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Delegatura de propiedad Industrial

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SOLICITUD

PATENTE DE INVENCIÓN

21 **EXPEDIENTE No.** 06-34461

54 **TÍTULO** DERIVADOS DE PIRROL CON ACTIVIDAD ANTIBACTERIANA

51 **CLASIFICACIÓN INTERNACIONAL** C07D 401/13, 401/14, 413/14, 417/14, 409/14, A61K 31/454, A61P 31/04

71 **SOLICITANTE** ASTRAZENECA AB

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(FORMA P-10)

55

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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL 13-04-2006

1 **SOLICITUD DE:**

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☒ Capítulo I. ☐ Capítulo II.

2 **SOLICITANTE (71)**	Nombre: ASTRAZENECA AB Dirección: S-1-51 85 Södertälje, Suecia Nacionalidad o Domicilio: Suecia Lugar de Constitución: Suecia Teléfono: Fax: E-mail	**IDENTIFICACION** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual____ Número ____
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4 **INVENTOR (ES) (72)**	Nombre: Alexander Louis BREEZE, Oluyinka Morenike GREEN, Kenneth Gregory HULL, Haihong NI, Sheila Irene HAUCK, George Byron MULLEN, Neil James HALES, David TIMMS Dirección: AstraZeneca R & D Alderley, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB); AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, Massachusetts 02451 (US); AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, Massachusetts 02451 (US); AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, Massachusetts 02451 (US); AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, Massachusetts 02451 (US); AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB); AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB) (Respectivamente) Nacionalidad o Domicilio: Reino Unido y Estados Unidos (Respectivamente)	

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

10 **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud. $463.000
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Fotocopia Autenticada
- [x] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar efectuado por la IPEA.
- [ ] Traducción del examen preliminar 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 12x12.
- [ ] 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.
- [x] Otros: Extracto para publicación y Tarjeta de Archivo Temático
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11 **FIGURA CARACTERÍSTICA:**

12 Solicito la concesión de la patente,

NOMBRE: JUAN PABLO CADENA SARMIENTO

FIRMA:

C.C. 80.410.337 de Usaquén T.P. 57492 del C.S.J.

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7 3

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(74) Agent: ASTRAZENECA; Global Intellectual Property, S-SE-151 85 Södertälje (SE).

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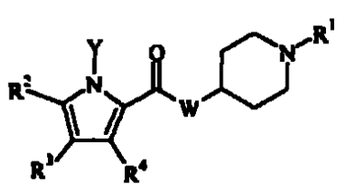
(54) Title: PYRROL DERIVATIVES WITH ANTIBACTERIAL ACTIVITY



(1)

(57) Abstract: Compounds of Formula (1) and their pharmaceutically acceptable salts are described: Formula (1) Processes for their preparation, pharmaceutical compositions containing them, their use as medicaments and their use in the treatment of bacterial infections are also described.

WO 2005/026149 A1

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

PYRROL DERIVATIVES WITH ANTIBACTERIAL ACTIVITY

The present invention relates to compounds which demonstrate antibacterial activity, processes for their preparation, pharmaceutical compositions containing them as the active ingredient, to their use as medicaments and to their use in the manufacture of medicaments for use in the treatment of bacterial infections in warm-blooded animals such as humans. In particular this invention relates to compounds useful for the treatment of bacterial infections in warm-blooded animals such as humans, more particularly to the use of these compounds in the manufacture of medicaments for use in the treatment of bacterial infections in warm-blooded animals such as humans.

The international microbiological community continues to express serious concern that the evolution of antibiotic resistance could result in strains against which currently available antibacterial agents will be ineffective. In general, bacterial pathogens may be classified as either Gram-positive or Gram-negative pathogens. Antibiotic compounds with effective activity against both Gram-positive and Gram-negative pathogens are generally regarded as having a broad spectrum of activity. The compounds of the present invention are regarded as effective against both Gram-positive and certain Gram-negative pathogens.

Gram-positive pathogens, for example Staphylococci, Enterococci, Streptococci and mycobacteria, are particularly important because of the development of resistant strains which are both difficult to treat and difficult to eradicate from the hospital environment once established. Examples of such strains are methicillin resistant *staphylococcus aureus* (MRSA), methicillin resistant coagulase negative staphylococci (MRCNS), penicillin resistant *Streptococcus pneumoniae* and multiple resistant *Enterococcus faecium*.

The preferred clinically effective antibiotic for treatment of last resort of such resistant Gram-positive pathogens is vancomycin. Vancomycin is a glycopeptide and is associated with various toxicities, including nephrotoxicity. Furthermore, and most importantly, antibacterial resistance to vancomycin and other glycopeptides is also appearing. This resistance is increasing at a steady rate rendering these agents less and less effective in the treatment of Gram-positive pathogens. There is also now increasing resistance appearing towards agents such as β-lactams, quinolones and macrolides used for the treatment of upper respiratory tract infections, also caused by certain Gram negative strains including *H.influenzae* and *M.catarrhalis*.

Consequently, in order to overcome the threat of widespread multi-drug resistant organisms, there is an on-going need to develop new antibiotics, particularly those with either a novel mechanism of action and/or containing new pharmacophoric groups.

Deoxyribonucleic acid (DNA) gyrase is a member of the type II family of topoisomerases that control the topological state of DNA in cells (Champoux, J. J.; 2001. Ann. Rev. Biochem. 70: 369-413). Type II topoisomerases use the free energy from adenosine triphosphate (ATP) hydrolysis to alter the topology of DNA by introducing transient double-stranded breaks in the DNA, catalyzing strand passage through the break and resealing the DNA. DNA gyrase is an essential and conserved enzyme in bacteria and is unique among topoisomerases in its ability to introduce negative supercoils into DNA. The enzyme consists of two subunits, encoded by *gyrA* and *gyrB*, forming an A_2B_2 tetrameric complex. The A subunit of gyrase (GyrA) is involved in DNA breakage and resealing and contains a conserved tyrosine residue that forms the transient covalent link to DNA during strand passage. The B subunit (GyrB) catalyzes the hydrolysis of ATP and interacts with the A subunit to translate the free energy from hydrolysis to the conformational change in the enzyme that enables strand-passage and DNA resealing.

Another conserved and essential type II topoisomerase in bacteria, called topoisomerase IV, is primarily responsible for separating the linked closed circular bacterial chromosomes produced in replication. This enzyme is closely related to DNA gyrase and has a similar tetrameric structure formed from subunits homologous to Gyr A and to Gyr B. The overall sequence identity between gyrase and topoisomerase IV in different bacterial species is high. Therefore, compounds that target bacterial type II topoisomerases have the potential to inhibit two targets in cells, DNA gyrase and topoisomerase IV; as is the case for existing quinolone antibacterials (Maxwell, A. 1997, Trends Microbiol. 5: 102-109).

DNA gyrase is a well-validated target of antibacterials, including the quinolones and the coumarins. The quinolones (*e.g.* ciprofloxacin) are broad-spectrum antibacterials that inhibit the DNA breakage and reunion activity of the enzyme and trap the GyrA subunit covalently complexed with DNA (Drlica, K., and X. Zhao, 1997, Microbiol. Molec. Biol. Rev. 61: 377-392). Members of this class of antibacterials may also inhibit topoisomerase IV and as a result, the primary target of these compounds varies among species. Although the quinolones are successful antibacterials, resistance generated primarily by mutations in the target (DNA gyrase and topoisomerase IV) is becoming an increasing problem in several organisms, including *S. aureus* and *Streptococcus pneumoniae* (Hooper, D. C., 2002, The

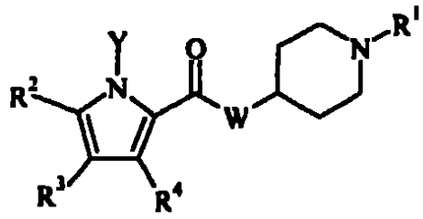
Lancet Infectious Diseases 2: 530-538). In addition, quinolones, as a chemical class, suffer from toxic side effects, including arthropathy that prevents their use in children (Lipsky, B. A. and Baker, C. A., 1999, Clin. Infect. Dis. 28: 352-364). Furthermore, the potential for cardiotoxicity, as predicted by prolongation of the QT_c interval, has been cited as a toxicity concern for quinolones.

There are several known natural product inhibitors of DNA gyrase that compete with ATP for binding the GyrB subunit (Maxwell, A. and Lawson, D.M. 2003, Curr. Topics in Med. Chem. 3: 283-303). The coumarins are natural products isolated from *Streptomyces spp.*, examples of which are novobiocin, clorobiocin and coumermycin A1. Although these compounds are potent inhibitors of DNA gyrase, their therapeutic utility is limited due to toxicity in eukaryotes and poor penetration in Gram-negative bacteria (Maxwell, A. 1997, Trends Microbiol. 5: 102-109). Another natural product class of compounds that targets the GyrB subunit is the cyclothialidines, which are isolated from *Streptomyces filipensis* (Watanabe, J. et al 1994, J. *Antibiot.* 47: 32-36). Despite potent activity against DNA gyrase, cyclothialidine is a poor antibacterial agent showing activity only against some eubacterial species (Nakada, N. 1993, *Antimicrob. Agents Chemother.* 37: 2656-2661).

Synthetic inhibitors that target the B subunit of DNA gyrase are known in the art. For example, coumarin-containing compounds are described in patent application number WO 99/35155, 5,6-bicyclic heteroaromatic compounds are described in patent application WO 02/060879, and pyrazole compounds are described in patent application WO 01/52845 (US patent US6,608.087).

We have discovered a new class of compounds which are useful for inhibiting DNA gyrase.

Therefore the current invention provides a compound of the formula (1) or a pharmaceutically acceptable salt thereof;



(1)

wherein:

W is O or NR^5;

Y is hydrogen;

R^1 is selected from R^1a, R^1b, R^1c, R^1d, R^1e and R^1f;

R^1a is a 4 to 7 membered saturated, partially unsaturated or unsaturated heterocyclic ring containing 1, 2, 3, or 4 heteroatoms independently selected from O, S and N (provided that such a ring does not contain O-O or S-S bonds), wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-, a ring sulphur atom may be optionally oxidised to form the S-oxide(s), and a ring nitrogen atom may be optionally oxidised to form the N-oxide, and wherein said ring may be optionally substituted by 1, 2 or 3 substituents independently selected from: nitro, cyano, sulfo, formyl, hydroxyiminomethyl, (2-6C)alkenyl, (2-6C)alkynyl, -CO(1-6C)alkyl, -COO(1-6C)alkyl (optionally substituted with -COO(1-6C)alkyl), trifluoromethyl, $-CONR^6R^7$, $-OCONR^6R^7$, $-N(R^7)COR^6$, $-CONHCH(CO_2R^7)R^6$, halo, hydroxy, carboxy, (1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo, cyano, nitro, -COO(1-6C)alkyl, -OCO(1-4C)alkyl, (1-6C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(1-4C)alkoxy-, (2-4C)alkenyloxy, trifluoromethyl, $-CONR^6R^7$, carboxy, -NHC(O)O(1-4C)alkyl, $-OCONR^6R^7$, $-C(=NOH)(1-4C)alkyl$, $-C(=NOH)NR^6R^7$, $-NHC(=NH)NR^6R^7$, $-NHC(O)NR^6R^7$, -NHC(O)(1-4C)alkyl, -NHC(O)heterocyclyl, -NHC(O)aryl, -NHS(O)p(1-4C)alkyl, -S(O)p(1-4C)alkyl, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$, and heterocyclyl], (3-6C)cycloalkyl (optionally substituted by 1 or 2 substituents selected from (1-6C)alkyl and the optional substituents described for (1-6C)alkyl hereinbefore), -O(1-6C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), -S(O)p(1-4C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), heterocyclyl, aryl, -NHC(O)O(1-4C)alkyl, $-C(=NOR^7)(1-4C)alkyl$, $-C(=NOR^7)NR^6R^7$, $-S(O)pNR^6R^7$, $-S(O)p(1-4C)alkylCONHR^7$, $-NR^7S(O)pNR^6R^7$, $-NR^7S(O)p(1-4C)alkyl$, $-NR^7S(O)p$-aryl, $-C(O)NHS(O)p(1-4C)alkyl$, -C(O)NHS(O)p-aryl, $-NR^6R^7$, $-CH_2CH(CO_2R^6)OH$, $-(1-4C)alkylCH(NR^6R^7)CO_2R^6$ and $-(1-4C)alkylCH(NR^6R^7)CO(NR^6R^7)$;

wherein any aryl or heterocyclyl group in any of the preceding values for substituents on R^1a may optionally be substituted by 1 or 2 substituents independently selected from (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, hydroxy, (1-4C)alkoxy, halo, cyano, nitro, carboxy, hydroxy(1-4C)alkyl-, (1-4C)alkoxy(1-4C)alkyl-, halo(1-4C)alkyl-, difluoromethyl, trifluoromethyl, trifluoromethoxy, formyl, -CO(1-4C)alkyl, -COO(1-4C)alkyl, $-C(O)NH_2$, -C(O)NH(1-4C)alkyl, -C(O)N[di(1-4C)alkyl], $-S(O)_2NH_2$, $-S(O)_2NH(1-4C)alkyl$ and $-S(O)_2N[di(1-4C)alkyl]$;

R^1b is an 8-10 membered bicyclic heterocyclic ring containing 1, 2, 3, or 4 heteroatoms independently selected from O, S and N (provided that such a ring does not contain O-O or S-S bonds), wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-, a ring sulphur atom may be optionally oxidised to form the S-oxide(s), and a ring nitrogen atom may be optionally oxidised to form the N-oxide, and wherein said ring may be optionally substituted by 1, 2 or 3 substituents independently selected from the substituents listed for R^1a above;

R^1c is a phenyl ring, substituted by 1, 2 or 3 substituents independently selected from the substituents listed for R^1a above;

R^1d is selected from $-CH_2R^1a$, $-C(O)R^1a$, $-OR^1a$, $S(O)qR^1a$ (wherein q is 1 or 2);

R^1e is selected from $-CH_2R^1b$, $-C(O)R^1b$, $-OR^1b$, $S(O)qR^1b$ (wherein q is 1 or 2);

R^1f is selected from $-CH_2R^1c$, $-C(O)R^1c$ $-OR^1c$, $S(O)qR^1c$ (wherein q is 1 or 2);

R^2 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, (2-4C)alkenyl, (2-4C)alkynyl, halo, cyano, fluoromethyl, difluoromethyl and trifluoromethyl;

R^3 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, (2-4C)alkenyl, (2-4C)alkynyl, halo, hydroxy, cyano, fluoromethyl, difluoromethyl trifluoromethyl, -CO(1-6C)alkyl, and (1-6C)alkoxy;

R^4 is selected from hydrogen, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, nitro, hydroxy, halo, cyano, (3-6C)cycloalkyl, -(1-6C)alkyl(3-6C)cycloalkyl, halo(1-4C)alkyl-, difluoromethyl, trifluoromethyl, -CO(1-6C)alkyl, and (1-6C)alkoxy;

R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-4C)alkenyl, (3-6C)cycloalkyl, -(1-4C)alkylC(O)O(1-4C)alkyl, hydroxy, amino, -NH(1-4C)alkyl, -N[di(1-4C)alkyl], (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy(1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl-, (1-4C)alkylthio(1-4C)alkyl-, hydroxy(1-4C)alkyl-, -(1-4C)alkylNH_2, -(1-4C)alkylNH(1-4C)alkyl, -(1-4C)alkylN[di(1-4C)alkyl], and -(1-4C)alkylheterocyclyl;

R^7 is independently at each occurrence selected from hydrogen and (1-6C)alkyl;

or R^6 and R^7 may together with the nitrogen to which they are attached form a 5 or 6-membered heterocyclyl ring, optionally substituted with 1 or 2 substituents independently selected from (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, hydroxy, (1-4C)alkoxy, halo, cyano, nitro, carboxy, hydroxy(1-4C)alkyl-, (1-4C)alkoxy(1-4C)alkyl-, halo(1-4C)alkyl-, difluoromethyl, trifluoromethyl, trifluoromethoxy, formyl, -CO(1-4C)alkyl, -COO(1-4C)alkyl, $-C(O)NH_2$, -C(O)NH(1-4C)alkyl, -C(O)N[di(1-4C)alkyl], $-S(O)_2NH_2$, $-S(O)_2$NH(1-4C)alkyl, $-S(O)_2$N[di(1-4C)alkyl] and -S(O)p(1-4C)alkyl;

R^5 is selected from hydrogen and (1-4C)alkyl;

p is (independently at each occurrence) 0, 1 or 2.

In a further aspect of the invention there is provided a compound of the formula (1) or a pharmaceutically-acceptable salt thereof, wherein:

W is O or NR^5;

Y is hydrogen or methyl;

R^1 is selected from R^1a, R^1b, R^1c, R^1d, R^1e and R^1f;

R^1a is a 4 to 7 membered saturated, partially unsaturated or unsaturated heterocyclic ring containing 1, 2, 3, or 4 heteroatoms independently selected from O, S and N (provided that such a ring does not contain O-O or S-S bonds), wherein said ring is substituted by 1, 2 or 3 substituents independently selected from:

nitro, cyano, (2-6C)alkenyl, (2-6C)alkynyl, -CO(1-6C)alkyl, -COO(1-6C)alkyl, -O(1-6C)alkyl, trifluoromethyl, $-CONR^6R^7$, $-OCONR^6R^7$, $-N(R^7)COR^6$, $-CONHCH(CO_2R^7)R^6$, halo, hydroxy, carboxy,

(1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo, cyano, nitro, -COO(1-6C)alkyl, -O(1-6C)alkyl, trifluoromethyl, $-CONR^6R^7$, carboxy, -NHC(O)O(1-4C)alkyl, -C(=NOH)(1-4C)alkyl, $-C(=NOH)NR^6R^7$, -S(O)p(1-4C)alkyl, $-S(O)pNR^6R^7$, $-NR^6R^7$, and heterocyclyl {optionally substituted by 1 or 2 substituents independently selected from (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, hydroxy, (1-4C)alkoxy, halo, cyano, nitro, carboxy, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, formyl, -CO(1-4C)alkyl, -COO(1-4C)alkyl, $-C(O)NH_2$, -C(O)NH(1-4C)alkyl, -C(O)N[di(1-4C)alkyl], $-S(O)_2NH_2$, $-S(O)_2NH(1-4C)alkyl$, $-S(O)_2N[di(1-4C)alkyl]$ and -S(O)p(1-4C)alkyl}],

heterocyclyl [optionally substituted by 1 or 2 substituents independently selected from (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, hydroxy, (1-4C)alkoxy, halo, cyano, nitro, carboxy, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, formyl, -CO(1-4C)alkyl, -COO(1-4C)alkyl, $-C(O)NH_2$, -C(O)NH(1-4C)alkyl, -C(O)N[di(1-4C)alkyl], $-S(O)_2NH_2$, $-S(O)_2NH(1-4C)alkyl$, $-S(O)_2N[di(1-4C)alkyl]$ and -S(O)p(1-4C)alkyl],

aryl [optionally substituted by 1 or 2 substituents independently selected from (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, hydroxy, (1-4C)alkoxy, halo, cyano, nitro, carboxy, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, halo(1-4C)alkyl, difluoromethyl,

trifluoromethyl, trifluoromethoxy, formyl, -CO(1-4C)alkyl, -COO(1-4C)alkyl, -C(O)NH_2, -C(O)NH(1-4C)alkyl, -C(O)N[di(1-4C)alkyl], -S(O)$_2NH_2$, -S(O)$_2$NH(1-4C)alkyl, -S(O)$_2$N[di(1-4C)alkyl] and -S(O)p(1-4C)alkyl], -NHC(O)O(1-4C)alkyl, -C(=NOR^7)(1-4C)alkyl, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alkyl (optionally substituted by hydroxy), -S(O)pNR^{6}R^7, -S(O)p(1-4C)alkylCONHR^7, -NR^{7}S(O)pNR^{6}R^7, -NR^{7}S(O)p(1-4C)alkyl, -NR^{7}S(O)p-aryl, -C(O)NHS(O)p(1-4C)alkyl, -C(O)NHS(O)p-aryl, -NR^{6}R^7, -CH_2CH(CO_2R^6)OH, -(1-4C)alkylCH(NR^{6}R^7)CO_2R^6, and -(1-4C)alkylCH(NR^{6}R^7)CO(NR^{6}R^7);

R^{1}b is an 8-10 membered bicyclic heterocyclic ring containing 1, 2, 3, or 4 heteroatoms independently selected from O, S and N (provided that such a ring does not contain O-O or S-S bonds), wherein said ring is substituted by 1, 2 or 3 substituents independently selected from the substituents listed for R^{1}a above;

R^{1}c is a phenyl ring, substituted by 1, 2 or 3 substituents independently selected from the substituents listed for R^{1}a above;

R^{1}d is selected from -CH_2R^{1}a, -C(O)R^{1}a, -OR^{1}a, S(O)qR^{1}a (wherein q is 1 or 2);

R^{1}e is selected from -CH_2R^{1}b, -C(O)R^{1}b, -OR^{1}b, S(O)qR^{1}b (wherein q is 1 or 2);

R^{1}f is selected from -CH_2R^{1}c, -C(O)R^{1}c -OR^{1}c, S(O)qR^{1}c (wherein q is 1 or 2);

R^2 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, (2-4C)alkenyl, (2-4C)alkynyl, halo, fluoromethyl, difluoromethyl and trifluoromethyl;

R^3 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, (2-4C)alkenyl, (2-4C)alkynyl, halo, hydroxy, cyano, fluoromethyl, difluoromethyl trifluoromethyl, -CO(1-6C)alkyl, and (1-6C)alkoxy;

R^4 is selected from hydrogen, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, nitro, hydroxy, halo, cyano, (3-6C)cycloalkyl, -(1-6C)alkyl(3-6C)cycloalkyl, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl, -CO(1-6C)alkyl, and (1-6C)alkoxy;

R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-6C)cycloalkyl, -(1-4C)alkylC(O)O(1-4C)alkyl, hydroxy, amino, (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy(1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylthio(1-4C)alkyl, hydroxy(1-4C)alkyl, -(1-4C)alkylNH_2, -(1-4C)alkylNH(1-4C)alkyl, -(1-4C)alkylN[di(1-4C)alkyl], and -(1-4C)alkylheterocyclyl;

R^7 is independently at each occurrence selected from hydrogen and (1-6C)alkyl;

or R^6 and R^7 may together form a 5 or 6-membered heterocyclyl ring, optionally substituted with 1 or 2 substituents independently selected from (1-4C)alkyl, (2-4C)alkenyl,

(2-4C)alkynyl, hydroxy, (1-4C)alkoxy, halo, cyano, nitro, carboxy, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, formyl, -CO(1-4C)alkyl, -COO(1-4C)alkyl, -C(O)NH_2, -C(O)NH(1-4C)alkyl, -C(O)N[di(1-4C)alkyl], -S(O)$_2NH_2$, -S(O)$_2$NH(1-4C)alkyl, -S(O)$_2$N[di(1-4C)alkyl] and -S(O)p(1-4C)alkyl;

R^5 is selected from hydrogen and (1-4C)alkyl;

p is (independently at each occurrence) 0, 1 or 2.

Therefore the current invention provides a compound of the formula (1) or a pharmaceutically acceptable salt thereof; wherein:

W is O or NR^5;

Y is hydrogen;

R^1 is selected from R^1a, R^1b, R^1c, R^1d, R^1e and R^1f;

R^1a is a 4 to 7 membered saturated, partially unsaturated or unsaturated heterocyclic ring containing 1, 2, 3, or 4 heteroatoms independently selected from O, S and N (provided that such a ring does not contain O-O or S-S bonds), wherein said ring is substituted by 1, 2 or 3 substituents independently selected from:

nitro, cyano, (2-6C)alkenyl, (2-6C)alkynyl, -CO(1-6C)alkyl, -COO(1-6C)alkyl (optionally substituted with -COO(1-6C)alkyl), trifluoromethyl, -CONR^{6}R^7, -OCONR^{6}R^7, -N(R^7)COR^6, -CONHCH(CO$_2$R^7)R^6, halo, hydroxy, carboxy,

(1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo, cyano, nitro, -COO(1-6C)alkyl, -OCO(1-4C)alkyl, (1-6C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(1-4C)alkoxy, (2-4C)alkenyloxy, trifluoromethyl, -CONR^{6}R^7, carboxy, -NHC(O)O(1-4C)alkyl, -OCONR^{6}R^7, -C(=NOH)(1-4C)alkyl, -C(=NOH)NR^{6}R^7, -S(O)p(1-4C)alkyl, -S(O)pNR^{6}R^7, -NHSO$_2$R^6, -NR^{6}R^7, and heterocyclyl],

(3-6C)cycloalkyl (optionally substituted by 1 or 2 substituents selected from (1-6C)alkyl and the optional substituents described for (1-6C)alkyl hereinbefore), -O(1-6C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), -S(O)p(1-4C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), heterocyclyl, aryl, -NHC(O)O(1-4C)alkyl, -C(=NOR^7)(1-4C)alkyl, -C(=NOR^7)NR^{6}R^7, -S(O)pNR^{6}R^7, -S(O)p(1-4C)alkylCONHR^7, -NR^{7}S(O)pNR^{6}R^7, -NR^{7}S(O)p(1-4C)alkyl, -NR^{7}S(O)p-aryl, -C(O)NHS(O)p(1-4C)alkyl, -C(O)NHS(O)p-aryl, -NR^{6}R^7, -CH$_2$CH(CO$_2$R^6)OH, -(1-4C)alkylCH(NR^{6}R^7)CO$_2$R^6 and -(1-4C)alkylCH(NR^{6}R^7)CO(NR^{6}R^7);

wherein any aryl or heterocyclyl group in any of the preceding values for substituents on R^1a may optionally be substituted by 1 or 2 substituents independently selected from (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, hydroxy, (1-4C)alkoxy, halo, cyano, nitro, carboxy, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, formyl, -CO(1-4C)alkyl, -COO(1-4C)alkyl, $-C(O)NH_2$, -C(O)NH(1-4C)alkyl, -C(O)N[di(1-4C)alkyl], $-S(O)_2NH_2$, $-S(O)_2NH(1-4C)alkyl$ and $-S(O)_2N[di(1-4C)alkyl]$;

R^1b is an 8-10 membered bicyclic heterocyclic ring containing 1, 2, 3, or 4 heteroatoms independently selected from O, S and N (provided that such a ring does not contain O-O or S-S bonds), wherein said ring is substituted by 1, 2 or 3 substituents independently selected from the substituents listed for R^1a above;

R^1c is a phenyl ring, substituted by 1, 2 or 3 substituents independently selected from the substituents listed for R^1a above;

R^1d is selected from $-CH_2R^1a$, $-C(O)R^1a$, $-OR^1a$, $S(O)qR^1a$ (wherein q is 1 or 2);

R^1e is selected from $-CH_2R^1b$, $-C(O)R^1b$, $-OR^1b$, $S(O)qR^1b$ (wherein q is 1 or 2);

R^1f is selected from $-CH_2R^1c$, $-C(O)R^1c$ $-OR^1c$, $S(O)qR^1c$ (wherein q is 1 or 2);

R^2 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, (2-4C)alkenyl, (2-4C)alkynyl, halo, fluoromethyl, difluoromethyl and trifluoromethyl;

R^3 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, (2-4C)alkenyl, (2-4C)alkynyl, halo, hydroxy, cyano, fluoromethyl, difluoromethyl trifluoromethyl, -CO(1-6C)alkyl, and (1-6C)alkoxy;

R^4 is selected from hydrogen, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, nitro, hydroxy, halo, cyano, (3-6C)cycloalkyl, -(1-6C)alkyl(3-6C)cycloalkyl, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl, -CO(1-6C)alkyl, and (1-6C)alkoxy;

R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-4C)alkenyl, (3-6C)cycloalkyl, -(1-4C)alkylC(O)O(1-4C)alkyl, hydroxy, amino, -NH(1-4C)alkyl, -N[di(1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy(1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylthio(1-4C)alkyl, hydroxy(1-4C)alkyl, $-(1-4C)alkylNH_2$, -(1-4C)alkylNH(1-4C)alkyl, -(1-4C)alkylN[di(1-4C)alkyl], and -(1-4C)alkylheterocyclyl;

R^7 is independently at each occurrence selected from hydrogen and (1-6C)alkyl;

or R^6 and R^7 may together with the nitrogen to which they are attached form a 5 or 6-membered heterocyclyl ring, optionally substituted with 1 or 2 substituents independently

selected from (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, hydroxy, (1-4C)alkoxy, halo, cyano, nitro, carboxy, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, formyl, -CO(1-4C)alkyl, -COO(1-4C)alkyl, -C(O)NH_2, -C(O)NH(1-4C)alkyl, -C(O)N[di(1-4C)alkyl], -$S(O)_2NH_2$, -$S(O)_2$NH(1-4C)alkyl, -$S(O)_2$N[di(1-4C)alkyl] and -S(O)p(1-4C)alkyl;

R^5 is selected from hydrogen and (1-4C)alkyl;

p is (independently at each occurrence) 0, 1 or 2.

In this specification the term alkyl includes both straight and branched chain alkyl groups but references to individual alkyl groups such as propyl are specific for the straight chain version only. An analogous convention applies to other generic terms. Unless otherwise stated the term alkyl advantageously refers to chains with 1-6 carbon atoms, preferably 1-4 carbon atoms. In this specification, the terms alkenyl, alkynyl and cycloalkenyl include all positional and geometrical isomers.

In this specification the term alkoxy means an alkyl group as defined hereinbefore linked to an oxygen atom.

Where optional substituents are chosen from 0, 1, 2 or 3 groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups. An analogous convention applies to substituents chose from 0, 1 or 2 groups; 1, 2 or 3 substituents; and 1 or 2 groups.

It is to be understood that where substituents contain two substituents on an alkyl chain, in which both are linked by a heteroatom (for example two alkoxy substituents), then these two substituents are not substituents on the same carbon atom of the alkyl chain. It will be understood that unstable compounds are not contemplated as part of this invention.

There follow particular and suitable values for certain substituents and groups referred to in this specification. These values may be used where appropriate with any of the definitions and embodiments disclosed hereinbefore, or hereinafter. For the avoidance of doubt each stated species represents a particular and independent aspect of this invention.

Where "R^6 and R^7 may together with the nitrogen to which they are attached form a 5 or 6-membered heterocyclyl ring" said "5 or 6-membered heterocyclyl ring" is a saturated, partially saturated or fully unsaturated, monocyclic ring one atom of which is the nitrogen atom to which R^6 and R^7 are attached, and the other atoms are either all carbon atoms or they are carbon atoms and 1, 2 or 3 heteroatoms chosen from nitrogen, sulphur or oxygen,

wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-, and a ring nitrogen atom or a ring sulphur atom may be optionally oxidised to form the N- and / or S-oxide(s). Examples and suitable values of "R^6 and R^7 may together with the nitrogen to which they are attached form a 5 or 6-membered heterocyclyl ring" are piperazinyl and morpholino.

Particular examples of "4 to 7 membered saturated, partially unsaturated or unsaturated heterocyclic ring containing 1, 2, 3, or 4 heteroatoms independently selected from O, S and N (provided that such a ring does not contain O-O or S-S bonds), wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-, a ring sulphur atom may be optionally oxidised to form the S-oxide(s), and a ring nitrogen atom may be optionally oxidised to form the N-oxide" include pyridinyl, *N*-oxopyridinyl, pyrimidinyl, thiazolyl, thiadiazolyl, tetrazolyl, imidazolyl, triazinyl, pyrrolidinyl, thienyl, furanyl, oxadiazolyl, isoxazolyl, oxazolyl and pyrrolyl.

Particular examples of an "8-10 membered bicyclic heterocyclic ring containing 1, 2, 3, or 4 heteroatoms independently selected from O, S and N (provided that such a ring does not contain O-O or S-S bonds), wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-, a ring sulphur atom may be optionally oxidised to form the S-oxide(s), and a ring nitrogen atom may be optionally oxidised to form the N-oxide" include quinolinyl, purinyl, benzothiazolyl, indolyl, 4-oxoquinolinyl, 2,7-naphthyridinyl and quinazolinyl.

Heterocyclyl is a saturated, partially saturated or unsaturated, optionally substituted monocyclic ring containing 5 to 7 atoms of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-, a ring sulphur atom may be optionally oxidised to form the S-oxide(s), and a ring nitrogen atom may be optionally oxidised to form the N-oxide. Examples and suitable values of the term heterocyclyl are morpholino, morpholinyl, piperidino, piperidyl, pyridyl, pyridyl-N-oxide, pyranyl, pyrrolyl, imidazolyl, thiazolyl, thienyl, dioxolanyl, thiadiazolyl, piperazinyl, isothiazolidinyl, triazolyl, tetrazolyl, pyrrolidinyl, 2-oxazolidinonyl, 5-isoxazolonyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, 3-oxopyrazolin-5-yl, tetrahydropyranyl, tetrahydrothiopyranyl, 1-oxotetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolinyl, isoxazolyl, 4-oxopydridyl, 2-oxopyrrolidyl, 4-oxothiazolidyl, furyl, thienyl, oxazolyl, oxadiazolyl, 2-[(5-oxo)-1-oxa-3,4-diazolyl] and 3-[oxa-2,4-diazolyl].

Suitably a heterocyclyl is morpholino, morpholinyl, piperidino, piperidyl, pyridyl, pyranyl, pyrrolyl, imidazolyl, thiazolyl, thienyl, thiadiazolyl, piperazinyl, isothiazolidinyl, 1,3,4-triazolyl, tetrazolyl, pyrrolidinyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolinyl, isoxazolyl, 4-oxopydridyl, 2-oxopyrrolidyl, 4-oxothiazolidyl, furyl, thienyl, oxazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl 2-[(5-oxo)-1-oxa-3,4-diazolyl] and 3-[oxa-2,4-diazolyl].

Conveniently heterocyclyl is oxazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, 2-[(5-oxo)-1-oxa-3,4-diazolyl], 3-[oxa-2,4-diazolyl], tetrazolyl, thiazolyl, thiadiazolyl, pyridyl, imidazolyl, furyl, thienyl, morpholine, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolinyl, and piperazinyl.

Suitable optional substituents for heterocyclyl as a saturated or partially saturated ring are, unless otherwise defined, 1, 2 or 3 substituents independently selected from halo, cyano, hydroxy, (1-4C)alkyl, (1-4C)alkoxy and (1-4C)alkylS(O)$_b$ (wherein b is 0, 1 or 2). Further suitable substituents for "heterocyclyl" as a saturated or partially saturated ring are 1, 2 or 3 substituents independently selected from fluoro, chloro, cyano, hydroxy, methyl, ethyl, methoxy, methylthio, methylsulfinyl and methylsulfonyl.

Suitable optional substituents for heterocyclyl as an unsaturated ring are, unless otherwise defined, 1, 2 or 3 substituents independently selected from halo, cyano, nitro, amino, hydroxy, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylS(O)$_b$ (wherein b is 0, 1 or 2), *N*-((1-4C)alkyl)amino and *N*,*N*-((1-4C)alkyl)$_2$amino. Further suitable optional substituents for "heterocyclyl" as an unsaturated ring are 1, 2 or 3 substituents independently selected from fluoro, chloro, cyano, nitro, amino, methylamino, dimethylamino, hydroxy, methyl, ethyl, methoxy, methylthio, methylsulfinyl and methylsulfonyl.

For the avoidance of doubt, optional substituents on heterocyclyl groups are generally substituents on carbon atoms of the ring, but may where appropriate be on an N atom, for example N-alkylpyridine.

Examples of (heterocyclyl)(1-4C)alkyl are morpholinomethyl, morpholinethyl, morpholinylmethyl, morpholinylethyl, piperidinomethyl, piperidinoethyl, piperidylmethyl, piperidylethyl, imidazolylmethyl, imidazolylethyl, tetrazolylmethyl, tetrazolylethyl, oxazolylmethyl, oxazolylethyl, 1,3,4-oxadiazolylmethyl, 1,2,4-oxadiazolylmethyl, 1,2,4-oxadiazolylethyl, pyridylmethyl, pyridylethyl, furylmethyl, furylethyl, (thienyl)methyl, (thienyl)ethyl, pyrazinylmethyl, pyrazinylethyl, piperazinylmethyl and piperazinylethyl.

Aryl is a partially saturated or unsaturated, mono or bicyclic carbon ring that contains 3-12 atoms; wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-. Particularly aryl is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. In another aspect aryl is a totally unsaturated ring. Suitable values for aryl include cyclopentenyl, cyclohexenyl, phenyl, naphthyl, indanyl or 1-oxoindanyl. Examples of aryl are optionally substituted phenyl and naphthyl.

Examples of aryl((1-4C))alkyl are benzyl, phenethyl, naphthylmethyl and naphthylethyl.

Examples of (1-4C)alkyl include methyl, ethyl, propyl, butyl, tert-butyl and isopropyl; examples of (1-6C)alkyl include (1-4C)alkyl, pentyl and hexyl; examples of (2-4C)alkenyl include vinyl, propenyl, allyl, but-2-enyl and but-3-enyl; examples of (3-4C)alkenyl include propenyl, allyl, but-2-enyl and but-3-enyl; examples of (2-6C)alkenyl include (2-4C)alkenyl, pent-2-enyl, pent-3-enyl, and hex-5-enyl; examples of (2-4C)alkynyl include ethynyl, prop-2-ynyl, but-2-ynyl and but-3-ynyl; examples of (2-6C)alkynyl include (2-4C)alkynyl, pent-3-ynyl and hex-4-ynyl; examples of (1-6C)alkoxy and -O(1-6C)alkyl include methoxy, ethoxy, propoxy, iso-propoxy, butoxy, tert-butoxy and pentoxy; examples of (1-4C)alkoxy include methoxy, ethoxy and propoxy; examples of (1-4C)alkoxy(1-4C)alkyl include methoxymethyl, ethoxymethyl, methoxyethyl and propoxymethyl; examples of (3-6C)cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; examples of -(1-6C)alkyl(3-6C)cycloalkyl include cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl; examples of halo groups include fluoro, chloro and bromo; examples of halo(1-4C)alkyl groups include fluoromethyl, fluoroethyl, chloromethyl, chloroethyl and bromomethyl; examples of hydroxy(1-4C)alkyl and hydroxy(1-6C)alkyl include hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 3-hydroxypropyl; examples of (1-4C)alkoxy-(1-4C)alkoxy and (1-6C)alkoxy-(1-6C)alkoxy include methoxymethoxy, 2-methoxyethoxy, 2-ethoxyethoxy and 3-methoxypropoxy; examples of (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxy include 2-(methoxymethoxy)ethoxy, 2-(2-methoxyethoxy)ethoxy; 3-(2-methoxyethoxy)propoxy and 2-(2-ethoxyethoxy)ethoxy; examples of (1-4C)alkyl$S(O)_p$- wherein p is 0, 1 or 2 include methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, methylsulfonyl and ethylsulfonyl; examples of (1-4C)alkylthio(1-4C)alkyl include methylthioethyl, methylthiomethyl, ethylthiomethyl, propylthiomethyl and propylthioethyl; examples of cyano(1-4C)alkyl include cyanomethyl, 1-cyanoethyl, 2-cyanoethyl and 3-cyanopropyl; examples of -CO(1-4C)alkyl include

methylcarbonyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl and tert-butylcarbonyl; examples of -CO(1-6C)alkyl include -CO(1-4C)alkyl and pentylcarbonyl; examples of -COO(1-4C)alkyl include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl and tert-butoxycarbonyl; examples of -COO(1-6C)alkyl include -COO(1-4C)alkyl and pentoxycarbonyl; examples of -OCO(1-4C)alkyl include methylcarbonyloxy, ethylcarbonyloxy, propylcarbonyloxy, isopropylcarbonyloxy and tert-butylcarbonyloxy; examples of -OCO(1-6C)alkyl include -OCO(1-4C)alkyl and pentylcarbonyloxy; examples of -(1-4C)alkylCOO(1-4C)alkyl include methoxycarbonylmethyl, ethoxycarbonylmethyl, methoxycarbonylethyl, propoxycarbonylmethyl, isopropoxycarbonylmethyl and tert-butoxycarbonylmethyl; examples of -NH(1-4C)alkyl include methylamino, ethylamino, propylamino and butylamino; examples of -N[di(1-4C)alkyl] include N,N-dimethylamino, N-methyl-N-ethylamino, N,N-diethylamino, and N,N-dipropylamino; examples of -(1-4C)alkylNH(1-4C)alkyl include methylaminomethyl, ethylaminomethyl, methylaminoethyl, propylaminomethyl and isopropylaminomethyl; examples of -(1-4C)alkylN[di(1-4C)alkyl] include N,N-dimethylaminomethyl, N,N-dimethylaminoethyl, N-methyl-N-ethylaminomethyl and dimethylaminopropyl; examples of -CONH(1-4C)alkyl include methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl, isopropylaminocarbonyl and tert-butylaminocarbonyl; examples of -CON[di(1-4C)alkyl] include N-dimethylaminocarbonyl and N-methyl-N-ethylaminocarbonyl; examples of $-S(O)_2NH(1-4C)alkyl$ include N-methylaminosulfonyl and N-ethylaminosulfonyl; examples of $-S(O)_2N[di(1-4C)alkyl]$ include N,N-dimethylaminosulfonyl, N,N-diethylaminosulfonyl and N-methyl-N-ethylaminosulfonyl; examples of -S(O)p(1-4C)alkyl include methylthio, methylsulfinyl, methylsulfonyl, ethylthio, propylthio, isopropylthio, ethylsulfinyl and ethylsulfonyl; examples of -NHC(O)(1-4C)alkyl include acetylamino and propionylamino; examples of -NHC(O)heterocyclyl include pyrimidin-2-ylcarbonylamino and piperazin-1-ylcarbonylamino; examples of -NHC(O)aryl include benzoylamino and naphth-3-ylcarbonylamino; examples of -NHS(O)p(1-4C)alkyl include mesylamino and isopropylsulphonylamino.

Within this specification composite terms are used to describe groups comprising more that one functionality such as $-(1-4C)alkylSO_2(1-4C)alkyl$. Such terms are to be interpreted in accordance with the meaning which is understood by a person skilled in the art for each component part. For example $-(1-4C)alkylSO_2(1-4C)alkyl$ includes

-methylsulphonylmethyl, -methylsulphonylethyl, -ethylsulphonylmethyl, and -propylsulphonylbutyl.

A compound of formula (I) may form stable acid or basic salts, and in such cases administration of a compound as a salt may be appropriate, and pharmaceutically acceptable salts may be made by conventional methods such as those described following.

Suitable pharmaceutically-acceptable salts include acid addition salts such as methanesulfonate, tosylate, α-glycerophosphate. fumarate, hydrochloride, citrate, maleate, tartrate and (less preferably) hydrobromide. Also suitable are salts formed with phosphoric and sulfuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, N-methylpiperidine, N-ethylpiperidine, procaine, dibenzylamine, N,N-dibenzylethylamine, tris-(2-hydroxyethyl)amine, N-methyl d-glucamine and amino acids such as lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically-acceptable salt is the sodium salt.

However, to facilitate isolation of the salt during preparation, salts which are less soluble in the chosen solvent may be preferred whether pharmaceutically-acceptable or not.

Within the present invention it is to be understood that a compound of the formula (I) or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which inhibits DNA gyrase and is not to be limited merely to any one tautomeric form utilised within the formulae drawings. The formulae drawings within this specification can represent only one of the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been possible to show graphically herein.

It will be appreciated by those skilled in the art that certain compounds of formula (I) contain an asymmetrically substituted carbon and/or sulphur atom, and accordingly may exist in, and be isolated in, optically-active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic or stereoisomeric form, or mixtures thereof, which form possesses properties useful in the inhibition of DNA gyrase, it being well known in the art how to prepare optically-active forms (for example, by resolution of the racemic form by

recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, by enzymatic resolution, by biotransformation, or by chromatographic separation using a chiral stationary phase) and how to determine efficacy for the inhibition of DNA gyrase by the standard tests described hereinafter.

It is also to be understood that certain compounds of the formula (I) and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which inhibit DNA gyrase.

As stated before, we have discovered a range of compounds that are good inhibitors of DNA gyrase. They have good physical and/or pharmacokinetic properties in general. The following compounds possess preferred pharmaceutical and/or physical and/or pharmacokinetic properties.

Particularly preferred compounds of the invention comprise a compound of formula (I), or a pharmaceutically-acceptable salt thereof, wherein the substituents W and R^1 to R^7 and other substituents mentioned above have values disclosed hereinbefore, or any of the following values (which may be used where appropriate with any of the definitions and embodiments disclosed hereinbefore or hereinafter):

In one embodiment of the invention are provided compounds of formula (I), in an alternative embodiment are provided pharmaceutically-acceptable salts of compounds of formula (I).

In one aspect of the invention, W is O. In another aspect, W is NR^5.

In one embodiment, R^1 is selected from R^1a.

In another embodiment, R^1 is selected from R^1b.

In another embodiment, R^1 is selected from R^1c.

In another embodiment, R^1 is selected from R^1d.

In another embodiment, R^1 is selected from R^1e.

In another embodiment, R^1 is selected from R^1f.

In one aspect R^1a is a 5 membered heterocyclic ring containing 1, 2, 3 or 4 heteroatoms independently selected from O, S and N (provided that such a ring does not contain any O-O or S-S bonds). In another aspect R^1a is a 5 membered heterocyclic ring containing 1, 2 or 3 heteroatoms independently selected from O, S and N (provided that such a ring does not contain any O-O or S-S bonds). In another aspect R^1a is a 5 membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, S and N

(provided that such a ring does not contain any O-O or S-S bonds). In another aspect R^1a is a 5 membered heterocyclic ring containing 1 heteroatom independently selected from O, S and N.

In one aspect R^1a is a 6 membered heterocyclic ring containing 1, 2, 3 or 4 heteroatoms independently selected from O, S and N (provided that such a ring does not contain any O-O or S-S bonds). In another aspect R^1a is a 6 membered heterocyclic ring containing 1, 2 or 3 heteroatoms independently selected from O, S and N (provided that such a ring does not contain any O-O or S-S bonds). In another aspect R^1a is a 6 membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, S and N (provided that such a ring does not contain any O-O or S-S bonds). In another aspect R^1a is a 6 membered heterocyclic ring containing 1 heteroatom independently selected from O, S and N.

Suitable values for R^1a as a 5-membered heterocyclyl ring include furyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, triazolyl, tetrazolyl, 1-oxa-3,4-diazolyl, 2-oxo-[1-oxa-3,4-diazolyl], oxa-2,4-diazolyl, thia-2,4-diazolyl and pyrrolyl.

Suitable values for R^1a as a 6-membered heterocyclyl ring include morpholinyl, thiomorpholinyl, pyridyl, pyrimidinyl, triazinyl, piperidinyl and piperazinyl.

Suitable values for R^1a as a 6-membered heterocyclyl ring include morpholinyl, thiomorpholinyl, pyridyl, pyridinonyl(for example pyridin-2(1*H*)-one), pyrimidinyl, pyrimidinonyl (for example pyrimidin-2(1*H*)-one), triazinyl, piperidinyl and piperazinyl.

Further suitable values for R^1a are imidazolyl, pyrimidinyl, pyridinyl, thiazolyl, triazinyl, pyrrolyl, thiadiazolyl and tetrazolyl.

R^1a is 5 or 6 membered saturated, partially unsaturated or unsaturated heterocyclic ring containing 1, 2, 3, or 4 heteroatoms independently selected from O, S and N (provided that such a ring does not contain O-O or S-S bonds), wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-, a ring sulphur atom may be optionally oxidised to form the S-oxide(s), and a ring nitrogen atom may be optionally oxidised to form the N-oxide.

R^1a is pyridinyl, *N*-oxopyridinyl, pyrimidinyl, thiazolyl, thiadiazolyl, tetrazolyl, imidazolyl, triazinyl, pyrrolidinyl, thienyl, furanyl, oxadiazolyl, isoxazolyl, oxazolyl or pyrrolyl.

R^1a is 5 or 6 membered saturated, partially unsaturated or unsaturated heterocyclic ring containing 1, 2, 3, or 4 heteroatoms independently selected from O, S and N (provided that such a ring does not contain O-O or S-S bonds), wherein a $-CH_2-$ group can optionally be

replaced by a -C(O)-, a ring sulphur atom may be optionally oxidised to form the S-oxide(s), and a ring nitrogen atom may be optionally oxidised to form the N-oxide, and wherein said ring may be optionally substituted by 1, 2 or 3 substituents independently selected from: nitro, cyano, sulfo, formyl, hydroxyiminomethyl, (2-6C)alkenyl, -CO(1-6C)alkyl, -COO(1-6C)alkyl trifluoromethyl, -CONR^{6}R^7, -N(R^7)COR^6, halo, hydroxy, carboxy, (1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, -OCO(1-4C)alkyl, (1-6C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(1-4C)alkoxy, (2-4C)alkenyloxy, -NHC(O)O(1-4C)alkyl, -NHC(=NH)NR^{6}R^7, -NHC(O)NR^{6}R^7, -NHC(O)(1-4C)alkyl, -NHC(O)heterocyclyl, -NHC(O)aryl, -NHS(O)p(1-4C)alkyl, -S(O)p(1-4C)alkyl, -S(O)pNR^{6}R^7, -NHSO$_2$R^6, -NR^{6}R^7, and heterocyclyl], (3-6C)cycloalkyl, -O(1-6C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), -S(O)p(1-4C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), heterocyclyl, -NHC(O)O(1-4C)alkyl, -C(=NOR^7)(1-4C)alkyl, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alkylCONHR^7, -C(O)NHS(O)p(1-4C)alkyl and -NR^{6}R^7; wherein any aryl or heterocyclyl group in any of the preceding values for substituents on R^{1}a may optionally be substituted by 1 or 2 substituents independently selected from (1-4C)alkyl and carboxy.

R^{1}a is pyridinyl, *N*-oxopyridinyl, pyrimidinyl, thiazolyl, thiadiazolyl, tetrazolyl, imidazolyl, triazinyl, pyrrolidinyl, thienyl, furanyl, oxadiazolyl, isoxazolyl, oxazolyl or pyrrolyl, wherein said R^{1}a may be optionally substituted by 1, 2 or 3 substituents independently selected from:
nitro, cyano, sulfo, formyl, hydroxyiminomethyl, (2-6C)alkenyl, -CO(1-6C)alkyl, -COO(1-6C)alkyl trifluoromethyl, -CONR^{6}R^7, -N(R^7)COR^6, halo, hydroxy, carboxy, (1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, -OCO(1-4C)alkyl, (1-6C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(1-4C)alkoxy, (2-4C)alkenyloxy, -NHC(O)O(1-4C)alkyl, -NHC(=NH)NR^{6}R^7, -NHC(O)NR^{6}R^7, -NHC(O)(1-4C)alkyl, -NHC(O)tetrahydrofuranyl, -NHC(O)phenyl, -NHS(O)p(1-4C)alkyl, -S(O)p(1-4C)alkyl, -S(O)pNR^{6}R^7, -NHSO$_2$R^6, -NR^{6}R^7, morpholino, 1,3-dioxo-1,3-dihydro-2H-isoindolyl and 1,3-dioxolanyl], cyclopropyl, -O(1-6C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), -S(O)p(1-4C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), tetrazolyl, 2-oxo-1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, morpholino, piperazinyl,

pyrrolidinyl, -NHC(O)O(1-4C)alkyl, -C(=NOR^7)(1-4C)alkyl, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alkylCONHR^7, -C(O)NHS(O)p(1-4C)alkyl and -NR^{6}R^7;
wherein any phenyl, tetrahydrofuranyl, morpholino, 1,3-dioxo-1,3-dihydro-2H-isoindolyl, 1,3-dioxolanyl, tetrazolyl, 2-oxo-1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, morpholino, piperazinyl, pyrrolidinyl, in any of the preceding values for substituents on R^{1}a may optionally be substituted by 1 or 2 substituents independently selected from (1-4C)alkyl and carboxy.

In one aspect R^{1}b is a 8 membered heterocyclic ring containing 1, 2, 3 or 4 heteroatoms independently selected from O, S and N (provided that such a ring does not contain any O-O or S-S bonds). In another aspect R^{1}b is a 8 membered heterocyclic ring containing 1, 2 or 3 heteroatoms independently selected from O, S and N (provided that such a ring does not contain any O-O or S-S bonds). In another aspect R^{1}b is a 8 membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, S and N (provided that such a ring does not contain any O-O or S-S bonds). In another aspect R^{1}b is a 8 membered heterocyclic ring containing 1 heteroatom independently selected from O, S and N.

In one aspect R^{1}b is a 9 membered heterocyclic ring containing 1, 2, 3 or 4 heteroatoms independently selected from O, S and N (provided that such a ring does not contain any O-O or S-S bonds). In another aspect R^{1}b is a 9 membered heterocyclic ring containing 1, 2 or 3 heteroatoms independently selected from O, S and N (provided that such a ring does not contain any O-O or S-S bonds). In another aspect R^{1}b is a 9 membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, S and N (provided that such a ring does not contain any O-O or S-S bonds). In another aspect R^{1}b is a 9 membered heterocyclic ring containing 1 heteroatom independently selected from O, S and N.

In one aspect R^{1}b is a 10 membered heterocyclic ring containing 1, 2, 3 or 4 heteroatoms independently selected from O, S and N (provided that such a ring does not contain any O-O or S-S bonds). In another aspect R^{1}b is a 10 membered heterocyclic ring containing 1, 2 or 3 heteroatoms independently selected from O, S and N (provided that such a ring does not contain any O-O or S-S bonds). In another aspect R^{1}b is a 10 membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, S and N (provided that such a ring does not contain any O-O or S-S bonds). In another aspect R^{1}b is a

10 membered heterocyclic ring containing 1 heteroatom independently selected from O, S and N.

Examples of R^1b as an 8-10 membered bicyclic heterocyclic ring containing 1, 2, 3, or 4 heteroatoms independently selected from O, S and N (provided that such a ring does not contain O-O or S-S bonds) include, for example, bicyclic benzo-fused systems containing a 5- or 6-membered heteroaryl ring containing one nitrogen atom and optionally 1-3 further heteroatoms chosen from oxygen, sulfur and nitrogen. Specific examples of such ring systems include, for example, indole, benzofuran, benzothiophene, benzimidazole, benzothiazole, benzisothiazole, benzoxazole, benzisoxazole, quinoline, quinoxaline, quinazoline, phthalazine, 1,4-benzoxazine, and cinnoline. Further examples of such ring systems are isomers of the above named examples, such as isoquinoline and isoindole; it will be understood that references to such ring systems are intended to encompass such isomers.

R^1b is a 10 membered bicyclic heterocyclic ring containing 1, 2 or 4 heteroatoms independently selected from S and N (provided that such a ring does not contain S-S bonds), wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-.

R^1b is quinolinyl, purinyl, benzothiazolyl, indolyl, 4-oxoquinolinyl, 2,7-naphthyridinyl or quinazolinyl.

R^1b is a 10 membered bicyclic heterocyclic ring containing 1, 2 or 4 heteroatoms independently selected from S and N (provided that such a ring does not contain S-S bonds), wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-, wherein said ring may be optionally substituted by 1, 2 or 3 substituents independently selected from: nitro, cyano, sulfo, formyl, hydroxyiminomethyl, (2-6C)alkenyl, -CO(1-6C)alkyl, -COO(1-6C)alkyl trifluoromethyl, $-CONR^6R^7$, $-N(R^7)COR^6$, halo, hydroxy, carboxy, (1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, -OCO(1-4C)alkyl, (1-6C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(1-4C)alkoxy, (2-4C)alkenyloxy, -NHC(O)O(1-4C)alkyl, $-NHC(=NH)NR^6R^7$, $-NHC(O)NR^6R^7$, -NHC(O)(1-4C)alkyl, -NHC(O)heterocyclyl, -NHC(O)aryl, -NHS(O)p(1-4C)alkyl, -S(O)p(1-4C)alkyl, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$, and heterocyclyl], (3-6C)cycloalkyl, -O(1-6C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), -S(O)p(1-4C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), heterocyclyl, -NHC(O)O(1-4C)alkyl, $-C(=NOR^7)$(1-4C)alkyl, $-C(=NOR^7)NR^6R^7$, -S(O)p(1-4C)alkylCONHR^7, -C(O)NHS(O)p(1-4C)alkyl and $-NR^6R^7$;

wherein any aryl or heterocyclyl group in any of the preceding values for substituents on R^1a may optionally be substituted by 1 or 2 substituents independently selected from (1-4C)alkyl and carboxy.

R^1b is quinolinyl, purinyl, benzothiazolyl, indolyl, 4-oxoquinolinyl, 2,7-naphthyridinyl or quinazolinyl wherein said R^1b may be optionally substituted by 1, 2 or 3 substituents independently selected from:
nitro, cyano, sulfo, formyl, hydroxyiminomethyl, (2-6C)alkenyl, -CO(1-6C)alkyl, -COO(1-6C)alkyl trifluoromethyl, $-CONR^6R^7$, $-N(R^7)COR^6$, halo, hydroxy, carboxy, (1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, -OCO(1-4C)alkyl, (1-6C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(1-4C)alkoxy, (2-4C)alkenyloxy, -NHC(O)O(1-4C)alkyl, $-NHC(=NH)NR^6R^7$, $-NHC(O)NR^6R^7$, -NHC(O)(1-4C)alkyl, -NHC(O)tetrahydrofuranyl, -NHC(O)phenyl, -NHS(O)p(1-4C)alkyl, -S(O)p(1-4C)alkyl, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$, morpholino, 1,3-dioxo-1,3-dihydro-2H-isoindolyl and 1,3-dioxolanyl], cyclopropyl, -O(1-6C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), -S(O)p(1-4C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), tetrazolyl, 2-oxo-1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, morpholino, piperazinyl, pyrrolidinyl, -NHC(O)O(1-4C)alkyl, $-C(=NOR^7)$(1-4C)alkyl, $-C(=NOR^7)NR^6R^7$, -S(O)p(1-4C)alkylCONHR^7, -C(O)NHS(O)p(1-4C)alkyl and $-NR^6R^7$;
wherein any phenyl, tetrahydrofuranyl, morpholino, 1,3-dioxo-1,3-dihydro-2H-isoindolyl, 1,3-dioxolanyl, tetrazolyl, 2-oxo-1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, morpholino, piperazinyl, pyrrolidinyl, in any of the preceding values for substituents on R^1a may optionally be substituted by 1 or 2 substituents indcpendently selected from (1-4C)alkyl and carboxy.

Further examples of R^1b as an 8-10 membered heterocyclic ring include 5/5-, 5/6 and 6/6 bicyclic ring systems containing heteroatoms in both of the rings. Further examples of R^1b as an 8-10 membered heterocyclic ring include bicyclic heteroaryl ring systems with at least one bridgehead nitrogen and optionally a further 1-3 heteroatoms chosen from oxygen, sulfur and nitrogen.

Specific examples of such ring systems include, for example, purine, naphthyridine, pyrido[2,3-d]pyrimidinyl, pyrimido[4,5-d]pyrimidinyl, indolizine, quinolizine, indazole, indan-2-yl, carbazole, pyrrolo[1,2-c]pyrimidine, pyrazolo[3,4-b]pyridine, 1H-pyrazolo[3,4-d]pyrimidine, thiadiazolo[3,4-b]pyridine, 1H-imidazo[4,5-b]pyridine,

azapurine, furazanopyrimidines, coumarin, benzopyran, thiazolo[4,5-d]pyrimidine, pyrido[2,3-b]pyrazin-3(2H)-one, H-pyrimido[5,4-b][1,4]oxazin-7(6H)-one, 3H-pyrrolo[1,2-a]pyrrole, pyrrolo[2,1-b]thiazole, 1H-imidazo[1,2-a]pyrrole, 1H-imidazo[1,2-a]imidazole, 1H,3H-pyrrolo[1,2-c]oxazole, 1H-imidazo[1,5-a]pyrrole, pyrrolo[1,2-b]isoxazole, imidazo[5,1-b]thiazole, imidazo[2,1-b]thiazole, indolizine, imidazo[1,2-a]pyridine, imidazo[1,5-a]pyridine, pyrazolo[1,5-a]pyridine, pyrrolo[1,2-b]pyridazine, pyrrolo[1,2-c]pyrimidine, pyrrolo[1,2-a]pyrazine, pyrrolo[1,2-a]pyrimidine, pyrido[2,1-c]-s-triazole, s-triazole[1,5-a]pyridine, imidazo[1,2-c]pyrimidine, imidazo[1,2-a]pyrazine, imidazo[1,2-a]pyrimidine, imidazo[1,5-a]pyrazine, imidazo[1,5-a]pyrimidine, imidazo[1,2-b]-pyridazine, s-triazolo[4,3-a]pyrimidine, imidazo[5,1-b]oxazole and imidazo[2,1-b]oxazole. Other specific examples of such ring systems include, for example, [1H]-pyrrolo[2,1-c]oxazine, [3H]-oxazolo[3,4-a]pyridine, [6H]-pyrrolo[2,1-c]oxazine and pyrido[2,1-c][1,4]oxazine. Other specific examples of 5/5- bicyclic ring systems are imidazooxazole or imidazothiazole, such as imidazo[5,1-b]thiazole, imidazo[2,1-b]thiazole, imidazo[5,1-b]oxazole or imidazo[2,1-b]oxazole.

Further examples of R^1b as an 8-10 membered heterocyclic ring include ring systems where one or both of the rings is partially or fully saturated, for example indoline, 1,3,4,6,9,9a-hexahydropyrido[2,1c][1,4]oxazin-8-yl, 1,2,3,5,8,8a-hexahydroimidazo[1,5a]pyridin-7-yl, 1,5,8,8a-tetrahydrooxazolo[3,4a]pyridin-7-yl, 1,5,6,7,8,8a-hexahydrooxazolo[3,4a]pyridin-7-yl, (7aS)[3H,5H]-1,7a-dihydropyrrolo[1,2c]oxazol-6-yl, (7aS)[5H]-1,2,3,7a-tetrahydropyrrolo[1,2c]imidazol-6-yl, (7aR)[3H,5H]-1,7a-dihydropyrrolo[1,2c]oxazol-6-yl, [3H,5H]-pyrrolo[1,2-c]oxazol-6-yl, [5H]-2,3-dihydropyrrolo[1,2-c]imidazol-6-yl, [3H,5H]-pyrrolo[1,2-c]thiazol-6-yl, [3H,5H]-1,7a-dihydropyrrolo[1,2-c]thiazol-6-yl, [5H]-pyrrolo[1,2-c]imidazol-6-yl, [1H]-3,4,8,8a-tetrahydropyrrolo[2,1-c]oxazin-7-yl, [3H]-1,5,8,8a-tetrahydrooxazolo[3,4-a]pyrid-7-yl, [3H]-5,8-dihydroxazolo[3,4-a]pyrid-7-yl and 5,8-dihydroimidazo[1,5-a]pyrid-7-yl.

The nomenclature used is that found in, for example, "Heterocyclic Compounds (Systems with bridgehead nitrogen)", W.L.Mosby (Interscience Publishers Inc., New York), 1961, Parts 1 and 2.

Further examples of suitable values for R^1b may be found in Handbook of Heterocyclic Chemistry 2nd Ed- by A.R. Katritzky and A.F. Pozharskii.

Suitable values for R^1b are quinolinyl, purinyl, benzothiazolyl and indolyl.

In one aspect R^1d is selected from $-CH_2R^1a$.

In another aspect R^1d is selected from $-C(O)R^1a$.

In another aspect R^1d is selected from $-OR^1a$.

In a further aspect R^1d is selected from $S(O)qR^1a$ (wherein q is 1 or 2).

R^1d is selected from $-CH_2R^1a$ or $-C(O)R^1a$.

In one aspect R^1e is selected from $-CH_2R^1b$.

In another aspect R^1e is selected from $-C(O)R^1b$.

In another aspect R^1e is selected from $-OR^1b$.

In a further aspect R^1e is selected from $S(O)qR^1b$ (wherein q is 1 or 2).

In one aspect R^1f is selected from $-CH_2R^1c$.

In another aspect R^1f is selected from $-C(O)R^1c$.

In another aspect R^1f is selected from $-OR^1c$.

In a further aspect R^1f is selected from $S(O)qR^1c$ (wherein q is 1 or 2).

In one aspect, R^1 contains one substituent selected from the optional substituents listed in any aspect or embodiment hereinbefore or hereinafter. In another aspect R^1 contains two substituents independently selected from the optional substituents listed in any aspect or embodiment hereinbefore or hereinafter. In a further aspect, R^1 is unsubstituted.

In one aspect the optional substituents for R^1 (wherein R^1 is selected from R^1a, R^1b, R^1c, R^1d, R^1e and R^1d) are selected from

nitro, cyano, (2-6C)alkenyl, (2-6C)alkynyl, -CO(1-6C)alkyl, -COO(1-6C)alkyl, -O(1-6C)alkyl, trifluoromethyl, $-CONR^6R^7$, $-OCONR^6R^7$, $-N(R^7)COR^6$, $-CONHCH(CO_2R^7)R^6$, halo, hydroxy, carboxy,

(1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo, cyano, nitro, -COO(1-6C)alkyl, -O(1-6C)alkyl, trifluoromethyl, $-CONR^6R^7$, carboxy, -NHC(O)O(1-4C)alkyl, -C(=NOH)(1-4C)alkyl, $-C(=NOH)NR^6R^7$, $-S(O)p(1-4C)alkyl$, $-S(O)pNR^6R^7$ and $-NR^6R^7$],

heterocyclyl [optionally substituted by 1 or 2 substituents independently selected from (1-4C)alkyl, hydroxy, (1-4C)alkoxy, halo, cyano, nitro, carboxy, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, (1-4C)alkylcarbonyl, (1-4C)alkoxycarbonyl, $-C(O)NH_2$, -C(O)NH(1-4C)alkyl,

-C(O)N[di(1-4C)alkyl], -S(O)$_2$NH$_2$, -S(O)$_2$NH(1-4C)alkyl, -S(O)$_2$N[di(1-4C)alkyl] and -S(O)p(1-4C)alkyl],

aryl [optionally substituted by 1 or 2 substituents independently selected from (1-4C)alkyl, hydroxy, (1-4C)alkoxy, halo, cyano, nitro, carboxy, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, (1-4C)alkylcarbonyl, (1-4C)alkoxycarbonyl, -C(O)NH$_2$, -C(O)NH(1-4C)alkyl, -C(O)N[di(1-4C)alkyl], -S(O)$_2$NH$_2$, -S(O)$_2$NH(1-4C)alkyl, -S(O)$_2$N[di(1-4C)alkyl] and -S(O)p(1-4C)alkyl], -NHC(O)O(1-4C)alkyl, -C(=NOR^7)(1-4C)alkyl, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alkyl (optionally substituted by hydroxy), -S(O)pNR^{6}R^7, -S(O)p(1-4C)alkylCONHR^7, -NR^{7}S(O)pNR^{6}R^7, -NR^{7}S(O)p(1-4C)alkyl, -NR^{7}S(O)p-aryl, -C(O)NHS(O)p(1-4C)alkyl, -C(O)NHS(O)p-aryl, -NR^{6}R^7, -CH$_2$CH(CO$_2$R^6)OH, -(1-4C)alkylCH(NR^{6}R^7)CO$_2$R^6 and -(1-4C)alkylCH(NR^{6}R^7)CO(NR^{6}R^7).

In another aspect the optional substituents for R^1 (wherein R^1 is selected from R^{1}a, R^{1}b, R^{1}c, R^{1}d, R^{1}e and R^{1}d) are selected from

nitro, cyano, (2-6C)alkenyl, (2-6C)alkynyl, -CO(1-6C)alkyl, -COO(1-6C)alkyl, -O(1-6C)alkyl, trifluoromethyl, -CONR^{6}R^7, -OCONR^{6}R^7, -N(R^7)COR^6, -CONHCH(CO$_2$R^7)R^6, halo, hydroxy, carboxy,

(1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo, -COO(1-6C)alkyl, -O(1-6C)alkyl, trifluoromethyl, -CONR^{6}R^7, -NHC(O)O(1-4C)alkyl, -C(=NOH)(1-4C)alkyl, -C(=NOH)NR^{6}R^7, -S(O)p(1-4C)alkyl, -S(O)pNR^{6}R^7 and - NR^{6}R^7],

heterocyclyl [optionally substituted by 1 or 2 substituents independently selected from (1-4C)alkyl, hydroxy, (1-4C)alkoxy, halo, cyano, nitro, carboxy, hydroxy(1-4C)alkyl, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, (1-4C)alkylcarbonyl, (1-4C)alkoxycarbonyl, -C(O)NH$_2$, -C(O)NH(1-4C)alkyl, -C(O)N[di(1-4C)alkyl], -S(O)$_2$NH$_2$, -S(O)$_2$NH(1-4C)alkyl, -S(O)$_2$N[di(1-4C)alkyl] and -S(O)p(1-4C)alkyl],

aryl [optionally substituted by 1 or 2 substituents independently selected from (1-4C)alkyl, hydroxy, (1-4C)alkoxy, halo, cyano, nitro, carboxy, hydroxy(1-4C)alkyl, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, (1-4C)alkylcarbonyl, (1-4C)alkoxycarbonyl, -C(O)NH$_2$, -C(O)NH(1-4C)alkyl, -C(O)N[di(1-4C)alkyl], -S(O)$_2$NH$_2$, -S(O)$_2$NH(1-4C)alkyl, -S(O)$_2$N[di(1-4C)alkyl] and -S(O)p(1-4C)alkyl],

-NHC(O)O(1-4C)alkyl, -C(=NOR^7)(1-4C)alkyl, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alkyl (optionally substituted by hydroxy), -S(O)pNR^{6}R^7, -S(O)p(1-4C)alkylCONHR^7, -NR^{7}S(O)pNR^{6}R^7, -NR^{7}S(O)p(1-4C)alkyl, -NR^{7}S(O)p-aryl, -C(O)NHS(O)p(1-4C)alkyl, -C(O)NHS(O)p-aryl and -NR^{6}R^7.

