar el compuesto del título (0.36g) como un aceite que se solidificó en reposo.

Espectro de masa: (API⁺): encontrado 332 (MH⁺). C₁₈H₂₅N₃O₃ requiere 331.

Descripción 3: (RS) Benzoxazol- 2- il- piperidin- 2- ilmetil- amina

20 El compuesto de la descripción 2 (0.36g) fue agitada en ácido trifluoroacético (10ml) que contenía agua (1 gota) durante 3 horas. El solvente fue removido a presión reducida y el residuo fue cromatografado en columna (Gel Sílice, 0- 1g0% (9:1 metanol/amoniaco) en eluyente de diclorometano) para proporcionar el compuesto del título (0.23g).

Espectro de masa: (API⁺): encontrado 232 (MH⁺). C₁₃H₁₇N₃O requiere 231

Descripción 4: (R)- 2- [(S)- 2- (benzooxazol- 2- ilaminometil)- piperidin- 1- il]- 2- fenil- etanol

Una mezcla de (R)- 2- [(S)- 2- aminometil- piperidin- 1. il]- 2- fenil- etanol (1.0g) (Froelich, Zhu, Jieping. J. Org. Chem. 1996, 61, 6700) y 2- clorobenzoxazol (0.66g) fueron

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combinados en tetrahidrofurano (40ml) que contenía trietilamina (0.43g) y agitados a temperatura ambiente durante 1 hora. La mezcla fue separada entre acetato etílico y agua, la fase orgánica fue separada, secada, y el solvente fue removido a presión reducida. El residuo fue cromatograficado en columna (Gel de Sílice, pentano al 3% en acetato etílico – acetato etílico) para proporcionar el compuesto del título (1.1g).

^1H NMR δ : 1.59 – 1.71 (4H, m), 1.91 (1H, t), 2.73(1H,m), 3.71(2H, m), 4.0(1H, m), 4.10(1H, m), 4.26(1H, m), 5.7 (1H, m), 7.03(1H, m), 7.23 – 7.26 (3H, m) y 7.32 – 7.40(4H, m). Espectro de masa (API^+). Encontrado 352 (MH^+) $\text{C}_{12}\text{H}_{25}\text{N}_3\text{O}_2$ requiere 351

10 **Descripción 5: Benzoxazol- 2- il- (s)- 1- piperidin- 2- ilmetil- amina**

El compuesto de la descripción 4 (1.15g) en etanol (60 ml) que contenía catalizador Pearlmans (0.23g) fue agitado bajo una atmósfera de hidrógeno (50psi) durante 24 horas. Se agregó catalizador Pearlmans adicional y se agito bajo hidrógeno a 50psi continua durante 12 horas más. La reacción fue filtrada a través de tierra de diatomeas, el filtrado

15 fue evaporado a presión reducida y el residuo fue cromatograficado en columna (Gel Sílice, eluyente 1:1 de acetato de etilo- acetato de etilo/metanol) para proporcionar el compuesto del título 80.49g) como un aceite.

^1H NMR δ : 1.16 – 1.85 (7H, m), 2.64 (1H, m), 2.85 – 2.99(1H,m), 3.11(2H, m), 3.55(1H, m), 7.00(1H, dd), 7.12(1H, m), 7.20 (1H, m), y 7.30 (1H, m), Espectro de masa (API^+).

20 Encontrado 232 (MH^+) $\text{C}_{13}\text{H}_{25}\text{N}_3\text{O}_2$ requiere 351

Descripción 6: (RS)- benzoxazol- 2- il- (4- bencil- morfolin- 3- ilmetil)- amina

A partir de (4- bencil- morfolin- 3- il)- metilamina (1g) (Morie, Toshiya; Kato,Shiro; Harada, Hiroshi; Yoshida, Naoyuki; Fujiwara, Iwao; Matsumoto, Jun- ichi., Chem. Pharm, Bull. 1995, 43, 1337- 47) y clorobenzoxazol (0.78g), se preparó el compuesto del título (0.77g) según el método de D4.

^1H NMR δ : 2.33 (1H, m), 2.73 – 2.80 (2H, m), 3.33 (1H, d), 3.51- 3.90 (6H, m), 4.10(1H, d), 5.58 (1H, s), 7.04(1H, m), 7.17 (1H, m), y 7.24 – 7.39 (7H, m), Espectro de masa (API^+). Encontrado 324 (MH^+) $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}_2$ requiere 323

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Descripción 7: (RS)- Benzoxazol- 2- il- morfolin- 3- ilmetil- amina

El compuesto del título (0.55g) se preparó a partir del compuesto de D6 según el método de D5.

¹H NMR δ: 2.93 – 3.23 (2H, m), 3.46 – 4.03 (7H, m), 6.95 – 7.23(4H, m), Espectro de masa (API⁺). Encontrado 234 (MH⁺) C₁₂H₁₅N₃O₂ requiere 233.

Descripción 8: Ester tert butílico del ácido (RS) 2- (1H- benzoimidazol- 2- ilaminometil- 1- carboxílico

Ester tert butílico del ácido (RS)- 2- aminometil- piperidina- 1- carboxílico (0.25g) y 2- clorobencimidazol (0.15g) fueron combinados y calentados a 100°C durante 48 horas.

Después de enfriar a temperatura ambiente la mezcla fue cromatografada (Gel de sílice, eluyente 1:4 de acetato de etilo/pentano, 1:1 de Caetano de etilo/pentano) para proporcionar el compuesto del título (0.1g)

¹H NMR δ: 1.47 (9H, m), 1.65 – 1.81 (7H, m), 2.85 (1H, t), 3.47 (2H, m), 3.91 (1H, d), 4.32 (1H, s), 7.04 (3H, m) y 7.29 (1H, s).

Espectro de masa (API⁺). Encontrado 331 (MH⁺) C₁₈H₂₆N₄O₂ requiere 330.

Descripción 9: Dihidrocloruro de (RS)- (1H- benzoimidazol- 2- il)piperidin- 2- ilmetil- amina

El compuesto de D8 (0.39) fue agitado en una mezcla de HCl 4M en dioxano/metanol (1:1) durante 4 horas. El solvente fue removido a presión reducida para proporcionar el compuesto del título (0.28) como una espuma.

Espectro de masa (API⁺). Encontrado 231 (MH⁺) C₁₃H₁₈N requiere 230.

Descripción 10: Ester tert butílico del ácido (RS) 2- (Quinolin- 2- ilaminometil)- piperidina- 1- carboxílico

El compuesto del título (0.1g) fue preparado a partir de Ester tert butílico del ácido (RS) 2- aminometil- piperidina- 1- carboxílico y 2- cloroquinolina (0.5g) según el procedimiento de D8.

Espectro de masa (API⁺). Encontrado 342 (MH⁺) C₂₀H₂₇N₃O₂ requiere 341

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Descripción 11: (RS)- piperidin- 2- ilmetil- quinolin- 2- il- amina

El compuesto del titulo (0.29) fue preparado a partir del compuesto de D10 según el método de D9. Después de remover el solvente el residuo fue disuelto en diclorometano, lavado con carbonato de hidrógeno de sodio saturado, la fase orgánica fue separada, secada y el solvente removido a presión reducida para proporcionar el compuesto del titulo.

^1H NMR δ : 1.20 – 1.96 (6H, m), 2.64 (1H, m), 2.85 (1H, m), 3.10 (1H, m), 3.35 (1H, m), 3.60 (1H, m), 5.17 (1H, m), 6.66 (1H, d), 7.19 (1H, dt), 7.48 – 7.58 (2H, m), 7.66 (1H, d) y 7.78 (1H, d).

Espectro de masa (API^+). Encontrado 242 (MH^+) $\text{C}_{15}\text{H}_{19}\text{N}_3$ requiere 241.



Descripción 12: Ester tert butílico del ácido (RS)- 2- (benzotiazol- 2- ilaminometil)- piperidina- 1- carboxílico

El compuesto del titulo (1.2g) después de cromatografía en columna (Gel Sílice, eluyente de éter dietílico/hexano- éter dietílico) fue preparado a partir de ester tert butílico del ácido (RS) 2- aminometil- piperidina- 1- carboxílico (2.0g) y clorobenzotiazol(1.5g) según el método de D2.

Espectro de masa (API^+). Encontrado 348 (MH^+) $\text{C}_{18}\text{H}_{25}\text{N}_3\text{O}_2\text{S}$ requiere 347.

Descripción 13: (RS)- benzotiazol- 2- il- piperidin- 2- ilmetil- amina

El compuesto de D12 (1.2) fue disuelto en metanol (60ml) y tratado con HCl 4N en dioxan (12ml). La mezcla fue agitada durante 4h, agregada a carbonato de hidrógeno de sodio que contiene agua y extraída con acetato de etilo (x3). La fase orgánica combinada fue secada y el solvente removido a presión reducida para obtener el compuesto del titulo (0.70g).

Espectro de masa (API^+). Encontrado 348 (MH^+) $\text{C}_{13}\text{H}_{17}\text{N}_3\text{S}$ requiere 347.



Descripción 14: Ester tert butílico del ácido 2- (RS)- (isoquinolin- 1- ilaminometil)- piperidina- 1- carboxílico

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El compuesto del título (0.76) fue preparado a partir de Ester tert butílico del ácido(RS)2-aminometil- piperidina- 1- carboxílico (1.6ml) y 1- cloroisoquinolina (0.8g) según el método utilizado para la preparación del compuesto de D8.

Espectro de masa (API⁺). Encontrado 342 (MH⁺) C₂₀H₂₇N₃O₂ requiere 341.

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Descripción 15: isoquinolin- 1- il- piperidin- 2- ilmetil- amina

El compuesto del título (0.39) fue preparado según el método de la descripción 13 a partir del compuesto de D14 (0.75g).

Espectro de masa (API⁺). Encontrado 242 (MH⁺) C₁₅H₁₉N₃ requiere 241.

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Descripción 16: Ester tert butílico del ácido (S)- 2- (quinolin- 2- ilaminometil)- piperidina- 1- carboxílico

El compuesto del título (0.11g) fue preparado a partir de éster tert butílico del ácido (S)2-aminometil- piperidina- 1- carboxílico (1.23g) y 2- cloroquinolina (1g) según el

15 procedimiento de D8.

Espectro de masa (API⁺). Encontrado 342 (MH⁺) C₂₀H₂₇N₃O₂ requiere 341.

Descripción 17: (S)- piperidin- 2- ilmetil- quinolin- 2- il- amina

El compuesto de D16 (0.11g) fue disuelto en diclorometano (10ml) y se agregó ácido trifluoroacético (1ml). La mezcla fue agitada durante 4h, vertida sobre hielo conteniendo carbonato de potasio y extraída con metanol al 10%/diclorometano (x3). Los extractos orgánicos combinados fueron secados y el solvente fue removido a presión reducida para obtener el compuesto del título (0.05g).

Espectro de masa (API⁺). Encontrado 242 (MH⁺) C₁₅H₁₉N₃ requiere 241.

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Descripción 18: Ester tert butílico del ácido (RS)- 2- (quinoxalin- 2- ilaminometil)- piperidina- 1- carboxílico

El compuesto del título (0.73g) fue preparado a partir de Ester tert butílico del ácido (RS)2-aminometil- piperidina- 1- carboxílico (1.ml) y 2- cloroquinoxalina (0.5g) según el

30 procedimiento de D8.

Espectro de masa (API⁺). Encontrado 343 (MH⁺) C₁₉H₂₆N₄O₂ requiere 342.

Descripción 19: (RS)- piperidin- 2- ilmetil- quinoxalin- 2- il- amina

El compuesto del titulo (0.36g) fue preparado a partir del compuesto de D18 (0.71g) según el método de D17.

Espectro de masa (API⁺). Encontrado 243 (MH⁺) C₁₄H₁₈N₄ requiere 242.

Descripción 20: Ester tert butílico del ácido (RS) 2- (pirimidin- 2- ilaminometil)- piperidina- 1- carboxílico

Un mezcla de éster tert butílico del ácido (RS) 2- aminometil- piperidina- 1- carboxílico (1.28g) y 2- cloropirimidina fue calentada a 100°C durante 48 horas. Después de enfriar a temperatura ambiente la mezcla fue cromatograficada en columna (Gel sílice, 0 – 10% (9:1 metanol/amoniaco) en eluyente de diclorometano) para proporcionar el compuesto del titulo (0.42) como un aceite.

Espectro de masa (API⁺). Encontrado 293 (MH⁺) C₁₅H₂₄N₄O₂ requiere 292.

Descripción 21: (RS)- piperidin- 2- ilmetil- pirimidin- 2- il- amina

El compuesto del titulo (0.350g) fue preparado a partir del compuesto de D20 (0.4g) según el método de D17.

Espectro de masa (API⁺). Encontrado 193 (MH⁺) C₁₀H₁₆N₄ requiere 192.

Descripción 22: Ester tert butílico del ácido (RS) 2- (pirazin- 2- ilaminometil)- piperidina- 1- carboxílico

El compuesto del titulo (0.18g) se preparó a partir de éster tert butílico del ácido (RS) 2- aminometil- piperidina- 1- carboxílico (0.54g) y 2- cloropirazina según el método de D20. Espectro de masa (API⁺). Encontrado 293 (MH⁺) C₁₅H₂₄N₄O₂ requiere 292.

Descripción 23: (RS)- piperidin- 2- ilmetil- pirazin- 2- il- amina

El compuesto del titulo (0.18g) fue preparado a partir del compuesto de D22 (0.08g) según el método de D17.

Espectro de masa (API⁺). Encontrado 193 (MH⁺) C₁₀H₁₆N₄ requiere 192

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Descripción 24: Ester tert butílico del ácido (s)- 2- (quinazolin- 4- ilminometil)- piperidina- 1- carboxílico

- 5 Ester tert butílico del ácido (S)- 2- aminometil- piperidina- 1- carboxílico (1.0g), 4- cloroquinoxalina (0.768g) y diisopropiletilamina (0.816ml) fueron disueltos en tetrahydrofurano (75ml) y calentados a reflujo durante 6 horas bajo una atmósfera de argón. Después de enfriar, la solución de reacción fue particionada entre acetato de etilo y agua. Las capas orgánicas fueron lavadas con una solución de carbonato de hidrógeno de sodio
- 10 saturado, salmuera saturada, secadas y evaporadas. El residuo fue cromatograficado sobre gel de Sílice, eluyendo con un gradiente de acetato de etilo al 50 a 100% en hexano. El compuesto del titulo fue obtenido como una espuma blanca (1.44g)
- 15 ¹H NMR δ: 1.40 (3H, s), 2.90 (1H, dt), 3.35 – 3.50 (1H, br), 3.9 – 4.05 (1H, br), 4.15- 4.3 (1H, br), 4.68 – 4.82 (1H, br), 6.9 – 7.2 (1H, br), 7.40 (1H, t), 7.65- 7.85 (3H, m), 8.65 (1H, s).

Descripción 25: (S)- 2- (quinazolin- 4- ilaminometil)- piridina

- Ester tert butílico del ácido (S)- 2- (quinazolin- 4- ilaminometil)- piperidina- 1- carboxílico fue disuelto en ácido trifluoroacetico (60ml) y agitado a temperatura ambiente durante 2
- 20 horas. Luego la solución fue evaporada y el residuo cromatograficado sobre gel de sílice, eluyendo con 0 a 10% (9:1 metanol – solución de amoniaco concentrado) en diclorometano. El compuesto del titulo fue obtenido como una espuma blanca (0.84g), MH⁺243

- 25 **Descripción 26: Ester tert butílico del ácido (S)- 2- [(6,7- difluoro- 3- metilquinoxalin- 2- ilamino)metil]- piperidina- 1- carboxílico**

- Ester tert butílico del ácido (S)- 2- aminometil- piperidina- 1- carboxílico (1.14g), y 2- cloro- 6,7- difluoro- 3- metilquinoxalina *Teng et al PCT Int. (2000), WO00/42026^{A1} 20000720 (1.14g)* fueron disueltos en DMF (2ml) y calentados a 90°C durante 3 días bajo
- 30 una atmósfera de argón. Después de enfriar, la solución de reacción fue particionada entre

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acetato de etilo y agua. La fase organica fue lavada con agua, saturada en salmuera, secada y evaporada. El residuo fue cromatograficado sobre gel de Sílice, eluyendo con un gradiente de 10 a 50% de acetato de etilo en hexano. El compuesto del titulo fue obtenido como una espuma rosada.

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Descripción 27: (S)- 2- [(6,7- difluoro- 3- metilquinoxalin- 2- ilamino)metil]- piperidina

Ester tert butilico del ácido de (S)- 2- [(6,7- difluoro- 3- metilquinoxalin- 2- ilamino)metil]- piperidina- 1- carboxilico fue disuelto en ácido trifluoroacetico (15ml) y agitado a

10 temperatura ambiente durante 3 horas. Luego la solución fue evaporada y el residuo cromatograficado sobre gel de sílice, eluyendo con un gradiente 0 a 10% (9:1 metanol – solución de amoniaco concentrado) en diclorometano. El compuesto del titulo fue obtenido como un sólido blanco (0.289), MH^+293 .

Descripción 28: Ester tert butilico del ácido (S)- 2- [(6,7- difluoroquinoxalin- 2- ilamino)metil]- piperidina- 1- carboxílico

Ester tert butilico del ácido (S)- 2- aminometil- piperidina- 1- carboxílico (0.607g), y 2 cloro- 6,7- difluoroquinoxalina *McQuaid. al. J. Med. Chem (1992), 35(18), 3319-24(0.569g)* fueron disueltos en dimetilformamida (1 ml) y calentados a 90°C durante 5

20 horas bajo una atmósfera de argón. Después de enfriar, la solución de reacción fue particionada entre acetato de etilo y agua. La capa orgánica fue lavada con agua, saturada con salmuera, secada y evaporada. El residuo fue cromatograficado sobre gel de sílice eluyendo con un gradiente de 10 a 50% de acetato de etilo en hexano. El compuesto del titulo fue obtenido como una espuma de color amarillo claro. (0.460g), MH^+379 .

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Descripción 29: (S)- 2- [(6,7- difluoroquinoxalin- 2- ilamino)metil]- piperidina

Ester tert butilico del ácido (S)- 2- [(6,7- difluoroquinoxalin- 2- ilamino)metil]- piperidina- 1- carboxilico fue disuelto en ácido trifluoroacetico (10ml) y agitado a temperatura ambiente durante 3 horas. Luego, la solución fue evaporada y el residuo fue

30 cromatograficado sobre gel de sílice, eluyendo con un gradiente 0 a 10% (9:1 metanol –

solución de amoníaco concentrado) en diclorometano. El compuesto del título fue obtenido como una espuma amarilla clara (0.286g), $MH^+ 279$.

Descripción 30: Ester tert butílico del ácido (R,S)- 2- [(6,7- difluoroquinoxalin- 2-ilamino)- metil]- pirrolidina- 1- carboxílico

Ester tert butílico del ácido (R,S)- 2- aminometil- pirrolidina- 1- carboxílico (3.0g) y 2-cloro- 6,7- difluoroquinoxalina (3.0g) fueron combinados en xileno (20ml) que contenía diisopropiletilamina (3ml) y calentados a 130°C durante 24 horas. El solvente fue removido a presión reducida y el residuo cromatograficado en columna (gel de Sílice, éter dietílico:

éter de petróleo 1:1) para proporcionar el compuesto del título (3.4g)

Espectro de masa (API^+): encontrado 365 (MH^+). $C_{18}H_{22}F_2N_4O_2$ requiere 364.

Descripción 31: (R,S)- 2- [(6,7- difluoroquinoxalin- 2- ilamino)- metil]- pirrolidina

El compuesto de D30 (.4g) se disolvió en diclorometano (100ml) y fue tratado con ácido trifluoroacético (15ml). Después de 3h se agregó más ácido trifluoroacético (40ml) y diclorometano (100ml). La mezcla fue agitada durante 48h, vertida en carbonato de hidrógeno de sodio acuoso de exceso, la fase orgánica fue separada, secada y el solvente fue removido a presión reducida. El residuo fue cromatograficado en columna (gel de sílice, 5% (9:1 metanol/amoniaco)/diclorometano para obtener el compuesto del

título(0.9g) espectro de masa (API^+): encontrado 265 (MH^+). $C_{13}H_{14}F_2N_4$ requiere 264.

^1H NMR δ : 1.56 (1H, m), 1.72 – 1.93 (3H, m), 2.96(2h, m), 3.28(1H, m), 3.49(1H, m), 3.64(1H, m), 7.39(1H, dd), 7.59(1H, dd) y 8.16(1H, s).

Descripción 32: Ester tert butílico del ácido (S)- 2- (quinazolin- 2- ilamino)metil- piperidina- 1- carboxílico

El compuesto del título (0.6g) fue preparado a partir de éster tert butílico del ácido (S)- 2- aminometil- piperidina- 1- carboxílico (0.68g) y 2- cloroquinazolina (0.53g) según el método de D30.

Espectro de masa (API^+): encontrado 343 (MH^+). $C_{19}H_{26}N_4O_2$ requiere 342.

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Descripción 33: (S)- 1- piperidin- 2- ilmetil- quinazolin- 2- il- amina

El compuesto del título (0.384g) fue preparado a partir del compuesto de D32 (0.6g) según el método de D31

- 5 Espectro de masa (API^+): encontrado 243 (MH^+). $\text{C}_{14}\text{H}_{18}\text{N}_4$ requiere 242. $^1\text{HNMR}$ δ : 1.18 – 1.65 (6H, m), 2.66 (1H, m), 3.08 – 3.23 (2H, m), 3.50(1H, m), 3.69(1H, m), 6.16(1h,br, s), 7.20(1H, t), 7.554 – 7.69(3H, m) y 8.91(1H, s).

Descripción 34: Ester tert butílico (S)- 2- ([1,5]naftiridin- 2- ilaminometil)- piperidina- 1- carboxílico.

El compuesto del título (0.48g) fue preparado a partir de éster tert butílico del ácido (S)- 2- aminometil- piperidina- 1- carboxílico (0.59g) y 2- cloro- 1,5- naftiridina *Rapoport, et al J. Org. Chem. (1971), 450- 4(0.40g)* según el procedimiento del método de D30.

Descripción 35: [1,5]naftiridin- 2- il- (S)- 1- piperidin- 2- ilmetil- amina

- 15 El compuesto del título (0.30g) fue preparado a partir del compuesto de D34 (0.48g) según el método de D31.

Espectro de masa (API^+): encontrado 243 (MH^+). $\text{C}_{14}\text{H}_{18}\text{N}_4$ requiere 242. $^1\text{HNMR}$ δ : 1.25 – 1.88 (6H, m), 2.68 (1H, m), 2.98 (1H, m), 3.16(1H, m), 3.37 – 3.50 (1H, m), 3.66(1H, m), 6.85(1H, d), 7.41 (1H,dd) 7.95(1H, t) y 8.58 (1H, m).

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Descripción 36: éster tert butílico del ácido (S)- 2- (1,8- naftiridin- 2- ilamino)metil- piperidina- 1- carboxílico

El compuesto del título (0.28g) fue preparado a partir de éster tert butílico del ácido (S)- 2- aminometil- piperidina- 1- carboxílico (0.35g) y 2- cloro- 1,8- naftiridina (0.19g) según el método de D30

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Espectro de masa (API^+): encontrado 343 (MH^+). $\text{C}_{19}\text{H}_{26}\text{N}_4\text{O}_2$ requiere 342.

Descripción 37: [1,8]naftiridin- 2- il- (S)- 1- piperidin- 2- ilmetil- amina

El compuesto del título (0.11g) fue preparado a partir del compuesto de D36 (0.28g) según el método de D31.

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Espectro de masa (API⁺): encontrado 243 (MH⁺). C₁₄H₁₈N₄ requiere 242.

Descripción 38: Ester tert butílico del ácido (RS) 2- (4- azabenzooxazol- 2- ilaminometil)- piperidina- 1- carboxílico

- 5 El compuesto del titulo (0.7g) fue preparado a partir de Ester tert butílico del ácido (RS)- 2- aminometil- piperidina- 1- carboxílico (0.64g) y metiltio- 4- azabenzoxazol Chu- Moyeret al J. Org. Chem (1995), 60(17), 5721- 5. (0.5g) según el método de D30.
Espectro de masa (API⁺): encontrado 333 (MH⁺). C₁₇H₂₄N₄O₃ requiere 332.

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- 10 **Descripción 39: (RS)- oxazolo[4,5- b]piridin- 2- il- piperidin- 2- ilmetil- amina**
El compuesto del titulo (0.55g) fue preparado a partir del compuesto de D38 (0.7g) según el método de D31
Espectro de masa (API⁺): encontrado 233 (MH⁺). C₁₂H₁₈N₄O requiere 232.

- 15 **Descripción 40: éster tert butílico del ácido ((S)- 1- {1- [2- (3- metil- [1,2,4]- oxadiazol- 5- il)- fenil]- metanoil}- piperidin- 2- ilmetil)- carboxílico**
Una mezcla de éster tert butílico del ácido (s)- 1- piperidin- 2- ilmetil- carbámico (2.0g) y el ácido 2- (3- metil- [1,2,4]oxadiazol- 5- il)- benzoico (1.9) en dimetilformaida (10ml) que contenía diisopropilietilamina (2.4ml) fue tratado con [O- (7- azabenzotriazol- 1- il)- 1,1, 3, 3- tetrametilurionium hexafluorofosfato] (3.55g) y agitado a 90°C durante 16 horas. El solvente fue removido a presión reducida y el residuo cromatograficado en columna (Gel de sílice, eluyente de éter dietílico) para proporcionar el compuesto del titulo (3.4g).
Espectro de masa (API⁺): encontrado 401 (MH⁺). C₂₁H₂₈N₄O₄ requiere 400

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- 25 **Descripción 41: 1- ((S)- 2- aminometil- piperidin- 1- il)- 1- [2- (3- metil- [1,2,4]oxadiazol- 5- il)- fenil]- metanona**
El compuesto del titulo (0.53g) fue preparado a partir del compuesto de D40 según el método de D13.
Espectro de masa (API⁺): encontrado 301 (MH⁺). C₁₆H₂₀N₄O₂ requiere 300.

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Descripción 42: éster dimetil- etílico del ácido metil- ((S)- 1- {1- [2- (3- metil- [1,2,4]oxadiazol- 5- il)- fenil]- metanoil)- piperidin- 2- ilmetil)- carbámico

Ester tert butílico del ácido ((S)- 1- {1- [2- (3- metil- [1,2,4]oxadiazol- 5- il)- fenil]- metanoil)- piperidin- 2- ilmetil)- carbámico (0.4g) en tetrahidrofurano (5ml) fue tratado

- 5 con hidruro de sodio (0.1g). Después que termino la evolución de hidrógeno se agregó yodometano (0.1m) y la reacción fue agitada durante 16 horas. La reacción fue apagada con hielo/agua, extraída con éter dietílico (x3), los extractos orgánicos combinados fueron secados y el solvente fue removido a presión reducida. El residuo fue cromatograficado en columna (gel de sílice, éter dietílico) para proporcionar el compuesto del titulo (0.2g).
- 10 Espectro de masa (API⁺): encontrado 415 (MH⁺). C₂₂H₃₀N₄O₄ requiere 414.



Descripción 43: 1- [(R)- 2- metilaminometil- piperidin- 1- il)- 1- [2- (3- metil- [1,2,4]oxadiazol- 5- il)- fenil]- metanona

El compuesto del titulo (0.15g) fue preparado a partir del compuesto de D42 según el método de D13.

- 15 Espectro de masa (API⁺): encontrado: 315(MH⁺). C₁₁H₁₂N₄ requiere 314g.

Descripción 44: éster tert butílico del ácido (S)- 2- [(6,7- difluoro- quinoxalin- 2- ilamino)- metil]- pirrolidina- 1- carboxílico

- 20 El compuesto (0.53g) fue preparado a partir de éster tert- butílico del ácido (S)- 2- aminometil- pirrolidina- 1- carboxílico (0.5g) y 2- cloro- 6,7- difluoroquinoxalina (0.5g) según el método de D-



Espectro de masa (API⁺): encontrado 365 (MH⁺). C₁₈H₂₂N₄O₂ requiere 364.

- 25 **Descripción 45: (S)- 2- [(6,7- difluoroquinoxalin- 2- ilamino)metil]- pirrolidina**

El compuesto del titulo (0.38g) fue preparado a partir del compuesto de D44 (0.53g) según el método de D31

Espectro de masa (API⁺): encontrado 265 (MH⁺). C₁₃H₁₈F₂N₄ requiere 264

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Descripción 46: éster tert butílico del ácido (RS)- 3- [(6,7- difluoro- 2- quinoxalin- 2- ilamino)- metil]morfolina- 4- carboxílico

El compuesto del título (0.58g) fue preparado a partir de éster tert butílico del ácido 2- aminometilmorfolina- 4- carboxílico (0.82g) y 2- cloro- 6,7- difluoroquinoxalina (0.76g) según el método de D30.

Espectro de masa (API^+): encontrado 381 (MH^+). $C_{18}H_{22}N_4O_4$ requiere 380.

Descripción 47: (6,7- difluoro- quinoxalin- 2- il)morfolin- 3- ilmetil- amina

El compuesto del título de D46 (0.58g) fue disuelto en ácido trifluoroacético y agitado durante 3 horas. El solvente fue removido a presión reducida y el residuo fue particionado entre carbonato de hidrógeno de sodio acuoso y acetato de etilo. La fase orgánica fue separada y secada, el solvente fue removido a presión reducida y el residuo fue cromatograficado en columna (gel sílice, 0- 10% (9:1 metanol/amoniaco) en diclorometano, eluyente) para proporcionar el compuesto del título (0.327g)

Espectro de masa (API^+): encontrado 281 (MH^+). $C_{13}H_{14}F_2N_4O$ requiere 280.

Descripción 48: éster tert butílico del ácido 2- (pirido[2,3- b]pirazin- 2- ilaminometil)- piperidina- 1- carboxílico y éster tert butílico del ácido 2- (pirido[2,3- b]- pirazin- 3- ilaminometil)- piperidina- 1- carboxílico

Una mezcla de éster tert butílico del ácido (S)- 2- aminometil- piperidina- 1- carboxílico (1.0g) y una mezcla 2:1 de 2- cloro- pirido[2,3- b+piperazina y 3- cloro- pirido[2,3- b]pirazina (0.8g) fueron combinadas y calentadas a 90°C durante 18 horas. La mezcla fue diluida con acetato de etilo y lavada con carbonato de hidrógeno de sodio acuoso y agua, la fase orgánica secada y el solvente removido a presión reducida. El residuo fue cromatograficado en columna (gel sílice, diclorometano 0 a 6% etanol en diclorometano, incrementos del 1%) para proporcionar como el compuesto de mayor velocidad éster tert butílico del ácido 2- (pirido[2,3- b]pirazin- 2- ilaminometil)- piperidina- 1- carboxílico (0.48g). Espectro de masa (API^+): encontrado 344 (MH^+). $C_{17}H_{25}N_5O_2$ requiere 343 y éster tert butílico del ácido 2- (pirido[2,3- b]pirazin- 3- ilaminometil)- piperidina- 1- carboxílico

(0.3g) Espectro de masa (API^+): encontrado 344 (MH^+). $C_{17}H_{25}N_5O_2$ requiere 343.

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Descripción 49: sal de trifluoroacetato de piperidin- 2- ilmetil- pirido[2,3- b]pirazin- 2- il- amina

Éster tert butílico del ácido 2- (pirido[2,3- b]pirazin- 2- ilaminometil)- piperidina- 1-

- 5 carboxílico (0.48g) fue disuelto en diclorometano (3ml), enfriado (baño maría) y tratado con ácido trifluoroacetico (2ml). La mezcla fue agitada durante 3 horas a temperatura ambiente, el solvente fue removido a presión reducida y el residuo fue co- evaporado con tolueno para proporcionar el compuesto del titulo (0.45g).

Espectro de masa (API^+): encontrado 244 (MH^+). $C_{13}H_{17}N_5$ requiere 243

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Descripción 50: sal de trifluoroacetato de piperidina- 2- ilmetil- pirido[2,3- b]pirazin- 3- il- amina

El compuesto del titulo (0.3g) fue preparado a partir de éster tert butílico del ácido 2- (pirido[2,3- b]pirazin- 3- ilaminometil)- piperidina- 1- carboxílico (0.3g) según el método

- 15 de la descripción 49

Espectro de masa (API^+): encontrado 244 (MH^+). $C_{13}H_{17}N_5$ requiere 243.

Descripción 51: éster tert butílico del ácido 2- tioureidometil- piperidina- 1- carboxílico

- 20 Se agregó por goteo cloruro de benzoilo (1.2ml) a tiocianato de sodio (0.90g) en acetona (50ml). Cuando la adición se termino, la mezcla fue sometida a reflujo durante 15 minutos, enfriada a temperatura ambiente y se agregó éster tert butílico del ácido (RS) 2- aminometil- piperidina- 1- carboxílico (2.0g) en acetona (5ml). La mezcla fue sometida a reflujo durante 2 horas, enfriada a temperatura ambiente y el solvente fue removido a
- 25 presión reducida. El residuo fue cromatograficado en columna (gel sílice, 0 – 10% (9:1 metanol/amoniaco) en eluyente de diclorometano) para proporcionar el producto del titulo (1.95g).

Espectro de masa (API^+): encontrado 274 (MH^+). $C_{12}H_{23}N_3O_2S$ requiere 273

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Descripción 52: éster tert butílico del ácido 2- [(4- fenil- tiazol- 2- ilamino)- metil]- piperidina- 1- carboxílico

El compuesto de la descripción 51 (1.95g) fue disuelto en etanol (100ml) que contenía trietilamina (0.99ml). Se agregó bromuro de fenacilo (1.42g) y la mezcla fue agitada

- 5 durante 16 horas. El solvente fue removido a presión reducida y el residuo fue particionado entre acetato de etilo y agua. La fase orgánica fue separada y el solvente removido a presión reducida. El residuo fue cromatograficado en columna (gel sílice, eluyente de diclorometano) para proporcionar el compuesto del titulo (2.42g).

Espectro de masa (API^+): encontrado 274 (MH^+). $C_{20}H_{27}N_3O_2S$ requiere 273.

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Descripción 53: (4- fenil- tiazol- 2- il)- piperidin- 2- ilmetil- amina

El compuesto del titulo (1.55g) fue preparado a partir del compuesto de D52 (2.42g) según el método de D47.

Espectro de masa (API^+): encontrado 174 (MH^+). $C_{15}H_{19}N_3O_2S$ requiere 173.

- 15 **Descripción 54: éster tert butílico del ácido 2- [(5- ciano- piridin- 2- ilamino)- metil]- piperidina- 1- carboxílico**

El compuesto del titulo (1.54g) fue preparado a partir de éster tert butílico del ácido (S)- 2- aminometil- piperidina- 1- carboxílico (2.0g) y 2- cloro- 5- cianopiridina (1.29g) en presencia de diisopropiletilamina (1.21g) según el método de D28.

- 20 Espectro de masa (API^+): encontrado 317 (MH^+). $C_{17}H_{24}N_4O_2$ requiere 316.

Descripción 55: 6- [(piperidin- 2- ilmetil)- amino]- nicotinonitrilo

El compuesto del titulo (1.56g) fue preparado a partir del compuesto de D54 (1.53g) y ácido trifluoroacetico según el método de D29.

- 25 Espectro de masa (API^+): encontrado 217 (MH^+). $C_{12}H_{16}N_4$ requiere 216.

Descripción 56: éster tert butílico del ácido 2- [(4- trifluorometil- pirimidin- 2- ilamino)- metil]- piperidina- 1- carboxílico

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El compuesto del título (0.298g) fue preparado a partir del éster tert butílico del ácido (S)- 2- aminometil- piperidina- 1- carboxílico (1.0g) y 2- cloro- 4- trifluoropirimidina (0.85g) según el método de D28.

Espectro de masa (API^+): encontrado 361 (MH^+). $C_{16}H_{23}N_4O_2$ requiere 360.

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Descripción 57: piperidin- 2- ilmetil- (4- trifluorometil- pirimidin- 2- il)- amina

El compuesto del título (0.25g) fue preparado a partir del compuesto de D56 (0.29g) y el ácido trifluoroacético según el método de D29.

Espectro de masa (API^+): encontrado 261 (MH^+). $C_{11}H_{15}F_3N_4$ requiere 260.

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Descripción 58: éster tert butílico del ácido ((S)- 1- {1- [4- (4- fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanoil}- carbámico

El compuesto del título (3.96g) fue preparado a partir del éster tert butílico del ácido (S)- 1- piperidin- 2- ilmetil- carbámico (2.14g) y 4- (4- fluoro- fenil)- 1- metil- 1H- pirazol- 3- il-

15 carboxílico (2.20g) según el método de D40

Espectro de masa (API^+): encontrado 417 (MH^+). $C_{22}H_{29}N_4O_3$ requiere 416.

Descripción 59: éster dimetil- etílico del ácido ((S)- 1- {1- [4- (4- fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanoil}- piperidin- 2- ilmetil)- metil- carbámico

20 El compuesto del título (2.0g) fue preparado a partir del compuesto de la descripción 58 (3.85g) según el método de D42.

Espectro de masa (API^+): encontrado 431 (MH^+). $C_{23}H_{31}FN_4O_3$ requiere 430.



Descripción 60: 1- [4- (4- fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- 1- ((S)- 2- metilaminometil- piperidin- 1- il)- metanona

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El compuesto del título (0.15g) fue preparado a partir del compuesto de D59 (0.50g) según el método de D29.

Descripción 61: éster tert butílico del ácido (S)- 2- [(3- ciano- piridin- 2- ilamino)- metil]- piperidina- 1- carboxílico

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El compuesto del título (0.66g) se preparó a partir de éster tert butílico del ácido (S)- 2-aminometil- piperidina- 1- carboxílico (1.55g) y 2- cloro- 3- cianopiridina (1.0g) según el método de D28.

Espectro de masa (API^+): encontrado 317 (MH^+). $C_{17}H_{24}N_4O_2$ requiere 316.

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Descripción 63: éster tert butílico del ácido (S)- 2- [(4- ciano- piridin- 2- ilamino)- metil]- piperidina- 1- carboxílico

El compuesto del título (0.24g) fue preparado a partir del éster tert butílico del ácido (S)- 2-aminometil- piperidina- 1- carboxílico (1.14g) y 2- cloro- 4- cianopiridina (0.74g) según el método de D28.

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Espectro de masa (API^+): encontrado 317 (MH^+). $C_{17}H_{24}F_3N_4O_2$ requiere 316.

Descripción 64: 4- ciano- 2- [(S)- 1- piperidin- 2- ilmetil]- aminol- piridina

El compuesto del título (0.17g) fue preparado a partir del compuesto de D63 (0.243g) y el ácido trifluoroacético según el método de D29.

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Espectro de masa (API^+): encontrado 271 (MH^+). $C_{12}H_{16}N_4$ requiere 216.

Descripción 65: carbonato tert butílico del ácido (S)2- [(5- bromo- pirimidin- 2- ilamino)- metil]- piperidina- 1- carboxílico

Éster tert butílico del ácido (S)- 2- aminometil- piperidina- 1- carboxílico (1g), 5- bromo- 2- cloropirimidina (0.9g) fueron combinados en xileno (20ml) que contenía carbonato de potasio (1.29g) y diisopropiletilamina (2.43g) y calentados a reflujo durante 48h. La mezcla fue enfriada a temperatura ambiente, filtrada y el solvente fue removido a presión reducida.

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El residuo fue cromatografiado en columna (gel sílice, pentano – 25% acetato de

etilo/pentano). Las fracciones apropiadas fueron recolectadas, el solvente fue removido a presión reducida para proporcionar el compuesto (1.43g) como una goma incolora.

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Espectro de masa (API^+): encontrado 272 (MH^+ tert BOC). $C_{10}H_{14}N_4Br$ requiere 371.

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Descripción 66: (S) (5- bromo- pirimidin- 2- il)- piperidin- 2- ilmetil- amina

El compuesto del título (1.40g) fue preparado a partir del compuesto de D65 (2.1g) según el método de D9.

- 5 Espectro de masa (API^+): encontrado 272 (MH^+). $C_{10}H_{14}N_4Br$ requiere 271.

Descripción 67: éster tert butílico del ácido (S) 2- [(3- ciano – 6,7- difluoro- quinolin- 2- ilamino)- metil]- piperidina- 1- carboxílico

- 10 Éster tert butílico del ácido (S)- 2- aminometil- piperidina- 1- carboxílico (1.1g) y 2- cloro- 3- ciano- 5,6- difluoroquinona (1.12g) según el método de D28 fueron combinados en xileno (15ml) que contenía carbonato de potasio (4.0g) y diisopropiletilamina (4ml) y hervidos durante 20 horas. La mezcla de reacción fue enfriada a temperatura ambiente, filtrada y el solvente fue removido a presión reducida. El residuo fue cromatograficado en columna (gel sílice, eluyente de diclorometano). Para proporcionar el compuesto del título
15 (1.8g), después de combinar las fracciones apropiadas.

Espectro de masa (API^+): encontrado 403 (MH^+). $C_{21}H_{24}F_2N_4O_2$ requiere 402.

- 20 **Descripción 68: (S)6,7- difluoro- 2- [(piperidin- 2- ilmetil)- amino]- quinolina- 3- carbonitrilo**

El compuesto del título (1.40g) fue preparado a partir del compuesto de D67 (1.8g) según el método de D9

Espectro de masa (API^+): encontrado 303 (MH^+ tert BOC). $C_{16}H_{11}F_2N_4$ requiere 302.

- 25 **Descripción 69: carbonato tert butílico del ácido (S)2- [(5- bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- carboxílico**

- 30 Éster tert butílico del ácido (S)- 2- aminometil- pirrolidina- 1- carboxílico (2g), 5- bromo- 2- cloropirimidina (1.93g) fueron combinados en xileno (40ml) que contenía carbonato de potasio (2.76g) y diisopropiletilamina (5.23ml) y calentados a reflujo durante 20h. La mezcla fue enfriada a temperatura ambiente, filtrada y el solvente fue removido a presión

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reducida. El residuo fue cromatograficado en columna (gel de sílice, pentano – 25% acetato de etilo/pentano). Las fracciones recolectadas fueron apropiadas, el solvente fue removido a presión reducida para proporcionar el compuesto del titulo (1.78g) como una goma incolora.

5 Espectro de masa (API⁺): encontrado 257 (MH⁺ tert BOC). C₁₄H₂₁Br N₄O₂ requiere 357.

Descripción 70: (S)(5- bromo- pirimidin- 2- il)- pirrolidin- 2- ilmetil- amina

El compuesto del titulo (1.40g) fue preparado a partir del compuesto de D69 (1.78g) según el método de D9.

10 Espectro de masa (API⁺): encontrado 258 (MH⁺). C₉H₁₂N₄Br requiere 257.

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Descripción 71: ácido 3- (1- {(S)- 2- [(6,7- difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- metanoil)- benzoico

Éster metílico del ácido 3- (1- {(S)- 2- [(6,7- difluoro- quinoxalin- 2- ilamino)- metil]-

15 piperidin- 1- il}- metanoil)- benzoico (0.5g) fue disuelto en metanol (15ml) y agitado con hidroxido de sodio 1M (1.7ml). La mezcla de reacción fue agitada durante 12 h, se agregó hidroxido de sodio 1M adicional (1.7ml) y la agitación continuo durante 24 horas mas. La mezcla de reacción fue diluida con agua y lavada con acetato de etilo. La fase acuosa fue acidificada con ácido clorhídrico 2M y extraida con acetato de etilo (x3). La fase orgánica
20 combinada fue secada (MgSO₄), filtrada y el solvente fue removido a presión reducida para proporcionar el compuesto del titulo (0.463g) como un sólido amarillo.

Espectro de masa (API⁺): encontrado 427 (MH⁺). C₂₂H₂₀ F₂N₄O₂ requiere 426.

Q

Descripción 72: ácido 1,1,1- trifluorometanosulfonico, éster 5- bromo- piridin- 2- ilo

25 A una solución de 5- bromo- 2- piridona (3g) en diclorometano (60ml) y piridina (60ml) a 0°C bajo argón se agregó por goteo anhídrido sulfónico de trifluorometano (5.4g). La mezcla resultante fue calentada a temperatura ambiente y después de 20h fue evaporada y el residuo cromatograficado sobre gel de sílice eluyendo con acetato de etilo para

465
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proporcionar el producto del título (3.5g) como un aceite amarillo. ¹HNMR δ: 7.10 (1H, d, j=8 Hz), 8.00 (1H, dd, 2.4 y 8 Hz), 8.46 (1H, d, J=2.4 Hz).

Descripción 73: éster tert butlico del ácido (S)- 2- [(5- bromopiridin- 2- ilamino)- metil]- pirrolidina- 1- carboxílico

El producto del título (0.22g) fue obtenido a partir de éster tert butlico del ácido (S)- 2- aminometil- pirrolidina- 1- carboxílico (1g) y el compuesto de D72 (1.7g) según el método de D69

Espectro de masa (Electroatomización LC/MS), API⁺: encontrado 356 (MH⁺). C₁₅H₂₂N₃O₂ requiere 355.

Descripción 74: (5- bromo- piridin- 2- il)- (S)- 1- pirrolidin- 2- ilmetilamina

A una solución del compuesto de D73 (0.49) en diclorometano (40ml) a temperatura ambiente se agregó ácido trifluoroacético (5ml). Después de 48h, la mezcla de reacción fue evaporada y particionada entre cloroformo e hidróxido de sodio 1M. La capa acuosa fue extraída con cloroformo y los extractos combinados fueron secados y evaporados para proporcionar el compuesto del título (0.33g) como un aceite anaranjado. ¹HNMR δ: 1.44 – 1.48 (1H, m), 1.72 – 1.81 (3H, m), 2.05 (2H, m), 3.09 – 3.13 (1H, m), 3.35 – 3.41 (2H, m), 4.99 (1H, d, J=9 Hz), 7.43 (1H, dd, J=3 y 9 Hz), 8.08 (1H, d, J = 3 Hz).

Descripción 75: N- (4- bencil- morfolin- 3- ilmetil)- 2,2,2- trifluoroacetamida

A (4- bencil- morfolin- 3- il) metilamina (7.34g) en diclorometano (240ml) se agregó trietilamino (5.83ml), seguido por adición por goteo de anhídrido trifluoroacético (8.23g) durante 25 minutos a 0°C bajo argón. La mezcla de reacción fue dejada alcanzar la temperatura ambiente y después de agitar durante 18h, fue disuelta en diclorometano y lavada con carbonato de hidrógeno de sodio acuoso saturado. La fase orgánica fue separada, secada y evaporada para proporcionar una goma de color marrón la cual fue purificada sobre gel de sílice, eluyendo con mezclas de acetato de etilo- pentano para proporcionar el producto del título (5.17g) como una goma anaranjada

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Espectro de masa (API^+): encontrado 303 (MH^+). $\text{C}_{14}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_2$ requiere 302.

Descripción 76: 2,2,2- trifluoro- N- morfolin- 3- ilmetilacetamida

Al compuesto de D75 (1.62g) en metanol (40ml) se agregó negro de paladio (0.45g) y ácido formico (10 gotas) y la mezcla fue agitada a temperatura ambiente durante 16h. Se agregó más negro de paladio (0.2225g) y ácido fórmico (10 gotas) y después de 1h, la mezcla de reacción fue filtrada a través de tierra de diatomeas y el filtrado fue evaporado a una goma naranja. La re- evaporación a partir de diclorometano proporcionó el compuesto del titulo (1.4g) como un sólido rosado.

Espectro de masa (API^+): encontrado 213 (MH^+). $\text{C}_7\text{H}_{11}\text{F}_3\text{N}_2\text{O}_2$ requiere 212.

Descripción 77: éster tert butílico del ácido 3- [(2,2,2- trifluoro- etanoilamino)- metil]- morfolina- 4- carboxílico

Una mezcla del compuesto de D76 (1.75g), trietilamona (2.25ml) y dicarbonato di- tert- butílico (3.59g) en diclorometano (75ml) fue agitada a temperatura ambiente durante 18h. La mezcla de reacción fue diluida con diclorometano y lavada sucesivamente con ácido clorhídrico, agua y salmuera, secada y evaporada a una goma. La cromatografía sobre gel de Sílice eluyendo con mezclas de acetato de etilo- pentano proporcionó el compuesto del titulo (1.70g) como un sólido amarillo claro. Espectro de masa (API^+): encontrado 213

($\text{MH}^+ - \text{'Boc'}^+$). $\text{C}_{12}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_4$ requiere 312.

Descripción 78: éster tert butílico del ácido 3- aminometil- morfolina- 4- carboxílico

Una mezcla del compuesto de D77 (1.7g) y carbonato de potasio (3.77g) en metanol (80 ml) y agua (27ml) fue agitada a temperatura ambiente durante 4h y luego calentada a 50°C durante 2h mas. La mezcla de reacción fue concentrada para remover el metanol, diluida con agua y extraída con acetato de etilo (x3) y diclorometano (x4). Los extractos combinados fueron secados y evaporados para proporcionar el producto del titulo (0.79) como una goma amarilla. Espectro de masa (API^+): encontrado 116 ($\text{MH}^+ - \text{'Boc'}$).

$\text{C}_{10}\text{H}_{20}\text{N}_2\text{O}_2$ requiere 216.

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Descripción 79: éster tert butílico del ácido 3- [(5- bromo- pirimidin- 2- ilamino)- metil]- morfolina- 4- carboxílico.

El compuesto del título (1.19g) fue obtenido a partir de D78 (0.97) y 5- bromo- 2- cloropirimidina 80.87g) según el método de D30. Espectro de masa (API^+): encontrado 273 ($MH^+ - ^1Boc$). $C_{14}H_{21}^{79}BrN_4O_3$ requiere 372.