In another aspect the optional substituents for R^1 (wherein R^1 is selected from R^{1}a, R^{1}b, R^{1}c, R^{1}d, R^{1}e and R^{1}d) are selected from
nitro, cyano, -CO(1-6C)alkyl, -COO(1-6C)alkyl, -O(1-6C)alkyl, trifluoromethyl, -CONR^{6}R^7, -OCONR^{6}R^7, -N(R^7)COR^6, -CONHCH(CO$_2$R^7)R^6, halo, hydroxy, carboxy, (1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo, -COO(1-6C)alkyl, -O(1-6C)alkyl, trifluoromethyl, -CONR^{6}R^7, -S(O)p(1-4C)alkyl, -S(O)pNR^{6}R^7 and - NR^{6}R^7], heterocyclyl [optionally substituted by 1 or 2 substituents independently selected from (1-4C)alkyl, hydroxy, (1-4C)alkoxy, halo, cyano, nitro, carboxy, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl and trifluoromethoxy], aryl [optionally substituted by 1 or 2 substituents independently selected from (1-4C)alkyl, hydroxy, (1-4C)alkoxy, halo, cyano, nitro, carboxy, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl and trifluoromethoxy], -NHC(O)O(1-4C)alkyl, -C(=NOR^7)(1-4C)alkyl, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alkyl (optionally substituted by hydroxy), -S(O)pNR^{6}R^7, -S(O)p(1-4C)alkylCONHR^7, -NR^{7}S(O)pNR^{6}R^7, -NR^{7}S(O)p(1-4C)alkyl, -NR^{7}S(O)p-aryl, -C(O)NHS(O)p(1-4C)alkyl, -C(O)NHS(O)p-aryl and -NR^{6}R^7.

In another aspect the optional substituents for R^1 (wherein R^1 is selected from R^{1}a, R^{1}b, R^{1}c, R^{1}d, R^{1}e and R^{1}d) are selected from
nitro, cyano, -CO(1-6C)alkyl, -COO(1-6C)alkyl, -O(1-6C)alkyl, trifluoromethyl, -CONR^{6}R^7, -OCONR^{6}R^7, -N(R^7)COR^6, halo, hydroxy, carboxy, (1-6C)alkyl, heterocyclyl, aryl, -NHC(O)O(1-4C)alkyl, -C(=NOR^7)(1-4C)alkyl, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alkyl (optionally substituted by hydroxy), -S(O)pNR^{6}R^7, -S(O)p(1-4C)alkylCONHR^7, -NR^{7}S(O)pNR^{6}R^7, -NR^{7}S(O)p(1-4C)alkyl, -NR^{7}S(O)p-aryl, -C(O)NHS(O)p(1-4C)alkyl, -C(O)NHS(O)p-aryl and -NR^{6}R^7.

In another aspect the optional substituents for R^1 (wherein R^1 is selected from R^{1}a, R^{1}b, R^{1}c, R^{1}d, R^{1}e and R^{1}d) are selected from
nitro, cyano, -CO(1-6C)alkyl, -COO(1-6C)alkyl, -O(1-6C)alkyl, trifluoromethyl, -CONR^{6}R^7, -OCONR^{6}R^7, -N(R^7)COR^6, halo, hydroxy, carboxy, (1-6C)alkyl, heterocyclyl, aryl,

-NHC(O)O(1-4C)alkyl, -C(=NOR^7)(1-4C)alkyl, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alkyl (optionally substituted by hydroxy), -S(O)pNR^{6}R^7, -S(O)p(1-4C)alkylCONHR^7, -NR^{7}S(O)pNR^{6}R^7, -NR^{7}S(O)p(1-4C)alkyl, -NR^{7}S(O)p-aryl, and -NR^{6}R^7.

In another aspect the optional substituents for R^1 (wherein R^1 is selected from R^{1}a, R^{1}b, R^{1}c, R^{1}d, R^{1}e and R^{1}d) are selected from
nitro, cyano, -CO(1-4C)alkyl, -COO(1-4C)alkyl, -O(1-4C)alkyl, trifluoromethyl, -CONR^{6}R^7, -N(R^7)COR^6, fluoro, chloro, bromo, hydroxy, carboxy, (1-4C)alkyl, heterocyclyl, -NHC(O)O(1-4C)alkyl, -C(=NOR^7)(1-4C)alkyl, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alkyl (optionally substituted by hydroxy), -S(O)p(1-4C)alkylCONHR^7, and -NR^{6}R^7.

In another aspect the optional substituents for R^1 (wherein R^1 is selected from R^{1}a, R^{1}b, R^{1}c, R^{1}d, R^{1}e and R^{1}d) are selected from
nitro, cyano, -CO(1-6C)alkyl, -COO(1-6C)alkyl (optionally substituted with -COO(1-4C)alkyl), trifluoromethyl, -CONR^{6}R^7, -OCONR^{6}R^7, -N(R^7)COR^6, -CONHCH(CO$_2$R^7)R^6, halo, hydroxy, carboxy, (1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo, cyano, nitro, -COO(1-6C)alkyl, -OCO(1-4C)alkyl, (1-6C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(1-4C)alkoxy, (2-4C)alkenyloxy, trifluoromethyl, -CONR^{6}R^7, carboxy, -NHC(O)O(1-4C)alkyl, -OCONR^{6}R^7, -C(=NOH)(1-4C)alkyl, -C(=NOH)NR^{6}R^7, -S(O)p(1-4C)alkyl, -S(O)pNR^{6}R^7, -NHSO$_2$R^6, -NR^{6}R^7, and heterocyclyl],
(3-6C)cycloalkyl (optionally substituted by 1 or 2 substituents selected from (1-6C)alkyl and the optional substituents described for (1-6C)alkyl hereinbefore), -O(1-6C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), -S(O)p(1-4C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), heterocyclyl, -NHC(O)O(1-4C)alkyl, -C(=NOR^7)(1-4C)alkyl, -C(=NOR^7)NR^{6}R^7, -S(O)pNR^{6}R^7, -NR^{7}S(O)p(1-4C)alkyl, -NR^{7}S(O)p-aryl, -C(O)NHS(O)p(1-4C)alkyl, -C(O)NHS(O)p-aryl, and -NR^{6}R^7;
wherein any heterocyclyl or aryl group in any of the preceding values for substituents on R^{1}a may optionally be substituted by 1 or 2 substituents independently selected from (1-4C)alkyl, hydroxy, (1-4C)alkoxy, halo, cyano, nitro, carboxy, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, formyl, -CO(1-4C)alkyl, -COO(1-4C)alkyl, -C(O)NH$_2$, -C(O)NH(1-4C)alkyl, -C(O)N[di(1-4C)alkyl], -S(O)$_2$NH$_2$, -S(O)$_2$NH(1-4C)alkyl and -S(O)$_2$N[di(1-4C)alkyl].

In another aspect the optional substituents for R^1 (wherein R^1 is selected from R^1a, R^1b, R^1c, R^1d, R^1e and R^1d) are selected from
nitro, cyano, -CO(1-6C)alkyl, -COO(1-6C)alkyl (optionally substituted with -COO(1-4C)alkyl), trifluoromethyl, $-CONR^6R^7$, $-OCONR^6R^7$, $-N(R^7)COR^6$, $-CONHCH(CO_2R^7)R^6$, halo, carboxy, (1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo, cyano, nitro, -COO(1-6C)alkyl, -OCO(1-4C)alkyl, (1-6C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(1-4C)alkoxy, (2-4C)alkenyloxy, trifluoromethyl, $-CONR^6R^7$, carboxy, -NHC(O)O(1-4C)alkyl, $-OCONR^6R^7$, -C(=NOH)(1-4C)alkyl, $-C(=NOH)NR^6R^7$, -S(O)p(1-4C)alkyl, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$, and heterocyclyl],
(3-6C)cycloalkyl (optionally substituted by 1 or 2 substituents selected from (1-6C)alkyl and the optional substituents described for (1-6C)alkyl hereinbefore), -O(1-6C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), -S(O)p(1-4C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), heterocyclyl, -NHC(O)O(1-4C)alkyl, $-C(=NOR^7)$(1-4C)alkyl, $-C(=NOR^7)NR^6R^7$, $-S(O)pNR^6R^7$, $-NR^7S(O)p$(1-4C)alkyl, -C(O)NHS(O)p(1-4C)alkyl, and $-NR^6R^7$;
wherein any heterocyclyl or aryl group in any of the preceding values for substituents on R^1a may optionally be substituted by 1 or 2 substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy, halo, cyano, nitro, carboxy, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl and trifluoromethoxy.

In another aspect the optional substituents for R^1 (wherein R^1 is selected from R^1a, R^1b, R^1c, R^1d, R^1e and R^1d) are selected from
nitro, cyano, -CO(1-6C)alkyl, -COO(1-6C)alkyl (optionally substituted with -COO(1-4C)alkyl), trifluoromethyl, $-CONR^6R^7$, $-OCONR^6R^7$, $-N(R^7)COR^6$, halo, carboxy, (1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo, -COO(1-6C)alkyl, -OCO(1-4C)alkyl, (1-6C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(1-4C)alkoxy, (2-4C)alkenyloxy, trifluoromethyl, $-CONR^6R^7$, carboxy, -NHC(O)O(1-4C)alkyl, $-OCONR^6R^7$, -C(=NOH)(1-4C)alkyl, $-C(=NOH)NR^6R^7$, -S(O)p(1-4C)alkyl, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$, and heterocyclyl], (3-6C)cycloalkyl (optionally substituted by 1 or 2 substituents selected from (1-6C)alkyl and the optional substituents described for (1-6C)alkyl hereinbefore), -O(1-6C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore),

-S(O)p(1-4C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), heterocyclyl, -NHC(O)O(1-4C)alkyl, -C(=NOR^7)(1-4C)alkyl, -C(=NOR^7)NR^{6}R^7, -S(O)pNR^{6}R^7, -NR^{7}S(O)p(1-4C)alkyl, -C(O)NHS(O)p(1-4C)alkyl, and -NR^{6}R^7;

wherein any heterocyclyl or aryl group in any of the preceding values for substituents on R^{1}a may optionally be substituted by 1 or 2 substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy, halo, cyano, nitro, carboxy, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl and trifluoromethoxy.

In another aspect the optional substituents for R^1 (wherein R^1 is selected from R^{1}a, R^{1}b, R^{1}c, R^{1}d, R^{1}e and R^{1}d) are selected from

nitro, cyano, sulfo, formyl, hydroxyiminomethyl, (2-6C)alkenyl, -CO(1-6C)alkyl, -COO(1-6C)alkyl trifluoromethyl, -CONR^{6}R^7, -N(R^7)COR^6, halo, hydroxy, carboxy, (1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, -OCO(1-4C)alkyl, (1-6C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(1-4C)alkoxy, (2-4C)alkenyloxy, -NHC(O)O(1-4C)alkyl, -NHC(=NH)NR^{6}R^7, -NHC(O)NR^{6}R^7, -NHC(O)(1-4C)alkyl, -NHC(O)heterocyclyl, -NHC(O)aryl, -NHS(O)p(1-4C)alkyl, -S(O)p(1-4C)alkyl, -S(O)pNR^{6}R^7, -NHSO$_2$R^6, -NR^{6}R^7, and heterocyclyl], (3-6C)cycloalkyl, -O(1-6C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), -S(O)p(1-4C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), heterocyclyl, -NHC(O)O(1-4C)alkyl, -C(=NOR^7)(1-4C)alkyl, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alkylCONHR^7, -C(O)NHS(O)p(1-4C)alkyl and -NR^{6}R^7; wherein any aryl or heterocyclyl group in any of the preceding values for substituents on R^{1}a may optionally be substituted by 1 or 2 substituents independently selected from (1-4C)alkyl and carboxy.

In another aspect the optional substituents for R^1 (wherein R^1 is selected from R^{1}a, R^{1}b, R^{1}c, R^{1}d, R^{1}e and R^{1}d) are selected from

nitro, cyano, sulfo, formyl, hydroxyiminomethyl, (2-6C)alkenyl, -CO(1-6C)alkyl, -COO(1-6C)alkyl trifluoromethyl, -CONR^{6}R^7, -N(R^7)COR^6, halo, hydroxy, carboxy, (1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, -OCO(1-4C)alkyl, (1-6C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(1-4C)alkoxy, (2-4C)alkenyloxy, -NHC(O)O(1-4C)alkyl, -NHC(=NH)NR^{6}R^7, -NHC(O)NR^{6}R^7, -NHC(O)(1-4C)alkyl, -NHC(O)tetrahydrofuranyl, -NHC(O)phenyl, -NHS(O)p(1-4C)alkyl, -S(O)p(1-4C)alkyl, -S(O)pNR^{6}R^7, -NHSO$_2$R^6, -NR^{6}R^7, morpholino,

1,3-dioxo-1,3-dihydro-2H-isoindolyl and 1,3-dioxolanyl], cyclopropyl, -O(1-6C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), -S(O)p(1-4C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), tetrazolyl, 2-oxo-1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, morpholino, piperazinyl, pyrrolidinyl, -NHC(O)O(1-4C)alkyl, -C(=NOR^7)(1-4C)alkyl, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alkylCONHR^7, -C(O)NHS(O)p(1-4C)alkyl and -NR^{6}R^7;
wherein any phenyl, tetrahydrofuranyl, morpholino, 1,3-dioxo-1,3-dihydro-2H-isoindolyl, 1,3-dioxolanyl, tetrazolyl, 2-oxo-1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, morpholino, piperazinyl, pyrrolidinyl, in any of the preceding values for substituents on R^{1}a may optionally be substituted by 1 or 2 substituents independently selected from (1-4C)alkyl and carboxy.

In another aspect R^1 is substituted by 2 substituents; wherein one substituent is selected from carboxy, -CONHSO$_2$Me and -CONHR^6 (wherein R^6 is selected from any of the values listed in any aspect or embodiment hereinbefore or hereinafter) and wherein the other substituent is selected from
(1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo, cyano, nitro, -COO(1-6C)alkyl, -OCO(1-4C)alkyl, (1-6C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(1-4C)alkoxy, (2-4C)alkenyloxy, trifluoromethyl, -CONR^{6}R^7, carboxy, -NHC(O)O(1-4C)alkyl, -OCONR^{6}R^7, -C(=NOH)(1-4C)alkyl, -C(=NOH)NR^{6}R^7, -S(O)p(1-4C)alkyl, -S(O)pNR^{6}R^7, -NHSO$_2$R^6, -NR^{6}R^7, and heterocyclyl], -O(1-6C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore) and -S(O)p(1-4C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), wherein R^6 and R^7 are selected from any of the values listed in any aspect or embodiment hereinbefore or hereinafter.

In another aspect R^1 is substituted by 2 substituents; wherein one substituent is selected from carboxy, -CONHSO$_2$Me and -CONHR^6 (wherein R^6 is selected from -OMe, hydrogen, amino and 3-4C alkenyl); and wherein the other substituent is selected from (1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo, cyano, nitro, -COO(1-6C)alkyl, -OCO(1-4C)alkyl, (1-6C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(1-4C)alkoxy, (2-4C)alkenyloxy, trifluoromethyl, -CONR^{6}R^7, carboxy, -NHC(O)O(1-4C)alkyl, -OCONR^{6}R^7, -C(=NOH)(1-4C)alkyl, -C(=NOH)NR^{6}R^7, -S(O)p(1-4C)alkyl, -S(O)pNR^{6}R^7, -NHSO$_2$R^6, -NR^{6}R^7, and heterocyclyl],

-O(1-6C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore) and -S(O)p(1-4C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), wherein R^6 and R^7 are selected from any of the values listed in any aspect or embodiment hereinbefore or hereinafter.

In another aspect R^1 is substituted by 2 substituents; wherein one substituent is selected from carboxy, $-CONHSO_2Me$ and $-CONHR^6$ (wherein R^6 is selected from -OMe, hydrogen, amino, (3-4C alkenyl and $-SO_2Me$); and wherein the other substituent is selected from

(1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo, cyano, nitro, -COO(1-6C)alkyl, -OCO(1-4C)alkyl, (1-6C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(1-4C)alkoxy, (2-4C)alkenyloxy, trifluoromethyl, $-CONR^6R^7$, carboxy, -NHC(O)O(1-4C)alkyl, $-OCONR^6R^7$, -C(=NOH)(1-4C)alkyl, $-C(=NOH)NR^6R^7$, -S(O)p(1-4C)alkyl, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$, and heterocyclyl], -O(1-6C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore) and -S(O)p(1-4C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), wherein R^6 is selected from hydrogen and (1-4C)alkyl, and R^7 is hydrogen or methyl, or wherein R^6 and R^7 together from a piperidine, morpholine or piperazine ring, which ring may optionally be substituted with methyl on an available carbon or nitrogen atom (provided a nitrogen atom is not thereby quaternised) and a carbon atom may optionally be oxidised to form a carbonyl group.

R^1 is selected from R^1a, R^1b, R^1c and R^1d; wherein

R^1a is a 5 or 6 membered saturated, partially unsaturated or unsaturated heterocyclic ring containing 1, 2, 3, or 4 heteroatoms independently selected from O, S and N (provided that such a ring does not contain O-O or S-S bonds), wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-, a ring sulphur atom may be optionally oxidised to form the S-oxide(s), and a ring nitrogen atom may be optionally oxidised to form the N-oxide, and wherein said ring may be optionally substituted by 1, 2 or 3 substituents independently selected from: nitro, cyano, sulfo, formyl, hydroxyiminomethyl, (2-6C)alkenyl, -CO(1-6C)alkyl, -COO(1-6C)alkyl trifluoromethyl, $-CONR^6R^7$, $-N(R^7)COR^6$, halo, hydroxy, carboxy, (1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, -OCO(1-4C)alkyl, (1-6C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(1-4C)alkoxy, (2-4C)alkenyloxy, -NHC(O)O(1-4C)alkyl, $-NHC(=NH)NR^6R^7$, $-NHC(O)NR^6R^7$, -NHC(O)(1-4C)alkyl, -NHC(O)heterocyclyl, -NHC(O)aryl, -NHS(O)p(1-4C)alkyl,

-S(O)p(1-4C)alkyl, -S(O)pNR^{6}R^7, -NHSO$_2$R^6, -NR^{6}R^7, and heterocyclyl], (3-6C)cycloalkyl, -O(1-6C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), -S(O)p(1-4C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), heterocyclyl, -NHC(O)O(1-4C)alkyl, -C(=NOR^7)(1-4C)alkyl, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alkylCONHR^7, -C(O)NHS(O)p(1-4C)alkyl, and -NR^{6}R^7, wherein any aryl or heterocyclyl group in any of the preceding values for substituents on R^{1}a may optionally be substituted by 1 or 2 substituents independently selected from (1-4C)alkyl and carboxy;

R^{1}b is a 10 membered bicyclic heterocyclic ring containing 1, 2 or 4 heteroatoms independently selected from S and N (provided that such a ring does not contain S-S bonds), wherein a -CH$_2$- group can optionally be replaced by a -C(O)-, and wherein said ring may be optionally substituted by 1, 2 or 3 substituents independently selected from the substituents listed for R^{1}a above;

R^{1}c is a phenyl ring, substituted by 1, 2 or 3 substituents independently selected from the substituents listed for R^{1}a above;

R^{1}d is selected from -CH$_2$R^{1}a, and -C(O)R^{1}a.

R^1 is selected from R^{1}a, R^{1}b, R^{1}c and R^{1}d; wherein

R^{1}a is pyridinyl, *N*-oxopyridinyl, pyrimidinyl, thiazolyl, thiadiazolyl, tetrazolyl, imidazolyl, triazinyl, pyrrolidinyl, thienyl, furanyl, oxadiazolyl, isoxazolyl, oxazolyl or pyrrolyl, wherein said R^{1}a may be optionally substituted by 1, 2 or 3 substituents independently selected from:
nitro, cyano, sulfo, formyl, hydroxyiminomethyl, (2-6C)alkenyl, -CO(1-6C)alkyl, -COO(1-6C)alkyl trifluoromethyl, -CONR^{6}R^7, -N(R^7)COR^6, halo, hydroxy, carboxy, (1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, -OCO(1-4C)alkyl, (1-6C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(1-4C)alkoxy, (2-4C)alkenyloxy, -NHC(O)O(1-4C)alkyl, -NHC(=NH)NR^{6}R^7, -NHC(O)NR^{6}R^7, -NHC(O)(1-4C)alkyl, -NHC(O)tetrahydrofuranyl, -NHC(O)phenyl, -NHS(O)p(1-4C)alkyl, -S(O)p(1-4C)alkyl, -S(O)pNR^{6}R^7, -NHSO$_2$R^6, -NR^{6}R^7, morpholino, 1,3-dioxo-1,3-dihydro-2H-isoindolyl and 1,3-dioxolanyl], cyclopropyl, -O(1-6C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), -S(O)p(1-4C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), tetrazolyl, 2-oxo-1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, morpholino, piperazinyl,

pyrrolidinyl, -NHC(O)O(1-4C)alkyl, -C(=NOR^7)(1-4C)alkyl, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alkylCONHR^7, -C(O)NHS(O)p(1-4C)alkyl and -NR^{6}R^7;

wherein any phenyl, tetrahydrofuranyl, morpholino, 1,3-dioxo-1,3-dihydro-2H-isoindolyl, 1,3-dioxolanyl, tetrazolyl, 2-oxo-1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, morpholino, piperazinyl, pyrrolidinyl, in any of the preceding values for substituents on R^{1}a may optionally be substituted by 1 or 2 substituents independently selected from (1-4C)alkyl and carboxy;

R^{1}b is R^{1}b is quinolinyl, purinyl, benzothiazolyl, indolyl, 4-oxoquinolinyl, 2,7-naphthyridinyl or quinazolinyl, and wherein said R^{1}b may be optionally substituted by 1, 2 or 3 substituents independently selected from the substituents listed for R^{1}a above;

R^{1}c is a phenyl ring, substituted by 1, 2 or 3 substituents independently selected from the substituents listed for R^{1}a above;

R^{1}d is selected from -CH$_2$R^{1}a, and -C(O)R^{1}a.

In one aspect R^2 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, fluoromethyl, difluoromethyl and trifluoromethyl.

In another aspect R^2 is selected from (1-4C)alkyl, cyclopropyl, halo, and trifluoromethyl.

In another aspect R^2 is selected from (1-4C)alkyl, halo, and trifluoromethyl.

In another aspect R^2 is selected from (1-4C)alkyl, chloro and bromo.

In another aspect R^2 is selected from (1-4C)alkyl, halo and cyano.

In a further aspect R^2 is selected from methyl, ethyl, isopropyl and chloro.

In another aspect R^2 is selected from methyl, ethyl, isopropyl, chloro and cyano.

In one aspect R^3 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, cyano, fluoromethyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl.

In another aspect R^3 is selected from hydrogen, (1-4C)alkyl, halo, cyano, trifluoromethyl and -CO(1-4C)alkyl.

In another aspect R^3 is selected from hydrogen, (1-4C)alkyl, halo, cyano, trifluoromethyl and -COMe.

In another aspect R^3 is selected from hydrogen, (1-4C)alkyl, halo, cyano and -CO(1-6C)alkyl.

In another aspect R^3 is selected from hydrogen, methyl, ethyl, chloro, bromo, cyano, trifluoromethyl and -COMe.

In a further aspect R^3 is selected from hydrogen, methyl, ethyl, chloro, bromo, cyano and -COMe.

In one aspect R^4 is selected from hydrogen, (1-4C)alkyl, nitro, hydroxy, halo, cyano, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl, -CO(1-4C)alkyl, and (1-4C)alkoxy.

In another aspect R^4 is selected from hydrogen, (1-4C)alkyl, halo, cyano, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl.

In another aspect R^4 is selected from hydrogen, (1-4C)alkyl, halo, cyano, fluoromethyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl.

In another aspect R^4 is selected from hydrogen, (1-4C)alkyl, halo, cyano, trifluoromethyl and -COMe.

In another aspect R^4 is selected from hydrogen, (1-4C)alkyl, halo and cyano.

In another aspect R^4 is selected from hydrogen, methyl, ethyl, chloro, bromo, cyano and -COMe.

In a further aspect R^4 is selected from hydrogen, methyl, ethyl, chloro, bromo and cyano.

In another aspect R^4 is selected from hydrogen, chloro, methyl, ethyl and cyano.

A preferred value of R^4 as halo(1-4C)alkyl is fluoromethyl.

In one aspect R^5 is hydrogen or methyl.

In one aspect R^5 is hydrogen. In another aspect R^5 is methyl.

In one aspect R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-6C)cycloalkyl, -(1-4C)alkylC(O)O(1-4C)alkyl, hydroxy, amino, -NH(1-4C)alkyl, -(N[di(1-4C)alkyl], (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl, -(1-4C)alkylNH_2, -(1-4C)alkylNH(1-4C)alkyl, -(1-4C)alkylN[di(1-4C)alkyl], and -(1-4C)alkylheterocyclyl.

In another aspect R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-4C)alkenyl, (3-6C)cycloalkyl, -(1-4C)alkylC(O)O(1-4C)alkyl, hydroxy, amino, -NH(1-4C)alkyl, -(N[di(1-4C)alkyl], (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl, -(1-4C)alkylNH_2, -(1-4C)alkylNH(1-4C)alkyl, -(1-4C)alkylN[di(1-4C)alkyl], and -(1-4C)alkylheterocyclyl.

In another aspect R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-6C)cycloalkyl, -(1-4C)alkylC(O)O(1-4C)alkyl, hydroxy, amino, -NH(1-4C)alkyl, -(N[di(1-4C)alkyl], (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl, and -(1-4C)alkylheterocyclyl.

In another aspect R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-4C)alkenyl, (3-6C)cycloalkyl, -(1-4C)alkylC(O)O(1-4C)alkyl, hydroxy, amino, -NH(1-4C)alkyl, -(N[di(1-4C)alkyl], (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl, and -(1-4C)alkylheterocyclyl.

In another aspect R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, cyclopropyl, -(1-4C)alkylC(O)O(1-4C)alkyl, amino, -NHMe, $-NMe_2$, (1-4C)alkoxy, and -(1-4C)alkylheterocyclyl.

In another aspect R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-4C)alkenyl, cyclopropyl, -(1-4C)alkylC(O)O(1-4C)alkyl, amino, -NHMe, $-NMe_2$, (1-4C)alkoxy, and -(1-4C)alkylheterocyclyl.

In another aspect R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, cyclopropyl, -(1-4C)alkylC(O)OMe, amino, -NHMe, $-NMe_2$, (1-4C)alkoxy, and -(1-4C)alkylheterocyclyl.

In another aspect R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, allyl, cyclopropyl, -(1-4C)alkylC(O)OMe, amino, -NHMe, $-NMe_2$, (1-4C)alkoxy, and -(1-4C)alkylheterocyclyl.

When R^6 is -(1-4C)alkylheterocyclyl, the heterocyclyl group is preferably selected from morpholinyl, piperidinyl, piperazinyl, thiomorpholinyl and tetrahydropyranyl. Such a heterocyclyl group may optionally be substituted with a methyl group.

R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-4C)alkenyl, (3-6C)cycloalkyl, -(1-4C)alkylC(O)O(1-4C)alkyl, hydroxy, amino, -N[di(1-4C)alkyl], (1-4C)alkoxy and -(1-4C)alkylheterocyclyl.

R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-4C)alkenyl, cyclopropyl, -(1-4C)alkylC(O)O(1-4C)alkyl, hydroxy, amino, -N[di(1-4C)alkyl], (1-4C)alkoxy and -(1-4C)alkylmorpholino.

In another aspect, R^6 and R^7 together with the nitrogen to which they are attached form a 5-membered heterocyclyl ring, optionally substituted with 1 or 2 substituents independently selected from (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, hydroxy, (1-4C)alkoxy, halo, cyano, nitro, carboxy, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, formyl, (1-4C)alkylcarbonyl, (1-4C)alkoxycarbonyl, $-C(O)NH_2$, -C(O)NH(1-4C)alkyl, -C(O)N[di(1-4C)alkyl], $-S(O)_2NH_2$, $-S(O)_2NH(1-4C)alkyl$, $-S(O)_2N[di(1-4C)alkyl]$ and -S(O)p(1-4C)alkyl.

In another aspect, R^6 and R^7 together with the nitrogen to which they are attached form a 5-membered heterocyclyl ring, optionally substituted with 1 or 2 substituents independently selected from (1-4C)alkyl, hydroxy, (1-4C)alkoxy, halo, cyano, nitro, carboxy, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl and trifluoromethoxy.

In another aspect, R^6 and R^7 together with the nitrogen to which they are attached form a 5-membered heterocyclyl ring, optionally substituted with 1 or 2 substituents independently selected from (1-4C)alkyl, hydroxy, (1-4C)alkoxy, halo, cyano, nitro and carboxy.

In another aspect, R^6 and R^7 together with the nitrogen to which they are attached form a 5-membered heterocyclyl ring, optionally substituted with 1 or 2 substituents independently selected from (1-4C)alkyl and halo.

In another aspect, R^6 and R^7 together with the nitrogen to which they are attached form a 5-membered heterocyclyl ring, optionally substituted with 1 or 2 substituents independently selected from formyl, (1-4C)alkylcarbonyl, (1-4C)alkoxycarbonyl, $-C(O)NH_2$, -C(O)NH(1-4C)alkyl, -C(O)N[di(1-4C)alkyl], $-S(O)_2NH_2$, $-S(O)_2NH$(1-4C)alkyl, $-S(O)_2N$[di(1-4C)alkyl] and -S(O)p(1-4C)alkyl.

In another aspect, R^6 and R^7 together with the nitrogen to which they are attached form a 6-membered heterocyclyl ring, optionally substituted with 1 or 2 substituents independently selected from (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, hydroxy, (1-4C)alkoxy, halo, cyano, nitro, carboxy, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, formyl, (1-4C)alkylcarbonyl, (1-4C)alkoxycarbonyl, $-C(O)NH_2$, -C(O)NH(1-4C)alkyl, -C(O)N[di(1-4C)alkyl], $-S(O)_2NH_2$, $-S(O)_2NH$(1-4C)alkyl, $-S(O)_2N$[di(1-4C)alkyl] and -S(O)p(1-4C)alkyl.

In another aspect, R^6 and R^7 together with the nitrogen to which they are attached form a 6-membered heterocyclyl ring, optionally substituted with 1 or 2 substituents independently selected from (1-4C)alkyl, hydroxy, (1-4C)alkoxy, halo, cyano, nitro, carboxy, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl and trifluoromethoxy.

In another aspect, R^6 and R^7 together with the nitrogen to which they are attached form a 6-membered heterocyclyl ring, optionally substituted with 1 or 2 substituents

independently selected from (1-4C)alkyl, hydroxy, (1-4C)alkoxy, halo, cyano, nitro and carboxy.

In another aspect, R^6 and R^7 together with the nitrogen to which they are attached form a 6-membered heterocyclyl ring, optionally substituted with 1 or 2 substituents independently selected from (1-4C)alkyl and halo.

In another aspect, R^6 and R^7 together with the nitrogen to which they are attached form a 6-membered heterocyclyl ring, optionally substituted with 1 or 2 substituents independently selected from formyl, (1-4C)alkylcarbonyl, (1-4C)alkoxycarbonyl, $-C(O)NH_2$, -C(O)NH(1-4C)alkyl, -C(O)N[di(1-4C)alkyl], $-S(O)_2NH_2$, $-S(O)_2NH(1-4C)alkyl$, $-S(O)_2N[di(1-4C)alkyl]$ and -S(O)p(1-4C)alkyl.

When R^6 and R^7 together with the nitrogen to which they are attached form a 5-membered heterocyclyl ring, suitable values for such a ring are pyrrolidine, pyrazole, pyrrole, tetrazole, imidazole, imidazoline and triazole. Further suitable values are the afore-mentioned rings wherein a ring carbon atom is oxidised to form a carbonyl group, such as 2-pyrrolidone.

When R^6 and R^7 together with the nitrogen to which they are attached form a 6-membered heterocyclyl ring, suitable values for such a ring are morpholinyl, piperidinyl, piperazinyl, thiomorpholinyl and tetrahydropyridinyl. Further suitable values are the afore-mentioned rings wherein a ring carbon atom is oxidised to form a carbonyl group, such as 2-piperidinone, 2-piperazinone and 2-tetrahydropyridone.

R^6 and R^7 may together with the nitrogen to which they are attached form a 5 or 6-membered heterocyclyl ring, optionally substituted with 1 or 2 substituents independently selected from (1-4C)alkyl.

R^6 and R^7 may together with the nitrogen to which they are attached form piperazinyl or morpholino optionally substituted with 1 or 2 subatituents independently selected from (1-4C)alkyl.

In one aspect R^7 is independently at each occurrence selected from hydrogen and (1-4C)alkyl.

In a further aspect of the invention R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-4C)alkenyl, (3-6C)cycloalkyl, -(1-4C)alkylC(O)O(1-4C)alkyl, hydroxy, amino, -N[di(1-4C)alkyl], (1-4C)alkoxy and -(1-4C)alkylheterocyclyl;

R^7 is independently at each occurrence selected from hydrogen and (1-6C)alkyl;

or R^6 and R^7 may together with the nitrogen to which they are attached form a 5 or 6-membered heterocyclyl ring, optionally substituted with 1 or 2 substituents independently selected from (1-4C)alkyl.

In one embodiment is provided a compound of the formula (1) or a pharmaceutically-acceptable salt thereof, wherein:

Y is H;

W is O;

R^1 is selected from R^1a and R^1b;

R^2 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, fluoromethyl, difluoromethyl and trifluoromethyl;

R^3 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, cyano, fluoromethyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl;

R^4 is selected from hydrogen, (1-4C)alkyl, halo, cyano, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl;

R^6 is indepedently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-6C)cycloalkyl, -(1-4C)alkylC(O)O(1-4C)alkyl, hydroxy, amino, -NH(1-4C)alkyl, -(N[di(1-4C)alkyl], (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl, and -(1-4C)alkylheterocyclyl;

R^7 is independently at each occurrence selected from hydrogen and (1-4C)alkyl.

In another embodiment is provided a compound of the formula (1) or a pharmaceutically-acceptable salt thereof, wherein:

Y is H;

W is O;

R^1 is selected from R^1a and R^1b, optionally substituted by 1 or 2 substituents independently selected from nitro, cyano, -CO(1-6C)alkyl, -COO(1-6C)alkyl (optionally substituted with -COO(1-4C)alkyl), trifluoromethyl, $-CONR^6R^7$, $-OCONR^6R^7$, $-N(R^7)COR^6$, $-CONHCH(CO_2R^7)R^6$, halo, hydroxy, carboxy, (1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo, cyano, nitro, -COO(1-6C)alkyl, -OCO(1-4C)alkyl, (1-6C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(1-4C)alkoxy, (2-4C)alkenyloxy, trifluoromethyl, $-CONR^6R^7$, carboxy, -NHC(O)O(1-4C)alkyl, $-OCONR^6R^7$, -C(=NOH)(1-4C)alkyl, $-C(=NOH)NR^6R^7$, -S(O)p(1-4C)alkyl, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$, and heterocyclyl],

(3-6C)cycloalkyl (optionally substituted by 1 or 2 substituents selected from (1-6C)alkyl and the optional substituents described for (1-6C)alkyl hereinbefore), -O(1-6C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), -S(O)p(1-4C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), heterocyclyl, -NHC(O)O(1-4C)alkyl, -C(=NOR^7)(1-4C)alkyl, -C(=NOR^7)NR^{6}R^7, -S(O)pNR^{6}R^7, -NR^{7}S(O)p(1-4C)alkyl, -NR^{7}S(O)p-aryl, -C(O)NHS(O)p(1-4C)alkyl, -C(O)NHS(O)p-aryl, and -NR^{6}R^7;

wherein any heterocyclyl or aryl group in any of the preceding values for substituents on R^{1}a may optionally be substituted by 1 or 2 substituents independently selected from (1-4C)alkyl, hydroxy, (1-4C)alkoxy, halo, cyano, nitro, carboxy, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, formyl, -CO(1-4C)alkyl, -COO(1-4C)alkyl, -C(O)NH$_2$, -C(O)NH(1-4C)alkyl, -C(O)N[di(1-4C)alkyl], -S(O)$_2$NH$_2$, -S(O)$_2$NH(1-4C)alkyl and -S(O)$_2$N[di(1-4C)alkyl];

R^2 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, fluoromethyl, difluoromethyl and trifluoromethyl;

R^3 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, cyano, fluoromethyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl;

R^4 is selected from hydrogen, (1-4C)alkyl, halo, cyano, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl;

R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-4C)alkenyl, (3-6C)cycloalkyl, -(1-4C)alkylC(O)O(1-4C)alkyl, hydroxy, amino, -NH(1-4C)alkyl, -(N[di(1-4C)alkyl], (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl, and -(1-4C)alkylheterocyclyl;

R^7 is independently at each occurrence selected from hydrogen and (1-4C)alkyl; and

p is (independently at each occurrence) 0, 1 or 2.

In another embodiment is provided a compound of the formula (1) or a pharmaceutically-acceptable salt thereof, wherein:

Y is H;

W is O;

R^1 is selected from R^{1}a and R^{1}b, optionally substituted by 1 or 2 substituents independently selected from nitro, cyano, -CO(1-6C)alkyl, -COO(1-6C)alkyl, -O(1-6C)alkyl, trifluoromethyl, -CONR^{6}R^7, -OCONR^{6}R^7, -N(R^7)COR^6, -CONHCH(CO$_2$R^7)R^6, halo, hydroxy, carboxy, (1-6C)alkyl, heterocyclyl, aryl, -NHC(O)O(1-4C)alkyl,

-C(=NOR^7)(1-4C)alkyl, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alkyl (optionally substituted by hydroxy), -S(O)pNR^{6}R^7, -S(O)p(1-4C)alkylCONHR^7, -NR^{7}S(O)pNR^{6}R^7, -NR^{7}S(O)p(1-4C)alkyl, -NR^{7}S(O)p-aryl, -C(O)NHS(O)p(1-4C)alkyl, -C(O)NHS(O)p-aryl and -NR^{6}R^7;

R^2 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, fluoromethyl, difluoromethyl and trifluoromethyl;

R^3 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, cyano, fluoromethyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl;

R^4 is selected from hydrogen, (1-4C)alkyl, halo, cyano, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl;

R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-6C)cycloalkyl, -(1-4C)alkylC(O)O(1-4C)alkyl, hydroxy, amino, -NH(1-4C)alkyl, -(N[di(1-4C)alkyl], (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl, and -(1-4C)alkylheterocyclyl;

R^7 is independently at each occurrence selected from hydrogen and (1-4C)alkyl; and

p is (independently at each occurrence) 0, 1 or 2.

In another embodiment is provided a compound of the formula (I) or a pharmaceutically-acceptable salt thereof, wherein:

Y is H;

W is O;

R^1 is selected from R^{1}a and R^{1}b, optionally substituted by 1 or 2 substituents independently selected from nitro, cyano, -CO(1-6C)alkyl, -COO(1-6C)alkyl (optionally substituted with -COO(1-4C)alkyl), trifluoromethyl, -CONR^{6}R^7, -OCONR^{6}R^7, -N(R^7)COR^6, halo, carboxy, (1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo, -COO(1-6C)alkyl, -OCO(1-4C)alkyl, (1-6C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(1-4C)alkoxy, (2-4C)alkenyloxy, trifluoromethyl, -CONR^{6}R^7, carboxy, -NHC(O)O(1-4C)alkyl, -OCONR^{6}R^7, -C(=NOH)(1-4C)alkyl, -C(=NOH)NR^{6}R^7, -S(O)p(1-4C)alkyl, -S(O)pNR^{6}R^7, -NHSO$_2$R^6, -NR^{6}R^7, and heterocyclyl], (3-6C)cycloalkyl (optionally substituted by 1 or 2 substituents selected from (1-6C)alkyl and the optional substituents described for (1-6C)alkyl hereinbefore), -O(1-6C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), -S(O)p(1-4C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), heterocyclyl, -NHC(O)O(1-4C)alkyl, -C(=NOR^7)(1-4C)alkyl,

-C(=NOR^7)NR^{6}R^7, -S(O)pNR^{6}R^7, -NR^{7}S(O)p(1-4C)alkyl, -C(O)NHS(O)p(1-4C)alkyl, and -NR^{6}R^7;

wherein any heterocyclyl or aryl group in any of the preceding values for substituents on R^{1}a may optionally be substituted by 1 or 2 substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy, halo, cyano, nitro, carboxy, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl and trifluoromethoxy;

R^2 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, fluoromethyl, difluoromethyl and trifluoromethyl;

R^3 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, cyano, fluoromethyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl;

R^4 is selected from hydrogen, (1-4C)alkyl, halo, cyano, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl;

R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-4C)alkenyl, (3-6C)cycloalkyl, -(1-4C)alkylC(O)O(1-4C)alkyl, hydroxy, amino, -NH(1-4C)alkyl, -(N[di(1-4C)alkyl], (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl, and -(1-4C)alkylheterocyclyl;

R^7 is independently at each occurrence selected from hydrogen and (1-4C)alkyl; and

p is (independently at each occurrence) 0, 1 or 2.

In another embodiment is provided a compound of the formula (1) or a pharmaceutically-acceptable salt thereof, wherein:

Y is H;

W is O;

R^1 is selected from R^{1}a and R^{1}b, optionally substituted by 1 or 2 substituents independently selected from nitro, cyano, -CO(1-4C)alkyl, -COO(1-4C)alkyl, -O(1-4C)alkyl, trifluoromethyl, -CONR^{6}R^7, -N(R^7)COR^6, fluoro, chloro, bromo, hydroxy, carboxy, (1-4C)alkyl, heterocyclyl, -NHC(O)O(1-4C)alkyl, -C(=NOR^7)(1-4C)alkyl, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alkyl (optionally substituted by hydroxy), -S(O)p(1-4C)alkylCONHR^7, and -NR^{6}R^7;

R^2 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, fluoromethyl, difluoromethyl and trifluoromethyl;

R^3 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, cyano, fluoromethyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl;

R^4 is selected from hydrogen, (1-4C)alkyl, halo, cyano, fluoromethyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl;

R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-6C)cycloalkyl, -(1-4C)alkylC(O)O(1-4C)alkyl, hydroxy, amino, -NH(1-4C)alkyl, -(N[di(1-4C)alkyl], (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl, and -(1-4C)alkylheterocyclyl;

R^7 is independently at each occurrence selected from hydrogen and (1-4C)alkyl; and

p is (independently at each occurrence) 0, 1 or 2.

In another embodiment is provided a compound of the formula (1) or a pharmaceutically-acceptable salt thereof, wherein:

Y is H;

W is O;

R^1 is selected from imidazolyl, pyrimidinyl, pyridinyl, thiazolyl, triazinyl, pyrrolyl, thiadiazolyl, tetrazolyl, quinolinyl, purinyl, benzothiazolyl and indolyl; optionally substituted by 1 or 2 substituents independently selected from nitro, cyano, -CO(1-4C)alkyl, -COO(1-4C)alkyl, -O(1-4C)alkyl, trifluoromethyl, -CONR^{6}R^7, -N(R^7)COR^6, fluoro, chloro, bromo, hydroxy, carboxy, (1-4C)alkyl, heterocyclyl, -NHC(O)O(1-4C)alkyl, -C(=NOR^7)(1-4C)alkyl, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alkyl (optionally substituted by hydroxy), -S(O)p(1-4C)alkylCONHR^7, and -NR^{6}R^7;

R^2 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, fluoromethyl, difluoromethyl and trifluoromethyl;

R^3 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, cyano, fluoromethyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl;

R^4 is selected from hydrogen, (1-4C)alkyl, halo, cyano, fluoromethyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl;

R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-6C)cycloalkyl, -(1-4C)alkylC(O)O(1-4C)alkyl, hydroxy, amino, -NH(1-4C)alkyl, -(N[di(1-4C)alkyl], (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl, and -(1-4C)alkylheterocyclyl;

R^7 is independently at each occurrence selected from hydrogen and (1-4C)alkyl; and

p is (independently at each occurrence) 0, 1 or 2.

In another embodiment is provided a compound of the formula (1) or a pharmaceutically-acceptable salt thereof, wherein:

Y is H;

W is O;

R^1 is selected from imidazolyl, pyrimidinyl, pyridinyl, thiazolyl, triazinyl, pyrrolyl, thiadiazolyl, tetrazolyl, quinolinyl, purinyl, benzothiazolyl and indolyl; optionally substituted by 2 substituents; wherein one substituent is selected from carboxy, $-CONHSO_2Me$ and $-CONHR^6$ and wherein the other substituent is selected from (1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo, cyano, nitro, -COO(1-6C)alkyl, -OCO(1-4C)alkyl, (1-6C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(1-4C)alkoxy, (2-4C)alkenyloxy, trifluoromethyl, $-CONR^6R^7$, carboxy, $-NHC(O)O(1\text{-}4C)alkyl$, $-OCONR^6R^7$, $-C(=NOH)(1\text{-}4C)alkyl$, $-C(=NOH)NR^6R^7$, $-S(O)p(1\text{-}4C)alkyl$, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$, and heterocyclyl], -O(1-6C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore) and $-S(O)p(1\text{-}4C)alkyl$ (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore);

R^2 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, fluoromethyl, difluoromethyl and trifluoromethyl;

R^3 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, cyano, fluoromethyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl.

R^4 is selected from hydrogen, (1-4C)alkyl, halo, cyano, fluoromethyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl;

R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-4C)alkenyl, (3-6C)cycloalkyl, -(1-4C)alkylC(O)O(1-4C)alkyl, hydroxy, amino, -NH(1-4C)alkyl, -(N[di(1-4C)alkyl], (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl, and -(1-4C)alkylheterocyclyl;

R^7 is independently at each occurrence selected from hydrogen and (1-4C)alkyl; and

p is (independently at each occurrence) 0, 1 or 2.

In another embodiment is provided a compound of the formula (1) or a pharmaceutically-acceptable salt thereof, wherein:

Y is H;

W is O;

R^1 is selected from imidazolyl, pyrimidinyl, pyridinyl, thiazolyl, triazinyl, pyrrolyl, thiadiazolyl, tetrazolyl, quinolinyl, purinyl, benzothiazolyl and indolyl; optionally substituted by 1 or 2 substituents independently selected from nitro, cyano, -CO(1-4C)alkyl,

-COO(1-4C)alkyl, -O(1-4C)alkyl, trifluoromethyl, -CONR^{6}R^7, -N(R^7)COR^6, fluoro, chloro, bromo, hydroxy, carboxy, (1-4C)alkyl, heterocyclyl, -NHC(O)O(1-4C)alkyl, -C(=NOR^7)(1-4C)alkyl, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alkyl (optionally substituted by hydroxy), -S(O)p(1-4C)alkylCONHR^7, and -NR^{6}R^7;

R^2 is selected from (1-4C)alkyl, chloro and bromo;

R^3 is selected from hydrogen, methyl, ethyl, chloro, bromo, cyano, trifluoromethyl and -COMe;

R^4 is selected from hydrogen, methyl, ethyl, chloro, bromo, cyano and -COMe;

R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, cyclopropyl, -(1-4C)alkylC(O)OMe, amino, -NHMe, -NMe$_2$, (1-4C)alkoxy, and -(1-4C)alkylheterocyclyl;

R^7 is independently at each occurrence selected from hydrogen and (1-4C)alkyl; and

p is (independently at each occurrence) 0, 1 or 2.

In another embodiment is provided a compound of the formula (1) or a pharmaceutically-acceptable salt thereof, wherein:

Y is H;

W is O;

R^1 is selected from imidazolyl, pyrimidinyl, pyridinyl, thiazolyl, triazinyl, pyrrolyl, thiadiazolyl, tetrazolyl, quinolinyl, purinyl, benzothiazolyl and indolyl; optionally substituted by 2 substituents; wherein one substituent is selected from carboxy, -CONHSO$_2$Me and -CONHR^6 (wherein R^6 is selected from -OMe, hydrogen, amino and 3-4C alkenyl); and wherein the other substituent is selected from (1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo, cyano, nitro, -COO(1-6C)alkyl, -OCO(1-4C)alkyl, (1-6C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(1-4C)alkoxy, (2-4C)alkenyloxy, trifluoromethyl, -CONR^{6}R^7, carboxy, -NHC(O)O(1-4C)alkyl, -OCONR^{6}R^7, -C(=NOH)(1-4C)alkyl, -C(=NOH)NR^{6}R^7, -S(O)p(1-4C)alkyl, -S(O)pNR^{6}R^7, -NHSO$_2$R^6, -NR^{6}R^7, and heterocyclyl], -O(1-6C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore) and -S(O)p(1-4C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore);

R^2 is selected from (1-4C)alkyl, chloro and bromo;

R^3 is selected from hydrogen, methyl, ethyl, chloro, bromo, cyano, trifluoromethyl and -COMe;

R^4 is selected from hydrogen, methyl, ethyl, chloro, bromo, cyano and -COMe;

R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, allyl, cyclopropyl, -(1-4C)alkylC(O)OMe, amino, -NHMe, -NMe_2, (1-4C)alkoxy, and -(1-4C)alkylheterocyclyl;

R^7 is independently at each occurrence selected from hydrogen and (1-4C)alkyl; and

p is (independently at each occurrence) 0, 1 or 2.

In another embodiment is provided a compound of the formula (1) or a pharmaceutically-acceptable salt thereof, wherein:

Y is H;

W is O;

R^1 is selected from imidazolyl, pyrimidinyl, pyridinyl, thiazolyl, triazinyl, pyrrolyl, thiadiazolyl, tetrazolyl, quinolinyl, purinyl, benzothiazolyl and indolyl; optionally substituted by 1 or 2 substituents independently selected from nitro, cyano, -CO(1-4C)alkyl, -COO(1-4C)alkyl, -O(1-4C)alkyl, trifluoromethyl, -$CONR^6R^7$, fluoro, chloro, bromo, hydroxy, carboxy, (1-4C)alkyl, heterocyclyl, -NHC(O)O(1-4C)alkyl, -$C(=NOH)NR^6R^7$, -S(O)p(1-4C)alkyl (optionally substituted by hydroxy), -S(O)p(1-4C)alkylCONHMe, and -NR^6R^7;

R^2 is selected from (1-4C)alkyl, chloro and bromo;

R^3 is selected from hydrogen, methyl, ethyl, chloro, bromo, cyano, trifluoromethyl and -COMe;

R^4 is selected from hydrogen, methyl, ethyl, chloro, bromo, cyano and -COMe;

R^6 and R^7 together form a 5- or 6-membered heterocyclyl ring, optionally substituted with 1 or 2 substituents independently selected from (1-4C)alkyl, hydroxy, (1-4C)alkoxy, halo, cyano, nitro, carboxy, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl and trifluoromethoxy; and

p is (independently at each occurrence) 0, 1 or 2.

In one embodiment is provided a compound of the formula (1) or a pharmaceutically-acceptable salt thereof, wherein:

Y is H;

W is NR^5;

R^1 is selected from R^1a and R^1b;

R^2 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, fluoromethyl, difluoromethyl and trifluoromethyl;

R^3 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, cyano, fluoromethyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl.

R^4 is selected from hydrogen, (1-4C)alkyl, halo, cyano, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl;

R^5 is hydrogen or methyl;

R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-6C)cycloalkyl, -(1-4C)alkylC(O)O(1-4C)alkyl, hydroxy, amino, -NH(1-4C)alkyl, -(N[di(1-4C)alkyl], (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl, and -(1-4C)alkylheterocyclyl;

R^7 is independently at each occurrence selected from hydrogen and (1-4C)alkyl.

In another embodiment is provided a compound of the formula (I) or a pharmaceutically-acceptable salt thereof, wherein:

Y is H;

W is NR^5;

R^1 is selected from R^1a and R^1b, optionally substituted by 1 or 2 substituents independently selected from nitro, cyano, -CO(1-6C)alkyl, -COO(1-6C)alkyl (optionally substituted with -COO(1-4C)alkyl), trifluoromethyl, $-CONR^6R^7$, $-OCONR^6R^7$, $-N(R^7)COR^6$, $-CONHCH(CO_2R^7)R^6$, halo, hydroxy, carboxy, (1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo, cyano, nitro, -COO(1-6C)alkyl, -OCO(1-4C)alkyl, (1-6C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(1-4C)alkoxy, (2-4C)alkenyloxy, trifluoromethyl, $-CONR^6R^7$, carboxy, -NHC(O)O(1-4C)alkyl, $-OCONR^6R^7$, -C(=NOH)(1-4C)alkyl, $-C(=NOH)NR^6R^7$, -S(O)p(1-4C)alkyl, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$, and heterocyclyl], (3-6C)cycloalkyl (optionally substituted by 1 or 2 substituents selected from (1-6C)alkyl and the optional substituents described for (1-6C)alkyl hereinbefore), -O(1-6C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), -S(O)p(1-4C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), heterocyclyl, -NHC(O)O(1-4C)alkyl, $-C(=NOR^7)$(1-4C)alkyl, $-C(=NOR^7)NR^6R^7$, $-S(O)pNR^6R^7$, $-NR^7S(O)p$(1-4C)alkyl, $-NR^7S(O)p$-aryl, -C(O)NHS(O)p(1-4C)alkyl, -C(O)NHS(O)p-aryl, and $-NR^6R^7$;

wherein any heterocyclyl or aryl group in any of the preceding values for substituents on R^1a may optionally be substituted by 1 or 2 substituents independently selected from (1-4C)alkyl,

hydroxy, (1-4C)alkoxy, halo, cyano, nitro, carboxy, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, formyl, -CO(1-4C)alkyl, -COO(1-4C)alkyl, -C(O)NH_2, -C(O)NH(1-4C)alkyl, -C(O)N[di(1-4C)alkyl], -$S(O)_2NH_2$, -$S(O)_2$NH(1-4C)alkyl and -$S(O)_2$N[di(1-4C)alkyl];

R^2 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, fluoromethyl, difluoromethyl and trifluoromethyl;

R^3 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, cyano, fluoromethyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl;

R^4 is selected from hydrogen, (1-4C)alkyl, halo, cyano, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl;

R^5 is hydrogen or methyl;

R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-4C)alkenyl, (3-6C)cycloalkyl, -(1-4C)alkylC(O)O(1-4C)alkyl, hydroxy, amino, -NH(1-4C)alkyl, -(N[di(1-4C)alkyl], (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl, and -(1-4C)alkylheterocyclyl;

R^7 is independently at each occurrence selected from hydrogen and (1-4C)alkyl; and

p is (independently at each occurrence) 0, 1 or 2.

In another embodiment is provided a compound of the formula (1) or a pharmaceutically-acceptable salt thereof, wherein:

Y is H;

W is NR^5;

R^1 is selected from R^1a and R^1b, optionally substituted by 1 or 2 substituents independently selected from nitro, cyano, -CO(1-6C)alkyl, -COO(1-6C)alkyl, -O(1-6C)alkyl, trifluoromethyl, -$CONR^6R^7$, -$OCONR^6R^7$, -$N(R^7)COR^6$, -$CONHCH(CO_2R^7)R^6$, halo, hydroxy, carboxy, (1-6C)alkyl, heterocyclyl, aryl, -NHC(O)O(1-4C)alkyl, -$C(=NOR^7)$(1-4C)alkyl, -$C(=NOR^7)NR^6R^7$, -S(O)p(1-4C)alkyl (optionally substituted by hydroxy), -S(O)pNR^6R^7, -S(O)p(1-4C)alkylCONHR^7, -NR^7S(O)pNR^6R^7, -NR^7S(O)p(1-4C)alkyl, -NR^7S(O)p-aryl, -C(O)NHS(O)p(1-4C)alkyl, -C(O)NHS(O)p-aryl and -NR^6R^7;

R^2 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, fluoromethyl, difluoromethyl and trifluoromethyl;

R^3 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, cyano, fluoromethyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl.

R^4 is selected from hydrogen, (1-4C)alkyl, halo, cyano, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl;

R^5 is hydrogen or methyl;

R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-6C)cycloalkyl, -(1-4C)alkylC(O)O(1-4C)alkyl, hydroxy, amino, -NH(1-4C)alkyl, -(N[di(1-4C)alkyl], (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl, and -(1-4C)alkylheterocyclyl;

R^7 is independently at each occurrence selected from hydrogen and (1-4C)alkyl; and

p is (independently at each occurrence) 0, 1 or 2.

In another embodiment is provided a compound of the formula (1) or a pharmaceutically-acceptable salt thereof, wherein:

Y is H;

W is NR^5;

R^1 is selected from R^1a and R^1b, optionally substituted by 1 or 2 substituents independently selected from nitro, cyano, -CO(1-6C)alkyl, -COO(1-6C)alkyl (optionally substituted with -COO(1-4C)alkyl), trifluoromethyl, $-CONR^6R^7$, $-OCONR^6R^7$, $-N(R^7)COR^6$, halo, carboxy, (1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo, -COO(1-6C)alkyl, -OCO(1-4C)alkyl, (1-6C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(1-4C)alkoxy, (2-4C)alkenyloxy, trifluoromethyl, $-CONR^6R^7$, carboxy, -NHC(O)O(1-4C)alkyl, $-OCONR^6R^7$, -C(=NOH)(1-4C)alkyl, $-C(=NOH)NR^6R^7$, -S(O)p(1-4C)alkyl, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$, and heterocyclyl], (3-6C)cycloalkyl (optionally substituted by 1 or 2 substituents selected from (1-6C)alkyl and the optional substituents described for (1-6C)alkyl hereinbefore), -O(1-6C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), -S(O)p(1-4C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), heterocyclyl, -NHC(O)O(1-4C)alkyl, $-C(=NOR^7)$(1-4C)alkyl, $-C(=NOR^7)NR^6R^7$, $-S(O)pNR^6R^7$, $-NR^7S(O)p$(1-4C)alkyl, -C(O)NHS(O)p(1-4C)alkyl, and $-NR^6R^7$;

wherein any heterocyclyl or aryl group in any of the preceding values for substituents on R^1a may optionally be substituted by 1 or 2 substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy, halo, cyano, nitro, carboxy, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl and trifluoromethoxy;

R^2 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, fluoromethyl, difluoromethyl and trifluoromethyl;

R^3 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, cyano, fluoromethyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl;

R^4 is selected from hydrogen, (1-4C)alkyl, halo, cyano, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl;

R^5 is hydrogen or methyl;

R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-4C)alkenyl, (3-6C)cycloalkyl, -(1-4C)alkylC(O)O(1-4C)alkyl, hydroxy, amino, -NH(1-4C)alkyl, -(N[di(1-4C)alkyl], (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl, and -(1-4C)alkylheterocyclyl;

R^7 is independently at each occurrence selected from hydrogen and (1-4C)alkyl; and

p is (independently at each occurrence) 0, 1 or 2.

In another embodiment is provided a compound of the formula (I) or a pharmaceutically-acceptable salt thereof, wherein:

Y is H;

W is NR^5;

R^1 is selected from R^1a and R^1b, optionally substituted by 1 or 2 substituents independently selected from nitro, cyano, -CO(1-4C)alkyl, -COO(1-4C)alkyl, -O(1-4C)alkyl, trifluoromethyl, $-CONR^6R^7$, $-N(R^7)COR^6$, fluoro, chloro, bromo, hydroxy, carboxy, (1-4C)alkyl, heterocyclyl, -NHC(O)O(1-4C)alkyl, $-C(=NOR^7)$(1-4C)alkyl, $-C(=NOR^7)NR^6R^7$, -S(O)p(1-4C)alkyl (optionally substituted by hydroxy), -S(O)p(1-4C)alkylCONHR^7, and $-NR^6R^7$;

R^2 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, fluoromethyl, difluoromethyl and trifluoromethyl;

R^3 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, cyano, fluoromethyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl.

R^4 is selected from hydrogen, (1-4C)alkyl, halo, cyano, fluoromethyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl;

R^5 is hydrogen or methyl;

R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-6C)cycloalkyl, -(1-4C)alkylC(O)O(1-4C)alkyl, hydroxy, amino, -NH(1-4C)alkyl,

-(N[di(1-4C)alkyl], (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl, and -(1-4C)alkylheterocyclyl;

R^7 is independently at each occurrence selected from hydrogen and (1-4C)alkyl; and

p is (independently at each occurrence) 0, 1 or 2.

In another embodiment is provided a compound of the formula (1) or a pharmaceutically-acceptable salt thereof, wherein:

Y is H;

W is NR^5;

R^1 is selected from imidazolyl, pyrimidinyl, pyridinyl, thiazolyl, triazinyl, pyrrolyl, thiadiazolyl, tetrazolyl, quinolinyl, purinyl, benzothiazolyl and indolyl; optionally substituted by 1 or 2 substituents independently selected from nitro, cyano, -CO(1-4C)alkyl, -COO(1-4C)alkyl, -O(1-4C)alkyl, trifluoromethyl, $-CONR^6R^7$, $-N(R^7)COR^6$, fluoro, chloro, bromo, hydroxy, carboxy, (1-4C)alkyl, heterocyclyl, -NHC(O)O(1-4C)alkyl, $-C(=NOR^7)$(1-4C)alkyl, $-C(=NOR^7)NR^6R^7$, -S(O)p(1-4C)alkyl (optionally substituted by hydroxy), -S(O)p(1-4C)alkylCONHR^7, and $-NR^6R^7$;

R^2 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, fluoromethyl, difluoromethyl and trifluoromethyl;

R^3 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, cyano, fluoromethyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl.

R^4 is selected from hydrogen, (1-4C)alkyl, halo, cyano, fluoromethyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl;

R^5 is hydrogen or methyl;

R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-6C)cycloalkyl, -(1-4C)alkylC(O)O(1-4C)alkyl, hydroxy, amino, -NH(1-4C)alkyl, -(N[di(1-4C)alkyl], (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl, and -(1-4C)alkylheterocyclyl;

R^7 is independently at each occurrence selected from hydrogen and (1-4C)alkyl; and

p is (independently at each occurrence) 0, 1 or 2.

In another embodiment is provided a compound of the formula (1) or a pharmaceutically-acceptable salt thereof, wherein:

Y is H;

W is NR^5;

R^1 is selected from imidazolyl, pyrimidinyl, pyridinyl, thiazolyl, triazinyl, pyrrolyl, thiadiazolyl, tetrazolyl, quinolinyl, purinyl, benzothiazolyl and indolyl; optionally substituted by 2 substituents; wherein one substituent is selected from carboxy, $-CONHSO_2Me$ and $-CONHR^6$ and wherein the other substituent is selected from

(1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo, cyano, nitro, -COO(1-6C)alkyl, -OCO(1-4C)alkyl, (1-6C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(1-4C)alkoxy, (2-4C)alkenyloxy, trifluoromethyl, $-CONR^6R^7$, carboxy, -NHC(O)O(1-4C)alkyl, $-OCONR^6R^7$, -C(=NOH)(1-4C)alkyl, $-C(=NOH)NR^6R^7$, -S(O)p(1-4C)alkyl, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$, and heterocyclyl], -O(1-6C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore) and -S(O)p(1-4C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore);

R^2 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, fluoromethyl, difluoromethyl and trifluoromethyl;

R^3 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, halo, cyano, fluoromethyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl.

R^4 is selected from hydrogen, (1-4C)alkyl, halo, cyano, fluoromethyl, difluoromethyl, trifluoromethyl and -CO(1-4C)alkyl;

R^5 is hydrogen or methyl;

R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-4C)alkenyl, (3-6C)cycloalkyl, -(1-4C)alkylC(O)O(1-4C)alkyl, hydroxy, amino, -NH(1-4C)alkyl, -(N[di(1-4C)alkyl], (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl, and -(1-4C)alkylheterocyclyl;

R^7 is independently at each occurrence selected from hydrogen and (1-4C)alkyl; and

p is (independently at each occurrence) 0, 1 or 2.

In another embodiment is provided a compound of the formula (I) or a pharmaceutically-acceptable salt thereof, wherein:

Y is H;

W is NR^5;

R^1 is selected from imidazolyl, pyrimidinyl, pyridinyl, thiazolyl, triazinyl, pyrrolyl, thiadiazolyl, tetrazolyl, quinolinyl, purinyl, benzothiazolyl and indolyl; optionally substituted by 1 or 2 substituents independently selected from nitro, cyano, -CO(1-4C)alkyl, -COO(1-4C)alkyl, -O(1-4C)alkyl, trifluoromethyl, $-CONR^6R^7$, $-N(R^7)COR^6$, fluoro, chloro,

bromo, hydroxy, carboxy, (1-4C)alkyl, heterocyclyl, -NHC(O)O(1-4C)alkyl, -C(=NOR^7)(1-4C)alkyl, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alkyl (optionally substituted by hydroxy), -S(O)p(1-4C)alkylCONHR^7, and -NR^{6}R^7;

R^2 is selected from (1-4C)alkyl, chloro and bromo;

R^3 is selected from hydrogen, methyl, ethyl, chloro, bromo, cyano, trifluoromethyl and -COMe;

R^4 is selected from hydrogen, methyl, ethyl, chloro, bromo, cyano and -COMe;

R^5 is hydrogen or methyl;

R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, cyclopropyl, -(1-4C)alkylC(O)OMe, amino, -NHMe, -NMe$_2$, (1-4C)alkoxy, and -(1-4C)alkylheterocyclyl;

R^7 is independently at each occurrence selected from hydrogen and (1-4C)alkyl; and

p is (independently at each occurrence) 0, 1 or 2.

In another embodiment is provided a compound of the formula (1) or a pharmaceutically-acceptable salt thereof, wherein:

Y is H;

W is NR^5;

R^1 is selected from imidazolyl, pyrimidinyl, pyridinyl, thiazolyl, triazinyl, pyrrolyl, thiadiazolyl, tetrazolyl, quinolinyl, purinyl, benzothiazolyl and indolyl; optionally substituted by 2 substituents; wherein one substituent is selected from carboxy, -CONHSO$_2$Me and -CONHR^6 (wherein R^6 is selected from -OMe, hydrogen, amino and 3-4C alkenyl); and wherein the other substituent is selected from (1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo, cyano, nitro, -COO(1-6C)alkyl, -OCO(1-4C)alkyl, (1-6C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(1-4C)alkoxy, (2-4C)alkenyloxy, trifluoromethyl, -CONR^{6}R^7, carboxy, -NHC(O)O(1-4C)alkyl, -OCONR^{6}R^7, -C(=NOH)(1-4C)alkyl, -C(=NOH)NR^{6}R^7, -S(O)p(1-4C)alkyl, -S(O)pNR^{6}R^7, -NHSO$_2$R^6, -NR^{6}R^7, and heterocyclyl], -O(1-6C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore) and -S(O)p(1-4C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore);

R^2 is selected from (1-4C)alkyl, chloro and bromo;

R^3 is selected from hydrogen, methyl, ethyl, chloro, bromo, cyano, trifluoromethyl and -COMe;

R^4 is selected from hydrogen, methyl, ethyl, chloro, bromo, cyano and -COMe;

R^5 is hydrogen or methyl;

R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, allyl, cyclopropyl, -(1-4C)alkylC(O)OMe, amino, -NHMe, -NMe_2, (1-4C)alkoxy, and -(1-4C)alkylheterocyclyl;

R^7 is independently at each occurrence selected from hydrogen and (1-4C)alkyl; and

p is (independently at each occurrence) 0, 1 or 2.