Descripción 80: (5- bromo- pirimidin- 2- il)- morfolin- 3- ilmetilamina

Al compuesto de D79 (1.15g) en diclorometano (45 ml) a 0°C se agregó ácido trifluoroacético (5ml) y la mezcla de reacción luego se agito a temperatura ambiente durante 2h. La solución resultante fue vertida sobre hielo y una solución de carbonato de potasio acuoso saturado, y luego extraída con diclorometano (x2). Los extractos orgánicos fueron secados y evaporados para proporcionar el producto del título (0.85g) como un sólido blancuzco. Espectro de masa (API^+): encontrado 273 (MH^+). $C_9H_{13}^{79}BrN_4O$ requiere 272

Descripción 81: éster tert butílico del ácido (S)- 2- [(4- ciano- 2,6- difluoro- fenilamino)- metil]- piperidina- 1- carboxílico

Éster tert butílico del ácido (S)- 2- aminometil- piperidina- 1- carboxílico (1.36g) y 3,4,5- trifluorobenzonitrilo (1.00g) fueron calentados bajo argón en xileno (10 ml) que contenía diisopropiletilamino (3.3 ml) durante 16h. La fase orgánica fue lavada con salmuera, secada y evaporada para proporcionar un sólido el cual fue triturado con pentano- éter para proporcionar el producto del título (0.16 g) como un polvo blancuzco. La cromatografía de licores madre sobre gel de sílice eluyendo con mezclas de acetato de etilo-pentano proporcionó el producto del título adicional. Espectro de masa (API^+): encontrado 252 ($MH^+ - ^1Boc$). $C_{18}H_{15}F_2N_3O_2$ requiere 351.

Descripción 82: 3,5- difluoro- 4- [((s)- 1- piperidin- 2- ilmetil)- amino]- benzonitrilo

Se agregó ácido trifluoroacético a una solución de D81 (1.05g) en diclorometano (27 ml) a 0°C. La reacción fue dejada alcanzar la temperatura ambiente, agitada durante 4h y luego vertida en carbonato de potasio acuoso saturado. La fase acuosa fue extraída con

diclorometano y los extractos combinados secados y evaporados para proporcionar el compuesto del título (0.59) como un sólido blancuzco. Espectro de masa (API^+): encontrado 252 (MH^+). $C_{13}H_{15}F_2N_3$ requiere 251.

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5 **Descripción 83: éster tert butílico del ácido (S)- 2- [(4- ciano- 2,6- difluoro- fenilamino)- metil]- pirrolidina- 1- carboxílico**

El compuesto del título (0.295g) fue obtenido a partir de éster tert butílico del ácido (S)- 2- aminometil- pirrolidina- 1- carboxílico (0.402g) y 3,4,5- trifluorobenzonitrilo (0.314g) utilizando un procedimiento similar a aquel descrito en la descripción 81. Espectro de masa (API^+): encontrado 238 (MH^+ Boc). $C_{12}H_{21}F_2N_3O_2$ requiere 337.

15 **Descripción 85: éster tert butílico del ácido (s)- 2- [(5- etil- pirimidin- 2- ilamino)- metil]- pirrolidina- 1- carboxílico**

El compuesto del título (0.10g) fue obtenido a partir de éster tert butilico del ácido (S)- 2- aminometil- pirrolidina- 1- carboxílico (0.75g) y 2- cloro- 5- etil pirimidina (0.53g) utilizando un procedimiento similar a aquel descrito en la descripción 81. Espectro de masa (Electroatomización LC/MS): encontrado 307 (MH^+). $C_{16}H_{26}N_4O_2$ requiere 306.

20 **Descripción 86: (5- etil- pirimidin- 2- il)- (S)- 1- pirrolidin- 2- ilmetilamina**

El compuesto del título (0.07g) fue obtenido a partir del compuesto de D85 (0.10g) utilizando el metodo de D9. Espectro de masa (Electroatomización LC/MS): encontrado 207 (MH^+). $C_{11}H_{18}N_4$ requiere 206.

25 **Descripción 87: éster tert butílico del ácido (S)- 2- [(2,2,2- trifluoro- etanoilamino)- metil]- pirrolidina- 1- carboxílico**

A una solución de éster tert butílico del ácido (S)- 2- aminometil- pirrolidina- 1- carboxílico (1.3g) en diclorometano (50 ml) que contiene trietilamina (1.4 ml) se agregó anhídrido trifluoroacético (1.6g) por goteo bajo argón. Después de 16h a temperatura ambiente la mezcla de reacción fue diluida con diclorometano y lavada con salmuera. La capa acuosa fue extraída con diclorometano y los extractos combinados fueron secados y evaporados.

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La cromatografía del residuo sobre gel de sílice eluyendo con mezclas de pentano- acetato de etilo proporcionó el compuesto del título (1.43g) como un aceite anaranjado ¹HNMR δ: 1.30 – 1.50 (1H, m), 1.47 (9H, s), 1.60 – 1.75 (1H, m), 1.80 – 1.95 (2H, m), 2.00 - 2.10 (1H, m), 3.22 – 3.30 (1H, m), 3.30 – 3.55 (3H, m), 9.03 (1H, br s).

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Descripción 88: éster tert butílico del ácido (S)- 2- {[metil- (2,2,2- trifluoro- etanoil)- amino]- metil}- pirrolidina- 1- carboxílico

Se agregó hidruro de sodio (0.23g, dispersión al 60% en aceite) a una solución del compuesto de D87 (1.4g) en dimetilformamida (30 ml) bajo argón. Después de una 1h, se agregó yodometano y la mezcla de reacción fue agitada durante 16h más antes de ser particionada entre acetato de etilo y agua. La capa acuosa fue extraída con acetato de etilo y los extractos combinados fueron lavados con salmuera, secados y evaporados para proporcionar el compuesto del título (1.6g) como un aceite anaranjado. Espectro de masa (API⁺): encontrado 311 (MH⁺). C₁₃H₂₁F₃N₂O₃ requiere 310.

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Descripción 89: éster tert butílico del ácido (S)- 2- metilaminometil- pirrolidina- 1- carboxílico

Una mezcla del compuesto de D88 (1.47g) y carbonato de potasio (20ml) en metanol (50 ml) fue agitada a temperatura ambiente durante 20h. Después de remover el metanol al vacío, el residuo fue particionado entre cloroformo y agua. La capa acuosa fue extraída con cloroformo y los extractos combinados fueron secados y evaporados para proporcionar el producto del título (0.82g) como un aceite anaranjado.

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Descripción 90: éster tert butílico del ácido (S)- 2- {[5- bromo- pirimidin- 2- il)- metil- amino]- metil}- pirrolidina- 1- carboxílico

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El producto del título (0.85g) fue obtenido a partir del compuesto de D89 (0.82g) y 5- bromo- 2- cloropirimidina (0.77g) en una manera similar a aquella descrita en el procedimiento de la descripción 81. Espectro de masa (API⁺): encontrado 371 (MH⁺). C₁₅H₂₃⁷⁹BrN₄O₂ requiere 370.

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Descripción 91: (5- bromo- pirimidin- 2- il)- metil- (S)- 1- pirrolidin- 2- il)metilamina

Una solución del compuesto de D90 (0.82g) en diclorometano (50 ml) y ácido trifluoroacético (10 ml) fue agitada a temperatura ambiente durante 20h, evaporada y particionada entre acetato de etilo e hidróxido de sodio 1M. La fase orgánica fue separada, secada y evaporada para proporcionar el producto del título como un aceite anaranjado. (0.54g). Espectro de masa (API^+): encontrado 271 (MH^+). $\text{C}_{10}\text{H}_{15}^{79}\text{BrN}_4$ requiere 270.

Descripción 92: éster tert butílico del ácido (S)- 2- [(5- acetil- pirimidin- 2- ilamino)- metil]- pirrolidina- 1- carboxílico

El compuesto del título (0.57) se preparó a partir del compuesto de D69 (1.06g) (1-etoxivinil)tributil-estaño (1.2 ml) y tetraquis (trifenilfosfina)paladio (0) (0.172g) según el método del ejemplo 171. Espectro de masa (API^+): encontrado 321 (MH^+). $\text{C}_{16}\text{H}_{24}\text{N}_4\text{O}_3$ requiere 320.

Descripción 93: 1- {2- [((S)- 1- pirrolidin- 2- ilmetil)- amino]- pirimidin- 5- il}- etanona

A una solución del compuesto de D92 (0.57) en diclorometano (18ml) a 0°C se agregó por goteo ácido trifluoroacético (2ml). La mezcla de reacción fue agitada a temperatura ambiente durante 2h, y evaporada para proporcionar el compuesto del título como una goma amarilla (1.13g). Espectro de masa (API^+): encontrado 221 (MH^+). $\text{C}_{11}\text{H}_{16}\text{N}_4\text{O}$ requiere 220.

Descripción 94: éster tert butílico del ácido (S)- 2- [(5- cloro- pirimidin- 2- ilamino)- metil]- pirrolidina- 1- carboxílico

Éster tert butílico del ácido (S)- 2- aminometil pirrolidina- 1- carboxílico (3.38g), 2,5-dicloropirimidina (2.5g), carbonato de potasio (4.67g) y diisopropiletilamina (8.79 ml) fueron calentados en xileno (60 ml) a 100°C durante 3.75h. La mezcla de reacción enfriada fue filtrada y el filtrado fue evaporado a una goma la cual fue cromatografiada sobre gel de sílice, eluyendo con fracciones de acetato de etilo- pentano, para proporcionar el compuesto del título como un sólido amarillo claro (2.55g). Espectro de masa (API^+): encontrado 213 ($\text{MH}^+ \text{Boc}$). $\text{C}_{14}\text{H}_{21}^{35}\text{ClN}_4\text{O}_2$ requiere 312.

1779
173

Descripción 95: (5- cloro- pirimidin- 2- il)- (S)- 1- pirrolidin- 2- ilmetilamina

El compuesto de D94 (2.5g) fue disuelto en diclorometano (63 ml), enfriado a 0°C y se agregó por goteo ácido trifluoroacético (7m). La mezcla de reacción fue agitada a temperatura ambiente durante 2h, enfriado a 0°C y se agregó más ácido trifluoroacético (3 ml). Después de 2h a temperatura ambiente la mezcla fue cuidadosamente vertida en carbonato de potasio saturado helado y la capa orgánica fue separada. La fase acuosa fue extraída con diclorometano (x4) y los extractos combinados fueron secados y evaporados para proporcionar el producto del título (1.74g) como un sólido anaranjado. Espectro de masa (Electroatomización LC/MS): encontrado 213 (MH⁺). C₉H₁₃³⁵ClN₄ requiere 212.

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Descripción 96: éster tert butílico del ácido (S)- 2- [(5- ciano- piridin- 2- ilamino)- metil]- pirrolidina- 1- carboxílico

Éster tert butílico del ácido (S)- 2- aminometil- pirrolidina- 1- carboxílico (0.3g), 6- cloronicotinonitrilo (0.21g), carbonato de potasio (0.41 g) y diisopropiletilamina (0.78 ml) fueron calentados en xileno a 130°C durante 26h, enfriados y la mezcla fue filtrada a través de tierra de diatomeas. El filtrado fue evaporado y el residuo cromatograficado sobre gel de sílice, eluyendo con mezclas de acetato de etilo- hexano para proporcionar el compuesto del título 80.2g).

Espectro de masa (API⁺): encontrado 303 (MH⁺). C₁₆H₂₂N₄O₂ requiere 302.

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Descripción 97: 6- [((S)- 1- pirrolidin- 2- ilmetil)- amino]- nicotinonitrilo

Una solución del compuesto de D96 (0.2g) en diclorometano (20 ml) y ácido trifluoroacético (2.5 ml) fue agitada a temperatura ambiente durante 2h, evaporanda y particionada entre diclorometano e hidroxido de sodio 1M. La fase acuosa fue extraída con diclorometano y los extractos combinados secados y evaporados para proporcionar el compuesto del título como una goma (0.137g). Espectro de masa (Electroatomización LC/MS): encontrado 203 (MH⁺). C₁₁H₁₄N₄ requiere 202.

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Descripción 98: 6- metilsulfonil- pirimidin- 4- il éster del ácido 1,1,1- trifluorometanosulfónico

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A una solución de 6- metil- 2- metilsulfanil- pirimidin- 4- ol (1g) en diclorometano 840 ml) que contiene trietilamino (1.35 ml) a 0°C bajo argón se agregó por goteo anhídrido trifluorometanosulfónico (1.46 ml). La solución resultante fue dejada alcanzar la temperatura ambiente y fue agitada durante 16h antes de ser particionada entre diclorometano y solución de carbonato de hidrógeno de sodio acuoso saturado. La fase orgánica fue lavada con salmuera, secada y evaporada y el residuo cromatograficado sobre gel de sílice, eluyendo con mezclas de acetato de etilo- pentano, para proporcionar el compuesto del titulo (0.8g). ¹HNMR δ: 2.53 (3H, s), 2.55 (3H, s), 6.63 (1H, s).

10 **Descripción 99: 2,2,2- trifluoro- N- (S)- 1- pirrolidin- 2- ilmetil- acetamida**

El compuesto del titulo (2.31g) fue obtenido a partir de D87 (5.5g) utilizando el método de D97. ¹HNMR δ: 1.30 – 1.50 (1H, m), 1.70 – 1.95 (3H, m), 2.20 (1H, br s), 2.85 – 2.90 (1H, m), 2.94 - 2.97 (1H, m), 3.07 – 3.12 (1H, m), 3.37 – 3.39 (1H, m), 3.44 - 3.48 (1H, m), 7.15 (1H, br s).

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Descripción 100: 2,2,2: trifluoro- N- ((S)- 1- {1- [5- (4- fluorofenil)- 2- metil- tiazol- 4- il]- metanoil}- pirrolidin- 2- ilmetil)- acetamida

El compuesto del titulo (3.48g) fue obtenido a partir de D99 (2.31g) y el ácido 5- (4- fluorofenil)- 2- metil- tiazol- 4- carboxílico (3.08g) utilizando el método del ejemplo 229.

20 Espectro de masa (Electroatomización LC/MS): encontrado 416 (MH⁺). C₁₈H₁₇F₄N₃O₂S requiere 415.

Descripción 101: 1- ((S)- 2- aminometil- pirrolidin- 1- il)- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona

25 El compuesto del titulo (2.45g) fue obtenido a partir del compuesto de DI00 (3.84g) utilizando un procedimiento similar a aquel descrito en D78. Espectro de masa (Electroatomización LC/MS): encontrado 320 (MH⁺). C₁₆H₁₈FN₃OS requiere 319.

30 **Descripción 102: éster tert butílico del ácido 3- [(2,2,2- trifluoro- etanoilamino)- metil- morfolina- 4- carboxílico**

125

El compuesto del título (0.56g) fue obtenido a partir del compuesto de D77 (0.55g) y yometano (0.12 ml) utilizando un método similar a aquel de la descripción 88. Espectro de masa (API⁺): encontrado 227 (MH⁺ 'Boc). C₁₃H₂₁F₃ N₃O₄ requiere 326.

5 **Descripción 103: éster tert butílico del ácido 3- metilaminometil- morfolin- 4- carboxílico**

El compuesto del título (0.29g) fue obtenido a partir del compuesto de D102 (0.56g) utilizando el método de la descripción 89.

10 **Descripción 104: éster tert butílico del ácido 3- {(5- bromo- pirimidin- 2- il)- metil- amino]- metil}morfolina- 4- carboxílico**

El compuesto del título (0.3g) fue obtenido a partir del compuesto de D103 (0.29g) y 5- bromo- 2- cloropirimidina 80.26g) utilizando el método de la descripción 81. Espectro de masa (Electroatomización LC/MS): encontrado 287 (MH⁺ - 'Boc). C₁₅H₂₃ ⁷⁹BrN₃ requiere 386.

Descripción 105: (5- bromo- pirimidin- 2- il)- metil- morfolin- 3- ilmetil- amina

El compuesto del título (0.19g) fue obtenido a partir del compuesto de D104 (0.3g) según el método de descripción 91. Espectro de masa (API⁺): encontrado 287 (MH⁺). C₁₀H₁₅ ⁷⁹BrN₄O requiere 286.

Ejemplo1: 1- [2- (benzoxazol- 2- ilaminometil)- piperidin- 1- il]- 1- (2- metil- 5- fenil- tiazol- 4- il)- metanona

La amina de D3 (0.11g), trietilamina (0.05g) y cloruro de 2- metil- 5- fenil- tiazol- 4- carbonilo (0.12g) fueron combinados en diclorometano (5ml)y agitados durante 16 horas.

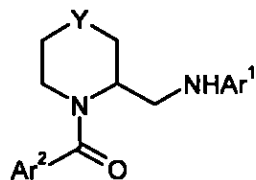
La fase orgánica fue lavada con agua, filtrada a través de un tubo de filtro de separación de fase Whatman, el solvente fue removido a presión reducida para proporcionar el compuesto del título (0.13g) después de cromatografía en columna (gel de Sílice, 0 -10% (9:1 metanol/amoniaco)en eluyente de diclorometano. Espectro de masa (API⁺): encontrado 443 (MH⁺). C₂₄H₂₂N₄O₂S requiere 432.

~~122~~

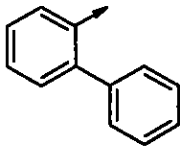
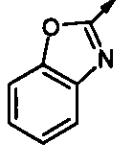
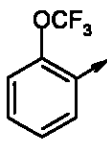
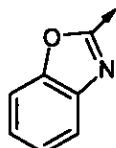
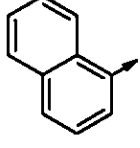
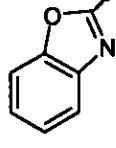
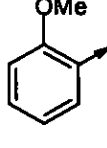
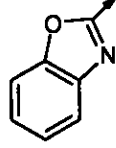
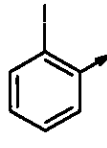
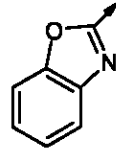
126

Los compuestos de los siguientes ejemplos fueron preparados a partir de la amina apropiada y cloruro ácido utilizando un procedimiento similar a aquel descrito en el ejemplo 1.

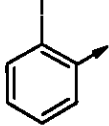
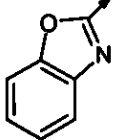
5



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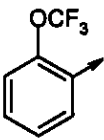
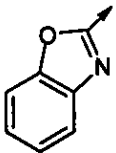
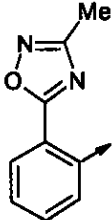
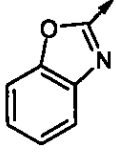
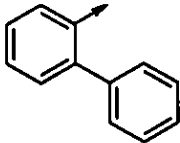
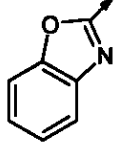
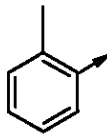
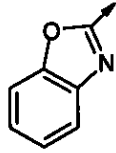
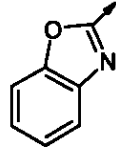
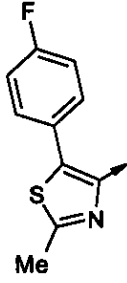
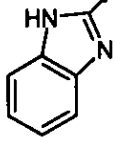
Ejemplo	Amina	Y	Ar ²	Ar ¹	Espectro de Masa (Electroatomización LC/MS) API ⁺
<u>2</u>	<u>D3</u>	CH ₂			Encontrado 412 (MH ⁺). C ₂₆ H ₂₅ N ₃ O ₂ requiere 411
<u>3</u>	<u>D3</u>	CH ₂			Encontrado 418 (MH ⁺). C ₂₃ H ₂₃ N ₅ O ₃ requiere 417
<u>4</u>	<u>D3</u>	CH ₂			Encontrado 420 (MH ⁺). C ₂₁ H ₂₀ F ₃ N ₃ O ₃ requiere 419
<u>5</u>	<u>D3</u>	CH ₂			Encontrado 386 (MH ⁺). C ₂₄ H ₂₃ N ₃ O ₂ requiere 385
<u>6</u>	<u>D3</u>	CH ₂			Encontrado 366 (MH ⁺). C ₂₁ H ₂₃ N ₃ O ₃ requiere 365
<u>7</u>	<u>D3</u>	CH ₂			Encontrado 462 (MH ⁺).

4/17/29
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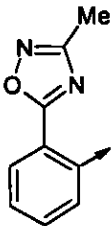
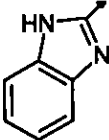
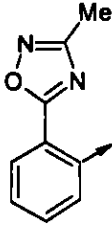
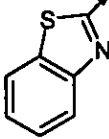
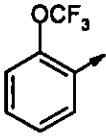
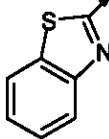
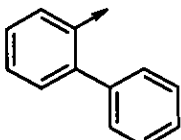
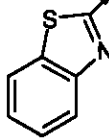
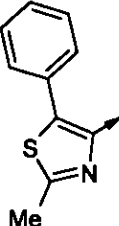
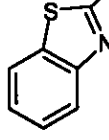
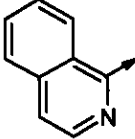
					$C_{20}H_{20}N_3O_2$ require 461
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179

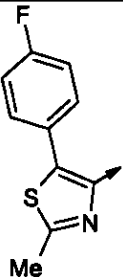
<u>8</u>	<u>D5</u>	CH ₂			Encontrado 420 (MH ⁺). C ₂₁ H ₂₀ F ₃ N ₃ O ₃ requiere 419
<u>9</u>	<u>D5</u>	CH ₂			Encontrado 418 (MH ⁺). C ₂₃ H ₂₃ N ₅ O ₃ requiere 417
<u>10</u>	<u>D5</u>	CH ₂			Encontrado 412 (MH ⁺). C ₂₆ H ₂₅ N ₃ O ₂ requiere 411
<u>11</u>	<u>D5</u>	CH ₂			Encontrado 462 (MH ⁺). C ₂₀ H ₂₀ N ₃ O ₂ requiere 461
<u>12</u>	<u>D3</u>	CH ₂	Ph		Encontrado 336 (MH ⁺). C ₂₀ H ₂₁ N ₃ O ₂ requiere 335
<u>13</u>	<u>D9</u>	CH ₂			Encontrado 450 (MH ⁺). C ₂₄ H ₂₄ FN ₅ OS requiere 449

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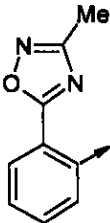
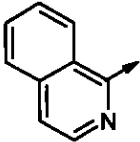
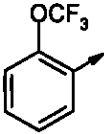
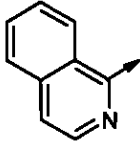
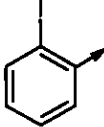
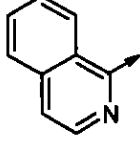
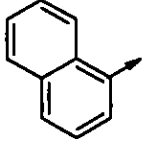
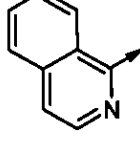
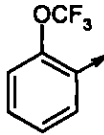
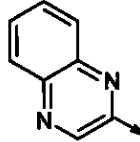
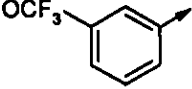
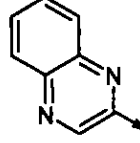
<u>14</u>	<u>D9</u>	CH ₂			Encontrado 417 (MH ⁺). C ₂₃ H ₂₄ N ₆ O ₂ requiere 416
<u>15</u>	<u>D13</u>	CH ₂			Encontrado 434 (MH ⁺). C ₂₃ H ₂₃ N ₅ O ₂ S requiere 433
<u>16</u>	<u>D13</u>	CH ₂			Encontrado 436 (MH ⁺). C ₂₁ H ₂₀ F ₃ N ₃ O ₂ S requiere 435
<u>17</u>	<u>D13</u>	CH ₂			Encontrado 428 (MH ⁺). C ₂₆ H ₂₅ N ₃ OS requiere 427
<u>18</u>	<u>D13</u>	CH ₂			Encontrado 449 (MH ⁺). C ₂₄ H ₂₄ N ₄ OS ₂ requiere 448
<u>19</u>	<u>D15</u>	CH ₂			Encontrado 461 (MH ⁺). C ₂₆ H ₂₅ FN ₄ OS requiere 460

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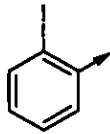
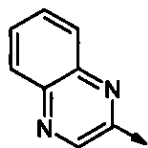
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182

<u>20</u>	<u>D15</u>	CH ₂			Encontrado 428 (MH ⁺). C ₂₅ H ₂₅ N ₅ O ₂ requiere 427
<u>21</u>	<u>D15</u>	CH ₂			Encontrado 430 (MH ⁺). C ₂₃ H ₂₂ F ₃ N ₃ O ₂ requiere 429
<u>22</u>	<u>D15</u>	CH ₂			Encontrado 472 (MH ⁺). C ₂₂ H ₂₂ IN ₃ O requiere 471
<u>23</u>	<u>D15</u>	CH ₂			Encontrado 396 (MH ⁺). C ₂₆ H ₂₅ N ₃ O requiere 395
<u>24</u>	<u>D19</u>	CH ₂			Encontrado 431 (MH ⁺). C ₂₂ H ₂₁ F ₃ N ₄ O ₂ requiere 430
<u>25</u>	<u>D19</u>	CH ₂			Encontrado 431 (MH ⁺). C ₂₂ H ₂₁ F ₃ N ₄ O ₂ requiere 430
<u>26</u>	<u>D19</u>	CH ₂			Encontrado 473 (MH ⁺). C ₂₁ H ₂₁ IN ₄ O requiere 472