In another embodiment is provided a compound of the formula (I) or a pharmaceutically-acceptable salt thereof, wherein:

Y is H;

W is NR^5;

R^1 is selected from imidazolyl, pyrimidinyl, pyridinyl, thiazolyl, triazinyl, pyrrolyl, thiadiazolyl, tetrazolyl, quinolinyl, purinyl, benzothiazolyl and indolyl; optionally substituted by 1 or 2 substituents independently selected from nitro, cyano, -CO(1-4C)alkyl, -COO(1-4C)alkyl, -O(1-4C)alkyl, trifluoromethyl, -$CONR^6R^7$, -$N(R^7)COR^6$, fluoro, chloro, bromo, hydroxy, carboxy, (1-4C)alkyl, heterocyclyl, -NHC(O)O(1-4C)alkyl, -$C(=NOR^7)$(1-4C)alkyl, -$C(=NOR^7)NR^6R^7$, -S(O)p(1-4C)alkyl (optionally substituted by hydroxy), -S(O)p(1-4C)alkylCONHR^7, and -NR^6R^7;

R^2 is selected from (1-4C)alkyl, chloro and bromo;

R^3 is selected from hydrogen, methyl, ethyl, chloro, bromo, cyano, trifluoromethyl and -COMe;

R^4 is selected from hydrogen, methyl, ethyl, chloro, bromo, cyano and -COMe;

R^5 is hydrogen or methyl;

R^6 and R^7 together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclyl ring, optionally substituted with 1 or 2 substituents independently selected from (1-4C)alkyl, hydroxy, (1-4C)alkoxy, halo, cyano, nitro, carboxy, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, halo(1-4C)alkyl, difluoromethyl, trifluoromethyl and trifluoromethoxy; and

p is (independently at each occurrence) 0, 1 or 2.

In one embodiment of the invention there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from R^1a, R^1b, R^1c and R^1d; wherein

R^1a is a 5 or 6 membered saturated, partially unsaturated or unsaturated heterocyclic ring containing 1, 2, 3, or 4 heteroatoms independently selected from O, S and N (provided

that such a ring does not contain O-O or S-S bonds), wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-, a ring sulphur atom may be optionally oxidised to form the S-oxide(s), and a ring nitrogen atom may be optionally oxidised to form the N-oxide, and wherein said ring may be optionally substituted by 1, 2 or 3 substituents independently selected from: nitro, cyano, sulfo, formyl, hydroxyiminomethyl, (2-6C)alkenyl, -CO(1-6C)alkyl, -COO(1-6C)alkyl trifluoromethyl, $-CONR^6R^7$, $-N(R^7)COR^6$, halo, hydroxy, carboxy, (1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, -OCO(1-4C)alkyl, (1-6C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(1-4C)alkoxy, (2-4C)alkenyloxy, -NHC(O)O(1-4C)alkyl, $-NHC(=NH)NR^6R^7$, $-NHC(O)NR^6R^7$, -NHC(O)(1-4C)alkyl, -NHC(O)heterocyclyl, -NHC(O)aryl, -NHS(O)p(1-4C)alkyl, -S(O)p(1-4C)alkyl, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$, and heterocyclyl], (3-6C)cycloalkyl, -O(1-6C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), -S(O)p(1-4C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), heterocyclyl, -NHC(O)O(1-4C)alkyl, $-C(=NOR^7)$(1-4C)alkyl, $-C(=NOR^7)NR^6R^7$, -S(O)p(1-4C)alkylCONHR^7, -C(O)NHS(O)p(1-4C)alkyl, and $-NR^6R^7$, wherein any aryl or heterocyclyl group in any of the preceding values for substituents on R^1a may optionally be substituted by 1 or 2 substituents independently selected from (1-4C)alkyl and carboxy;

R^1b is a 10 membered bicyclic heterocyclic ring containing 1, 2 or 4 heteroatoms independently selected from S and N (provided that such a ring does not contain S-S bonds), wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-, and wherein said ring may be optionally substituted by 1, 2 or 3 substituents independently selected from the substituents listed for R^1a above;

R^1c is a phenyl ring, substituted by 1, 2 or 3 substituents independently selected from the substituents listed for R^1a above;

R^1d is selected from $-CH_2R^1a$, and $-C(O)R^1a$;

R^2 is selected from (1-4C)alkyl, halo and cyano;

R^3 is selected from hydrogen, (1-4C)alkyl, halo, cyano and -CO(1-6C)alkyl;

R^4 is selected from hydrogen, (1-4C)alkyl, halo and cyano;

R^5 is selected from hydrogen and (1-4C)alkyl;

R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-4C)alkenyl, (3-6C)cycloalkyl, -(1-4C)alkylC(O)O(1-4C)alkyl, hydroxy, amino, -N[di(1-4C)alkyl], (1-4C)alkoxy and -(1-4C)alkylheterocyclyl;

R^7 is independently at each occurrence selected from hydrogen and (1-4C)alkyl;

or R^6 and R^7 may together with the nitrogen to which they are attached form a 5 or 6-membered heterocyclyl ring, optionally substituted with 1 or 2 substituents independently selected from (1-4C)alkyl; and

p is (independently at each occurrence) 0, 1 or 2.

In one embodiment of the invention there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from R^1a, R^1b, R^1c and R^1d; wherein

R^1a is pyridinyl, *N*-oxopyridinyl, pyrimidinyl, thiazolyl, thiadiazolyl, tetrazolyl, imidazolyl, triazinyl, pyrrolidinyl, thienyl, furanyl, oxadiazolyl, isoxazolyl, oxazolyl or pyrrolyl, wherein said R^1a may be optionally substituted by 1, 2 or 3 substituents independently selected from:
nitro, cyano, sulfo, formyl, hydroxyiminomethyl, (2-6C)alkenyl, -CO(1-6C)alkyl, -COO(1-6C)alkyl trifluoromethyl, $-CONR^6R^7$, $-N(R^7)COR^6$, halo, hydroxy, carboxy, (1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, -OCO(1-4C)alkyl, (1-6C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(1-4C)alkoxy, (2-4C)alkenyloxy, -NHC(O)O(1-4C)alkyl, $-NHC(=NH)NR^6R^7$, $-NHC(O)NR^6R^7$, -NHC(O)(1-4C)alkyl, -NHC(O)tetrahydrofuranyl, -NHC(O)phenyl, -NHS(O)p(1-4C)alkyl, -S(O)p(1-4C)alkyl, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$, morpholino, 1,3-dioxo-1,3-dihydro-2H-isoindolyl and 1,3-dioxolanyl], cyclopropyl, -O(1-6C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), -S(O)p(1-4C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), tetrazolyl, 2-oxo-1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, morpholino, piperazinyl, pyrrolidinyl, -NHC(O)O(1-4C)alkyl, $-C(=NOR^7)$(1-4C)alkyl, $-C(=NOR^7)NR^6R^7$, $-S(O)p(1-4C)alkylCONHR^7$, $-C(O)NHS(O)p(1-4C)alkyl$ and $-NR^6R^7$;
wherein any phenyl, tetrahydrofuranyl, morpholino, 1,3-dioxo-1,3-dihydro-2H-isoindolyl, 1,3-dioxolanyl, tetrazolyl, 2-oxo-1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, morpholino, piperazinyl, pyrrolidinyl, in any of the preceding values for substituents on R^1a may optionally be substituted by 1 or 2 substituents independently selected from (1-4C)alkyl and carboxy;

R^1b is R^1b is quinolinyl, purinyl, benzothiazolyl, indolyl, 4-oxoquinolinyl, 2,7-naphthyridinyl or quinazolinyl, and wherein said R^1b may be optionally substituted by 1, 2 or 3 substituents independently selected from the substituents listed for R^1a above;

R^1c is a phenyl ring, substituted by 1, 2 or 3 substituents independently selected from the substituents listed for R^1a above;

R^1d is selected from $-CH_2R^1a$, and $-C(O)R^1a$;

R^2 is selected from methyl, ethyl, isopropyl, chloro and cyano;

R^3 is selected from hydrogen, methyl, ethyl, chloro, bromo, cyano and -COMe;

R^4 is selected from hydrogen, chloro, methyl, ethyl and cyano;

R^5 is hydrogen or methyl;

R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-4C)alkenyl, cyclopropyl, -(1-4C)alkylC(O)O(1-4C)alkyl, hydroxy, amino, -N[di(1-4C)alkyl], (1-4C)alkoxy and -(1-4C)alkylmorpholino;

R^7 is independently at each occurrence selected from hydrogen and (1-4C)alkyl;

or R^6 and R^7 may together with the nitrogen to which they are attached form piperazinyl or morpholino optionally substituted with 1 or 2 substituents independently selected from (1-4C)alkyl;

p is (independently at each occurrence) 0, 1 or 2.

Preferred compounds of the invention are the compounds of the Examples, each of which provides a further independent aspect of the invention. In further aspects, the present invention also comprises any two or more compounds of the Examples.

Particular Examples are Examples 11, 20, 109, 114, 140, 141, 151, 176, 181, 208, 225, 227, 228, 278, 285, 292, 342, 343 and 344 or a pharmaceutically acceptable salt thereof.

Process

In a further aspect the present invention provides a process for preparing a compound of formula (1) or a pharmaceutically-acceptable salt thereof.

If not commercially available, the necessary starting materials for the procedures such as those described above may be made by procedures which are selected from standard organic chemical techniques, techniques which are analogous to the synthesis of known, structurally similar compounds, or techniques which are analogous to the above described procedure or the procedures described in the examples.

It is noted that many of the starting materials for synthetic methods as described above are commercially available and/or widely reported in the scientific literature, or could be made from commercially available compounds using adaptations of processes reported in the scientific literature. The reader is further referred to Advanced Organic Chemistry, 4th

Edition, by Jerry March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in compounds. The instances where protection is necessary or desirable are known to those skilled in the art, as are suitable methods for such protection. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Greene, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991).

Examples of a suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, a silyl group such as trimethylsilyl or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively a silyl group such as trimethylsilyl may be removed, for example, by fluoride or by aqueous acid; or an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation in the presence of a catalyst such as palladium-on-carbon.

A suitable protecting group for an amino group, for example R^a of formula (2a) herein below, is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for

example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine or 2-hydroxyethylamine, or with hydrazine.

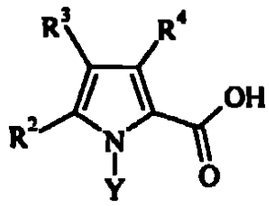
The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art, or they may be removed during a later reaction step or work-up.

The skilled organic chemist will be able to use and adapt the information contained and referenced within the above references, and accompanying Examples therein and also the Examples herein, to obtain necessary starting materials, and products.

Thus, the present invention also provides that the compounds of the formula (1) and pharmaceutically-acceptable salts thereof, can be prepared by a process as follows (wherein the variables are as defined above unless otherwise stated):

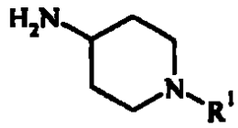
Another aspect of the present invention provides a process for preparing a compound of formula (1) or a pharmaceutically acceptable salt thereof which process (wherein R^2,R^3,R^4 are, unless otherwise specified, as defined in formula (1)) comprises of:

a) reacting an acid of the formula (2):



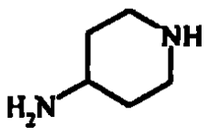
(2)

(wherein Y is H or a suitable protecting group) or an activated derivative thereof; with an amine of formula (3); or



(3)

b) reacting an acid of the formula (2) or an activated derivative thereof, with an amine of formula (4) (suitably protected on the piperidine nitrogen), removal of the protecting group, followed by reaction with a compound of formula (5);



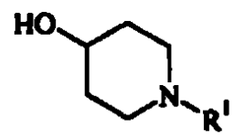
(4)

$X–R^1$

(5)

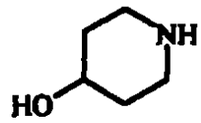
wherein X is a displaceable group; or

c) reacting an acid of the formula (2) or an activated derivative thereof, with an alcohol of formula (6); or



(6)

d) reacting an acid of the formula (2) or an activated derivative thereof, with an alcohol of formula (7) (suitably protected on the piperidine nitrogen), removal of the protecting group, followed by reaction with a compound of formula (8);



(7)

(8)

wherein X is a displaceable group; and thereafter if necessary:

i) converting a compound of the formula (1) into another compound of the formula (1);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt.

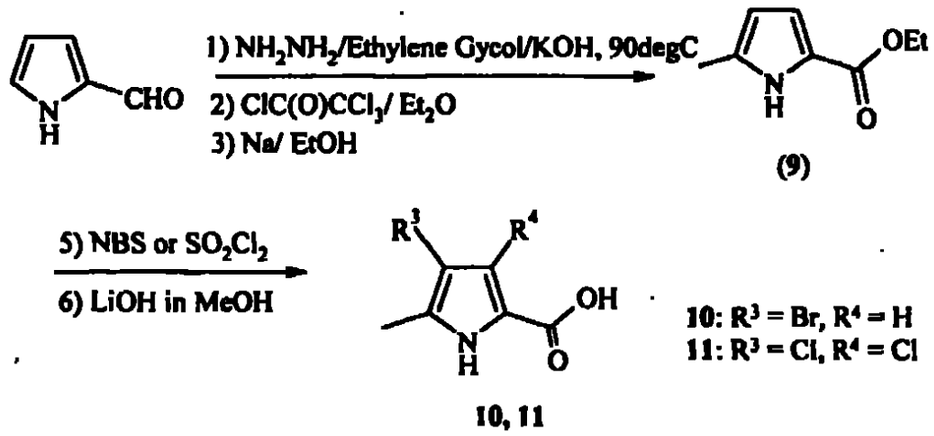
X is a displaceable group, suitable values for X are for example, a chloro, bromo or iodo group.

Specific reaction conditions for the above reaction are as follows.

Acids of formula (2) and amines of formula (3) or formula (4) may be coupled together in the presence of a suitable coupling reagent. Standard peptide coupling reagents known in the art can be employed as suitable coupling reagents, or for example HATU, carbonyldiimidazole, 1-ethyl-3-(3-dimethylaminopropyl)carbodi-imide hydrochloride (EDCI) and dicyclohexyl-carbodiimide (DCCI), optionally in the presence of a catalyst such as 1-hydroxy-7-azabenzotriazole, HOAT, dimethylaminopyridine or 4-pyrrolidinopyridine, optionally in the presence of a base for example triethylamine, di-isopropylethylamine, pyridine, or 2,6-di-alkyl-pyridines such as 2,6-lutidine or 2,6-di-tert-butylpyridine. Suitable solvents include dimethylacetamide, dichloromethane, N-methylpyrrolidone, tetrahydrofuran and dimethylformamide. The coupling reaction may conveniently be performed at a temperature in the range of 0 °C to 40 °C.

Suitable activated derivatives of acids of formula (2) include active esters, for example pentafluorophenyl esters, acid halides, for example acid chlorides, and acid fluorides. The reaction of these types of compounds with amines is well known in the art, for example they may be reacted in the presence of a base, such as those described above, and in a suitable solvent, such as those described above. The reaction may conveniently be performed at a temperature in the range of 0 °C to 40 °C.

A compound of formula (2) may be prepared by functionalisation of a substituted pyrrole compound which are commercially available or they are known compounds or they are prepared by processes known in the art, for example by processes such as those shown in Scheme 1 for Y = H.



(9)

10, 11

10: R^3 = Br, R^4 = H
11: R^3 = Cl, R^4 = Cl

Scheme 1

For example, compounds of the formula (10) (R^3 is Br and R^4 is H) may be made by bromination of a compound of formula (9) with a brominating agent such as N-bromosuccinimide and other brominating reagents known in the art, in an inert organic chlorinated solvent such as dichloromethane or 1,2-dichloroethane, followed by treatment with an aqueous base, such as, aqueous sodium hydroxide.

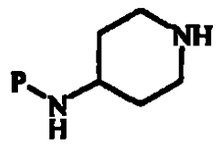
For example, compounds of the formula (11) (R^3 and R^4 are both chloro) may be made by chlorination of a compound of formula (9) with a chlorinating agent such as sulphuryl chloride and other chlorinating reagents known in the art, in an inert organic chlorinated solvent such as carbon tetrachloride, dichloromethane or 1,2-dichloroethane followed by treatment with an aqueous base, such as, aqueous lithium hydroxide in methanol. Alternatively diethyl ether may be used instead of the chlorinated solvent. The mono chlorinated compound can be formed in a similar manner.

Conveniently, carbon tetrachloride (CCl_4) is used as a solvent as the compound (11) then precipitates from the reaction mixture. The process of conversion of compound (9) to compound (11) using sulphuryl chloride in carbon tetrachloride is novel and forms a further independent aspect of the invention.

Compound (9) may also be prepared in a one pot procedure by following the procedure described in Curran, T. P.; Keaney, M. T., *J Org Chem* 1996, 61 (25), 9068.

Compounds of the formula (2) containing other functional groups may be made by processes analogous to those illustrated in Scheme 1 above, or by processes known in the art (see for example Heterocyclic Chemistry, 4th Ed., J.A. Joule and K. Mills, Blackwell Science; Heterocyclic Chemistry, T.L. Gilchrist, Adison Wesley Longman, 1997) or by processes illustrated in the Examples hereinafter.

Compounds of formula (3) are prepared by processes known in the art and may be made by coupling of a compound of the formula (4) (suitably protected on the amine nitrogen as shown below, formula (4-P)) with a compound of the formula (5).



(4-P)

The skilled person will thus recognise that in order to form the compound of formula (1):

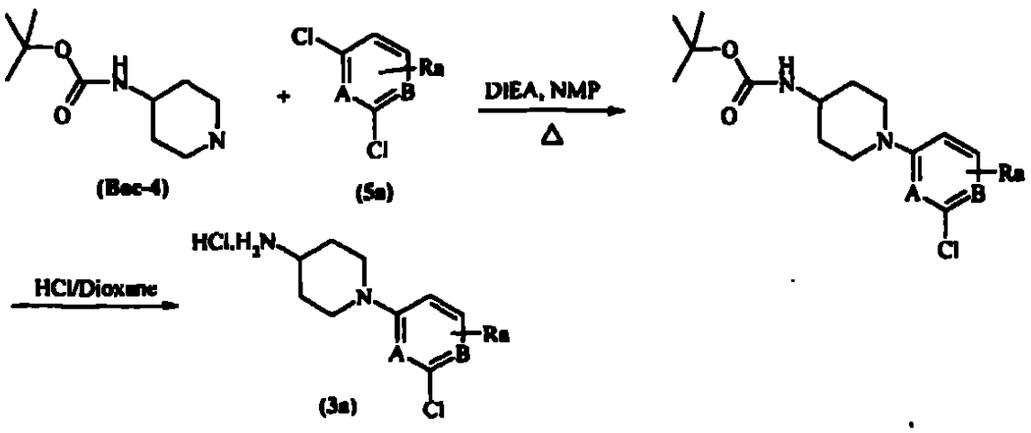
either suitably protected versions of the compounds of formulae (4) and (5) are reacted together to form a compound of formula (3) which is then (once deprotected where necessary) coupled to the compound of formula (2);

or a suitably protected version of the compound of formula (4) is coupled to the compound of formula (2) and then (once deprotected where necessary) reacted with the compound of formula (5).

Compounds of formula (4) are commercially available, or known in the art, or may be made by processes known in the art.

Compounds of formula (5) are commercially available, or known in the art, or may be made by processes known in the art.

For example when the compound of formula (5) (X = Cl) is a compound of formula (5a), coupling to (4) may be carried out as shown in Scheme 2 (where the protecting group P for the amine group is a Boc group).



Scheme 2

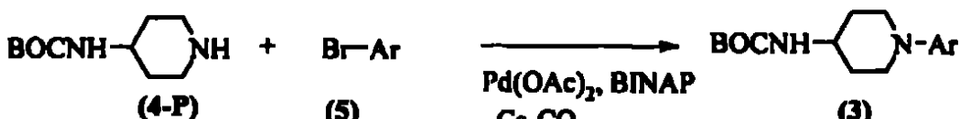
A and B are selected from carbon and nitrogen, thus a compound of the formula (5a) may be a phenyl, pyridine or pyrimidine derivative.

Ra is a ring substituent which falls within the definition of formula (1).

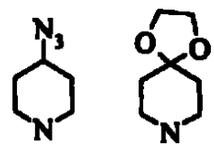
Compounds of the formula (3) wherein R^1 is another heterocycle, for example triazine, thiazole, and thiadiazole may be made by analogous processes.

Suitable protecting groups for the coupling reaction shown above are for example carbamate protecting groups such as Boc (tert-butoxycarbonyl) or other suitable protecting groups known in the art or mentioned hereinbefore.

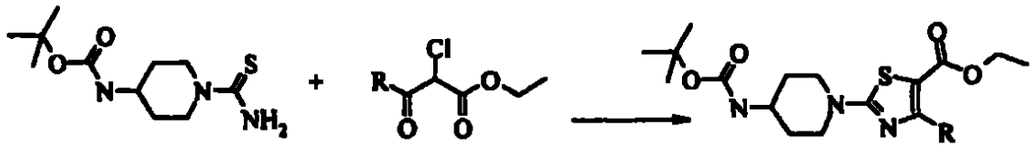
Compounds of formula (3) wherein R^1 is phenyl, or a heterocycle such as for example furan, thiophene or pyridine, may be made by coupling of a protected version of a compound of formula (4) (i.e. a compound of formula (4-P)) with a suitable compound of formula (5), for example where X is halo such as Br, using palladium catalysed amination reaction known in the art. (see for example Hartwig, J.F.; *Angew. Chem. Int. Ed*, 1998, *37*, 2046-2067, *Topics in Chemistry*, 219, 2002, Alex R. Muci; Stephen L. Buchwald; Artis Klapars et al. *J. Am. Chem. Soc*, 2001, 123, 7727-7729). This process is illustrated in the scheme below.



Alternatively, a precursor to a compound of formula (4) might be used, for example, azide or acetal derivatives such as those shown below.



Compounds of formula (3) wherein R^1 is another heterocycle, for example thiazole, may also be made by a cyclisation reaction of a suitable (N-protected) derivative of a compound of formula (4). This process is illustrated in the scheme below for R^1 is thiazole, where a thiourea derivative of a compound of formula (12) is reacted with a halodicarbonyl derivative (13) (wherein R is an optional substituent on R^1 as hereinbefore defined) to give the N-protected compound of formula (14). Suitably such a reaction may be carried out in an alcohol solvent such as methanol or ethanol, suitably at elevated temperature. The N-protecting group (a BOC group in the illustrative scheme below) may then be removed under appropriate conditions known in the art.



(12) (13) (14)

Reaction of a compound of the formula (2) with a compound of the formula (6) (process c) or a compound of the formula (7) (process d) above may be carried out for example using coupling reagents such as triphenylphosphine and diethylazodicarboxylate (DEAD), or other reagents well known in the art to promote ester bond formation.

A compound of the formula (6) may be formed by reaction of a compound of the formula (7) with a compound of the formula (8) as described above.

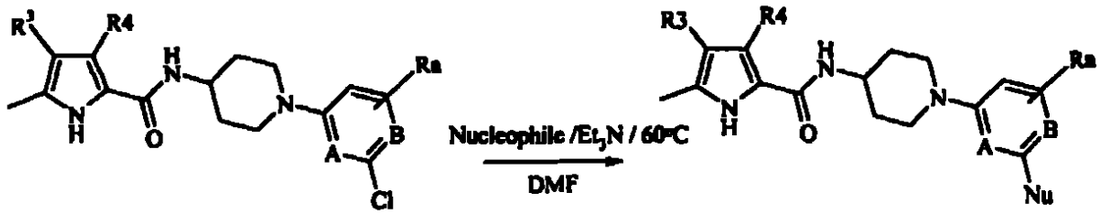
Where a compound of the formula (8) is X-R^1d, X-R^1e or X-R^1f (wherein R^1d to R^1f are as defined hereinbefore and contain a CH_2 group), coupling to a compound of the formula (4) or (7) (protected as necessary) may suitably be carried out using a reductive amination reaction, using a reagent such as sodium triacetoxyborohydride, for example as shown in Scheme 3 for R^1d:

(4)

P is protecting group

Scheme 3

Compounds of formula (1) may be combined with nucleophiles (for example R-SH and R-OH and R-NH_2) according to Scheme 4 to form other compounds of the formula 1:



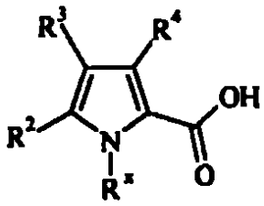
Scheme 4

Ra is a ring substituent which falls within the definition of formula (1).

Alternatively, where B in Scheme 4 above is carbon, the equivalent reaction may be carried out where the nucleophile is ROH, in the presence of alkali metals such as sodium or potassium, under reflux conditions.

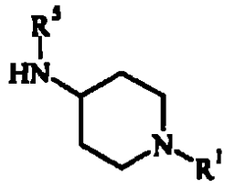
In a further aspect of the invention there is provided a process for preparing a compound of formula (1) or a pharmaceutically acceptable salt thereof which process (wherein variable groups are, unless otherwise specified, as defined in formula (1)) comprises of:

a) for compounds of formula (1) where W is NR^5; reacting an acid of the formula (2a):



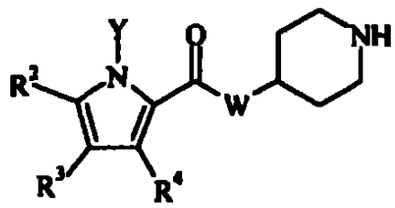
(2a)

(wherein R^x is hydrogen or a suitable protecting group) or an activated derivative thereof; with an amine of formula (3a); or



(3a)

b) reacting a compound of formula (4a):



(4a)

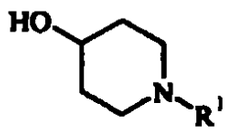
with a compound of formula (5a):

$X\text{-}R^1$

(5a)

wherein X is a displaceable group;

c) for compounds of formula (I) where W is O; reacting an acid of the formula (2a) or an activated derivative thereof, with an alcohol of formula (6a); or



(6a)

and thereafter if necessary:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt.

X is a displaceable group, suitable values for X are for example, a chloro, bromo or iodo group.

Process conditions and generic schemes for the synthesis of intermediates are given herein above.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention, for example substituents on the ring R^1, illustrated as Ra in the Schemes above, may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. The reagents used to introduce such ring substituents are either commercially available or are made by processes known in the art. Alternatively, starting materials where R^1 is already substituted may be commercially available.

Introduction of substituents into the ring of R^1 may convert one compound of the formula (I) into another compound of the formula (I). Such reactions and modifications

include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents , oxidation of substituents, esterification of substituents, amidation of substituents, formation of heteroaryl rings. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of alkoxides, diazotization reactions followed by introduction of thiol group, alcohol group, halogen group. Examples of modifications include; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

The removal of any protecting groups and the formation of a pharmaceutically-acceptable salt are within the skill of an ordinary organic chemist using standard techniques. Further information on these steps has been added above.

When an optically active form of a compound of the invention is required, it may be obtained by carrying out one of the above procedures using an optically active starting material (formed, for example, by asymmetric induction of a suitable reaction step), or by resolution of a racemic form of the compound or intermediate using a standard procedure, or by chromatographic separation of diastereoisomers (when produced). Enzymatic techniques may also be useful for the preparation of optically active compounds and/or intermediates.

Similarly, when a pure regioisomer of a compound of the invention is required, it may be obtained by carrying out one of the above procedures using a pure regioisomer as a starting material, or by resolution of a mixture of the regioisomers or intermediates using a standard procedure.

According to a further feature of the invention there is provided a compound of the formula (I), or a pharmaceutically-acceptable salt thereof for use in a method of treatment of the human or animal body by therapy.

We have found that compounds of the present invention inhibit bacterial DNA gyrase and are therefore of interest for their antibacterial effects.

According to a further feature of the present invention there is provided a method for producing an antibacterial effect in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically-acceptable salt thereof.

According to a further feature of the invention there is provided a method for inhibition of bacterial DNA gyrase in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a

compound of formula (1) or a pharmaceutically acceptable salt thereof as defined hereinbefore.

According to a further feature of the invention there is provided a method of treating a bacterial infection in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1) or a pharmaceutically acceptable salt thereof as defined hereinbefore.

A further feature of the present invention is a compound of formula (1) and pharmaceutically acceptable salts thereof for use as a medicament. Suitably the medicament is an antibacterial agent.

Conveniently this is a compound of formula (1), or a pharmaceutically acceptable salt thereof, for use as a medicament for producing an antibacterial effect in a warm-blooded animal such as a human being.

Conveniently this is a compound of formula (1), or a pharmaceutically acceptable salt thereof, for use as a medicament for inhibiting bacterial DNA gyrase in a warm-blooded animal, such as a human being.

Particularly this is a compound of formula (1), or a pharmaceutically acceptable salt thereof, for use as a medicament for treating a bacterial infection in a warm-blooded animal such as a human being.

According to a further aspect of the invention there is provided the use of a compound of formula (1), or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the production of an anti-bacterial effect in a warm-blooded animal such as a human being.

According to a further aspect of the invention there is provided the use of a compound of formula (1), or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in inhibition of bacterial DNA gyrase in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided the use of a compound of formula (1), or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of a bacterial infection in a warm-blooded animal such as a human being.

According to a further aspect of the invention there is provided a compound of formula (1), or a pharmaceutically acceptable salt thereof for use in the production of an anti-bacterial effect in a warm-blooded animal such as a human being.

According to a further aspect of the invention there is provided a compound of formula (1), or a pharmaceutically acceptable salt thereof for use in inhibition of bacterial DNA gyrase in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided a compound of formula (1), or a pharmaceutically acceptable salt thereof for use in the treatment of a bacterial infection in a warm-blooded animal such as a human being.

In order to use a compound of the formula (1) or a pharmaceutically-acceptable salt thereof, (hereinafter in this section relating to pharmaceutical composition "a compound of this invention") for the therapeutic (including prophylactic) treatment of mammals including humans, in particular in treating infection, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula (1) or a pharmaceutically-acceptable salt thereof, and a pharmaceutically-acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (1) as defined hereinbefore or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier for use in inhibition of bacterial DNA gyrase in an warm-blooded animal, such as a human being.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (1) as defined hereinbefore or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier for use in the treatment of a bacterial infection in an warm-blooded animal, such as a human being.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

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

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

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

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile

fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain or be co-administered (simultaneously, sequentially or separately) with one or more known drugs selected from other clinically useful antibacterial agents (for example, macrolides, quinolones, ß-lactams or aminoglycosides) and/or other anti-infective agents (for example, an antifungal triazole or amphotericin). These may include carbapenems, for example meropenem or imipenem, to broaden the therapeutic effectiveness. Compounds of this invention may also contain or be co-administered with bactericidal/permeability-increasing protein (BPI) products or efflux pump inhibitors to improve activity against gram negative bacteria and bacteria resistant to antimicrobial agents.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

In addition to its use in therapeutic medicine, compounds of formula (I) and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development

and standardisation of in-vitro and in-vivo test systems for the evaluation of the effects of inhibitors of DNA gyrase in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above other, pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

Enzyme Potency Testing Methods

Compounds were tested for inhibition of GyrB ATPase activity using an ammonium molybdate/malachite green-based phosphate detection assay (Lanzetta, P. A., L. J. Alvarez, P. S. Reinach, and O. A. Candia, 1979, 100: 95-97). Assays were performed in multiwell plates in 100µl reactions containing: 50 mM TRIS buffer pH 7.5, 75 mM ammonium acetate, 5.5 mM magnesium chloride, 0.5 mM ethylenediaminetetraacetic acid, 5% glycerol, 1 mM 1,4-Dithio-DL-threitol, 200 nM bovine serum albumin, 16 µg/ml sheared salmon sperm DNA, 4 nM *E. coli* GyrA, 4 nM *E. coli* GyrB, 250 µM ATP, and compound in dimethylsulfoxide. Reactions were quenched with 150 µL of ammonium molybdate/malachite green detection reagent containing 1.2 mM malachite green hydrochloride, 8.5 mM ammonium molybdate tetrahydrate, and 1 M hydrochloric acid. Plates were read in an absorbance plate reader at 625 nm and percent inhibition values were calculated using dimethylsulfoxide (2%)-containing reactions as 0% inhibition and novobiocin-containing (2 µM) reactions as 100% inhibition controls. Compound potency was based on IC_{50} measurements determined from reactions performed in the presence of 10 different compound concentrations.

Compounds of the Examples generally have an IC_{50} of <20µg/ml.

Bacterial Susceptibility Testing Methods

Compounds were tested for antimicrobial activity by susceptibility testing in liquid media. Compounds were dissolved in dimethylsulfoxide and tested in 10 doubling dilutions in the susceptibility assays. The organisms used in the assay were grown overnight on suitable agar media and then suspended in a liquid medium appropriate for the growth of the organism. The suspension was a 0.5 McFarland and a further 1 in 10 dilution was made into the same liquid medium to prepare the final organism suspension in 100 µL. Plates were incubated under appropriate conditions at 37 degrees C for 24 hrs prior to reading. The Minimum Inhibitory Concentration was determined as the lowest drug concentration able to reduce growth by 80% or more.

Example 130 had an MIC of 2μg/ml against *Streptococcus pneumoniae*.

The invention is now illustrated but not limited by the following Examples in which unless otherwise stated :-

(i) evaporations were carried out by rotary evaporation in-vacuo and work-up procedures were carried out after removal of residual solids by filtration;

(ii) operations were carried out at ambient temperature, that is typically in the range 18-26 °C and without exclusion of air unless otherwise stated, or unless the skilled person would otherwise work under an inert atmosphere;

(iii) column chromatography (by the flash procedure) was used to purify compounds and was performed on Merck Kieselgel silica (Art. 9385) unless otherwise stated;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the structure of the end-products of the invention were generally confirmed by NMR and mass spectral techniques [proton magnetic resonance spectra were generally determined in DMSO-d_6 unless otherwise stated using a Bruker DRX-300 spectrometer operating at a field strength of 300 MHz. Chemical shifts are reported in parts per million downfield from tetramethysilane as an internal standard (δ scale) and peak multiplicities are shown thus: s, singlet; d, doublet; AB or dd, doublet of doublets; dt, doublet of triplets; dm, doublet of multiplets; t, triplet, m, multiplet; br, broad; fast-atom bombardment (FAB) mass spectral data were generally obtained using a Platform spectrometer (supplied by Micromass) run in electrospray and, where appropriate, either positive ion data or negative ion data were collected]or using Agilent 1100series LC/MSD equipped with Sedex 75ELSD, run in APCI mode and, where appropriate, either positive ion data or negative ion data were collected; optical rotations were determined at 589 nm at 20 °C for 7.6 mM solutions in methanol using a Perkin Elmer Polarimeter 341; REVERSE PHASE HPLC carried out using YMC Pack ODS-AQ(100x20 mmID, S-5μ particle size, 12 nm pore size)

(vi) each intermediate was purified to the standard required for the subsequent stage and was characterised in sufficient detail to confirm that the assigned structure was correct; purity was assessed by HPLC, TLC, or NMR and identity was determined by infra-red spectroscopy (IR), mass spectroscopy or NMR spectroscopy as appropriate;

(vii) in which the following abbreviations may be used :-

DMF is N,N-dimethylformamide; DMA is N,N-dimethylacetamide; TLC is thin layer chromatography; HPLC is high pressure liquid chromatography; MPLC is medium pressure liquid chromatography; DMSO is dimethylsulfoxide; $CDCl_3$ is deuterated chloroform; MS is

mass spectroscopy; ESP (or ES) is electrospray; EI is electron impact; CI is chemical ionisation; APCI is atmospheric pressure chemical ionisation; EtOAc is ethyl acetate; MeOH is methanol; DEAD is diethylazodicarboxylate; DIEA is diisopropylethlamine; mCPBA is meta-chloroperoxybenzoic acid; TFA is trifluoroacetic acid; HATU is N-[(dimethylamino)-1H,2,3-triazolo[4,5-b-]pyridin-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate N-oxide; HOAT is 1-hydroxy-7-azabenzotriazole; EDC is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; TEA is triethylamine; NMP is N-methylpyrrolidinone; Pd(dba) is bis(dibenzylidineacetone)palladium; Dppf is 1,1'bis(diphenylphosphine)ferrocene; THF is tetrahydrofuran; EtOH is ethanol; LCMS is liquid chromatography/mass spectrometry; DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene; DCM is dichloromethane;

(viii) temperatures are quoted as °C;

(ix) Smith Microwave Synthesizer refers to an equipment that uses microwave energy to heat organic reactions in a short period of time; it was used according to the manufacturers instruction and was obtained from Personal Chemistry Uppsala AB; and

(x) Kugelrohr distillation refers to a piece of equipment that distils liquids and heats sensitive compounds using air-bath oven temperature; it was used according to the manufacturers instruction and was obtained from Buchi, Switzerland or Aldrich, Milwaukee, USA.

Intermediate 1: 3,4-Dichloro-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride

tert-Butyl 4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidine-1-carboxylate (Intermediate 2, 1.978 g, 5.257 mol) was treated with 4 M HCl in dioxane (20 ml), and the reaction was stirred at room temperature for 1.5 h. The reaction mixture was concentrated under reduced pressure to give the desired material as a pink solid (1.61 g, 98% yield).

MS (ES$^-$): 274.08, 276.08 for $C_{11}H_{15}Cl_2N_3O$

^{1}H NMR δ: 1.71 (m, 2H); 1.95 (m, 2H); 2.18 (s, 3H); 2.99 (m, 2H); 3.27 (m, 2H); 3.99 (m, 1H); 7.64 (d, 1H); 8.67 (brs, 1H); 12.16 (s, 1H)

Intermediate 2: *tert*-Butyl 4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidine-1-carboxylate

3,4-Dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid (Intermediate 3, 3.0 g, 0.016 mol), *tert*-butyl 4-aminopiperidine-1-carboxylate (3.1 g, 0.016 mol), and Et_3N (2.2 ml, 0.032 mol) were combined in DMF (20 ml) and stirred under N_2 for 5 minutes. HATU (6.47 g, 0.017 mol) was added in one portion, and the reaction was stirred at room temperature for 5 h. The reaction mixture was diluted with EtOAc and H_2O. The organic phase was washed with 1 N HCl, and the combined aqueous portions were extracted once with EtOAc. The combined organic portions were washed sequentially with saturated $NaHCO_3$ and saturated NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a brown solid. Most of the crude material was isolated by trituration with EtOAc/hexanes to give an off-white solid. The remaining material was chromatographed on silica, eluting with 3:1, 2:1, and 1:1 EtOAc/hexanes to give a light brown solid that was triturated with EtOAc, collected and combined with the other triturated material to give a total of 1.978 g of the desired product.

MS (ES$^-$): 374.33, 376.34 for $C_{16}H_{23}Cl_2N_3O_3$

^{1}H NMR δ: 1.16 (s, 9H); 1.20 (m, 2H); 1.53 (m, 2H); 1.93 (s, 3H); 2.65 (m, 2H); 3.65 (m, 3H); 6.97 (d, 1H); 11.72 (s, 1H)

Intermediate 3: 3,4-Dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid

Ethyl 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylate (Intermediate 4, 7.765 g, 0.03496 mol) was dissolved in MeOH (80 ml) and DCM (10 ml) and slowly added to a 70 °C solution of 2 N LiOH (105 ml, 0.21 mol). After 2 h, the reaction mixture was cooled to room temperature and then in an ice bath, followed by acidification with 2 N HCl. The mixture was stirred at 0 °C for 1 h, and a purple solid was filtered, washed with water and lyophilized overnight to give 4.314 g (0.0222 mol, 64% yield) of the desired product.

MS (ES$^-$): 192.13, 194.13 for $C_6H_5Cl_2NO_2$

^{1}H NMR δ: 2.17 (s, 3H)

Intermediate 4: Ethyl 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylate

A solution of ethyl 5-methyl-1*H*-pyrrole-2-carboxylate (Intermediate 20) (7.00 g, 0.0457 mol) in tetrachloromethane (30 ml) was cooled to 0 °C under nitrogen. The rubber septum used in the apparatus was pierced with a needle, and SO_2Cl_2 (7.8 ml, 0.096 mol) was then added dropwise over 25 minutes. Within 1 hr, the reaction mixture had formed a slurry. The

solid was collected by suction filtration, washed with cold tetrachloromethane, and dried under vacuum overnight to give the title product as a peach coloured solid (7.84 g, 0.0353 mol, 77% yield).

MS (ES⁻): 222.00, 224.00 for $C_8H_9Cl_2NO_2$

^{1}H NMR δ: 1.34-1.40 (t, 3H); 2.28 (s, 3H); 4.32-4.38 (m, 2H)

Intermediate 5: Ethyl 4-methoxy-3-oxobutanoate

The title compound was prepared in a manner analogous to Intermediate 123 starting from 2,2-dimethyl-1,3-dioxane-4,6-dione and methoxyacetyl chloride.

MS (APCI) MH+: 161,162 for $C_7H_{12}O_4$

^{1}H NMR($CDCl_3$) δ: 1.12-1.26 (t, 3H); 3.26 (s, 3H); 3.51 (s, 2H); 4.03-4.16 (brs, 4H).

Intermediate 6: Ethyl 2-chloro-4-methoxy-3-oxobutanoate

The title compound was prepared in a manner analogous to Intermediate 124 starting from ethyl 4-methoxy-3-oxobutanoate (Intermediate 5) and sulfuryl chloride.

MS (APCI) MH^+: 193,195 for $C_7H_{11}ClO_4$

^{1}H NMR ($CDCl_3$) δ:1.10-1.12 (t, 3H); 3.22 (s, 3H); 3.22 (s, 3H); 4.22-4.25 (s, 2H); 4.08-4.19 (q, 2H); 4.48 (s, 1H)

Intermediate 7: *N*-(2,6-Dichloropyrimidin-4-yl)acetamide

4-Amino-2,6-dichloropyrimidine (500 mg, 3.05 mmol) was refluxed in acetic anhydride (10 ml) for 3 h. Upon cooling to room temperature, the reaction mixture was cooled in an ice bath and basified to pH 8 with 10% aqueous $NaHCO_3$. The phases were separated, and the aqueous portion was extracted twice with EtOAc. The combined organic portions were dried over Na_2SO_4, filtered, and concentrated to give an off-white solid (503.7 mg, 2.44 mmol, 80% yield).

MS (ES⁻): 204.08, 206.08 for $C_6H_5Cl_2N_3O$

^{1}H NMR δ: 2.15 (s, 3H); 8.07 (s, 1H); 11.56 (brs, 1H)

Intermediate 8: 4-Chloro-5-methyl-1*H*-pyrrole-2-carboxylic acid

Lithium hydroxide (2 M, 4 ml) was warmed to 50 °C and a solution of ethyl 4-chloro-5-methyl-1*H*-pyrrole-2-carboxylate (Intermediate 9, 0.30 g, 1.60 mmol) in MeOH was added to it. The reaction was heated to 80 °C and stirred for two hours. The MeOH was removed and

the aqueous solution was cooled to 0 °C and acidified with 30% HCl. The precipitated product (0.23 g, 92%) was filtered and dried.

MS (ES): 160 (M+1) for $C_6H_6ClNO_2$

^{1}H NMR ($CDCl_3$) δ: 2.25 (s, 3H); 6.85 (s, 1H); 8.98 (brs, 1H)

Intermediate 9: Ethyl 4-chloro-5-methyl-1*H*-pyrrole-2-carboxylate

N-Chlorosuccinimide (0.67 g, 5.08 mmol) was added to a solution of ethyl 5-methyl-1*H*-pyrrole-2-carboxylate (**Intermediate 20**) (0.65 g, 4.23 mmol) in chloroform (20 ml). The reaction was warmed to 40 °C and stirred for 4 hours, then poured to a beaker containing 2 N NaOH (20 ml) at 0 °C. The layers were separated and the aqueous layer was extracted with chloroform (x3). The combined organic extracts were dried over magnesium sulfate and concentrated. The resultant off-white solid was purified by flash chromatography (hexanes/EtOAc, 16:1) to give the title product as a white solid (0.3 g, 38%).

MS (ES): 188 (M+1) for $C_8H_{10}ClNO_2$

^{1}H NMR ($CDCl_3$) δ: 1.34 (t, 3H); 2.27 (s, 3H); 4.30 (q, 2H); 6.76 (s, 1H); 9.07 (brs, 1H)

Intermediate 10: 4-Bromo-5-ethyl-1*H*-pyrrole-2-carboxylic acid

This intermediate was synthesised from ethyl 4-bromo-5-ethyl-1*H*-pyrrole-2-carboxylate (**Intermediate 11**) by an analogous method to **Intermediate 8**.

MS (ES): 218 (M+1) for $C_7H_8BrN_2$

^{1}H NMR ($CDCl_3$) δ: 1.11 (t, 3H); 2.54 (q, 2H); 6.67 (s, 1H); 11.94 (brs, 1H); 12.38 (s, 1H)

Intermediate 11: Ethyl 4-bromo-5-ethyl-1*H*-pyrrole-2-carboxylate

N-Bromosuccinimide (5.86 g, 0.033 mol) was added to a solution of ethyl 5-ethyl-1*H*-pyrrole-2-carboxylate (**Intermediate 12**, 5.0 g, 0.03 mol) in DCM (85 ml) at 0 °C, and the reaction was stirred for 30 minutes then poured to a chilled beaker containing 2 N NaOH (50 ml). The layers were separated and the aqueous layer was extracted with DCM (x3). The combined organic extracts were washed with water and brine, dried over magnesium sulfate and concentrated. The resultant dark brown solid was purified by flash chromatography (hexanes/EtOAc, 10:1) to give the title product as a white solid (5.0 g, 68%).

MS (ES): 247 (M+1) for $C_9H_{12}BrNO_2$

^{1}H NMR ($CDCl_3$) δ: 1.04 (t, 3H); 1.14 (t, 3H); 2.46 (q, 2H); 4.10 (q, 2H); 6.64 (s, 1H); 8.68 (brs, 1H)

Intermediate 12: Ethyl 5-ethyl-1*H*-pyrrole-2-carboxylate

Absolute EtOH (6 ml) was added to a 21 wt% solution of sodium ethoxide in EtOH (0.33 ml, 1.05 mmol) followed by the portion-wise addition of 2,2,2-trichloro-1-(5-ethyl-1*H*-pyrrol-2-yl)ethanone (*J.Chem.Soc. Perkin Trans 1*, 1996, 03) (2.1 g, 8.75 mmol) under nitrogen. The resulting yellow solution was stirred at room temperature for 30 minutes. Then the reaction was concentrated to give light orange oil. Hydrochloric acid (3 M, 2.5 ml) and diethyl ether (8 ml) were added to the oil and layers separated. The aqueous layer was extracted with diethyl ether (x2) and the combined organic extracts were washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and concentrated to give the desired product as a white solid (1.27 g, 86%).

MS (ES): 168 (M+1) for $C_9H_{13}NO_2$

^{1}H NMR ($CDCl_3$) δ: 1.18 (t, 3H); 1.27 (t, 3H); 2.59 (q, 2H); 4.23 (q, 2H); 5.89 (s, 1H); 6.64 (s, 1H); 8.68 (brs, 1H)

Intermediate 13: 4-Cyano-5-methyl-1*H*-pyrrole-2-carboxylic acid

Lithium hydroxide (2 N, 2 ml) was warmed to 40 °C and a solution of ethyl 4-cyano-5-methyl-1*H*-pyrrole-2-carboxylate (**Intermediate 14**, 0.16 g) in 2 ml of MeOH was added. The reaction temperature was gradually increased to 90 °C and the reaction was stirred at that temperature for 2 hours. Then MeOH was removed and the remaining aqueous solution was cooled to 0 °C and acidified with 3 M HCl (pH ~ 2). The acidic solution was extracted with EtOAc, the combined organic extracts were dried over magnesium sulfate and concentrated to give brown solid (0.07 g, crude).

MS (ES): 151 (M+1) for $C_7H_6N_2O_2$

^{1}H NMR δ: 2.33 (s, 3H); 7.01 (s, 1H); 12.47 (s, 1H)

Intermediate 14: Ethyl 4-cyano-5-methyl-1*H*-pyrrole-2-carboxylate

Ethyl 4-formyl-5-methyl-1*H*-pyrrole-2-carboxylate (**Intermediate 15**, 0.2 g, 1.1 mmol) and hydroxylamine hydrochloride (0.08 g, 1.1 mmol) were dissolved in EtOH (10 ml) and refluxed for 1.5 hours. The mixture was concentrated under vacuum to give yellow solid, which was dissolved in DMF (5 ml) before addition of $SOCl_2$ (0.35 ml) at 0 °C. The solvent was removed under vacuum after the completion of the reaction and the residue was partitioned between water and EtOAc. The layers were separated and the aqueous layer was

extracted with EtOAc twice. The combined organic extracts were dried over $MgSO_4$ and concentrated to give brown solid (0.16 g, crude).

MS (ES): 179 (M+1) for $C_9H_{10}N_2O_2$

Intermediate 15: Ethyl 4-formyl-5-methyl-1*H*-pyrrole-2-carboxylate

Trimethoxymethane (1.18 ml, 10.78 mmol) was added to a solution of ethyl 5-methyl-1*H*-pyrrole-2-carboxylate (Intermediate 20) (0.5 g, 3.26 mmol) in TFA (2.5 ml) at 0 °C. The reaction was stirred at that temperature for 10 mins then quenched with cold water (20 ml). The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over magnesium sulfate and concentrated to give yellow solid which was purified by flash chromatography (10% to 20 % EtOAc in hexanes, 0.25 g).

MS (ES): 182 (M+1) for $C_9H_{11}NO_3$

^{1}H NMR ($CDCl_3$) δ: 1.37 (t, 3H); 2.61 (s, 3H); 4.34 (q, 2H); 7.24 (s, 1H); 9.51 (brs, 1H); 9.88 (s, 1H).

Intermediate 16: tert-Butyl 1-[4-(aminocarbonyl)-6-chloropyridin-2-yl]piperidin-4-ylcarbamate

tert-Butyl piperidin-4-ylcarbamate (500 mg, 2.62 mmol), was dissolved in anhydrous N, N'-dimethyl acetamide (4 ml). 2,6-Dichloroisonicotinamide (522 mg, 2.62 mmol) was added, followed by N, N-dimethyl isopropylethylamine (465 µl,2.62 mmol). Using a Smith Microwave Synthesizer, the mixture was subjected to single-mode microwave at 150 °C for 20 minutes. H_2O (50 ml) and EtOAc (100 ml) were added, the EtOAc layer was washed (4 x 50 ml), dried over Na_2SO_4 and concentrated in vacuo to give the title product as a brown solid. (760 mg).

MS (ES, M+H): 355 for $C_{16}H_{23}ClN_4O_3$

^{1}H NMR δ:1.42 (m, 2H); 1.53 (s, 9H); 1.94 (m, 2H); 3.12 (m, 2H); 3.45 (s, 1H); 3.70 (m, 1H); 4.34 (m, 2H); 7.07 (s, 1H); 7.26 (s, 1H); 7.81 (s, 1H); 8.49 (s, 1H).

Intermediate 17: Pentafluorophenyl 4-bromo-5-methyl-1H-pyrrole-2-carboxylate

4-Bromo-5-methyl-1H-pyrrole-2-carboxylic acid (Intermediate 18, 2.16 g, 10.59 mmol) was dissolved an THF (10 ml). Pentafluorophenol and EDC (2.03 g, 10.59 mmol) were added and the mixture was stirred at room temperature for 6 h. The solvent was removed under vacuum and EtOAc (50 ml) was added. The organic phase was washed with water, 10% Na_2CO_3 (2 x

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25 ml), water (50 ml) and brine (50 ml), dried over Na_2SO_4 and concentrated in vacuo to give the title compound as an off white solid (2.23 g).

MS (ESI, M+H): 368,371 for $C_{12}H_5BrF_5NO_2$

^{1}H NMR δ: 2.39 (s, 3H); 7.46 (d, 1H); 12.06 (s, 1H)

^{19}F NMR δ: -151.5 to –192.7ppm

Intermediate 18: 4-Bromo-5-methyl-1H-pyrrole-2-carboxylic acid

Ethyl 4-bromo-5-methyl-1H-pyrrole-2-carboxylate (Intermediate 19, 16.5 g, 71.09 mmol) was dissolved anhydrous THF (100 ml) and was added to a preheated solution of 2 N lithium hydroxide (500 ml) at 70 °C. The mixture was heated at 70 °C for 4 h and the solvent was removed in vacuo and the crude aqueous solution was cooled in an ice-bath and slowly acidified with 3 N HCl. The precipitate was extracted with EtOAc (3x100 ml), the organic extracts were washed with water, brine and dried with Na_2SO_4, treated with decolourizing charcoal for 1 h, filtered over celite and concentrated in vacuo. The brown solid was filtered and washed well with n-hexanes and dried in vacuo. (13 g).

MS (APCI, M+H): 205 for $C_6H_6BrNO_2$

^{1}H NMR δ: 2.27 (s, 3H); 6.74 (d, 1H); 12.06 (s, 1H); 12.57 (s, 1H).

Intermediate 19: Ethyl 4-bromo-5-methyl-1H-pyrrole-2-carboxylate

Ethyl 5-methyl-1H-pyrrole-2-carboxylate (Intermediate 20, 12.3 g, 0.803 mmol) was dissolved in anhydrous DCM and cooled to –5 °C. N-bromosuccinimide (14.23 g; 0.0803 mmol) was added and the reaction stirred for 10 min and then poured into ice-cold 2 N sodium hydroxide (500 ml). The brown solution was extracted with EtOAc (2 x 150 ml), the combined organic extracts were washed with water, brine and dried over Na_2SO_4, then concentrated in vacuo to give a brown solid which was dried under vacuum. (16.5 g).

MS (ES, M+H): 233 for $C_8H_{10}BrNO_2$

^{1}H NMR δ: 1.32 (t, 3H); 2.1 (s, 3H); 4.371 (q, 2H); 6.23 (d, 1H); 11.54 (s, 1H).

Intermediate 20: Ethyl 5-methyl-1H-pyrrole-2-carboxylate

Sodium (2.79 g, 0.121 mmol) was dissolved in anhydrous EtOH (100 ml), then 2,2,2-trichloro-1-(5-methyl-1H-pyrrol-2-yl)ethanone (Intermediate 21, 22.5 g, 0.099 mmol) was added in small portions. The dark brown solution was stirred at room temperature for 30 minutes then concentrated under vacuum to a small volume. The mixture was cooled in an ice

bath and 3 N HCl was added slowly then extracted with diethyl ether (3 x 100 ml). The ether extracts were washed with 10% $NaHCO_3$, water and brine, dried over Na_2SO_4 and concentrated in vacuo to give the title compound as a brown solid. (15.04 g).

^{1}H NMR δ: 1.32 (t, 3H); 2.1 (s, 3H); 4.371 (q, 2H); 5.96 (dd, 1H); 6.78 (dd, 1H); 11.67 (s, 1H).

In an alternative procedure, Ethyl 5-methyl-1H-pyrrole-2-carboxylate (Intermediate 20) was synthesized in one pot according to Curran, T. P.; Keaney, M. T., *J Org Chem* 1996, 61 (25), 9068.

Intermediate 21: 2,2,2-Trichloro-1-(5-methyl-1H-pyrrol-2-yl)ethanone

2-Methyl-1H-pyrrole (Intermediate 22, 10 g, 0.123 mmol) in anhydrous diethyl ether (30 ml) was added dropwise over 1 h to a stirred solution of triacetyl chloride (29 g, 0.16 mmol) in anhydrous Et_2O (100 ml). The mixture was stirred for a further 1 h then K_2CO_3 (10 g/30 ml) was added slowly through a dropping funnel. The organic phase was dried over Na_2SO_4 and treated with decolourizing charcoal (3 g) for 30 minutes at room temperature. The resulting purple solution was concentrated and triturated with n-hexanes to give the title compound as a purple solid. (16.72 g).

^{1}H NMR ($CDCl_3$) δ: 2.36 (s, 3H); 6.04 (dd, 1H); 7.45 (dd, 1H); 10.344 (s, 1H).

Intermediate 22: 2-Methyl-1H-pyrrole

Potassium hydroxide (50 g, 0.89 mmol) was added to a solution of ethylene glycol (750 ml) and 1H-pyrrole-2-carbaldehyde (50 g,0.53 mmol). Hydrazine hydrate (37 ml, 0.745 mmol) was added slowly over 15 minutes. The reaction mixture was refluxed at 90 °C for 90 minutes. The mixture was cooled to room temperature and cold water (250 ml) was added. The aqueous mixture was extracted with DCM (250 ml). The organic phase was washed with water (250 ml), dried over Na_2SO_4 and concentrated in vacuo. Kugelrohr distillation gave the title compound as a clear colourless liquid (29.75 g).

^{1}H NMR δ: 2.1 (s, 3H); 5.77 (s, 1H); 5.9 (dd, 1H); 6.25 (dd, 1H); 10.54 (s, 1H).

Intermediate 23: Methyl 2-{4-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-6-chloroisonicotinate

tert-Butyl piperidin-4-ylcarbamate (972 mg, 4.85 mmol), was dissolved in anhydrous NMP (5 ml). Methyl 2,6-dichloroisonicotinate (Intermediate 24, 1 g, 4.85 mmol) was added followed

by TEA (675 µl, 4.85 mmol). The mixture was heated under microwave conditions at 150 °C for 10 minutes. Water (50 ml) and EtOAc (100 ml) were added, the aqueous phase was treated with solid NaCl and extracted with EtOAc (4 x 100 ml). The EtOAc layer was dried, concentrated in vacuo and purified by flash chromatography eluting with hexane: EtOAc (4:1) to give the title product as an off-white solid. (1.4 g).

MS (ES, M+H): 370 for $C_{17}H_{24}ClN_3O_4$

^{1}H NMR δ: 1.38 (m, 2H); 1.49 (s, 9H); 1.93 (m, 2H); 2.29 (m, 1H); 3.17 (m, 2H); 3.48 (s, 1H); 3.94 (s, 3H); 4.38 (m, 2H); 7.02 (s, 1H); 7.31 (s, 1H); 7.81 (s, 1H); 8.49 (s, 1H)

Intermediate 24: Methyl 2,6-dichloroisonicotinate

2,6-Dichloroisonicotinic acid was (5 g, 26.04 mmol) was suspended in anhydrous toluene (75 ml). Thionyl chloride (19 ml, 260.4 mmol) was added and the mixture was heated to reflux for 4 h. The excess thionyl chloride was removed and solvent was removed in vacuo. Anhydrous MeOH (25 ml) was added and reaction was stirred for a further 4 h. Solvents were removed in vacuo to give a white coloured solid which was dried under vacuum (4.8 g).

MS (APCI, M+H): 206 for $C_7H_5Cl_2NO_2$

^{1}H NMR δ: 4.10 (s, 3H); 8.15 (s, 2H).

Intermediate 25: Ethyl 4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-3-oxobutanoate

The title compound was prepared in a manner analogous to Intermediate 123 starting from 2,2-dimethyl-1,3-dioxane-4,6-dione and (1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)acetyl chloride.

MS (APCI) MH^+: 276, 277 for $C_{14}H_{13}NO_5$

^{1}H NMR ($CDCl_3$) δ: 1.18-1.22 (t, 3H); 3.85 (s, 2H); 4.10-4.13 (q, 2H); 4.71 (s, 2H); 7.89-7.93 (brs, 4H).

Intermediate 26: 2-Chloro-6-(4-hydroxypiperidin-1-yl)isonicotinonitrile

2,6-Dichloroisoniconitrile (200 mg, 1.15 mmol) and 4-hydroxypiperidine(117 mg, 1.15 mmol) were dissolved in NMP (3 ml). TEA (160 µl, 1.15 mmol) was added. Using a Smith Microwave Synthesizer, the mixture was subjected to single-mode microwave at 150 °C for 20 minutes. The brown mixture was extracted with EtOAc and was washed with water (3x15 ml). The organic phase was dried over Na_2SO_4 and concentrated in vacuo. (250 mg).

MS (ES, M+H): 238 for $C_{11}H_{12}ClN_3O$

Intermediate 27; 3-Cyano-5-ethyl-1H-pyrrole-2-carboxylic acid methyl ester

3-Cyano-5-ethyl-1H-pyrrole-2-carboxylic acid (Intermediate 31) (500 mg) was dissolved in anhydrous THF (5 ml) and cooled to 0 °C. (Trimethylsilyl)diazomethane /ether (2 ml) was added. The mixture was stirred at room temperature under nitrogen gas for 1 h. The solvent was removed in vacuo and MeOH was added. The mixture was stirred for a further 15 min, the solvent was removed in vacuo and the solid was dried under vacuum to give the title compound (580 mg).

MS (ES) MH^+: 177 for $C_9H_{10}N_2O_2$

Intermediate 28; 3-Cyano-5-methyl-1H-pyrrole-2-carboxylic acid methyl ester

The title compound was prepared by a procedure analogous to Intermediate 27 starting from 3-cyano-5-methyl-1H-pyrrole-2-carboxylic acid (Intermediate 32).

MS (ES) MH^+: 164 for $C_8H_8N_2O_2$

Intermediate 29; 5-Methyl-1H-pyrrole-2-carboxylic acid

The title compound was synthesised by an analogous method to Intermediate 18 starting from ethyl 5-methyl-1H-pyrrole-2-carboxylate (Intermediate 20).

MS (ES): 250 (MH) dimer for $C_6H_7NO_2$

^1H NMR δ: 2.24 (s, 3H); 5.92 (s, 1H); 6.68 (s, 1H); 11.55 (s, 1H); 12.05 (s, 1H)

Intermediate 30; 5-Ethyl-1H-pyrrole-3-carbonitrile

Iodoethane (3.99 g, 25.61 mmol) was added to a solution of 1-isocyanomethanesulfonyl-4-methyl-benzene (5 g, 25.61 mmol) in anhydrous THF (20 ml). The mixture was cooled to –78 °C and potassium tert-butoxide (31 ml of a 1 M solution in THF, 31 mmol) was added dropwise over 15 minutes. The mixture was warmed to room temperature over 1 h. Water (50 ml) was added and the solution was extracted with diethylether and dried over Na_2SO_4 and evaporated to dryness. The resulting brown oily material was used without purification.

The resulting 1-(1-Isocyano-propane-1-sulfonyl)-4-methyl-benzene (4.29 g, 19.05 mmol) and acrylonitrile (1.26 ml, 19.05 mmol) were stirred in anhydrous THF (20 ml). The mixture was cooled to 0 °C and potassium tert-butoxide in THF (38.1 ml, 38.1 mmol) was added dropwise. The mixture was heated to reflux for 2 h then left at room temperature overnight, and then concentrated in vacuo. EtOAc (30 ml)was added to the brown solid and the mixture was stirred at room temperature for a few hours, filtered and the solid washed well with EtOAc.

The EtOAc solution was concentrated in vacuo and purified by flash chromatography eluting with EtOAc/n-hexanes mixture: 3:2 to afford the title compound. (0.856 g).

MS (APCI, M+): 119,121 for $C_7H_8N_2$

^{1}H NMR ($CDCl_3$) δ: 1.43 (m, 3H); 2.79 (m, 2H); 6.24 (s, 1H); 7.35 (s, 1H); 8.91 (s, 1H).

Intermediate 31: 3-Cyano-5-ethyl-1H-pyrrole-2-carboxylic acid

Silver nitrate (1.41 g, 8.3 mmol) in water (100 ml) was added to a solution of 5-ethyl-2-formyl-1H-pyrrole-3-carbonitrile (**Intermediate 58**) (819 mg, 5.53 mmol) in 1 N sodium hydroxide (100 ml) in the dark. The mixture was heated at 100 °C in the dark for 1 h. The reaction mixture was cooled to room temperature and acidified with 65% aqueous nitric acid. The yellow/brown solution was extracted with EtOAc, dried over sodium sulfate and concentrated in vacuo to give the title compound (600 mg).

^{1}H NMR δ: 1.03 (m, 3H); 2.37 (m, 2H); 6.39 (d, 1H); 8.03 (brs, 1H); 12.45 (s, 1H).

Intermediate 32: 3-Cyano-5-methyl-1H-pyrrole-2-carboxylic acid

The title compound was prepared by a procedure analogous to **Intermediate 31** starting from 5-methyl-2-formyl-1H-pyrrole-3-carbonitrile (preparation: *J. Med. Chem.* 1998, 41(6) 808-820).

^{1}H NMR δ: 2.26 (s, 3H); 6.46 (d, 1H); 12.58 (s, 1H); 13.47 (brs, 1H).

Intermediate 33: 4-Bromo-3-cyano-5-ethyl-1H-pyrrole-2-carboxylic acid

N-Bromosuccinimide (289 mg, 1.63 mmol) was added to a cooled solution of 3-cyano-5-ethyl-1H-pyrrole-2-carboxylic acid methyl ester (**Intermediate 27**; 290 mg, 1.63 mmol) in anhydrous DCM at 0 °C. The mixture was stirred at 0 °C for 30 minutes. The mixture was poured into a cold solution of 2 N sodium hydroxide (15 ml) and extracted with DCM. The combined extracts were washed with water (2 x 15 ml), dried over sodium sulphate and concentrated in vacuo to give small amounts of title compound. The aqueous phase was acidified, extracted with EtOAc, concentrated in vacuo to give the title compound as a creamy brown solid (240 mg).

^{1}H NMR δ: 1.03 (m, 3H); 3.46 (m, 2H); 13.16 (s, 1H); 13.82 (brs, 1H).

Intermediate 34: 4-Bromo-3-cyano-5-methyl-1H-pyrrole-2-carboxylic acid

The title compound was prepared by a procedure analogous to Intermediate 33 starting from 3-cyano-5-methyl-1H-pyrrole-2-carboxylic acid methyl ester (Intermediate 28).

^{1}H NMR δ: 2.03 (m, 3H); 13.05 (s, 1H).

Intermediate 35: Ethyl 2-chloro-4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-3-oxobutanoate

The title compound was prepared in a manner analogous to Intermediate 124 starting from ethyl 4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-3-oxobutanoate (Intermediate 25) and sulfuryl chloride.

MS (APCI) MH^+: 313 for $C_{14}H_{12}ClNO_5$

^{1}H NMR ($CDCl_3$) δ: 1.24-1.33 (t, 3H); 4.20-4.28 (q, 2H); 4.43 (q, 2H); 4.88 (s, 2H); 5.07 (s, 1H); 5.76 (s, 1H); 6.0 (s, 1H); 7.88-7.96 (brs, 6H).

Intermediate 36: Ethyl 2-(4-aminopiperidin-1-yl)-4-(methoxymethyl)-1,3-thiazole-5-carboxylate hydrochloride

The title compound was prepared in a manner analogous to Intermediate 126 starting from *tert*-butyl [1-(aminocarbonothioyl)piperidin-4-yl]carbamate (Intermediate 125) and ethyl 2-chloro-4-methoxy-3-oxobutanoate (Intermediate 6).

MS (ES) (M+H): 300,301 for $C_{13}H_{22}ClN_3O_3S$

Intermediate 37: 4-Bromo-5-isopropyl-1H-pyrrole-2-carboxylic acid

Intermediate 37 was synthesised by according to Elder, T et al. *Synth. Commun.* 1989,19 (5&6) 763-767 and references therein; Kelly, TR et al. *Tetrahedron.*1984, 40 (22) 4569.

Intermediate 38: tert-Butyl [1-(3-nitropyridin-2-yl)piperidin-4-yl]carbamate

Anhydrous TEA (0.76 ml, 5.49 mmol) was added to piperidin-4-yl-carbamic acid tert-butyl ester (1 g, 5 mmol) and 2-chloro-3-nitro-pyridine (0.791 g, 5 mmol) in anhydrous NMP (3 ml). Using a Smith Microwave Synthesizer, the mixture was subjected to single-mode microwave at 150 °C for 10 minutes. The brown solution was partitioned between EtOAc and water and the organic phase was washed several times with water, dried over sodium sulphate and concentrated in vacuo to give the title compound as a yellow solid (1.35 g).

MS (ES): 323 (MH^+) for $C_{15}H_{22}N_4O_4$

^{1}H NMR δ: 1.37 (s, 9H); 1.48 (m, 2H); 1.96 (m, 2H); 3.18 (m, 2H); 3.7 (m, 1H); 3.86 (m, 2H); 7.05 (m, 2H); 8.33 (m, 2H)

Intermediate 39: 1-(3-Nitropyridin-2-yl)piperidin-4-amine hydrochloride salt

A solution of 4 N hydrochloric acid in dioxane (10 ml) was added to tert-butyl [1-(3-nitropyridin-2-yl)piperidin-4-yl]carbamate (**Intermediate 38**; 1.3 g, 4.2 mmol).The mixture was stirred at room temperature for 1 h under nitrogen gas. The solvent was removed in vacuo to give the title compound as a yellow powder (500 mg).

MS (APCI): MH^+ 222 for $C_{11}H_{15}N_3O_2$

^{1}H NMR δ:1.76 (m, 2H); 2.10 (m, 2H); 3.18 (m, 2H); 3.82 (m, 12H); 3. 3.83 (m, 2H); 7.02 (m, 1H); 8.39 (m, 1H); 8.48 (m, 1H); 9.32 (b, 2H)

Intermediate 40: 2,6-Dichloro-N-(2-morpholin-4-yl-ethyl)-isonicotinamide

HATU (989 mg, 2.6 mmol), HOAT (354 mg, 2.6 mmol) and DIEA (907 µl, 5.21 mmol) were added to a stirred solution of 2,6-dichloroisonicotinic acid (500 mg, 2.60 mmol) in anhydrous DMA (4 ml). The mixture was stirred for 10 minutes after which 2-morpholin-4-yl-ethylamine (420 µl, 2.86 mmol) was added. The mixture was stirred at room temperature for 12 h and the mixture was partitioned between EtOAc and water. The EtOAc layer was washed well with water, dried over sodium sulphate and concentrated in vacuo to give the title compound as an oil (830 mg).

MS (ES) MH^+: 304

Intermediate 41: 2-(2,6-Dichloro-pyridin-4-ylsulfanyl)-N-methyl-acetamide

2,6-Dichloro-pyridin-4-ylamine (1 g, 6.13 mmol) in concentrated hydrochloric acid (5 ml) was cooled to 0 °C. Sodium nitrite (465 mg, 6.75 mmol) in water (10 ml) was added slowly whilst keeping the temperature at less than 5 °C. The mixture was stirred at low temperature for 20 minutes. N-Methylmercaptoacetamide (645 mg, 6.13 mmol) was added slowly, stirred at low temperature for 10 minutes and heated at 90 °C for 1 h. The yellow solution was cooled and extracted with EtOAc, washed with water, dried in vacuo and purified silica chromatography eluting with EtOAc/hexane mixture to give the title compound (855 mg).

^{1}H NMR δ: 2.55 (s, 3H); 3.94 (s, 2H); 7.55 (s, 2H)

Intermediate 42: tert-Butyl {1-[4-(aminocarbonyl)-6-cyanopyridin-2-yl]piperidin-4-yl}carbamate

tert-Butyl {1-[4-(aminocarbonyl)-6-chloropyridin-2-yl]piperidin-4-yl}carbamate (Intermediate 16) (100 mg, 0.282 mmol), copper cyanide (101 mg, 1.13 mmol), Pd(dba) (103 mg, 0.11 mmol) and Dppf (250 mg, 0.45 mmol) were placed in anhydrous dioxane (5 ml) under argon. The mixture was heated at 100 °C for 5 h, then diluted with EtOAc (20 ml) and filtered through celite. The mixture was washed with sodium bicarbonate (2 x 20 ml), brine(20 ml), dried over sodium sulphate and concentrated in vacuo. The brown residue was purified by flash chromatography eluting with DCM and MeOH mixtures to give the title compound as a brown solid (61 mg).

MS (ES): 346 (MH^+) for $C_{17}H_{23}N_5O_3$

^1H NMR δ: 1.27 (m, 2H); 1.38 (s, 9H); 1.78 (m, 2H); 3.03 (m, 2H); 3.52 (m, 1H); 4.24 (m, 2H); 7.79 (s, 1H); 8.22 (s, 1H).

Intermediate 43: Thiophene-2-carboxylic acid-2-chloro-pyridinyl-3-yl ester

TEA (1.2 ml, 8.49 mmol) was added to 2-chloro-3-pyridinol (1 g, 7.72 mmol) and 2-thiophenecarbonyl chloride (1.13 g, 7.72 mmol) in anhydrous toluene (10 ml). The mixture was heated at 100 °C for 25 minutes. The solvent was removed in vacuo and the mixture was partitioned between EtOAc and water, washed with water (x1), dried over sodium sulphate and dried in vacuo to give an oil which was triturated with n-hexanes to give the title compound as an off-white solid (1.85 g).

^1H NMR δ: 7.42 (m, 1H); 7.70 (m, 1H); 8.09 (m, 1H); 8.14 (m, 1H); 8.26 (m, 1H); 8.52 (m, 1H).

Intermediate 44: N-[6-Chloro-2-(methylthio)pyrimidin-4-yl]acetamide

Acetic anhydride (10.4 ml, 0.11 mol) was added to 6-chloro-2-(methylthio)pyrimidin-4-amine (2.5 g, 0.01 mol) and the reaction mixture was refluxed at 135 °C for 5 hr. The reaction mixture was cooled to room temperature and basified to pH 7 with saturated sodium bicarbonate solution (20 ml). The mixture was partitioned between EtOAc and water, the organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated to give the title compound (2.62 g).

MS (ES): 218 (MH^+) for $C_7H_8ClNO_3S$

Intermediate 45: tert-Butyl 1-[6-amino-2-(methylthio)pyrimidin-4-yl]piperidin-4-ylcarbamate

TEA (0.243 ml, 1.74 mmol) and 6-chloro-2-(methylthio)pyrimidin-4-amine (0.309 g, 1.74 mmol) were added to a solution of tert-butyl piperidin-4-ylcarbamate (0.35 g, 1.74 mmol) in NMP (4 ml). Using a Smith Microwave Synthesizer, the mixture was subjected to single-mode microwave at 150 °C for 90 minutes. The mixture was partitioned between water and EtOAc and washed (x2) with water. The organic phase was dried over magnesium sulphate and concentrated to give the title compound (0.294 g).

MS (ES) (MH^+): 340 for $C_{16}H_{26}N_4O_2S$

Intermediate 46: 6-(4-Aminopiperidin-1-yl)-2-(methylthio)pyrimidin-4-amine hydrochloride

4 N Hydrogen chloride in dioxane(3 ml) was added to tert-butyl 1-[6-amino-2-(methylthio)pyrimidin-4-yl]piperidin-4-ylcarbamate (Intermediate 45, 0.29 mg 0.86 mmol). The mixture was stirred at room temperature for 90 minutes. The solvent was removed in vacuo to afford the title compound (238 mg).

MS (ES) (MH^+): 240 for $C_{10}H_{17}N_5S$

Intermediate 47: 2,6-Dichloro-N-methoxy-N-methylisonicotinamide

HATU (1.97 g, 5.20 mmol), HOAT (707 mg, 5.20 mmol) and DIEA (1.77 ml, 10.5 mmol) were added to 2, 6-dichloroisonicotinic acid (1 g, 5.20 mmol) in anhydrous DMF (5 ml). The mixture was stirred for 5 minutes, then N-methyl methoxylamine hydrochloride (507 mg, 5.20 mmol) was added in one portion followed by DIEA (800 µl, 5.2 mmol). The reaction was stirred for 30 minutes, then the crude product was partitioned between EtOAc (50 ml) and water (50 ml) and the organic level washed with water (3 x 50 ml). The organic phase was dried over sodium sulphate and concentrated in vacuo. The crude product was purified by flash chromatography eluting with EtOAc: n-hexanes (2:3) to afford the title compound (1.12 g).

MS (APCI, M+H): 235 for $C_8H_8Cl_2N_2O_2$

^{1}H NMR δ: 3.29 (s, 3H); 3.61 (s, 3H); 7.77 (s, 2H)

Intermediate 48: 1-(2,6-Dichloropyridin-4-yl)ethanone

2,6-Dichloro-N-methoxy-N-methylisonicotinamide (Intermediate 47, 780 mg, 3.3 mmol) in anhydrous diethylether (13 ml) was cooled to –78 °C. Methyllithium (1.6 M solution in diethyl ether (5.2 ml, 8.3 mmol) was added dropwise. The mixture was stirred at –78 °C for 1 h and quenched with ammonium chloride solution, followed by warming to room temperature. The reaction mixture was diluted with water (20 ml) and extracted with diethyl ether (2 x 30 ml), dried over sodium sulphate and concentrated in vacuo to give the title compound (575 mg).

MS (APCI, M+H): 191 for $C_7H_5Cl_2O$

^{1}H NMR δ: 2.66 (s, 3H); 7.96 (s, 2H)

Intermediate 49: tert-Butyl 1-[6-chloro-4-(hydrazinocarbonyl)pyridin-2-yl]piperidin-4-ylcarbamate

Hydrazine (0.55 ml 17.0 mmol) was added to a solution of methyl 2-{4-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-6-chloroisonicotinate (Intermediate 23, 0.15 g, 0.40 mmol) in isopropanol (3 ml). The mixture was stirred at room temperature overnight then the isopropanol was removed in vacuo to give the title product (130 mg).

MS (ES, MH): 370,368 for $C_{17}H_{25}Cl_2N_4O_3$

Intermediate 50: tert-Butyl 1-[6-chloro-4-(5-oxo-2,5-dihydro-1,3,4-oxadiazol-2-yl)pyridin-2-yl]piperidin-4-ylcarbamate

N, N'-Carbonyldiimidazole (0.12 g, 0.82 mmol) was added to a solution of tert-butyl 1-[6-chloro-4-(hydrazinocarbonyl)pyridin-2-yl]piperidin-4-ylcarbamate (Intermediate 49, 0.15 g, 0.41 mmol) in DMF (3 ml). The mixture was stirred at room temperature overnight and was purified by semi-preparative HPLC eluting with CH_3CN/H_2O (0.1% TFA) mixtures to afford the title compound (0.125 g).

MS (ES, MH): 396,394 for $C_{18}H_{23}ClN_4O_4$

Intermediate 51: 5-[2-(4-Aminopiperidin-1-yl)-6-chloropyridin-4-yl]-1,3,4-oxadiazol-2(5*H*)-one hydrochloride

4 N Hydrochloric acid in dioxane (3 ml) was added to tert-butyl 1-[6-chloro-4-(5-oxo-2,5-dihydro-1,3,4-oxadiazol-2-yl)pyridin-2-yl]piperidin-4-ylcarbamate (Intermediate 50, 0.12

mg, 0.32 mmol). The mixture was stirred at room temperature for 45 min, then concentrated in vacuo to afford the title compound (100 mg).

MS (ES, MH): 296,294 for $C_{13}H_{15}ClN_4O_2$

Intermediate 52: *tert*-Butyl 4-{[(4-bromo-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidine-1-carboxylate

Title compound was synthesized by an analogous method to **Intermediate 2**, starting from 4-bromo-5-methyl-1H-pyrrole-2-carboxylic acid (**Intermediate 18**).

MS (ESP): 386.1 (M+H) for $C_{16}H_{24}BrN_3O_3$

^{1}H NMR δ: 1.34 (m, 2H); 1.41 (s, 9H); 1.74 (d, 2H); 2.13 (s, 3H); 2.84 (m, 2H); 3.92 (m, 3H); 6.81 (s, 1H); 7.75 (d, 1H); 11.67 (s, 1H).

Intermediate 53: tert-Butyl 1-(6-chloro-4-cyanopyridin-2-yl)piperidin-4-ylcarbamate

TEA (0.20 ml, 1.44 mmol) and 2,6-dichloroisonicotinonitrile (0.25 g, 1.44 mmol) were added to a solution of tert-butyl piperidin-4-ylcarbamate (0.28 g, 1.44 mmol) in NMP (2 ml). Using a Smith Microwave Synthesizer, the mixture was subjected to single-mode microwave at 150 °C for 10 minutes. The crude mixture was partitioned between water and EtOAc and washed (x2) with water. The extracts were combined dried over $MgSO_4$ and concentrated to give the title compound (400 mg).

MS (ES): 337 (MH^+) for $C_{17}H_{22}ClN_3O_2$

Intermediate 54: tert-Butyl 1-{4-[amino(hydroxyimino)methyl]-6-chloropyridin-2-yl}piperidin-4-ylcarbamate

TEA (0.24 ml,1.78 mmol) was added to a solution of tert-butyl 1-(6-chloro-4-cyanopyridin-2-yl)piperidin-4-ylcarbamate (**Intermediate 53**, 0.4 g, 1.19 mmol) in MeOH (2 ml), followed by the addition of hydroxylamine hydrochloride (0.82 g, 1.19 mmol). The mixture was refluxed for 4 h, then the solvent was removed in vacuo to give the desired product.(410 mg).

MS (ES): 370 (MH^+) for $C_{17}H_{25}ClN_4O_3$

Intermediate 55 : tert-Butyl 1-[6-chloro-4-(1,2,4-oxadiazol-3-yl)pyridin-2-yl]piperidin-4-ylcarbamate

Boron trifluoroetherate (0.1 ml) was added to a solution of tert-butyl 1-{4-[amino (hydroxyimino)methyl]-6-chloropyridin-2-yl}piperidin-4-ylcarbamate (**Intermediate 54**)

(0.254 g, 0.69 mmol) in 1,1,1-triethoxyethane (1.5 ml) at room temperature. The mixture was refluxed for 10 minutes. The mixture was purified by flash chromatography on silica gel eluting with (n-hexanes:EtOAc; 70:30) to afford the title compound (50 mg).
MS (ES) : 380 (MH^+) for $C_{18}H_{23}ClN_4O_3$

Intermediate 56: 1-[6-Chloro-4-(1,2,4-oxadiazol-3-yl)pyridin-2-yl]piperidin-4-amine hydrochloride

Tert-butyl 1-[6-chloro-4-(1,2,4-oxadiazol-3-yl)pyridin-2-yl]piperidin-4-ylcarbamate (Intermediate 55) (50 mg 0.13 mmol) was dissolved in 4 N HCl in dioxane (2 ml). The mixture was stirred at room temperature for 2 h. The solvent was concentrated in vacuo to afford the crude title compound which was used without further purification (74 mg).
MS (ES): 280 (MH^+) for $C_{13}H_{15}ClN_4O$

Intermediate 57: 4-Bromo-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride

Title compound was synthesized by an analogous method to Intermediate 1, starting from *tert*-butyl 4-{[(4-bromo-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidine-1-carboxylate (Intermediate 52).
MS (ESP): 286.1 (M+H) for $C_{11}H_{16}BrN_3O$
^{1}H NMR δ: 1.36 (m, 2H); 1.74 (d, 2H); 2.13 (s, 3H); 2.83 (m, 2H); 3.85-4.05 (m, 3H); 6.81 (s, 1H); 7.75 (d, 1H); 11.66 (s, 1H).

Intermediate 58: 5-Ethyl-2-formyl-1H-pyrrole-3-carbonitrile

$POCl_3$ (3.3 ml, 35.67 mmol) was added to 1,2-dichloroethane (4 ml), then anhydrous DMF (2.75 ml, 35.67 mmol) was added very slowly. The mixture was stirred at room temperature for ~10 minutes. 5-Ethyl-1H-pyrrole-3-carbonitrile (Intermediate 30, 856 mg, 7.13 mmol) in 1,2-dichloroethane (2 ml) was added dropwise and the mixture was heated at 80 °C for ~30 minutes. The mixture was cooled to room temperature and sodium acetate (2.5 g/5 ml) was added and the mixture was stirred for 1 h. The brown/black emulsion was extracted with DCM (4 x 50 ml). The combined organic phase was washed with water (2 x 50 ml) dried over Na_2SO_4 and concentrated in vacuo to give the title compound. (819 mg).
^{1}H NMR ($CDCl_3$) δ: 1.52 (m, 3H); 2.81 (m, 2H); 6.46 (s, 1H); 9.65 (s, 1H); 9.96 (s, 1H).

Intermediate 59: Ethyl 4,5-dichloro-1H-pyrrole-2-carboxylate

The title compound was prepared in a manner analogous to **Intermediate 20** starting from 2,2,2-trichloro-1-(4,5-dichloro-1H-pyrrol-2-yl)ethanone (**Intermediate 60**).

MS (ES): MH^+ 207, 209 for $C_7H_7Cl_2NO_2$

Intermediate 60: 2,2,2-Trichloro-1-(4,5-dichloro-1H-pyrrol-2-yl)ethanone

A solution of sulfuryl chloride (11.3 ml, 0.14 mol) in ether (5 ml) at 0 °C was added to a solution of 2,2,2-trichloro-1-(1H-pyrrol-2-yl)ethanone (15.0 g, 0.07 mol) in diethyl ether (10 ml). The mixture was left to stir at room temperature overnight. The solvent was removed under vacuum. The crude mixture was partitioned between ether and 10% aqueous K_2CO_3. The organic phase was concentrated in vacuo and was purified by flash chromatography on silica eluting gradient (2 – 5% EtOAc in hexane) to give the title compound (17.0 g).

^1H NMR (500 MHz, $CDCl_3$) δ: : 7.42 (d, 1H); 13.85 (s, 1H)

Intermediate 61: 4,5-Dichloro-1H-pyrrole-2-carboxylic acid

A solution of lithium hydroxide in water (2 N, 0.80 ml, 0.16 mol) was added to a stirred solution of a mixture of ethyl 4,5-dichloro-1H-pyrrole-2-carboxylate (**Intermediate 59**; 7.0 g, 0.033 mol) in THF (15 ml) at room temperature. The mixture was stirred at 50 °C for 8 h over 2 days. The reaction mixture was acidified with 10% HCl solution to a pH ~ 2 and partitioned between EtOAc and water. The organic layer was dried over $MgSO_4$and concentrated in vacuo to give the title compound (4.0 g).

MS(ES): MH^+ 178 for $C_5H_3Cl_2NO_2$

^1H NMR (500 MHz) δ: : 7.06 (s, 1H); 12.43 (s, 1H); 13.43 (s, 1H)

Intermediate 62: 2-Chloro-6-(4-hydroxypiperidin-1-yl)isonicotinamide

The title compound was prepared in a manner analogous to **Intermediate 26** starting from 2,6-dichloroisonicotinamide and 4-hydroxypiperidine (both commercially available).

MS (LCMS): 255

Intermediate 63: 2-Chloro-6-[4-(methylamino)piperidin-1-yl]isonicotinonitrile

2,6-Dichloroisoniconitrile (1.28 g, 7.38 mmol) and DIEA (3.85 ml) were added to piperidin-4-one (1 g, 7.38 mmol) in anhydrous DMA (8 ml) was added. Using a Smith Microwave Synthesizer, the mixture was subjected to single-mode microwave at 150 °C for 20 minutes in

two batches. The batches were combined and diluted with EtOAc (100 ml) and washed with water (3 x 50 ml). The organic phase was dried over Na_2SO_4 and concentrated in vacuo to give a brown solid corresponding [LCMS indicated the expected mass (236)] to 2-chloro-6-(4-oxopiperidin-1-yl)isonicotinonitrile (1.58 g).

Methylamine (2.65 ml, 5.3 mmol) was added to a solution of 2-chloro-6-(4-oxopiperidin-1-yl)isonicotinonitrile (Intermediate 26; 500 mg, 2.12 mmol) in anhydrous THF (4 ml). The mixture was stirred for 30 minutes and sodium triacetoxyborohydride (674 mg, 3.18 mmol) was added. The mixture was stirred at room temperature for 18 h, then concentrated in vacuo, diluted with EtOAc and washed with 1 N NaOH, water and brine. The organic phase was dried over Na_2SO_4 then concentrated in vacuo to give a brown oil which was dried under vacuum to yield the title compound (507 mg).

MS (ES): 251 for $C_{12}H_{15}ClN_4$

^{1}H NMR δ: 1.21 (m, 2H); 1.90 (m, 2H); 2.32 (s, 3H); 2.61 (m, 1H); 3.12 (m, 2H); 4.14 (m, 2H); 7.10 (s, 1H); 7.39 (s, 1H)

Intermediate 64: 1-[6-Chloro-4-(1*H*-tetrazol-5-yl)pyridin-2-yl]-*N*-methylpiperidin-4-amine

Sodium azide (131 mg, 2.02 mmol) and NH_4Cl (108 mg, 2.02 mmol) were added to a solution of 2-chloro-6-[4-(methylamino)piperidin-1-yl]isonicotinonitrile (Intermediate 63, 507 mg, 2.02 mmol) in anhydrous DMF (3 ml). The mixture was heated at 120 °C under nitrogen gas for 1 h where LCMS showed the expected mass. The mixture was filtered and was purified by semi-preparative HPLC eluting with acetonitrile/water (0.1% TFA) and the title compound was concentrated in vacuo to give a hygroscopic brown solid (220 mg).

MS (ES): (MH^+)294 for $C_{12}H_{16}ClN_7$

Intermediate 65: 1-[6-Chloro-4-(1-methyl-1*H*-tetrazol-5-yl)pyridin-2-yl]-*N*-methylpiperidin-4-amine

Sodium azide (225 mg, 3.47 mmol) and ammonium chloride (186 mg, 3.47 mmol) were added to a solution of 2,6-dichloroisoniconitrile (500 mg, 2.89 mmol) in anhydrous DMF (3 ml). The mixture was heated at 120 °C under nitrogen gas for 1 h. The mixture was cooled to room temperature and K_2CO_3 (798 mg, 5.78 mmol) was added. The resulting mixture was stirred for 30 minutes after which iodomethane (270 µl, 4.33 mmol) was added. The mixture was stirred at room temperature for 18 h, diluted with EtOAc and washed with water and

brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo to give a brown solid 2,6-dichloro-4-(2-methyl-2H-tetrazol-5-yl)-pyridine (486 mg).

tert-Butyl piperidin-4-ylcarbamate (87 mg, 0.44 mmol) and DIEA (76 µl, 0.44 mmol) were added to a solution of 2,6-dichloro-4-(2-methyl-2H-tetrazol-5-yl)-pyridine (100 mg, 0.44 mmol) in anhydrous NMP (2 ml). Using a Smith Microwave Synthesizer, the mixture was subjected to single-mode microwave at 150 °C for 15 minutes, diluted with EtOAc (25 ml) and washed with water (4 x 25 ml). The organic phase was dried over Na_2SO_4 and concentrated in vacuo to give a brown solid. This sample was treated with 4 N HCl/dioxane (8 ml) for 45 minutes. The solvent was removed under reduced pressure and the material was dried in vacuo.

MS (ES): MH^+294, for $C_{12}H_{16}ClN_7O$

Intermediate 66: tert-Butyl [1-(6-chloropyridin-2-yl)piperidin-4-yl]carbamate

TEA (0.13 ml, 0.99 mmol) and 2,6-dichloropyridine (0.14 g, 0.99 mmol) were added to a solution of tert-butyl piperidin-4-ylcarbamate (0.20 g, 0.99 mmol) in NMP (2 ml) at room temperature. Using a Smith Microwave Synthesizer, the mixture was subjected to single-mode microwave at 150 °C for 30 minutes. The mixture was diluted with EtOAc and washed with water three times. The organic phase was dried over magnesium sulfate and concentrated to give the title compound. (300 mg).

MS (ES) : 337 (MH^+) for $C_{17}H_{22}ClN_3O_2$

Intermediate 67: 2-Bromo-5-(ethylthio)-1,3,4-thiadiazole

tert-Butyl nitrite (2.20 ml, 1.91 g, 18.50 mmol) was added dropwise to a mixture of copper (II) bromide (3.32 g, 14.86 mmol) in acetonitrile (30 ml). A solution of 5-(ethylthio)-1,3,4-thiadiazol-2 amine (2.00 g, 12.40 mmol) in acetonitrile (66 ml) was added and the mixture was heated at 65 °C. After approximately three hours, the mixture was cooled, diluted with water, and extracted with ether. The organic phase was dried ($MgSO_4$), and concentrated under vacuum. The crude material was purified by flash chromatography using 10% EtOAc/hexanes to give 2.15g of the title product.

MS (ESP): 226 (MH^+) for $C_4H_5BrN_2S_2$

Intermediate 68: tert-Butyl {1-[6-(acetylamino)-2-(methylthio)pyrimidin-4-yl]piperidin-4-yl}carbamate

TEA (0.32 ml, 2.28 mmol) and N-[6-chloro-2-(methylthio)pyrimidin-4-yl]acetamide (Intermediate 44, 0.50 g, 2.28 mmol) were added to a solution of tert-butyl piperidin-4-ylcarbamate (0.46 g, 2.28 mmol) in NMP (2 ml) at room temperature. Using a Smith Microwave Synthesizer, the mixture was subjected to single-mode microwave at 150 °C for 10 minutes. The mixture was partitioned between water and EtOAc. The layers were separated and the organic layer was washed with water two more times. The organic phase was dried over magnesium sulfate and concentrated to give the title compound (816 mg).

MS (ES) : 381 (MH^+) for $C_{18}H_{28}N_4O_3S$

Intermediate 69: N-[6-(4-Aminopiperidin-1-yl)-2-(methylthio)pyrimidin-4-yl]acetamide hydrochloride

tert-Butyl {1-[6-(acetylamino)-2-(methylthio)pyrimidin-4-yl]piperidin-4-yl}carbamate (Intermediate 68) (816 mg, 2.15 mmol) was dissolved in 4 N HCl/Dioxane (10 ml). The mixture was stirred at room temperature for 2 h. Excess 4 N HCl/Dioxane was removed by concentrating under vacuo to give the title compound as a bright yellow coloured solid. (790 mg).

MS (ES) : 281 (MH^+) for $C_{13}H_{20}N_4OS$

Intermediate 70: 2-(4-Aminopiperidin-1-yl)-6-chloroisonicotinamide hydrochloride salt

4 N HCl/ Dioxane solution (6 ml) was added to tert-butyl 1-[4-(aminocarbonyl)-6-chloropyridin-2-yl]piperidin-4-ylcarbamate (Intermediate 16, 100 mg, 0.282 mmol). The mixture was stirred at room temperature for 90 minutes. The solvent was removed in vacuo and the anhydrous diethylether (25 ml) was added. The solvent was removed in vacuo and light yellow solid that resulted was dried under vacuum for several hours to give the title compound as an off-white solid (87 mg).

MS (ES): 255 for $C_{11}H_{15}ClN_4O$

^1H NMR δ: 1.56 (m, 2H); 2.08 (m, 2H); 2.35 (m, 2H); 3.27 (m, 1H); 4.35 (m, 2H); 7.00 (s, 1H); 7.21 (s, 1H); 7.68 (s, 1H); 7.90 (s, 1H); 8.20 (b, 3H).

Intermediate 71: 4-Chloro-5-ethyl-1*H*-pyrrole-2-carboxylic acid

Title compound was synthesized from ethyl 4-chloro-5-ethyl-1*H*-pyrrole-2-carboxylate (**Intermediate 72**) by an analogous method to **Intermediate 8**.

MS (ESP): 172.1 (M-H) for $C_7H_8ClNO_2$

Intermediate 72: Ethyl 4-chloro-5-ethyl-1*H*-pyrrole-2-carboxylate

Title compound was synthesized from ethyl 5-ethyl-1*H*-pyrrole-2-carboxylate (**Intermediate 12**) by an analogous method to **Intermediate 9**.

MS (ESP): 200.1 (M-H) for $C_9H_{12}ClNO_2$

Intermediate 73: 3,4-Dichloro-5-ethyl-1*H*-pyrrole-2-carboxylic acid

Title compound was synthesized from ethyl 3,4-dichloro-5-ethyl-1*H*-pyrrole-2-carboxylate (**Intermediate 74**) by an analogous method to **Intermediate 8**.

MS (ESP): 208.1 (M+H) for $C_7H_7Cl_2NO_2$

Intermediate 74: Ethyl 3,4-dichloro-5-ethyl-1*H*-pyrrole-2-carboxylate

Title compound was synthesized from ethyl 5-ethyl-1*H*-pyrrole-2-carboxylate (**Intermediate 12**) by an analogous method to **Intermediate 4**.

MS (ESP): 234.1 (M-H) for $C_9H_{11}Cl_2NO_2$

Intermediate 75: 4-Chloro-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid

Title compound was synthesized from ethyl 4-chloro-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (**Intermediate 76**) by an analogous method to **Intermediate 8**.

MS (ESP): 172 (M-H) for $C_7H_8ClNO_2$

Intermediate 76: Ethyl 4-chloro-3,5-dimethyl-1*H*-pyrrole-2-carboxylate

Title compound was synthesized from ethyl 3,5-dimethyl-1*H*-pyrrole-2-carboxylate (commercially available) by an analogous method to **Intermediate 9**.

MS (ESP): 200 (M-H) for $C_9H_{12}ClNO_2$

Intermediate 77: Ethyl 2-(4-aminopiperidin-1-yl)-4-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1,3-thiazole-5-carboxylate hydrochloride

The title compound was prepared in a manner analogous to **Intermediate 126** starting from *tert*-butyl [1-(aminocarbonothioyl)piperidin-4-yl]carbamate (**Intermediate 125**) and ethyl 2-chloro-4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-3-oxobutanoate (**Intermediate 35**).

MS (ES) $(M+H)^+$: 416 for $C_{20}H_{23}ClN_4O_4S$

Intermediates 78-80

The following compounds were prepared in a manner analogous to **Intermediate 126** starting from *tert*-butyl [1-(aminocarbonothioyl)piperidin-4-yl]carbamate (**Intermediate 125**) and the starting materials listed.

Intermediate	Compound	M/Z	SM
Intermediate 78	Ethyl 2-(4-aminopiperidin-1-yl)-4-(trifluoromethyl)-1,3-thiazole-5-carboxylate hydrochloride salt	323	Ethyl 2-chloro-4,4,4-trifluoro-3-oxobutanoate (commercially available)
Intermediate 79	Ethyl 2-(4-aminopiperidin-1-yl)-4-(methoxymethyl)-1,3-thiazole-5-carboxylate hydrochloride	300,301	Ethyl 2-chloro-4-methoxy-3-oxobutanoate (Intermediate 6)
Intermediate 80	Ethyl 2-(4-aminopiperidin-1-yl)-4-butyl-1,3-thiazole-5-carboxylate hydrochloride salt	311	Ethyl 2-bromo-3-oxoheptanoate (Intermediate 85)

Intermediate 81: 2-(4-Aminopiperidin-1-yl)-1,3-thiazole-5-carboxamide hydrochloride

Title compound was synthesized from *tert*-butyl 1-[5-(aminocarbonyl)-1,3-thiazol-2-yl]piperidin-4-ylcarbamate (**Intermediate 82**) by an analogous method to **Intermediate 1**.

MS (ESP): 227 (M+H) for $C_9H_{14}N_4OS$

Intermediate 82: *tert*-Butyl 1-[5-(aminocarbonyl)-1,3-thiazol-2-yl]piperidin-4-ylcarbamate

Title compound was synthesized by an analogous method to **Intermediate 38** by coupling *tert*-butyl piperidin-4-ylcarbamate (commercially available) with 2-bromo-1,3-thiazole-5-carboxamide (*J. Am. Chem. Soc.* 1952, *74*, 5799).

MS (ESP): 327 (M+H) for $C_{14}H_{22}N_4O_3S$

Intermediate 83: Methyl 2-chloro-6-(methylthio)isonicotinate

Methyl 2,6-dichloroisonicotinate (300 mg, 1.45 mmol) was dissolved in anhydrous DMF. Sodium thiomethoxide (102 mg, 1.45 mmol) was added and the mixture was stirred at room temperature for 4 h. The mixture was diluted with EtOAc and washed with water (x3), brine (x1) and dried over sodium sulfate and concentrated in vacuo to afford title compound (294 mg).

MS (ES) (M+H): 218 for $C_8H_8ClNO_2S$

^{1}H NMR δ: 2.73 (s, 3H); 4.04 (t, 3H); 7.64 (s, 1H); 7.79 (s, 1H)

Intermediate 84: Methyl 2-chloro-6-(methylsulfinyl)isonicotinate

Methyl 2-chloro-6-(methylthio)isonicotinate (**Intermediate 83**; 290 mg), was dissolved in anhydrous DCM (5 ml). mCPBA (345 mg) was added and the mixture was stirred at room temperature for 90 minutes. The mixture was diluted with EtOAc and washed with water, 10% sodium thiosulfate, water, brine and dried over sodium sulfate. The mixture was concentrated in vacuo and purified by flash chromatography eluting with EtOAc: Hexane (7:3) to afford the title compound (129 mg).

MS (ES) (M+H): 224 for $C_8H_8ClNO_3S$

^{1}H NMR δ: 2.97 (s, 3H); 4.04 (s, 3H); 8.06 (s, 1H); 8.29 (s, 1H)

Intermediate 85: Ethyl 2-bromo-3-oxoheptanoate

Ethyl 3-oxoheptanoate (**Intermediate 94**; 5g, 29.03mmol) was dissolved in anh.CH_3CN (75ml) and cooled to 0°C. $CuBr_2$ was added, followed by addition of (hydroxy(tosyloxy) iodo)benzene (Koser's reagent). The mixture was warmed to room temperature over 1 h, after which the reaction was quenched with water (100ml). The blue solution was extracted with DCM and combined organic phase was washed well with water, brine and dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash chromatography eluting with a gradient of 10%-50% Hexane/EtOAc, followed by Kugelrohr distillation affording the title compound (3.5g).

^{1}H NMR δ: 0.75-0.93 (m, 3H); 1.13-1.25 (m, 5H); 1.38-1.64 (m, 2H); 2.43-2.50 (m, 2H); 3.5-3.69 (s, 2H); 5.54 (s, 1H).

Intermediate 92: 2,6-Dioxo-1,2,3,6-tetrahydropyrimidine-4-carbaldehyde monohydrate

The title compound (9.53 g) was prepared according to the procedure of Johnson et al (Johnson, Treat B.; Schroeder, Elmer F. *J. Am. Chem. Soc.* 1931, *53*,1989-1994).

^{1}H NMR δ: 6.75 (brs, 2H); 9.60 (s, 1H); 10.61 (s, 1H); 10.99 (s, 1H)

Intermediate 93: Methyl 2-(4-aminopiperidin-1-yl)-6-chloroisonicotinate hydrochloride salt

Methyl 2-{4-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-6-chloroisonicotinate (Intermediate 23, 1.81 g, 4.9 mmol) was dissolved in 4 N HCl/dioxane (200 ml). The mixture was stirred at room temperature for 2 h. The solvent was removed under vacuum to give the title compound (1.5 g).

MS (LCMS): 269

Intermediate 94: Ethyl 3-oxoheptanoate

The title compound was prepared in a manner analogous to Intermediate 123 from valeryl chloride and 2,2-dimethyl-1,3-dioxane-4,6-dione (both commercially available).

^{1}H NMR δ: 0.7-0.96 (m, 3H); 1.06-1.31 (m, 5H); 1.36-1.58 (m, 2H); 2.43-2.50 (m, 2H); 3.5-3.69 (s, 2H); 3.99-4.22 (m, 2H).

Intermediate 95: N-[1-(Aminocarbonothioyl)piperidin-4-yl]-3,4-dichloro-5-methyl-1H-pyrrole-2-carboxamide

The title compound was prepared by a procedure analogous to Intermediate 125 starting from 3,4-dichloro-5-methyl-N-piperidin-4-yl-1H-pyrrole-2-carboxamide (Intermediate 90, 0.5 g, 2 mmol). The product was concentrated to a solid which was purified on a silica flash column (gradient elution from 0 - 5 % MeOH in DCM over 30 min). Purification yielded a white solid (0.22 g).

^{1}H NMR δ: 1.41 - 1.56 (m, 2H); 1.80 (dd, J=12.81, 3.20 Hz, 2H); 2.17 (s, 3H); 3.08 - 3.22 (m, 2H); 3.96 - 4.11 (m, 1H); 4.43 (d, J=15.07 Hz, 2H); 7.27 (d, J=7.72 Hz, 1H); 7.32 - 7.47 (m, 2H); 11.96 (s, 1H).

Intermediate 96: Methyl 2-chloro-6-(ethylthio)pyrimidine-4-carboxylate

A solution of ethanethiol (0.30 g, 4.8 mmol) in THF (1 ml) was added dropwise to a solution of methyl 2,6-dichloropyrimidine-4-carboxylate (1 g, 4.8 mmol), THF (8 ml) and TEA (0.49

g, 4.8 mmol) at 0 °C under nitrogen. The mixture was stirred for 2 h and slowly warmed to room temperature. The mixture was diluted with EtOAc (50 ml) and water (10 ml). The organic layer was separated, dried over sodium sulfate, filtered and concentrated in vacuo to afford the title compound (1.1 g).

MS (ESP): 431 (M+H) for $C_8H_9ClN_2O_2S$

^{1}H NMR δ: 1.38 (t, 3H); 3.29 (q, 2H); 3.96 (s, 3H); 7.97 (s, 1H).

Intermediate 97: 4-Chloro-2-butyl-6-methylpyrimidine

Using the procedure of Papet, Anne-Lure et. al., (*Synthesis* 1993 (5), 478-481) the title compound (1.28 g) was prepared from 2-butyl-6-methylpyrimidin-4-ol (**Intermediate 98**, 4 g, 32.85 mmol).

MS (ES) (M+H): 184 for $C_9H_{13}ClN_2$

^{1}H NMR δ: 1.10 (m, 3H); 1.57 (m, 2H); 1.80 (m, 2H); 2.37 (s, 3H); 2.99 (m, 2H); 6.67 (s, 1H)

Intermediate 98: 2-Butyl-6-methylpyrimidin-4-ol

Pentanimidamide hydrochloride (3.2 g) (prepared according to Garigipati, R. S.; *Tetrahedron Lett* 1990, 31 (14), 1969) was treated with ethyl acetoacetate (3.05 g) in a modified procedure using sodium (1.62 g) in anhydrous EtOH (50 ml) as base (as described in Salimbeni, Aldo; et al. *J. Med. Chem.* (1995), 38(24), 4806-20) affording the title compound (4.04 g).

MS (ES) (M+H): 166 for $C_9H_{14}N_2O$

^{1}H NMR δ: 0.80 (m, 3H); 1.31 (m, 2H); 1.63 (m, 2H); 2.25 (s, 3H); 2.41 (m, 2H); 6.29 (s, 1H)

Intermediate 99: *tert*-Butyl [1-(2-butyl-6-methylpyrimidin-4-yl)piperidin-4-yl]carbamate

Prepared in a manner analogous to **Intermediate 38** starting from 4-chloro-2-butyl-6-methylpyrimidine (**Intermediate 97**) and *tert*-butyl piperidin-4-ylcarbamate.

MS (ES) (M+H): 349 for $C_{19}H_{32}N_4O_2$

^{1}H NMR δ: 0.93 (m, 3H); 1.33 (m, 2H); 1.45 (s, 9H); 1.70 (m, 2H); 1.82 (m, 2H); 2.02 (m, 1H); 2.25 (s, 3H); 2.61 (m, 4H); 3.03 (m, 2H); 3.39 (m, 2H); 3.66 (m, 1H); 4.20 (m, 2H); 6.58 (s, 1H); 6.93 (d, 1H); 6.29.

Intermediate 100: 6-{4-[(*tert*-Butoxycarbonyl)amino]piperidin-1-yl}-2-butylpyrimidine-4-carboxylic acid

tert-Butyl [1-(2-butyl-6-methylpyrimidin-4-yl)piperidin-4-yl]carbamate (1.08 g) (Intermediate 99) was dissolved in anhydrous pyridine (25 ml). Selenium dioxide (1.72 g) was added and the mixture was heated at 120 °C for 4 h. The black solution was diluted with water (40 ml), filtered through a bed of celite. The filtrate was acidified with 1 N HCl and extracted with EtOAc, washed well with water, dried over sodium sulfate and concentrated in vacuo. The crude material was purified by flash chromatography eluting with trichloromethane/MeOH/ammonium hydroxide (9:1:1) to afford the title compound (241 mg).

MS (ES) (M+H): 378 for $C_{19}H_{30}N_4O_4$

^{1}H NMR δ: 0.74 (t, 3H); 1.12 (m, 4H); 1.20 (s, 9H); 1.49 (m, 2H); 1.65 (m, 2H); 2.54 (m, 1H); 2.9 (m, 2H); 3.45 (m, 2H); 4.18 (m, 2H); 6.69 (d, 1H); 6.82 (s, 1H)

Intermediates 101 to 109 were prepared by the following general method:

The 4-(*N*-BOC amino)-piperidine (1.00 equivalent, 5.00 mmol), palladium (II) acetate (0.10 equiv), BINAP (*rac*-2,2'-bis(diphenylphosphinio)-1,1'-binaphthyl, 0.10 equiv), caesium carbonate (1.40 equiv) and aryl halide starting material shown in the following table (1.00 equiv) were combined. The solids were degassed and placed under argon. Toluene (10 ml) was added and the mixture was stirred at 100 °C for approximately 16 h. The mixture was filtered, and the filtrate was concentrated under vacuum. The crude product was purified by silica gel flash column chromatography.

The Aryl halide starting materials shown in the table below for Intermediates 101 to 109 are commercially available, except for methyl 6-bromopyridine-2-carboxylate (Intermediate 158) and methyl 5-bromothiophene-2-carboxylate (Intermediate 159) which were formed by esterification of commercially available acids.

Intermediate 101: Methyl 5-{4-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}thiophene-2-carboxylate

Intermediate 102: Methyl 5-{4-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}-2-furoate

Intermediate 103: Methyl 3-{4-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}benzoate

Intermediate 104: Methyl 3-bromo-5-{4-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}benzoate

Intermediate 105: Ethyl 5-{4-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}nicotinate

Intermediate 106: Methyl 5-{4-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}nicotinate

Intermediate 107: Methyl 6-{4-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}pyridine-2-carboxylate

Intermediate 108: Methyl 3-{4-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}-5-morpholin-4-ylbenzoate

Intermediate 109: Methyl 3-{4-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}-5-(4-methylpiperazin-1-yl)benzoate

Intermediate	Aryl Halide Starting Material	^{1}H NMR δ	m/z
101	Methyl 5-bromothiophene-2-carboxylate (Intermediate 159)	1.38 (s, 9H); 1.43-1.53 (m, 2H); 1.78-1.81 (m, 2H); 3.00 (t, 2H); 3.45 (m, 1H); 3.55-3.60 (m, 2H); 3.70 (s, 3H); 6.17 (d, 1H); 6.90 (d, 1H); 7.49 (d, 1H).	341
102	Methyl 5-bromo-2-furoate	1.32-1.43 (m, 11H); 1.75-1.77 (m, 2H); 2.91 (t, 2H); 3.42 (m, 1H); 3.61-3.65 (m, 2H); 3.68 (s, 3H); 5.43 (d, 1H); 6.89 (d, 1H); 7.21 (d, 1H).	325
103	Methyl 3-bromobenzoate	1.38 (s, 9H); 1.42-1.51 (m, 2H); 1.78-1.82 (m, 2H); 2.77 (t, 2H); 3.40 (m, overlapping with water, 1H); 3.65-3.70 (m, 2H); 3.82 (s, 3H); 6.86 (d, 1H); 7.22 (m, 1H); 7.33 (d, 2H); 7.43 (br s, 1H).	335
104	Methyl 3,5-dibromobenzoate	1.38 (s, 9H); 1.43-1.48 (m, 2H); 1.76-1.79 (m, 2H); 2.84 (t, 2H); 3.43 (m, 1H); 3.70-3.74 (m, 2H); 3.83 (s, 3H); 6.85 (d, 1H); 7.35 (br s, 2H); 7.39 (s, 1H).	413, 415
105	Ethyl 5-bromonicotinate	1.33 (t, 3H); 1.39 (s, 9H); 1.43-1.52 (m, 2H); 1.79-1.83 (m, 2H); 2.86 (t, 2H); 3.39 (m, 1H); 3.75-3.79 (m, 2H); 4.33 (q, 2H); 6.88 (d, 1H); 7.65 (m, 1H); 8.45 (m, 1H); 8.53 (m, 1H).	350

Intermediate	Aryl Halide Starting Material	^{1}H NMR δ	m/z
106	Methyl 5-bromonicotinate	1.26-1.34 (m, 2H); 1.38 (s, 9H); 1.76-1.80 (m, 2H); 2.91 (t, 2H); 3.49 (m, 1H); 3.82 (s, 3H); 4.25-4.30 (m, 2H); 6.84 (d, 1H); 7.07 (d, 1H); 7.26 (d, 1H); 7.65 (t, 1H).	336
107	Methyl 6-bromopyridine-2-carboxylate (Intermediate 158)	1.26-1.34 (m, 2H); 1.39 (s, 9H); 1.76-1.80 (m, 2H); 2.91 (t, 2H); 3.50 (m, 1H); 3.82 (s, 3H); 4.26-4.30 (m, 2H); 6.85 (d, 1H); 7.08 (d, 1H); 7.26 (d, 1H); 7.65 (t, 1H).	336
108	Methyl 3-bromo-5-{4-[(tert-butoxy carbonyl)amino]piperidin-1-yl}benzoate (Intermediate 104)	1.32-1.52 (m, 11H); 1.77 (d, 2H); 2.72 (t, 2H); 3.02-3.15 (m, 4H); 3.31 (s, 3H); 3.34-3.47 (m, 1H); 3.64 (d, 2H); 3.58-3.74 (m, 4H); 3.79 (s, 3H); 6.70 (s, 1H); 6.84 (d, 1H); 6.89 (s, 1H); 6.93 (s, 1H).	420
109	Methyl 3-bromo-5-{4-[(tert-butoxy carbonyl)amino]piperidin-1-yl}benzoate (Intermediate 104)	1.32-1.53 (m, 11H); 1.77 (d, 2H); 2.21 (s, 3H); 2.37-2.47 (m, 4H); 2.72 (t, 2H); 3.07-3.20 (m, 4H); 3.35-3.41 (m, 1H); 3.64 (d, 2H); 3.79 (s, 3H); 6.69 (s, 1H); 6.85 (d, 1H); 6.91 (d, 2H).	433

Intermediates 110 to 118 were made by deprotection of Intermediates 101 to 109 by treatment with an excess of 4 N HCl in THF, a procedure analogous to that used in Intermediate 46. The resulting crude material was used without further purification.

Intermediate 110: Methyl 5-(4-aminopiperidin-1-yl)thiophene-2-carboxylate hydrochloride

MS (APCI) (MH^+): 241 for $C_{11}H_{16}N_2O_2S$; SM: Intermediate 101

Intermediate 111: Methyl 5-(4-aminopiperidin-1-yl)-2-furoate hydrochloride

MS (ES) (MH^+): 225 for $C_{11}H_{16}N_2O_3$; SM: Intermediate 102

Intermediate 112: Methyl 3-(4-aminopiperidin-1-yl)benzoate hydrochloride

MS (ES) (MH^+): 235 for $C_{13}H_{18}N_2O_2$; SM: Intermediate 103

Intermediate 113: Methyl 3-(4-aminopiperidin-1-yl)-5-bromobenzoate hydrochloride

MS (ESP) (M, MH^{+2}): 313, 315 for $C_{13}H_{17}BrN_2O_2$; SM: Intermediate 104

Intermediate 114: Ethyl 5-(4-aminopiperidin-1-yl)nicotinate hydrochloride

MS (ESP) (MH^+): 250 for $C_{13}H_{19}N_3O_2$; SM: Intermediate 105

Intermediate 115: Methyl 5-(4-aminopiperidin-1-yl)nicotinate hydrochloride

MS (ESP) (MH^+): 236 for $C_{12}H_{17}N_3O_2$; SM: Intermediate 106

Intermediate 116: Methyl 6-(4-aminopiperidin-1-yl)pyridine-2-carboxylate hydrochloride

MS (ESP) (MH^+): 236 for $C_{12}H_{17}N_3O_2$; SM: Intermediate 107

Intermediate 117: Methyl 3-(4-aminopiperidin-1-yl)-5-morpholin-4-ylbenzoate hydrochloride

MS (ESP): 320 (MH^+) for $C_{17}H_{25}N_3O_3$; SM: Intermediate 108

Intermediate 118: Methyl 3-(4-aminopiperidin-1-yl)-5-(4-methylpiperazin-1-yl)benzoate hydrochloride

MS (ESP): 333 (MH^+) for $C_{18}H_{28}N_4O_2$; SM: Intermediate 109

Intermediate 119: Ethyl 3-bromoisoxazole-5-carboxylate

Dibromoformaldoxime (407 mg, 2.07 mmol) (prepared via the procedure of JC Rohloff, et. al., Tetrahedron Lett 1992, 33:3113-6), and ethyl propiolate (311 mg, 3.17 mmol) were dissolved in 10 ml of 50% aqueous EtOH. While stirring, a solution of 243 mg (2.43 mmol) of potassium bicarbonate in 5 ml of water was added dropwise over 1 h. The resulting solution was stirred for an additional 4 h, diluted with 25 ml of water, and extracted with chloroform (3 x 25 ml). The combined organic extract was dried over sodium sulfate and concentrated in vacuo to a colourless oil, 345 mg (78% yield) as a 7:1 mixture of the 5- and 4-carboxylates.

^1H NMR ($CDCl_3$) δ: 1.34 (t, 3H, J = 7.16Hz), 4.30 & 4.37 (2q, 2H, J = 7.16 Hz), 6.92 & 8.81 (2s, 1H, ratio 7:1).

Intermediate 120: 3-Bromoisoxazole-5-carboxylic acid

A solution of 442 mg (2.0 mmol) of ethyl 3-bromoisoxazole-5-carboxylate (Intermediate 119) and 5.0 ml of 1 N sodium hydroxide in 10 ml of MeOH was stirred at ambient temperature for 5 h, then acidified with 6.0 ml of 1 N hydrochloric acid, diluted with 25 ml of water and extracted with EtOAc (3 x 25 ml). The combined organic extract was dried over magnesium sulfate and concentrated in vacuo to give the title compound as a white solid (310 mg).

MS, 0.30 (ES⁻) 189.99/191.99/193.17; $C_4H_2BrNO_3$ 191.97

^{1}H NMR δ: 7.46 (s, 1H)

Intermediate 121: Methyl 6-aminopyridine-2-carboxylate

6-Aminopyridine-2-carboxylic acid (5.0 g, 36 mmol) was dissolved in 50 ml of MeOH. To this was added acetyl chloride (9.0 ml, 126 mmol) in 50 ml of MeOH. The reaction was heated to reflux overnight. Concentrate to an orange oil and partition with EtOAc and water. The organic portions were washed with brine, dried ($MgSO_4$) and concentrated to a yellow solid.

^{1}H NMR δ: 3.79 (s, 3H); 6.32 (s, 2H); 6.64 (d, J=8.29 Hz, 1H); 7.18 (d, J=7.35 Hz, 1H); 7.51 (dd, J=8.29, 7.35 Hz, 1H).

Intermediate 122: Methyl 6-aminopyridine-2-carboxylate 1-oxide hydrochloride

Methyl 6-aminopyridine-2-carboxylate (**Intermediate 121**, 3.3 g, 22 mmol) was dissolved in acetone and to this was added a solution of mCPBA (5.9 g, 23.5 mmol) in acetone. After stirring overnight, the acetone was removed and the residue was suspended in 3 N HCl. The precipitate was filtered off to give the HCl salt (3.57 g, 87%).

MS (ES): 169 $(M+H)^+$.

^{1}H NMR δ: 3.91 (s, 3H); 7.20 (dd, J=7.25, 1.60 Hz, 1H); 7.39 (dd, J=8.85, 1.70 Hz, 1H); 7.82 (dd, J=8.95, 7.25 Hz, 1H).

Intermediate 123: Ethyl 4-(2-methoxyethoxy)-3-oxobutanoate

2,2-Dimethyl-1,3-dioxane-4,6-dione (1.72 g) was suspended in anhydrous pyridine (20 ml) and cooled to 0 °C. (2-methoxyethoxy)acetyl chloride (2 g) was added slowly. The mixture was stirred at room temperature for 3 h. The mixture was poured into 2 N HCl (30 ml) and extracted with DCM (x3). The combined organic phase was washed with water, brine, dried over sodium sulfate and concentrated in vacuo. The orange oil was dissolved in EtOH (20 ml) and was refluxed for 7 h. The solvent was removed in vacuo and the brown oil was Kugelrohr distilled affording the title compound as a colourless oil (1.55 g).

MS (ES) (M+H): 204 for $C_9H_{16}O_5$

^{1}H NMR ($CDCl_3$) δ: 1.58 (m, 2H); 1.92 (m, 2H); 2.18 (s, 3H); 2.80 (s, 3H); 3.18 (m, 2H); 3.76 (s, 3H); 4.12 (m, 1H); 4.29 (m, 2H); 7.08 (s, 1H); 7.22 (d, 1H); 7.34 (s, 1H); 11.96 (s, 1H); 12.17 (s, 1H)

Intermediate 124: Ethyl 2-chloro-4-(2-methoxyethoxy)-3-oxobutanoate

Ethyl 4-(2-methoxyethoxy)-3-oxobutanoate (Intermediate 123) (0.5 g) was dissolved in anhydrous DCM (5 ml). Sulfuryl chloride (430 mg) was added dropwise at room temperature. The mixture was stirred for 6 h. The crude mixture was diluted with EtOAc (50 ml) and washed well with water and brine, dried over sodium sulfate and concentrated in vacuo to afford the title compound as a light orange oil (414 mg).

MS (ES) (M+H): 238 for $C_9H_{15}ClO_5$

^{1}H NMR ($CDCl_3$) δ: 1.70 (m, 3H); 3.70 (s, 3H); 4.18 (m, 4H); 4.62 (m, 2H); 4.71 (s, 1H)

Intermediate 125: *tert*-Butyl [1-(aminocarbonothioyl)piperidin-4-yl]carbamate

tert-Butyl piperidin-4-ylcarbamate (5.5 g) was dissolved in anhydrous DCM (75 ml). H-Fluoren-9-ylmethyl isothiocyanatidocarbonate (Fmoc isothiocyanate; 7.75 g) was added in small portions at room temperature after which time a white precipitate formed. The mixture was stirred at room temperature for 90 min. The solvent was removed in vacuo and the crude mixture was treated with 10% piperidine in MeOH (100 ml) for 12 h. The mixture was concentrated in vacuo and triturated with n-hexanes. The white crystalline material was filtered and washed well with n-hexanes and dried in vacuo to afford the title compound (6.55 g).

MS (ES) (M+H): 260 for $C_{12}H_{21}N_3O_2S$

^{1}H NMR δ: 1.24 (m, 2H); 1.38 (s, 9H); 1.67 (m, 2H); 2.99 (m, 2H); 3.33 (m, 1H); 4.15 (m, 2H); 6.52 (d, 1H); 7.72 (s, 2H).

Intermediate 126: Ethyl 2-(4-aminopiperidin-1-yl)-4-[(2-methoxyethoxy)methyl]-1,3-thiazole-5-carboxylate hydrochloride

tert-Butyl [1-(aminocarbonothioyl)piperidin-4-yl]carbamate (Intermediate 125, 400 mg) was dissolved in anhydrous EtOH (5 ml). Ethyl 2-chloro-4-(2-methoxyethoxy)-3-oxobutanoate (Intermediate 124, 368 mg) was added and the mixture was heated at 90 °C for 18 h. Partial removal of Boc group was detected. Solvent was removed in vacuo and the dried material was treated with 4 N HCl/dioxane for 2 h. Solvent was removed in vacuo to give a brown/yellow solid which was dried to afford the title compound which was used without further purification(508 mg).

MS (ES) (M+H): 343 for $C_{15}H_{24}ClN_3O_4S$

Intermediate 127: Methyl 6-azidopyridine-2-carboxylate 1-oxide

Methyl 6-aminopyridine-2-carboxylate 1-oxide hydrochloride (Intermediate 122, 3.34 g, 16 mmol) was dissolved in 10% HCl (aqueous) and cooled to 5 °C. An aqueous solution of $NaNO_2$ (1.5 g, 21 mmol) was added dropwise maintaining temperature below 5 °C. After 15 minutes of stirring, an aqueous solution of NaN_3 (1.4 g, 21 mmol) was added dropwise maintaining temperature below 5 °C. The reaction was stirred at 5 °C for 30 minutes and slowly warmed to room temperature. The product was extracted with DCM and then the aqueous layer was basified (with 50% NaOH to pH 13) and then extracted again with DCM. Drying ($MgSO_4$) and removal of solvent yielded a yellow oil (2.6 g, 82%).

^{1}H NMR δ: 3.89 (s, 3H); 7.61 (dd, 1H); 7.78 (dd, J=8.85, 1.70 Hz, 1H); 8.02 (dd, J=8.95, 7.25 Hz, 1H).

Intermediate 128: Methyl 5-cyano-1-hydroxy-1H-pyrrole-2-carboxylate

A solution of methyl 6-azidopyridine-2-carboxylate 1-oxide (Intermediate 127, 2.6 g, 13 mmol) in isopropanol was bubbled with nitrogen for 20 minutes followed heating to reflux for 16 hours. The solution was concentrated to a red oil (2.55 g, 99%).

^{1}H NMR δ: 3.81 (s, 3H); 6.75 (d, J=4.90 Hz, 1H); 6.87 (d, J=4.90 Hz, 1H).

Intermediate 129: Methyl 5-cyano-1H-pyrrole-2-carboxylate

A 20% solution of $TiCl_3$ (25 ml, 32 mmol) in water was added to a solution of methyl 5-cyano-1-hydroxy-1H-pyrrole-2-carboxylate (Intermediate 128, 2.55 g, 15 mmol) in MeOH. The reaction was heated to an external temperature of 70 °C for 3 hours. The reaction mixture was concentrated to remove MeOH and the residue was partitioned with EtOAc and water. The organic portion was dried with $MgSO_4$ and concentrated to an orange oil.

^{1}H NMR δ: 3.79 - 3.87 (m, 3H); 6.88 (dd, J=3.86, 2.35 Hz, 1H); 7.02 (dd, J=3.77, 2.07 Hz, 1H); 13.42 (s, 1H).

Intermediate 130: Methyl 3,4-dichloro-5-cyano-1H-pyrrole-2-carboxylate

Methyl 5-cyano-1H-pyrrole-2-carboxylate (Intermediate 129, 0.95 g, 6.3 mmol) was dissolved in anhydrous DCM and cooled to 0 °C. TEA was added dropwise and stirred for several minutes followed by the dropwise addition of SO_2Cl_2. The reaction was stirred for 20 minutes at 0 °C before warming to room temperature. The reaction mixture was diluted with

water and extracted. The organic portion was dried with $MgSO_4$ and concentrated to a yellow solid (1.32 g, 96%).

^{1}H NMR δ: 3.80 - 3.91 (m, 3H); 14.25 (s, 1H).

Intermediate 131: 3,4-Dichloro-5-cyano-1H-pyrrole-2-carboxylic acid

The title compound was prepared by a procedure analogous to **Intermediate 3** starting from methyl 3,4-dichloro-5-cyano-1H-pyrrole-2-carboxylate (**Intermediate 130**).

^{1}H NMR δ: 14.02 (s, 1H).

Intermediate 132: 3,4-Dichloro-5-cyano-1H-pyrrole-2-carbonyl chloride

3,4-Dichloro-5-cyano-1H-pyrrole-2-carboxylic acid (**Intermediate 131**, 0.9 g, 0.2 mmol) was dissolved in excess thionyl chloride (5 ml) and heated to reflux for 30 minutes. The reaction mixture was concentrated and the residue was dissolved in THF and concentrated (x2). The solid (0.82 g, 89%) was pumped to dryness and stored under argon.

^{1}H NMR ($CDCl_3$) δ: 12.39 (s, 1H).

Intermediate 133: Methyl 2-{4-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-1,3-thiazole-5-carboxylate

tert-Butyl piperidin-4-ylcarbamate (4.5 g, 22 mmol), methyl 2-bromo-1,3-thiazole-5-carboxylate (5.0 g, 22 mmol), and diisopropylethylamine (3.8 ml, 22 mmol) were suspended in anhydrous DMF and heated to an external temperature of 130 °C for 1.5 hours. The DMF was removed and the solid was partitioned with EtOAc and water. The combined organic extracts were washed with brine, dried with $MgSO_4$ and concentrated to a yellow solid (7.05 g, 94%).

^{1}H NMR δ: 1.34 - 1.41 (m, 9H); 1.41 - 1.47 (m, 2H); 1.82 (dd, J=12.81, 2.83 Hz, 2H); 3.15 - 3.28 (m, 2H); 3.54 (s, 1H); 3.74 (s, 3H); 3.83 - 3.95 (m, 2H); 6.93 (d, J=7.72 Hz, 1H); 7.85 (s, 1H).

Intermediate 134: Methyl 2-(4-aminopiperidin-1-yl)-1,3-thiazole-5-carboxylate

Methyl 2-{4-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-1,3-thiazole-5-carboxylate (**Intermediate 133**, 6.92 g, 20 mmol) was dissolved in excess 4 M HCl in dioxane. After several minutes a white precipitate formed and after 1 hour the reaction was complete. The precipitate was filtered off, washed with ether and dried, yielding the di-HCl salt,

monohydrate 6.03 g, 96%). The solid was then dissolved in sat. $NaHCO_3$ put in the continuous extractor with DCM overnight. The organic portion was dried with $MgSO_4$ and concentrated to a white solid (3.84 g, 83%).

^{1}H NMR δ: 1.19 - 1.33 (m, 2H); 1.57 (s, 2H); 1.70 - 1.83 (m, 2H); 2.76 - 2.89 (m, 1H); 3.12 - 3.25 (m, 2H); 3.74 (s, 3H); 3.87 (dt, J=13.09, 3.72 Hz, 2H); 7.84 (s, 1H).

Intermediate 135: Methyl 4-{4-[(tert-butoxycarbonyl)amino]piperidin-1-yl}quinoline-2-carboxylate

The title compound was prepared by a procedure analogous to Intermediate 133 starting with methyl 4-chloroquinoline-2-carboxylate (WO 9505378). The product was purified on a silica gel flash column (0 → 5% MeOH in DCM) followed by recrystallization from EtOAc.

^{1}H NMR δ: 1.37 - 1.44 (m, 9H); 1.63 - 1.78 (m, 2H); 1.93 (s, 1H); 1.98 (d, J=7.54 Hz, 1H); 2.96 (t, J=11.11 Hz, 2H); 3.56 (d, J=12.25 Hz, 3H); 3.93 (s, 3H); 7.03 (d, J=7.54 Hz, 1H); 7.52 (s, 1H); 7.64 - 7.74 (m, 1H); 7.80 (td, J=7.63, 1.32 Hz, 1H); 7.99 (d, J=7.91 Hz, 1H); 8.07 (d, J=7.54 Hz, 1H).

Intermediate 136: Methyl 4-(4-aminopiperidin-1-yl)quinoline-2-carboxylate hydrochloride

The title compound was prepared by a procedure analogous to Intermediate 134 starting from methyl 4-{4-[(tert-butoxycarbonyl)amino]piperidin-1-yl}quinoline-2-carboxylate (Intermediate 135). The product was obtained as the monohydrochloride salt.

^{1}H NMR δ: 1.89 (d, J=10.17 Hz, 2H); 2.19 (s, 2H); 3.45 - 3.60 (m, 3H); 4.05 (s, 3H); 4.24 (d, J=13.00 Hz, 2H); 7.59 (s, 1H); 7.75 (t, J=7.63 Hz, 1H); 7.97 - 8.05 (m, 1H); 8.12 (d, J=8.48 Hz, 1H); 8.34 (d, J=8.48 Hz, 1H); 8.60 (s, 2H).

Intermediates 137-142

The following quinolines were prepared via the method of FR Alexandre, et.al., Tetrahedron 2003, 59: 1413

Intermediate 137: Ethyl 4-chloro-8-methoxyquinoline-2-carboxylate

Intermediate 138 : Methyl 4-chloro-8-fluoroquinoline-2-carboxylate

Intermediate 139: Methyl 4-chloro-8-methylquinoline-2-carboxylate

Intermediate 140: Methyl 4-chloro-6-fluoroquinoline-2-carboxylate

Intermediate 141: Methyl 4,8-dichloroquinoline-2-carboxylate

Intermediate 142:Ethyl 2-chloro-oxazole-4-carboxylate

Under a nitrogen atmosphere, 1.70 ml (14.3 mmol) of tert-butyl nitrite was added to a suspension of 1.65 g (12.3 mmol) of copper(II) chloride in 50 ml of acetonitrile. The resulting suspension was heated to 75 °C, then 1.60 g (10.2 mmol) of ethyl 2-aminooxazole-4-carboxylate (G Crank & MJ Foulis, J Med Chem 1971, 14:1075-1077) was added in portions over 20 min (gas evolution). After stirring for an additional 30 min, the reaction was allowed to cool to ambient temperature, diluted with 50 ml of EtOAc, and extracted with water (2 x 25 ml). The organic layer was dried over $MgSO_4$ and concentrated in vacuo to a dark oily solid. Flash chromatography through neutral silica gel using a 3:1 mixture of hexane and EtOAc gave 1.27 g (71%) of the title compound, which crystallized from hexane as white needles.

m/z (ES+): 176/177.

^{1}H NMR ($CDCl_3$) δ: 1.47 (t, 3H, J = 7.16); 4.48 (q, 2H, J = 7.16); 6.92 & 8.28 (s, 1H).

Intermediates 143 to 148

The following compounds in the below table were made by deprotection of Intermediates 149 to 154 by treatment with an excess of 4 N HCl in THF, a procedure analogous to that used in Intermediate 46. The resulting crude material was used without further purification.

Intermediate	Compound	MS (ESP)(MH^+)	SM
Intermediate 143	Methyl 3-allyl-5-(4-aminopiperidin-1-yl)benzoate hydrochloride	275 for $C_{16}H_{22}N_2O_2$	Intermediate 149
Intermediate 144	Methyl 3-(4-aminopiperidin-1-yl)-5-(2,3-dihydroxypropyl)- benzoate hydrochloride	309 for $C_{16}H_{24}N_2O_4$	Intermediate 150
Intermediate 145	Dimethyl 5-(4-aminopiperidin-1-yl)isophthalate hydrochloride	293 for $C_{15}H_{20}N_2O_4$	Intermediate 151
Intermediate 146	Dimethyl 2-(4-aminopiperidin-1-yl)terephthalate hydrochloride	293 for $C_{15}H_{20}N_2O_4$	Intermediate 152
Intermediate 147	Methyl 4-(4-aminopiperidin-1-yl)pyridine-2-carboxylate hydrochloride	236 for $C_{12}H_{17}N_3O_2$	Intermediate 153
Intermediate 148	Methyl 5-(4-aminopiperidin-1-yl)nicotinate 1-oxide hydrochloride	252 for $C_{12}H_{17}N_3O_3$	Intermediate 154

Intermediate 149: Methyl 3-allyl-5-{4-[(tert-butoxycarbonyl)amino]piperidin-1-yl}benzoate

Methyl 3-bromo-5-{4-[(tert-butoxycarbonyl)amino]piperidin-1-yl}benzoate (Intermediate 104, 300 mg, 0.73 mmol), tris(dibenzylidineacetone)dipalladium (0) (26 mg, 0.03 mmol), trifurylphosphine (14 mg, 0.06 mmol) were weighed into a flask and placed under argon. NMP (3 ml) was added, followed by the dropwise addition of allyltributyl tin (0.25 ml, 0.80 mmol). The mixture was stirred at 100 °C. After 64 h, the mixture was diluted with EtOAc and washed sequentially with water followed by brine. The organic phase was dried over $MgSO_4$ and concentrated to dryness. The crude material was purified by chromatography on silica gel using 25% EtOAc/hexanes to give 174 mg of the title product.

MS (ESP) (MH^+): 375 for $C_{21}H_{30}N_2O_4$

^1H NMR δ: 1.38 (s, 9H); 1.42-1.51 (m, 2H); 1.78-1.81 (m, 2H); 2.76 (t, 2H); 3.34-3.40 (m overlapping water, 3H); 3.64-3.68 (m, 2H); 3.81 (S, 3H); 5.04-5.13 (m, 2H); 5.94 (m, 1H); 6.86 (d, 1H); 7.05 (s, 1H); 7.17 (s, 1H); 7.28 (s, 1H).

Intermediate 150: Methyl 3-{4-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-5-(2,3-dihydroxypropyl)benzoate

The title compound was prepared from methyl 3-allyl-5-{4-[(tert-butoxycarbonyl)amino] piperidin-1-yl}benzoate (Intermediate 149) and AD-mix β using the method described in J. Org. Chem. 1992, 57, 2768.

MS (ESP) (MH^+): 409 for $C_{21}H_{32}N_2O_6$

^1H NMR ($CDCl_3$) δ: 1.47 (s, 9H); 1.51-1.55 (m overlapping water, 2H); 1.89 (t, 1H); 2.05-2.09 (m, 3H); 2.71-2.80 (m, 2H); 2.82-2.92 (m, 2H); 3.53 (m, 1H); 3.65-3.75 (m, 4H); 3.90 (s, 3H); 3.97 (m, 1H); 4.48 (m, 1H); 6.98 (s, 1H); 7.38 (s, 1H); 7.48 (s, 1H).

Intermediates 151 to 154

The following compounds were prepared by the following general method: The 4-(N-BOC amino)-piperidine (1.00 equivalent, 5.00 mmol), palladium (II) acetate (0.10 equiv), BINAP (rac-2,2'-bis(diphenylphosphinio)-1,1'-binaphthyl, 0.10 equiv), cæsium carbonate (1.40 equiv) and aryl halide (1.00 equiv) were combined. The solids were degassed and placed under argon. Toluene (10 ml) was added and the mixture was stirred at 100 °C for approximately 16 h. The mixture was filtered, and the filtrate was concentrated under vacuum. The crude product was purified by silica gel flash column chromatography.