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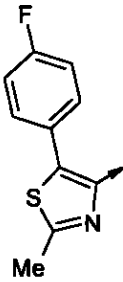
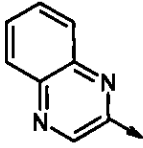
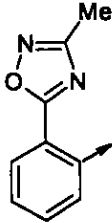
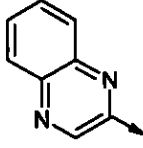
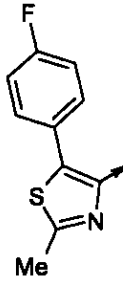
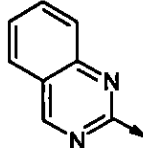
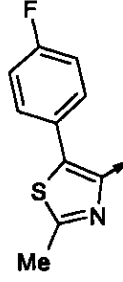
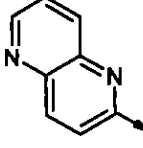
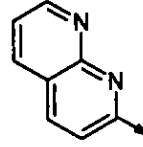
183

					
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②

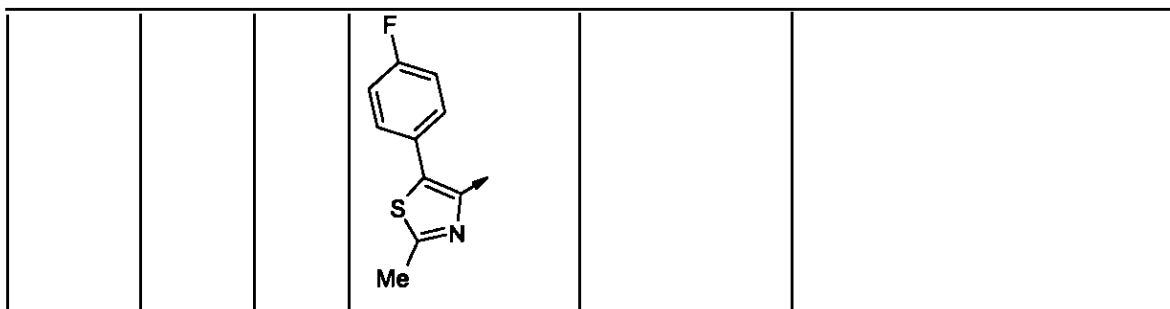
③

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184

<u>27</u>	<u>D19</u>	CH ₂			Encontrado 462 (MH ⁺). C ₂₅ H ₂₄ FN ₅ OS requiere 461
<u>28</u>	<u>D19</u>	CH ₂			Encontrado 429 (MH ⁺). C ₂₄ H ₂₄ N ₆ O ₂ requiere 428
<u>29</u>	<u>D33</u>	CH ₂			Encontrado 462 (MH ⁺). C ₂₅ H ₂₄ FN ₅ OS requiere 461
<u>30</u>	<u>D35</u>	CH ₂			Encontrado 462 (MH ⁺). C ₂₅ H ₂₄ FN ₅ OS requiere 461
<u>31</u>	<u>D37</u>	CH ₂			Encontrado 462 (MH ⁺). C ₂₅ H ₂₄ FN ₅ OS requiere 461

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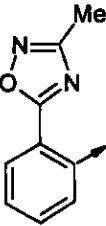
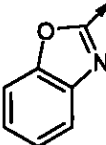
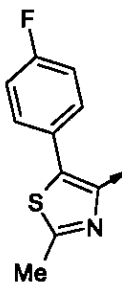
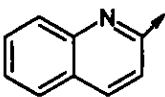
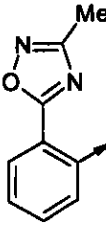
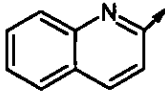
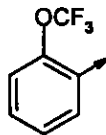
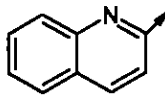
**Ejemplo 32: 1- [(S)- 2- (Benzooxazol- 2- ilaminometil)- piperidin- 1- il]- 1- [5- (4-
5 fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona**

Una mezcla de amina D5 (0.05g), ácido 2- metil- 5- fenil- tiazol- 4- carboxílico (0.026g) y diisopropiletilamina (0.06ml) en dimetilformamida (5ml) fue tratada con [hexafluorofosfato de O- (7- azabenzotriazol- 1- il)- 1,1,3,3- tetrametiluronio] (0.042g) y la mezcla fue agitada durante 48 horas. La mezcla fue diluida con acetato de etilo, lavada con carbonato de hidrógeno de sodio y agua, secada, el solvente fue removido a presión reducida y el residuo fue sometido a cromatografía en columna (gel de sílice, diclorometano – metanol al 1%/diclorometano) para proporcionar el compuesto del título (0.05g).

Espectro de Masa (API⁺): Encontrado 451 (MH⁺). C₂₄H₂₃FN₄O₂S requiere 450.

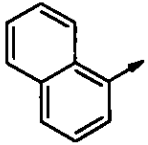
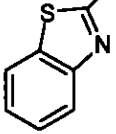
Los compuestos de los siguientes Ejemplos fueron preparados a partir de la amina y el ácido apropiados utilizando procedimientos similares a aquellos descritos en el Ejemplo 32.

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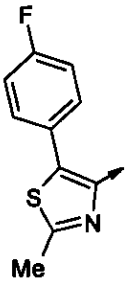
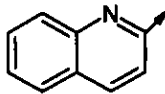
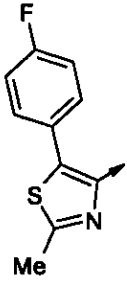
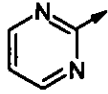
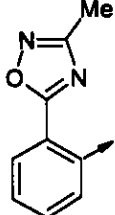
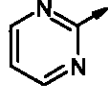
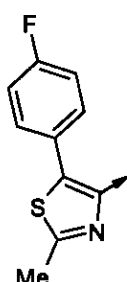
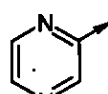
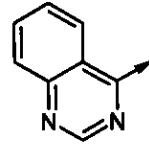
Ejemplo	Amina	Y	Ar ²	Ar ¹	Espectro de Masa (Electroatomización LC/MS), API ⁺
<u>33</u>	<u>D7</u>	O			Encontrado 420 (MH ⁺). C ₂₂ H ₂₁ N ₅ O ₄ requiere 419
<u>34</u>	<u>D11</u>	CH ₂			Encontrado 461 (MH ⁺). C ₂₆ H ₂₅ FN ₄ OS requiere 460
<u>35</u>	<u>D11</u>	CH ₂			Encontrado 428 (MH ⁺). C ₂₅ H ₂₅ N ₅ O ₂ requiere 427 Preparado como la sal de HCl
<u>36</u>	<u>D11</u>	CH ₂			Encontrado 430 (MH ⁺). C ₂₃ H ₂₂ F ₃ N ₃ O ₂ requiere 429 Preparado como la sal de HCl
<u>37</u>	<u>D13</u>	CH ₂			Encontrado 402 (MH ⁺). C ₂₄ H ₂₃ N ₃ OS requiere 401

180

187

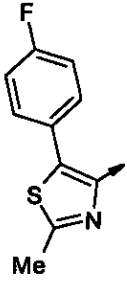
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188
188

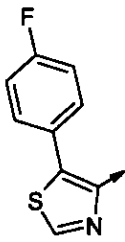
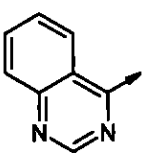
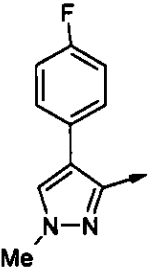
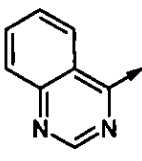
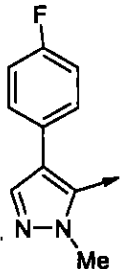
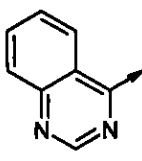
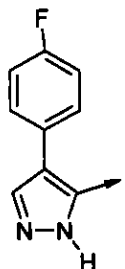
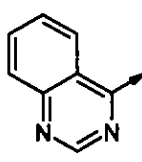
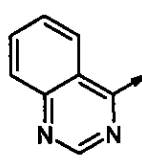
<u>38</u>	<u>D17</u>	CH ₂			Encontrado 461 (MH ⁺). C ₂₆ H ₂₅ FN ₄ OS requiere 460
<u>39</u>	<u>D21</u>	CH ₂			Encontrado 412 (MH ⁺). C ₂₁ H ₂₂ FN ₅ OS requiere 411
<u>40</u>	<u>D21</u>	CH ₂			Encontrado 379 (MH ⁺). C ₂₀ H ₂₂ N ₆ O ₂ requiere 378
<u>41</u>	<u>D23</u>	CH ₂			Encontrado 412 (MH ⁺). C ₂₁ H ₂₂ FN ₅ OS requiere 411
<u>42</u>	<u>D25</u>	CH ₂			Encontrado 462 (MH ⁺). C ₂₅ H ₂₄ FN ₅ OS requiere 461

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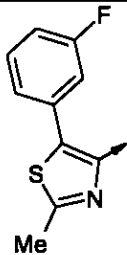
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190

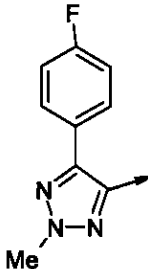
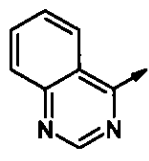
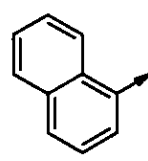
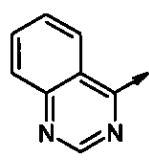
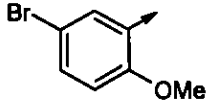
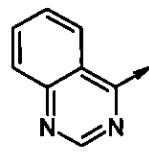
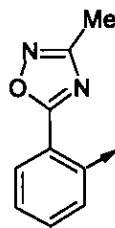
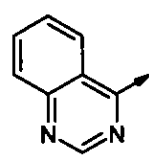
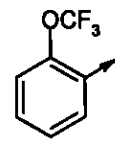
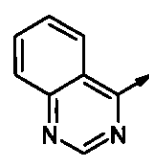
<u>43</u>	<u>D25</u>	CH ₂			Encontrado 448 (MH ⁺). C ₂₄ H ₂₂ FN ₅ OS requiere 447
<u>44</u>	<u>D25</u>	CH ₂			Encontrado 445 (MH ⁺). C ₂₅ H ₂₅ FN ₆ O requiere 444
<u>45</u>	<u>D25</u>	CH ₂			Encontrado 445 (MH ⁺). C ₂₅ H ₂₅ FN ₆ O requiere 444
<u>46</u>	<u>D25</u>	CH ₂			Encontrado 431 (MH ⁺). C ₂₄ H ₂₃ FN ₆ O requiere 430
<u>47</u>	<u>D25</u>	CH ₂			Encontrado 462 (MH ⁺). C ₂₅ H ₂₄ FN ₅ OS requiere 461

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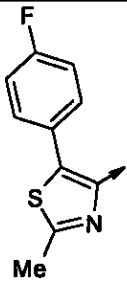
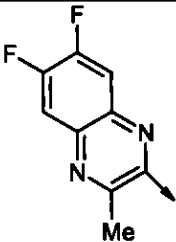
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142

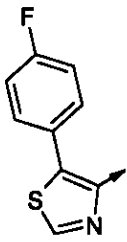
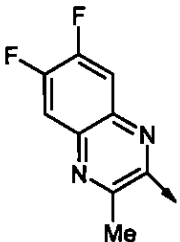
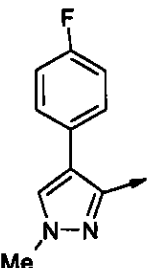
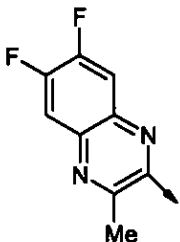
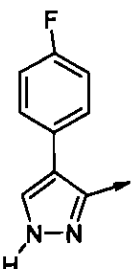
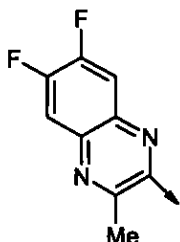
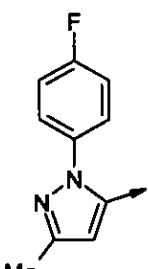
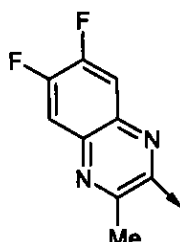
<u>48</u>	<u>D25</u>	CH ₂			Encontrado 446 (MH ⁺). C ₂₄ H ₂₄ FN ₇ O requiere 445
<u>49</u>	<u>D25</u>	CH ₂			Encontrado 397 (MH ⁺). C ₂₅ H ₂₄ N ₄ O requiere 396
<u>50</u>	<u>D25</u>	CH ₂			Encontrado 456 (MH ⁺). C ₂₂ H ₂₃ ⁷⁹ BrN ₄ O ₂ requiere 455
<u>51</u>	<u>D25</u>	CH ₂			Encontrado 429 (MH ⁺). C ₂₄ H ₂₄ N ₆ O ₂ requiere 428
<u>52</u>	<u>D25</u>	CH ₂			Encontrado 431 (MH ⁺). C ₂₂ H ₂₁ F ₃ N ₄ O ₂ requiere 430
<u>53</u>	<u>D27</u>	CH ₂			Encontrado 512 (MH ⁺). C ₂₆ H ₂₄ F ₃ N ₅ OS requiere 511

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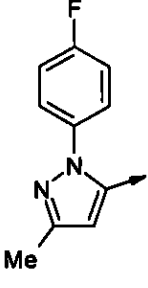
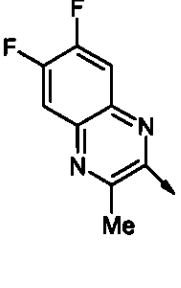
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194

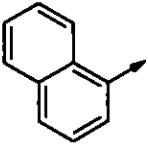
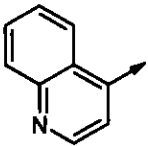
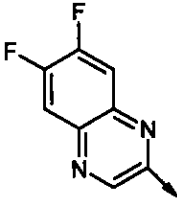
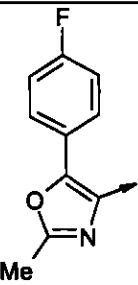
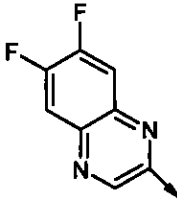
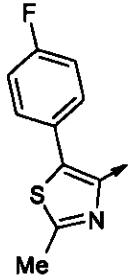
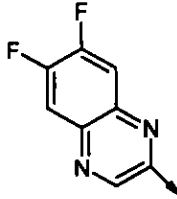
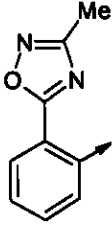
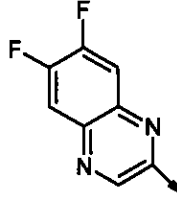
<u>54</u>	<u>D27</u>	CH ₂			Encontrado 498 (MH ⁺). C ₂₅ H ₂₂ F ₃ N ₅ OS requiere 497
<u>55</u>	<u>D27</u>	CH ₂			Encontrado 495 (MH ⁺). C ₂₆ H ₂₅ F ₃ N ₆ O requiere 494
<u>56</u>	<u>D27</u>	CH ₂			Encontrado 481 (MH ⁺). C ₂₅ H ₂₃ F ₃ N ₆ O requiere 480
<u>57</u>	<u>D27</u>	CH ₂			Encontrado 495 (MH ⁺). C ₂₆ H ₂₅ F ₃ N ₆ O requiere 494
<u>58</u>	<u>D27</u>	CH ₂			Encontrado 495 (MH ⁺). C ₂₆ H ₂₅ F ₃ N ₆ O requiere 494

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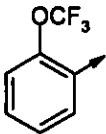
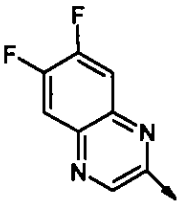
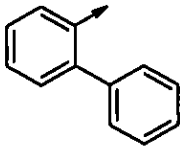
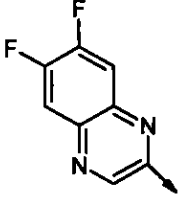
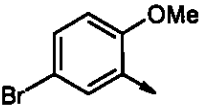
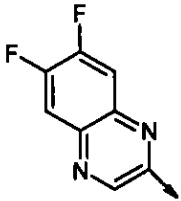
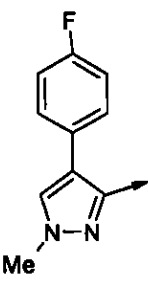
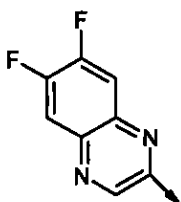
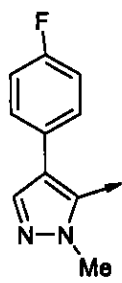
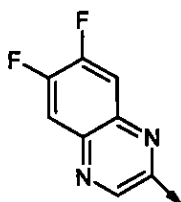
145

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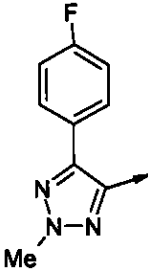
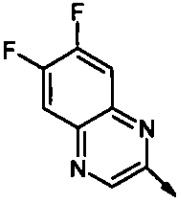
146

<u>59</u>	<u>D27</u>	CH ₂			Encontrado 447 (MH ⁺). C ₂₆ H ₂₄ F ₂ N ₄ O requiere 446
<u>60</u>	<u>D29</u>	CH ₂			Encontrado 434 (MH ⁺). C ₂₄ H ₂₁ F ₂ N ₅ O requiere 433
<u>61</u>	<u>D29</u>	CH ₂			Encontrado 482 (MH ⁺). C ₂₅ H ₂₂ F ₃ N ₅ O ₂ requiere 481
<u>62</u>	<u>D29</u>	CH ₂			Encontrado 498 (MH ⁺). C ₂₅ H ₂₂ F ₃ N ₅ OS requiere 497
<u>63</u>	<u>D29</u>	CH ₂			Encontrado 465 (MH ⁺). C ₂₄ H ₂₂ F ₂ N ₆ O ₂ requiere 464

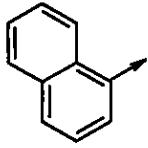
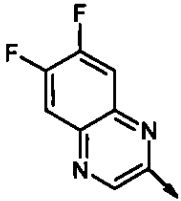
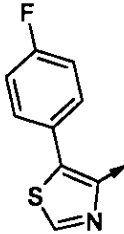
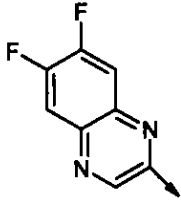
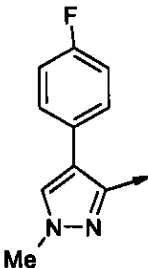
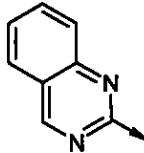
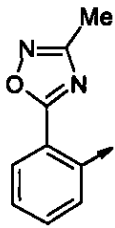
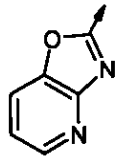
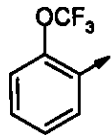
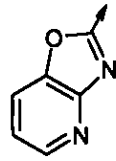
15/9/8
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<u>64</u>	<u>D29</u>	CH ₂			Encontrado 467 (MH ⁺). C ₂₂ H ₁₉ F ₅ N ₄ O ₂ requiere 466
<u>65</u>	<u>D29</u>	CH ₂			Encontrado 459 (MH ⁺). C ₂₇ H ₂₄ F ₂ N ₄ O requiere 458
<u>66</u>	<u>D29</u>	CH ₂			Encontrado 491 (MH ⁺). C ₂₂ H ₂₁ ⁷⁹ BrF ₂ N ₄ O ₂ requiere 490
<u>67</u>	<u>D29</u>	CH ₂			Encontrado 481 (MH ⁺). C ₂₅ H ₂₃ F ₃ N ₆ O requiere 480
<u>68</u>	<u>D29</u>	CH ₂			Encontrado 481 (MH ⁺). C ₂₅ H ₂₃ F ₂ N ₆ O requiere 480
<u>69</u>	<u>D29</u>	CH ₂			Encontrado 482 (MH ⁺).

~~149~~
148

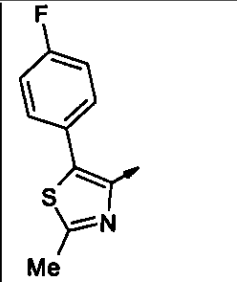
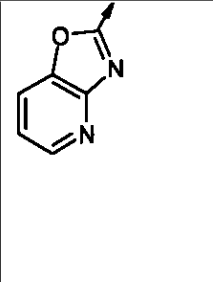
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1/200
199

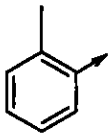
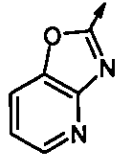
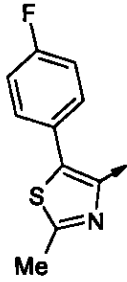
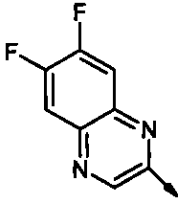
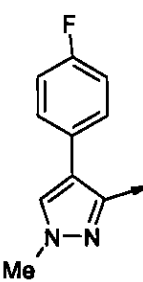
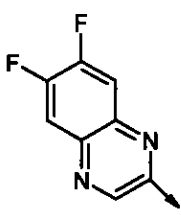
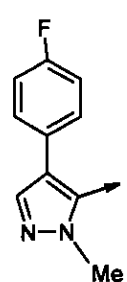
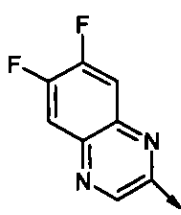
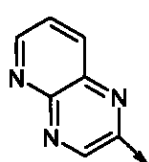
<u>70</u>	<u>D29</u>	CH ₂			Encontrado 433 (MH ⁺). C ₂₅ H ₂₂ F ₂ N ₄ O requiere 432
<u>71</u>	<u>D29</u>	CH ₂			Encontrado 484 (MH ⁺). C ₂₄ H ₂₀ F ₃ N ₅ OS requiere 483
<u>72</u>	<u>D33</u>	CH ₂			Encontrado 445 (MH ⁺). C ₂₅ H ₂₅ FN ₆ O requiere 444
<u>73</u>	<u>D39</u>	CH ₂			Encontrado 419 (MH ⁺). C ₂₂ H ₂₂ N ₆ O ₃ requiere 418
<u>74</u>	<u>D39</u>	CH ₂			Encontrado 421 (MH ⁺). C ₂₀ H ₁₉ F ₃ N ₄ O ₃ requiere 420
<u>75</u>	<u>D39</u>	CH ₂			Encontrado 452 (MH ⁺). C ₂₃ H ₂₂ FN ₅ O ₂ S requiere 451

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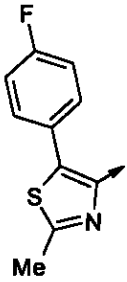
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201

<u>76</u>	<u>D39</u>	CH ₂			Encontrado 463 (MH ⁺). C ₁₉ H ₁₉ N ₄ O ₂ requiere 462
<u>77</u>	<u>D47</u>	O			Encontrado 500 (MH ⁺). C ₂₄ H ₂₀ F ₃ N ₅ O ₂ S requiere 499
<u>78</u>	<u>D47</u>	O			Encontrado 483 (MH ⁺). C ₂₄ H ₂₁ F ₃ N ₆ O ₂ requiere 482
<u>79</u>	<u>D47</u>	O			Encontrado 483 (MH ⁺). C ₂₄ H ₂₁ F ₃ N ₆ O ₂ requiere 482
<u>80</u>	<u>D49</u>	CH ₂			Encontrado 463 (MH ⁺). C ₂₄ H ₂₃ FN ₆ OS requiere 462

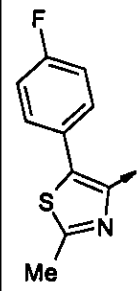
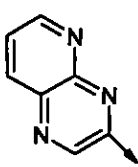
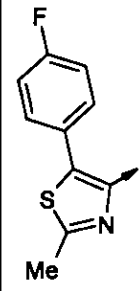
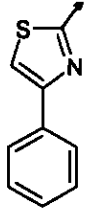
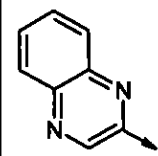
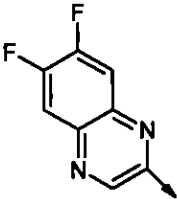
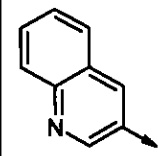
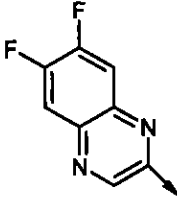
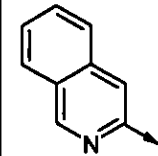
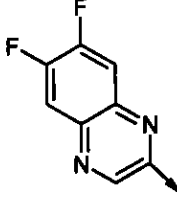
21202

202

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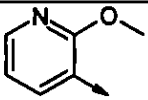
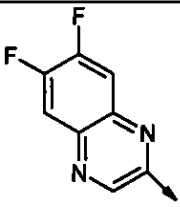
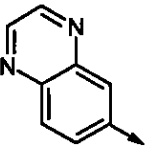
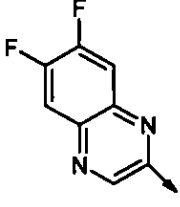
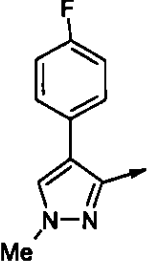
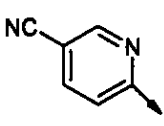
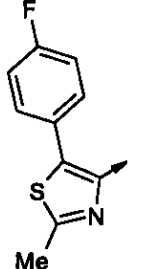
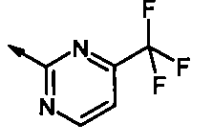
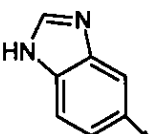
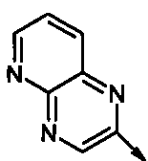