Intermediate	Compound	^{1}H NMR δ	M+1	SM
Intermediate 151	Dimethyl 5-(4-tert-butoxy carbonylamino piperidin-1-yl)isophthalate	1.37 (s, 9H); 1.42-1.50 (m, 2H); 1.76-1.87 (m, 2H); 2.85 (t, 2H); 3.45 (br s, 1H overlapping with water peak); 3.66-3.79 (m, 2H); 3.85 (s, 6H); 6.84 (m, 1H); 7.66 (s, 2H); 7.85 (s, 1H).	393	Dimethyl 5-bromo isophthalate
Intermediate 152	Dimethyl 2-(4-tert-butoxy carbonylamino piperidin-1-yl)terephthalate	1.46 (s, 9H); 1.54-1.67 (m, 2H); 2.03-2.07 (m, 2H); 2.88 (t, 2H); 3.28-3.33 (m, 2H); 3.61 (m, 1H); 3.91 (s, 3H); 3.93 (s, 3H); 4.50 (m, 1H); 7.60-7.74 (m, 3H).	393	Dimethyl 2-bromo terephthalate
Intermediate 153	Methyl 4-(4-tert-butoxy carbonylamino piperidin-1-yl) pyridine-2-carboxylate	1.45 (s, 9H); 1.89 (br s, 1H); 2.00-2.04 (m, 3H); 3.07 (t, 2H); 3.72 (m, 1H); 3.76-3.92 (m, 2H); 3.97 (s, 3H); 4.51 (br s, 1H); 6.76 (m, 1H); 7.55 (d, 1H); 8.34 (d, 1H).	336	Intermediate 155
Intermediate 154	Methyl 5-(4-tert-butoxy carbonylamino piperidin-1-yl) nicotinate 1-oxide	1.46 (s, 9H); 1.51-1.56 (m, 2H); 2.05-2.10 (m, 2H); 2.99 (t, 2H); 3.65-3.69 (m, 2H); 3.95 (s, 3H); 4.48 (m, 1H); 7.42 (s, 1H); 8.00 (s, 1H); 8.35 (s, 1H).	352	Intermediate 156

Intermediate 155: Methyl 4-iodopyridine-2-carboxylate

This was prepared from the corresponding carboxylic acid as described under **Intermediates 101-109.**

MS (ESP) (MH^+): 264 for $C_7H_6INO_2$

Intermediate 156: Methyl 5-bromonicotinate-1-oxide

A solution of mCPBA (70%, 4.46 g, 18.11 mmol) in DCM (100 ml) was added to a solution of methyl 5-bromonicotinate (3.11 g, 15.09 mmol) in DCM (100 ml). After stirring at room

temperature for several hours, additional mCPBA (6.6 g, 26.77 mmol) was added (in portions) to drive the reaction to completion. After 4 days, the reaction mixture was sequentially washed with a saturated solution of sodium bicarbonate followed by water. The organic phase was dried over $MgSO_4$, and concentrated to dryness. The crude material was purified by chromatography on silica gel using 50 % EtOAc/hexanes to 100% EtOAc to give 1.16 g of the title product.

MS (ESP) (M^+, MH^{2+}): 232, 234 for $C_7H_6BrNO_3$

^{1}H NMR δ: 3.89 (s, 3H); 7.95 (s, 1H); 8.52 (s, 1H); 8.85 (s, 1H).

Intermediate 157: Methyl [2-({4-[(tert-butoxycarbonyl)amino]piperidin-1-yl}carbonyl) hydrazinol(oxo)acetate

A solution of tert-butyl piperidin-4-ylcarbamate (comm. available) (1.0 g, 5.0 mmol), TEA (2.0 g, 20 mmol) and DCM (30 ml) was added dropwise to phosgene (20 %) in toluene (comm. available)(10 ml, ~ 20 mmol) at 0 °C. The resultant mixture was allowed to slowly warm to room temperature while stirring overnight. The mixture was filtered to remove solid material and the filtrate was concentrated under reduced pressure to yield the carbamoyl chloride (1.2 g). The crude carbamoyl chloride (1.2 g, 5.0 mmol), TEA (0.70 ml, 5.0 mmol), methyl hydrazino(oxo)acetate (0.59 g, 5 mmol, reference: J. Med. Pharm. Chem. 1961, vol. 4,(2), p. 259) and THF (20 ml) were combined and heated at 60 °C for 24 h. The mixture was cooled to room temperature and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (DCM/acetone, 5:1 ratio with 1% MeOH) to yield 462 mg of the title compound.

MS (ESP): 345.1 (M+H) for $C_{14}H_{24}N_4O_6$

^{1}H NMR δ: 1.03 (m, 2H); 1.44 (s, 9H); 1.73 (d, 2H); 2.85 (t, 2H); 3.45 (m, 1H); 3.85 (s, 3H); 3.92 (d, 2H); 6.94 (d, 1H); 8.72 (s, 1H); 10.48 (s, 1H).

Intermediate 158: Methyl 6-bromopyridine-2-carboxylate

6-Bromopicolinic acid (411 mg, 2.03 mmol) was slurried in anhydrous MeOH (6 ml). Concentrated sulfuric acid (0.3 ml) was added and the resulting solution was stirred at room temperature for approximately 3 h. EtOAc was added, followed by a saturated solution of sodium bicarbonate. The phases were separated, and the organic phase was washed with water, dried over $MgSO_4$, and concentrated to dryness. The crude ester (313 mg) was used without further purification.

MS (ESP) (M, MH^{+2}) 216, 218 for $C_7H_6NO_2$

Intermediate 159: Methyl 5-bromothiophene-2-carboxylate

This was made from the corresponding carboxylic acid as described in **Intermediate 158**.

MS (APCI) (M, MH^{+2}) 221, 223 for $C_6H_5BrO_2S$

Intermediate 160: Methyl 5-{4-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-1,3,4-oxadiazole-2-carboxylate

TEA (0.20 ml, 1.34 mmol), para-toluenesulfonyl chloride (255 mg, 1.34 mmol), methyl [2-({4-[(tert-butoxycarbonyl)amino]piperidin-1-yl}carbonyl)hydrazino](oxo)acetate (**Intermediate 157**) (460 mg, 1.34 mmol) and DCM (8 ml) were combined and stirred overnight. The mixture was diluted with DCM (150 ml) and washed with water (10 ml). The organic phase was separated, dried over sodium sulfate, filtered and concentrated. The crude residue was purified by flash column chromatography (DCM/acetone, 8:1 ratio with 1% MeOH) to yield 342 mg of the title compound.

MS (ESP): 326.9 (M+H) for $C_{14}H_{22}N_4O_5$

^{1}H NMR δ: 1.46 (s, 9H); 1.50 (m, 2H); 1.89 (d, 2H); 3.29 (t, 2H); 3.57 (m, 1H); 3.92 (d, 2H); 3.95 (s, 3H); 7.02 (d, 1H).

Intermediates 161 and 162

The following compounds were prepared in a manner analogous to **Intermediate 98** starting from ethyl acetoacetate and the SMs listed. The resulting crude material was used without further purification.

Intermediate	Compound	M/Z	SM
Intermediate 161	2-Cyclopropyl-6-methylpyrimidin-4-ol	151	cyclopropane carboximidamide hydrochloride
Intermediate 162	2-*tert*-Butyl-6-methylpyrimidin-4-ol	167	2,2-dimethylpropanimidamide hydrochloride

Intermediates 163-165

The following compounds were prepared in a manner analogous to **Intermediate 97** starting from pyrimidinols listed. The resulting crude material was used without further purification.

Intermediate	Compound	M/Z	1H NMR	SM
Intermediate 163	4-Chloro-2-cyclopropyl-6-methylpyrimidine	168	0.83 (m, 2H); 0.93 (m, 2H); 2.03 (m, 1H); 2.29 (s, 3H); 7.21 (s, 1H)	2-Cyclopropyl-6-methylpyrimidin-4-ol (Intermediate 161)
Intermediate 164	4-Chloro-2-isopropyl-6-methylpyrimidine	170	1.27 (d, 6H); 2.49 (s, 3H); 3.17 (q, 1H); 7.50 (s, 1H)	2-Isopropyl-6-methylpyrimidin-4-ol (commercially available)
Intermediate 165	2-*tert*-Butyl-4-chloro-6-methyl pyrimidine	184	1.48 (s, 9H); 2.49 (s, 3H); 6.98 (s, 1H)	2-*tert*-Butyl-6-methylpyrimidin-4-ol (Intermediate 162)

Intermediates 166-168

The following compounds were prepared in a manner analogous to Intermediate 99 starting from *tert*-butyl piperidin-4-ylcarbamate and the SMs listed.

Intermediate	Compound	M/Z	1H NMR	SM
Intermediate 166	*tert*-Butyl [1-(2-cyclopropyl-6-methylpyrimidin-4-yl)piperidin-4-yl]carbamate	332		4-Chloro-2-cyclopropyl-6-methylpyrimidine (Intermediate 163)
Intermediate 167	*tert*-Butyl [1-(2-isopropyl-6-methylpyrimidin-4-yl)piperidin-4-yl]carbamate	334	1.23 (d, 6H); 1.4 (s, 9H); 2.26 (s, 3H); 3.20 (q, 1H); 3.09 (m, 2H); 3.43 (m, 2H); 3.67 (m, 3H); 4.46 (m, 2H); 6.56 (s, 1H); 7.1 (d, 1H)	4-Chloro-2-isopropyl-6-methylpyrimidine (Intermediate 164)

Intermediate	Compound	M/Z	1H NMR	SM
Intermediate 168	*tert*-Butyl [1-(2-*tert*-butyl-6-methylpyrimidin-4-yl)piperidin-4-yl]carbamate	349	1.33 (s, 9H); 1.44-1.51 (s, 9H); 1.89 (m, 2H); 2.35 (s, 3H); 3.09 (m, 2H); 3.43 (s, 2H); 3.67 (m, 1H); 4.46 (m, 2H); 6.64 (s, 1H); 6.9 (d, 1H)	2-*tert*-Butyl-4-chloro-6-methylpyrimidine (Intermediate 165)

Intermediates 169-171

The following compounds were prepared in a manner analogous to **Intermediate 100** starting from the SMs listed.

Intermediate	Compound	M/Z	SM
Intermediate 169	6-{4-[(*tert*-Butoxycarbonyl) amino]piperidin-1-yl}-2-cyclopropylpyrimidine-4-carboxylic acid	363	*tert*-butyl [1-(2-cyclopropyl-6-methylpyrimidin-4-yl)piperidin-4-yl]carbamate (Intermediate 166)
Intermediate 170	6-{4-[(*tert*-Butoxycarbonyl) amino]piperidin-1-yl}-2-isopropylpyrimidine-4-carboxylic acid	364	*tert*-butyl [1-(2-isopropyl-6-methylpyrimidin-4-yl)piperidin-4-yl]carbamate (Intermediate 167)
Intermediate 171	6-{4-[(*tert*-Butoxycarbonyl) amino]piperidin-1-yl}-2-*tert*-butylpyrimidine-4-carboxylic acid	378	*tert*-butyl [1-(2-*tert*-butyl-6-methylpyrimidin-4-yl)piperidin-4-yl]carbamate (Intermediate 168)

Intermediates 172-174

The following compounds were prepared in a manner analogous to **Intermediate 70** starting from the SMs listed.

Intermediate	Compound	M/Z	SM
Intermediate 172	6-(4-Aminopiperidin-1-yl)-2-cyclopropylpyrimidine-4-carboxylic acid hydrochloride salt	263	6-{4-[(*tert*-butoxycarbonyl) amino]piperidin-1-yl}-2-cyclopropylpyrimidine-4-carboxylic acid (Intermediate 169)
Intermediate 173	6-(4-Aminopiperidin-1-yl)-2-isopropylpyrimidine-4-carboxylic acid hydrochloride salt	264	6-{4-[(*tert*-butoxycarbonyl) amino]piperidin-1-yl}-2-isopropylpyrimidine-4-carboxylic acid (Intermediate 170)
Intermediate 174	6-(4-Aminopiperidin-1-yl)-2-*tert*-butylpyrimidine-4-carboxylic acid hydrochloride salt	278	6-{4-[(*tert*-butoxycarbonyl) amino]piperidin-1-yl}-2-*tert*-butylpyrimidine-4-carboxylic acid (Intermediate 171)

Intermediates 175 - 195

The following compounds were prepared in a manner analogous to Intermediate 16 starting from tert-butyl piperidin-4-ylcarbamate and the haloheteroaryl starting materials listed below (commercially available unless otherwise stated).

Intermediate	Compound	M/Z	SM
Intermediate 175	Ethyl 2-{4-[(*tert*-butoxycarbonyl) amino] piperidin-1-yl}-3-cyano-6-methylisonicotinate	409	ethyl 2-chloro-3-cyano-6-methylisonicotinate
Intermediate 176	*tert*-Butyl [1-(3-cyanopyridin-2-yl)piperidin-4-yl]carbamate	303	2-chloronicotinonitrile
Intermediate 177	*tert*-Butyl (1-quinolin-2-ylpiperidin-4-yl)carbamate	328	2-chloroquinoline
Intermediate 178	*tert*-Butyl [1-(6-methoxy-3-nitro pyridin-2-yl)piperidin-4-yl]carbamate	353	2-chloro-6-methoxy-3-nitropyridine

Intermediate	Compound	M/Z	SM
Intermediate 179	*tert*-Butyl [1-(4-acetyl-6-chloropyridin-2-yl)piperidin-4-yl]carbamate	353	1-(2,6-Dichloropyridin-4-yl)ethanone (Intermediate 48)
Intermediate 180	*tert*-Butyl {1-[6-(trifluoromethyl) pyridin-2-yl]piperidin-4-yl}carbamate	346	2-chloro-6-(trifluoromethyl) pyridine
Intermediate 181	*tert*-Butyl {1-[3-(aminocarbonyl)-6-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl}carbamate	391	2-chloro-6-(trifluoromethyl) nicotinamide
Intermediate 182	*tert*-Butyl {1-[3-cyano-6-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl}carbamate	371	2-chloro-6-(trifluoromethyl) nicotinonitrile
Intermediate 183	*tert*-Butyl [1-(3-chloropyridin-2-yl)piperidin-4-yl]carbamate	313	2,3-dichloropyridine
Intermediate 184	*tert*-Butyl [1-(4-cyanopyridin-2-yl)piperidin-4-yl]carbamate	303	2-chloroisonicotino nitrile
Intermediate 185	*tert*-Butyl {1-[5-(trifluoromethyl) pyridin-2-yl]piperidin-4-yl}carbamate	347	2-chloro-5-(trifluoromethyl) pyridine
Intermediate 186	*tert*-Butyl {1-[5-(aminocarbonyl) pyridin-2-yl]piperidin-4-yl}carbamate	321	6-chloronicotinamide
Intermediate 187	*tert*-Butyl [1-(6-bromopyridin-2-yl)piperidin-4-yl]carbamate	357	2,6-dibromopyridine
Intermediate 188	6-{4-[(*tert*-Butoxycarbonyl)amino] piperidin-1-yl}-2-chloronicotinic acid	357	2,6-dichloronicotinic acid
Intermediate 189	*tert*-Butyl (1-pyrimidin-2-ylpiperidin-4-yl)carbamate	278	2-chloropyrimidine
Intermediate 190	Methyl 2-{4-[(*tert*-butoxycarbonyl) amino]piperidin-1-yl}-6-methylpyrimidine-4-carboxylate	349	methyl 2-chloro-6-methylpyrimidine-4-carboxylate
Intermediate 191	*tert*-Butyl [1-(7*H*-purin-6-yl)piperidin-4-yl]carbamate	318	6-chloro-7H-purine

Intermediate	Compound	M/Z	SM
Intermediate 192	Methyl 6-{4-[(*tert*-butoxycarbonyl) amino]piperidin-1-yl}-2-chloropyrimidine-4-carboxylate	270	methyl 2,6-dichloropyrimidine-4-carboxylate
Intermediate 193	*tert*-Butyl [1-(6-chloro-4-{[(2-morpholin-4-ylethyl)amino] carbonyl}pyridin-2-yl)piperidin-4-yl]carbamate	468	2,6-Dichloro-N-(2-morpholin-4-yl-ethyl)-isonicotinamide (Intermediate 40)
Intermediate 194	*tert*-Butyl [1-(6-chloro-4-{[(3-morpholin-4-ylpropyl)amino] carbonyl}pyridin-2-yl)piperidin-4-yl]carbamate	481	2,6-Dichloro-N-(3-morpholin-4-yl-propyl)-isonicotinamide (Intermediate 196)
Intermediate 195	*tert*-Butyl [1-(6-chloro-4-{[2-(methylamino)-2-oxoethyl]thio}pyridin-2-yl)piperidin-4-yl]carbamate	415	2-(2,6-Dichloro-pyridin-4-ylsulfanyl)-N-methyl-acetamide (Intermediate 41)

Intermediate 196: 2,6-Dichloro-N-(3-morpholin-4-yl-propyl)-isonicotinamide

The title compound was prepared by the procedure of Intermediate 40 from 3-morpholin-4-yl-propan-1-amine and 2,6-dichloroisonicotinic acid (both commercially available).

MS (ES) (M+H): 318 for $C_{13}H_{17}Cl_2N_3O_2$

Intermediates 197-220

The following compounds were prepared in a manner analogous to Intermediate 70 from SMs listed below. The resulting crude material was used without further purification.

Intermediate	Compound	M/Z	SM
Intermediate 197	1-[2-(4-Aminopiperidin-1-yl)-6-chloropyridin-4-yl]ethanone hydrochloride salt	253	*tert*-butyl [1-(4-acetyl-6-chloropyridin-2-yl)piperidin-4-yl]carbamate (Intermediate 179)

Intermediate	Compound	M/Z	SM
Intermediate 198	2-(4-Aminopiperidin-1-yl)-6-cyanoisonicotinamide hydrochloride salt	246	tert-Butyl {1-[4-(aminocarbonyl)-6-cyanopyridin-2-yl]piperidin-4-yl}carbamate (Intermediate 42)
Intermediate 199	Ethyl 2-(4-aminopiperidin-1-yl)-3-cyano-6-methylisonicotinate hydrochloride salt	308	ethyl 2-{4-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}-3-cyano-6-methylisonicotinate (Intermediate 175)
Intermediate 200	2-(4-Aminopiperidin-1-yl)nicotinonitrile hydrochloride salt	202	*tert*-butyl [1-(3-cyanopyridin-2-yl)piperidin-4-yl]carbamate (Intermediate 176)
Intermediate 201	1-Quinolin-2-ylpiperidin-4-amine hydrochloride salt	228	*tert*-butyl (1-quinolin-2-ylpiperidin-4-yl)carbamate (Intermediate 177)
Intermediate 202	1-(6-Methoxy-3-nitropyridin-2-yl)piperidin-4-amine hydrochloride salt	253	*tert*-butyl [1-(6-methoxy-3-nitropyridin-2-yl)piperidin-4-yl]carbamate (Intermediate 178)
Intermediate 203	2-(4-Aminopiperidin-1-yl)-6-chloroisonicotinonitrile hydrochloride salt	237	tert-Butyl 1-(6-chloro-4-cyanopyridin-2-yl)piperidin-4-ylcarbamate (Intermediate 53)
Intermediate 204	1-[6-(Trifluoromethyl) pyridin-2-yl]piperidin-4-amine hydrochloride salt	246	*tert*-butyl {1-[6-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl}carbamate (Intermediate 180)
Intermediate 205	2-(4-Aminopiperidin-1-yl)-6-(trifluoromethyl) nicotinamide hydrochloride salt	291	*tert*-butyl {1-[3-(aminocarbonyl)-6-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl}carbamate (Intermediate 181)

Intermediate	Compound	M/Z	SM
Intermediate 206	2-(4-Aminopiperidin-1-yl)-6-(trifluoromethyl) nicotinonitrile hydrochloride salt	271	*tert*-butyl {1-[3-cyano-6-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl}carbamate (Intermediate 182)
Intermediate 207	1-(3-Chloropyridin-2-yl)piperidin-4-amine hydrochloride salt	213	*tert*-butyl [1-(3-chloropyridin-2-yl)piperidin-4-yl]carbamate (Intermediate 183)
Intermediate 208	2-(4-Aminopiperidin-1-yl)isonicotinonitrile hydrochloride salt	202	*tert*-butyl [1-(4-cyanopyridin-2-yl)piperidin-4-yl]carbamate (Intermediate 184)
Intermediate 209	1-[5-(Trifluoromethyl) pyridin-2-yl]piperidin-4-amine hydrochloride salt	247	*tert*-butyl {1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl}carbamate (Intermediate 185)
Intermediate 210	6-(4-Aminopiperidin-1-yl)nicotinamide hydrochloride salt	221	*tert*-butyl {1-[5-(aminocarbonyl)pyridin-2-yl]piperidin-4-yl}carbamate (Intermediate 186)
Intermediate 211	1-(6-Bromopyridin-2-yl)piperidin-4-amine hydrochloride salt	257	*tert*-butyl [1-(6-bromopyridin-2-yl)piperidin-4-yl]carbamate (Intermediate 187)
Intermediate 212	[1-(6-Chloropyridin-2-yl)piperidin-4-yl]amine hydrochloride salt	213	*tert*-butyl [1-(6-chloropyridin-2-yl)piperidin-4-yl]carbamate (Intermediate 66)
Intermediate 213	6-(4-Aminopiperidin-1-yl)-2-chloronicotinic acid hydrochloride salt	257	6-{4-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}-2-chloronicotinic acid (Intermediate 188)
Intermediate 214	1-Pyrimidin-2-ylpiperidin-4-amine hydrochloride salt	278	*tert*-butyl (1-pyrimidin-2-ylpiperidin-4-yl)carbamate (Intermediate 189)

Intermediate	Compound	M/Z	SM
Intermediate 215	Methyl 2-(4-aminopiperidin-1-yl)-6-methylpyrimidine-4-carboxylate hydrochloride salt	249	methyl 2-{4-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}-6-methylpyrimidine-4-carboxylate (Intermediate 190)
Intermediate 216	1-(7*H*-Purin-6-yl)piperidin-4-amine hydrochloride salt	218	*tert*-butyl [1-(7*H*-purin-6-yl)piperidin-4-yl]carbamate (Intermediate 191)
Intermediate 217	Methyl 6-(4-aminopiperidin-1-yl)-2-chloropyrimidine-4-carboxylate hydrochloride salt	270	methyl 6-{4-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}-2-chloropyrimidine-4-carboxylate (Intermediate 192)
Intermediate 218	2-(4-Aminopiperidin-1-yl)-6-chloro-*N*-(2-morpholin-4-ylethyl)isonicotinamide hydrochloride salt	368	*tert*-butyl [1-(6-chloro-4-{1-[(2-morpholin-4-ylethyl)amino] carbonyl}pyridin-2-yl)piperidin-4-yl]carbamate (Intermediate 193)
Intermediate 219	2-(4-Aminopiperidin-1-yl)-6-chloro-*N*-(3-morpholin-4-ylpropyl)isonicotinamide hydrochloride salt	381	*tert*-butyl [1-(6-chloro-4-{[(3-morpholin-4-ylpropyl)amino]carbonyl}pyridin-2-yl)piperidin-4-yl]carbamate (Intermediate 194)
Intermediate 220	2-{[2-(4-Aminopiperidin-1-yl)-6-chloropyridin-4-yl]thio}-*N*-methylacetamide hydrochloride salt	315	*tert*-butyl [1-(6-chloro-4-{[2-(methylamino)-2-oxoethyl]thio}pyridin-2-yl)piperidin-4-yl]carbamate (Intermediate 195)

Intermediate 221: Ethyl 2,4-dibromo-1,3-thiazole-5-carboxylate

A solution of 14 ml of 1.6 N *n*-butylithium in hexane was added slowly to a solution of diisopropylamine (3.1 ml, 22 mmol) in 80 ml THF cooled in a dry ice/acetone bath under an

inert atmosphere. The solution was warmed to 0 °C and re-cooled to –70 °C. A solution of 2,5-dibromothiazole in 20 ml THF was added and the mixture was stirred for 30 min before adding ethyl chloroformate (2.1 ml, 22 mmol). After warming to room temperature, the mixture was quenched with aqueous $NaHCO_3$ and diluted with EtOAc. The EtOAc was separated and washed with water and brine. Drying ($MgSO_4$) and removal of solvent gave an oil that was purified by chromatography (1:1 hexanes-DCM followed by gradient elution to 100% DCM) to give 4.5 g of product as an oil that slowly solidified.

MS (ES): 316 (M+H)

^{1}H NMR ($CDCl_3$) δ: 1.4 (t, 3H); 4.4 (q, 2H).

Intermediate 222: Ethyl 4-bromo-2-{4-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}-1,3-thiazole-5-carboxylate

A solution of ethyl 2,4-dibromo-1,3-thiazole-5-carboxylate (Intermediate 221) (4.5 g, 14.3 mmol), carbamic acid, 4-piperidinyl-, 1,1-dimethylethyl ester (2.86 g, 14.3 mmol), and diisopropylethylamine (2.6 ml, 14.5 mmol) in 45 ml dioxane was heated at 100 °C for 4 hours. The mixture was partitioned between EtOAc and water. The EtOAc was separated and washed with brine. Drying ($MgSO_4$) and removal of solvent gave an oil that was chromatographed on silica gel (1:1 hexanes-DCM followed by gradient elution to 100% DCM and then to 8% MeOH in DCM) to give 2.1 gm of product.

MS (ES): 378, 380 (M+H)

^{1}H NMR δ: 1.24 (t, J=7.06Hz, 3H); 1.33 - 1.47 (m, 11H); 1.80 (s, 2H); 3.13 - 3.31 (m, 2H); 3.54 (s, 1H); 3.83 (s, 2H); 4.19 (q, J=7.10Hz, 2H); 6.95 (d, J=7.91Hz, 1H)

Intermediate 223: Ethyl 2-{4-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}-4-cyano-1,3-thiazole-5-carboxylate

A solution of ethyl 4-bromo-2-{4-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}-1,3-thiazole-5-carboxylate (Intermediate 222) (1.3 g, 2.9 mmol), $Zn(CN)_2$ (250 mg, 2.2 mmol), tris(dibenzylidineaceetone)dipalladium(0) (125 mg, 0.13 mmol) and 1,1'-bis(diphenylphosphino) ferrocene (151 mg, 13 mmol) in 20 ml DMF under argon was heated at 130 °C for 1 hour in a microwave reactor. Solvent was removed and the residue was taken up in EtOAc and washed with water and brine. Drying ($MgSO_4$) and removal of solvent gave an oil that was chromatographed on silica gel (DCM followed by gradient elution to 5% MeOH in DCM) to give 1.9 g of product as a yellow solid.

^{1}H NMR δ: 1.28 (t, *J*=7.06Hz, 3H); 1.31 - 1.52 (m, 11H); 1.72 - 1.95 (m, 2H); 3.19 - 3.33 (m, 2H); 3.54 (s, 1H); 3.89 (d, *J*=13.19Hz, 2H); 4.29 (q, *J*=7.16Hz, 2H); 6.95 (s, 1H).

Intermediate 224 3,4-Dichloro-5-methyl-1*H*-pyrrole-2-carbonyl chloride

A solution of 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid (**Intermediate 3**) in 50 ml $SOCl_2$ was heated at reflux for 30 min. Solvent was removed and the residue was dried in vacuo.

^{1}H NMR ($CDCl_3$) δ: 9.0 (s, 1H); 2.4 (s, 3H).

Examples

Example 1: *tert*-Butyl 2-[(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)methyl]-1-methyl-1*H*-imidazol-4-ylcarbamate

A mixture of 3,4-dichloro-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (**Intermediate 1**, 243 mg, 0.777 mmol) and *tert*-butyl 2-formyl-1-methyl-1*H*-imidazol-4-ylcarbamate (WO03/002567) (175 mg, 0.777 mmol) in THF (15 ml) was stirred at room temperature for 10 minutes. Sodium triacetoxyborohydride (494 mg, 2.33 mmol) was then added in two portions, and the reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with EtOAc and 10% aqueous Na_2CO_3. The aqueous layer was extracted with EtOAc, the combined organic portions were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 398 mg of a pale yellow solid, 100 mg of which was dissolved in DMSO and purified by preparatory HPLC using a gradient of 20-95% CH_3CN/H_2O (0.1% TFA) to give the TFA salt of the title compound.

MS (ES$^-$): 483.30, 485.37 for $C_{21}H_{30}Cl_2N_6O_3$

^{1}H NMR δ: 1.55 (s, 9H); 1.95 (m, 2H); 2.09 (s, 3H); 2.32 (s, 3H); 3.18 (m, 2H); 3.43 (m, 2H); 3.67 (s, 3H); 3.93 (m, 1H); 4.38 (s, 2H); 7.36 (d, 1H); 7.99 (s, 1H); 11.89 (brs, 1H).

Example 2: 3,4-Dichloro-5-methyl-*N*-{1-[2-(methylsulfonyl)pyrimidin-4-yl]piperidin-4-yl}-1*H*-pyrrole-2-carboxamide

A suspension of 3,4-dichloro-5-methyl-*N*-{1-[2-(methylthio)pyrimidin-4-yl]piperidin-4-yl}-1*H*-pyrrole-2-carboxamide (**Example 306**, 200 mg, 0.5 mmol) in anhydrous DCM (8 ml) was treated with 70% mCPBA (250 mg, 1 mmol). The resulting solution was stirred under

nitrogen for 1 h then diluted with DCM and washed with 10% aqueous $NaHCO_3$ solution. The aqueous portion was extracted once with DCM, and the combined organic portions were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 215 mg of an off-white solid. The crude material was purified by preparatory HPLC using a gradient of 20-60% acetonitrile/water (0.1% TFA) to give the TFA salt of the title compound (103.1 mg).

MS (ES$^+$): 430.11, 432.11 for $C_{16}H_{19}Cl_2N_5O_3S$

^{1}H NMR δ: 1.29 (m, 2H); 1.66 (m, 2H); 1.92 (s, 3H); 2.94 (m, 2H); 3.04 (s, 3H); 3.21 (m, 2H); 3.84 (m, 1H); 6.87 (d, 1H); 7.02 (d, 1H); 8.07 (d, 1H); 11.73 (s, 1H).

Example 3: 3,4-Dichloro-5-methyl-*N*-{1-[2-(methylsulfinyl)pyrimidin-4-yl]piperidin-4-yl}-1*H*-pyrrole-2-carboxamide

A suspension of 3,4-dichloro-5-methyl-*N*-{1-[2-(methylthio)pyrimidin-4-yl]piperidin-4-yl}-1*H*-pyrrole-2-carboxamide (Example 306, 114.6 mg, 0.2863 mmol) in anhydrous DCM (5 ml) at 0 °C was treated with 70% mCPBA (77.6 mg, 0.314 mmol). The reaction was stirred at 0 °C for 30 minutes and was then quenched with 10% aqueous Na_2SO_3 solution. The phases were separated, and the aqueous portion was extracted with DCM. The combined organic portions were washed with dilute aqueous Na_2CO_3 solution and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a pale yellow oil that was purified by preparatory HPLC using a gradient of 20-60% CH_3CN/H_2O (0.1% TFA) to give the TFA salt of the title compound (67.0 mg).

MS (ES$^+$): 414.15, 416.15 for $C_{16}H_{19}Cl_2N_5O_2S$

^{1}H NMR δ: 1.43 (m, 2H); 1.81 (m, 2H); 2.07 (s, 3H); 2.69 (s, 3H); 3.06 (m, 2H); 4.02 (m, 2H); 4.22 (m, 1H); 6.85 (d, 1H); 7.16 (d, 1H); 7.81 (d, 1H); 11.87 (s, 1H).

Example 4: *N*-[1-(6-Amino-2-chloropyrimidin-4-yl)piperidin-4-yl]-3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxamide

3,4-Dichloro-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (Intermediate 1, 500 mg, 1.6 mmol), 4-amino-2,6-dichloropyrimidine (262 mg, 1.6 mmol), and Et_3N (0.45 ml, 3.2 mmol) were combined in DMF (15 ml) and heated at 100 °C under nitrogen for 1 h. Upon cooling to room temperature, the reaction was diluted with EtOAc and water. The aqueous phase was extracted twice with EtOAc, and the combined organic portions were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced

pressure to give a brown oil. Approximately 1 ml DMF was added to the oil, followed by the slow addition of water. Trituration resulted in a light brown solid (212 mg) that was collected by filtration. 66 mg of this crude material was purified by preparatory HPLC using a gradient of 20-60% CH_3CN/H_2O (0.1% TFA) to give the TFA salt of the title compound (21 mg).

MS (ES$^-$): 401.12, 403.13, 405.13 for $C_{15}H_{17}Cl_3N_6O$

^{1}H NMR δ: 1.38 (m, 2H); 1.76 (m, 2H); 2.10 (s, 3H); 2.97 (m, 2H); 3.94 (m, 1H); 4.35 (m, 2H); 5.66 (s, 2H); 6.68 (m, 1H); 7.12 (d, 1H); 11.89 (s, 1H).

Example 5: *N*-{1-[6-(Acetylamino)-2-chloropyrimidin-4-yl]piperidin-4-yl}-3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxamide

3,4-Dichloro-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (**Intermediate 1**, 280 mg, 0.896 mmol), *N*-(2,6-dichloropyrimidin-4-yl)acetamide (**Intermediate 7**, 184.5 mg, 0.896 mmol), and TEA (0.25 ml, 1.79 mmol) were combined in DMF (6 ml) and heated at 100 °C under nitrogen for 1 h. Upon cooling to room temperature, the reaction was diluted with EtOAc and water. The phases were separated, and the aqueous portion was extracted twice with EtOAc. The combined organic portions were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a brown liquid (some DMF still present), which was triturated with water. The resulting light brown solid (76 mg) was purified by preparatory HPLC using a gradient of 20-60% CH_3CN/H_2O (0.1% TFA) to give the TFA salt of the title compound (20 mg).

MS (ES$^-$): 445.14, 447.14, 448.14 for $C_{17}H_{19}Cl_3N_6O_2$

^{1}H NMR δ: 1.45 (m, 2H); 1.82 (m, 2H); 2.01 (s, 3H); 2.11 (s, 3H); 3.09 (m, 2H); 4.04 (m, 2H); 4.22 (m, 1H); 7.15 (d, 1H); 7.30 (s, 1H); 10.67 (s, 1H); 11.90 (s, 1H)

Example 6: Methyl 2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylate

A solution of methyl 2,4-dichloropyrimidine-6-carboxylate (commercially available) (0.95 g, 4.6 mmol) in DMF (5 ml) was added dropwise to a solution of 3,4-dichloro-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (**Intermediate 1**, 0.43 g, 4.6 mmol) and TEA (0.92 g, 9.2 mmol) in DMF (10 ml) under nitrogen. The resultant mixture was stirred for 1 h at room temperature. Water (50 ml) was added to the stirred reaction mixture and the material that precipitated was collected and washed with water/acetonitrile (1:1, 15

ml) to give 1.9 g of the title compound. An analytical sample was purified by reversed-phase HPLC (water/acetonitrile gradient, 20-95%).

MS (ESP): 446.3 (M+H) for $C_{17}H_{18}Cl_3N_5O_3$

^{1}H NMR δ: 1.73-1.83 (m, 2H); 2.14 (d, 2H); 2.39 (s, 3H); 3.40-3.52 (m, 2H); 4.09 (s, 3H); 4.30-4.45 (m, 2H); 4.60-4.80 (m, 1H); 7.46 (d, 1H); 7.60 (s, 1H); 12.2 (s, 1H).

Example 7: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-(methylthio)pyrimidine-4-carboxylic acid

Sodium thiomethoxide (0.275 g, 3.94 mmol) was added to a solution of methyl 2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylate (Example 6, 0.44 g, 0.99 mmol) in DMF (3 ml) under nitrogen. The resultant mixture was stirred at room temperature for 18 h. The reaction was quenched by addition of water (5 ml) and 1 N HCl (5 ml), then diluted with EtOAc (100 ml) and the organic phase was separated. The aqueous phase was extracted with EtOAc (30 ml) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude residue was purified by preparative reversed-phase HPLC (water/acetonitrile gradient, 10-95%) to yield 275 mg of the title compound.

MS (ESP): 444.3 (M+H) for $C_{17}H_{19}Cl_2N_5O_3S$

^{1}H NMR δ: 1.40-1.60 (m, 2H); 1.80 (d, 2H); 2.06 (s, 3H); 2.39 (s, 3H); 3.09 (t, 2H); 4.0-4.15 (m, 1H); 4.10-4.50 (m, 2H); 5.50-6.50 (br s, 1H); 6.90 (s, 1H); 7.11 (d, 1H); 11.85 (s, 1H).

Example 8: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-*N*-methoxy-2-(methylthio)pyrimidine-4-carboxamide

HATU (197 mg, 0.52 mmol) was added to a solution of TEA (0.14 ml, 1.0 mmol), 6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-(methylthio)pyrimidine-4-carboxylic acid (Example 7, 230 mg, 0.52 mmol) and methoxylamine hydrochloride (43 mg, 0.52 mmol) in DMF (3 ml) under nitrogen. The resultant mixture was stirred overnight at room temperature, then diluted with EtOAc (50 ml) and water (10 ml) and the organic phase was separated. The organic phase was washed with 1 N HCl (5 ml), saturated $NaHCO_3$ solution (5 ml) and brine (5 ml). The aqueous layers were back extracted with EtOAc (25 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum to give 400 mg of crude product. which was purified

by preparative reversed-phase HPLC (water/acetonitrile gradient, 20-95%) to give 200 mg of the title compound.

MS (ESP): 473.3 (M+H) for $C_{18}H_{22}Cl_2N_6O_3S$

^{1}H NMR δ: 1.42-1.52 (m, 2H); 1.80-1.88 (m, 2H); 2.10 (s, 3H); 2.44 (s, 3H); 3.16 (t, 2H); 3.61 (s, 3H); 4.00-4.14 (m, 1H); 4.20-4.50 (m, 2H); 6.94 (s, 1H); 7.16 (d, 1H); 11.70 (s, 1H); 11.90 (s, 1H).

Example 9: Methyl 6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-morpholin-4-ylpyrimidine-4-carboxylate

A solution of methyl 2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylate (Example 6, 300 mg, 0.67 mmol), morpholine (58 mg, 0.67 mmol) and TEA (0.09 ml, 0.67 mmol) in DMF (3 ml) were stirred at 60 °C under nitrogen for 4 hours. The mixture was cooled to room temperature and diluted with EtOAc (75 ml) and water (10 ml). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield 320 mg of the title compound. An analytical sample was purified by reversed-phase HPLC (water/acetonitrile gradient, 20-95%).

MS (ESP): 497.4 (M+H) for $C_{21}H_{26}Cl_2N_6O_4$

^{1}H NMR δ: 1.40-1.58 (m, 2H); 1.81 (d, 2H); 2.10 (s, 3H); 3.06 (t, 2H); 3.58 (br s, 8H); 3.75 (s, 3H); 3.95-4.10 (m, 1H); 4.15-4.40 (m, 2H); 6.65 (s, 1H); 7.16 (d, 1H); 11.90 (s, 1H).

Example 10: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-*N*-methoxy-2-(methylsulfonyl)pyrimidine-4-carboxamide

mCPBA (70%, 104 mg, 0.42 mmol) was added to a suspension of 6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-*N*-methoxy-2-(methylthio)pyrimidine-4-carboxamide (Example 8, 100 mg, 0.21 mmol) in DCM (15 ml) and the resultant mixture was stirred for 3 h. The reaction mixture was diluted with DCM (50 ml), washed with saturated Na_2CO_3 solution (10 ml), dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by reversed-phase HPLC (water/acetonitrile gradient, 15-95%).

MS (ESP): 505.3 (M+H) for $C_{18}H_{22}Cl_2N_6O_5S$

^{1}H NMR δ: 1.45-1.62 (m, 2H); 1.88 (d, 2H); 2.11 (s, 3H); 3.15-3.35 (m, 2H); 3.33 (s, 3H); 3.66 (s, 3H); 4.02-4.18 (m, 2H); 4.45-4.70 (m, 1H); 7.18 (d, 1H); 7.40 (s, 1H); 11.91 (s, 1H); 11.98 (s, 1H).

Example 11: 2-Chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-*N*-methoxypyrimidine-4-carboxamide

The title compound was synthesised by an analogous method to Example 8 starting from 2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylic acid (Example 32) and methoxylamine hydrochloride.

MS (ESP): 461.2 (M+H) for $C_{17}H_{19}Cl_3N_6O_3$

^{1}H NMR δ: 1.45-1.59 (m, 2H); 1.89 (d, 2H); 2.15 (s, 3H); 3.12-3.30 (m, 2H); 3.65 (s, 3H); 4.04-4.17 (m, 2H); 4.35-4.62 (m, 1H); 7.20 (d, 1H); 7.26 (s, 1H); 11.95 (s, 2H).

Example 12: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-*N*-methoxy-2-morpholin-4-ylpyrimidine-4-carboxamide

The title compound was synthesised by an analogous method to Example 8 starting from 6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-morpholin-4-ylpyrimidine-4-carboxylic acid (Example 310) and methoxylamine hydrochloride.

MS (ESP): 512.4 (M+H) for $C_{21}H_{27}Cl_2N_7O_4$

^{1}H NMR δ: 1.40-1.65 (m, 2H); 1.81 (d, 2H); 2.10 (s, 3H); 3.03 (t, 2H); 3.50-3.70 (m, 8H); 3.62 (s, 3H); 3.90-4.10 (m, 1H); 4.15-4.32 (m, 2H); 6.57 (s, 1H); 7.15 (d, 1H); 11.61 (s, 1H); 11.90 (s, 1H).

Example 13: 2-Chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-*N*-(2-morpholin-4-ylethyl)pyrimidine-4-carboxamide

A solution of methyl 2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylate (Example 6: 380 mg, 0.85 mmol), 2-morpholin-4-ylethanamine (222 mg, 1.70 mmol) and TEA (0.12 ml, 0.85 mmol) in DMF (3 ml) were stirred at 60 °C under nitrogen for 18 hours. The mixture was cooled to room temperature and diluted with EtOAc (75 ml) and water (10 ml). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by reversed-phase HPLC (water/acetonitrile gradient, 5-95%) provided 110 mg of the title compound.

MS (ESP): 544.5 (M+H) for $C_{22}H_{28}Cl_3N_7O_3$

^{1}H NMR δ: 1.40-1.55 (m, 2H); 1.88 (d, 2H); 2.11 (s, 3H); 2.95-3.30 (m, 6H); 3.40-3.65 (m, 6H); 3.70-4.50 (m, 5H); 7.18 (d, 1H); 7.26 (s, 1H); 8.86 (t, 1H); 11.94 (s, 1H).

Example 14: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-(methylsulfonyl)pyrimidine-4-carboxylic acid

mCPBA (70%, 164 mg, 0.67 mmol) was added to a suspension of 6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-(methylthio)pyrimidine-4-carboxylic acid (Example 7, 151 mg, 0.34 mmol) in DCM (15 ml) at 0 °C and the resultant mixture was stirred for 3 h. The mixture was allowed to slowly warm to room temperature over the 3 h period. The reaction mixture was diluted with DCM (50 ml), dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by reversed phase HPLC (water/acetonitrile gradient, 5-95%) to yield 32 mg of the title compound.

MS (ESP): 476.1 (M+H) for $C_{17}H_{19}Cl_2N_5O_5S$

^{1}H NMR δ: 1.45-1.59 (m, 2H); 1.89 (d, 2H); 2.11 (s, 3H); 3.10-3.30 (m, 2H); 3.27 (s, 3H); 4.00-4.15 (m, 2H); 4.48-4.70 (m, 1H); 7.18 (d, 1H); 7.46 (s, 1H); 11.92 (s, 1H); 13.80 (s, 1H).

Example 15: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-*N*-methoxy-2-(methylsulfinyl)pyrimidine-4-carboxamide

mCPBA (70%, 86 mg, 0.35 mmol) was added to a suspension of 6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-*N*-methoxy-2-(methylthio)pyrimidine-4-carboxamide (Example 8, 166 mg, 0.35 mmol) in DCM (12 ml) at 0 °C and the resultant mixture was stirred for 2 h. The reaction mixture was diluted with DCM (50 ml), washed with Na_2SO_3 solution (5%, 10 ml), dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by reversed-phase HPLC (water/acetonitrile gradient, 10-95%) gave 45 mg of the title product.

MS (ESP): 489.1 (M+H) for $C_{18}H_{22}Cl_2N_6O_4S$

^{1}H NMR δ: 1.40-1.60 (m, 2H); 1.88 (d, 2H); 2.11 (s, 3H); 2.84 (s, 3H); 3.21 (t, 2H); 3.64 (s, 3H); 4.00-4.15 (m, 2H); 4.40-4.80 (m, 1H); 7.18 (d, 1H); 7.25 (s, 1H); 11.91 (s, 2H).

Example 16: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-[(2-hydroxyethyl)thio]pyrimidine-4-carboxylic acid

A suspension of methyl 2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylate (Example 6, 150 mg, 0.34 mmol), 2-mercaptoethanol (31 mg, 0.40 mmol) and potassium carbonate (139 mg, 1.01 mmol) in DMF (3 ml) were stirred at 65 °C under nitrogen for 3 hours. The mixture was cooled to room temperature and diluted with EtOAc (75 ml) and 1 N HCl (3 ml). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated under vacuum. Purification of the residue by reversed-phase HPLC (water/acetonitrile gradient, 10-95%) gave 39 mg of the title compound.

MS (ESP): 474.2 (M+H) for $C_{18}H_{21}Cl_2N_5O_4S$

^{1}H NMR δ: 1.40-1.55 (m, 2H); 1.83 (d, 2H); 2.11 (s, 3H); 3.07-3.20 (m, 4H); 3.52- 3.62 (m, 2H); 4.00-4.40 (m, 5H); 7.00 (s, 1H); 7.16 (d, 1H); 11.90 (s, 1H).

Example 17: Methyl 6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-[(2-hydroxyethyl)thio]pyrimidine-4-carboxylate

The title compound was also isolated from Example 16.

MS (ESP): 488.2 (M+H) for $C_{19}H_{23}Cl_2N_5O_4S$

^{1}H NMR δ: 1.40-1.55 (m, 2H); 1.84 (d, 2H); 2.11 (s, 3H); 3.05-3.22 (m, 4H); 3.56 (t, 2H); 4.00-4.40 (m, 4H); 7.00 (s, 1H); 7.16 (d, 1H); 11.91 (s, 1H).

Example 18: 2-Chloro-6-(4-{[(4-chloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)isonicotinamide

Diisopropylethylamine (0.34 ml, 2.0 mmol), EDC (0.121 g, 0.63 mmol) and HOAT (0.086 g, 0.63 mmol) were added to a stirred solution of 4-chloro-5-methyl-1*H*-pyrrole-2-carboxylic acid (Intermediate 8, 0.1 g, 0.63 mmol) in DMF (2 ml) at room temperature. The resultant solution was stirred for 15 mins then a solution of 2-(4-aminopiperidin-1-yl)-6-chloroisonicotinamide hydrochloride (Intermediate 70, 0.19 g, 0.75 mmol) in 3 ml of DMF was added. The reaction was concentrated after 2 hours and the residue was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc (x2), the combined organic layers were washed with 1 N HCl, water and brine, then dried over magnesium sulfate and concentrated under vacuum. The residue was purified by reverse phase chromatography (water/acetonitrile gradient, 20-95%) to give the title product as a white solid.

MS (ES): 396 (M+1) for $C_{17}H_{19}Cl_2N_5O_2$

^{1}H NMR δ: 1.46 (m, 2H); 1.82 (m, 2H); 2.13 (s, 3H); 3.04 (t, 2H); 4.03 (m, 1H); 4.25 (m, 2H); 6.74 (s, 1H); 6.97 (s, 1H); 7.19 (s, 1H); 7.69 (m, 2H); 8.15 (s, 1H); 11.59 (brs, 1H)

Example 19: 2-(4-{[(4-Bromo-5-ethyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-chloroisonicotinamide

Diisopropylethylamine (0.28 ml, 1.64 mmol), EDC (0.088 g, 0.46 mmol) and HOAT (0.063 g, 0.46 mmol) were added to a stirred solution of 4-bromo-5-ethyl-1*H*-pyrrole-2-carboxylic acid (**Intermediate 10**, 0.1 g, 0.46 mmol) in DMF (1.5 ml) at room temperature. The resultant solution was stirred for 30 mins and a solution of 2-(4-aminopiperidin-1-yl)-6-chloroisonicotinamide hydrochloride (**Intermediate 70**, 0.14 g, 0.55 mmol) in 3 ml of DMF was added. The reaction was stirred overnight, then concentrated under vacuum and the residue was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc (x2) and the combined organic extracts were washed with 1 N HCl, water and brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by reverse phase chromatography to give the desired product as a white solid.

MS (ES): 456 (M+1) for $C_{18}H_{21}BrClN_5O_2$

^{1}H NMR δ: 1.09 (t, 3H); 1.47 (m, 2H); 1.82 (m, 2H); 3.04 (t, 2H); 3.30 (q, 2H); 4.03 (m, 1H); 4.25 (m, 2H); 6.79 (s, 1H); 6.97 (s, 1H); 7.19 (s, 1H); 7.69 (s, 1H); 7.76 (d, 1H); 8.15 (s, 1H); 11.64 (brs, 1H)

Example 20: 2-Chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)isonicotinamide

Diisopropylethylamine (0.063 ml, 0.37 mmol), EDC (0.095 g, 0.31 mmol) and HOAT (0.042 g, 0.31 mmol) were added to a stirred solution of 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid (**Intermediate 3**, 0.060 g, 0.31 mmol) in DMF (1.0 ml) at room temperature. The resultant solution was stirred for 30 mins and a solution of 2-(4-aminopiperidin-1-yl)-6-chloroisonicotinamide hydrochloride (**Intermediate 70**, 0.096 g, 0.37 mmol) in 1 ml of DMF was added. The reaction was stirred overnight, then concentrated under vacuum and the residue was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc (x2) and the combined organic extracts were washed with 1 N HCl, water and brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by reverse phase chromatography to give the desired product as a white solid (40 mg).

MS (ES): 431 (M+1) for $C_{17}H_{18}Cl_3N_5O_2$

^{1}H NMR δ: 1.56 (m, 2H); 1.88 (m, 2H); 2.17 (s, 3H); 3.11 (t, 2H); 4.10 (m, 1H); 4.25 (m, 2H); 6.97 (s, 1H); 7.18 (s, 1H); 7.23 (d, 1H); 7.69 (s, 1H); 8.14 (s, 1H); 11.95 (s, 1H)

Example 21: 2-Chloro-6-(4-{[(4-cyano-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)isonicotinamide

Diisopropylethylamine (0.1 ml, 0.56 mmol), EDC (0.09 g, 0.46 mmol) and HOAT (0.064 g, 0.46 mmol) were added to a stirred solution of 4-cyano-5-methyl-1*H*-pyrrole-2-carboxylic acid (**Intermediate 13**, 0.07 g, 0.47 mmol) in DMF (1.5 ml) at room temperature. The resultant solution was stirred for 30 mins and a solution of 2-(4-aminopiperidin-1-yl)-6-chloroisonicotinamide hydrochloride (**Intermediate 70**, 0.16 g, 0.56 mmol) in 1 ml of DMF was added. The reaction was stirred overnight, then concentrated under vacuum and the residue was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc (x2) and the combined organic extracts were washed with 1 N HCl, water and brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by reverse phase chromatography to give the desired product as a white solid (13 mg).

MS (ES): 387 (M+1) for $C_{18}H_{19}ClN_6O_2$

^{1}H NMR δ: 1.48 (m, 2H); 1.84 (m, 2H); 2.31 (s, 3H); 3.05 (t, 2H); 4.04 (m, 1H); 4.26 (m, 2H); 6.98 (s, 1H); 7.03 (s, 1H); 7.19 (s, 1H); 7.69 (s, 1H); 7.98 (d, 1H); 8.15 (s, 1H); 12.23 (s, 1H)

Example 22: 2-Chloro-6-(4-{[(4-chloro-5-ethyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)isonicotinamide

Title compound was synthesized by an analogous method to **Example 18** by coupling 2-(4-aminopiperidin-1-yl)-6-chloroisonicotinamide hydrochloride (**Intermediate 70**) with 4-chloro-5-ethyl-1*H*-pyrrole-2-carboxylic acid (**Intermediate 71**).

MS (ES): 410 (M+1) for $C_{18}H_{21}Cl_2N_5O_2$

^{1}H NMR δ: 1.10 (t, 3H); 1.45 (m, 2H); 1.83 (m, 2H); 2.54 (q, 2H); 3.04 (t, 2H); 4.03 (m, 1H); 4.27 (m, 2H); 6.73 (d, 1H); 6.97 (s, 1H); 7.19 (s, 1H); 7.69 (s, 1H); 7.76 (d, 1H); 8.15 (s, 1H); 11.57 (s, 1H)

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Example 23: 2-Chloro-6-(4-{[(3,5-dimethyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)isonicotinamide

Title compound was synthesized by an analogous method to **Example 18** using 2-(4-aminopiperidin-1-yl)-6-chloroisonicotinamide hydrochloride (**Intermediate 70**) and 3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid (commercially available).

MS (ES): 476 (M+1) for $C_{18}H_{22}ClN_5O_2$

^{1}H NMR δ: 1.46 (m, 2H); 1.87 (m, 2H); 2.13 (s, 3H); 2.19 (s, 3H); 3.09 (t, 2H); 4.03 (m, 1H); 4.23 (m, 2H); 5.63 (s, 1H); 6.97 (s, 1H); 7.00 (d, 1H); 7.19 (s, 1H); 7.69 (s, 1H); 8.15 (s, 1H); 10.69 (s, 1H)

Example 24: 2-Chloro-6-(4-{[(3,4-dichloro-5-ethyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)isonicotinamide

Title compound was synthesized by an analogous method to **Example 18** by coupling 2-(4-aminopiperidin-1-yl)-6-chloroisonicotinamide hydrochloride (**Intermediate 70**) with 3,4-dichloro-5-ethyl-1*H*-pyrrole-2-carboxylic acid (**Intermediate 73**).

MS (ES): 446 (M+1) for $C_{18}H_{20}Cl_2N_5O_2$

^{1}H NMR δ: 1.12 (t, 3H); 1.56 (m, 2H); 1.87 (m, 2H); 2.56 (q, 2H); 3.11 (t, 2H); 4.06 (m, 1H); 4.24 (m, 2H); 6.97 (s, 1H); 7.18 (s, 1H); 7.25 (d, 1H); 7.69 (s, 1H); 8.14 (s, 1H); 11.92 (s, 1H)

Example 25: 2-Chloro-6-(4-{[(3-ethyl-4,5-dimethyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)isonicotinamide

Title compound was synthesized by an analogous method to **Example 18** by coupling 2-(4-aminopiperidin-1-yl)-6-chloroisonicotinamide hydrochloride (**Intermediate 70**) with 3-ethyl-4,5-dimethyl-1*H*-pyrrole-2-carboxylic acid (commercially available).

MS (ES): 404 (M+1) for $C_{20}H_{26}Cl_3N_5O_2$

^{1}H NMR δ: 0.97 (t, 3H); 1.43 (m, 2H); 1.82 (s, 3H); 1.90 (m, 2H); 2.08 (s, 3H); 2.65 (q, 2H); 3.07 (t, 2H); 3.99 (m, 1H); 4.22 (m, 2H); 6.96 (s, 1H); 7.06 (d, 1H); 7.18 (s, 1H); 7.68 (s, 1H); 8.14 (s, 1H); 10.48 (s, 1H)

Example 26: 2-Chloro-6-(4-{[(3,4-diethyl-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)isonicotinamide

Title compound was synthesized by an analogous method to Example 18 by coupling 2-(4-aminopiperidin-1-yl)-6-chloroisonicotinamide hydrochloride (Intermediate 70) with 3,4-diethyl-5-methyl-1*H*-pyrrole-2-carboxylic acid (commercially available).

MS (ES): 418 (M+1) for $C_{21}H_{28}ClN_5O_2$

^{1}H NMR δ: 0.94- 1.04 (m, 6H); 1.43 (m, 2H); 1.90 (m, 2H); 2.08 (s, 3H); 2.28 (q, 2H); 2.63 (q, 2H); 3.07 (t, 2H); 4.08 (m, 1H); 4.20 (m, 2H); 6.96 (s, 1H); 7.07 (d, 1H); 7.18 (s, 1H); 7.66 (s, 1H); 8.14 (s, 1H); 10.51 (s, 1H)

Example 27: 2-Chloro-6-(4-{[(4-chloro-3,5-dimethyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)isonicotinamide

Title compound was synthesized by an analogous method to Example 18 by coupling 2-(4-aminopiperidin-1-yl)-6-chloroisonicotinamide hydrochloride (Intermediate 70) with 4-chloro-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid (Intermediate 75).

MS (ES): 408 (M-1) for $C_{18}H_{21}Cl_2N_5O_2$

^{1}H NMR δ: 1.47 (m, 2H); 1.87 (m, 2H); 2.13 (s, 3H); 2.16 (s, 3H); 3.10 (t, 2H); 4.00 (m, 1H); 4.21 (m, 2H); 6.96 (s, 1H); 7.18 (s, 1H); 7.20 (d, 1H); 7.68 (s, 1H); 8.14 (s, 1H); 11.17 (s, 1H)

Example 28: 2-Chloro-6-(4-{[(4-cyano-3,5-dimethyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)isonicotinamide

Title compound was synthesized by an analogous method to Example 18 by coupling 2-(4-aminopiperidin-1-yl)-6-chloroisonicotinamide hydrochloride (Intermediate 70) with 4-cyano-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid (commercially available).

MS (ES): 399 (M-1) for $C_{19}H_{21}ClN_6O_2$

^{1}H NMR δ: 1.48 (m, 2H); 1.86 (m, 2H); 2.25 (s, 3H); 2.28 (s, 3H); 3.08 (t, 2H); 4.01 (m, 1H); 4.21 (m, 2H); 6.96 (s, 1H); 7.18 (s, 1H); 7.40 (d, 1H); 7.68 (s, 1H); 8.13 (s, 1H); 11.77 (s, 1H)

Example 29: 2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxamide

Diisopropylethylamine (0.19 ml, 1.12 mmol), EDC (0.098 g, 0.51 mmol) and HOAT (0.070 g, 0.51 mmol) were added to a stirred solution of 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid (Intermediate 3, 0.1 g, 0.51 mmol) in DMF (1.5 ml) at room temperature.

The resultant solution was stirred for 30 mins and 2-(4-aminopiperidin-1-yl)-1,3-thiazole-5-carboxamide hydrochloride (Intermediate 81; 0.163 g, 0.62 mmol) was added. The reaction was stirred at room temperature overnight under nitrogen. The reaction was stirred overnight, then concentrated under vacuum and the residue was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with 1 N HCl, water and brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by reverse phase chromatography (water/acetonitrile gradient, 20-95%) to give the desired product as a white solid (50 mg).

MS (ES): 402 (M+1) for $C_{15}H_{17}Cl_2N_5O_2S$

^{1}H NMR δ: 1.58 (m, 2H); 1.82 (m, 2H); 2.11 (s, 3H); 3.17 (t, 2H); 3.81 (m, 2H); 3.97 (m, 1H); 7.07 (brs, 1H); 7.20 (d, 1H); 7.61 (brs, 1H); 7.71 (s, 1H); 11.90 (s, 1H)

Example 30: 2-(4-{[(3,4-Dichloro-5-ethyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxamide

Title compound was synthesized by an analogous method to Example 29 by coupling 3,4-dichloro-5-ethyl-1*H*-pyrrole-2-carboxylic acid (Intermediate 73) with 2-(4-aminopiperidin-1-yl)-1,3-thiazole-5-carboxamide hydrochloride (Intermediate 81).

MS (ES): 416 (M+1) for $C_{16}H_{19}Cl_2N_5O_2S$

^{1}H NMR δ: 1.11 (t, 3H); 1.66 (m, 2H); 1.89 (m, 2H); 2.56 (q, 2H); 3.24 (t, 2H); 3.81 (m, 2H); 4.06 (m, 1H); 7.14 (brs, 1H); 7.31 (d, 1H); 7.71 (brs, 1H); 7.78 (s, 1H); 11.94 (s, 1H)

Example 31: 6-(4-{[(4-Bromo-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-chloropyrimidine-4-carboxylic acid

Lithium hydroxide (2 M, 4 ml) was warmed to 40 °C and a solution of methyl 6-(4-{[(4-bromo-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-chloropyrimidine-4-carboxylate (Example 73, 0.180 g, 0.394 mmol) in MeOH was added. The reaction was stirred at 40 °C for 30 mins. The MeOH was removed and the aqueous solution was cooled to 0 °C and it was acidified with 6 M HCl. The acidic solution was extracted with EtOAc, dried over $MgSO_4$ and concentrated to give pink solid (0.15 g, 86%). An analytical sample was purified by reversed phase HPLC (acetonitrile/water (0.1% TFA), 20-95%).

MS (ES): 443 (M+1) for $C_{16}H_{17}BrClN_5O_3$

^{1}H NMR δ: 1.45 (m, 2H); 1.88 (m, 2H); 2.12 (s, 3H); 3.17 (m, 2H); 3.81 (m, 2H); 4.06 (m, 1H); 6.79 (s, 1H); 7.37 (s, 1H); 7.76 (d, 1H); 11.67 (s, 1H)

Example 32: 2-Chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylic acid

Title compound was synthesized from methyl 2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylate (Example 6) by an analogous method to Example 31.

MS (ES): 432 (M+1) for $C_{16}H_{16}Cl_3N_5O_3$

^{1}H NMR δ: 1.57 (m, 2H); 1.91 (m, 2H); 2.17 (s, 3H); 3.21 (m, 2H); 4.11 (m, 1H); 4.36 (m, 2H); 7.22 (d, 1H); 7.33 (s, 1H); 11.96 (s, 1H)

Example 33: 6-(4-{[(4-Bromo-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-chloro-*N*-methoxypyrimidine-4-carboxamide

Title compound was synthesized by an analogous method to Example 8 by coupling 6-(4-{[(4-bromo-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-chloropyrimidine-4-carboxylic acid (Example 31) with methoxylamine hydrochloride (commercially available).

MS (ES): 473 (M+1) for $C_{17}H_{20}BrClN_6O_3$

^{1}H NMR δ: 1.43 (m, 2H); 1.85 (m, 2H); 2.10 (s, 3H); 3.24 (m, 2H); 3.16 (t, 3H); 4.06 (m, 1H); 4.71 (m, 2H); 6.79 (s, 1H); 7.26 (s, 1H); 7.74 (d, 1H); 11.65 (s, 1H); 11.94 (s, 1H)

Example 34: 6-(4-{[(4-Bromo-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-*N*-methoxy-2-(methylthio)pyrimidine-4-carboxamide

Title compound was synthesized by an analogous method to Example 8 by coupling 6-(4-{[(4-bromo-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-(methylthio)pyrimidine-4-carboxylic acid (Example 35) with methoxylamine hydrochloride (commercially available).

MS (ES): 484 (M+1) for $C_{18}H_{23}BrN_6O_3S$

^{1}H NMR δ: 1.38 (m, 2H); 1.84 (m, 2H); 2.11 (s, 3H); 2.50 (s, 3H); 3.10 (t, 2H); 3.67 (s, 3H); 4.03 (m, 1H); 4.37 (m, 2H); 6.78 (s, 1H); 6.95 (s, 1H); 7.74 (d, 1H); 11.66 (s, 1H); 11.75 (s, 1H)

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Example 35: 6-(4-{[(4-Bromo-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-(methylthio)pyrimidine-4-carboxylic acid

Title compound was synthesized from methyl 6-(4-{[(4-bromo-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-chloropyrimidine-4-carboxylate (**Example 73**) by an analogous method to **Example 7**.

MS (ES): 455 (M+1) for $C_{17}H_{20}BrN_5O_3S$

^{1}H NMR δ: 1.44 (m, 2H); 1.86 (m, 2H); 2.12 (s, 3H); 2.46 (s, 3H); 3.12 (t, 2H); 4.06 (m, 1H); 4.36 (m, 2H); 6.79 (s, 1H); 7.06 (s, 1H); 7.75 (d, 1H); 11.67 (s, 1H); 11.66 (s, 1H)

Example 36: 6-(4-{[(4-Bromo-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-chloropyrimidine-4-carboxamide

Title compound was synthesized by an analogous method to **Example 8** by coupling 6-(4-{[(4-bromo-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-chloropyrimidine-4-carboxylic acid (**Example 31**) with 2 M ammonia in MeOH.

MS (ES): 443 (M+1) for $C_{16}H_{18}BrClN_6O_2$

^{1}H NMR δ: 1.45 (m, 2H); 1.90 (m, 2H); 2.12 (s, 3H); 3.18 (t, 2H); 4.06 (m, 1H); 4.39 (m, 2H); 6.79 (s, 1H); 7.30 (s, 1H); 7.79 (d, 1H); 7.83 (s, 1H); 7.95 (s, 1H); 11.68 (s, 1H)

Example 37: 2-Chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxamide

Title compound was synthesized by an analogous method to **Example 8** by coupling 2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylic acid (**Example 32**) with 2 M ammonia in MeOH.

MS (ES): 431 (M+1) for $C_{16}H_{17}Cl_3N_6O_2$

^{1}H NMR δ: 1.56 (m, 2H); 1.90 (m, 2H); 2.16 (s, 3H); 3.30 (t, 2H); 4.12 (m, 1H); 4.36 (m, 2H); 7.23 (d, 1H); 7.30 (s, 1H); 7.82 (s, 1H); 7.94 (s, 1H); 11.97 (s, 1H)

Example 38: 6-(4-{[(4-Bromo-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-(methylthio)pyrimidine-4-carboxamide

Title compound was synthesized by an analogous method to **Example 8** by coupling 6-(4-{[(4-bromo-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-(methylthio) pyrimidine-4-carboxylic acid (**Example 35**) with 2 M ammonia in MeOH (commercially available).

MS (ES): 454 (M+1) for $C_{17}H_{21}BrN_6O_2S$

^{1}H NMR δ: 1.43 (m, 2H); 1.88 (m, 2H); 2.12 (s, 3H); 2.46 (s, 3H); 3.11 (t, 2H); 4.04 (m, 1H); 4.45 (brs, 2H); 6.78 (s, 1H); 7.04 (s, 1H); 7.74 (s, 2H); 7.93 (s, 1H); 11.67 (s, 1H).

Example 39: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-*N*,2-dimethoxypyrimidine-4-carboxamide

The title compound was synthesised by an analogous method to Example 8 starting from 6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-methoxypyrimidine-4-carboxylic acid (Example 311) and methoxylamine hydrochloride.

MS (ES): 457 (M+1) for $C_{18}H_{22}Cl_2N_6O_4$

^{1}H NMR δ: 1.52 (m, 2H); 1.88 (m, 2H); 2.16 (s, 3H); 3.17 (t, 2H); 3.67 (s, 3H); 3.87 (s, 3H); 4.09 (m, 1H); 4.32 (m, 2H); 6.96 (s, 1H); 7.22 (d, 1H); 11.81 (s, 1H); 11.96 (s, 1H)

Example 40: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-ethoxy-*N*-methoxypyrimidine-4-carboxamide

The title compound was synthesised by an analogous method to Example 8 starting from 6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-ethoxypyrimidine-4-carboxylic acid (Example 312) and methoxylamine hydrochloride.

MS (ES): 471 (M+1) for $C_{19}H_{24}Cl_2N_6O_4$

^{1}H NMR δ: 1.28 (t, 3H); 1.52 (m, 2H); 1.88 (m, 2H); 2.16 (s, 3H); 3.16 (t, 2H); 3.66 (s, 3H); 4.09 (m, 1H); 4.32 (m, 2H); 4.32 (q, 2H); 6.95 (s, 1H); 7.22 (d, 1H); 11.80 (s, 1H); 11.96 (s, 1H)

Example 41: 3,4-Dichloro-*N*-[1-(4-chloro-6-methoxy-1,3,5-triazin-2-yl)piperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide

A solution of 2,4-dichloro-6-methoxy-1,3,5-triazine (commercially available)(0.05 g, 0.32 mmol) in DMF (0.5 ml) was added to a solution of 3,4-dichloro-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (Intermediate 1, 0.1 g, 0.32 mmol) and TEA (0.06 g, 0.64 mmol) in DMF (1.5 ml). The resultant mixture was stirred for 1 h at room temperature, then was diluted with water and extracted with EtOAc. During the aqueous workup, some of the product precipitated and was collected by suction filtration. The organic extract was dried over magnesium sulphate, filtered and concentrated to give the desired product with small amount of impurities.

MS (ESP): 419 (M+1) for $C_{15}H_{17}Cl_3N_6O_2$

^{1}H NMR δ: 1.54 (m, 2H); 1.90 (m, 2H); 2.16 (s, 3H); 3.10 (t, 2H); 3.88 (t, 3H); 4.08 (m, 1H); 4.45 (t, 2H); 7.25 (d, 1H); 12.01 (s, 1H).

Example 42: 2-(4-{[(4-Bromo-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-chloroisonicotinamide

4 N HCl/ dioxane solution (10 ml) was added to tert-butyl 1-[4-(aminocarbonyl)-6-chloropyridin-2-yl]piperidin-4-ylcarbamate (**Intermediate 16**,100 mg, 0.282 mmol). The mixture was stirred at room temperature for 90 minutes. The solvent was removed in vacuo and the anhydrous diethylether (25 ml) was added. The solvent was removed in vacuo and light brown solid that resulted was dried under vacuum for several hours. LCMS indicated a pure product 2-(4-aminopiperidin-1-yl)-6-chloroisonicotinamide hydrochloride salt (MS M+H:255). Pentafluorophenyl 4-bromo-5-methyl-1H-pyrrole-2-carboxylate (**Intermediate 17**)(104 mg, 0.282 mmol), and N,N-diisopropyl ethylamine (98 µl, 0.564 mmol) were added to 2-(4-aminopiperidin-1-yl)-6-chloroisonicotinamide hydrochloride salt (82 mg, 0.282 mmol) in anhydrous DMA (4 ml). The mixture was stirred at room temperature 18 h and was filtered and purified by semi- preparative HPLC using CH_3CN/H_2O (0.1% TFA) to give the title compound (28 mg).

MS (ES, M+H): 442 for $C_{17}H_{19}ClN_5O_2$

^{1}H NMR δ: 1.25 (m, 2H); 1.62 (m, 2H); 1.93 (s, 3H); 2.83 (m, 2H); 3.88 (m, 1H); 4.29 (m, 2H); 6.64 (d, 1H); 6.8 (s, 1H); 6.99 (s, 1H); 7.47 (s, 1H); 7.78 (s, 1H); 7.96 (s, 1H); 11.54 (s, 1H).

Example 43: Methyl 2-(4-{[(4-bromo-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-6-chloroisonicotinate

Pentafluorophenyl 4-bromo-5-methyl-1H-pyrrole-2-carboxylate (**Intermediate 17**, 1.81 g, 4.90 mmol) and TEA (682 µl, 4.9 mmol) were added to methyl 2-(4-aminopiperidin-1-yl)-6-chloroisonicotinate hydrochloride salt (**Intermediate 93**; 1.5 g, 4.90 mmol) in anhydrous DMA (10 ml). The mixture was stirred at room temperature18 h then partitioned between EtOAc and water. The organic layer was washed with water, dried over Na_2SO_4 and concentrated under vacuum. The solid material was purified by flash chromatography eluting with EtOAc / n-hexanes mixture (7:3) to give the title compound as a brown solid (1.7 g).

MS (ES, M+H): 456 for $C_{18}H_{21}BrClN_4O_3$

^{1}H NMR δ:1.39 (m, 2H); 1.82 (m, 2H); 2.11 (s, 3H); 3.00 (m, 2H); 3.86 (s, 3H); 3.99 (m, 1H); 4.23 (d, 2H); 6.80 (d, 1H); 6.96 (s, 1H); 7.21 (s, 1H); 7.73 (d, 1H); 11.26 (s, 1H)

Example 44: 2-(4-{[(4-Bromo-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-chloroisonicotinic acid

Methyl 2-(4-{[(4-bromo-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-chloroisonicotinate (Example 43, 1.7 g, 3.72 mmol) was dissolved in THF (10 ml). 2 N lithium hydroxide (10 ml) was added and the reaction was stirred at room temperature for 3 h. The mixture was acidified with 1 N HCl and was extracted with EtOAc (3x50 ml), dried over Na_2SO_4 and concentrated in vacuo.

MS (ES, M+H): 442 for $C_{17}H_{18}BrN_4O_3$

^{1}H NMR δ:1.29 (m, 2H); 1.72 (m, 2H); 2.04 (s, 3H); 2.91 (m, 2H); 3.89 (m, 1H); 4.13 (d, 2H); 6.70 (d, 1H); 6.84 (s, 1H); 7.10 (s, 1H); 7.65 (d, 1H); 11.26 (s, 1H)

Example 45: 2-(4-{[(4-Bromo-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-chloro-N-methoxyisonicotinamide

2-(4-{[(4-Bromo-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-chloroisonicotinic acid (Example 44, 150 mg, 0.34 mmol); HATU, (129 mg, 0.34 mmol); HOAT (46.25 mg; 0.34 mmol); N, N-diisopropyl ethylamine (116 µl, 0.68 mmol) were stirred in anhydrous DMF (3 ml) for 30 minutes. Methoxylamine hydrochloride (28.4 mg, 0.340 mmol), N, N-diisopropyl ethylamine (58 µl, 0.340 mmol) were added. The mixture was stirred at room temperature for 18 h and the crude mixture was filtered, then purified by semi-prep reverse phase HPLC eluting with CH_3CN/H_2O (0.1% TFA). (23 mg).

MS (ES, M+H): 472 for $C_{18}H_{21}BrClN_5O_3$

^{1}H NMR δ: 1.36 (m, 2H); 1.78 (m, 2H); 2.08 (s, 3H); 2.96 (m, 2H); 3.66 (s, 3H); 3.96 (m, 1H); 4.17 (d, 2H); 6.76 (d, 1H); 6.82 (s, 1H); 7.02 (s, 1H); 7.71 (d, 1H); 11.63 (s, 1H); 11.92 (s, 1H)

Example 46: 3,4-Dichloro-N-(1-{6-chloro-4-[(1E)-N-hydroxyethanimidoyl]pyridin-2-yl}piperidin-4-yl)-5-methyl-1H-pyrrole-2-carboxamide

N-[1-(4-Acetyl-6-chloropyridin-2-yl)piperidin-4-yl]-3,4-dichloro-5-methyl-1H-pyrrole-2-carboxamide (Example 115)(49 mg, 0.114 mmol) was dissolved in EtOH (2 ml). Pyridine (74 µl, 0.913 mmol) was added followed by hydroxylamine hydrochloride (63.4 mg, 0.913

mmol). The mixture was stirred at room temperature overnight. The product was purified by semi-prep reverse phase HPLC eluting with CH_3CN/H_2O (0.1% TFA). (28 mg).

MS (ES, M+H): 446 for $C_{18}H_{20}Cl_3N_5O_2$

^{1}H NMR δ: 146 (m, 2H); 1.83 (s, 3H); 2.10 (s, 3H); 2.15 (s, 3H); 3.02 (m, 2H); 3.99 (m, 1H); 4.17 (d, 2H); 6.83 (s, 1H); 6.91 (s, 1H); 7.20 (s, 1H); 11.65 (s, 1H); 11.93 (s, 1H)

Example 47: N-(1-{4-[Amino(hydroxyimino)methyl]-6-chloro-2-pyridinyl}-4-piperidinyl)-3,4-dichloro-5-methyl-1H-pyrrole-2-carboxamide

3,4-Dichloro-N-[1-(6-chloro-4-cyanopyridin-2-yl)piperidin-4-yl]-5-methyl-1H-pyrrole-2-carboxamide (Example 95; 150 mg, 0.362 mmol) was dissolved in MeOH (5 ml) and TEA (100 µl, 0.724 mmol) was added. Hydroxylamine hydrochloride (25.2 mg, 0.362 mmol) was added and the mixture was refluxed for 1 h. The solvent was removed in vacuo and the resulting precipitate was dissolved in DMSO and purified by semi preparative reverse phase HPLC eluting with CH_3CN/H_2O (0.1% TFA). (80 mg).

MS (ES, M+H): 447 for $C_{17}H_{19}Cl_3N_6O_2$

^{1}H NMR δ: 1.35 (m, 2H); 1.73 (m, 2H); 2.06 (s, 3H); 2.94 (m, 2H); 3..89 (m, 1H); 4.07 (d, 2H); 6.04 (brm, 2H); 6.78 (s, 1H); 6.95 (s, 1H); 7.13 (d, 1H); 9.98 (s, 1H); 11.85 (s, 1H)

Example 48: 1-[6-Chloro-4-(1H-tetrazol-5-yl)pyridin-2-yl]piperidin-4-yl 3,4-dichloro-5-methyl-1H-pyrrole-2-carboxylate

1-(6-Chloro-4-cyanopyridin-2-yl)piperidin-4-yl 3,4-dichloro-5-methyl-1H-pyrrole-2-carboxylate (Example 308, 64 mg, 0.154 mmol), sodium azide (12 mg, 0.185 mmol) and ammonium chloride (8.3 mg, 0.154 mmol) were dissolved in anhydrous DMF (2 ml) and the mixture was heated at 120 °C for 8 h. The mixture was filtered and purified my semi-preparative reverse phase HPLC eluting with CH_3CN/H_2O (0.1% TFA)(48 mg).

MS (ES, M+H): 456 for $C_{17}H_{16}Cl_3N_7O_2$

^{1}H NMR δ: 1.67 (m, 2H); 1.91 (m, 2H); 2.16 (s, 3H); 3.66 (m, 2H); 3.79 (m, 2H); 5.19 (m, 1H); 7.17 (s, 1H); 7.39 (s, 1H); 12.24 (s, 1H)

Example 49: 3,4-Dichloro-5-methyl-*N*-[1-(1-methyl-5-nitro-1*H*-imidazol-2-yl)piperidin-4-yl]-1*H*-pyrrole-2-carboxamide

TEA (0.26 ml, 1.86 mmol) was added to a mixture of 2-bromo-1-methyl-5-nitro-*1H*-imidazole (G.B. Barlin, *J. Chem. Soc. B*, 1967, 641; 126 mg, 0.61 mmol,) and 3,4-dichloro-5-

methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (Intermediate 1), 191 mg, 0.61 mmol) in 1-methyl-2-pyrrolidinone (1.5 ml). Using a Smith Microwave Synthesizer, the mixture was subjected to single-mode microwave at 150 °C for 30 min. EtOAc was added and the solution was washed with water (2X). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The crude material was purified by chromatography on silica gel using 50% EtOAc/hexanes to give 158 mg of the title product.

MS (ESP): 401 (MH^+) for $C_{15}H_{18}Cl_2N_6O_3$

^{1}H-NMR δ: 1.73-1.86 (m, 2H); 1.97-2.01 (m, 2H); 2.25 (s, 3H); 3.18 (t, 2H); 3.56-3.64 (m, 2H); 3.71 (s, 3H); 4.08 (m, 1H); 7.34 (d, 1H); 8.02 (s, 1H); 12.19 (s, 1H).

Example 50: 3,4-Dichloro-5-methyl-*N*-[1-(1-methyl-4-nitro-1*H*-imidazol-2-yl)piperidin-4-yl]-1*H*-pyrrole-2-carboxamide

Using a procedure similar to that used in Example 52, 30 mg of the title product was obtained starting from 2-bromo-1-methyl-4-nitro-*1H*-imidazole (G.B. Barlin, *J. Chem. Soc. B*, 1967, 641).

MS (ESP): 401 (MH^+) for $C_{15}H_{18}Cl_2N_6O_3$

^{1}H-NMR δ: 1.76-1.86 (m, 2H); 1.98-2.01 (m, 2H); 2.26 (s, 3H); 3.02 (t, 2H); 3.42-3.52 (m overlapping water, 2H); 3.65 (s, 3H); 4.03 (m, 1H); 7.35 (d, 1H); 8.28 (s, 1H); 12.06 (s, 1H).

Example 51: 1-*tert*-Butyl 2-methyl (2*S*)-4-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrrolidine-1,2-dicarboxylate

N-BOC-*trans*-4-Hydroxy-L-proline methylester (0.20 g, 0.81 mM) and 3,4-dichloro-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide (free base of Intermediate 1), 0.16 g, 0.81 mM) were stirred in 1,2-dichloroethane (3.5 ml). Sodium triacetoxyborohydride (0.24 g, 1.1 mM) was added followed by acetic acid (0.05 ml). The reaction was stirred under nitrogen at room temperature overnight then diluted with ether and washed with 1 N sodium hydroxide. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated to give an orange oil. The oil was chromatographed using EtOAc to give the desired product as a light yellow solid.

MS (ESP): 503 (MH^+) for $C_{22}H_{32}Cl_2N_4O_5$

^{1}H-NMR ($CDCl_3$) δ: 1.39 and 1.45 (2s, 9H, rotamers); 1.71-1.92 (m, 1H); 1.92-2.10 (m, 2H); 2.10-2.34 (m, 5H); 2.41-2.61 (m, 1H); 2.67-2.94 (m, 3H); 3.21 (t, 1H); 3.71 (s, 3H); 3.81-4.01 (m, 2H); 4.19-4.31 (m, 1H); 6.58 (d, 1H); 9.59 (brs, 1H).

Example 52: Methyl 4-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-L-prolinate

1-*tert*-Butyl 2-methyl (2*S*)-4-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl] amino}piperidin-1-yl)pyrrolidine-1,2-dicarboxylate (**Example 51**, 0.16 g, 0.32 mM) was stirred in 4 N hydrogen chloride in dioxane (4.0 ml) at room temperature for twenty minutes. The orange mixture was concentrated then dissolved in a small amount of MeOH/ DCM, diluted with DCM, and washed with sodium bicarbonate. The organic layer was dried over $MgSO_4$, filtered and concentrated to give an orange solid (0.130 g).

MS (ESP): 403 (MH^+) for $C_{17}H_{24}Cl_2N_4O_3$

^{1}H-NMR ($CDCl_3$) δ: 1.51-1.70 (m, 2H); 1.70-1.82 (m, 1H); 1.89-2.04 (m, 2H); 2.18-2.34 (m, 5H); 2.36-2.48 (m, 1H); 2.77-3.01 (m, 4H); 3.07-3.20 (m, 1H); 3.72 (s, 3H); 3.77-3.95 (m, 2H).

Example 53: 4-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-L-proline

A 2 N solution of lithium hydroxide was heated to 70 °C. Methyl 4-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-L-prolinate (**Example 52**, 0.081 g, 0.20 mM) in acetonitrile (1.1 ml) and water (0.4 ml) was added to the solution and stirred at 70 °C for ten minutes then ambient temperature for twenty minutes. 1 N Hydrogen chloride was added and a minor impurity was extracted using EtOAc. The aqueous layer was lyophilized to give an orange solid that was purified by HPLC eluting CH_3CN/H_2O (0.1% TFA). Relevant fractions were collected, concentrated and lyophilized to give the desired product as a light orange solid (0.039 g).

MS (ESP): 389 (MH^+) for $C_{16}H_{22}Cl_2N_4O_3$

^{1}H-NMR (D_2O) δ: 1.80-2.02 (m, 2H); 2.11-2.33 (m, 6H); 2.85-3.04 (m, 1H); 3.15-3.41 (m, 2H); 3.48-3.73 (m, 3H); 3.92 (t, 1H); 4.04-4.20 (m, 2H); 4.27 (t, 1H).

Example 54: 4-Bromo-5-methyl-*N*-[1-(3-nitro-2-pyridinyl)-4-piperidinyl]-1H-pyrrole-2-carboxamide

1-(3-Nitropyridin-2-yl)piperidin-4-amine hydrochloride salt (**Intermediate 39**) (41 mg, 1.35 mmol) and TEA (37 µl,1.35 mmol) were added to pentafluorophenyl 4-bromo-5-methyl-1H-pyrrole-2-carboxylate (**Intermediate 17**): (50 mg,1.35 mmol) in anhydrous DMA (1 ml). The mixture was stirred at room temperature overnight. The crude mixture was filtered and

purified by semi-preparative HPLC using CH_3CN/H_2O (0.1% TFA) to yield the title compound as a yellow solid (26 mg).

MS (ES) MH^+: 410 for $C_{16}H_{18}Br N_5O_3$

^1H NMR δ: 1.25 (m, 2H); 1.53 (m, 2H); 1.79 (s, 3H); 2.82 (m, 2H); 3.43 (m, 2H); 3.74 (m, 1H); 6.4 (d, 1H); 6.83 (m, 1H); 7.58 (d, 1H); 7.96 (d, 1H); 8.16 (d, 1H); 11.39 (s, 1H).

Examples 55-69

The following compounds were synthesized by an analogous method to Example 54 starting from pentafluorophenyl 4-bromo-5-methyl-1H-pyrrole-2-carboxylate (Intermediate 17) and the starting materials given in the table below.

Examples 55-69:

Example 55: Ethyl 2-(4-{[(4-bromo-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-1-piperidinyl)-3-cyano-6-methylisonicotinate

Example 56: 4-Bromo-N-[1-(3-cyano-2-pyridinyl)-4-piperidinyl]-5-methyl-1H-pyrrole-2-carboxamide

Example 57: 4-Bromo-5-methyl-N-[1-(2-quinolinyl)-4-piperidinyl]-1H-pyrrole-2-carboxamide

Example 58: 4-Bromo-N-[1-(6-methoxy-3-nitro-2-pyridinyl)-4-piperidinyl]-5-methyl-1H-pyrrole-2-carboxamide

Example 59: 4-Bromo-N-[1-(6-chloro-4-cyano-2-pyridinyl)-4-piperidinyl]-5-methyl-1H-pyrrole-2-carboxamide

Example 60: 4-Bromo-5-methyl-N-{1-[6-(trifluoromethyl)-2-pyridinyl]-4-piperidinyl}-1H-pyrrole-2-carboxamide

Example 61: 2-(4-{[(4-Bromo-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-1-piperidinyl)-6-(trifluoromethyl)nicotinamide

Example 62: 4-Bromo-N-[1-[3-cyano-6-(trifluoromethyl)-2-pyridinyl]-4-piperidinyl}-5-methyl-1H-pyrrole-2-carboxamide

Example 63: 4-Bromo-N-[1-(3-chloro-2-pyridinyl)-4-piperidinyl]-5-methyl-1H-pyrrole-2-carboxamide

Example 64: 4-Bromo-N-[1-(4-cyano-2-pyridinyl)-4-piperidinyl]-5-methyl-1H-pyrrole-2-carboxamide

Example 65: 4-Bromo-5-methyl-N-[1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-4-yl]-1H-pyrrole-2-carboxamide

Example 66: 6-(4-[[(4-Bromo-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-1-piperidinyl)nicotinamide Example 67: 4-Bromo-N-[1-(6-bromopyridin-2-yl)piperidin-4-yl]-5-methyl-1H-pyrrole-2-carboxamide

Example 68: 4-Bromo-N-[1-(6-chloro-2-pyridinyl)-4-piperidinyl]-5-methyl-1H-pyrrole-2-carboxamide

Example 69: 6-(4-[[(4-Bromo-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-1-piperidinyl)-2-chloronicotinic acid

Example	^{1}H NMR δ	m/z	SM
55	1.5 (t, 3H); 1.8 (m, 2H); 2.1 (m, 2H); 2.3 (s, 3H); 2.6 (s, 3H); 3.3 (m, 2H); 4.2 (m, 1H); 4.4 (m, 2H); 4.6 (m, 2H); 7.0 (d, 1H); 7.4 (s, 1H); 11.6 (s, 1H).	474	Ethyl 2-(4-aminopiperidin-1-yl)-3-cyano-6-methylisonicotinate hydrochloride salt (Intermediate 199)
56	1.5 (m, 2H); 1.8 (m, 2H); 2.1 (s, 3H); 3.1 (m, 2H); 3.3 (m, 2H); 3.9 (m, 1H); 4.41 (m, 2H); 6.8 (d, 1H); 6.9 (d, 1H); 7.8 (d, 1H); 8.0 (d, 1H); 8.4 (d, 1H); 11.6 (s, 1H).	388	2-(4-Aminopiperidin-1-yl)nicotinonitrile hydrochloride salt (Intermediate 200)
57	1.4 (m, 2H); 1.8 (m, 2H); 2.0 (s, 3H); 3.1 (m, 2H); 2.9 (m, 2H); 4.0 (m, 1H); 4.4 (m, 2H); 6.6 (d, 1H); 7.3 (m, 1H); 7.8 (bm, 4H); 8.2 (m, 1H); 8.4 (d, 1H); 11.6 (s, 1H).	415	1-Quinolin-2-ylpiperidin-4-amine hydrochloride salt (Intermediate 201)
58	1.5 (m, 2H); 1.8 (m, 2H); 2.0 (s, 3H); 3.0 (m, 2H); 3.7 (m, 2H); 3.8 (s, 3H); 3.9 (m, 1H); 6.2 (d, 1H); 6.7 (s, 1H); 6.9 (d, 1H); 8.2 (d, 1H); 11.6 (s, 1H).	440	1-(6-Methoxy-3-nitropyridin-2-yl)piperidin-4-amine hydrochloride salt (Intermediate 202)
59	1.30 (m, 2H); 1.7 (m, 2H); 1.93 (s, 3H); 2.83 (m, 2H); 3.88 (m, 1H); 4.29 (m, 2H); 6.64 (d, 1H); 6.8 (s, 1H); 6.99 (s, 1H); 7.27 (s, 1H); 7.7 (d, 1H); 11.54 (s, 1H).	420	2-(4-Aminopiperidin-1-yl)-6-chloroisonicotinonitrile hydrochloride salt (Intermediate 203)

Example	^{1}H NMR δ	m/z	SM
60	1.29 (m, 2H); 1.70 (m, 2H); 1.97 (s, 3H); 2.86 (m, 2H); 3.89 (m, 1H); 4.13 (m, 2H); 6.92 (s, 1H); 7.09 (d, 1H); 7.61 (m, 2H); 11.58 (s, 1H).	433	1-[6-(Trifluoromethyl) pyridin-2-yl]piperidin-4-amine hydrochloride salt (Intermediate 204)
61	1.43 (m, 2H); 1.72 (m, 2H); 2.03 (s, 3H); 2.91 (m, 2H); 3.75 (m, 3H); 6.70 (s, 1H); 7.08 (s, 1H); 7.61 (d, 1H); 7.75 (d, 2H); 7.91 (m, 1H); 11.54 (s, 1H).	476	2-(4-Aminopiperidin-1-yl)-6-(trifluoromethyl) nicotinamide hydrochloride salt (Intermediate 205)
62	1.43 (m, 2H); 1.78 (m, 2H); 1.99 (s, 3H); 2.96 (m, 2H); 3.91 (m, 1H); 4.22 (m, 1H); 6.63 (s, 1H); 7.16 (d, 1H); 7.66 (d, 1H); 8.24 (d, 1H); 11.50 (s, 1H).	458	2-(4-Aminopiperidin-1-yl)-6-(trifluoromethyl) nicotinonitrile hydrochloride salt (Intermediate 206)
63	1.58 (m, 2H); 1.76 (m, 2H); 2.00 (s, 3H); 2.2.71 (m, 2H); 3.61 (d, 2H); 3.84 (m, 1H); 6.75 (s, 1H); 6.91 (s, 1H); 7.66 (m, 1H); 8.03 (m, 1H); 11.55 (s, 1H).	399	1-(3-Chloropyridin-2-yl)piperidin-4-amine hydrochloride salt (Intermediate 207)
64	1.17 (m, 2H); 1.62 (m, 2H); 1.97 (s, 3H); 2.95 (m, 2H); 3.84 (m, 1H); 4.19 (d, 2H); 6.64 (d, 1H); 7.09 (d, 1H); 7.4 (s, 1H); 7.8 (d, 1H); 8.34 (d, 1H); 11.68 (s, 1H).	389	2-(4-Aminopiperidin-1-yl)isonicotinonitrile hydrochloride salt (Intermediate 208)
65	1.45 (m, 2H); 1.85 (m, 2H); 2.10 (s, 3H); 2.35 (s, 3H); 2.97 (m, 2H); 3.82 (s, 3H); 4.10 (m, 1H); 4.7 (d, 2H); 6.85 (s, 1H); 7.56 (s, 1H); 7.85 (d, 1H); 11.68 (s, 1H).		1-[5-(Trifluoromethyl) pyridin-2-yl]piperidin-4-amine hydrochloride salt (Intermediate 209)
66	1.35 (m, 2H); 1.77 (m, 2H); 2.10 (s, 3H); 3.10 (m, 2H); 4.12 (m, 1H); 4.45 (d, 2H); 6.82 (bra, 1H); 7.18 (d, 1H); 7.71 (s, 1H); 7.92 (s, 1H); 7.99 (dd 1H); 8.58 (d, 1H); 11.69 (s, 1H).	406	6-(4-Aminopiperidin-1-yl)nicotinamide hydrochloride salt (Intermediate 210)

Example	^{1}H NMR δ	m/z	SM
67	1.13 (m, 2H); 1.53 (m, 2H); 1.87 (s, 3H); 2.67 (m, 2H); 3.70 (m, 1H); 3.92 (d, 2H); 6.50 (d, 1H); 6.60 (d 1H); 6.67 (d, 1H); 7.17 (dd, 1H); 7.49 (d 1H); 11.40 (s, 1H).	443	1-(6-Bromopyridin-2-yl)piperidin-4-amine hydrochloride salt (Intermediate 211)
68	1.28 (m, 2H); 1.68 (m, 2H); 2.02 (s, 3H); 2.83 (m, 2H); 3.87 (m, 1H); 4.09 (d, 2H); 6.52 (d, 1H); 6.70 (m, 2H); 7.41 (m, 1H); 7.63 (d, 1H); 11.52 (s, 1H)	399	[1-(6-Chloropyridin-2-yl)piperidin-4-yl]amine hydrochloride salt (Intermediate 212)
69	1.27 (m, 2H); 1.72 (m, 2H); 2.01 (s, 3H); 2.94 (m, 2H); 3.90 (m, 1H); 4.18 (d, 2H); 6.69 (s, 1H); 6.76 (d, 1H); 7.65 (d, 1H); 7.88 (d, 1H); 11.55 (s, 1H); 12.53 (s, 1H).	443	6-(4-Aminopiperidin-1-yl)-2-chloronicotinic acid hydrochloride salt (Intermediate 213)

Examples 70-73

The following compounds were synthesized by an analogous method to **Example 54** using pentafluorophenyl 4-bromo-5-methyl-1H-pyrrole-2-carboxylate (**Intermediate 17**) and the starting materials given in the table below.

Example 70: 4-Bromo-5-methyl-N-[1-(2-pyrimidinyl)-4-piperidinyl]-1H-pyrrole-2-carboxamide

Example 71: Methyl 2-(4-{[(4-bromo-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-1-piperidinyl)-6-methyl-4-pyrimidinecarboxylate

Example 72: 4-Bromo-5-methyl-N-[1-(7H-purin-6-yl)piperidin-4-yl]-1H-pyrrole-2-carboxamide

Example 73: Methyl 6-(4-{[(4-bromo-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-1-piperidinyl)-2-chloro-4-pyrimidinecarboxylate

Example	^{1}H NMR δ	m/z	SM
70	1.17 (m, 2H); 1.62 (m, 2H); 1.97 (s, 3H); 2.95 (m, 2H); 3.84 (m, 1H); 4.19 (d, 2H); 6.64 (d, 1H); 7.09 (d, 1H); 7.4 (s, 1H); 7.8 (d, 1H); 8.34 (d, 1H); 11.68 (s, 1H).	365	1-Pyrimidin-2-ylpiperidin-4-amine hydrochloride salt (Intermediate 214)

Example	^{1}H NMR δ	m/z	SM
71	1.45 (m, 2H); 1.85 (m, 2H); 2.10 (s, 3H); 2.35 (s, 3H); 2.97 (m, 2H); 3.82 (s, 3H); 4.10 (m, 1H); 4.7 (d, 2H); 6.85 (s, 1H); 7.56 (s, 1H); 7.85 (d, 1H); 11.68 (s, 1H).	438	Methyl 2-(4-aminopiperidin-1-yl)-6-methylpyrimidine-4-carboxylate hydrochloride salt (Intermediate 215)
72	1.29 (m, 2H); 1.77 (m, 2H); 2.05 (s, 3H);3.99 (m, 1H); 4.96 (m, 2H); 6.60 (d, 1H); 7.55 (s, 1H); 7.96 (d, 1H); 8.13 (d, 1H); 8.86 (brs, 2H); 11.46 (s, 1H); 12.76 (brs, 1H)	406	1-(7*H*-Purin-6-yl)piperidin-4-amine hydrochloride salt (Intermediate 216)
73	1.21 (m, 2H); 1.71 (m, 2H); 1.91 (s, 3H); 2.97 (m, 2H); 3.30 (m, 2H); 3.67 (s, 3H); 3.92 (m, 1H); 6.49 (s, 1H); 7.16 (s, 1H); 7.53 (d, 1H); 11.46 (s, 1H)	458	Methyl 6-(4-aminopiperidin-1-yl)-2-chloropyrimidine-4-carboxylate hydrochloride salt (Intermediate 217)

Examples 74-85

The following compounds were synthesized by an analogous method to Example 45, starting from 2-(4-{[(4-bromo-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-chloroisonicotinic acid (Example 44) and the commercially available amines given in the table below.

Example 74: 2-(4-{[(4-Bromo-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-1-piperidinyl)-6-chloro-N-cyclopropylisonicotinamide

Example 75: 2-(4-{[(4-Bromo-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-1-piperidinyl)-6-chloro-N-methylisonicotinamide

Example 76: Methyl 2-{[2-(4-{[(4-bromo-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-1-piperidinyl)-6-chloroisonicotinoyl]amino}acetate

Example 77: 2-(4-{[(4-Bromo-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-1-piperidinyl)-6-chloro-N-hydroxyisonicotinamide

Example 78: 4-Bromo-N-{1-[6-chloro-4-(hydrazinocarbonyl)-2-pyridinyl]-4-piperidinyl}-5-methyl-1H-pyrrole-2-carboxamide

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Example 79: 4-Bromo-N-{1-[6-chloro-4-[(4-methyl-1-piperazinyl)carbonyl]-2-pyridinyl}-4-piperidinyl)-5-methyl-1H-pyrrole-2-carboxamide

Example 80: 4-Bromo-N-{1-[6-chloro-4-[(2,2-dimethylhydrazino)carbonyl]-2-pyridinyl]-4-piperidinyl)-5-methyl-1H-pyrrole-2-carboxamide

Example 81: 4-Bromo-N-{1-[6-chloro-4-(4-morpholinylcarbonyl)-2-pyridinyl]-4-piperidinyl}-5-methyl-1H-pyrrole-2-carboxamide

Example 82: 2-(4-{[(4-Bromo-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-1-piperidinyl)-6-chloro-N,N-dimethylisonicotinamide

Example 83: 2-(4-{[(4-Bromo-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-1-piperidinyl)-6-chloro-N-methoxy-N-methylisonicotinamide

Example 84: 2-(4-{[(4-Bromo-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-1-piperidinyl)-6-chloro-N-[3-(4-morpholinyl)propyl]isonicotinamide

Example 85: 2-(4-{[(4-Bromo-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-1-piperidinyl)-6-chloro-N-[2-(4-morpholinyl)ethyl]isonicotinamide

Example	Amine	^{1}H NMR δ	m/z
74	Cyclopropylamine	0.28 (m, 2H); 0.40 (m, 2H); 0.97 (m, 2H); 1.6 (m, 2H); 1.87 (s, 3H); 2.51 (m, 1H); 2.69 (m, 2H); 3.60 (m, 1H); 4.18 (d, 2H); 3.69 (s, 1H); 3.91 (d, 2H); 6.43 (s, 1H); 6.58 (s, 1H); 6.78 (s, 1H); 7.36 (d, 1H); 8.21 (d, 1H); 11.26 (s, 1H)	482
75	Methylamine	1.59 (m, 2H); 2.01 (m, 2H); 2.32 (s, 3H); 2.96 (m, 1H); 3.27 (m, 2H); 4.18 (m, 1H); 4.41 (d, 2H); 6.99 (d, 1H); 7.12 (s, 2H); 7.33 (s, 1H); 7.92 (d, 1H); 8.79 (d, 1H); 11.81 (s, 1H)	456
76	Amino-acetic acid methyl ester . HCl	1.56 (m, 2H); 1.91 (m, 2H); 2.15 (s, 3H); 3.14 (m, 2H); 3.41 (s, 3H); 3.69 (m, 1H); 4.08 (m, 2H); 4.4 (m, 2H); 6.85 (m, 1H); 7.07 (s, 1H); 7.94 (d, 1H); 11.81 (s, 1H)	512
77	Hydroxylamine. HCl	1.27 (m, 2H); 1.7 (m, 2H); 2.03 (s, 3H); 2.84 (m, 2H); 3.88 (m, 1H); 4.07 (d, 2H); 6.68 (d, 1H); 6.76 (s, 1H); 6.93 (s, 1H); 7.60 (d, 1H); 9.12 (d, 1H); 11.27 (s, 1H); 11.47 (s;1H).	457

Example	Amine	^{1}H NMR δ	m/z
78	Hydrazine	1.29 (m, 2H); 1.71 (m, 2H); 2.03 (s, 3H); 2.89 (m, 2H); 2.69 (m, 2H); 3.87 (m, 1H); 4.13 (d, 2H); 5.48 (brm, 2H); 6.69 (d, 1H); 6.84 (s, 1H); 7.05 (s, 1H); 7.64 (d, 1H); 9.95 (d, 1H); 11.55 (s, 1H)	456
79	1-methyl-piperazine	1.35 (m, 2H); 1.78 (m, 2H); 2.09 (s, 3H); 2.75 (s, 3H); 2.96 (m, 4H); 3.95 (m, 1H); 4.17 (d, 2H); 4.41 (m, 1H); 6.61 (d, 1H); 6.76 (m, 2H); 7.72 (d, 1H); 11.60 (s, 1H)	525
80	N,N-dimethyl hydrazine	1.36 (m, 2H); 1.78 (m, 2H); 2.09 (s, 3H); 2.54 (s, 6H); 2.94 (m, 2H); 3.31 (m, 2H); 4.10 (m, 1H); 4.33 (d, 2H); 6.76 (d, 1H); 6.85 (s, 1H); 7.03 (s, 1H); 7.71 (d, 1H); 9.55, (s, 1H); 11.62 (s, 1H)	485
81	morpholine	1.32 (m, 2H); 1.75 (m, 2H); 2.07 (s, 3H); 2.92 (m, 2H); 3.12 (m, 2H); 3.22 (m, 2H); 3.30 (m, 2H); 3.47 (m, 4H); 3.94 (m, 1H); 4.05 (m, 1H); 4.16 (m, 2H); 6.57 (s, 1H); 6.74 (m, 2H); 7.67 (d, 1H); 11.60 (s, 1H)	512
82	dimethylamine	1.51 (m, 2H); 1.92 (m, 2H); 2.26 (s, 3H); 3.01 (s, 3H); 3.09 (s, 3H); (m, 2H); 3.15 (m, 21H); 3.44 (d, 4H); 4.10 (m, 1H); 4.36 (d, 2H); 6.73 (s, 1H); 6.93 (d, 2H); 7.87 (d, 1H); 11.78 (s, 1H)	468
83	O, N- Dimethyl-hydroxylamine	1.35 (m, 2H); 1.76 (m, 2H); 2.11 (s, 3H); 2.95 (m, 2H); 3.20 (s, 3H); 3.56 (s, 3H); 3.95 (m, 1H); 4.19 (d, 2H); 6.67 (s, 1H); 6.77 (s, 1H); 6.88 (s, 1H); 7.71 (d, 1H); 11.64 (s, 1H)	486
84	3-Morpholin-4-yl-propylamine	1.33 (m, 2H); 1.70 (m, 4H); 2.08 (s, 3H); 2.94 (m, 4H); 3.24 (m, 2H); 3.38 (m, 2H); 3.51 (m, 6H); 3.87 (m, 2H); 4.12 (m, 1H); 6.74 (s, 1H); 6.91 (s, 1H); 7.04 (s 1H); 7.61 (s 1H); 8.66 (d, 1H); 11.51 (s, 1H).	569

Example	Amine	^{1}H NMR δ	m/z
85	2-Morpholin-4-yl-ethylamine	1.24 (m, 2H); 1.66 (m, 2H); 2.05 (s, 3H); 2.93 (m, 4H); 3.24 (m, 2H); 3.4 (m, 8H); 3.79 (m, 2H); 4.13 (m, 1H); 6.71 (a, 1H); 6.88 (s, 1H); 7.04 (s 1H); 7.66 (d, 1H); 8.78 (m, 1H); 11.58 (s, 1H).	555

Examples 86-88

The following examples were synthesised by an analogous method to Example 48 from the starting materials given in the table below.

Example 86: 4-Bromo-5-methyl-N-{1-[4-(1H-1,2,3,4-tetrazol-5-yl)-2-pyridinyl]-4-piperidinyl}-1H-pyrrole-2-carboxamide

Example 87: 4-Bromo-N-{1-[6-chloro-4-(1H-1,2,3,4-tetrazol-5-yl)-2-pyridinyl]-4-piperidinyl}-5-methyl-1H-pyrrole-2-carboxamide

Example 88: 3,4-Dichloro-N-{1-[6-chloro-4-(1H-1,2,3,4-tetrazol-5-yl)-2-pyridinyl]-4-piperidinyl}-5-methyl-1H-pyrrole-2-carboxamide

Example	^{1}H NMR δ	m/z	SM
86	1.30 (m, 2H); 1.7 (m, 2H); 1.93 (s, 3H); 2.83 (m, 2H); 3.88 (m, 1H); 4.29 (m, 2H); 6.64 (d, 1H); 6.8 (s, 1H); 6.99 (s, 1H); 7.27 (s, 1H); 7.7 (d, 1H); 11.54 (s, 1H).	433	4-Bromo-N-[1-(4-cyano-2-pyridinyl)-4-piperidinyl]-5-methyl-1H-pyrrole-2-carboxamide (Example 64)
87	1.24 (m, 2H); 1.66 (m, 2H); 1.99 (s, 3H); 2.88 (m, 2H); 3.84 (m, 1H); 4.08 (d, 1H); 6.55 (s, 1H); 6.96 (s, 1H); 7.16 (s, 1H); 7.53 (d, 1H); 11.28 (s, 1H).	467	4-Bromo-N-[1-(6-chloro-4-cyano-2-pyridinyl)-4-piperidinyl]-5-methyl-1H-pyrrole-2-carboxamide (Example 59)
88	1.32 (m, 2H); 1.71 (m, 2H); 2.04 (s, 3H); 2.97 (m, 2H); 3.88 (m, 1H); 4.13 (d, 2H); 6.97 (s, 1H); 7.15 (d, 1H); 7.29 (s, 1H); 11.58 (s, 1H).	457	3,4-Dichloro-*N*-[1-(6-chloro-4-cyanopyridin-2-yl)piperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide (Example 95)

Examples 89-95

The following compounds were made according to the method of Example 18, by coupling the amine derivative of tert-butyl 1-[4-(aminocarbonyl)-6-chloropyridin-2-yl]piperidin-4-ylcarbamate (Intermediate 16) with the relevant carboxylic acid given in the table below.

Example 89: 2-(4-{[(4-Acetyl-3-cyano-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-1-piperidinyl)-6-chloroisonicotinamide

Example 90: 2-Chloro-6-(4-{[(3-cyano-5-ethyl-1H-pyrrol-2-yl)carbonyl]amino}-1-piperidinyl)isonicotinamide

Example 91: 2-(4-{[(4-Bromo-3-cyano-5-ethyl-1H-pyrrol-2-yl)carbonyl]amino}-1-piperidinyl)-6-chloroisonicotinamide

Example 92: 2-(4-{[(4-Bromo-3-cyano-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-1-piperidinyl)-6-chloroisonicotinamide

Example 93: 2-Chloro-6-(4-{[(3-cyano-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-1-piperidinyl)isonicotinamide

Example 94: 2-Chloro-6-(4-{[(5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-1-piperidinyl) isonicotinamide

Example	Acid	^{1}H NMR δ	m/z
89	4-Acetyl-3-cyano-5-methyl-1H-pyrrole-2-carboxylic acid (commercially available)	1.36 (m, 2H); 1.79 (m, 2H); 2.32 (s, 6H); 2.89 (m, 2H); 3.88 (m, 1H); 4.12 (m, 2H); 6.86 (s, 1H); 7.07 (s, 1H); 7.47 (s, 1H); 7.92 (m, 2H); 12.36 (s, 1H)	429
90	3-Cyano-5-ethyl-1H-pyrrole-2-carboxylic acid (Intermediate 31)	0.96 (t, 3H); 1.29 (m, 2H); 1.70 (m, 2H); 2.90 (m, 2H); 3.14 (m, 2H); 3.81 (m, 1H); 4.02 (d, 2H); 6.14 (s, 1H); 6.77 (s, 1H); 6.96 (s, 1H); 7.50 (s, 1H); 7.65 (m, 1H); 11.70 (s, 1H).	401
91	4-Bromo-3-cyano-5-ethyl-1H-pyrrole-2-carboxylic acid (Intermediate 33)	1.14 (t, 3H); 1.51 (m, 2H); 1.89 (m, 2H); 2.61 (m, 2H); 3.12 (m, 2H); 4.22 (m, 3H); 6.93 (s, 1H); 7.17 (s, 1H); 7.69 (s, 1H); 8.05 (s, 1H); 8.17 (m, 1H); 12.39 (s, 1H).	481

Example	Acid	^{1}H NMR δ	m/z
92	4-Bromo-3-cyano-5-methyl-1H-pyrrole-2-carboxylic acid (Intermediate 34)	1.15 (m, 2H); 1.60 (m, 2H); 1.88 (m, 3H); 2.72 (m, 2H); 3.70 (m, 1H); 3.91 (m, 2H); 6.59 (s, 1H); 6.89 (s, 1H); 7.33 (s, 1H); 7.65 (d, 1H); 7.85 (m, 1H); 12.06 (s, 1H).	467
93	3-Cyano-5-methyl-1H-pyrrole-2-carboxylic acid (Intermediate 32)	1.31 (m, 2H); 1.74 (m, 2H); 2.07 (s, 3H); 2.96 (m, 2H); 3.89 (m, 1H); 4.07 (d, 2H); 6.09 (s, 1H); 6.78 (d, 1H); 7.00 (s, 1H); 7.58 (s, 1H); 7.71 (s, 1H); 7.99 (s, 1H); 11.88 (s, 1H).	389
94	5-Methyl-1H-pyrrole-2-carboxylic acid (Intermediate 29)	1.33 (m, 2H); 1.70 (m, 2H); 2.09 (s, 3H); 2.88 (m, 2H); 3.95 (m, 1H); 4.18 (m, 2H); 5.70 (s, 1H); 6.49 (d, 1H); 6.88 (s, 1H); 7.14 (s, 1H); 7.49 (m, 2H); 8.05 (s, 1H); 11.03 (s, 1H).	362

Example 95: 3,4-Dichloro-*N*-[1-(6-chloro-4-cyanopyridin-2-yl)piperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide

The title compound was prepared from 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid (**Intermediate 3**) and 2-(4-aminopiperidin-1-yl)-6-chloroisonicotinonitrile hydrochloride salt (**Intermediate 203**) in a manner analogous to **Example 18**.

MS (ES, M+H): 411,413 for $C_{17}H_{16}Cl_3N_5O$

Examples 96 and 97

The following compounds were made by an analogous method to **Example 18** using 1-(3-nitropyridin-2-yl)piperidin-4-amine hydrochloride salt (**Intermediate 39**) as a starting material.

Example 96: 4,5-Dichloro-N-[1-(3-nitro-2-pyridinyl)-4-piperidinyl]-1H-pyrrole-2-carboxamide

Example 97: 4-Bromo-5-isopropyl-N-[1-(3-nitro-2-pyridinyl)-4-piperidinyl]-1H-pyrrole-2-carboxamide

Example	Acid	^{1}H NMR δ	m/z
96	4,5, Dichloro-1H-pyrrole-2-carboxylic acid (Intermediate 61)	1.55 (m, 2H); 1.92 (m, 2H); 3.2 (m, 2H); 3.82 (m, 2H); 4.1 (m, 1H); 6.8 (d, 1H); 6.95 (m, 1H); 8.1 (d, 1H); 8.3 (d, 1H); 8.5 (d, 1H); 11.39 (s, 1H).	386
97	4-Bromo-5-isopropyl-1H-pyrrole-2-carboxylic acid (Intermediate 37)	1.33 (m, 6H); 1.71 (m, 2H); 2.03 (m, 2H); 3.26 (m, 3H); 3.89 (m, 2H); 4.18 (m, 1H); 6.9 (d, 1H); 7.01 (q, 1H); 8.09 (d, 1H); 8.40 (dd, 1H); 8.63 (dd, 1H); 11.77 (s, 1H)	435

Example 98: 3,4-Dichloro-N-[1-(6-chloro-2-pyridinyl)-4-piperidinyl]-5-methyl-1H-pyrrole-2-carboxamide

The title compound was synthesised by an analogous method to Example 42 starting from [1-(6-chloropyridin-2-yl)piperidin-4-yl]amine hydrochloride salt (Intermediate 212; 1 mmol) and 3,4-dichloro-5-methyl-1H-pyrrole-2-carboxylic acid (Intermediate 3, 1 mmol).

MS (ES): 410 (MH^+) for $C_{16}H_{17}Cl_3N_4O$

^{1}H NMR δ: 1.38 (m, 2H); 1.76 (m, 2H); 2.10 (s, 3H); 2.94 (m, 2H); 3.92 (m, 1H); 4.10 (m, 2H); 6.57 (d, 1H); 6.71 (d, 1H); 7.08 (d, 1H); 7.42 (m, 1H); 11.71 (s, 1H).

Example 99: 2-Chloro-6-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-1-piperidinyl)-N-[2-(4-morpholinyl)ethyl]isonicotinamide

The title compound was synthesised by an analogous method to Example 18 from 2-(4-aminopiperidin-1-yl)-6-chloro-*N*-(2-morpholin-4-ylethyl)isonicotinamide hydrochloride salt (Intermediate 218) and 3,4-dichloro-5-methyl-1H-pyrrole-2-carboxylic acid (Intermediate 3).

MS (ES): 543 (MH^+) for $C_{23}H_{29}Cl_3N_6O_3$

^{1}H NMR δ: 1.42 (m, 2H); 1.86 (m, 2H); 2.13 (s, 3H); 3.04 (m, 4H); 3.22 (m, 2H); 3.40 (m, 8H); 3.93 (m, 3H); 4.13 (m, 2H); 3.96 (m, 2H); 6.89 (s, 1H); 7.09 (s, 1H); 7.21 (d, 1H); 8.76 (d, 1H); 11.84 (s, 1H).

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Example 100: 2-Chloro-6-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-1-piperidinyl)-N-[3-(4-morpholinyl)propyl]isonicotinamide

The title compound was synthesised by an analogous method to **Example 99** starting from 2-(4-aminopiperidin-1-yl)-6-chloro-*N*-(3-morpholin-4-ylpropyl)isonicotinamide hydrochloride salt (**Intermediate 219**) and 3,4-dichloro-5-methyl-1H-pyrrole-2-carboxylic acid (**Intermediate 3**).

MS (ES): 559 (MH^+) for $C_{24}H_{31}Cl_3N_6O_3$

^{1}H NMR δ: 1.28 (m, 2H); 1.69 (m, 4H); 1.92 (s, 3H); 2.76 (m, 6H); 3.05 (m, 2H); 3.21 (m, 2H); 3.37 (d, 2H); 3.72 (m, 3H); 3.96 (m, 2H); 6.61 (s, 1H); 6.87 (s, 1H); 7.00 (s, 1H); 8.49 (d, 1H); 11.63 (s, 1H).

Example 101: 3,4-Dichloro-N-[1-(6-chloro-4-{[2-(methylamino)-2-oxoethyl]sulfanyl}-2-pyridinyl)-4-piperidinyl]-5-methyl-1H-pyrrole-2-carboxamide

The title compound was synthesised by an analogous method to **Example 18** starting from 2-{[2-(4-aminopiperidin-1-yl)-6-chloropyridin-4-yl]thio}-*N*-methylacetamide hydrochloride salt (**Intermediate 220**) and 3,4-dichloro-5-methyl-1H-pyrrole-2-carboxylic acid (**Intermediate 3**).

MS (ES): 492 (MH^+) for $C_{19}H_{22}Cl_3N_5O_2S$

^{1}H NMR δ: 1.41 (m, 2H); 1.79 (m, 2H); 2.11 (s, 3H); 2.54 (s, 3H); 2.92 (m, 2H); 3.64 (s, 2H); 3.89 (m, 2H); 4.12 (m, 1H); 6.51 (s, 1H); 6.59 (s, 1H); 7.11 (s 1H); 8.08 (m, 1H); 11.90 (s, 1H).

Example 102: 4-Bromo-N-[1-(6-chloro-4-{[2-(methylamino)-2-oxoethyl]sulfanyl}-2-pyridinyl)-4-piperidinyl]-5-methyl-1H-pyrrole-2-carboxamide

The title compound was prepared by analogous method to **Example 18** starting from 2-{[2-(4-aminopiperidin-1-yl)-6-chloropyridin-4-yl]thio}-*N*-methylacetamide hydrochloride salt (**Intermediate 220**) and 4-bromo-5-methyl-1H-pyrrole-2-carboxylic acid (**Intermediate 18**).

MS (ES): 502 (MH^+) for $C_{19}H_{23}BrClN_5O_2S$

^{1}H NMR δ: 1.33 (m, 2H); 1.70 (m, 2H); 2.07 (s, 3H); 2.41 (s, 3H); 2.58 (m, 2H); 3.64 (s, 2H); 3.89 (m, 2H); 4.17 (m, 1H); 6.42 (s, 1H); 6.62 (s, 1H); 6.71 (s, 1H); 7.67 (s 1H); 7.97 (m, 1H); 11.51 (s, 1H).

Example 103: 2-Cyano-6-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-1-piperidinyl)isonicotinamide

The title compound was synthesised by an analogous method to Example 18 starting from 2-(4-aminopiperidin-1-yl)-6-cyanoisonicotinamide hydrochloride salt (Intermediate 198) and 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid (Intermediate 3).

MS (ES): 423 (MH^+) for $C_{18}H_{18}Cl_2N_5O_2$

^{1}H NMR δ: 1.36 (m, 2H); 1.64 (m, 2H); 2.01 (s, 3H); 2.17 (m, 2H); 2.90 (m, 2H); 4.08 (m, 2H); 4.32 (m, 3H); 7.05 (d, 1H); 7.67 (s, 1H); 8.06 (s, 1H); 11.73 (s, 1H).

Example 104: 2-(4-{[(4-Bromo-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-1-piperidinyl)-3-hydroxy-1-pyridiniumolate

Anhydrous TEA (0.23 ml,1.65 mmol) was added to piperidin-4-yl-carbamic acid tert-butyl ester (300 mg,1.65 mmol) and thiophene-2-carboxylic acid-2-chloro-pyridinyl-3-yl ester (Intermediate 43, 119 mg, 0.5 mmol) in anhydrous NMP (2 ml). The mixture was heated in a pressure bottle at 165 °C for 18 h. The brown solution was partitioned between EtOAc and water and the organic phase was washed several times with water, dried over sodium sulphate and concentrated in vacuo to give 2-{4-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}pyridin-3-yl thiophene-2-carboxylate (170 mg, LCMS:420). This compound was treated with 4 N hydrochloric acid in dioxane for 45 minutes, solvent removed in vacuo and dried to give 2-(4-aminopiperidin-1-yl)pyridin-3-yl thiophene-2-carboxylate as a white solid. The white solid (0.421 mmol) was dissolved in anhydrous NMP (3 ml), and pentafluorophenyl 4-bromo-5-methyl-1H-pyrrole-2-carboxylate (Intermediate 17) (75 mg, 0.21 mmol) was added followed by TEA (64 µl, 0.46 mmol). The mixture was stirred at room temperature for 18 h and the crude mixture was filtered and purified by semi-preparative HPLC eluting with CH_3CN/H_2O (0.1% TFA) to give the title compound (30 mg) (spontaneous oxidation and hydrolysis to give the title compound occurred).

MS (ES): 398 (MH^+) for $C_{16}H_{19}BrN_4O_3$

^{1}H NMR δ: 1.29 (m, 2H); 1.47 (m, 2H); 1.82 (s, 3H); 3.72 (m, 1H); 3.90 (m, 2H); 6.47 (d, 1H); 6.78 (m, 1H); 7.07 (m, 1H); 7.42 (d, 1H); 7.57 (d, 1H); 9.16 (m, 3H); 11.32 (s, 1H).

Example 105: 4-Bromo-N-[1-(6-methoxy-2-pyridinyl)-4-piperidinyl]-5-methyl-1H-pyrrole-2-carboxamide

tert-Butyl [1-(6-chloropyridin-2-yl)piperidin-4-yl]carbamate (Intermediate 66) (300 mg, 0.99 mmol) was dissolved in 0.5 M solution of sodium methoxide in MeOH (9 ml, 4.45 mmol) at room temperature and the mixture was refluxed for 72 h. The solvent was removed in vacuo, extracted with EtOAc then washed with water. The organic phase was concentrated in vacuo and treated with 4 N hydrochloric acid in dioxane (10 ml) for 2 h. The solvent was removed in vacuo and dried to remove excess hydrochloric acid. The solid was dissolved in NMP (3 ml) and pentafluorophenyl 4-bromo-5-methyl-1H-pyrrole-2-carboxylate (Intermediate 17) (80 mg,0.216 mmol) and TEA (137 µl, 0.9 mmol) were added. The mixture was stirred at room temperature for 2 h and the mixture was purified by semi-preparative HPLC using a gradient of 15-95% CH_3CN/H_2O (0.1% TFA) to give the title compound (23 mg).

MS (ES): 395 (MH^+) for $C_{17}H_{21}BrN_4O_2$

^{1}H NMR δ: 1.31 (m, 2H); 1.67 (m, 2H); 2.03 (s, 3H);2.78 (m, 2H); 3.67 (s, 3H); 3.87 (m, 1H); 4.10 (d, 2H); 5.97 (d, 1H); 6.24 (d, 1H); 6.77 (d, 1H); 7.32 (t, 1H); 7.63 (d, 1H); 11.54 (s, 1H)

Example 106: 4-Bromo-N-{1-[6-chloro-4-(5-oxo-2,5-dihydro-1,3,4-oxadiazol-2-yl)pyridin-2-yl]piperidin-4-yl}-5-methyl-1H-pyrrole-2-carboxamide

TEA (0.10 ml, 0.70 mmol) and 5-[2-(4-aminopiperidin-1-yl)-6-chloropyridin-4-yl]-1,3,4-oxadiazol-2(5H)-one hydrochloride (Intermediate 51, 0.10 g, 0.33 mmol) were added to a solution of pentafluorophenyl 4-bromo-5-methyl-1H-pyrrole-2-carboxylate (Intermediate 17) (0.12 g, 0.33 mmol) in DMA (2 ml). The mixture was stirred at room temperature overnight and was purified by semi-preparative HPLC eluting with water/acetonitrile and TFA mixtures to give the title compound (18 mg).

MS (ES): 480 (MH^+) for $C_{18}H_{18}ClBrN_6O_3$

^{1}H NMR δ: 1.42 (m, 2H); 1.84 (m, 2H); 2.16 (s, 3H); 3.05 (m, 2H); 4.02 (m, 1H); 4.29 (d, 2H); 6.84 (d, 1H); 6.93 (s, 1H); 7.11 (s, 1H); 7.79 (d, 1H); 11.70 (s, 1H); 12.96 (s, 1H)

Example 107: 4-Bromo-N-{1-[(4-bromo-5-methyl-1H-pyrrol-2-yl)carbonyl]-4-piperidinyl}-5-methyl-1H-pyrrole-2-carboxamide

The title compound was obtained as a by-product during the synthesis of Example 44 (69 mg).

MS (ES):471 (MH^+) for $C_{17}H_{20}Br_2N_4O_2$

^{1}H NMR δ: 1.34 (m, 2H); 1.74 (m, 2H); 1.93 (s, 3H); 2.02 (s, 3H); 2.84 (m, 2H); 3.93 (m, 1H); 4.26 (d, 2H); 6.40 (d, 1H); 6.78 (d, 1H); 7.73 (d, 1H); 11.48 (s, 1H)

Example 108: 3,4-Dichloro-N-{1-[6-chloro-4-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2-pyridinyl]-4-piperidinyl}-5-methyl-1H-pyrrole-2-carboxamide

N, N'-Carbonyldimidazole (0.021 g, 0.13 mmol) was added to a stirred solution of 3,4-dichloro-N-{1-[6-chloro-4-(hydrazinocarbonyl)pyridin-2-yl]piperidin-4-yl}-5-methyl-1H-pyrrole-2-carboxamide (Example 309) (30 mg, 0.06 mmol) in DMF (2 ml). The mixture was stirred at room temperature for 6 h. The mixture was filtered and purified by semi-preparative HPLC eluting with CH_3CN/H_2O (0.1% TFA) mixtures to give the title compound (15 mg).

MS (ES): 471 (MH^+) for $C_{18}H_{17}Cl_2N_6O_3$

^{1}H NMR δ: 1.47 (m, 2H); 1.84 (m, 2H); 2.15 (m, 3H); 3.06 (m, 2H); 4.01 (m, 1H); 4.18 (d, 2H); 6.87 (s, 1H); 7.02 (s, 1H); 7.20 (d, 1H); 11.91 (s, 1H); 12.87 (s, 1H).

Example 109: 1-[4-(Aminocarbonyl)-6-chloro-2-pyridinyl]-4-piperidinyl 4-bromo-5-methyl-1H-pyrrole-2-carboxylate

2-chloro-6-(4-hydroxypiperidin-1-yl)isonicotinamide (Intermediate 62; 123 mg, 0.48 mmol), 4-bromo-5-methyl-1H-pyrrole-2-carboxylic acid (Intermediate 18)(98 mg, 0.48 mmol) and triphenylphosphine (138 mg, 0.53 mmol) were stirred in anhydrous THF and cooled to 0 °C. DEAD (83 µl, 0.53 mmol) was added and the mixture was stirred at room temperature for 18 h. The mixture was filtered, diluted with EtOAc and washed with water and dried over sodium sulphate and concentrated in vacuo. The crude product was purified by flash chromatography eluting with EtOAc/hexane (4:1) to afford the title compound (11 mg).

MS (ES): 441 (MH^+) for $C_{17}H_{18}BrClN_4O_3$

^{1}H NMR δ: 1.69 (m, 2H); 1.97 (m, 2H); 2.24 (s, 3H); 3.58 (m, 2H); 3.91 (m, 2H); 5.18 (m, 1H); 6.86 (d, 1H); 7.03 (s, 1H); 7.25 (s, 1H); 7.73 (d, 1H); 8.17 (s, 1H); 12.08 (s, 1H)

Example 110: 1-[6-Chloro-4-(1H-tetrazol-5-yl)pyridin-2-yl]piperidin-4-yl 4-bromo-5-methyl-1H-pyrrole-2-carboxylate

The title compound was synthesised by an analogous method to Example 48 starting from 1-(6-chloro-4-cyanopyridin-2-yl)piperidin-4-yl-4-bromo-5-methyl-1H-pyrrole-2-carboxylate (Example 330).

MS (ES): 468 (MH^+) for $C_{17}H_{17}BrClN_7O_2$

^{1}H NMR δ: 1.69 (m, 2H); 1.97 (m, 2H); 2.24 (s, 3H); 3.58 (m, 2H); 3.91 (m, 2H); 5.18 (m, 1H); 6.86 (d, 1H); 7.03 (s, 1H); 7.25 (s, 1H); 7.73 (d, 1H); 8.17 (s, 1H); 12.08 (s, 1H)

Example 111: 3,4-Dichloro-N-{1-[6-chloro-4-(1,2,4-oxadiazol-3-yl)-2-pyridinyl]-4-piperidinyl}-5-methyl-1H-pyrrole-2-carboxamide

Diisopropylethylamine (0.04 ml, 0.46 mmol), HOAT (0.03 g, 0.23 mmol) and HATU (0.08 g, 0.23 mmol) were added to a stirred solution of 3,4-dichloro-5-methyl-1H-pyrrole-2-carboxylic acid (Intermediate 3, 0.04 g, 0.23 mmol) in DMF (2 ml) at room temperature. The resulting solution was stirred for 5 minutes and 1-[6-chloro-4-(1,2,4-oxadiazol-3-yl)pyridin-2-yl]piperidin-4-amine hydrochloride (Intermediate 56) (0.074 g, 0.23 mmol) was added. The mixture was stirred at room temperature for 1 h and was filtered and purified by semi-preparative HPLC eluting with CH_3CN/H_2O (0.1% TFA) mixtures to give the title compound (100 mg).

MS (ES):457 (MH^+) for $C_{18}H_{17}Cl_3N_6O_2$

^{1}H NMR δ: 1.50 (m, 2H); 1.84 (m, 2H); 2.13 (s, 3H); 3.09 (m, 2H); 4.04 (m, 1H); 4.20 (d, 2H); 7.08 (s, 1H); 7.20 (d, 1H); 7.28 (s, 1H); 9.80 (s, 1H); 11.91 (s, 1H)

Example 112: 1-[6-Chloro-4-(1,2,4-oxadiazol-3-yl)-2-pyridinyl]-4-piperidinyl 3,4-dichloro-5-methyl-1H-pyrrole-2-carboxylate

$BF_3.Et_2O$ (0.1 ml) was added to a solution of 1-{4-[amino(hydroxyimino)methyl]-6-chloropyridin-2-yl}piperidin-4-yl 3,4-dichloro-5-methyl-1H-pyrrole-2-carboxylate (Example 114) (0.07 g, 0.15 mmol) in 1,1,1-triethoxyethane (1.0 ml) at room temperature. The mixture was stirred at room temperature for 1 h. The mixture was purified by semi-preparative HPLC eluting with CH_3CN/H_2O (0.1% TFA) mixtures to give the title compound (21 mg).

MS (ES):458 (MH^+) for $C_{18}H_{16}Cl_3N_5O_3$

^{1}H NMR δ: 1.66 (m, 2H); 1.90 (m, 2H); 2.17 (s, 3H); 3.67 (m, 2H); 3.79 (m, 2H); 5.18 (m, 1H); 7.09 (s, 1H); 7.31 (s, 1H); 9.80 (s, 1H); 12.23 (s, 1H)

Example 113: 2-Chloro-6-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-1-piperidinyl)-N-methoxyisonicotinamide

The title compound was synthesised by an analogous method to Example 45 starting from 2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)isonicotinic acid (Example 153) and methoxylamine hydrochloride.

MS (ES): 462 (MH^+) for $C_{18}H_{20}Cl_3N_5O_3$

^{1}H NMR δ: 1.46 (m, 2H); 1.84 (m, 2H); 2.15 (s, 3H); 3.05 (m, 2H); 3.68 (s, 3H); 4.00 (m, 1H); 4.16 (d, 2H); 6.82 (s, 1H); 7.04 (s, 1H); 7.1 9 (d, 1H); 11.91 (s, 1H)

Example 114: 1-{4-[Amino(hydroxyimino)methyl]-6-chloro-2-pyridinyl}-4-piperidinyl 3,4-dichloro-5-methyl-1H-pyrrole-2-carboxylate

The title compound was synthesized by an analogous method to Example 47 from 1-(6-chloro-4-cyanopyridin-2-yl)piperidin-4-yl 3,4-dichloro-5-methyl-1H-pyrrole-2-carboxylate (Example 308).

MS (ES): 446 (MH^+) for $C_{17}H_{18}Cl_3N_5O_3$

^{1}H NMR δ: 1.48 (m, 2H); 1.72 (m, 2H); 2.04 (s, 3H); 3.43 (m, 2H); 3.60 (d, 2H); 5.01 (m, 1H); 6.72 (s, 1H); 6.90 (s, 1H); 7.35 (s, 2H); 9.91 (s, 1H); 12.09 (s, 1H)

Example 115: N-[1-(4-Acetyl-6-chloro-2-pyridinyl)-4-piperidinyl]-3,4-dichloro-5-methyl-1H-pyrrole-2-carboxamide

The title compound was synthesized by an analogous method to Example 18 starting from 1-[2-(4-aminopiperidin-1-yl)-6-chloropyridin-4-yl]ethanone hydrochloride salt (Intermediate 197) and 3,4-dichloro-5-methyl-1H-pyrrole-2-carboxylic acid (Intermediate 3).

MS (ES): 431 (MH^+) for $C_{18}H_{19}Cl_3N_4O_2$

^{1}H NMR δ: 1.46 (m, 2H); 1.84 (m, 2H); 2.14 (s, 3H); 2.55 (s, 3H); 3.05 (m, 2H); 4.00 (m, 1H); 4.21 (d, 2H); 6.94 (s, 1H); 7.18 (s, 1H); 7.21 (s, 1H); 11.91 (s, 1H)

Example 116: N-[1-(4-Acetyl-6-chloro-2-pyridinyl)-4-piperidinyl]-4-bromo-5-methyl-1H-pyrrole-2-carboxamide

The title compound was synthesized by an analogous method to Example 42 starting from 1-1-[2-(4-aminopiperidin-1-yl)-6-chloropyridin-4-yl]ethanone hydrochloride salt (Intermediate 197) and 4-Bromo-5-methyl-1H-pyrrole-2-carboxylic acid (Intermediate 18).

MS (ES): 441 (MH^+) for $C_{18}H_{20}BrClN_5O_2$

^{1}H NMR δ: 1.38 (m, 2H); 1.80 (m, 2H); 2.11 (s, 3H); 2.57 (s, 3H); 2.99 (m, 2H); 3.97 (m, 1H); 4.26 (d, 2H); 6.78 (s, 1H); 6.94 (s, 1H); 7.18 (s, 1H); 7.73 (d. 1H); 11.64 (s, 1H)

Example 117: 2-Chloro-N-methoxy-6-(4-{[(5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-1-piperidinyl)isonicotinamide

The title compound was synthesised by an analogous method to **Example 45** starting from 2-chloro-6-(4-{[(5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)isonicotinic acid (**Example 332**) and methoxylamine hydrochloride.

MS (ES): 392 (MH^+) for $C_{18}H_{22}BrClN_5O_3$

^{1}H NMR δ: 1.36 (m, 2H); 1.76 (m, 2H); 2.12 (s, 3H); 2.96 (m, 2H); 3.66 (s, 3H); 3.96 (m, 1H); 4.20 (m, 2H); 5.72 (s, 3H); 6.59 (s, 1H); 6.81 (s, 1H); 7.03 (s, 1H); 7.56 (d 1H); 11.11 (s, 1H); 11.92 (s, 1H)

Example 118: N-{1-[6-Amino-2-(methylsulfanyl)-4-pyrimidinyl]-4-piperidinyl}-3,4-dichloro-5-methyl-1H-pyrrole-2-carboxamide

Diisopropylethylamine (0.21 ml, 1.25 mmol) and HATU (0.239 g, 0.63 mmol) were added to a stirred solution of 3,4-dichloro-5-methyl-1H-pyrrole-2-carboxylic acid (**Intermediate 3**) (0.122 g, 0.63 mmol) in DMF (2 ml). The resultant solution was stirred for 5 minutes, 6-(4-amino-piperidin-1-yl)-2-(methylthio)pyrimidin-4-amine hydrochloride (**Intermediate 46**) (0.2 g, 0.63 mmol) was added and the mixture was stirred at room temperature for 18 h. The crude mixture was filtered and purified by semi-preparative HPLC eluting with CH_3CN/H_2O (0.1% TFA) to give the title product (42 mg).

MS (ES): 417 (MH^+) for $C_{16}H_{20}Cl_2N_6OS$

^{1}H NMR δ: 1.22 (m, 2H); 1.61 (m, 2H); 1.92 (s, 3H); 2.84 (m, 2H); 3.78 (m 4H); 5.25 (s, 1H); 5.52 (s, 1H); 6.50 (m, 2H); 11.72 (s, 1H)

Example 119: N-{1-[6-(Acetylamino)-2-(methylsulfanyl)-4-pyrimidinyl]-4-piperidinyl}-3,4-dichloro-5-methyl-1H-pyrrole-2-carboxamide

The title compound was synthesised by an analogous method to **Example 118** starting from N-[6-(4-aminopiperidin-1-yl)-2-(methylthio)pyrimidin-4-yl]acetamide hydrochloride (**Intermediate 69**) and 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid (**Intermediate 3**).

MS (ES): 456 (MH^+) for $C_{16}H_{20}Cl_2N_6OS$

^{1}H NMR δ: 1.39 (m, 2H); 1.78 (m, 2H); 1.99 (s, 3H); 2.10 (s, 3H); 2.36 (s, 3H); 2.99 (m, 2H); 3.95 (m, 1H); 4.23 (m, 2H); 7.09 (s, 1H); 7.15 (d, 1H); 7.50 (q, 1H); 8.46 (dd, 1H); 10.31 (s, 1H); 11.88 (s, 1H)

Example 120: N-{1-[6-(Acetylamino)-2-(methylsulfinyl)-4-pyrimidinyl]-4-piperidinyl}-3,4-dichloro-5-methyl-1H-pyrrole-2-carboxamide

mCPBA (0.11 g, 0.133 mmol) was added to a stirred solution of N-{1-[6-(acetylamino)-2-(methylthio)pyrimidin-4-yl]piperidin-4-yl}-3,4-dichloro-5-methyl-1H-pyrrole-2-carboxamide (Example 119), 0.15 g, 0.33 mmol) in DCM (2 ml). The mixture was stirred at room temperature for 3 hr and was purified by semi-preparative HPLC eluting with CH_3CN/H_2O (0.1% TFA) to afford the title compound (5 mg).