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<u>81</u>	<u>D50</u>	CH ₂			Encontrado 463 (MH ⁺). C ₂₄ H ₂₃ FN ₆ OS requiere 462
<u>82</u>	<u>D53</u>	CH ₂			Encontrado 493 (MH ⁺). C ₂₆ H ₂₅ FN ₄ OS ₂ requiere 492
<u>83</u>	<u>D29</u>	CH ₂			Encontrado 435 (MH ⁺).C ₂₃ H ₂₀ F ₂ N ₆ O requiere 434
<u>84</u>	<u>D29</u>	CH ₂			Encontrado 434 (MH ⁺). C ₂₄ H ₂₁ F ₂ N ₅ O requiere 433
<u>85</u>	<u>D29</u>	CH ₂			Encontrado 434 (MH ⁺). C ₂₄ H ₂₁ F ₂ N ₅ O requiere 433

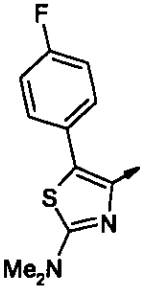
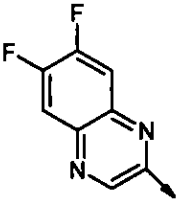
1/205

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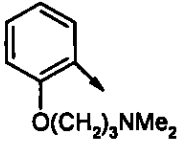
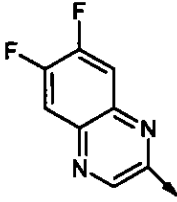
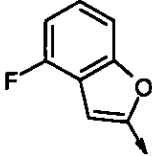
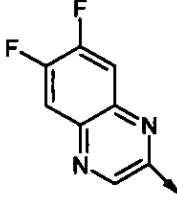
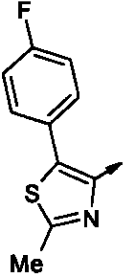
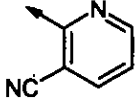
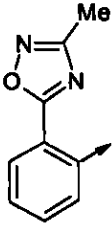
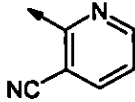
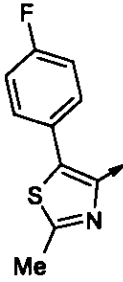
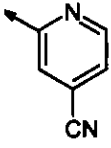
<u>86</u>	<u>D29</u>	CH ₂			Encontrado 414 (MH ⁺). C ₂₁ H ₂₁ F ₂ N ₅ O ₂ requiere 413
<u>87</u>	<u>D29</u>	CH ₂			Encontrado 435 (MH ⁺). C ₂₃ H ₂₀ F ₂ N ₆ O requiere 434
<u>88</u>	<u>D55</u>	CH ₂			Encontrado 419 (MH ⁺). C ₂₃ H ₂₃ FN ₆ O requiere 418
<u>89</u>	<u>D57</u>	CH ₂			Encontrado 480 (MH ⁺). C ₂₂ H ₂₁ F ₄ N ₅ OS requiere 479
<u>90</u>	<u>D49</u>	CH ₂			Encontrado 388 (MH ⁺). C ₂₁ H ₂₁ N ₇ O requiere 387
<u>91</u>	<u>D29</u>	CH ₂			Encontrado 527 (MH ⁺). C ₂₆ H ₂₅ F ₃ N ₆ OS requiere 526

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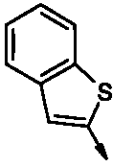
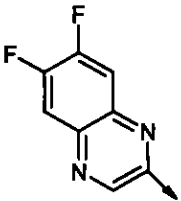
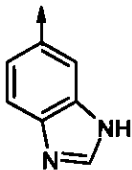
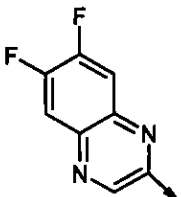
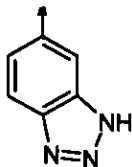
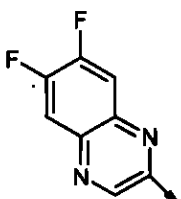
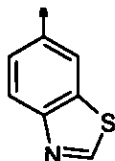
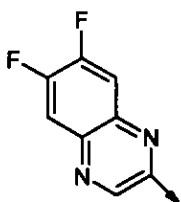
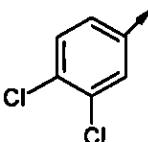
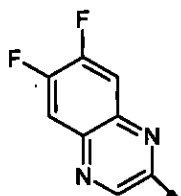
705

			 <chem>CN1C=NC(S1)=c2ccc(F)cc2</chem>	 <chem>Nc1nc2cc(F)c(F)cc2n1</chem>	
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1208
206

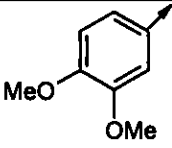
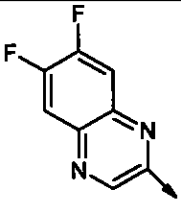
<u>92</u>	<u>D29</u>	CH ₂			Encontrado 484 (MH ⁺). C ₂₆ H ₃₁ F ₂ N ₅ O ₂ requiere 483
<u>109</u>	<u>D29</u>	CH ₂			Encontrado 441 (MH ⁺). C ₂₃ H ₁₉ F ₃ N ₄ O ₂ requiere 440
<u>110</u>	<u>D62</u>	CH ₂			Encontrado 436 (MH ⁺). C ₂₃ H ₂₂ FN ₅ OS requiere 435
<u>111</u>	<u>D62</u>	CH ₂			Encontrado 403 (MH ⁺). C ₂₂ H ₂₂ N ₆ O ₂ requiere 402
<u>112</u>	<u>D64</u>	CH ₂			Encontrado 436 (MH ⁺). C ₂₃ H ₂₂ FN ₅ OS requiere 435

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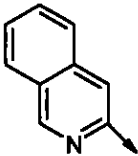
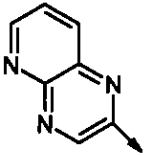
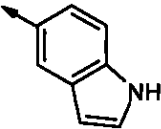
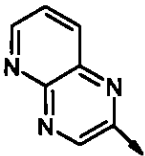
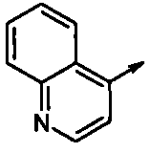
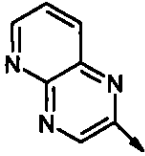
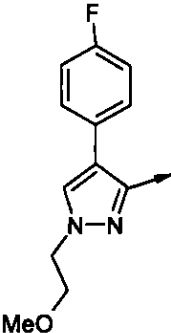
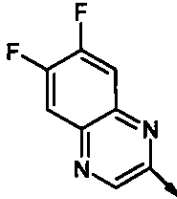
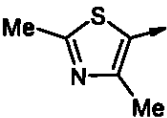
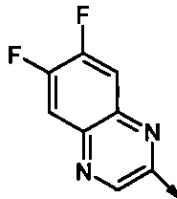
<u>113</u>	<u>D29</u>	CH ₂			Encontrado 439 (MH ⁺). C ₂₃ H ₂₀ F ₂ N ₄ OS requiere 438
<u>114</u>	<u>D29</u>	CH ₂			Encontrado 423 (MH ⁺). C ₂₂ H ₂₀ F ₂ N ₆ O requiere 422
<u>115</u>	<u>D29</u>	CH ₂			Encontrado 424 (MH ⁺). C ₂₁ H ₁₉ F ₂ N ₇ OS requiere 423
<u>116</u>	<u>D29</u>	CH ₂			Encontrado 440 (MH ⁺). C ₂₂ H ₁₉ F ₂ N ₅ OS requiere 439
<u>117</u>	<u>D29</u>	CH ₂			Encontrado 452 (MH ⁺). C ₂₁ H ₁₈ Cl ₂ F ₂ N ₄ O requiere 451
<u>118</u>	<u>D29</u>	CH ₂			Encontrado 443 (MH ⁺). C ₂₃ H ₂₄ F ₂ N ₄ O ₃ requiere 442

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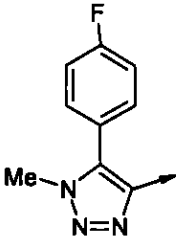
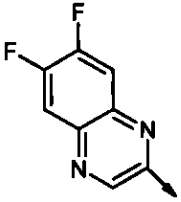
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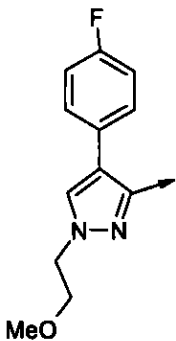
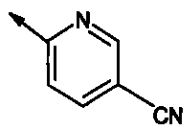
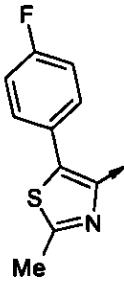
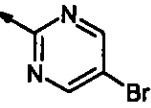
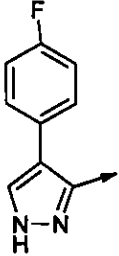
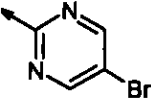
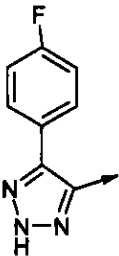
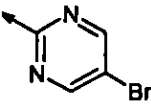
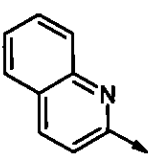
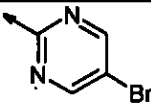
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<u>121</u>	<u>D49</u>	CH ₂			Encontrado 399 (MH ⁺). C ₂₃ H ₂₂ N ₆ O requiere 49
<u>122</u>	<u>D49</u>	CH ₂			Encontrado 387 (MH ⁺). C ₂₂ H ₂₂ N ₆ O requiere 386
<u>123</u>	<u>D49</u>	CH ₂			Encontrado 399 (MH ⁺). C ₂₃ H ₂₂ N ₆ O requiere 498
<u>124</u>	<u>D29</u>	CH ₂			Encontrado 525 (MH ⁺). C ₂₇ H ₂₇ F ₃ N ₆ O ₂ requiere 524
<u>125</u>	<u>D29</u>	CH ₂			Encontrado 418 (MH ⁺). C ₂₀ H ₂₁ F ₂ N ₅ OS requiere 417
<u>126</u>	<u>D29</u>	CH ₂			Encontrado 482 (MH ⁺). C ₂₄ H ₂₂ F ₃ N ₇ O requiere 481

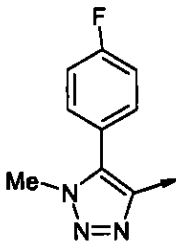
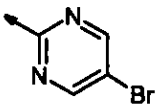
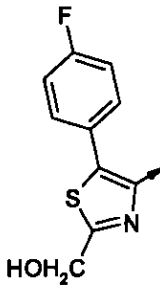
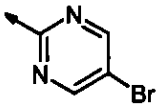
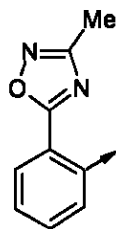
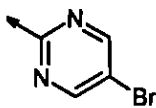
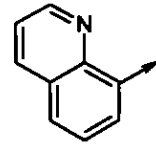
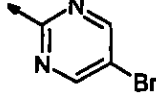
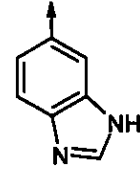
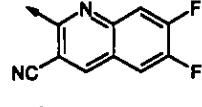
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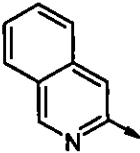
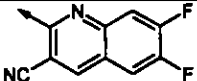
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<u>128</u>	<u>D66</u>	CH ₂			Encontrado 490 (MH ⁺). C ₂₁ H ₂₁ ⁷⁹ BrFN ₅ OS requiere 489
<u>129</u>	<u>D66</u>	CH ₂			Encontrado 459 (MH ⁺). C ₂₀ H ₂₀ ⁷⁹ BrFN ₆ O requiere 458
<u>130</u>	<u>D66</u>	CH ₂			Encontrado 460 (MH ⁺). C ₁₉ H ₁₉ BrFN ₇ O requiere 459
<u>131</u>	<u>D66</u>	CH ₂			Encontrado 426 (MH ⁺). C ₂₀ H ₂₀ ⁷⁹ BrN ₅ O requiere 425

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<u>132</u>	<u>D66</u>	CH ₂			Encontrado 474 (MH ⁺). C ₂₀ H ₂₁ ⁷⁹ BrFN ₇ O requiere 473
<u>133</u>	<u>D66</u>	CH ₂			Encontrado 506 (MH ⁺). C ₂₁ H ₂₁ ⁷⁹ BrFN ₅ O ₂ S requiere 505
<u>134</u>	<u>D66</u>	CH ₂			Encontrado 457 (MH ⁺). C ₂₀ H ₂₁ ⁷⁹ BrFN ₆ O ₂ requiere 456
<u>135</u>	<u>D66</u>	CH ₂			Encontrado 426 (MH ⁺). C ₂₀ H ₂₀ ⁷⁹ BrFN ₅ O requiere 425
<u>136</u>	<u>D68</u>	CH ₂			Encontrado 447 (MH ⁺). C ₂₄ H ₂₀ F ₂ N ₆ O requiere 446
<u>137</u>	<u>D68</u>	CH ₂			Encontrado 458 (MH ⁺). C ₂₆ H ₂₁ F ₂ N ₅ O

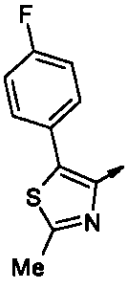
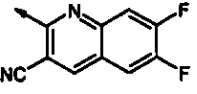
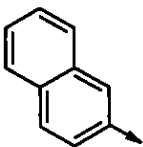
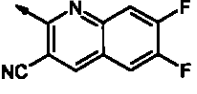
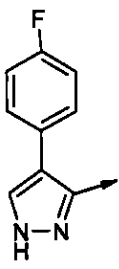
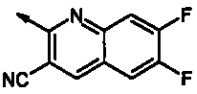
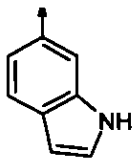
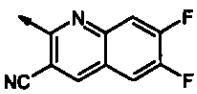
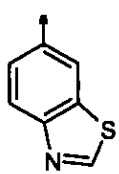
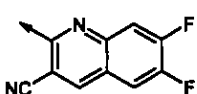
1/21/9

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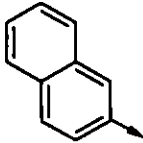
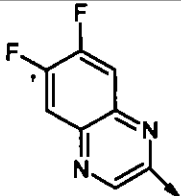
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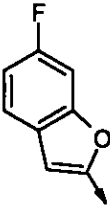
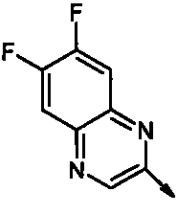
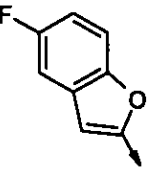
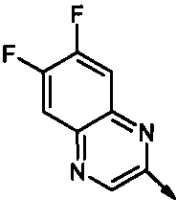
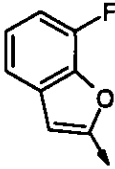
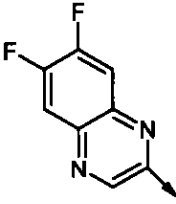
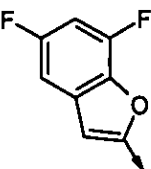
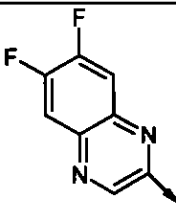
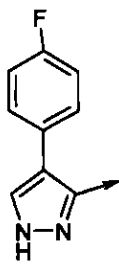
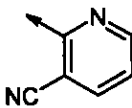
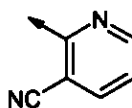
<u>138</u>	<u>D68</u>	CH ₂			Encontrado 522 (MH ⁺). C ₂₇ H ₂₂ F ₃ N ₅ OS requiere 521
<u>139</u>	<u>D68</u>	CH ₂			Encontrado 457 (MH ⁺). C ₂₇ H ₂₂ F ₂ N ₄ O requiere 456
<u>140</u>	<u>D68</u>	CH ₂			Encontrado 491 (MH ⁺). C ₂₆ H ₂₁ F ₃ N ₆ O requiere 490
<u>141</u>	<u>D68</u>	CH ₂			Encontrado 446 (MH ⁺). C ₂₅ H ₂₁ F ₂ N ₅ O requiere 445
<u>142</u>	<u>D68</u>	CH ₂			Encontrado 464 (MH ⁺). C ₂₄ H ₁₉ F ₂ N ₃ OS requiere 463
<u>143</u>	<u>D29</u>	CH ₂			Encontrado 433 (MH ⁺). C ₂₅ H ₂₂ F ₂ N ₄ O requiere 432

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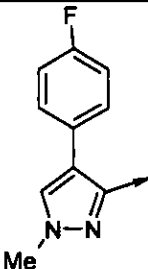
					
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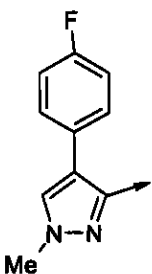
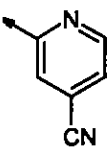
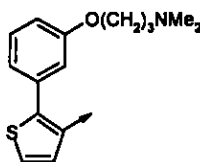
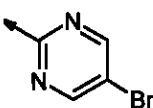
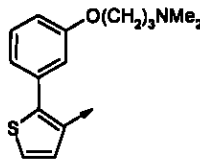
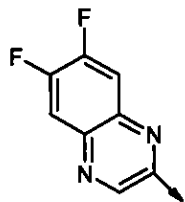
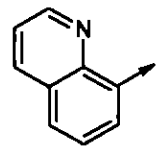
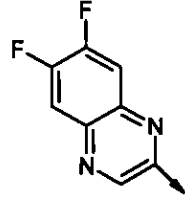
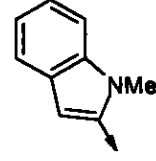
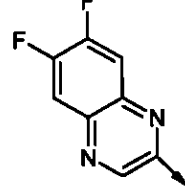
<u>144</u>	<u>D29</u>	CH ₂			Encontrado 441 (MH ⁺). C ₂₃ H ₁₉ F ₃ N ₄ O ₂ requiere 440
<u>145</u>	<u>D29</u>	CH ₂			Encontrado 441 (MH ⁺). C ₂₃ H ₁₉ F ₃ N ₄ O ₂ requiere 440
<u>146</u>	<u>D29</u>	CH ₂			Encontrado 441 (MH ⁺). C ₂₃ H ₁₉ F ₃ N ₄ O ₂ requiere 440
<u>147</u>	<u>D29</u>	CH ₂			Encontrado 459 (MH ⁺). C ₂₃ H ₁₈ F ₄ N ₄ O ₂ requiere 458
<u>148</u>	<u>D62</u>	CH ₂			Encontrado 405 (MH ⁺). C ₂₂ H ₂₁ FN ₆ O requiere 404
<u>149</u>	<u>D62</u>	CH ₂			Encontrado 419 (MH ⁺). C ₂₃ H ₂₃ FN ₆ O requiere 418

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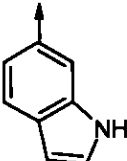
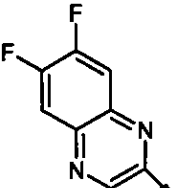
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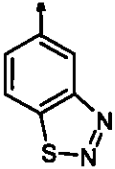
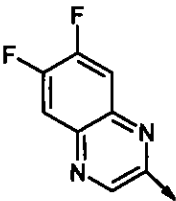
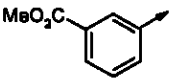
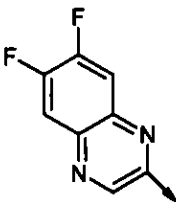
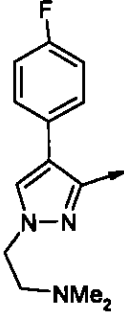
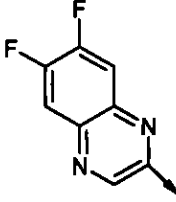
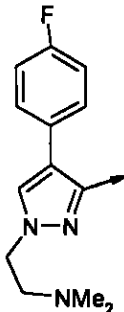
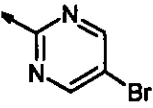
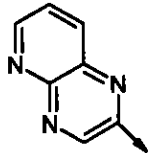
<u>150</u>	<u>D64</u>	CH ₂			Encontrado 419 (MH ⁺). C ₂₃ H ₂₃ FN ₆ O requiere 418
<u>151</u>	<u>D66</u>	CH ₂			Encontrado 558 (MH ⁺). C ₂₆ H ₃₂ ⁷⁹ BrN ₅ O ₂ S requiere 557
<u>152</u>	<u>D29</u>	CH ₂			Encontrado 566 (MH ⁺). C ₃₀ H ₃₃ F ₂ N ₅ O ₂ S requiere 565
<u>153</u>	<u>D29</u>	CH ₂			Encontrado 427 (MH ⁺). C ₂₀ H ₂₀ BrN ₅ O requiere 426
<u>154</u>	<u>D29</u>	CH ₂			Encontrado 436 (MH ⁺). C ₂₄ H ₂₃ F ₂ N ₅ O requiere 435
<u>155</u>	<u>D29</u>	CH ₂			Encontrado 422 (MH ⁺). C ₂₃ H ₂₁ F ₂ N ₅ O requiere 421

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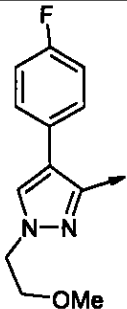
					
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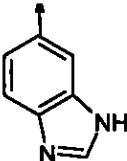
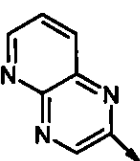
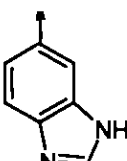
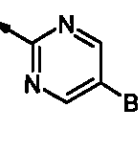
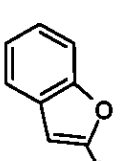
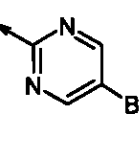
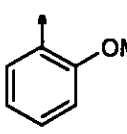
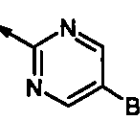
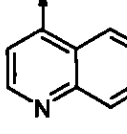
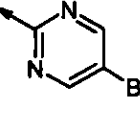
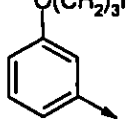
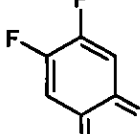
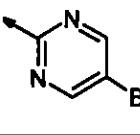
<u>156</u>	<u>D29</u>	CH ₂			Encontrado 441 (MH ⁺). C ₂₁ H ₁₈ F ₂ N ₆ OS requiere 440
<u>157</u>	<u>D29</u>	CH ₂			Encontrado 441 (MH ⁺). C ₂₃ H ₂₂ F ₂ N ₄ O ₃ requiere 440
<u>158</u>	<u>D29</u>	CH ₂			Encontrado 538 (MH ⁺). C ₂₈ H ₃₀ F ₃ N ₇ O requiere 537
<u>159</u>	<u>D29</u>	CH ₂			Encontrado 530 (MH ⁺). C ₂₄ H ₂₉ ⁷⁹ BrFN ₇ O requiere 529
<u>160</u>	<u>D49</u>	CH ₂			Encontrado 490 (MH ⁺). C ₂₆ H ₂₈ FN ₇ O ₂ requiere 489

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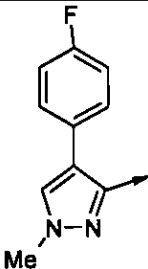
					
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212

<u>161</u>	<u>D49</u>	CH ₂			Encontrado 388 (MH ⁺). C ₂₁ H ₂₁ N ₇ O requiere 387
<u>162</u>	<u>D66</u>	CH ₂			Encontrado 415 (MH ⁺). C ₁₈ H ₁₉ ⁷⁹ BrN ₆ O requiere 414
<u>163</u>	<u>D66</u>	CH ₂			Encontrado 415 (MH ⁺). C ₁₉ H ₁₉ ⁷⁹ BrN ₄ O ₂ requiere 414
<u>164</u>	<u>D66</u>	CH ₂			Encontrado 405 (MH ⁺). C ₁₈ H ₂₁ ⁷⁹ BrN ₄ O ₂ requiere 404
<u>165</u>	<u>D66</u>	CH ₂			Encontrado 426 (MH ⁺). C ₂₀ H ₂₀ ⁷⁹ BrN ₅ O requiere 425
<u>166</u>	<u>D29</u>	CH ₂			Encontrado 484 (MH ⁺). C ₂₆ H ₃₁ F ₂ N ₅ O ₂ requiere 483
<u>170</u>	<u>D66</u>	CH ₂			Encontrado 473 (MH ⁺). C ₂₁ H ₂₂ ⁷⁹ BrFN ₆ O requiere 472