MS (ES): 473 (MH^+) for $C_{18}H_{22}Cl_2N_6O_3S$

^1H NMR δ: 1.42 (m, 2H); 1.86 (m, 2H); 2.06 (s, 3H); 2.13 (s, 3H); 2.76 (s, 3H); 4.02 (m, 4H); 7.21 (d, 1H); 7.42 (s, 1H); 10.81 (s, 1H); 11.94 (s, 1H)

Example 121: N-{1-[6-(Acetylamino)-2-(methylsulfonyl)pyrimidin-4-yl]piperidin-4-yl}-3,4-dichloro-5-methyl-1H-pyrrole-2-carboxamide

The title compound was synthesised by an analogous method to Example 120 starting from N-{1-[6-(acetylamino)-2-(methylsulfinyl)-4-pyrimidinyl]-4-piperidinyl}-3,4-dichloro-5-methyl-1H-pyrrole-2-carboxamide (Example 120).

MS (ES): 489 (MH^+) for $C_{18}H_{22}Cl_2N_6O_4S$

^1H NMR δ: 1.48 (m, 2H); 1.87 (m, 2H); 2.08 (s, 3H); 2.14 (s, 3H); 3.13-3.26 (m, 2H); 3.29 (s, 3H); 4.04 (m, 2H); 4.18 (m, 1H); 7.20 (d, 1H); 7.51 (s, 1H); 10.89 (s, 1H); 11.93 (s, 1H)

Example 122: 4-Bromo-5-methyl-*N*-{1-[(1-methyl-1*H*-imidazol-2-yl)methyl]piperidin-4-yl}-1*H*-pyrrole-2-carboxamide

Title compound was synthesized by an analogous method to Example 1 by coupling 4-bromo-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (Intermediate 57) with 1-methyl-1*H*-imidazole-2-carbaldehyde (commercially available).

MS (ESP): 380.1 (M+H) for $C_{16}H_{22}BrN_5O$

^1H NMR δ: 1.45 (m, 2H); 1.72 (d, 2H); 2.04 (m, 2H); 2.12 (s, 3H); 2.75 (d, 2H); 3.50 (s, 2H); 3.65 (s, 3H); 3.72 (m, 1H); 6.74 (s, 1H); 6.81 (s, 1H); 7.00 (s, 1H); 7.69 (d, 1H); 11.62 (s, 1H).

Example 123: Ethyl 2-(4-{[(4-bromo-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-1,3-thiazole-4-carboxylate

4-Bromo-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (Intermediate 57, 0.41 g, 1.27 mmol), sodium bicarbonate (0.42 g, 1.78 mmol) and ethyl 2-bromo-1,3-thiazole-4-carboxylate (0.30 g, 1.27 mmol) were combined in DMF (5 ml) under nitrogen and heated at 50 °C for 18 h. The mixture was cooled to room temperature and diluted with EtOAc (75 ml) and water (10 ml). The organic layer was separated, dried over sodium sulphate, filtered and concentrated under vacuum. Purification by flash chromatography (MeOH/ DCM, 10%) provided 275 mg of the title compound.

MS (ESP): 439.2 (M-H) for $C_{17}H_{21}BrN_4O_3S$

^{1}H NMR δ: 1.28 (t, 3H); 1.56 (m, 2H); 1.87 (d, 2H); 2.14 (s, 3H); 3.18 (t, 2H); 3.81-4.10 (m, 3H); 4.24 (q, 2H); 6.83 (s, 1H); 7.71 (s, 1H); 7.81 (d, 1H); 11.54 (s, 1H).

Example 124: 4-Bromo-5-methyl-*N*-[1-(1,3-thiazol-2-yl)piperidin-4-yl]-1*H*-pyrrole-2-carboxamide

Title compound was synthesized by an analogous method to **Example 123** by coupling 4-bromo-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (Intermediate 57) with 2-bromo-1,3-thiazole (commercially available).

MS (ESP): 369.1 (M+H) for $C_{14}H_{17}BrN_4OS$

^{1}H NMR δ: 1.57 (m, 2H); 1.86 (d, 2H); 2.14 (s, 3H); 3.16 (t, 2H); 3.87-4.10 (m, 3H); 6.82 (s, 1H); 6.86 (s, 1H); 7.19 (s, 1H); 7.81 (d, 1H); 11.68 (s, 1H).

Example 125: *N*-[1-(1,3-Benzothiazol-2-yl)piperidin-4-yl]-4-bromo-5-methyl-1*H*-pyrrole-2-carboxamide

Title compound was synthesized by an analogous method to **Example 123** by coupling 4-bromo-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (Intermediate 57) with 2-bromo-1,3-benzothiazole (commercially available).

MS (ESP): 419.1 (M+H) for $C_{18}H_{19}BrN_4OS$

^{1}H NMR δ: 1.58 (q, 2H); 1.91 (d, 2H); 2.14 (s, 3H); 3.31 (t, 2H); 3.95-4.15 (m, 3H); 6.82 (s, 1H); 7.07 (t, 1H); 7.28 (t, 1H); 7.47 (d, 1H); 7.76-7.82 (m, 2H); 11.70 (s, 1H).

Example 126: Ethyl 5-(4-{[(4-bromo-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-1,3,4-thiadiazole-2-carboxylate

Title compound was synthesized by an analogous method to Example 123 by coupling 4-bromo-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (Intermediate 57) with 5-chloro-[1,3,4]thiadiazole-2-carboxylic acid ester (Demaree, P et. al. *Can. J. Chem* 1977, 55(2) 243-50).

MS (ESP): 442.0 (M+H) for $C_{16}H_{20}BrN_5O_3S$

^{1}H NMR δ: 1.32 (t, 3H); 1.58 (m, 2H); 1.92 (d, 2H); 2.14 (s, 3H); 3.41 (t, 2H); 3.85-4.10 (m, 3H); 4.36 (q, 2H); 6.82 (s, 1H); 7.82 (d, 1H); 11.70 (s, 1H).

Example 127: 2-(4-{[(4-Bromo-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxamide

Title compound was synthesized by an analogous method to Example 123 by coupling 4-bromo-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (Intermediate 57) with 2-bromo-1,3-thiazole-5-carboxamide (*J. Am. Chem. Soc.* 1952, *74*, 5799).

MS (ESP): 412.0 (M+H) for $C_{15}H_{18}BrN_5O_2S$

^{1}H NMR δ: 1.54 (m, 2H); 1.86 (d, 2H); 2.14 (s, 3H); 3.21 (t, 2H); 3.87-4.10 (m, 3H); 6.82 (s, 1H); 7.16 (s, 1H); 7.64 (s, 1H); 7.79 (s, 1H); 7.81 (d, 1H); 11.69 (s, 1H).

Example 128: 5-(4-{[(4-Bromo-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3,4-thiadiazole-2-carboxylic acid

Title compound was synthesized from ethyl 5-(4-{[(4-bromo-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3,4-thiadiazole-2-carboxylate (Example 126) by an analogous method to Example 31.

MS (ESP): 414.0 (M+H) for $C_{14}H_{16}BrN_5O_3S$

^{1}H NMR δ: 1.58 (m, 2H); 1.87 (d, 2H); 2.14 (s, 3H); 3.28 (t, 2H); 3.88 (d, 2H); 4.01 (m, 1H); 6.82 (s, 1H); 7.84 (d, 1H); 8.82 (s, 1H); 11.71 (s, 1H).

Example 129: 2-(4-{[(4-Bromo-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-4-carboxylic acid

Title compound was synthesized from ethyl 2-(4-{[(4-bromo-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-4-carboxylate (Example 123) by an analogous method to Example 31.

MS (ESP): 413.0 (M+H) for $C_{15}H_{17}BrN_4O_3S$

^{1}H NMR δ: 1.56 (m, 2H); 1.86 (d, 2H); 2.14 (s, 3H); 3.17 (t, 2H); 3.90 (d, 2H); 4.00 (m, 1H); 6.83 (s, 1H); 7.64 (s, 1H); 7.85 (d, 1H); 8.20 (s, 1H); 11.72 (s, 1H).

Example 130: 4-Bromo-*N*-[1-(4-cyano-1,3-thiazol-2-yl)piperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide

Title compound was synthesized by an analogous method to Example 123 by coupling 4-bromo-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (Intermediate 57) with 2-bromo-1,3-thiazole-4-carbonitrile (*Tetrahedron Lett.* 1977, *18 (21)*, 1813).

MS (ESP): 394.0 (M+H) for $C_{15}H_{16}BrN_5OS$

^{1}H NMR δ: 1.56 (m, 2H); 1.88 (d, 2H); 2.14 (s, 3H); 3.24 (t, 2H); 3.89 (d, 2H); 4.02 (m, 1H); 6.82 (s, 1H); 7.81 (d, 1H); 7.98 (s, 1H); 11.69 (s, 1H).

Example 131: 4-Bromo-5-methyl-*N*-[1-(1-methyl-1*H*-tetrazol-5-yl)piperidin-4-yl]-1*H*-pyrrole-2-carboxamide

Title compound was synthesized by an analogous method to Example 123 by coupling 4-bromo-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (Intermediate 57) with 5-bromo-1-methyl-1*H*-tetrazole (*Can. J. Chem.* 1971, *49*, 2139).

MS (ESP): 368.0 (M+H) for $C_{13}H_{18}BrN_7O$

^{1}H NMR δ: 1.66 (m, 2H); 1.85 (d, 2H); 2.14 (s, 3H); 3.10 (t, 2H); 3.64 (d, 2H); 3.89 (s, 3H); 3.99 (m, 1H); 6.85 (s, 1H); 7.84 (d, 1H); 11.68 (s, 1H).

Example 132: 4-Bromo-*N*-[1-(5-cyano-1,3-thiazol-2-yl)piperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide

Title compound was synthesized by an analogous method to Example 123 by coupling 4-bromo-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (Intermediate 57) with 2-bromo-1,3-thiazole-5-carbonitrile (*Tetrahedron Lett.* 1977, *21*, 1813).

MS (ESP): 394.0 (M+H) for $C_{15}H_{16}BrN_5OS$

^{1}H NMR δ: 1.56 (m, 2H); 1.90 (d, 2H); 2.14 (s, 3H); 3.35 (t, 2H); 3.97 (d, 2H); 4.05 (m, 1H); 6.82 (s, 1H); 7.82 (d, 1H); 8.04 (s, 1H); 11.70 (s, 1H).

Example 133: 2-(4-{[(4-Bromo-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-4-carboxamide

Title compound was synthesized by an analogous method to Example 123 by coupling 4-bromo-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (Intermediate 57) with 2-bromo-1,3-thiazole-4-carboxamide (*J. Am. Chem. Soc.* 1952, *74*, 5799).

MS (ESP): 412.0 (M+H) for $C_{15}H_{18}BrN_5O_2S$

^{1}H NMR δ: 1.57 (m, 2H); 1.86 (d, 2H); 2.14 (s, 3H); 3.18 (t, 2H); 3.90-4.10 (m, 3H); 6.82 (s, 1H); 7.39 (s, 1H); 7.40 (s, 1H); 7.46 (s, 1H); 7.81 (d, 1H); 11.68 (s, 1H).

Example 134: Methyl 6-chloro-4-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)quinoline-2-carboxylate

A solution of 3,4-dichloro-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (Intermediate 1; 59 mg, 0.21 mmol), methyl 4,6-dichloroquinoline-2-carboxylate (FR Alexandre, et. al., Tetrahedron 2003, 59: 1413; 57 mg 0.22 mmol) and diisopropylethylamine (0.10 ml) in DMF (2.0 ml) was heated in a microwave reactor to 180 °C for 30 minutes. The reaction was diluted with 50 ml of EtOAc, then extracted with 25 ml of 1 N NaOH, 2 x 25 ml of water, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude solid was flash chromatographed through neutral silica gel using EtOAc as the eluent to give 37 mg of the title compound; crystallization from MeOH gave a white solid.

MS(ES+): 494.95/496.95/498.90 for $C_{22}H_{21}Cl_3N_4O_3$

^{1}H NMR δ: 1.85 (m, 2H); 1.954 (m, 2H); 2.10 (s, 3H); 2.98 (m, 2H); 3.49 (m, 2H); 3.85 (s, 3H); 3.97 (m, 1H); 7.24 (d, 1H, J = 7.91); 7.50 (s, 1H); 7.75 (m, 1H); 7.87 (s, 1H); 8.02 (d, 1H, J = 9.04); 11.93 (s, 1H).

Example 135: 4-Bromo-5-methyl-*N*-(1-{[4-(trifluoromethyl)-1*H*-indol-2-yl]carbonyl}piperidin-4-yl)-1*H*-pyrrole-2-carboxamide

Title compound was synthesized by an analogous method to Intermediate 2 by coupling 4-bromo-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (Intermediate 57) with 4-(trifluoromethyl)-1*H*-indole-2-carboxylic acid (*J. Am. Chem. Soc.* 1957, *79*, 1745).

MS (ESP): 497.0 (M+H) for $C_{21}H_{20}BrF_3N_4O_2$

^{1}H NMR δ: 1.50 (q, 2H); 1.93 (d, 2H); 2.14 (s, 3H); 3.23 (m, 2H); 4.07 (m, 1H); 4.40 (m, 2H); 6.77 (s, 1H); 6.83 (s, 1H); 7.37 (t, 1H); 7.46 (d, 1H); 7.74 (d, 1H); 7.83 (d, 1H); 11.70 (s, 1H); 12.23 (s, 1H).

Example 136: 4-Bromo-N-{1-[6-chloro-4-(1H-1,2,3,4-tetraazol-5-yl)-2-pyridinyl]-4-piperidinyl}-N,5-dimethyl-1H-pyrrole-2-carboxamide

The title compound was synthesised by an analogous method to Example 18 starting from 1-[6-chloro-4-(1*H*-tetrazol-5-yl)pyridin-2-yl]-*N*-methylpiperidin-4-amine (Intermediate 64) and pentafluorophenyl 4-bromo-5-methyl-1H-pyrrole-2-carboxylate (Intermediate 17).

MS (ES): 481 (M+H) for $C_{18}H_{20}BrIN_8O$

^{1}H NMR δ: 1.54 (m, 4H); 2.04 (s, 3H); 2.72 (s, 3H); 2.95 (t, 2H); 4.21 (d, 2H); 4.46 (t, 1H); 6.30 (s, 1H); 7.01 (s, 1H); 7.17 (s, 1H); 11.29 (s, 1H).

Example 137: 4-Bromo-N-{1-[6-chloro-4-(2-methyl-2H-1,2,3,4-tetraazol-5-yl)-2-pyridinyl]-4-piperidinyl}-5-methyl-1H-pyrrole-2-carboxamide

The title compound was synthesised by an analogous method to Example 42 starting from 1-[6-chloro-4-(1-methyl-1*H*-tetrazol-5-yl)pyridin-2-yl]-*N*-methylpiperidin-4-amine (Intermediate 65) and pentafluorophenyl 4-bromo-5-methyl-1H-pyrrole-2-carboxylate (Intermediate 17).

MS (ES): 481 (M+H) for $C_{18}H_{20}BrClN_8O$

^{1}H NMR δ: 1.49 (m, 2H); 1.87 (m, 2H); 2.14 (s, 3H); 3.11 (m, 2H); 4.06 (m, 1H); 4.31 (m, 2H); 4.34 (s, 3H); 6.82 (s, 1H); 7.07 (s, 1H); 7.16 (s, 1H); 7.78 (d, 1H); 11.68 (s, 1H).

Example 138: Ethyl 2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-4-(hydroxymethyl)-1,3-thiazole-5-carboxylate

Ethyl 2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-4-(methoxymethyl)-1,3-thiazole-5-carboxylate (Example 276; 50 mg; 0.105 mmol) was dissolved in anhydrous DCM and cooled to –78 °C. 1 M Boron tribromide/ DCM (105 µl; 0.105 mmol) was added dropwise. The mixture was stirred at -78 °C for 15 min, then at room temperature for 4 h. The mixture was diluted with DCM, washed with water and dried over Na_2SO_4. Organic phase was concentrated in vacuo giving the title compound (20 mg).

MS (ES) MH+: 461 for $C_{18}H_{22}Cl_2N_4O_4S$

^{1}H NMR δ: 1.16-1.19 (t, 3H); 1.56-1.61 (brs, 2H); 1.84-1.87 (d, 2H); 2.11 (s, 3H); 3.24 (t, 2H); 3.88 (d, 2H); 4.00 (brs, 1H); 4.11-4.13 (q, 2H); 4.55 (s, 1H); 7.21-7.23 (d, 1H); 11.91 (s, 1H).

Example 139: 2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-[2-(dimethylamino)ethoxy]isonicotinic acid

Sodium (155 mg, 6.74 mmol) and 2-(dimethylamino)ethanol (0.677 ml, 6.74 mmol) were stirred together in DMF (1.5 ml). Methyl 2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)isonicotinate (Example 333; 200 mg, 0.449 mmol) was added. The reaction mixture was refluxed overnight, then brought to room temperature and acidified with 10% HCl. The reaction mixture was partitioned between EtOAc and water. The organic layer was washed with water, then with brine, dried over sodium sulfate and concentrated to give the desired product. The crude product was purified by reversed phase HPLC eluting with water/acetonitrile/TFA mixtures to afford the desired product (60 mg).

MS (ES): 484 (MH^+) for $C_{21}H_{27}Cl_2N_5O_4$

^{1}H NMR δ: 1.57 (m, 2H); 1.88 (m, 2H); 2.17 (s, 3H); 2.85 (s, 6H); 3.09 (m, 2H); 4.07 (m, 1H); 4.24 (m, 2H); 4.55 (m, 2H); 6.46 (s, 1H); 6.83 (s, 1H); 7.20 (d, 1H); 9.52 (brs, 1H); 11.98 (s, 1H); 13.41 (brs, 1H)

Examples 140-147

The following compounds were synthesized by an analogous method to Example 139, starting from methyl 2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)isonicotinate (Example 333) and the commercially available alcohols given in the table below.

Example 140: 2-Butoxy-6-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)isonicotinic acid

Example 141: 2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-(2-methoxyethoxy)isonicotinic acid

Example 142: 2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-(2-hydroxyethoxy)isonicotinic acid Example 143: 2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-[2-(2-hydroxyethoxy)ethoxy]isonicotinic acid

Example 144: 2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-[2-(2-methoxyethoxy)ethoxy]isonicotinic acid

Example 145: 2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-(2-isopropoxyethoxy)isonicotinic acid

Example 146: 2-[2-(Allyloxy)ethoxy]-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl) carbonyl]amino}piperidin-1-yl)isonicotinic acid

Example 147: 2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-(2-morpholin-4-ylethoxy)isonicotinic acid

Examples	Alcohol	^{1}H NMR δ	m/z
140	butan-1-ol	0.94 (t, 3H); 1.44 (m, 2H); 1.61 (m, 2H); 1.76 (m, 2H); 1.95 (m, 2H); 2.22 (s, 3H); 3.15 (m, 2H); 4.05 (m, 1H); 4.24 (m, 2H); 6.38 (s, 1H); 6.76 (s, 1H); 7.23 (d, 1H); 11.98 (s, 1H); 13.31 (brs, 1H)	469
141	2-methoxy ethanol	1.38 (m, 2H); 1.67 (m, 2H); 1.98 (s, 3H); 2.84 (m, 2H); 3.10 (s, 3H); 3.45 (m, 2H); 3.85 (m, 2H); 3.99 (m, 2H); 4.17 (m, 2H); 6.19 (s, 1H); 6.57 (s, 1H); 7.02 (d, 1H); 11.76 (s, 1H); 13.12 (s, 1H).	471
142	ethylene glycol	1.56 (m, 2H); 1.60 (m, 2H); 2.17 (s, 3H); 2.57 (m, 2H); 3.69 (m, 2H); 4.04 (m, 1H); 4.24 (m, 4H); 6.38 (s, 1H); 6.75 (s, 1H); 7.21 (d, 1H); 11.96 (s, 1H); 13.31 (brs, 1H)	457
143	2,2'-oxydiethanol	1.63 (m, 2H); 1.93 (m, 2H); 2.24 (s, 3H); 3.13 (m, 2H); 3.53 (m, 4H); 3.79 (m, 2H); 4.07 (m, 1H); 4.25 (m, 2H); 4.39 (m, 2H); 6.45 (s, 1H); 6.82 (s, 1H); 7.27 (d, 1H); 12.02 (s, 1H); 13.38 (brs, 1H).	501
144	2-(2-methoxy ethoxy) ethanol	1.56 (m, 2H); 1.85 (m, 2H); 2.16 (s, 3H); 3.06 (m, 2H); 3.23 (s, 3H); 3.45 (m, 2H); 3.54 (m, 2H); 3.71 (m, 2H); 4.03 (m, 1H); 4.18 (m, 2H); 6.37 (s, 1H); 6.75 (s, 1H); 7.20 (d, 1H); 11.95 (s, 1H); 13.31 (brs, 1H).	499
145	2-isopropoxy ethanol	1.31 (m, 6H); 1.79 (m, 2H); 2.08 (m, 2H); 2.40 (s, 3H); 3.29 (m, 2H); 3.79 (q, 1H); 3.90 (m, 2H); 4.26 (m, 1H); 4.45 (m, 2H); 4.53 (m, 2H); 6.60 (s, 1H); 6.98 (s, 1H); 7.43 (d, 1H); 12.18 (s, 1H); 13.54 (brs, 1H).	515

Examples	Alcohol	^{1}H NMR δ	m/z
146	2-(allyloxy) ethanol	1.67 (m, 2H); 1.96 (m, 2H); 2.28 (s, 3H); 3.17 (m, 2H); 3.81 (t, 2H); 4.09 (m, 2H); 4.11 (m, 1H); 4.29 (m, 2H); 4.46 (m, 2H); 5.26 (dd, 1H); 5.34 (dd, 1H); 5.98 (m, 1H); 6.49 (s, 1H); 6.86 (s, 1H); 7.43 (d, 1H); 12.06 (s, 1H); 13.41 (brs, 1H).	497
147	2-morpholin-4-ylethanol	1.54 (m, 2H); 1.65 (m, 1H); 1.87 (m, 2H); 2.19 (s, 3H); 2.46 (m, 4H); 2.67 (m, 2H); 2.99 (m, 1H); 3.05 (m, 2H); 3.57 (m, 4H); 4.04 (m, 1H); 4.18 (m, 2H); 4.33 (m, 2H); 6.36 (s, 1H); 6.75 (s, 1H); 7.37 (d, 1H).	526

Example 148: 2-*tert*-Butoxy-2-oxoethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-(2-methoxyethoxy)isonicotinate

tert-Butyl chloroacetate (28 mg, 0.190 mmol) was added to a solution of 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-(2-methoxyethoxy)isonicotinic acid (60 mg, 0.127 mmol) (Example 141) in DMF (2 ml), followed by the addition of caesium fluoride (47 mg, 0.313 mmol). The resulting mixture was stirred at room temperature for 24 hr. The mixture was filtered and purified by HPLC eluting with water/acetonitrile/TFA mixtures to afford the desired product (20 mg).

MS (ES): 585 (MH^+) for $C_{26}H_{34}Cl_2N_4O_7$

^{1}H NMR δ: 0.96 (s, 9H); 1.37 (m, 2H); 1.67 (m, 2H); 1.97 (s, 3H); 2.85 (m, 2H); 3.09 (s, 3H); 3.44 (m, 2H); 3.84 (m, 1H); 3.99 (m, 2H); 4.14 (m, 3H); 5.73 (s, 1H); 6.16 (s, 1H); 6.55 (s, 1H); 7.00 (d, 1H); 11.75 (s, 1H).

Example 149: 2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-6-[2-(dimethylamino)ethoxy]-*N*-methoxyisonicotinamide

The title compound was prepared as described for Example 8 from 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-[2-(dimethylamino)ethoxy] isonicotinic acid (Example 139) acid and *O*-methylhydroxylamine hydrochloride.

MS (ES): 513 (MH^+) for $C_{22}H_{30}Cl_2N_6O_4$

^{1}H NMR δ: 1.56 (m, 2H); 1.88 (m, 2H); 2.17 (s, 3H); 2.85 (s, 6H); 3.08 (m, 2H); 3.70 (s, 3H); 4.19 (m, 1H); 4.52 (d, 2H); 4.54 (m, 2H); 6.34 (s, 1H); 6.69 (s, 1H); 7.20 (d, 1H); 11.85 (s, 1H); 11.98 (s, 1H).

Example 150: 2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-[2-(propionyloxy)ethoxy]isonicotinic acid

2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-(2-hydroxyethoxy)isonicotinic acid (**Example 142**) (199 mg, 0.435 mmol) was dissolved in DCM (3 ml). Propanoyl chloride (37.83 µl, 0.435 mmol) was added dropwise and the resulting mixture stirred at room temperature for 2.5 h. The mixture was diluted with EtOAc and washed with water. The aqueous phase was extracted with EtOAc, and the combined organic phase was dried over sodium sulfate and concentrated in vacuo to give the desired product. The crude product was dissolved in DMSO and purified by reversed phase HPLC, eluting with water/acetonitrile/TFA mixtures to afford the desired product (35 mg).

MS (ES): 513 (MH^+) for $C_{22}H_{26}Cl_2N_4O_6$

^{1}H NMR δ: 1.01 (t, 3H); 1.57 (m, 2H); 1.87 (m, 2H); 2.17 (s, 3H); 2.31 (m, 2H); 3.07 (m, 2H); 4.05 (m, 1H); 4.23 (m, 2H); 4.33 (m, 2H); 4.44 (m, 2H); 6.40 (s, 1H); 6.79 (s, 1H); 7.43 (d, 1H); 12.17 (s, 1H); 13.62 (m, 1H).

Example 151: 2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-*N*-methoxy-6-(methylsulfonyl)isonicotinamide

2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-*N*-methoxy-6-(methylsulfinyl)isonicotinamide (**Example 152**) (90 mg, 0.185 mmol) was dissolved in anhydrous DCM (5 ml). mCPBA (32 mg, 0185 mmol) was added and the mixture was stirred at room temperature for 12 h. The crude mixture was diluted and washed with 10% sodium thiosulfate, water, brine and dried over sodium sulfate and concentrated in vacuo. The brown oil was purified by flash chromatography eluting with acetonitrile/water (0.1% TFA) to give the title compound (11 mg).

MS (ES) (M+H): 504 for $C_{19}H_{23}Cl_2N_3O_5S$

^{1}H NMR δ: 1.53 (m, 2H); 1.83 (m, 2H); 2.03 (s, 3H); 2.97 (m, 2H); 3.12 (s, 3H); 3.62 (s, 3H); 4.07 (m, 1H); 4.28 (m, 2H); 7.16 (d, 1H); 7.30 (s, 2H); 11.87 (s, 1H); 12.05 (s, 1H).

Example 152: 2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-*N*-methoxy-6-(methylsulfinyl)isonicotinamide

Methyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-(methylsulfinyl)isonicotinate (**Example 334**; 200 mg, 0.422 mmol) was dissolved in anhydrous THF (5 ml) and treated with 2 N lithium hydroxide (10 ml) with stirring for 45

minutes. The mixture was cooled in an ice bath and acidified with 1 N HCl. The aqueous solution was extracted with EtOAc. The organic phase was washed with water, dried over sodium sulfate and concentrated in vacuo to give the acid derivative as a brown solid (LCMS showed a peak of 459). This acid (95 mg, 0.207 mmol) was treated with methoxyamine hydrochloride (17.3 mg, 0.207 mmol) in a manner analogous to Example 8 to afford the title compound. (30 mg).

MS (ES) (M+H): 488 for $C_{19}H_{23}Cl_2N_5O_4S$

^{1}H NMR δ: 1.58 (m, 2H); 1.92 (m, 2H); 2.18 (s, 3H); 2.80 (s, 3H); 3.18 (m, 2H); 3.76 (s, 3H); 4.12 (m, 1H); 4.29 (m, 2H); 7.08 (s, 1H); 7.22 (d, 1H); 7.34 (s, 1H); 11.96 (s, 1H); 12.17 (s, 1H)

Example 153: 2-Chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)isonicotinic acid

The title compound was prepared in a manner analogous to Example 44 from methyl 2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl] amino}piperidin-1-yl)isonicotinate (Example 333).

MS (ES) (M+H): 431 for $C_{17}H_{17}Cl_3N_4O_3$

^{1}H NMR δ: 1.64 (m, 2H); 2.00 (m, 2H); 2.46 (s, 3H); 3.46 (m, 2H); 4.40 (m, 1H); 4.55 (m, 2H); 7.21 (s, 1H); 7.27 (s, 1H); 7.59 (d, 1H); 12.13 (s, 1H); 14.06 (brs, 1H).

Example 154: 2-{2-[(*tert*-Butoxycarbonyl)amino]ethoxy}-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylic acid

Sodium hydride (0.097 g, 4.02 mmol) was added to a stirred solution of *tert*-butyl 2-hydroxyethylcarbamate (0.62 ml, 4.02 mmol) in THF at 0 °C under a nitrogen atmosphere. This mixture was stirred for 15 minutes at 0 °C and warmed to room temperature. Methyl 2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylate (Example 6, 0.30 g, 0.67 mmol) was added to the reaction mixture and the resultant mixture was stirred overnight. The reaction was quenched with water (10 ml) and the THF was removed under reduced pressure. The aqueous solution was acidified with 1 N HCl and extracted with EtOAc. The combined extract was washed with water and brine, dried over magnesium sulfate, filtered and concentrated to give a brown oil which was purified by purified by semi-preparative reverse phase HPLC eluting with acetonitrile/water (0.1% TFA).

MS (ES) MH^+: 557 for $C_{23}H_{30}Cl_2N_6O_6$

^1H NMR δ: 1.36 (s, 9H); 1.53 (m, 2H); 1.89 (m, 2H); 2.16 (s, 3H); 3.20 (m, 2H); 3.27 (m, 2H); 4.09 (m, 1H); 4.24 (t, 2H); 4.53 (brs, 2H); 7.00 (t, 1H); 7.05 (s, 1H); 7.23 (d, 1H); 11.96 (s, 1H).

Example 155-162

The following compounds were synthesized by an analogous method to **Example 154** starting from commercially available alcohols and sodium hydride, and reacting the alkoxide generated in situ with methyl 2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylate (**Example 6**). The commercially available alcohols are given in the table below.

Example 155: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-(2-methoxyethoxy)pyrimidine-4-carboxylic acid

Example 156: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-[2-(methylthio)ethoxy]pyrimidine-4-carboxylic acid

Example 157: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-(2-morpholin-4-ylethoxy)pyrimidine-4-carboxylic acid

Example 158: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-(2-hydroxyethoxy)pyrimidine-4-carboxylic acid

Example 159: 2-Butoxy-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylic acid

Example 160: 2-(2-Aminoethoxy)-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylic acid

Example 161: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-[2-(dimethylamino)ethoxy]pyrimidine-4-carboxylic acid

Example 162: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-[3-(dimethylamino)propoxy]pyrimidine-4-carboxylic acid

Example	Alcohol	^1H NMR δ	m/z
155	2-methoxy ethanol	1.54 (m, 2H); 1.88 (m, 2H); 2.16 (s, 3H); 3.18 (m, 2H); 3.28 (s, 3H); 3.62 (t, 2H); 4.08 (brs, 1H); 4.33 (m, 2H); 4.37 (t, 2H); 7.03 (s, 1H); 7.22 (d, 1H); 11.96 (s, 1H).	472

Example	Alcohol	^{1}H NMR δ	m/z
156	2-(methylthio) ethanol	1.53 (m, 2H); 1.89 (m, 2H); 2.13 (s, 3H); 2.16 (s, 3H); 2.82 (t, 2H); 3.19 (t, 2H); 4.09 (brs, 1H); 4.35 (m, 2H); 4.42 (t, 2H); 7.04 (s, 1H); 7.23 (d, 1H); 11.96 (s, 1H).	488
157	2-morpholin-4-ylethanol	1.52 (m, 2H); 1.95 (m, 2H); 2.16 (s, 3H); 3.20 (t, 2H); 3.56 (brs, 2H); 3.73 (brs, 2H); 3.94 (brs, 2H); 4.09 (brs, 2H); 4.35 (brs, 3H); 4.61 (brs, 4H); 7.10 (s, 1H); 7.25 (d, 1H); 12.01 (s, 1H).	527
158	ethylene glycol	1.52 (m, 2H); 1.87 (m, 2H); 2.15 (s, 3H); 3.17 (t, 2H); 3.66 (t, 2H); 4.07 (m, 1H); 4.26 (t, 2H); 4.35 (brs, 2H); 7.02 (s, 1H); 7.21 (d, 1H); 11.95 (s, 1H).	458
159	butan-1-ol	0.92 (t, 3H); 1.39 (m, 2H); 1.53 (m, 2H); 1.67 (m, 2H); 1.80 (m, 2H); 2.16 (s, 3H); 3.22 (m, 2H); 4.10 (m, 2H); 4.28 (t, 2H); 4.45 (brs, 1H); 7.05 (s, 1H); 7.23 (d, 1H); 11.97 (s, 1H)	470
160	3-(dimethylamino) propan-1-ol	1.52 (m, 2H); 1.89 (m, 2H); 2.02 (m, 2H); 2.16 (s, 3H); 2.80 (s, 3H); 2.81 (s, 3H); 3.18 (m, 4H); 4.09 (m, 1H); 4.31 (t, 2H); 4.58 (m, 2H); 7.05 (s, 1H); 7.21 (d, 1H); 9.36 (brs, 1H); 11.98 (s, 1H).	499
161	2-aminoethanol	1.53 (m, 2H); 1.91 (m, 2H); 2.17 (s, 3H); 3.21 (m, 4H); 4.13 (m, 1H); 4.35 (brs, 2H); 4.43 (t, 2H); 7.10 (s, 1H); 7.22 (d, 1H); 7.96 (brs, 2H); 11.98 (s, 1H).	457
162	2-(dimethylamino) ethanol	1.52 (m, 2H); 1.92 (m, 2H); 2.16 (s, 3H); 2.85 (s, 6H); 3.21 (t, 2H); 3.49 (brs, 2H); 4.10 (m, 1H); 4.33 (brs, 2H); 4.58 (m, 2H); 7.11 (s, 1H); 7.23 (d, 1H); 9.88 (brs, 1H); 11.99 (s, 1H).	485

Example 163: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-[2-(methylsulfonyl)ethoxy]pyrimidine-4-carboxylic acid

The title compound was synthesized by an analogous method to **Example 14** starting from 6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-[2-(methylthio)ethoxy]pyrimidine-4-carboxylic acid (**Example 156**).

MS (ES) MH^+: 520 for $C_{19}H_{23}Cl_2N_5O_6S$

^1H NMR δ: 1.54 (m, 2H); 1.88 (m, 2H); 2.16 (s, 3H); 3.00 (s, 3H); 3.14 (t, 2H); 3.55 (m, 2H); 4.03 (m, 1H); 4.28 (m, 2H); 4.55 (t, 2H); 7.01 (s, 1H); 7.16 (d, 1H); 11.90 (s, 1H).

Examples 164-168

The following compounds were synthesized by an analogous method to **Example 8** starting from the corresponding carboxylic acid derivatives and methoxylamine hydrochloride. The starting carboxylic acid derivatives are given in the table below.

Example 164: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-*N*-methoxy-2-(2-methoxyethoxy)pyrimidine-4-carboxamide

Example 165: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-*N*-methoxy-2-[2-(methylthio)ethoxy]pyrimidine-4-carboxamide

Example 166: 2-Butoxy-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-*N*-methoxypyrimidine-4-carboxamide

Example 167: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-[2-(dimethylamino)ethoxy]-*N*-methoxypyrimidine-4-carboxamide

Example 168: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-(2-hydroxyethoxy)-*N*-methoxypyrimidine-4-carboxamide

Example	SM	^1H NMR δ	m/z
164	6-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl] amino}piperidin-1-yl)-2-(2-methoxyethoxy)pyrimidine-4-carboxylic acid (Example 155)	1.52 (m, 2H); 1.88 (m, 2H); 2.16 (s, 3H); 3.21 (t, 2H); 3.28 (s, 3H); 3.61 (t, 2H); 3.66 (s, 3H); 4.08 (m, 1H); 4.33 (m, 2H); 4.41 (t, 2H); 6.96 (s, 1H); 7.22 (d, 1H); 11.84 (brs, 1H); 11.96 (s, 1H).	501

Example	SM	^{1}H NMR δ	m/z
165	6-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl] amino}piperidin-1-yl)-2-[2-(methylthio)ethoxy]pyrimidine-4-carboxylic (Example 156)	1.52 (m, 2H); 1.88 (m, 2H); 2.13 (s, 3H); 2.16 (s, 3H); 2.81 (t, 2H); 3.17 (t, 2H); 3.67 (s, 3H); 4.08 (m, 1H); 4.31 (m, 2H); 4.44 (t, 2H); 6.97 (s, 1H); 7.22 (d, 1H); 11.84 (brs, 1H); 11.96 (s, 1H).	517
166	2-butoxy-6-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylic acid (Example 159)	0.92 (t, 3H); 1.40 (m, 2H); 1.51 (m, 2H); 1.66 (m, 2H); 1.88 (m, 2H); 2.16 (s, 3H); 3.17 (t, 2H); 3.66 (t, 3H); 4.08 (m, 1H); 4.27 (t, 2H); 4.38 (brs, 2H); 6.95 (s, 1H); 7.22 (d, 1H); 11.81 (brs, 1H); 11.96 (s, 1H)	499
167	6-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl] amino}piperidin-1-yl)-2-[2-(dimethylamino)ethoxy] pyrimidine-4-carboxylic acid (Example 161)	1.50 (m, 2H); 1.89 (m, 2H); 2.16 (s, 3H); 2.83 (s, 3H); 2.85 (s, 3H); 3.19 (t, 2H); 3.69 (s, 3H); 4.08 (m, 1H); 4.31 (m, 2H); 4.65 (t, 2H); 7.03 (s, 1H); 7.20 (d, 1H); 11.85 (s, 1H); 11.97 (s, 1H); 2H buried underneath water peak	514
168	6-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl] amino}piperidin-1-yl)-2-(2-hydroxyethoxy)pyrimidine-4-carboxylic acid (Example 158)	1.52 (m, 2H); 1.88 (m, 2H); 2.16 (s, 3H); 3.17 (t, 2H); 3.67 (s, 3H); 3.68 (t, 2H); 4.10 (m, 1H); 4.30 (t, 2H); 4.35 (m, 2H); 6.96 (s, 1H); 7.21 (d, 1H); 11.81 (s, 1H); 11.95 (s, 1H)	487

Example 169: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-(2,3-dihydroxypropoxy)-*N*-methoxypyrimidine-4-carboxamide

6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-[(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]-*N*-methoxypyrimidine-4-carboxamide (Example 313; 0.60 g, 1.08 mmol) was dissolved in THF/water (4:1; 2.5 ml) and cooled to 0 °C. TFA (0.1 ml) was added to the solution which was then slowly warmed to room temperature and stirred overnight. The mixture was neutralized with concentrated ammonium hydroxide and the THF

was removed in vacuo. The mixture was diluted with water (4 ml), extracted with DCM, and the organic layers dried over magnesium sulfate. The mixture was concentrated in vacuo and crude product was purified by reverse phase chromatography eluting with acetonitrile/water (0.1% TFA) (33 mg).

MS (ES) MH^+: 517 for $C_{20}H_{26}Cl_2N_6O_6$

^1H NMR δ: 1.52 (m, 2H); 1.88 (m, 2H); 2.16 (s, 3H); 3.18 (t, 2H); 3.43 (d, 2H); 3.67 (s, 3H); 4.08 (m, 1H); 4.17 (m, 2H); 4.30 (m, 2H); 4.35 (m, 1H); 6.96 (s, 1H); 7.22 (d, 1H); 11.81 (s, 1H); 11.96 (s, 1H).

Example 170: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-*N*-methoxy-2-[2-(methylsulfonyl)ethoxy]pyrimidine-4-carboxamide

6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-*N*-methoxy-2-[2-(methylthio)ethoxy]pyrimidine-4-carboxamide (**Example 165**, 0.10 g, 0.19 mmol) was suspended in DCM (5 ml) and cooled to 0 °C. mCPBA (0.067 g, 0.387 mmol, 70 %) was added, then the reaction was warmed to room temperature and stirred for 4 h. A further equivalent of mCPBA was added and the mixture was stirred overnight. A solution of sodium sulfite (5 %, 3 ml) was added and the layers separated. The aqueous phase was extracted with EtOAc and the combined organic extract was dried over magnesium sulfate and concentrated to give a white solid which was purified by reverse phase chromatography eluting with (20 % to 75 % acetonitrile in water, 0.1% TFA) affording the title compound (44 mg).

MS (ES) MH^+: 549 for $C_{20}H_{26}Cl_2N_6O_6S$

^1H NMR δ: 1.52 (m, 2H); 1.88 (m, 2H); 2.15 (s, 3H); 3.05 (s, 3H); 3.18 (t, 2H); 3.60 (t, 2H); 3.67 (s, 3H); 4.10 (m, 1H); 4.32 (m, 2H); 4.64 (t, 2H); 7.00 (s, 1H); 7.21 (d, 1H); 11.86 (s, 1H); 11.95 (s, 1H).

Example 171: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-*N*-methoxy-2-{2-[(methylsulfonyl)amino]ethoxy}pyrimidine-4-carboxamide

Methane sulfonyl chloride (0.032 ml, 0.412 mmol) was added dropwise to a solution of 2-(2-aminoethoxy)-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-*N*-methoxypyrimidine-4-carboxamide (**Example 319**, 0.20 g, 0.412 mmol), TEA (0.11 ml, 0.824 mmol) and DMF (3 ml) at 0 °C. The reaction was stirred for 15 minutes at 0 °C then quenched with water. The aqueous phase was extracted with EtOAc, washed with saturated sodium bicarbonate solution, water and brine. It was dried over magnesium sulfate and

concentrated to give brown solid, which was purified by reverse phase HPLC (30% to 35% acetonitrile in water, 0.1 % TFA) affording the title compound (70 mg).

MS (ES) MH^+: 564 for $C_{20}H_{27}Cl_2N_7O_6S$

^1H NMR δ: 1.52 (m, 2H); 1.88 (m, 2H); 2.16 (s, 3H); 2.93 (s, 3H); 3.18 (t, 2H); 3.29 (m, 2H); 3.67 (s, 3H); 4.20 (m, 1H); 4.32 (m, 2H); 4.34 (t, 2H); 6.98 (s, 1H); 7.23 (m, 2H); 11.82 (s, 1H); 11.97 (s, 1H).

Example 172: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-*N*-methoxy-2-oxo-2,3-dihydropyrimidine-4-carboxamide

The title compound was synthesized by an analogous method to Example 8 starting from 6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-oxo-2,3-dihydropyrimidine-4-carboxylic acid (Example 173) and methoxylamine hydrochloride.

MS (ES) MH^+: 443 for $C_{17}H_{20}Cl_2N_6O_4$

^1H NMR δ: 1.54 (m, 2H); 1.90 (m, 2H); 2.17 (s, 3H); 3.25 (m, 2H); 3.71 (s, 3H); 4.10 (m, 2H); 4.39 (br s, 1H); 6.55 (s, 1H); 7.24 (d, 1H); 11.97 (s, 1H); 12.11 (s, 1H); 1H underneath water peak.

Example 173: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-oxo-2,3-dihydropyrimidine-4-carboxylic acid

The title compound was synthesized by an analogous method to Example 154 starting from 2-furylmethanol (commercially available) and sodium hydride, and reacting the alkoxide generated in situ with methyl 2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylate (Example 6). Purification of the crude material by reversed-phase HPLC resulted in hydrolysis of the desired product to form the title compound.

MS (ES) MH^+: 414 for $C_{16}H_{17}Cl_2N_5O_4$

^1H NMR δ: 1.54 (m, 2H); 1.90 (m, 2H); 2.16 (s, 3H); 3.26 (m, 2H); 3.71 (s, 3H); 4.09 (m, 2H); 4.49 (br s, 1H); 6.68 (s, 1H); 7.24 (d, 1H); 11.97 (s, 1H); 1H buried underneath water peak.

Example 174: 2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-6-methoxypyrimidine-4-carboxylic acid

Lithium hydroxide (2 M, 4 ml) was warmed to 40 °C and a solution of methyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-methoxypyrimidine-4-carboxylate (**Example 315**, 0.30 g, 0.68 mmol) in MeOH was added. The reaction temperature was increased to 60 °C and it was stirred at that temperature for 3 h. The MeOH was removed, the aqueous solution was cooled to 0 °C and then acidified with 1 N HCl. The precipitate was collected by suction filtration and washed with EtOAc to give the title compound (0.13 g).

MS (ES) MH^+: 428 for $C_{17}H_{19}Cl_2N_5O_4$

^1H NMR δ: 1.54 (m, 2H); 1.90 (m, 2H); 2.17 (s, 3H); 3.24 (t, 2H); 3.89 (s, 3H); 4.04 (m, 1H); 4.49 (d, 2H); 6.50 (s, 1H); 7.22 (d, 1H); 11.97 (s, 1H); 13.23 (s, 1H).

Example 175: 2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-*N*,6-dimethoxypyrimidine-4-carboxamide

The title compound was synthesized by an analogous method to **Example 8** starting from 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-methoxypyrimidine-4-carboxylic acid (**Example 174**) and methoxylamine hydrochloride.

MS (ES) MH^+: 457 for $C_{18}H_{22}Cl_2N_6O_4$

^1H NMR δ: 1.51 (m, 2H); 1.87 (m, 2H); 2.16 (s, 3H); 3.11 (t, 2H); 3.69 (s, 3H); 3.86 (s, 3H); 4.06 (m, 1H); 4.67 (brs, 2H); 6.45 (s, 1H); 7.20 (d, 1H); 11.83 (s, 1H); 11.96 (s, 1H).

Example 176: 2-(Butylthio)-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl] amino}piperidin-1-yl)pyrimidine-4-carboxylic acid

A suspension of sodium hydride (239.5 mg, 9.98 mmol) in THF (5 ml) was cooled to 0 °C and treated with a solution of 1-butanethiol (1.0 g, 0.011 mol) in THF (5 ml). The reaction mixture was allowed to warm to room temperature slowly. Concentration under reduced pressure gave a white solid (1.02 g), which was presumed to be the sodium salt of the thiol. methyl 2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylate (**Example 6**) (500 mg, 1.12 mmol) and the sodium salt of the thiol (627 mg, 5.6 mmol) were combined in DMF (12 ml) and heated at 90 °C under nitrogen for 1 h. Upon cooling to room temperature, the reaction solution was diluted with EtOAc and water and then acidified with 1 N HCl. The aqueous portion was extracted with EtOAc, and

the combined organic portions were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a brown oil. Some of the crude material was purified by preparatory HPLC using a gradient of 20-60% acetonitrile/water (0.1% TFA) to give the TFA salt of the title compound (50 mg).

MS (ES^+): 486.22, 488.22

^{1}H NMR δ: 0.83 (t, 3H); 1.32 (m, 2H); 1.4 (m, 2H); 1.58 (m, 2H); 1.81 (m, 2H); 2.10 (s, 3H); 3.0 (t, 2H); 3.14 (m, 2H); 4.04 (m, 2H); 4.27 (m, 1H); 6.98 (s, 1H); 7.16 (d, 1H); 11.90 (s, 1H); carboxylic acid proton not visible

Examples 177 - 181

The following compounds were synthesized by an analogous method to Example 176 from commercially available thiols and sodium hydride by reacting the sodium salt generated in situ with methyl 2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylate (Example 6). The relevant thiols are given in the table below.

Example 177: 2-({2-[(*tert*-Butoxycarbonyl)amino]ethyl}thio)-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylic acid

Example 178: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-[(2,3-dihydroxypropyl)thio]pyrimidine-4-carboxylic acid

Example 179: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-(isobutylthio)pyrimidine-4-carboxylic acid

Example 180: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-(isopropylthio)pyrimidine-4-carboxylic acid

Example 181: 2-(*tert*-Butylthio)-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylic acid

Example	Starting Material	^{1}H NMR δ	m/z
177	tert-butyl N-(2-mercaptoethyl) carbamate	1.25 (m, 2H); 1.30 (s, 9H); 1.49 (m, 2H); 1.83 (m, 2H); 2.11 (s, 3H); 3.03 (m, 2H); 3.18 (m, 2H); 4.05 (m, 2H); 4.27 (m, 1H); 6.99 (s, 1H); 7.0 (t, 1H); 7.15 (d, 1H); 11.91 (s, 1H); carboxylic acid proton not visible	571

Example	Starting Material	^{1}H NMR δ	m/z
178	3-mercapto-1,2-propanediol	1.48 (m, 2H); 1.82 (m, 2H); 2.10 (s, 3H); 2.91 (d, 2H); 2.96 (d, 2H); 3.14 (m, 2H); 3.6 (m, 1H); 4.03 (m, 2H); 4.29 (m, 1H); 7.00 (s, 1H); 7.15 (d, 1H); 11.90 (s, 1H); carboxylic acid proton not visible	504
179	2-methyl-1-propanethiol	0.90 (d, 6H); 1.46 (m, 2H); 1.84 (m, 2H); 2.11 (s, 3H); 2.91 (d, 2H); 3.15 (m, 2H); 3.7-4.3 (overlapping multiplets, 4H); 7.00 (s, 1H); 7.17 (d, 1H); 11.90 (s, 1H); carboxylic acid proton not visible	484
180	2-propanethiol	1.28 (d, 6H); 1.49 (m, 2H); 1.82 (m, 2H); 2.10 (s, 3H); 3.14 (m, 2H); 3.77 (m, 1H); 4.04 (m, 2H); 4.28 (m, 1H); 6.99 (s, 1H); 7.18 (d, 1H); 11.93 (s, 1H); carboxylic acid proton not visible	472
181	tert-butyl mercaptan	1.43 (m, 4H); 1.50 (s, 9H); 1.82 (m, 2H); 2.10 (s, 3H); 3.11 (m, 2H); 4.05 (m, 2H); 4.24 (m, 1H); 6.98 (s, 1H); 7.16 (d, 1H); 11.90 (s, 1H); carboxylic acid proton not visible.	484

Examples 182 - 185

The following compounds were synthesized by an analogous method to Example 8 by coupling the acids in the table below with methoxylamine hydrochloride.

Example 182: *tert*-Butyl 2-({4-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-[(methoxyamino)carbonyl]pyrimidin-2-yl}thio)ethylcarbamate

Example 183: 2-(Butylthio)-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-*N*-methoxypyrimidine-4-carboxamide

Example 184: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-2-(isopropylthio)-*N*-methoxypyrimidine-4-carboxamide

Example 185: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-2-[(2-hydroxyethyl)thio]-*N*-methoxypyrimidine-4-carboxamide

Example	Acid	^{1}H NMR δ	m/z
182	2-({2-[(tert-butoxycarbonyl) amino]ethyl}thio)-6-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)pyrimidine-4-carboxylic acid (Example 177)	1.38 (m, 2H); 1.46 (s, 9H); 1.60 (m, 2H); 1.94 (m, 2H); 2.23 (s, 3H); 3.1 (m, 2H); 3.24 (m, 2H); 4.15 (m, 2H); 4.39 (m, 1H); 7.11 (s, 1H); 7.3 (overlapping triplet and doublet, 2H); 11.85 (s, 1H); 12.03 (s, 1H)	600
183	2-(butylthio)-6-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)pyrimidine-4-carboxylic acid (Example 176)	0.81 (t, 3H); 1.33 (m, 2H); 1.5 (m, 2H); 1.57 (m, 2H); 1.81 (m, 2H); 2.10 (s, 3H); 3.01 (t, 2H); 3.15 (m, 2H); 3.61 (s, 3H); 4.05 (m, 2H); 4.21 (m, 1H); 6.92 (s, 1H); 7.18 (d, 1H); 11.68 (s, 1H); 11.90 (s, 1H)	513
184	6-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl] amino}piperidin-1-yl)-2-(isopropylthio)pyrimidine-4-carboxylic acid (Example 180)	1.27 (d, 6H); 1.48 (m, 2H); 1.81 (m, 2H); 2.10 (s, 3H); 3.12 (m, 2H); 3.88 (m, 1H); 4.03 (m, 2H); 4.27 (m, 1H); 6.92 (s, 1H); 7.15 (d, 1H); 11.68 (brs, 1H); 11.90 (s, 1H)	501
185	6-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl] amino}piperidin-1-yl)-2-[(2-hydroxyethyl)thio]pyrimidine-4-carboxylic acid (Example 16)	1.44 (m, 2H); 1.82 (m, 2H); 2.11 (s, 3H); 3.1-3.16 (overlapping triplet and multiplet, 4H); 3.55 (t, 2H); 4.02 (m, 2H); 4.26 (m, 1H); 6.94 (s, 1H); 7.15 (d, 1H); 11.67 (s, 1H); 11.90 (s, 1H)	501

Examples 186 - 189

The following compounds were synthesized by an analogous method to Example 10 by oxidizing the thioethers in the table above with mCPBA.

Example 186: *tert*-Butyl 2-({4-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl] amino}piperidin-1-yl)-6-[(methoxyamino)carbonyl]pyrimidin-2-yl}sulfonyl) ethylcarbamate

Example 187: 2-(Butylsulfonyl)-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl] amino}piperidin-1-yl)-*N*-methoxypyrimidine-4-carboxamide

Example 188: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-2-(isopropylsulfonyl)-*N*-methoxypyrimidine-4-carboxamide

Example 189: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-[(2-hydroxyethyl)sulfonyl]-*N*-methoxypyrimidine-4-carboxamide

Example	Starting material	^{1}H NMR δ	m/z
186	Example 182	1.11 (t, 2H); 1.30 (s, 9H); 1.53 (m, 2H); 1.88 (m, 2H); 2.11 (s, 3H); 3.22 (m, 2H); 3.71 (m, 2H); 4.08 (m, 2H); 4.58 (m, 1H); 6.97 (t, 1H); 7.17 (d, 1H); 7.41 (s, 1H); 11.89 (s, 1H); 11.92 (s, 1H)	634
187	Example 183	0.81 (t, 3H); 1.37 (m, 2H); 1.55 (m, 2H); 1.86 (m, 2H); 2.11 (s, 3H); 3.2 (m, 2H); 3.6 (m, 2H); 3.66 (s, 3H); 4.08 (m, 2H); 4.55 (m, 1H); 7.17 (d, 1H); 7.39 (s, 1H); 11.91 (s, 1H); 11.97 (s, 1H)	545
188	Example 184	1.16 (d, 6H); 1.53 (m, 2H); 1.87 (m, 2H); 2.11 (s, 3H); 3.24 (m, 2H); 3.66 (s, 3H); 4.08 (m, 2H); 4.25 (m, 1H); 4.55 (m, 1H); 7.17 (d, 1H); 7.39 (s, 1H); 11.91 (s, 1H); 11.95 (s, 1H)	531
189	Example 185	1.49 (m, 2H); 1.87 (m, 2H); 2.11 (s, 3H); 3.23 (m, 2H); 3.66 (s, 3H); 3.76 (t, 2H); 4.08 (m, 2H); 4.60 (m, 1H); 7.17 (d, 1H); 7.38 (s, 1H); 11.67 (s, 1H); 11.91 (s, 1H); 11.96 (s, 1H)	535

Example 190: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-2-(isopropylthio)pyrimidine-4-carboxamide

6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-(isopropylthio)pyrimidine-4-carboxylic acid (**Example 180**; 200 mg, 0.423 mmol), ammonia solution (2 M in MeOH, 0.43 ml, 0.846 mmol), TEA (0.06 ml, 0.423 mmol), and HATU (161 mg, 0.42 mmol) were combined in DMF (3 ml) and stirred at room temperature for 1 h. The reaction was diluted with EtOAc and water, and the organic portion was washed sequentially with 1 N HCl, saturated sodium bicarbonate, and brine. The organic portion was dried over sodium sulfate, filtered and concentrated to give an off-white solid (312 mg). The crude

material was purified by preparatory HPLC using a gradient of 40-70% acetonitrile/water (0.1% TFA) over 14 minutes to give the title compound as a white solid.

MS (ES⁺): 469.06, 471.18

^{1}H NMR δ: 1.27 (d, 6H); 1.49 (m, 2H); 1.82 (m, 2H); 2.10 (s, 3H); 3.12 (m, 2H); 3.86 (m, 3H); 4.04 (m, 2H); 4.25 (m, 1H); 6.97 (s, 1H); 7.15 (d, 1H); 7.68 (s, 1H); 7.78 (s, 1H); 11.90 (s, 1H).

Example 191: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-*N*-methoxy-2-pyrrolidin-1-ylpyrimidine-4-carboxamide

The title compound was synthesized by an analogous method to Example 8 starting from 6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-pyrrolidin-1-ylpyrimidine-4-carboxylic acid (Example 335) and methoxylamine hydrochloride.

MS (ES⁺): 494.67, 496.66

^{1}H NMR δ: 1.49 (m, 2H); 1.85 (m, 6H); 2.11 (s, 3H); 3.17 (m, 2H); 3.67 (s, 3H); 3.7 (m, 4H); 4.04 (m, 2H); 4.28 (m, 1H); 6.67 (s, 1H); 7.17 (d, 1H); 11.86 (s, 1H); 11.91 (s, 1H)

Example 192: 3,4-Dichloro-*N*-{1-[2-chloro-6-(hydrazinocarbonyl)pyrimidin-4-yl]piperidin-4-yl}-5-methyl-1*H*-pyrrole-2-carboxamide

Methyl 2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylate (Example 6) (500 mg, 1.12 mmol), hydrazine (0.035 ml, 1.12 mmol), and TEA (0.16 ml, 1.12 mmol) were combined in DMF (3 ml) and stirred at room temperature. Within 1.5 h, a white precipitate had formed. The reaction was stirred for another 30 minutes, and then the precipitate was collected by suction filtration to give 377 mg of the title compound. 100 mg of the crude material was purified by preparatory HPLC, using a gradient of 40-70% acetonitrile/water (0.1% TFA) over 14 minutes to give 23 mg of the title compound.

MS (ES⁺): 446.21, 448.20

^{1}H NMR δ: 1.47 (m, 2H); 1.84 (m, 2H); 2.11 (s, 3H); 3.1 (m, 2H); 4.06 (m, 2H); 4.35 (m, 2H); 4.77 (m, 1H); 7.16 (d, 1H); 7.18 (s, 1H); 9.85 (m, 1H); 11.91 (s, 1H)

Example 193: *N*-Allyl-2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxamide

Methyl 2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylate (**Example 6**) (100 mg, 0.224 mmol) in anhydrous THF (3 ml) was treated with allylamine (0.025 ml, 0.336 mmol), sodium *tert*-butoxide (32.29 mg, 0.336 mmol), $Pd(Dppf)_2Cl_2$- DCM complex (9.14 mg, 0.0112 mmol) and Dppf (18.61 mg, 0.0336 mmol). The reaction was heated at 80 °C for 2 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated to give a rust-coloured solid. The crude material was purified by preparatory HPLC, using a gradient of 35-75% acetonitrile/water (0.1% TFA) to give 12 mg pale brown solid.

MS (ES$^+$): 471.47

^{1}H NMR δ: 1.47 (m, 2H); 1.84 (m, 2H); 2.11 (s, 3H); 3.18 (m, 2H); 3.79 (t, 2H); 4.02 (m, 2H); 4.3 (m, 1H); 5.02 (t, 2H); 5.8 (m, 1H); 7.16 (d, 1H); 7.24 (s, 1H); 8.7 (t, 1H); 11.91 (s, 1H)

Example 194: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-2-piperazin-1-ylpyrimidine-4-carboxylic acid

The title compound was synthesized by an analogous method to **Example 310** starting from methyl 6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-piperazin-1-ylpyrimidine-4-carboxylate (**Example 317**) and 2 N lithium hydroxide.

MS (ES$^+$): 480.29, 482.28

^{1}H NMR δ: 1.41 (m, 2H); 1.81 (m, 2H); 2.11 (s, 3H); 3.08 (m, 4H); 3.75 (m, 4H); 4.01 (m, 2H); 4.23 (m, 2H); 4.48 (m, 1H); 6.68 (s, 1H); 7.14 (d, 1H); 8.71 (m, 1H); 11.92 (s, 1H); carboxylic acid proton not visible

Example 195: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-*N*-methoxy-2-piperazin-1-ylpyrimidine-4-carboxamide

The title compound was synthesized by an analogous method to **Example 8** starting from 6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-piperazin-1-ylpyrimidine-4-carboxylic acid (**Example 194**) and methoxylamine hydrochloride.

MS (ES$^+$): 509.70, 511.67

^{1}H NMR δ: 1.41 (m, 2H); 1.81 (m, 2H); 2.11 (s, 3H); 3.06 (m, 4H); 3.63 (s, 3H); 3.75-4.0 (overlapping multiplets, 6H); 4.23 (m, 2H); 4.55 (m, 1H); 6.62 (s, 1H); 7.15 (d, 1H); 8.75 (m, 1H); 11.69 (s, 1H); 11.93 (s, 1H)

Example 196: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-(4-methylpiperazin-1-yl)pyrimidine-4-carboxylic acid

The title compound was synthesized by an analogous method to Example 310 starting from methyl 6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-(4-methylpiperazin-1-yl)pyrimidine-4-carboxylate (Example 318) and 2 N lithium hydroxide.

MS (ES$^-$): 494.31, 496.3

^{1}H NMR δ: 1.44 (m, 2H); 1.83 (m, 2H); 2.11 (s, 3H); ~2.4 (s, 3H); 3.17 (m, 4H); 3.6-4.1 (overlapping multiplets, 8H); 4.38 (m, 1H); 7.15 (d, 1H); 7.27 (s, 1H); 11.91 (s, 1H)

Example 197: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-*N*-methoxy-2-(4-methylpiperazin-1-yl)pyrimidine-4-carboxamide

The title compound was synthesized by an analogous method to Example 8 starting from 6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-(4-methylpiperazin-1-yl)pyrimidine-4-carboxylic acid(Example 196) and methoxylamine hydrochloride.

MS (ES$^-$): 523.72, 525.65

^{1}H NMR δ: 1.44 (m, 2H); 1.81 (m, 2H); 2.11 (s, 3H); 2.76 (s, 3H); 2.94 (m, 2H); 3.06 (m, 2H); 3.39 (m, 2H); 3.63 (s, 3H); 3.9 (m, 2H); 4.23 (m, 2H); 4.55 (m, 1H); 4.77 (m, 2H); 6.64 (s, 1H); 7.13 (d, 1H); 7.27 (s, 1H); 11.71 (s, 1H); 11.92 (s, 1H)

Example 198: 2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-(ethylsulfonyl)-*N*-methoxypyrimidine-4-carboxamide

The title compound was synthesized by an analogous method to Example 10 starting from 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-(ethylthio)-*N*-methoxypyrimidine-4-carboxamide (Example 203) and mCPBA.

MS (ES$^-$): 517.62, 519.61

^{1}H NMR δ: 1.13 (t, 3H); 1.44 (m, 2H); 1.85 (m, 2H); 2.11 (s, 3H); 3.14 (m, 2H); 3.41 (q, 2H); 3.67 (s, 3H); 4.05 (m, 2H); 4.77 (m, 1H); 7.15 (d, 1H); 7.34 (s, 1H); 11.92 (s, 1H); 12.16 (s, 1H)

Example 199: 3,4-Dichloro-*N*-[1-(2-chloro-6-cyanopyrimidin-4-yl)piperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide

A stock solution of trimethylsilyl polyphosphate (prepared according to Yokoyama, Masataka; Yoshida, Sayaka; Imamoto, Tsuneo. *Synthesis*, **1982**, *7*, 591-592) was prepared by combining P_2O_5 (10 g) and hexamethyldisiloxane (25 ml) in anhydrous toluene (50 ml) and heating the mixture at 80 °C until it became a clear solution (about 45 minutes). 2-Chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxamide (Example 37, 2.1 g, 4.8 mmol) was treated with trimethylsilyl polyphosphate (80 ml), and the reaction was heated at 80 °C for 5 h, after which the reaction was about 50% complete. No further reaction was apparent after adding more trimethylsilyl polyphosphate and letting the reaction stir an additional 2.5 days. Upon cooling to room temperature, the reaction was concentrated under reduced pressure until most of the solvent was removed. The remaining liquid was triturated with EtOAc and water to form a brown precipitate, which was mostly the amide precursor. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give the title compound as a yellow solid. About 20 mg was purified by preparatory HPLC, using a gradient of 35-75% acetonitrile/water (0.1% TFA), while the rest was carried on without further purification.

MS (ES^-): 436.17, 438.16

^{1}H NMR δ: 1.51 (m, 2H); 1.9 (m, 2H); 2.12 (s, 3H); 3.28 (m, 2H); 4.06 (m, 2H); 4.43 (m, 1H); 7.16 (d, 1H); 7.64 (s, 1H); 11.93 (s, 1H)

Example 200: *N*-(1-{6-[(*Z*)-Amino(hydroxyimino)methyl]-2-chloropyrimidin-4-yl}piperidin-4-yl)-3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxamide

3,4-Dichloro-*N*-[1-(2-chloro-6-cyanopyrimidin-4-yl)piperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide (Example 199, 150 mg, 0.36 mmol), hydroxylamine hydrochloride (25 mg, 0.36 mmol) and TEA (0.05 ml, 0.36 mmol) were combined in MeOH (5 ml), and the reaction was heated at 80 °C for 2 h. The reaction was diluted with EtOAc and washed with water. The aqueous portion was extracted with EtOAc, and the combined organic portions were dried (sodium sulfate), filtered and concentrated to give a pale yellow solid. The crude material was purified by preparatory HPLC, using a gradient of 35-75% acetonitrile/water (0.1% TFA) to give 53 mg of the title compound.

MS (ES^+): 446.06, 448.05

^{1}H NMR δ: 1.50 (m, 2H); 1.84 (m, 2H); 2.11 (s, 3H); 3.16 (m, 2H); 4.06 (m, 2H); 4.21 (m, 1H); 7.08 (s, 1H); 7.16 (d, 1H); 10.36 (bra, 1H); 11.91 (s, 1H)

Example 201: Methyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-6-(ethylthio)pyrimidine-4-carboxylate

The title compound was synthesized by a method analogous to Example 9 by coupling methyl 2-chloro-6-(ethylthio)pyrimidine-4-carboxylate (Intermediate 96) with 3,4-dichloro-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (Intermediate 1).

MS (ESP): 472.56 (M+H) for $C_{19}H_{23}Cl_2N_5O_3S$

^{1}H NMR δ: 1.31 (t, 3H); 1.52 (m, 2H); 1.90 (d, 2H); 2.17 (s, 3H); 3.05-3.25 (m, 4H); 3.83 (s, 3H); 4.10 (m, 1H); 4.57 (d, 2H); 6.95 (s, 1H); 7.25 (d, 1H); 12.0 (s, 1H).

Example 202: 2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-6-(ethylthio)pyrimidine-4-carboxylic acid

The title compound was synthesized from methyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-(ethylthio)pyrimidine-4-carboxylate (Example 201) by a method analogous to Example 31.

MS (ESP): 458.2 (M+H) for $C_{18}H_{21}Cl_2N_5O_3S$

^{1}H NMR δ 1.25 (t, 3H); 1.50 (m, 2H); 1.85 (d, 2H); 2.11 (s, 3H); 3.03-3.20 (m, 4H); 4.05 (m, 1H); 4.20 (br s, 1H); 4.54 (d, 2H); 6.86 (s, 1H); 7.14 (d, 1H); 11.90 (s, 1H).

Example 203: 2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-(ethylthio)-*N*-methoxypyrimidine-4-carboxamide

The title compound was synthesized by an analogous method to Example 8 starting from 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-(ethylthio)pyrimidine-4-carboxylic acid (Example 202) and methoxylamine hydrochloride.

MS (ESP): 487.5 (M+H) for $C_{19}H_{24}Cl_2N_6O_3S$

^{1}H NMR δ: 1.24 (t, 3H); 1.46 (m, 2H); 1.82 (d, 2H); 2.11 (s, 3H); 3.02-3.11 (m, 4H); 3.62 (s, 3H); 4.05 (m, 1H); 4.60 (d, 2H); 6.83 (s, 1H); 7.14 (d, 1H); 11.83 (s, 1H); 11.90 (s, 1H).

Example 204: 2-Chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-*N*-(methylsulfonyl)pyrimidine-4-carboxamide

A solution of methanesulfonamide (40 mg, 0.44 mmol) and DMF (0.5 ml) was added to a suspension of sodium hydride (95%) (11 mg, 0.44 mmol) and DMF (0.5 ml) under nitrogen. The mixture was stirred for 20 minutes at room temperature. A solution of methyl 2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)pyrimidine-4-carboxylate (**Example 6**, 47 mg, 0.11 mmol) in DMF (1 ml) was added dropwise to the mixture over 5 minutes. The mixture was stirred for 1 h at room temperature and for 3 h at 60 °C. The mixture was cooled to room temperature and concentrated under reduced pressure. The crude residue was purified by preparative reversed-phase HPLC (water/acetonitrile gradient, 10-90%) to afford the title compound (14 mg).