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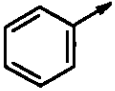
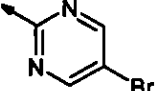
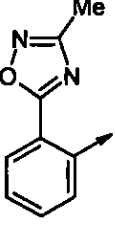
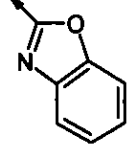
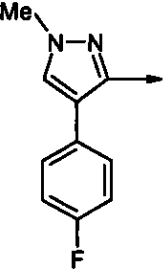
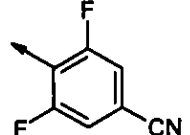
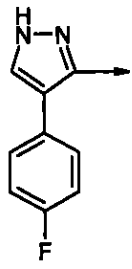
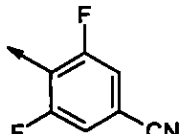
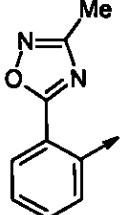
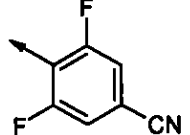
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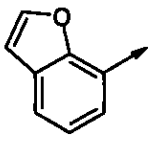
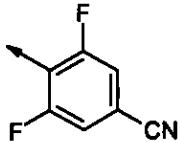
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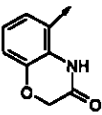
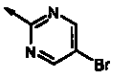
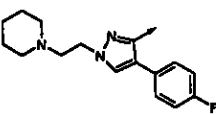
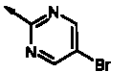
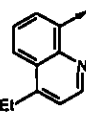
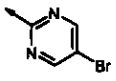
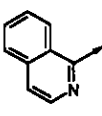
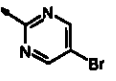
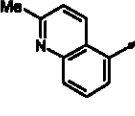
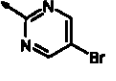
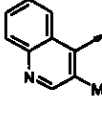
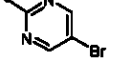
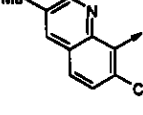
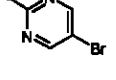
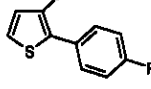
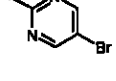
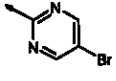
224

<u>175</u>	<u>D66</u>	CH ₂			Encontrado 375 (MH ⁺). C ₁₇ H ₁₉ ⁷⁹ BrN ₄ O requiere 374
<u>199</u>	<u>D7</u>	O			Encontrado 420 (MH ⁺). C ₂₂ H ₂₁ N ₅ O ₄ requiere 419
<u>204</u>	<u>D82</u>	CH ₂			Encontrado 454 (MH ⁺). C ₂₄ H ₂₂ F ₃ N ₅ O requiere 453
<u>206</u>	<u>D82</u>	CH ₂			Encontrado 438 (MH ⁺). C ₂₃ H ₂₁ F ₂ N ₅ O ₂ requiere 437
<u>207</u>	<u>D82</u>	CH ₂			Encontrado 396 (MH ⁺). C ₂₂ H ₁₉ F ₂ N ₃ O ₂ requiere 395
<u>230</u>	<u>D66</u>	CH ₂			Encontrado 446 (MH ⁺). C ₁₉ H ₂₀ ⁷⁹ BrN ₅ O ₃

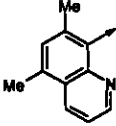
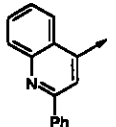
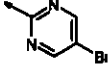
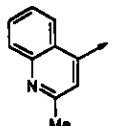
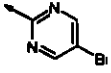
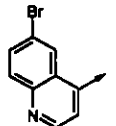
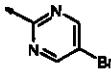
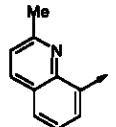
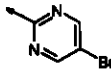
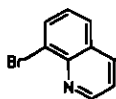
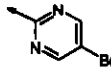
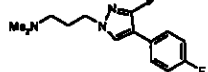
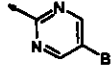
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					requiere 445
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<u>231</u>	<u>D66</u>	CH ₂			Encontrado 570 (MH ⁺). C ₂₇ H ₃₃ ⁷⁹ BrFN ₇ O requiere 569
<u>241</u>	<u>D66</u>	CH ₂			Encontrado 454 (MH ⁺). C ₂₂ H ₂₄ ⁷⁹ BrN ₅ O requiere 453
<u>242</u>	<u>D66</u>	CH ₂			Encontrado 448 (MH ⁺). C ₂₀ H ₂₀ ⁷⁹ BrN ₅ O requiere 447
<u>243</u>	<u>D66</u>	CH ₂			Encontrado 440 (MH ⁺). C ₂₁ H ₂₂ ⁷⁹ BrN ₅ O requiere 439
<u>244</u>	<u>D66</u>	CH ₂			Encontrado 440 (MH ⁺). C ₂₁ H ₂₂ ⁷⁹ BrN ₅ O requiere 439
<u>245</u>	<u>D66</u>	CH ₂			Encontrado 443 (MH ⁺). C ₁₇ H ₁₇ ⁷⁹ Br ³⁵ Cl ₂ N ₄ O requiere 442
<u>246</u>	<u>D66</u>	CH ₂			Encontrado 474 (MH ⁺). C ₂₁ H ₂₁ ⁷⁹ Br ³⁵ ClN ₅ O requiere 473
<u>259</u>	<u>D80</u>	O			Encontrado 476 (MH ⁺). C ₂₁ H ₁₉ ⁷⁹ BrFN ₃ O ₂ S requiere 475
<u>260</u>	<u>D66</u>	CH ₂			Encontrado 454 (MH ⁺). C ₂₂ H ₂₄ ⁷⁹ BrN ₅ O requiere 453

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227

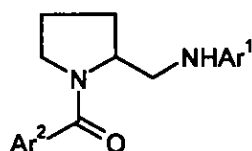
					
<u>261</u>	<u>D66</u>	CH ₂			Encontrado 502 (MH ⁺). C ₂₆ H ₂₄ ⁷⁹ BrN ₅ O requiere 501
<u>262</u>	<u>D66</u>	CH ₂			Encontrado 440 (MH ⁺). C ₂₁ H ₂₂ ⁷⁹ BrN ₅ O requiere 439
<u>263</u>	<u>D66</u>	CH ₂			Encontrado 504 (MH ⁺). C ₂₀ H ₁₉ ⁷⁹ Br ₂ N ₅ O requiere 503
<u>264</u>	<u>D66</u>	CH ₂			Encontrado 440 (MH ⁺). C ₂₁ H ₂₂ ⁷⁹ BrN ₅ O requiere 439
<u>265</u>	<u>D66</u>	CH ₂			Encontrado 504 (MH ⁺). C ₂₀ H ₁₉ ⁷⁹ Br ₂ N ₅ O requiere 503
<u>266</u>	<u>D66</u>	CH ₂			Encontrado 544 (MH ⁺). C ₂₅ H ₃₁ ⁷⁹ BrFN ₇ O requiere 543

Ejemplo 93: 1- {2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [4- (4- fluoro- fenil)- 2- H- pirazol- 3- il]- metanona

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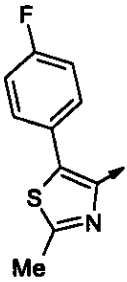
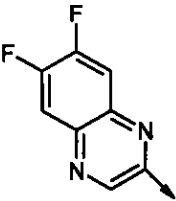
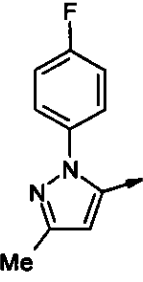
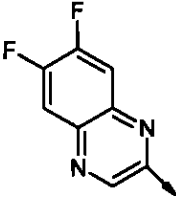
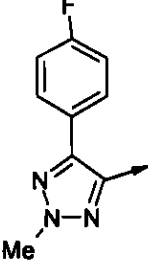
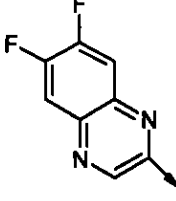
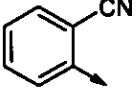
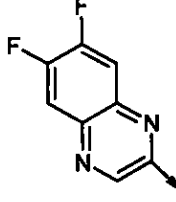
La amina de D31 (0.085g) en dimetilformamida (3ml) fue tratada con acido 4- (4- fluoro- fenil)- 2*H*- pirazola- 3- carboxílico (0.125g), diisopropiletilamina (0.07ml) y [hexafluorofosfato de O- (7- azabenzotriazol- 1- il)- 1,1,3,3- tetrametiluronio] (0.11g). La mezcla fue agitada durante 48 horas. El solvente fue removido a presion reducida y el residuo extraido con diclorometano. El filtrado fue evaporado bajo presion reducida y el residuo sometido a cromatografia en columna (gel de silice, metanol al 3%/eter dietilico) para proporcionar el compuesto del titulo (0.1g).

Espectro de Masa (API⁺): Encontrado 453 (MH⁺). C₂₃H₁₉F₃N₆O requiere 452.

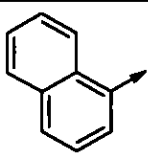
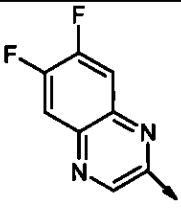


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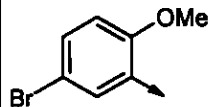
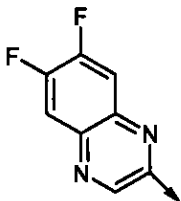
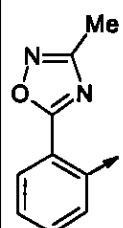
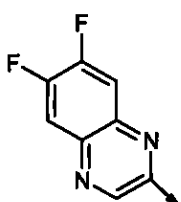
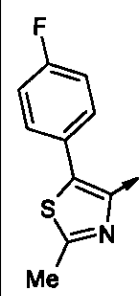
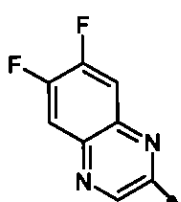
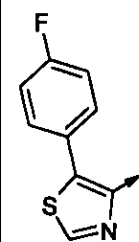
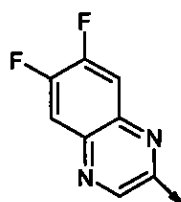
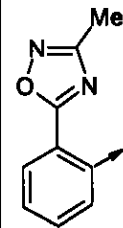
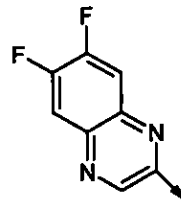
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Ejemplo	Amina	Ar ²	Ar ¹	Espectro de Masa (Electroatomización LC/MS), API ⁺
<u>94</u>	<u>D31</u>			Encontrado 484 (MH ⁺). C ₂₄ H ₂₀ F ₃ N ₅ OS requiere 483
<u>95</u>	<u>D31</u>			Encontrado 467 (MH ⁺). C ₂₄ H ₂₁ F ₃ N ₆ O requiere 466
<u>96</u>	<u>D31</u>			Encontrado 468 (MH ⁺). C ₂₃ H ₂₀ F ₃ N ₇ O requiere 467
<u>97</u>	<u>D31</u>			Encontrado 394 (MH ⁺). C ₂₁ H ₁₇ F ₂ N ₅ O requiere 393
<u>98</u>	<u>D31</u>			Encontrado 419 (MH ⁺).

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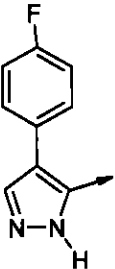
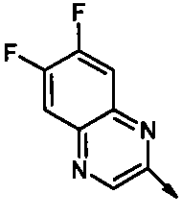
				$C_{24}H_{20}F_2N_4O$ requires 418
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232
231

<u>99</u>	<u>D31</u>			Encontrado 478 (MH ⁺). C ₂₁ H ₁₉ F ₂ N ₄ O ₂ requiere 477
<u>100</u>	<u>D31</u>			Encontrado 451 (MH ⁺). C ₂₃ H ₂₀ F ₂ N ₆ O ₂ requiere 450
<u>101</u>	<u>D45</u>			Encontrado 484 (MH ⁺). C ₂₄ H ₂₀ F ₃ N ₅ OS requiere 483
<u>102</u>	<u>D45</u>			Encontrado 470 (MH ⁺). C ₂₃ H ₁₈ F ₃ N ₅ OS requiere 469
<u>103</u>	<u>D45</u>			Encontrado 451 (MH ⁺). C ₂₃ H ₂₀ F ₂ N ₆ O ₂ requiere 450
<u>104</u>	<u>D45</u>			Encontrado 453 (MH ⁺).

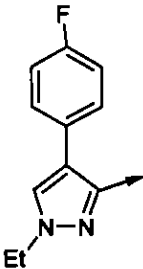
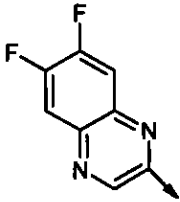
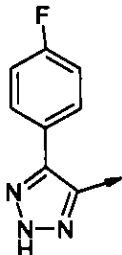
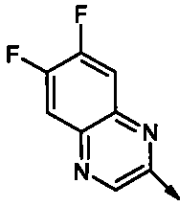
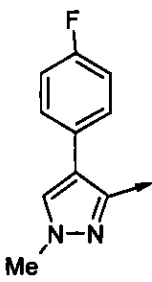
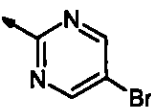
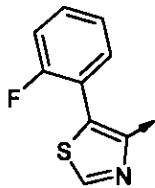
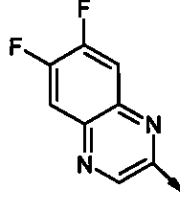
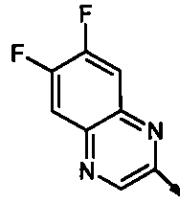
17/233

232

				$C_{23}H_{190}F_3N_6O$ require 452
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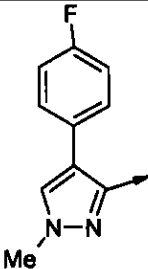


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233

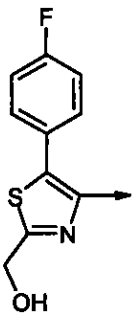
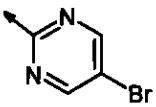
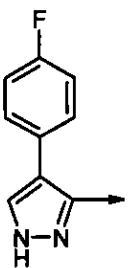
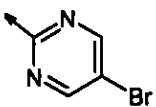
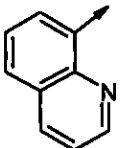
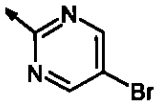
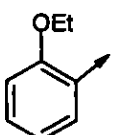
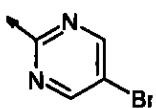
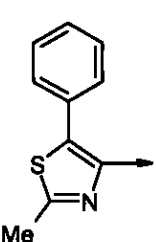
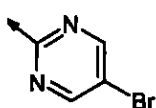
<u>119</u>	<u>D45</u>			Encontrado 481 (MH ⁺). C ₂₅ H ₂₃ F ₃ N ₆ O requiere 480
<u>120</u>	<u>D45</u>			Encontrado 454 (MH ⁺). C ₂₂ H ₁₈ F ₃ N ₇ O requiere 453
<u>167</u>	<u>D70</u>			Encontrado 459 (MH ⁺). C ₂₀ H ₂₀ ⁷⁹ BrFN ₆ O requiere 458
<u>168</u>	<u>D45</u>			Encontrado 470 (MH ⁺). C ₂₃ H ₁₈ F ₃ N ₅ OS requiere 469
<u>169</u>	<u>D45</u>			Encontrado 467 (MH ⁺). C ₂₄ H ₂₁ F ₃ N ₆ O requiere 466

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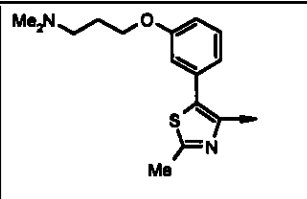
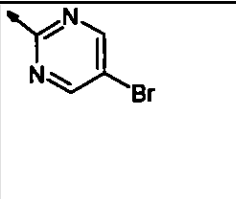
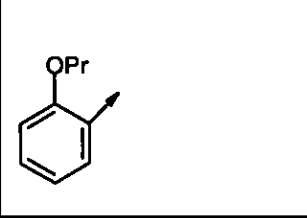
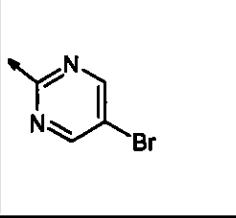
234

		 <chem>Cn1cc(C2=CC=CC=C2F)nn1</chem>		
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235

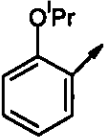
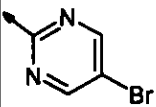
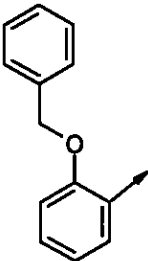
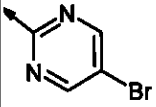
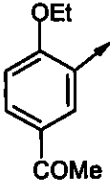
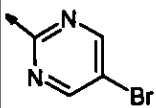
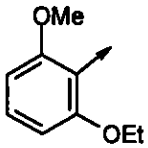
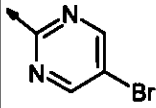
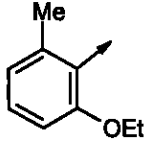
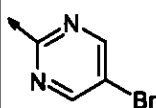
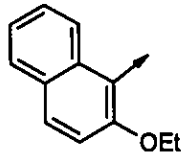
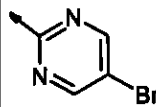
<u>176</u>	<u>D70</u>			Encontrado 514 (MNa ⁺). C ₂₀ H ₁₉ ⁷⁹ BrFN ₅ O ₂ S requiere 491
<u>177</u>	<u>D70</u>			Encontrado 445 (MH ⁺). C ₁₉ H ₁₈ ⁷⁹ BrFN ₆ O requiere 444
<u>178</u>	<u>D70</u>			Encontrado 434 (MNa ⁺). C ₁₉ H ₁₈ ⁷⁹ BrN ₅ O requiere 411
<u>179</u>	<u>D70</u>			Encontrado 405 (MH ⁺). C ₁₈ H ₂₁ ⁷⁹ BrN ₄ O ₂ requiere 404
<u>180</u>	<u>D70</u>			Encontrado 458 (MH ⁺). C ₂₀ H ₂₀ ⁷⁹ BrN ₅ OS requiere 457
<u>181</u>	<u>D70</u>			Encontrado 559 (MH ⁺). C ₂₅ H ₃₁ ⁷⁹ BrN ₆ O ₂ S

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236

				requiere 458
<u>182</u>	<u>D70</u>			Encontrado 419 (MH ⁺). C ₁₉ H ₂₃ ⁷⁹ BrN ₄ O ₂ requiere 418

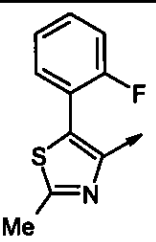
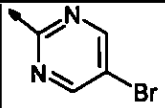
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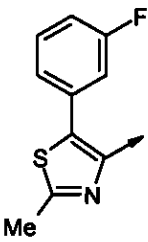
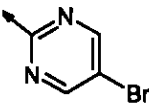
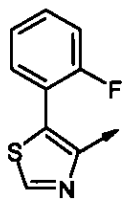
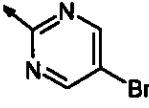
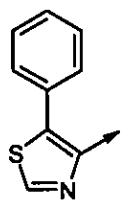
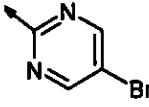
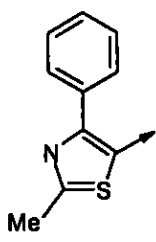
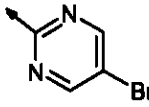
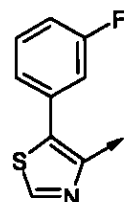
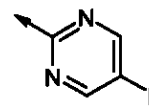
<u>183</u>	<u>D70</u>			Encontrado 419 (MH ⁺). C ₁₉ H ₂₃ ⁷⁹ BrN ₄ O ₂ requiere 418
<u>184</u>	<u>D70</u>			Encontrado 467 (MH ⁺). C ₂₃ H ₂₃ ⁷⁹ BrN ₄ O ₂ requiere 466
<u>185</u>	<u>D70</u>			Encontrado 447 (MH ⁺). C ₂₀ H ₂₃ ⁷⁹ BrN ₄ O ₃ requiere 446
<u>186</u>	<u>D70</u>			Encontrado 435 (MH ⁺). C ₁₉ H ₂₃ ⁷⁹ BrN ₄ O ₃ requiere 434
<u>187</u>	<u>D70</u>			Encontrado 419 (MH ⁺). C ₁₉ H ₂₃ ⁷⁹ BrN ₄ O ₂ requiere 418
<u>188</u>	<u>D70</u>			Encontrado 455 (MH ⁺). C ₂₂ H ₂₃ ⁷⁹ BrN ₄ O ₂ requiere 454
<u>189</u>	<u>D70</u>			Encontrado 476 (MH ⁺). C ₂₀ H ₁₉ ⁷⁹ BrFN ₅ OS

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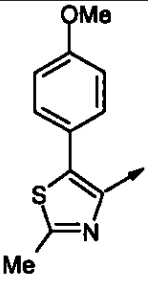
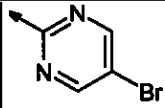
238

		 <chem>Cc1nc(s1)-c2ccccc2F</chem>	 <chem>Brc1ccncc1</chem>	requiere 475
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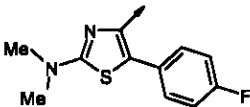
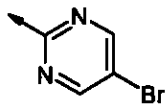
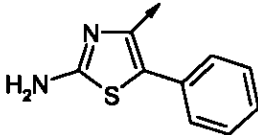
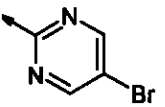
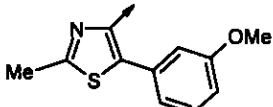
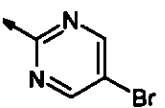
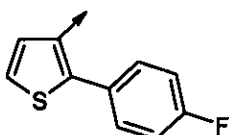
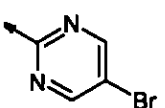
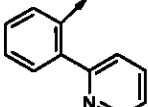
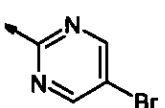
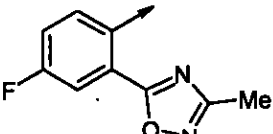
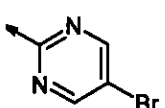
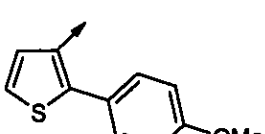
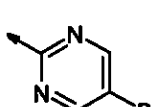
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<u>190</u>	<u>D70</u>			Encontrado 476 (MH ⁺). C ₂₀ H ₁₉ ⁷⁹ BrFN ₅ OS requiere 475
<u>191</u>	<u>D70</u>			Encontrado 462 (MH ⁺). C ₁₉ H ₁₇ ⁷⁹ BrFN ₅ OS requiere 461
<u>192</u>	<u>D70</u>			Encontrado 444 (MH ⁺). C ₁₉ H ₁₈ ⁷⁹ BrN ₅ OS requiere 443
<u>193</u>	<u>D70</u>			Encontrado 458 (MH ⁺). C ₂₀ H ₂₀ ⁷⁹ BrN ₅ OS requiere 457
<u>201</u>	<u>D70</u>			Encontrado 462 (MH ⁺). C ₂₀ H ₁₇ ⁷⁹ BrFN ₅ OS requiere 461
<u>202</u>	<u>D70</u>			Encontrado 488 (MH ⁺). C ₂₁ H ₂₂ ⁷⁹ BrN ₅ O ₂ S

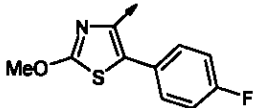
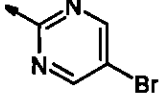
~~248~~
240

		 <chem>COc1ccc(cc1)-c2nc(C)s2</chem>	 <chem>Brc1ccncc1</chem>	requiere 487
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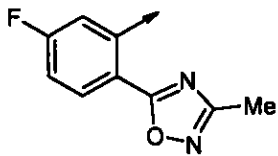
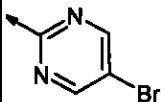
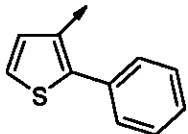
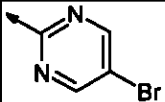
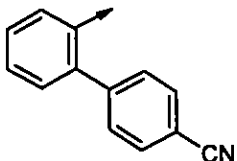
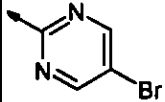
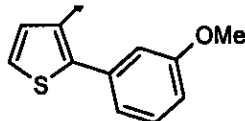
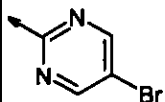
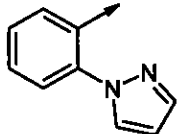
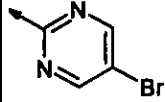
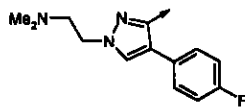
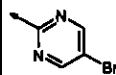
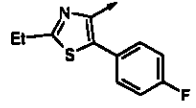
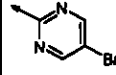
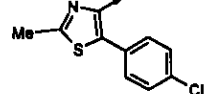
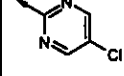
✓ 242
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<u>209</u>	<u>D70</u>			Encontrado 505 (MH ⁺). C ₂₁ H ₂₂ ⁷⁹ BrFN ₆ OS requiere 504
<u>210</u>	<u>D70</u>			Encontrado 459 (MH ⁺). C ₁₉ H ₁₉ ⁷⁹ BrN ₆ OS requiere 458
<u>211</u>	<u>D70</u>			Encontrado 488 (MH ⁺). C ₂₁ H ₂₂ ⁷⁹ BrN ₅ O ₂ S requiere 487
<u>212</u>	<u>D70</u>			Encontrado 461 (MH ⁺). C ₂₀ H ₁₈ ⁷⁹ BrFN ₄ OS requiere 460
<u>213</u>	<u>D70</u>			Encontrado 460 (MH ⁺). C ₂₁ H ₂₀ ⁷⁹ BrN ₅ O requiere 437
<u>214</u>	<u>D70</u>			Encontrado 461 (MH ⁺). C ₁₉ H ₁₈ ⁷⁹ BrFN ₆ O ₂ requiere 460
<u>215</u>	<u>D70</u>			Encontrado 473 (MH ⁺). C ₂₁ H ₂₁ ⁷⁹ BrN ₄ O ₂ requiere 472
<u>219</u>	<u>D70</u>			Encontrado 492 (MH ⁺). C ₂₀ H ₁₉ ⁷⁹ BrFN ₅ O ₂ S

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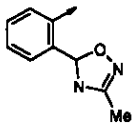
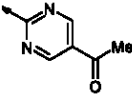
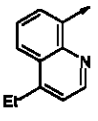
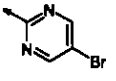
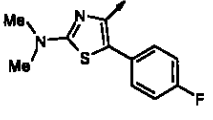
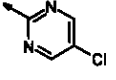
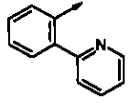
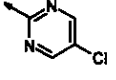
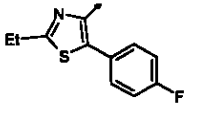
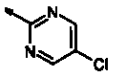
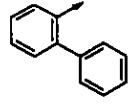
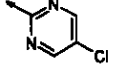
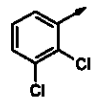
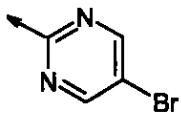
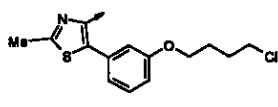
		 <chem>COc1nc(C)sc1-c2ccc(OC)cc2</chem>	 <chem>Brc1ccncc1</chem>	requiere 491
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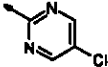
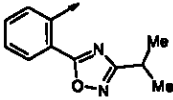
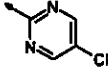
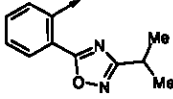
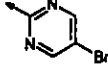
<u>220</u>	<u>D70</u>			Encontrado 461 (MH ⁺). C ₁₉ H ₁₈ ⁷⁹ BrFN ₆ O ₂ requiere 460
<u>221</u>	<u>D70</u>			Encontrado 443 (MH ⁺). C ₂₀ H ₁₉ ⁷⁹ BrN ₄ OS requiere 442
<u>222</u>	<u>D70</u>			Encontrado 462 (MH ⁺). C ₂₃ H ₂₀ ⁷⁹ BrN ₅ O requiere 461
<u>223</u>	<u>D70</u>			Encontrado 473 (MH ⁺). C ₂₁ H ₂₁ ⁷⁹ BrN ₄ O ₂ S requiere 472
<u>224</u>	<u>D70</u>			Encontrado 449 (MNa ⁺). C ₁₉ H ₁₉ ⁷⁹ BrN ₆ O requiere 426
<u>232</u>	<u>D70</u>			Encontrado 516 (MH ⁺). C ₂₃ H ₂₇ ⁷⁹ BrFN ₇ O requiere 415
<u>233</u>	<u>D70</u>			Encontrado 490 (MH ⁺). C ₂₁ H ₂₁ ⁷⁹ BrFN ₅ OS requiere 489
<u>247</u>	<u>D95</u>			Encontrado 448 (MH ⁺). C ₂₀ H ₁₉ ³⁵ Cl ₂ N ₅ OS requiere 447

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<u>248</u>	<u>D93</u>			Encontrado 407 (MH ⁺). C ₂₁ H ₂₂ N ₆ O ₃ requiere 406
<u>250</u>	<u>D70</u>			Encontrado 440 (MH ⁺). C ₂₁ H ₂₂ ⁷⁹ BrN ₅ O requiere 439
<u>251</u>	<u>D95</u>			Encontrado 461 (MH ⁺). C ₂₁ H ₂₂ ³⁵ ClFN ₆ OS requiere 460
<u>252</u>	<u>D95</u>			Encontrado 416 (MNa ⁺). C ₂₁ H ₂₀ ³⁵ ClN ₅ O requiere 393
<u>253</u>	<u>D95</u>			Encontrado 468 (MNa ⁺). C ₂₁ H ₂₁ ³⁵ ClFN ₅ OS requiere 445
<u>254</u>	<u>D95</u>			Encontrado 393 (MH ⁺). C ₂₂ H ₂₁ ³⁵ ClN ₄ O requiere 392
<u>255</u>	<u>D70</u>			Encontrado 429 (MH ⁺). C ₁₆ H ₁₅ ⁷⁹ Br ³⁵ Cl ₂ N ₄ O requiere 428
<u>256</u>	<u>D95</u>			Encontrado 520 (MH ⁺). C ₂₄ H ₂₇ ³⁵ Cl ₂ N ₅ O ₂ S requiere 519

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257	D95			Encontrado 427 (MH ⁺). C ₂₁ H ₂₃ ³⁵ ClN ₆ O ₂ requiere 426
258	D70			Encontrado 471 (MH ⁺). C ₂₁ H ₂₃ ⁷⁹ BrN ₆ O ₂ requiere 470

Ejemplo 105: 1- [2- (3- Metil- [1,2,4]oxadiazol- 5- il)- fenil]- 1- [(S)- 2- (oxazolo[4,5- b]]piridin- 2- ilaminometil)- piperidin- 1- il]- metanona

El compuesto de D41 (0.51g) y 2- metilsulfanil- oxazolo[4,5- b]piridina (0.25g) fueron combinados y calentados bajo argon a 90⁰ C durante 18 horas. La mezcla fue sometida a cromatografía en columna (metanol al 5%, eluyente de éter dietílico) para proporcionar el compuesto del titulo (026g).

Espectro de Masa (API⁺): Encontrado 419 (MH⁺). C₂₂H₂₂N₆O₃ requiere 418.

Ejemplo 106: 1- [2- (3- Metil- [1,2,4]oxadiazol- 5- il)- fenil]- 1- {(R)- 2- [(metil- oxazolo[4,5- b]piridin- 2- il- amino)- metil]piperidin- 1- il)- metanona

El compuesto del titulo (0.015g) fue preparado a partir del compuesto de D43 (0.15g) según el metodo del Ejemplo 105.

Espectro de Masa (API⁺): Encontrado 433 (MH⁺). C₂₃H₂₄N₆O₃ requiere 432.

Ejemplo 107: 6- [((S)- 1- {1- [4- (4- Fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanoil}- piperidin- 2- ilmetil)- metil- amino]- nicotinonitrilo

El compuesto del titulo (0.078g) fue preparado a partir del compuesto de D60 (0.45g) y 2- cloro- 5- cianopiridina (0.189g) según el metodo de D26.

Espectro de Masa (API⁺): Encontrado 433 (MH⁺). C₂₃H₂₄N₆O₃ requiere 432.

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Ejemplo 108: 1- ((S)- 2- {[(6,7- Difluoro- quinoxalin- 2- il)- metil- amino]- metil}- piperidin- 1- il)- 1- [4- (4- fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanona

El compuesto del título (0.031g) fue preparado a partir del compuesto de D60 (0.15g) y 2- cloro- 6,7- difluoroquinoxalina (0.091g) según el método de D26.

Espectro de Masa (API^+): Encontrado 495 (MH^+). $C_{26}H_{25}F_3N_6O$ requiere 494.

Ejemplo 171: 1- {2- [((S)- 1- {1- [4- (4- Fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanoil}- piperidin- 2- ilmetil)- amino]- pirimidin- 5- il}- etanona

Una mezcla de 1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il)- 1- [4- (4- fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanona (0.5g) y 1- etoxiviniltributylestano (0.42ml) tetraquis (trifenilfosfina)paladio[0] (0.06g) fue hervida en dioxano (8ml) durante 16 horas. Se agregó ácido clorhídrico 2N, la mezcla fue agitada durante 90 minutos, se agregó agua y la mezcla fue extraída (x3) con acetato de etilo. Los extractos combinados de acetato de etilo fueron secados, el solvente fue removido a presión reducida y el residuo fue sometido a cromatografía en columna (gel de sílice, acetato de etilo -> 2% metanol etilacetato) para proporcionar el compuesto del título (0.3g) como una espuma amarilla.

Espectro de Masa (API^+): Encontrado 437 (MH^+). $C_{23}H_{25}FN_6O_2$ requiere 436

Ejemplo 172: 1- [4- (4- Fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- 1- ((S)- 2- {[5- (1- hidroxil- etil)- pirimidin- 2- ilamino]- metil}- piperidin- 1- il)- metanona

1- {2- [((S)- 1- {1- [4- (4- Fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanoil}- piperidin- 2- ilmetil)- amino]- pirimidin- 5- il}- etanona (0.2g) fue disuelto en metanol (20ml) y se agregó borohidruro de sodio (0.4g). La reacción fue agitada durante la noche, se agregó agua y se continuó agitando durante 30 minutos. La mezcla de reacción fue extraída con acetato de etilo (x3), los extractos orgánicos fueron combinados, secados ($MgSO_4$) y el solvente fue removido a presión reducida para proporcionar el compuesto del título como una espuma incolora.

Espectro de Masa (API^+): Encontrado 439 (MH^+). $C_{23}H_{27}FN_6O_2$ requiere 438.

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Ejemplo 173: 2- [((S)- 1- {1- [4- (4- Fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanoil}- piperidin- 2- ilmetil)- amino]- pirimidina- 5- carbonitrilo

1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- piperidin- 1- il}- 1- [4- (4- fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanona (0.35g) en N- metilpirrolidinona (10ml) que contiene cianuro de cobre (I) (0.13g) fue calentada a reflujo durante 5 horas. La mezcla de reaccion fue diluida con agua, filtrada (tierra de diatomeas) y el filtrado fue extraido con acetato de etilo. La fase de acetato de etilo fue lavada con agua y salmuera, secada (MgSO₄), filtrada y el solvente fue removido a presion reducida. El residuo fue sometido a cromatografia en columna (gel de silice; acetato de etilo:pentano 1:1- > acetato de etilo eluyente), las fracciones apropiadas fueron combinadas y el solvente fue removido a presion reducida para proporcionar el compuesto del titulo (0.019g).

Espectro de Masa (API⁺): Encontrado 420 (MH⁺). C₂₂H₂₂FN₇O requiere 419

Ejemplo 174: 3- (1- {(S)- 2- [(6,7- Difluoro- quinoxalin- 2- ilamino)- metil]- piperidin- 1- il}- metanoil)- N- metil- benzamida

El compuesto de la descripcion 71 (0.10g) fue disuelto en dimetilformamida (5ml) que contiene HATU (0.095g) y diisopropiletilamina (0.131ul) y agitado durante 30 minutos. Se agrego metilamina (1M en tetrahidrofurano, 0.125ml) y se continuo agitando durante 16 horas. La mezcla de reaccion fue diluida con éter dietilico, lavada con agua (x3), saturada con salmuera y secada (MgSO₄). El solvente fue removido a presion reducida y el residuo fue sometido a cromatografia en columna (gel de sílice; acetato de etilo- > metanol al 10%: acetato de etilo) para proporcionar el compuesto del titulo 0.018g).

Espectro de Masa (API⁺): Encontrado 440 (MH⁺). C₂₃H₂₃F₂N₅O₂ requiere 439.

Ejemplo 194: 1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona

Una mezcla de la amina de D70 (0.070g), ácido 5- (4- fluoro- fenil)- 2- metil- tiazol- 4- carboxílico (0.065g), hidrocloreuro de 1- (3- dimetilaminopropil)- 3- etilcarbodiimida (EDC) (0.042g) e hidrato de 1- hidroxibenzotriazol (0.037g) en dimetilformamida (2ml)

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fue agitada a temperatura ambiente durante 18 horas, evaporada *al vacio* y el residuo fue particionado entre acetato de etilo y agua. La capa organica fue secada (Na_2SO_4), evaporada y el residuo sometido a cromatografia sobre gel de silice eluyendo con 30%-100% de acetato de etilo en gradiente de pentano para proporcionar el producto del titulo (0.083g) como un solido blanco.

Espectro de Masa (Electroatomización LC/MS), API^+ : Encontrado 476 (MH^+). $\text{C}_{20}\text{H}_{19}\text{BrFN}_3\text{OS}$ requiere 475.

Ejemplo 195: 1- {(S)- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1-[2- (3- metil- [1,2,4]oxadiazol- 5- il)- fenil]- metanona

El compuesto del titulo (0.053g) fue obtenido a partir de la amina de D70 (0.070g) y el acido 2- (3- metil- [1,2,4]oxadiazol- 5- il)- benzoico (0.056g) utilizando el metodo del Ejemplo 194.

Espectro de Masa (Electroatomización LC/MS): Encontrado 443 (MH^+). $\text{C}_{19}\text{H}_{19}^{79}\text{BrN}_6\text{O}_2$ requiere 442.

Ejemplo 196: 1- {(S)- 2- [(5- Bromo- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1-[5- (4- cloro- fenil)- 2- metil- tiazol- 4- il]- metanona

El compuesto del titulo (0.078g) fue obtenido a partir de la amina de D70 (0.077g) y el acido 5- (4- cloro- fenil)- 2- metil- tiazol- 4- carboxílico (0.076g) según el metodo del Ejemplo 32. Espectro de Masa (Electroatomización LC/MS), API^+ : Encontrado 492 (MH^+). $\text{C}_{20}\text{H}_{19}^{79}\text{Br}^{35}\text{CLN}_5\text{OS}$ requiere 491.

Ejemplo 197: 1- {(S)- 2- [(5- Bromo- piridin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1-[5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona

El compuesto del titulo (0.135g) fue obtenido a partir de la amina de D74 (0.11g) y el acido 5- (4- fluoro- fenil)- 2- metil- tiazol- 4- carboxílico (0.12g) según el metodo del Ejemplo 32. Espectro de Masa API^+ : Encontrado 475 (MH^+). $\text{C}_{21}\text{H}_{20}^{79}\text{BrFN}_4\text{OS}$ requiere 474.

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Ejemplo 198: 1- {(S)- 2- [(5- Bromo- piridin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [4- (4- fluoro- fenil)- 1- metil- 1*H*- pirazol- 3- il]- metanona

El compuesto del titulo (0.10g) fue obtenido a partir de la amina de D74 (0.11g) y el acido 4- (4- fluoro- fenil)- 1- metil- 1*H*- pirazol- 3- carboxílico (0.12g) según el metodo del

- 5 Ejemplo 32. Espectro de Masa API⁺: Encontrado 458 (MH⁺). C₂₁H₂₁⁷⁹BrFN₅O requiere 457.

Ejemplo 200: 1- {3- [(5- Bromo- pirimidin- 2- ilamino)- metil]- morfolin- 4- il}- 1- [4- (4- fluoro- fenil)- 1- metil- 1*H*- pirazol- 3- il]- metanona

- 10 El compuesto del titulo (0.393g) fue obtenido a partir del compuesto de D80 (0.3g) y el acido 4- (4- fluorofenil)- 1- metil- 1*H*- pirazol- 3- carboxílico (0.242g) según el metodo del Ejemplo 32. Espectro de Masa (API⁺): Encontrado 475 (MH⁺). C₂₀H₂₀⁷⁹BrFN₆O₂ requiere 474.

- 15 **Ejemplo 203:** 3,5- Difluoro- 4- [((S)- 1- {1- [5- (4- fluorofenil)- 2- metil- tiazol- 4- il]- metanoil}- piperidin- 2- ilmetil)- amino]- benzonitrilo

El compuesto del titulo (0.090g) fue obtenido a partir del compuesto de D82 (0.073g) y el acido 5- (4- fluorofenil)- 2- metil- tiazol- 4- carboxílico (0.069g) según el metodo del Ejemplo 32. Espectro de Masa (Electroatomización LC/MS): Encontrado 471.

- 20 C₂₄H₂₁F₃N₄OS requiere 470.

Ejemplo 208: 3,5- Difluoro- 4- [((S)- 1- {1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanoil}- pirrolidin- 2- ilmetil)- amino]- benzonitrilo

El compuesto del titulo (0.09g) fue obtenido a partir del compuesto de D84 y el acido 5- (4- fluoro- fenil)- 2- metil- tiazol- 4- carboxílico (0.095g) según el metodo del Ejemplo 32.

- 25 Espectro de Masa (Electroatomización LC/MS): Encontrado 457 (MH⁺). C₂₃H₁₉F₃N₄OS requiere 456.

Ejemplo 216: 1- {(S)- 2- [(5- Etil- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il}- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona

- 30

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El compuesto del título (0.05g) fue obtenido a partir del compuesto de D86 (0.07g) y el ácido 5- (4- fluoro- fenil)- 2- metil- tiazol- 4- carboxílico (0.068g) según el método del Ejemplo 32. Espectro de Masa (Electroatomización LC/MS): Encontrado 426 (MH⁺). C₂₂H₂₄FN₄OS requiere 425.

5

Ejemplo 217: 1- ((S)- 2- {[5- Bromo- pirimidin- 2- il)- metil- amino]- metil}- pirrolidin- 1- il)- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona

El compuesto del título (0.1g) fue obtenido a partir del compuesto de D91 (0.275g) y el ácido 5- (4- fluoro- fenil)- 2- metil- tiazol- 4- carboxílico (0.285g) según el método del

10 Ejemplo 32. Espectro de Masa (Electroatomización LC/MS): Encontrado 490 (MH⁺).

C₂₁H₂₁⁷⁹BrFN₅OS requiere 489.

Ejemplo 218: 1- ((S)- 2- {[5- Bromo- pirimidin- 2- il)- metil- amino]- metil}- pirrolidin- 1- il)- 1- [4- (4- fluoro- fenil)- 1- metil- 1H- pirazol- 3- il]- metanona

15 El compuesto del título (0.02g) fue obtenido a partir del compuesto de D91 (0.275g) y el ácido 4- (4- fluoro- fenil)- 1- metil- 1H- pirazol- 3- carboxílico (0.260g) según el método del Ejemplo 32. Espectro de Masa (Electroatomización LC/MS): Encontrado 473 (MH⁺). C₂₁H₂₂⁷⁹BrFN₆O requiere 472.

20 **Ejemplo 225: 1- {2- [((S)- 1- {1- [5- (4- Cloro- fenil)- 2- metil- tiazol- 4- il]- metanoil}- pirrolidin- 2- ilmetil)- amino]- pirimidin- 5- il)- etanona**

El producto del título (0.04g) fue obtenido a partir del compuesto de D93 (0.133g) y el ácido 5- (4- cloro- fenil)- 2- metil- tiazol- 4- carboxílico (0.076g) utilizando un procedimiento similar a aquel descrito en el Ejemplo 32. Espectro de Masa

25 (Electroatomización LC/MS): Encontrado 456 (MH⁺). C₂₂H₂₂³⁵ClN₅O₂S requiere 455.

Ejemplo 226: 1- {(S)- 2- [(5- Cloro- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il)- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona

El producto del título (0.095) fue obtenido a partir de la amina de D95 (0.064g) y el ácido

30 5- (4- fluorofenil)- 2- metil- tiazol- 4- carboxílico (0.071g) utilizando el método del

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Ejemplo 32. Espectro de Masa (Electroatomización LC/MS): Encontrado 432 (MH⁺).
C₂₀H₁₉³⁵ClFN₅OS requiere 431.

**Ejemplo 227: 1- {(S)- 2- [(5- Cloro- pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il)- 1-
5 [2- (3- metil- [1,2,4]oxadiazol- 5- il)- fenil]- metanona**

El compuesto del título (0.052) fue obtenido a partir de la amina de D95 (0.064g) y el ácido
2- (3- metil- [1,2,4]oxadiazol- 5- il)- benzoico (0.061g) según el método del Ejemplo 32.
Espectro de Masa (Electroatomización LC/MS): Encontrado 399 (MH⁺). C₁₉H₁₉³⁵ClN₆O₂
requiere 398.

**Ejemplo 228: 1- [(5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il)- 1- {(S)- 2- [(5- metil-
pirimidin- 2- ilamino)- metil]- pirrolidin- 1- il)- metanona**

Al compuesto del Ejemplo 194 (0.36g) en dimetilformamida se agregó cloruro de litio
(0.096g), estaño de tetrametilo (0.126ml) y diclorobis(trifenilfosfina) paladio (0) (0.035g) y
15 la mezcla resultante fue calentada a 100⁰C bajo argón durante 18 horas. Luego la reacción
fue evaporada, diluida con diclorometano, filtrada y el filtrado fue lavado con agua, secado
y evaporado. La cromatografía del residuo sobre gel de sílice, eluyendo con mezclas de
metanol- diclorometano, proporcionó el producto del título (0.2g) como un sólido amorfo
amarillo. Espectro de Masa (API⁺): Encontrado 412 (MH⁺). C₂₁H₂₂FN₅OS requiere 411.

**Ejemplo 229: 6- [((S)- 1- {1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il)- metanoil]-
pirrolidin- 2- ilmetil)- amino]- nicotinonitrilo**

Una mezcla de la amina de D97 (0.134g), ácido 5- (4- fluoro- fenil)- 2- metil- tiazol- 4-
carboxílico (0.172g), (EDC) (0.139g) y 1- hidroxibenzotriazol (0.01g) en diclorometano (8
25 ml) fue agitada a temperatura ambiente durante 7 días. La reacción fue lavada con solución
de bicarbonato de sodio acuoso saturado, secada y evaporada. La cromatografía del residuo
sobre gel de sílice, eluyendo con mezclas de acetato de etilo – hexano proporcionó el
producto del título (0.19g). Espectro de Masa (Electroatomización LC/MS): Encontrado
422 (MH⁺). C₂₂H₂₀FN₅OS requiere 421.

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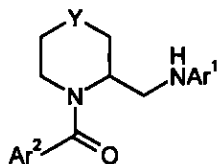
Ejemplo 234: 1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- 1- {(S)- 2- [(6- metil- 2- metilsulfanil- pirimidin- 4- ilamino)- metil]- pirrolidin- 1- il}- metanona

El producto del título (0.095g) fue obtenido a partir de la amina de D101 (0.15g) y el compuesto de D98 (0.14g) utilizando un método similar al descrito en D69. Espectro de
5 Masa (Electroatomización LC/MS): Encontrado 458 (MH^+). $C_{22}H_{24}FN_5OS_2$ requiere 457.

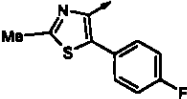
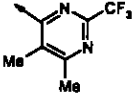
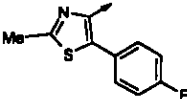
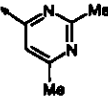
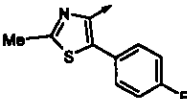
Ejemplo 235: 1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- 1- {(S)- 2- [(2- metilsulfanil- pirimidin- 4- ilamino)- metil]- pirrolidin- 1- il}- metanona

El compuesto del título (0.05g) fue obtenido a partir de la amina de D101 (0.15g) y 4-
10 cloro- 2- metilsulfanil- pirimidina (0.076g) utilizando un método similar al descrito en D69. Espectro de Masa (Electroatomización LC/MS): Encontrado 444 (MH^+).
 $C_{21}H_{22}FN_5OS_2$ requiere 443.

Los siguientes compuestos fueron preparados utilizando métodos similares a los descritos
15 en los Ejemplos 234 y 235.



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Ejemplo	Amina	Y	Ar ²	Ar ¹	Espectro de Masa (Electroatomización LC/MS), API ⁺
236	D101	Bond			Encontrado 494 (MH ⁺). C ₂₃ H ₂₃ F ₄ N ₅ OS requiere 493
237	D101	Bond			Encontrado 426 (MH ⁺). C ₂₂ H ₂₄ FN ₅ OS requiere 425
238	D101	Bond			Encontrado 466 (MH ⁺). C ₂₁ H ₁₉ F ₄ N ₅ OS requiere 465

Ejemplo 239: 1- (3- {(5- Bromo- pirimidin- 2- il)- metil- amino}- metil)- morfolin- 4- il)- 1- [5- (4- fluoro- fenil)- 2- metil- tiazol- 4- il]- metanona

El compuesto del titulo (0.056g) fue obtenido a partir del compuesto de D105 (0.095g) y el
5 acido 5- (4- fluorofenil)- 2- metil- tiazol- 4- carboxílico (0.10g) según el metodo del
Ejemplo 32. Espectro de Masa (Electroatomización LC/MS): Encontrado 506 (MH⁺).
C₂₁H₂₁⁷⁹BrFN₅O₂S requiere 505.

Ejemplo 240: 1- (3- {(5- Bromo- pirimidin- 2- il)- metil- amino}- metil)- morfolin- 4- il)- 1- [2- (4- fluoro- fenil)- tiofen- 3- il]- metanona

Al compuesto del titulo de D105 (0.095g) en diclorometano (8ml) que contenía trietilamina
(0.06ml) se agregó cloruro de 2- (4- fluorofenil- tiofeno- 3- carbonilo (0.084g). Después de
72 horas a temperatura ambiente la mezcla de reaccion fue lavada con salmuera, secada y
15 evaporada; el residuo fue cromatograficado sobre gel de sílice, eluyendo con mezclas de
acetato de metilo- pentano para proporcionar el producto del titulo (0.093g). Espectro de

+H₂SO₄
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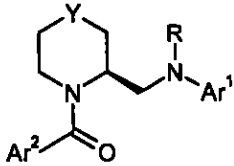
Masa (Electroatomización LC/MS): Encontrado 491 (MH⁺). C₂₁H₂₀⁷⁹BrFN₄O₂S requiere 490.

Ejemplo 249: 1- [5- (4- Fluoro- fenil)- 2- metil- tiazol- 4- il]- 1- {(S)- 2- [(5- trifluorometil- pirimidin- 2- ilamino)metil]- pirrolidin- 1- il}- metanona

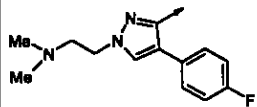
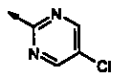
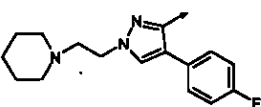
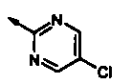
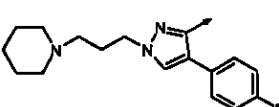
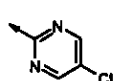
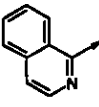
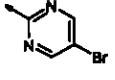
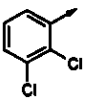
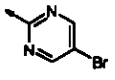
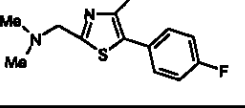
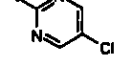
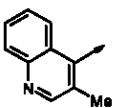
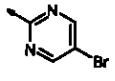
Al compuesto del Ejemplo 194 (0.36g) en dimetilformamida (5ml) se agregó trifluoroacetato de potasio (0.23g), yoduro de cobre (0.3g) y tolueno (5 ml) y la mezcla resultante fue calentada a reflujo bajo condiciones Dean- Stark durante 3 horas, antes de someter a reflujo durante 20 horas más. La mezcla de reacción fue enfriada, vertida en agua/éter y filtrada a través de tierra de diatomeas. La capa acuosa del filtrado fue extraída con éter, y los extractos de éter combinados fueron lavados con agua, secados y evaporados. La capa acuosa fue extraída nuevamente con diclorometano y el extracto fue evaporado. Los extractos combinados fueron cromatografiados sobre gel de sílice, eluyendo con mezclas de metanol- diclorometano, para proporcionar el compuesto del título (0.001g)

Espectro de Masa (Electroatomización LC/MS): Encontrado 466 (MH⁺). C₂₁H₁₉F₄N₅OS requiere 465.

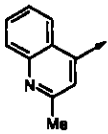
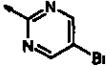
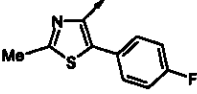
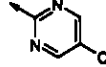
Los compuestos en la siguiente tabla fueron preparados utilizando los métodos descritos anteriormente.



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Ejemplo	X	R	Ar ²	Ar ¹	Espectro de Masa (Electroatomización LC/MS), API ⁺
<u>267</u>	<u>CH₂</u>	H			Encontrado 486 (MH ⁺). C ₂₄ H ₂₉ ³⁵ ClFN ₇ O requiere 485
<u>268</u>	<u>CH₂</u>	H			Encontrado 526 (MH ⁺). C ₂₇ H ₃₃ ³⁵ ClFN ₇ O requiere 525
<u>269</u>	<u>CH₂</u>	H			Encontrado 540 (MH ⁺). C ₂₈ H ₃₅ ³⁵ ClFN ₇ O requiere 539
<u>270</u>	<u>CH₂</u>	Me			Encontrado 440 (MH ⁺). C ₂₁ H ₂₂ ⁷⁹ BrN ₅ O requiere 439
<u>271</u>	<u>CH₂</u>	Me			Encontrado 457 (MH ⁺). C ₁₈ H ₁₉ ⁷⁹ Br ³⁵ Cl ₂ N ₄ O requiere 456
<u>272</u>	<u>CH₂</u>	H			Encontrado 489 (MH ⁺). C ₂₃ H ₂₆ ³⁵ ClFN ₆ OS requiere 488
<u>273</u>	<u>CH₂</u>	Me			Encontrado 454 (MH ⁺). C ₂₂ H ₂₄ ⁷⁹ BrN ₅ O requiere 453

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274	CH₂	Me			Encontrado 454 (MH ⁺). C ₂₂ H ₂₄ ⁷⁹ BrN ₅ O requiere 453
275	CH₂	H			Encontrado 446 (MH ⁺). C ₂₁ H ₂₁ ³⁵ CLFN ₅ OS requiere 445

Se entiende que el presente invento cubre todas las combinaciones de los grupos particulares y preferidos descritos en la presente.

5

Determinación de la Actividad Antagonista del Receptor de la Orexina- 1

La actividad antagonista del receptor de la orexina- 1 de los compuestos de la fórmula (I) fue determinada según el siguiente método experimental.

10 Método Experimental

Las células CHO- DG44 que expresan el receptor de la orexina- 1 humana fueron cultivadas en medio celular (médium MEM con sales de Earl) que contenía L- Glutamina 2 mM, 0.4 mg/mL de Sulfato G418 de GIBCO BRL y suero bovino fetal termo inactivado al 10% de Gibco BRL. Las células fueron sembradas a 20.000 células/100 ul/pozo en placas estériles de fondo translúcido de 96 pozos Costar las cuales han sido pre- recubiertas con 10 ug/pozo de poli- L- lisina de SIGMA. Las placas sembradas fueron incubadas durante la noche a 37°C en CO2 al 5%.

15

Los agonistas fueron preparados como concentraciones 1 mM en agua DMSO (1:1). Los valores EC50 (las concentraciones requeridas para producir respuesta máxima del 50%) fueron estimados utilizando diluciones logarítmicas decimales (Biomek 2000, Beckman) en amortiguador de Tyrode que contiene probenecid (Hepes 10 mM con NaCl

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145 mM, glucosa 10 mM, KCL 2.5 mM, CaCl₂ 1.5 mM, MgCl₂ 1.2 mM y probenecid 2.5 mM; pH 7.4). Los antagonistas fueron preparados como concentración 10 mM en DMSO (100%). Los valores IC₅₀ de antagonista (la concentración del compuesto necesaria para inhibir 50% de la respuesta agonista) fueron determinados contra orexina- A humana 3.0 nM utilizando diluciones logarítmicas en amortiguador de Tyrode que contiene DMSO al 10% y probenecid.

El día del ensayo 50 ul de medio celular que contenía probenecid (Sigma) y Fluo3AM (Texas Fluorescence Laboratories) fue agregado (Quadra, Tomtec) a cada pozo para proporcionar concentraciones finales de 2.5 mM y 4 uM, respectivamente. Las placas de 96 pozos fueron incubadas durante 60 minutos a 37°C en CO₂ al 5%. La solución de carga que contenía el tinte fue luego aspirada y las células fueron lavadas con 4x150 ul de amortiguador de Tyrode que contenía probenecid y gelatina al 1% (Denley Cell Wash). El volumen del amortiguador que quedo en cada pozo fue 125 ul. Se agregó antagonista o amortiguador (25 ul) (Quadra), las placas celulares fueron suavemente agitadas e incubadas a 37C en CO₂ al 5% durante 30 minutos. Las placas celulares fueron luego transferidas al instrumento Lector de Placas de Imágenes Fluorescentes (FLIPR, Dispositivos Moleculares). Antes de la adición del fármaco se tomó una imagen única de la placa celular (prueba de señal), para evaluar la consistencia de la carga de tinte. El protocolo de corrida utilizo 60 imágenes tomadas a intervalos de 1 segundo seguido por 24 imágenes más a intervalos de 5 segundos. Se agregaron agonistas (mediante FLIPR) después de 20 segundos (durante lectura continua). En cada pozo la fluorescencia máxima fue determinada sobre el periodo de ensayo completo y el promedio de las lecturas 1- 19 fue restado de esta cifra. El aumento máximo en fluorescencia fue graficado contra concentración del compuesto y la curva fue iterativamente ajustada utilizando un ajuste logístico de cuatro parámetros (tal como se describió por Bowen y Jerman, *TIPS*, 1995, 16, 413- 417) para generar un valor de efecto de concentración. Los valores Kb antagonistas fueron calculados utilizando la ecuación:

$$K_b = IC_{50} / (1 + ([3/EC_{50}])$$

Donde EC₅₀ fue la potencia de la orexina- A humana determinada en el ensayo (en términos nM) y IC₅₀ es expresado en términos molares.

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Los compuestos de los Ejemplos probados según este método obtuvieron valores pKb que oscilaban entre 6.7 y 9.7 para el receptor de la orexina- 1 clonada.

La actividad antagonista del receptor de la orexina- 2 de los compuestos de la fórmula (I) fue determinada según el siguiente método experimental.

5

Método Experimental

Células CHO- DG44 que expresan el receptor de la orexina- 2 humana fueron cultivadas en medio celular (medio MEM con sales de Earl) que contenía L- Glutamina 2 mM, 0.4 mg/mL de sulfato G418 de GIBCO BRL y suero bovino fetal termo inactivado de Gibco BRL. Las células fueron sembradas a 20.000 células/100 ul/pozo en placas esteriles de fondo translucido de 96 pozos de Costar las cuales fueron pre- revestidas con 10 ug/pozo de poli- L- lisina de SIGMA. Las placas sembradas fueron incubadas durante la noche a 37C en CO2 al 5%.

Los agonistas fueron preparados como concentraciones 1 mM en agua DMSO (1:1). Los valores EC50 (las concentraciones requeridas para producir respuesta máxima del 50%) fueron estimados utilizando diluciones logarítmicas (Biomek 2000, Beckman) en amortiguador de Tyrode que contiene probenecid (Hepes 10 mM con NaCl 145 mM, glucosa 10 mM, KCL 2.5 mM, CaCl2 1.5 mM, MgCl2 1.2 mM y probenecid 2.5 mM; pH 7.4). Los antagonistas fueron preparados como concentraciones 10 mM en DMSO (100%). Los valores IC50 de antagonista (la concentración del compuesto necesaria para inhibir 50% de la respuesta agonista) fueron determinados contra orexina- A humana 10.0 nM utilizando diluciones logarítmicas decimales en amortiguador de Tyrode que contiene DMSO al 10% y probenecid.

El día del ensayo 50 ul de medio celular que contenía probenecid (Sigma) y Fluo3AM (Texas Fluorescence Laboratories) fue agregado (Quadra, Tomtec) a cada pozo para proporcionar concentraciones finales de 2.5 mM y 4 uM, respectivamente. Las placas de 96 pozos fueron incubadas durante 60 minutos a 37°C en CO2 al 5%. La solución de carga que contenía el tinte fue luego aspirada y las células fueron lavadas con 4x150 ul de amortiguador de Tyrode que contenía probenecid y gelatina al 0.1% (Denley Cell Wash).

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El volumen del amortiguador que quedo en cada pozo fue 125 ul. Se agregó antagonista o amortiguador (25 ul) (Quadra), las placas celulares fueron suavemente agitadas e incubadas a 37°C en CO₂ al 5% durante 30 minutos. Las placas celulares fueron luego transferidas al instrumento Lector de Placas de Imágenes Fluorescentes (FLIPR, Dispositivos

- 5 Moleculares). Antes de la adición del fármaco se tomó una imagen única de la placa celular (prueba de señal), para evaluar la consistencia de la carga de tinte. El protocolo de corrida utilizó 60 imágenes tomadas a intervalos de 1 segundo seguido por 24 imágenes más a intervalos de 5 segundos. Se agregaron agonistas (mediante FLIPR) después de 20 segundos (durante lectura continua). En cada pozo la fluorescencia máxima fue
- 10 determinada sobre el periodo de ensayo completo y el promedio de las lecturas 1- 19 fue restado de esta cifra. El aumento máximo en fluorescencia fue graficado contra concentración del compuesto y la curva fue iterativamente ajustada utilizando un ajuste logístico de cuatro parámetros (tal como se describió por Bowen y Jerman, *TIPS*, 1995, 16, 413- 417) para generar un valor de efecto de concentración. Los valores Kb antagonistas
- 15 fueron calculados utilizando la ecuación:

$$K_b = IC_{50} / (1 + ([3/EC_{50}]))$$

Donde EC₅₀ fue la potencia de la orexina- A humana determinada en el ensayo (en términos nM) y IC₅₀ es expresado en términos molares.

- Los compuestos de los Ejemplos probados según este método tuvieron valores pK_b en el rango <6.3 – 9.1 en el receptor de la orexina- 1 clonada humana.
- 20

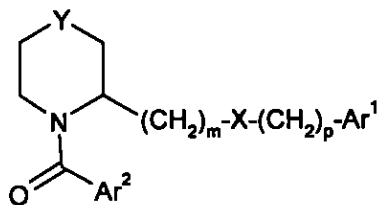
- La solicitud de la cual la descripción y las reivindicaciones hacen parte puede ser utilizada como una base para prioridad con respecto a cualquier solicitud subsiguiente. Las reivindicaciones de tal solicitud subsiguiente pueden ser dirigidas a cualquier característica
- 25 o combinación de características descritas en la presente. Estas pueden tomar la forma de reivindicaciones de producto, composición, proceso, o uso y pueden incluir, a manera de ejemplo y sin limitación las siguientes reivindicaciones:

REIVINDICACIONES

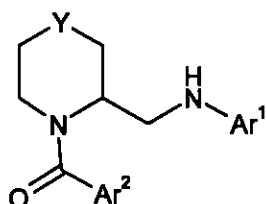
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1. Un compuesto de la fórmula (I):



- 5 Y representa un enlace, oxígeno, o un grupo $(\text{CH}_2)_n$, en donde n representa 1, 2 o 3
m representa 1, 2, o 3;
p representa 0 o 1;
X es NR, en donde R es H o C1- 4alquilo;
 Ar^1 es arilo, o un grupo heteroarilo mono o bicíclico que contiene hasta 3
- 10 heteroátomos seleccionados de N, O y S; cualquiera de los cuales puede ser opcionalmente substituido;
 Ar^2 representa fenilo o un grupo heterociclilo de 5 o 6 miembros que contiene hasta 3 heteroátomos seleccionados de N, O y S, en donde el grupo fenilo o heterociclilo es substituido por R^1 y substituyentes opcionales adicionales; o Ar^2 representa un grupo
- 15 bicíclico aromático o bicíclico heteroaromático opcionalmente substituido que contiene hasta 3 heteroátomos seleccionados de N, O y S;
 R^1 representa hidrógeno, C1- 4alcoxilo opcionalmente substituido, halo, ciano, C1- 6alquilo opcionalmente substituido, fenilo opcionalmente substituido, o un grupo fenilo heterociclilo de 5 o 6 miembros opcionalmente substituido que contiene hasta 4
- 20 heteroátomos seleccionados de N, O y S;
en donde cuando Y es un enlace, Ar^2 no puede ser 2- naftilo;
cuando Ar^1 es arilo p no es 1;
o una sal farmacéuticamente aceptable del mismo.
- 25 2. Un compuesto de la fórmula (Ia);



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en donde;

Y representa un enlace, oxígeno, o un grupo $(CH_2)_n$, en donde n representa 1, 2 o 3

5 Ar¹ es un grupo heteroarilo mono o biciclico que contiene hasta 3 heteroátomos seleccionados de N, O y S; cualquiera de los cuales puede ser opcionalmente sustituido;

Ar² representa fenilo o un grupo heterociclilo de 5 o 6 miembros que contiene hasta 3 heteroátomos seleccionados de N, O, y S, en donde el grupo fenilo o heterociclilo es
10 sustituido por R¹ y sustituyentes opcionales adicionales; o Ar² representa un grupo biciclico aromático o biciclico heteroaromático opcionalmente sustituido que contiene hasta 3 heteroátomos seleccionados de N, O y S;

R¹ representa hidrógeno, C1- 4alcoxilo opcionalmente sustituido, halo, ciano, C1- 6alquilo opcionalmente sustituido, fenilo opcionalmente sustituido, o un grupo fenilo
15 heterociclilo de 5 o 6 miembros opcionalmente sustituido que contiene hasta 4 heteroátomos seleccionados de N, O y S;

en donde cuando Y es un enlace entonces Ar² no puede ser 2- naftilo; o una sal farmacéuticamente aceptable del mismo.

20 3. Un compuesto según la reivindicación 1 o 2 en donde Y es un enlace, oxígeno o $(CH_2)_n$ donde n es 1 o 2.

4. Un compuesto según cualquier reivindicación precedente en donde Ar² representa un fenilo, piridilo, tiazolilo, pirazolilo, benzofurilo, naftilo, triazolilo, quinoxalinilo,
25 quinolinilo, isoquinolinilo, benzimidazolilo, benzotienilo, benzotriazolilo, benzotiazolilo, indolilo o tienilo opcionalmente sustituido.

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5. Un compuesto según cualquiera de las anteriores reivindicaciones en donde Ar¹ representa un benzoxazolilo, benzimidazolilo, quinoxalinilo, quinazolinilo, pirimidinilo, piridinilo, naftiridinilo, quinolinilo, piridopirimidina, tiazolilo, oxazolilpiridinilo, benzotiazolilo, isoquinolinilo o pirazinilo.

5

6. Un compuesto según cualquier reivindicación anterior en donde R¹ es seleccionado de trifluorometoxilo, metoxilo, etoxilo, halo, ciano o un grupo fenilo, piridilo, pirazolilo, pirimidinilo u oxadiazolilo opcionalmente substituido.

- 10 7. Un compuesto de la fórmula (I) tal como se definió en cualquiera de los Ejemplos 1 a 275, o una sal farmacéuticamente aceptable de cualquiera de los mismos.

8. Una composición farmacéutica que comprende un compuesto de la fórmula (I) tal como se definió en cualquiera de las reivindicaciones 1 a 7, o una sal farmacéuticamente aceptable del mismo, y un vehículo farmacéuticamente aceptable.

15

9. Un método para tratar o prevenir enfermedades o trastornos donde se requiere un antagonista de un receptor de la orexina humana, el cual comprende la administración a un sujeto en necesidad del mismo de una cantidad efectiva de un compuesto de la fórmula (I) tal como se definió en cualquiera de las reivindicaciones 1 a 7, o una sal farmacéuticamente aceptable del mismo.

20

PATENT COOPERATION TREATY

GlaxoSmithKline
Corporate IP

13 MAY 2003

Received NFSP

From the

INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

GIDDINGS, Peter John
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Corporate Intellectual Property
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GRANDE BRETAGNE

Corporate IP
Received BRENTFORD

06 MAY 2003

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

ATTY: ML

IPM: N/A

ATTY: CHEN

Date of mailing
(day/month/year)

02.05.2003

Applicant's or agent's file reference
SCH/P32809

IMPORTANT NOTIFICATION

International application No.
PCT/GB02/02042

International filing date (day/month/year)
02/05/2002

Priority date (day/month/year)
05/05/2001

Applicant

SMITHKLINE BEECHAM P.L.C. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

For the purpose of deciding whether the claimed invention is patentable or not, the elected Offices may apply criteria additional to or different from the criteria on which the international preliminary examination report is based (see Articles 27(5), 33(5)). Additional criteria may include e.g. exemptions from patentability and the requirements of enabling disclosure and of clarity and support of claims.

Name and mailing address of the IPEA/

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SCH/P32809	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB02/02042	International filing date (day/month/year) 02/05/2002	Priority date (day/month/year) 05/05/2001
International Patent Classification (IPC) or national classification and IPC C07D417/14		
Applicant SMITHKLINE BEECHAM P.L.C. et al.		
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 6 sheets, including this cover sheet. ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of sheets.		
3. This report contains indications relating to the following items: I ☒ Basis of the report II ☐ Priority III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV ☐ Lack of unity of invention V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI ☐ Certain documents cited VII ☐ Certain defects in the international application VIII ☐ Certain observations on the international application		
Date of submission of the demand 21/11/2002	Date of completion of this report 02.05.2003	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523658 apmu d Fax: +49 89 2399 - 4465	Authorized officer Cortés, J Telephone No. +49 89 2399 8206 	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB02/02042

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I. Basis of the report

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):*)

Description, pages:

1-89 as originally filed

Claims, No.:

1-9 as originally filed

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB02/02042

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 1 (part), 3-8 (all part), 9.

because:

- ☒ the said international application, or the said claims Nos. 9 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 1 (part), 3-8 (all part).

2. A meaningful International preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 4-9 (part)
	No: Claims 1-3 (part)
Inventive step (IS)	Yes: Claims 7 (part)
	No: Claims 1-6, 8, 9 (part)
Industrial applicability (IA)	Yes: Claims

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB02/02042

No: Claims 1-8 (part)

2. Citations and explanations
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB02/02042

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1). Present claims 1 and 3-9 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds where (referring to formula (I)) where m is 1; X is NR and p is 0. This is slightly larger than claim 2 due to having NR instead of NH. It is noted that this covers all of the examples.

2). Relevant prior art is provided by:

- (A) WO01/96302
- (B) WO02/44172
- (C) WO00/08015
- (D) WO00/12077
- (E) WO01/40231
- (F) Helv., Chim., Acta, 1992, pp109-123.
- (G) Chem. Pharm. Bull., 1984, pp3839-3847

No reasons are given for the provisos found in claim 1. The relevant prior art has not been cited (Rule 5.1 (a) (ii) PCT).

The claimed matter is assumed to be fully entitled to the priority of 05/05/91. The intermediate prior art documents (A) and (B) have therefore not been considered vis-à-vis inventive step.

- 3). The current application is novel vis-à-vis (A) and (B) on account of the lack of an amide linkage. The current application appears to be anticipated by (C)-(E) and (G). The current application is novel vis-à-vis (F) on account of the Ar² group.
- 4). The current application describes compounds which are orexin antagonists. None of (C)-(G) describe such an activity. Accordingly those claimed compounds which actually are orexin antagonists are inventive.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB02/02042

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It is, however, not credible that essentially all of the claimed matter solves the given problem. The expressions in the claims "optionally substituted", "heteroaryl", "heteroaromatic", "aryl" and derivatives thereof are non-limitative and are therefore not regarded as obvious modifications or equivalents of the examples which have been given in the description. Accordingly, the said expressions should be restricted in this respect to the particular meanings specified in the description e.g. page 4 and 5 (Article 6 PCT). Note that the list of optional substituents on page 5, line 28 currently only says "includes" which is not limitative.

- 5). Claim 9 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1 (iv) PCT. Consequently, no opinion is formulated with respect to the industrial applicability of the subject matter of this claim (Article 34(4)(a)(i)PCT). The precise scope of claim 9 is in any case not clear since the diseases or disorders are only defined by means of a functional definition.
- 6). Claim 2 lacks a reference to claim 1.
- 7). X in formula (I) should read NR.
- 8). In the table on page 86 X should presumably be Y.
- 9). Claim 7 refers to the description and is therefore not allowable.
- 10). The prior art documents (A)-(G) are not cited (Rule 5.1 (a) (ii) PCT).

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 02/02042

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D417/14 A61K31/445 C07D413/12 C07D413/14 C07D401/12
A61K31/505 C07D471/04 A61K31/5377 C07D401/14 C07D498/04
C07D403/14 A61P25/20 A61P9/10 A61P3/04

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

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

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

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 12077 A (SQUIBB BRISTOL MYERS CO) 9 March 2000 (2000-03-09) claim 5; examples 212,266,267,317	1,2
E	WO 02 44172 A (BRANCH CLIVE LESLIE ;JOHNSON CHRISTOPHER NORBERT (GB); SMITH ALEXA) 6 June 2002 (2002-06-06) claim 1	1,2
P,A	WO 01 96302 A (BRANCH CLIVE LESLIE ;JOHNSON CHRISTOPHER NORBERT (GB); THEWLIS KEV) 20 December 2001 (2001-12-20)	
X	WO 00 08015 A (APPLIED RESEARCH SYSTEMS ;BUCKLER DAVID (US); EL TAYER NABIL (US);) 17 February 2000 (2000-02-17) XXI on page 14. claim 4	1,2

	-/--	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

30 July 2002

Date of mailing of the international search report

21/08/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Gettins, M

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/02042

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 01 40231 A (SQUIBB BRISTOL MYERS CO ;VACCARO WAYNE (US); YAN LIN (US); ATWAL K) 7 June 2001 (2001-06-07) page 91; example 219 ---	1,2
X	MORI, MIWAKO ET AL: "New synthesis of pyrrolo-1,4-benzodiazepines by utilizing palladium-catalyzed carbonylation" CHEM. PHARM. BULL. (1984), vol. 32, no. 10, pages 3840-3847, XP001095476 Table I on page 3843 compound 17 where R is PhCO. ---	1,2
A	DEFOIN, ALBERT ET AL: "Asymmetric Diels-Alder cycloadditions with chiral carbamoyl dienophiles" HELV. CHIM. ACTA (1992), 75(1), 109-23 , XP001094556 example 16C -----	1,2

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 02/02042

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.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim9 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 8.4(a).

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

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

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

Remark on Protest

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

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 02 02042

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I.2

Present claims 1 and 3-9 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds where (referring to formula (I)) where M is 1; X is NR and p is 0. This is slightly larger than claim 2 due to having NR instead of NH. It is noted that this covers all of the examples.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No
PCT/GB 02/02042

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0012077	A	09-03-2000	AU 5675399 A EP 1109544 A1 WO 0012077 A1 US 6150356 A	21-03-2000 27-06-2001 09-03-2000 21-11-2000
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Folios 276, 277, 278, 279 ~~280~~
Extract Publications



2020
Bogotá, D.C.,

Doctor:
Carlos R. Olarte
Apoderado
SmithklineBeechamPLC.

Oficio N° 11429

ASUNTO:

Radicación N°	03-98005
Solicitud internacional	PCT/GB2002/02042
Fecha inicio fase nacional	05/12/2003
Trámite	011
Evento	379
Actuación	430
Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

☐ La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CRESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

26 DIC. 2003

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