MS (ESP): 507.3 (M-H) for $C_{17}H_{19}Cl_3N_6O_4S$

^{1}H NMR δ: 1.49 (m, 2H); 1.86 (d, 2H); 2.11 (s, 3H); 3.20 (m, 2H); 3.29 (s, 3H); 4.05 (m, 2H); 4.45 (m, 1H); 4.60-4.80 (br s, 1H); 7.17 (d, 1H); 7.30 (s, 1H); 11.91 (s, 1H).

Example 205: 2-Butyl-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)pyrimidine-4-carboxylic acid

(6-{4-[(*tert*-Butoxycarbonyl)amino]piperidin-1-yl}-2-butylpyrimidine-4-carboxylic acid) (**Intermediate 100**) was treated with 4 N HCl/dioxane for as described for **Intermediate 70**. The resulting hydrochloride salt, 6-(4-aminopiperidin-1-yl)-2-butylpyrimidine-4-carboxylic acid hydrochloride salt was coupled to 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid (**Intermediate 3**) in a manner analogous to **Example 29** to give the title compound.

MS (ES) (M+H): 454 for $C_{20}H_{25}Cl_2N_5O_3$

^{1}H NMR δ: 0.95 (t, 3H); 1.36 (m, 2H); 1.56 (m, 2H); 1.71 (m, 2H); 1.96 (m, 2H); 2.15 (s, 3H); 2.80 (m, 2H); 3.36 (b, 2H); 4.18 (m, 1H); 4.52 (m, 2H); 7.15 (s, 1H); 7.29 (d, 1H); 12.01 (s, 1H)

Examples 206-208

The following compounds were synthesized by an analogous method to **Example 29** from 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid (**Intermediate 3**) and the starting materials indicated.

Example 206: 2-Cyclopropyl-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl] amino}piperidin-1-yl)pyrimidine-4-carboxylic acid

Example 207: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-isopropylpyrimidine-4-carboxylic acid

Example 208: 2-*tert*-Butyl-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylic acid

Example	Starting material	^{1}H NMR δ	m/z
206	6-(4-aminopiperidin-1-yl)-2 cyclopropyl pyrimidine-4-carboxylic acid hydrochloride (Intermediate 172)	1.22 (m, 4H); 1.65 (m, 2H); 2.00 (m, 2H); 2.71 (s, 3H); 3.36 (m, 4H); 3.93 (m, 2H); 4.12 (m, 1H); 7.25 (d, 1H); 7.35 (s, 1H); 11.97 (s, 1H)	438
207	6-(4-aminopiperidin-1-yl)-2-isopropyl pyrimidine-4-carboxylic acid hydrochloride (Intermediate 173)	1.29 (d, 6H); 1.68 (m, 2H); 2.02 (m, 2H); 2.22 (s, 3H); 3.31 (m, 1H); 3.54 (m, 2H); 4.26 (m, 2H); 4.21 (m, 1H); 7.27 (d, 1H); 7.43 (s, 1H); 12.12 (s, 1H)	440
208	6-(4-aminopiperidin-1-yl)-2-tert-butyl pyrimidine-4-carboxylic acid hydrochloride (Intermediate 174)	1.29 (s, 9H); 1.58 (m, 2H); 1.93 (m, 2H); 2.11 (s, 3H); 3.32 (m, 2H); 4.17 (m, 2H); 4.21 (m, 1H); 7.06 (s, 1H); 7.18 (d, 1H); 12.02 (s, 1H)	454

Example 209-217

The following compounds were prepared by an analogous method to N-{1-[6-amino-2-(methylsulfanyl)-4-pyrimidinyl]-4-piperidinyl}-3,4-dichloro-5-methyl-1H-pyrrole-2-carboxamide (Example 118) starting from 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid (Intermediate 3) and the intermediates shown in the table below.

Example 209: Methyl 5-(4-{[(3,4-dichloro-5-methyl-1 *H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)thiophene-2-carboxylate

Example 210: Methyl 5-(4-{[(3,4-dichloro-5-methyl-1 *H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-2-furoate

Example 211 : Methyl 3-(4-{[(3,4-dichloro-5-methyl-1 *H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)benzoate

Example 212: Methyl 3-bromo-5-(4-{[(3,4-dichloro-5-methyl-1 *H*-pyrrol-2-yl)carbonyl] amino}piperidin-1-yl)benzoate

100

Example 213: Ethyl 5-(4-{[(3,4-dichloro-5-methyl-1 *H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)nicotinate

Example 214: Methyl 5-(4-{[(3,4-dichloro-5-methyl-1 *H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)nicotinate

Example 215: Methyl 6-(4-{[(3,4-dichloro-5-methyl-1 *H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)pyridine-2-carboxylate

Example 216: Methyl 3-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-5-morpholin-4-ylbenzoate

Example 217: Methyl 3-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-5-(4-methylpiperazin-1-yl)benzoate

Example	Starting material	^{1}H NMR δ	m/z
209	Intermediate 110	1.65-1.78 (m, 2H); 1.91-1.95 (m, 2H); 2.20 (s, 3H); 3.11-3.19 (m, 2H); 3.62-3.67 (m, 2H); 3.74 (s, 3H); 4.01 (m, 1H); 6.24 (d, 1H); 7.30 (d, 1H); 7.54 (d, 1H); 11.98 (s, 1H).	416
210	Intermediate 111	1.56-1.67 (m, 2H); 1.87-1.96 (m, 2H); 2.18 (s, 3H); 3.04 (t, 2H); 3.67-3.71 (m, 5H); 3.98 (m, 1H); 5.5 (d, 1H); 7.25-7.29 (m, 2H); 11.96 s, 1H).	400
211	Intermediate 112	1.61-1.71 (m, 2H); 1.90-1.94 (m, 2H); 2.18 (s, 3H); 2.94 (t, 2H); 3.70-3.75 (m, 2H); 3.84 (s, 3H); 3.96 (m, 1H); 7.23-7.70 (m, 5H); 11.96 (s, 1H).	410
212	Intermediate 113	1.57-1.68 (m, 2H); 1.87-1.91 (m, 2H); 2.18 (s, 3H); 2.99 (t, 2H); 3.76-3.80 (m, 2H); 3.85 (s, 3H); 3.98 (m, 1H); 7.25 (d, 1H); 7.38-7.43 (m, 3H); 11.9 (s, 1H).	489
213	Intermediate 114	1.33 (t, 3H); 1.57-1.73 (m, 2H); 2.08-2.12 (m, 2H); 2.20 (s, 3H); 2.94-3.03 (m, 2H); 3.62-3.66 (m, 2H); 4.09 (m, 1H); 4.32 (q, 2H); 6.52 (d, 1H); 7.70 (s, 1H); 8.39 (s, 1H); 8.60 (s, 1H); 9.26 (s, 1H).	425

Example	Starting material	^{1}H NMR δ	m/z
214	Intermediate 115	1.59-1.72 (m, 2H); 1.90-1.93 (m, 2H); 2.18 (s, 3H); 3.00 (t, 2H); 3.80-3.85 (m, 2H); 3.87 (s, 3H); 3.99 (m, 1H); 7.25 (d, 1H); 7.70 (s, 1H); 8.46 (S, 1H); 8.57 (s, 1H); 11.96 (s, 1H).	411
215	Intermediate 116	1.48-1.59 (m, 2H); 1.87-1.90 (m, 2H); 2.17 (s, 3H); 3.05 (t, 2H); 3.83 (s, 3H); 4.05 (m, 1H); 4.27-4.32 (m, 2H); 7.12 (d, 1H); 7.22 (d, 1H); 7.28 (d, 1H); 7.68 (t, 1H); 12.09 (s, 1H).	411
216	Intermediate 117	1.63 (m, 2H); 1.88 (d, 2H); 2.16 (s, 3H); 2.88 (t, 2H); 3.04-3.19 (m, 4H); 3.62-3.76 (m, 6H); 3.80 (s, 3H); 3.86-3.99 (m, 1H); 6.74 (s, 1H); 6.91 (s, 1H); 6.98 (s, 1H); 7.22 (d, 1H); 11.94 (s, 1H).	495
217	Intermediate 118	1.53-1.73 (q, 2H); 1.89 (d, 2H); 2.17 (s, 3H); 2.30-2.47 (m, 2H); 2.57-2.80 (m, 4H); 2.88 (t, 3H); 3.04-3.25 (m, 4H); 3.69 (d, 2H); 3.80 (s, 3H); 3.85-4.03 (m, 1H); 6.74 (s, 1H); 6.92 (s, 1H); 6.97 (s, 1H); 7.22 (d, 1H); 11.94 (s, 1H).	508

Example 218: Ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate

3,4-Dichloro-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (Intermediate 1; 0.500 g, 2.00 mmol), ethyl 2-bromo-4-methyl-1,3-thiazole-5-carboxylate (0.625 g, 2.00 mmol) and sodium bicarbonate (0.336 g, 2.00 mmol) were stirred in DMF (5 ml). The reaction was heated to 50 °C overnight. The solution was diluted by the addition of water and the resulting layers were separated. The aqueous layer was extracted with EtOAc (3x), and the organic layers were combined, dried over anhydrous magnesium sulfate, filtered and concentrated. Hexanes were added to the crude material, and the precipitate was filtered and rinsed with EtOAc to give the title compound as a beige solid (0.273 g).

MS (ESP): 445 (MH^+) for $C_{18}H_{22}Cl_2N_4O_3S$

^{1}H NMR ($CDCl_3$) δ: 1.32 (t, 3H); 1.62-1.72 (m, 2H); 2.12 (dd, 2H); 2.27 (s, 3H); 2.55 (s, 3H); 3.27 (dt, 2H); 4.11 (d, 2H); 4.13-4.33 (m, 3H); 6.57 (d, 1H); 9.41 (brs, 1H).

Examples 219 and 220

The following example was prepared by the general procedure of Example 218 using 3,4-dichloro-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (Intermediate 1) and the appropriate halide.

Example 219: Ethyl 5-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-1,3,4-thiadiazole-2-carboxylate

Example 220: 3,4-Dichloro-*N*-{1-[5-(ethylthio)-1,3,4-thiadiazol-2-yl]piperidin-4-yl}-5-methyl-1*H*-pyrrole-2-carboxamide

Example	Halide	^{1}H NMR δ	m/z
219	ethyl 5-chloro-1,3,4-thiadiazole-2-carboxylate	1.29 (t, 3H); 1.73 (m, 2H); 1.93 (d, 2H); 2.16 (s, 3H); 3.31-3.45 (hidden by H_2O peak, 2H); 3.99 (d, 2H); 4.00-4.16 (m, 1H); 4.34 (q, 2H); 7.28 (d, 1H); 11.95 (brs, 1H).	418
220	2-bromo-5-(ethylthio)-1,3,4-thiadiazole (Intermediate 67)	1.29 (t, 3H); 1.66 (m, 2H); 1.88 (d, 2H); 2.16 (s, 3H); 3.09-3.28 (overlapping with H_2O peak 2H); 3.77 (d, 2H); 3.91-4.14 (m, 1H); 7.27 (d, 1H); 11.93 (brs, 1H).	420

Examples 221 and 222:

Sulfoxide and sulphone derivatives of 3,4-Dichloro-*N*-{1-[5-(ethylthio)-1,3,4-thiadiazol-2-yl]piperidin-4-yl}-5-methyl-1*H*-pyrrole-2-carboxamide

3,4-Dichloro-*N*-{1-[5-(ethylthio)-1,3,4-thiadiazol-2-yl]piperidin-4-yl}-5-methyl-1*H*-pyrrole-2-carboxamide (Example 220; 2.873 g, 6.80 mmol) was stirred in DCM (42 ml) and cooled to –15 °C. mCPBA (2.51 g, 10.2 mmol) was added, and the reaction mixture was stirred at –15 °C for one hour, then warmed to room temperature. The yellow mixture was washed with 5% sodium thiosulfate (3x), 50 % sodium bicarbonate (1x) and brine (1x), dried over anhydrous magnesium sulfate, filtered, and concentrated to give a mixture of products. The yellow solid was further purified by semi-preparative HPLC (acetonitrile/water buffer (20:80 → 95:5)) to give peak 1 as the sulfoxide (0.040 g) and peak 2 as the sulphone (0.025 g).

Example 221: 3,4-Dichloro-*N*-{1-[5-(ethylsulphinyl)-1,3,4-thiadiazol-2-yl]piperidin-4-yl}-5-methyl-1*H*-pyrrole-2-carboxamide

MS (ESP): 436 (MH^+) for $C_{15}H_{19}Cl_2N_5O_2S_2$

^{1}H NMR δ: 1.17 (t, 3H); 1.69 (m, 2H); 1.92 (dd, 2H); 2.17 (s, 3H); 3.07-3.25 (m, 2H); 3.36-3.54 (m, 2H); 3.82-3.98 (m, 2H); 3.98-4.14 (m, 1H); 7.28 (d, 1H); 11.96 (s, 1H).

Example 222: 3,4-Dichloro-*N*-{1-[5-(ethylsulphonyl)-1,3,4-thiadiazol-2-yl]piperidin-4-yl}-5-methyl-1*H*-pyrrole-2-carboxamide

MS (ESP): 452 (MH^+) for $C_{15}H_{19}Cl_2N_5O_3S_2$

^{1}H NMR δ: 1.23 (t, 3H); 1.70 (m, 2H); 1.93 (dd, 2H); 2.17 (s, 3H); 3.44 (t, 2H); 3.55 (q, 2H); 3.93 (d, 2H); 4.01-4.19 (brs, 1H); 7.28 (d, 1H); 11.97 (s, 1H).

Example 223: 5-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3,4-thiadiazole-2-carboxylic acid

Ethyl 5-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3,4-thiadiazole-2-carboxylate (Example 219; 0.530 g, 1.2 mmol) and lithium hydroxide (0.117 g, 4.9 mmol) were stirred in dioxane (5 ml) and water (0.5 ml) and heated to 50 °C for thirty minutes. The solution was acidified (pH 4) using 1 N HCl resulting in a precipitate. The solids were collected and purified using semi-preparative HPLC to give the title compound (0.025 g).

MS (ESP): 404 (MH^+) for $C_{14}H_{15}Cl_2N_5O_3S$

^{1}H NMR δ: 1.62 (d, 2H); 1.86 (d, 2H): 2.16 (s, 3H); 3.11-3.27 (m, 2H); 3.78 (d, 2H); 3.93-4.08 (m, 1H); 7.55 (d, 1H).

Example 224: 3,4-Dichloro-5-methyl-*N*-[1-(1,3,4-thiadiazol-2-yl)piperidin-4-yl]-1*H*-pyrrole-2-carboxamide

5-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3,4-thiadiazole-2-carboxylic acid (Example 223; 0.250 g, 0.60 mmol) was stirred in 10 mM ammonium acetate (pH 8) (15 ml) and acetonitrile (15 ml) overnight. The mixture was concentrated then the residue was stirred in acetonitrile and filtered. The solid was dissolved in DMSO and purified using semi-preparative HPLC (10% ammonium acetate : water / acetonitrile (20:80-95:5)) to give the title compound as a white solid (0.092 g).

MS (ESP): 360 (MH^+) for $C_{13}H_{15}Cl_2N_5OS$

^{1}H NMR δ: 1.56-1.71 (m, 2H); 1.87 (d, 1H); 2.14 (s, 3H); 3.11-3.51 (overlapping with H_2O peak, 2H); 3.84 (d, 2H); 3.89-4.09 (m, 1H); 7.97 (brs, 1H); 8.79 (s, 1H).

Example 225: 4-(4-{[(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)quinoline-2-carboxylic acid

tert-Butyl 4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidine-1-carboxylate (Intermediate 2) (280 mg, 0.74 mmol) was suspended in 5 ml of 4.0 M HCl in dioxane and stirred for 2 h, then evaporated in vacuo to give a brown solid, which was dissolved in 20 ml of DMF. 4-Bromoquinoline-2-carboxylic acid (188 mg, 0.74 mmol) (prepared via the procedure of Y Kato, et. al., Tetrahedron Lett 2001, 42:4849-51), and sodium bicarbonate (554 mg, 6.6 mmol) were added and the resulting solution was heated under a nitrogen atmosphere with stirring for 20 h. Upon cooling to ambient temperature, the reaction was diluted with 25 ml of water, adjusted to pH 4 using concentrated HCl, filtered and the filtrate extracted with chloroform (2 x 25 ml). The combined organic extract was dried over sodium sulfate and concentrated in vacuo to a yellow solid, which was suspended in 10 ml of MeOH and collected by suction filtration, to afford the title compound as a yellow solid (64 mg).

m.p. 254-256°C.

MS(ES): 448.10/450.10 (MH+) for $C_{21}H_{20}Cl_2N_4O_3$

^{1}H NMR δ: 1.73 (m, 2H); 1.85 (m, 2H); 2.30 (s, 3H); 3.03 (m, 2H); 3.0 – 3.5 (br m, 1H); 3.55 (m, 2H); 3.94 (m, 1H): 7.13 (m, 1H); 7.35 (s, 1H); 7.47 (m, 1H); 7.85 (m, 1H); 7.97 (m, 1H); 11.82 (s, 1H).

Example 226: 3-(4-{[(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)isoxazole-5-carboxylic acid

The title compound was prepared via the procedure described in Example 1 from 182 mg (0.5 mmol) of 3,4-dichloro-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (Intermediate 1) and 103 mg (0.54 mmol) of 3-bromoisoxazole-5-carboxylic acid (Intermediate 120), to afford the title compound as a white solid, (65 mg).

m.p. 232-234 °C (EtOAc).

MS(ES) 343.19/345.24 (M-CO_2) MW 387.23 for $C_{15}H_{16}Cl_2N_4O_4$

^{1}H NMR δ: 1.52 (m, 2H); 1.88 (m, 2H); 2.22 (s, 3H); 2.91 (m, 1H); 3.20 (m, 2H); 3.68 (m, 1H); 4.06 (m, 1H); 4.11 (d, 1H, J = 6.0 Hz); 4.26 (m, 1H); 7.29 (d, 1H, J = 6.0 Hz); 12.03 (s, 1H).

Example 227: 2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylic acid

Methyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylate (Example 320, 250 mg, 0.60 mmol) was dissolved in THF (3 ml). 2 N lithium hydroxide solution in water (3 ml, 6.00 mmol) was added and the mixture was refluxed for 1 hr. The mixture was cooled to room temperature and acidified with 10% HCl solution. The mixture was extracted with EtOAc and organic layer was washed with water twice, dried over sodium sulfate and concentrated to give the desired product. The crude material was dissolved in DMF and purified by semi-preparative reverse phase HPLC eluting with acetonitrile/water (0.1% TFA). The desired fraction were collected and concentrated affording the title compound (28 mg).

MS (ES): 403 (MH^+) for $C_{15}H_{16}Cl_2N_4O_3S$

^{1}H NMR δ: 1.73 (m, 2H); 1.99 (m, 2H); 2.22 (s, 3H); 3.36 (m, 2H); 3.57 (m, 2H); 4.14 (m, 1H); 7.27 (d, 1H); 7.77 (s, 1H); 11.97 (s, 1H); 12.64 (s, 1H).

Example 228: 2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-1,3-thiazole-4-carboxylic acid

The title compound was prepared in a manner analogous to Example 227 from ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-4-carboxylate (Example 336).

MS (ES): 403 (MH^+) for $C_{15}H_{16}Cl_2N_4O_3S$

^{1}H NMR δ: 1.44 (m, 2H); 1.66 (m, 2H); 1.95 (s, 3H); 2.93 (m, 2H); 3.62 (m, 2H); 3.80 (m, 1H); 7.04 (d, 1H); 7.40 (s, 1H); 11.74 (s, 1H).

Example 229: 2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-*N*-methoxy-1,3-thiazole-5-carboxamide

2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-1,3-thiazole-5-carboxylic acid (Example 227, 100 mg, 0.25 mmol) was reacted with methoxylamine hydrochloride according to procedure described in Example 8 to afford the title compound (30 mg).

MS (ES): 432 (MH^+) for $C_{16}H_{19}Cl_2N_5O_3S$

^{1}H NMR δ: 1.54 (m, 2H); 1.78 (m, 2H); 2.07 (s, 3H); 3.24 (m, 2H); 3.57 (brs, 4H); 3.86 (m, 2H); 4.02 (m, 1H); 7.16 (d, 1H); 7.62 (s, 1H); 11.47 (s, 1H); 11.86 (s, 1H).

Example 230: 2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-*N*-methoxy-1,3-thiazole-4-carboxamide

Prepared in a manner analogous to Example 229 starting from 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-1,3-thiazole-4-carboxylic acid (Example 228).

MS (ES): 432 (MH^+) for $C_{16}H_{19}Cl_2N_5O_3S$

^{1}H NMR δ: 1.54 (m, 2H); 1.76 (m, 2H); 2.05 (s, 3H); 3.04 (m, 2H); 3.54 (s, 3H); 3.79 (m, 2H); 3.93 (m, 1H); 7.15 (d, 1H); 7.32 (s, 1H); 11.24 (s, 1H); 11.84 (s, 1H).

Example 231: 3,4-Dichloro-*N*-{1-[5-(hydrazinocarbonyl)-1,3-thiazol-2-yl]piperidin-4-yl}-5-methyl-1*H*-pyrrole-2-carboxamide

2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-1,3-thiazole-5-carboxylic acid (Example 227, 100 mg, 0.240 mmol) was dissolved in DMF (1 ml) and hydrazine (500 µL, 16.0 mmol). The mixture was stirred at room temperature for 2 h. The mixture was filtered and purified by semi-preparative reverse phase HPLC eluting with acetonitrile/water (0.1% TFA)(36 mg).

MS (ES): 417 (MH^+) for $C_{15}H_{18}Cl_2N_6O_2S$

^{1}H NMR δ: 1.62 (m, 2H); 1.89 (m, 2H); 2.17 (s, 3H); 3.29 (m, 2H); 3.47 (m, 2H); 3.89 (m, 2H); 4.04 (m, 1H); 7.26 (d, 1H); 7.80 (s, 1H); 9.92 (brs, 1H); 11.97 (s, 1H)

Example 232: 2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-*N*-(methylsulfonyl)-1,3-thiazole-5-carboxamide

2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylic acid (Example 227; 0.160 g, 0.397 mmol) was suspended in toluene (3 ml) and thionyl chloride (0.288 ml, 3.97 mmol) was added dropwise at room temperature. The solution was refluxed for 1 h. Excess thionyl chloride and toluene were removed in vacuo. The precipitate formed was dissolved in dioxane and methane sulfonamide (0.075 g, 0.794 mmol) was added. The mixture was stirred at 100 °C for 0.5 h after which DBU (0.119 ml, 0.794 mmol) was added. The mixture was stirred for a further 1 h at room temperature was acidified with 10% HCl solution. The mixture was extracted with EtOAc and washed with water. The organic layer was dried over sodium sulfate and conc in vacuo. The crude mixture dissolved in DMSO, and was purified by reverse phase HPLC eluting with acetonitrile/water (0.1% TFA) to afford the desired product. (15 mg).

MS (ES): 480 (MH^+) for $C_{16}H_{19}Cl_2N_5O_4S_2$

^{1}H NMR δ: 1.58 (m, 2H); 1.90 (m, 2H); 2.18 (s, 3H); 3.32 (m, 5H); 3.94 (m, 2H); 4.09 (m, 1H); 7.30 (d, 1H); 8.13 (s, 1H); 11.92 (brs, 1H); 11.98 (s, 1H)

Example 233: 3,4-Dichloro-5-methyl-*N*-{1-[5-(1*H*-tetrazol-5-yl)-1,3-thiazol-2-yl]piperidin-4-yl}-1*H*-pyrrole-2-carboxamide

To a solution of 3,4-dichloro-*N*-[1-(5-cyano-1,3-thiazol-2-yl)piperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide (Example 321, 0.100 g, 0.26 mmol) in DMF (3 ml) was added sodium azide (0.169 g, 2.60 mmol) followed by the addition of ammonium chloride (0.139 g, 2.60 mmol) at room temperature. The reaction was stirred at 120 °C for 3 hrs. The reaction mixture was cooled to room temperature, filtered and purified by reverse phase HPLC eluting with acetonitrile/water (0.1% TFA) (0.025 g).

MS (ES): 427 (MH^+) for $C_{15}H_{16}Cl_2N_8OS$

^{1}H NMR δ: 1.60 (m, 2H); 1.86 (m, 2H); 2.11 (s, 3H); 3.27 (m, 2H); 3.88 (m, 2H); 4.01 (m, 1H); 7.36 (d, 1H); 7.79 (s, 1H); 11.91 (s, 1H)

Example 234: 3,4-Dichloro-5-methyl-*N*-{1-[5-(1*H*-tetrazol-5-yl)-1,3-thiazol-2-yl]piperidin-4-yl}-1*H*-pyrrole-2-carboxamide

The title compound was prepared in a manner analogous to Example 233 from 3,4-dichloro-*N*-[1-(4-cyano-1,3-thiazol-2-yl)piperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide (Example 337).

MS (ES): 427 (MH^+) for $C_{15}H_{16}Cl_2N_8OS$

^{1}H NMR δ: 1.61 (m, 2H); 1.86 (m, 2H); 2.11 (s, 3H); 3.20 (m, 2H); 3.90 (m, 2H); 4.00 (m, 1H); 7.23 (d, 1H); 7.59 (s, 1H); 11.92 (s, 1H)

Example 235: *N*-(1-{4-[(*Z*)-Amino(hydroxylimino)methyl]-1,3-thiazol-2-yl}piperidin-4-yl)-3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxamide

To a solution of 3,4-dichloro-*N*-[1-(5-cyano-1,3-thiazol-2-yl)piperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide (Example 321, 0.100 g, 0.26 mmol) in MeOH (2 ml) was added TEA (50 µL, 0.26 mmol) followed by the addition of hydroxylamine hydrochloride (0.0182 g, 0.26 mmol) and treated as described in Example 47 to afford the title compound (0.049 g).

MS (ES): 417 (MH^+) for $C_{15}H_{18}Cl_2N_6O_2S$

^{1}H NMR δ: 1.63 (m, 2H); 1.91 (m, 2H); 2.17 (s, 3H); 3.32 (m, 2H); 3.89 (m, 2H); 4.07 (m, 1H); 7.27 (d, 1H); 7.88 (s, 1H); 10.46 (s, 1H); 11.98 (s, 1H)

Example 236: *N*-(1-{4-[(*E*)-Amino(hydroxyimino)methyl]-1,3-thiazol-2-yl}piperidin-4-yl)-3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxamide

Prepared in a manner analogous to Example 235 from 3,4-dichloro-*N*-[1-(4-cyano-1,3-thiazol-2-yl)piperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide (Example 337).

MS (ES): 417 (MH^+) for $C_{15}H_{18}Cl_2N_6O_2S$

^{1}H NMR δ: 1.62 (m, 2H); 1.90 (m, 2H); 2.18 (s, 3H); 3.23 (m, 2H); 3.94 (m, 2H); 4.07 (m, 1H); 7.29 (d, 1H); 7.82 (s, 1H); 8.84 (brs, 2H); 11.11 (s, 1H); 12.00 (s, 1H)

Example 237: 2-(4-{[(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-4-(hydroxymethyl)-1,3-thiazole-5-carboxylic acid

The title compound was prepared in a manner analogous to Example 31 from ethyl 2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-4-(hydroxymethyl)-1,3-thiazole-5-carboxylate (Example 138).

MS (ES) MH+: 433 for $C_{16}H_{18}Cl_2N_4O_4S$

^{1}H NMR δ: 1.59-1.67 (m, 1H); 1.89-1.93 (d, 2H); 2.18 (s, 3H); 3.23-3.29 (t, 2H); 2.18 (s, 3H); 3.23-3.29 (t, 2H); 3.91 (d, 2H); 4.07 (brs, 1H); 4.58 (s, 2H); 7.28-7.30 (d, 1H); 11.98 (s, 1H).

Example 238: 2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-4-[(2-methoxyethoxy)methyl]-1,3-thiazole-5-carboxylic acid

Prepared in an analogous manner to Example 129 starting from ethyl 2-(4-aminopiperidin-1-yl)-4-[(2-methoxyethoxy)methyl]-1,3-thiazole-5-carboxylate hydrochloride (Intermediate 126) and 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid (Intermediate 3). The ester product was submitted to hydrolysis using LiOH/THF at 65°C.

MS (ES) (M+H): 493 for $C_{19}H_{24}Cl_2N_4O_5S$

^{1}H NMR δ: 1.71 (m, 2H); 1.91 (m, 2H); 2.17 (s, 3H); 3.22 (s, 3H); 3.44 (b, 2H); 3.57 (m, 2H); 3.80 (m, 1H); 3.94 (m, 2H); 4.07-4.29 (m, 2H); 4.52 (m, 2H); 7.15 (s, 1H); 7.30 (d, 1H); 12.03 (s, 1H)

Examples 239-241

The following compounds were prepared in a manner analogous to Example 238 using 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid (Intermediate 3) and the starting materials given in the table below.

Example 239: 2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrolyl)carbonyl]amino}piperidin-1-yl)-4-(trifluoromethyl)-1,3-thiazole-5-carboxylic acid

Example 240: 4-Butyl-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-1,3-thiazole-5-carboxylic acid

Example 241: 2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-4-(methoxymethyl)-1,3-thiazole-5-carboxylic acid

Example	SM	^{1}H NMR δ	m/z
239	Ethyl 2-(4-aminopiperidin-1-yl)-4-(trifluoromethyl)-1,3-thiazole-5-carboxylate hydrochloride salt (Intermediate 78)	1.71 (m, 2H); 1.90 (m, 2H); 2.15 (s, 3H); 3.06 (b, 2H); 3.93 (m, 2H); 4.12 (m, 1H); 7.40 (d, 1H); 11.33 (s, 1H); 13.43 (b, 1H).	471
240	Ethyl 2-(4-aminopiperidin-1-yl)-4-(methoxymethyl)-1,3-thiazole-5-carboxylate hydrochloride (Intermediate 79)	1.42 (m, 2H); 1.67 (m, 2H); 1.95 (s, 3H); 3.09 (m, 5H); 3.67 (m, 2H); 3.82 (m, 1H); 4.34 (s, 2H); 7.08 (d, 1H); 11.74 (s, 1H); 12.54 (s, 1H)	447, 451
241	Ethyl 2-(4-aminopiperidin-1-yl)-4-butyl-1,3-thiazole-5-carboxylate hydrochloride salt (Intermediate 80)	1.29 (s, 9H); 1.58 (m, 2H); 1.93 (m, 2H); 2.11 (s, 3H); 3.32 (m, 2H); 4.17 (m, 2H); 4.21 (m, 1H); 7.06 (s, 1H); 7.18 (d, 1H); 12.02 (s, 1H)	459

Example 242: 4-[(Acetyloxy)methyl]-2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylic acid

2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-4-(hydroxymethyl)-1,3-thiazole-5-carboxylic acid (Example 237; 100 mg, 0.23 mmol) was dissolved in pyridine (2 ml) and cooled to 0°C. Acetic anhydride (21.8 µl, 0.230 mmol) was added and mixture was stirred at room temperature for 1 h. The mixture was diluted with

EtOAc and washed with water. Organic phase was dried over Na_2SO_4 and concentrated in vacuo to give the title compound (40 mg).

MS (ES) MH+: 477 for $C_{18}H_{20}Cl_2N_4O_5S$

^{1}H NMR δ: 1.60-1.63 (m, 2H); 1.86-1.91 (m, 4H); 2.03 (s, 2H); 2.18 (s, 3H); 3.16-3.24 (t, 2H); 3.83-3.87 (d, 2H); 4.02-4.03 (s, 1H); 5.25 (d, 1H).

Example 243: 4-[(Butyryloxy)methyl]-2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl) carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylic acid

The title compound was prepared in a manner analogous to Example 242 from 2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-4-(hydroxymethyl)-1,3-thiazole-5-carboxylic acid (Example 237) and butanoic anhydride.

MS (ES) MH+: 503 for $C_{20}H_{24}Cl_2N_4O_5S$

^{1}H NMR δ: 0.88-0.92 (t, 3H); 1.54-1.59 (m, 2H); 1.61-1.67 (m, 2H); 1.89-1.92 (d, 2H); 2.18 (s, 3H); 2.30-2.33 (t, 2H); 3.25-3.31 (t, 2H); 3.89-3.92 (d, 2H); 4.07 (m, 1H); 4.58 (s, 2H); 5.3 (s, 2H); 7.27-7.29 (d, 1H); 11.98 (s, 1H); 12.84 (s, 1H).

Example 244: 4-{[(2-Carboxybenzoyl)amino]methyl}-2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylic acid

Ethyl 2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-4-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1,3-thiazole-5-carboxylate (Example 277; 194 mg, 0.32 mmol) in anhydrous THF (2 ml) was added 2 N LiOH (0.82 ml). The mixture was stirred at room temperature for 4 h. The mixture was acidified to pH 3 and the precipitate that formed was diluted with water and extracted with EtOAc, dried over Na_2SO_4 and concentrated in vacuo to give the title compound (160 mg).

MS (ES) MH+: 580 for $C_{24}H_{23}Cl_2N_5O_6S$

^{1}H NMR δ: 1.71-1.73 (d, 2H); 1.96-1.99 (d, 2H); 2.23 (s, 3H); 3.23 (s, 1H); 3.31-3.37 (brs, 3H); 4.01-4.03 (d, 2H); 4.13 (m, 1H); 4.67 (s, 2H); 7.37-7.39 (d, 1H); 7.54-7.69 (m, 3H); 7.76-7.78 (d, 1H); 12.06 (s, 1H); 12.88 (s, 1H).

Example 245: 2-(4-{[(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-4-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1,3-thiazole-5-carboxylic acid

4-{[(2-Carboxybenzoyl)amino]methyl}-2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylic acid (Example 244;100 mg;

0.17 mmol) was stirred with 4 N HCl/Dioxane (3 ml) at room temperature for 8 h. The mixture was concentrated in vacuo and the resulting solid was purified by reversed phase HPLC eluting with water/acetonitrile/ammonium acetate buffer mixtures giving the title compound (31 mg).

MS (ES) MH+: 564 for $C_{24}H_{21}Cl_2N_5O_5S$

^{1}H NMR δ: 1.55-1.60 (m, 2H); 1.79-1.81 (d, 2H); 2.29 (s, 3H); 3.03-3.08 (t, 2H); 3.61-3.64 (d, 2H); 3.98-3.99 (m, 1H); 5.13 (s, 2H); 7.88-7.89 (d, 1H); 7.94-8.01 (m, 4H).

Example 246: Ethyl 4-(aminomethyl)-2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylate

Ethyl 2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-4-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1,3-thiazole-5-carboxylate (Example 277; 1.43 g, 2.42 mmol) in EtOH (10 ml) was added hydrazine hydrate (0.174 ml; 3.63 mmol) and refluxed for 14 h. The reaction mixture cooled to room temperature and concentrated in vacuo, diluted with DCM and acidified with 10% HCl, washed with H_2O. The precipitate was filtered and dried in vacuo to give the title compound (600 mg).

MS (ES) MH+: 461 for $C_{18}H_{23}Cl_2N_5O_3S$

Example 247: 4-(Aminomethyl)-2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylic acid

The title compound was prepared in a manner analogous to Example 31 from ethyl 4-(aminomethyl)-2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylate (Example 246) and LiOH/ THF.

MS (ES) MH+: 434 for $C_{16}H_{19}Cl_2N_5O_3S$

^{1}H NMR δ: 1.42-1.57 (d, 2H); 1.63 (s, 6H); 1.75-1.83 (d, 2H); 2.10 (s, 3H); 3.03-3.10 (t, 2H); 3.74-3.79 (m, 4H); 3.93 (m, 1H); 8.22 (d, 1H); 9.32 (brs, 1H)

Example 248: 4-({[Amino(imino)methyl]amino}methyl)-2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylic acid

Ethyl 4-(aminomethyl)-2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylate (Example 246) (300 mg, 0.652 mmol) was dissolved in NMP (2 ml). di-tert-butyl [(Z)-1H-pyrazol-1-ylmethylylidene] biscarbamate(1.01 g, 3.26 mmol) was added and the mixture was stirred at 50 °C for 18 h

(LCMS:702, 705). 4 N HCl/Dioxane (10 ml) was added and mixture was heated at 50 °C for 5 h. The solvent was removed in vacuo and the residual material was diluted with EtOAc, washed with sodium bicarbonate. Organic layer was filtered and dried over Na_2SO_4 and concentrated in vacuo to give the ethyl ester (320 mg): (LCMS:502,505). Ethyl ester (185 mg, 0.3 mmol) was dissolved in THF (3 ml) and 2 N LiOH (1.84 ml, 3.6 mmol) was heated at 50 °C for 4 h. The solvent was removed in vacuo and residual material was acidified to pH 3. The precipitate was filtered, washed with water, extracted with EtOAc, dried over Na_2SO_4 and concentrated in vacuo affording the title compound (47 mg).

MS (ES) MH+: 434 for $C_{17}H_{21}Cl_2N_7O_3S$

^{1}H NMR δ: 1.61 (m, 2H); 1.88 (m, 2H); 2.15 (s, 3H); 3.14 (t, 2H); 3.82-3.84 (d, 2H); 4.00 (brs, 1H); 4.40 (s, 2H); 6.60 (s, 2H); 7.33 (d, 1H); 8.12 (s, 1H); 12.09 (s, 1H).

Example 249: 2-(4-{[(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-4-{[(methylsulfonyl)amino]methyl}-1,3-thiazole-5-carboxylic acid

Ethyl 4-(aminomethyl)-2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-1,3-thiazole-5-carboxylate (**Example 246**; 312 mg, 0.677 mmol) was dissolved in DCM and methanesulfonyl chloride (65 µl; 0.844 mmol) was added slowly. The reaction was stirred at room temperature for 16 h, diluted with DCM, washed well with water dried over Na_2SO_4 and concentrated in vacuo to give the title compound as a light brown thick oil (350 mg)- (LCMS (ES) MH+: 538). The ethyl ester product was hydrolysed with lithium hydroxide/THF in a manner analogous to **Example 31** to give the title compound (30 mg).

MS (ES) MH+: 512 for $C_{17}H_{21}Cl_2N_5O_3S_2$

^{1}H NMR δ: 1.51-1.60 (q, 2H); 1.82-1.85 (m, 2H); 2.11 (s, 3H); 2.79 (s, 3H); 3.14-3.21 (t, 2H); 3.83-3.86 (d, 2H); 4.00 (s, 1H); 4.40 (s, 2H); 7.29 (d, 1H); 12.00 (s, 1H).

Example 250: 4-({[(tert-Butylamino)carbonyl]amino}methyl)-2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylic acid

Ethyl 4-(aminomethyl)-2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-1,3-thiazole-5-carboxylate (**Example 246**; 200 mg; 0.424 mmol) was dissolved in DCM (4 ml). tert-Butyl isocyanate (130 mg; 1.28 mmol) was added and the mixture stirred at room temperature for 1 h. The solvent was removed in vacuo and the ester

(215 mg), LCMS :561 was treated with LiOH/THF in a manner analogous to Example 31 to give the title compound (290 mg).

MS (ES) MH+: 533 for $C_{21}H_{28}Cl_2N_6O_4S$

^{1}H NMR δ: 1.21 (s, 9H); 1.60-1.68 (m, 2H); 1.90-1.93 (m, 2H); 2.18 (s, 3H); 3.25-3.28 (m, 2H); 3.95-3.98 (d, 2H); 4.05-4.10 (m, 1H); 4.34 (s, 2H); 5.92 (s, 1H); 6.06 (s, 1H); 7.49-7.51 (d, 1H).

Example 251: 2-(4-{[(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-4-({[(ethylamino)carbonyl]amino}methyl)-1,3-thiazole-5-carboxylic acid

The title compound was prepared in a manner analogous to Example 250 from ethyl 4-(aminomethyl)-2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylate (Example 246) and ethyl isocyanate.

MS (ES) MH+: 506 for $C_{19}H_{24}Cl_2N_6O_4S$

^{1}H NMR δ: 0.95-1.00 (t, 3H); 1.60-1.69 (m, 2H); 1.91 (m, 2H); 2.18 (s, 3H); 2.97-3.04 (q, 2H); 3.20-3.24 (t, 2H); 3.90-3.94 (d, 2H); 4.05-4.06 (m, 1H); 4.34 (s, 2H); 6.13 (brs, 1H); 6.42 (brs, 1H); 7.41-7.44 (d, 1H).

Example 252: 4-[(Butyrylamino)methyl]-2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylic acid

The title compound was prepared in a manner analogous to Example 242 from 4-(aminomethyl)-2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-1,3-thiazole-5-carboxylic acid (Example 247) and butanoic anhydride.

MS (ES) MH+: 504 for $C_{20}H_{25}Cl_2N_5O_4S$

^{1}H NMR δ: 0.77-0.81 (t, 3H); 1.40-1.48 (m, 2H); 1.53-1.59 (m, 2H); 1.82-1.85 (d, 2H); 2.00-2.04 (t, 2H); 2.11 (s, 3H); 3.16-3.20 (t, 2H); 3.84-3.87 (d, 2H); 3.97-4.02 (m, 1H); 4.37-4.38 (d, 2H); 7.26-7.28 (d, 1H); 8.02 (s, 1H); 11.98 (brs, 1H); 12.64 (brs, 1H).

Example 253: 2-(4-{[(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-4-{[(tetrahydrofuran-3-ylcarbonyl)amino]methyl}-1,3-thiazole-5-carboxylic acid

Ethyl 4-(aminomethyl)-2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-1,3-thiazole-5-carboxylate (Example 246; 200 mg; 0.434 mmol) was dissolved in anhydrous DMF (2 ml). HATU 165 mg; 0.434 mmol) was added followed by diisopropylethylamine (149 µl, 0.868 mmol). The reaction mixture was stirred for 10 minutes

and tetrahydrofuran-3-carboxylic acid (50 mg; 0.434 mmol) and reaction was stirred at room temperature for 2.5 h. The mixture was diluted with EtOAc, washed well with water, dried over Na_2SO_4 and concentrated in vacuo to give the title compound as an off-white solid (220 mg)- (LCMS (ES) MH+: 558, 561). The ethyl ester product was hydrolysed with lithium hydroxide/THF in a manner analogous to **Example 31** to give the title compound (25 mg).

MS (ES) MH+: 533 for $C_{21}H_{25}Cl_2N_5O_5S$

^{1}H NMR δ: 1.68 (m, 2H); 1.92-1.97 (m, 3H); 2.00-2.07 (m, 2H); 2.25 (s, 3H); 2.97-3.07 (m, 1H); 3.22-3.30 (m, 2H); 3.66-3.72 (m, 2H); 3.74-3.79 (m, 1H); 3.86-3.94 (m, 2H); 4.08 (m, 1H); 4.47-4.49 (d, 1H); 7.59-7.62 (d, 1H); 9.05 (s, 1H)

Example 254: 2-(4-{[(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-sulfonic acid

3,4-Dichloro-5-methyl-N-[1-(1,3-thiazol-2-yl)piperidin-4-yl]-1H-pyrrole-2-carboxamide (**Example 329**; 692 mg, 1.93 mmol) was dissolved in anhydrous DCM. Chlorosulfonic acid (513 µl, 7.7 mmol) was added slowly and the mixture was heated at 60 °C for 2 h. The mixture was cooled to 0 °C and water was added, whereupon a brown solid separated. This was filtered and washed well with water, dried in vacuo to give the title compound (393 mg).

MS (ES) MH+: 441 for $C_{14}H_{16}Cl_2N_4O_4S_2$

^{1}H NMR δ: 1.83 (m, 2H); 2.06 (m, 2H); 2.28 (s, 3H); 3.46 (m, 2H); 3.94 (m, 3H); 7.10 (s, 1H); 7.41 (d, 1H); 12.19 (s, 1H)

Example 255: N-{1-[5-(Aminosulfonyl)-1,3-thiazol-2-yl]piperidin-4-yl}-3,4-dichloro-5-methyl-1H-pyrrole-2-carboxamide

0.5 M ammonia /dioxane (10 ml, 5 mmol) was added to 2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-sulfonic acid (**Example 254**; 100 mg, 0.226 mmol) in a pressure bottle. The mixture was stirred at room temperature for 4 h. Excess solvent was removed in vacuo and the brown solid was dried in vacuo to give the title compound (56 mg).

MS (ES) MH+: 438 for $C_{14}H_{16}Cl_2N_4O_4S_2$

^{1}H NMR δ: 1.75 (m, 2H); 1.92 (m, 2H); 2.18 (s, 3H); 3.27 (m, 2H); 3.86 (m, 2H); 4.10 (m, 1H); 7.01 (s, 1H); 7.14 (d, 1H); 7.34 (s, 2H); 12.07 (s, 1H)

Example 256: 3,4-Dichloro-N-{1-[5-(hydroxymethyl)-1,3,4-thiadiazol-2-yl]piperidin-4-yl}-5-methyl-1H-pyrrole-2-carboxamide

A solution of ethyl 5-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3,4-thiadiazole-2-carboxylate (Example 219, 280 mg, 0.65 mmol) in THF (5 ml) was cooled to 0 °C and treated with diisobutylaluminium hydride (1.3 ml, 1.95 mmol) dropwise over 5 min. The reaction was kept in the ice bath and allowed to slowly warm to room temperature while stirring overnight. LC-MS indicated that the reaction was complete. The reaction was quenched with aqueous Rochelle salt, and the resultant mixture was diluted with EtOAc (10 ml) and stirred vigorously for 2 h. The layers were separated, and the aqueous portion was extracted with EtOAc. The combined organic portions were dried (Na_2SO_4), filtered, and concentrated to give a pale orange oil. The crude material was purified by preparatory HPLC (35-75% CH_3CN/H_2O, 0.1% TFA, 14 min.) to give 17 mg of the title compound.

MS (ES$^+$): 390.07 for $C_{14}H_{17}Cl_2N_5O_2S$

^{1}H NMR δ: 1.6 (m, 2H); 1.82 (m, 2H); 2.11 (s, 3H); 3.21 (t, 2H); 3.96 (m, 3H); 7.2 (d, 1H); 11.9 (s, 1H)

Example 257: 3-Quinolinecarboxylic acid, 1-[4-[[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino]-1-piperidinyl]-1,4-dihydro-4-oxo-, ethyl ester

A solution of N-(1-aminopiperidin-4-yl)-3,4-dichloro-5-methyl-1H-pyrrole-2-carboxamide (Intermediate 89, 400 mg ,1.4 mmol) and ethyl (2Z)-3-ethoxy-2-(2-fluorobenzoyl)acrylate (WO 2000040561 A1, 370 mg, 1.4 mmol) in 20 ml EtOH was stirred at room temperature for 2 hours. After dilution with 100 ml water, solids were filtered and dried in vacuo. The solids were suspended in 20 ml dioxane containing DBU (300 µl) and the mixture was heated in a microwave reactor at 120 °C for 3 hours. Solvent was removed and the residue was dissolved in EtOAc before being washed wit water and brine. Drying ($MgSO_4$) and removal of solvent followed by trituration with hot EtOAc gave 160 mg of product as a white solid.

MS (ES): 491.0 $(M+H)^+$, MS (ES): 489.2 $(M-H)^-$.

^{1}H NMR δ: 1.31 (t, J=7.16 Hz, 3H); 1.78 - 2.12 (m, 4H); 2.14 - 2.30 (m, 3H); 3.12 (s, 2H); 3.34 - 3.50 (m, 2H); 4.05 (s, 1H); 4.14 - 4.37 (m, 2H); 7.26 (d, J=7.72 Hz, 1H); 7.49 (t, J=7.54 Hz, 1H); 7.71 - 7.95 (m, 1H); 8.07 - 8.31 (m, 2H); 8.97 (s, 1H); 12.04 (s, 1H).

Example 258: 1-{4-[[(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

A suspension of 3-quinolinecarboxylic acid, 1-[4-[[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino]-1-piperidinyl]-1,4-dihydro-4-oxo-, ethyl ester (**Example 257**, 67 mg, 0.14 mmol) in 5 ml MeOH and 150 µl (0.15 mmol) of aqueous 1 N NaOH was heated at 80 °C for 40 min in a microwave reactor. A solution aqueous 1 N HCl (150 µl) was added affording a mass of solid precipitate. The mixture was taken up in hot water and insoluble material was filtered to afford 19 mg of product as a white solid.

MS (ES): 463 $(M+H)^+$, MS (ES): 461 $(M-H)^-$.

^{1}H NMR δ: 2.03 (s, 4H); 2.19 (s, 3H); 3.18 (s, 2H); 3.53 (s, 2H); 4.09 (s, 1H); 7.25 (s, 1H); 7.69 (s, 1H); 8.01 (s, 1H); 8.39 (s, 2H); 9.37 (s, 1H); 11.82 - 12.44 (m, 1H); 15.25 (s, 1H).

Example 259: 3,4-Dichloro-N-[1-(3-formyl-1H-pyrrol-1-yl)piperidin-4-yl]-5-methyl-1H-pyrrole-2-carboxamide

A mixture of *N*-(1-aminopiperidin-4-yl)-3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxamide (**Intermediate 89**; 67 mg, 0.14 mmol), 2,5-dimethoxytetrahydrofuran-3-carbaldehyde (100 µl, 4.2 mg), and sodium acetate (0.35 g, 4.1 mmol) in 30 ml acetic acid was heated at 70 °C for 2 hours. Solvent was removed and the residue was portioned between EtOAc and aqueous Na_2CO_3. Insoluble material was removed by filtering through diatomaceous earth rinsing through with EtOAc. The EtOAc from the filtrate was separated and washed with water and brine. Drying ($MgSO_4$) and removal of solvent gave a brown solid that was purified by normal phase chromatography (100% DCM with gradient elution to 2% MeOH in DCM) to give a material that was triturated with ether to afford 110 mg of a white solid.

MS (ES): 369 $(M+H)^+$, MS (ES): 367.2 $(M-H)^-$.

^{1}H NMR δ: 1.65 - 1.89 (m, 2H); 1.90 - 2.11 (m, 2H); 2.18 (s, 3H); 3.15 (dd, J=7.06, 3.30 Hz, 4H); 3.92 (s, 1H); 6.44 (dd, J=3.01, 1.88 Hz, 1H); 7.15 - 7.27 (m, 1H); 7.31 (d, J=7.72 Hz, 1H); 7.89 (t, J=1.88 Hz, 1H); 9.62 (s, 1H); 12.00 (s, 1H).

Example 260: 3,4-Dichloro-N-(1-{3-[(E)-(hydroxylimino)methyl]-1H-pyrrol-1-yl}piperidin-4-yl)-5-methyl-1H-pyrrole-2-carboxamide

A solution of 3,4-dichloro-N-[1-(3-formyl-1H-pyrrol-1-yl)piperidin-4-yl]-5-methyl-1H-pyrrole-2-carboxamide (**Example 259**, 151 mg, 0.41 mmol) and 50% aqueous hydroxylamine (55 µl, 0.83 mmol) in 5 ml EtOH was heated at 80 °C for 30 min. The mixture was diluted

with EtOAc and washed with brine. Drying ($MgSO_4$) and removal of solvent gave a solid that was purified by reverse phase HPLC (30-55% gradient CH_3CN in water with 0.1% TFA) to give product as a mixture of geometrical isomers.

MS (ES): 384 $(M+H)^+$, MS (ES): 282 $(M-H)^-$.

^1H NMR δ: 1.78 (m, 1H); 1.94 (m, 2H); 2.2 (s, 3H); 2.95 - 3.24 (m, 4H); 3.91 (m, 1H); 6.1 - 6.3 (2d, 1H); 6.9 and 7.1 (2s, 1H); 7.16 (s, 1H); 7.22 - 7.41 (m, 1H); 7.6 and 7.9 (2s, 1H); 10.9 and 10.4 (2s, 1H); 12.00 (s, 1H).

Example 261: 1-(4-{[(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1H-pyrrole-3-carboxylic acid

Solutions of 3,4-dichloro-N-[1-(3-formyl-1H-pyrrol-1-yl)piperidin-4-yl]-5-methyl-1H-pyrrole-2-carboxamide (Example 259, 90 mg, 0.24 mmol) in 10 ml acetone and $KMNO_4$ (39 mg, 0.24 mmol) in 3 ml water were combined and stirred at ambient temperature overnight. Due to incomplete conversion, solutions of $KMnO_4$ (15 and 20 mg) in 3 ml water were added at 5 hour intervals. The mixture was quenched with aqueous $NaHSO_3$ and partitioned between EtOAc and water. The EtOAc was separated and washed with brine. Drying ($MgSO_4$) and removal of solvent gave product as a white solid.

MS (ES): 384 $(M+H)^+$, MS (ES): 282 $(M-H)^-$.

^1H NMR δ: 1.79 (d, J=3.58 Hz, 2H); 1.86 - 2.04 (m, 2H); 2.18 (s, 3H); 3.11 (d, J=3.39 Hz, 4H); 3.77 - 4.05 (m, 1H); 6.22 - 6.42 (m, 1H); 7.05 (t, J=2.45 Hz, 1H); 7.31 (d, J=7.72 Hz, 1H); 7.58 (s, 1H); 11.96 (d, J=31.65 Hz, 2H).

Example 262: 1-(4-{[(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)isoquinoline-3-carboxylic acid

In a mixture of 20 ml THF, 5 ml H_2O, and 1 ml 50 wt % NaOH (aq) was dissolved methyl 1-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)isoquinoline-3-carboxylate (Example 301; 70 mg). The solution was stirred at 80 °C for 1 hr. The solution was cooled to room temperature, diluted with EtOAc and acidified with dilute HCl (aq). The EtOAc fraction was isolated, at which time a white solid precipitated from solution. The solid was collected by filtration and washed with acetonitrile to yield 50 mg white solid product.

MS (ES): 447 $(M+H)^+$.

^1H NMR δ: 1.90 (s, 2H); 1.98 - 2.12 (m, 2H); 2.19 (s, 3H); 3.14 (m, 2H); 3.82 (m, 2H); 4.04 (s, 1H); 7.31 (m, 1H); 7.77 (m, 2H); 8.06 - 8.21 (m, 2H); 12.02 (s, 1H); 12.79 (s, 1H).

Example 263: 1-(4-{[(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-4-methoxyisoquinoline-3-carboxylic acid

In a sealed high pressure container with a Teflon lining was combined ethyl 1-chloro-4-methoxyisoquinoline-3-carboxylate (EP 650961 A1; 390 mg, 1.55 mmol), 4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidinium trifluoroacetate (Intermediate 86; 1.7 g, 4.4 mmol), and K_2CO_3 (2.2 g) in 20 ml tert-butanol. The container was heated at 170 °C with stirring for 8 hours. The solution was concentrated by rotary evaporation and reconstituted with EtOAc. The organic layer was washed 4x with H_2O, and dried over $MgSO_4$. Crude ethyl 1-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-4-methoxyisoquinoline-3-carboxylate was purified by reverse phase Si yielding 20 mg of the intermediate ester. The ethyl ester was then hydrolyzed as in Example 262 to yield 13.5 mg white solid final product.

MS (ES): 477 $(M+H)^+$, MS (ES): 475 $(M-H)^-$.

^{1}H NMR δ: 1.81 - 1.97 (m, 2H); 2.01 (s, 2H); 2.14 - 2.26 (m, 3H); 3.06 (t, J=11.30 Hz, 2H); 3.71 (m, 2H); 3.93 (s, 3H); 4.03 (s, 1H); 7.40 (m, 1H); 7.73 - 7.89 (m, 2H); 8.10 - 8.22 (m, 2H); 12.12 (s, 1H).

Example 264: Ethyl 1-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2,7-naphthyridine-3-carboxylate

In a sealed high pressure container with a Teflon lining was combined ethyl 1-chloro-2,7-naphthyridine-3-carboxylate (280 mg, 1.18 mmol), 4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidinium trifluoroacetate (Intermediate 86; 957 mg), and K_2CO_3 (1.25 g) in 15 ml tert-butanol. The container was heated at 170 °C with stirring for 8 hours. The solution was concentrated by rotary evaporation and reconstituted with EtOAc. The organic layer was washed 4x with H_2O, and dried over $MgSO_4$. Product was purified on reverse phase Si to yield 36 mg white solid.

MS (ES): 476 $(M+H)^+$.

^{1}H NMR δ: 1.82 - 1.95 (m, 2H); 1.99 - 2.11 (m, 2H); 2.14 - 2.22 (m, 3H); 3.23 - 3.33 (m, 2H); 3.98 - 4.14 (m, 2H); 4.37 (m, 1H); 7.33 (d, J=7.54 Hz, 1H); 7.97 (d, J=5.28 Hz, 1H); 8.05 (s, 1H); 8.75 (d, J=5.28 Hz, 1H); 9.41 (s, 1H); 12.01 (s, 1H).

Example 265: 1-(4-{[(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2,7-naphthyridine-3-carboxylic acid

As described for the synthesis of Example 262, ethyl 1-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2,7-naphthyridine-3-carboxylate (Example 264; 30 mg) was hydrolyzed to yield 9.1 mg yellow solid.

MS (ES): 448 $(M+H)^+$, MS (ES): 446 $(M-H)^-$.

^{1}H NMR δ: 1.80 - 1.94 (m, 2H); 1.98 - 2.12 (m, 2H); 2.19 (s, 3H); 3.24 - 3.36 (m, 2H); 4.07 (d, J=13.57 Hz, 3H); 7.31 (d, J=8.29 Hz, 1H); 7.95 - 8.09 (m, 2H); 8.73 (d, J=5.28 Hz, 1H); 9.43 (s, 1H); 12.02 (s, 1H).

Example 266: Ethyl 4-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)quinazoline-2-carboxylate

As described for the synthesis of Example 264, ethyl 4-chloroquinazoline-2-carboxylate (690 mg), 4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidinium trifluoroacetate (Intermediate 86; 1.7 g), and K_2CO_3 (1.7 g) in 20 ml tert-butanol were combined to yield 662 mg grey solid.

MS (ES): 476 $(M+H)^+$.

^{1}H NMR δ: 1.34 (t, J=7.16 Hz, 3H); 1.79 (m, 2H); 2.01 (s, 2H); 2.18 (s, 3H); 4.17 (s, 1H); 4.33 - 4.46 (m, 4H); 7.33 (d, J=7.54 Hz, 1H); 7.68 (d, J=6.03 Hz, 1H); 7.88 - 7.98 (m, 1H); 8.06 (d, J=9.04 Hz, 1H); 12.03 (s, 1H).

Example 267: 4-(4-{[(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)quinazoline-2-carboxylic acid

As described for the synthesis of Example 262, ethyl 4-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)quinazoline-2-carboxylate (Example 266; 100 mg) was hydrolyzed to yield 32 mg white solid.

MS (ES): 448 $(M+H)^+$, MS (ES): 446 $(M-H)^-$.

^{1}H NMR δ: 1.60 - 1.75 (m, 2H); 1.75 - 1.90 (m, 2H); 2.15 - 2.24 (s, 3H); 3.70 - 3.86 (m, 2H); 4.23 (m, 1H); 4.53 (m, 2H); 7.41 (d, J=7.54 Hz, 1H); 7.69 (t, J=7.16 Hz, 1H); 7.92 - 8.04 (m, 2H); 8.10 (d, J=8.29 Hz, 1H); 12.11 (s, 1H).

Example 268: Methyl 4-amino-2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylate

A suspension of methyl N-cyano-4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidine-1-carbimidothioate (**Intermediate 91**, 1.78 g, 4.8 mmol) and methyl mercaptoacetate (0.43 ml, 4.8 mmol) with TEA (1.2 ml, 8.6 mmol) in MeOH was stirred at room temperature overnight. Reaction mixture was concentrated to 50% volume, the precipitate was filtered off and the solid was washed with MeOH and dried.

MS (ES): 432 $(M+H)^+$.

^{1}H NMR δ: 1.54 - 1.69 (m, 2H); 1.90 (dd, J=12.62, 2.83 Hz, 2H); 2.18 (s, 3H); 3.16 - 3.31 (m, 2H); 3.61 (s, 3H); 3.87 (d, J=14.69 Hz, 2H); 3.99 - 4.14 (m, 1H); 6.84 (s, 2H); 7.29 (d, J=7.91 Hz, 1H); 11.98 (s, 1H).

Example 269: 3,4-Dichloro-N-[1-(5-cyano-4-methoxy-1,3-thiazol-2-yl)piperidin-4-yl]-5-methyl-1H-pyrrole-2-carboxamide

A suspension of N-[1-(aminocarbonothioyl)piperidin-4-yl]-3,4-dichloro-5-methyl-1H-pyrrole-2-carboxamide (**Intermediate 95**, 0.22 g, 0.7 mmol) and tert-butyl chloro(cyano)acetate (0.12 g, 0.7 mmol) in MeOH was heated to 80 °C in the microwave reactor for 40 minutes. The product precipitated and was filtered off.

MS (ES): 414 $(M+H)^+$.

^{1}H NMR δ: 1.57 - 1.72 (m, 2H); 1.93 (dd, J=12.81, 3.01 Hz, 2H); 2.18 (s, 3H); 3.28 - 3.43 (m, 2H); 3.80 - 3.94 (m, 2H); 3.97 (s, 3H); 4.01 - 4.15 (m, 1H); 7.31 (d, J=7.72 Hz, 1H); 12.00 (s, 1H).

Example 270: 3,4-Dichloro-N-[1-(5-cyano-4-hydroxy-1,3-thiazol-2-yl)piperidin-4-yl]-5-methyl-1H-pyrrole-2-carboxamide

Iodotrimethylsilane (0.02 ml, 0.13 mmol) was added to a suspension of 3,4-dichloro-N-[1-(5-cyano-4-methoxy-1,3-thiazol-2-yl)piperidin-4-yl]-5-methyl-1H-pyrrole-2-carboxamide (**Example 269**, 0.04 g, 0.1 mmol) in DCM:$CHCl_3$ (1:1). After stirring for one hour the reaction was complete. Partitioning with EtOAc and water, drying organic portion with $MgSO_4$ and concentrating yielded a yellow oil which, after triturating with ether, gave a yellow solid.

MS (ES): 400 $(M+H)^+$.

^{1}H NMR δ: 1.65 (s, 2H); 1.84 - 1.95 (m, 2H); 2.08 - 2.20 (m, 3H); 3.77 - 3.90 (m, 2H); 4.09 (s, 2H); 4.41 (s, 1H); 7.25 - 7.39 (m, 1H); 12.00 (d, J=5.84 Hz, 1H); 12.48 (s, 1H).

Example 271: Methyl 2-(4-{[(3,4-dichloro-5-cyano-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-1,3-thiazole-5-carboxylate

TEA (0.06 ml, 0.5 mmol) was added to a solution of methyl 2-(4-aminopiperidin-1-yl)-1,3-thiazole-5-carboxylate (Intermediate 134, 0.1 g, 0.5 mmol)) in anhydrous THF. To this was added 3,4-dichloro-5-cyano-1H-pyrrole-2-carbonyl chloride (Intermediate 132, 0.1 g, 0.5 mmol) as a solution in anhydrous THF. After stirring 15 minutes, THF was removed. The product was partitioned with EtOAc and water. The organic portion was dried with $MgSO_4$ and concentrated to a yellow oil. Trituration with ether followed by filtration yielded a tan solid.

MS (ES): 428 $(M+H)^+$

^{1}H NMR δ: 1.65 (s, 2H); 1.87 (s, 2H); 3.09 (s, 1H); 3.25 - 3.40 (m, 2H); 3.75 (s, 3H); 3.95 (d, J=13.75 Hz, 2H); 7.87 (s, 2H).

Example 272: 2-(4-{[(3,4-Dichloro-5-cyano-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylic acid

The title compound was prepared by a procedure analogous to Intermediate 3 starting from methyl 2-(4-{[(3,4-dichloro-5-cyano-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylate (Example 271). The reaction mixture was concentrated to remove MeOH. Water was added and the pH was adjusted to pH 4 with $NaHCO_3$. The product was extracted with $CHCl_3$:isopropanol (3:1). Drying (MgSO4) and removal of solvent yielded a white solid. The was dried in drying pistol at 75 °C under vacuum.

MS (ES): 414 $(M+H)^+$.

^{1}H NMR δ: 1.66 (s, 2H); 1.91 (s, 2H); 3.36 (s, 2H); 3.94 (d, J=13.38 Hz, 2H); 4.09 (s, 1H); 7.76 - 7.91 (m, 1H); 8.04 (d, J=7.72 Hz, 1H); 12.64 (s, 1H); 13.86 (s, 1H).

Example 273: Methyl 4-(4-{[(3,4-dichloro-5-cyano-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)quinoline-2-carboxylate

The title compound was prepared by an analogous procedure to Example 271 starting from 3,4-dichloro-5-cyano-1H-pyrrole-2-carbonyl chloride (Intermediate 132) and methyl 4-(4-aminopiperidin-1-yl)quinoline-2-carboxylate hydrochloride (Intermediate 136).

^{1}H NMR δ: 1.95 (d, J=15.82 Hz, 2H); 2.99 - 3.14 (m, 2H); 3.38 (q, J=6.97 Hz, 2H); 3.54 - 3.69 (m, 2H); 3.94 (s, 4H); 7.55 (s, 1H); 7.69 (t, J=7.63 Hz, 1H); 7.76 - 7.86 (m, 1H); 7.96 - 8.11 (m, 2H).

Example 274: 4-(4-{[(3,4-Dichloro-5-cyano-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)quinoline-2-carboxylic acid

The title compound was prepared by an analogous procedure to **Intermediate 3** starting with methyl 4-(4-{[(3,4-dichloro-5-cyano-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl) quinoline-2-carboxylate (**Example 273**) and following the work-up procedure of **Example 272.**

MS (ES) $(M+H)^+$: 458

^{1}H NMR δ: 1.93 (s, 2H); 2.05 (s, 2H); 3.27 (s, 2H); 3.77 (s, 2H); 4.12 (s, 1H); 7.56 (s, 1H); 7.69 (s, 1H); 7.85 (s, 1H); 8.05 (s, 1H); 8.18 (d, J=8.67 Hz, 2H).

Example 275: N-Methoxy 8-fluoro-4-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)quinoline-2-carboxamide

The title compound was prepared from 8-fluoro-4-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)quinoline-2-carboxylic acid (**Example 280**) and O-methylhydroxylamine hydrochloride via the procedure described for **Example 8.**

MS(ES+): 494/496 for $C_{22}H_{22}Cl_2FN_5O_3$

^{1}H NMR δ:1.88 (m, 2H); 2.06 (m, 2H); 2.17 (s, 3H); 2.98 (m, 2H); 3.50 (m, 2H); 3.69 (s, 3H); 4.04 (m, 1H); 7.42 (m, 2H); 7.59 (s, 1H); 7.72 (m, 1H); 8.13 (s, 2H)

Example 276: Ethyl 2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-4-(methoxymethyl)-1,3-thiazole-5-carboxylate

The title compound was prepared from 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid (**Intermediate 3**) and ethyl 2-(4-aminopiperidin-1-yl)-4-(methoxymethyl)-1,3-thiazole-5-carboxylate hydrochloride (**Intermediate 36**) in a manner analogous to **Example 29.**

MS (ES) (M+H): 474 for $C_{19}H_{24}Cl_2N_4O_4S$

Example 277: Ethyl 2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-4-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1,3-thiazole-5-carboxylate

The title compound was prepared from 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid (Intermediate 3) and ethyl 2-(4-aminopiperidin-1-yl)-4-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1,3-thiazole-5-carboxylate hydrochloride (Intermediate 77) in a manner analogous to Example 29.

MS (ES) (M+H): 593 for $C_{26}H_{25}Cl_2N_5O_5S$

Example 278:6-Chloro-4-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)quinoline-2-carboxylic acid

Methyl 6-chloro-4-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl] amino}piperidin-1-yl)quinoline-2-carboxylate (Example 134; 20 mg) was dissolved in 6 ml of 2:1 THF/MeOH, 0.20 ml of 1 N NaOH was added and the resulting solution was stirred at ambient temperature for 20 h. Following neutralization with 0.25 ml of 1 N HCl, the reaction was diluted with 5 ml of water and filtered. The solid was washed with water and dried under vacuum, giving 18.4 mg of a light yellow granular solid.

MS(ES+): 480.94/482.94/484.94 for $C_{21}H_{19}Cl_3N_4O_3$

^{1}H NMR δ: 1.81 (m, 2H); 1.94 (m, 2H); 2.09 (s, 3H); 3.07 (m, 2H); 3.25 (s, 1H); 3.50 (m, 2H); 4.00 (m, 1H); 7.23 (d, 1H, J = 7.54); 7.48 (s, 1H); 7.74 (d, 1H, J = 9.04); 7.88 (s, 1H); 8.02 (d, 1H, J = 9.04); 11.93 (s, 1H).

Examples 279-283

The following compounds were prepared by an analogous method to Example 278.

Example	Compound	^{1}H NMR δ	m/z (ES^+)	SM
279	8-Methoxy-4-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl] amino}piperidin-1-yl)quinoline-2-carboxylic acid	1.86 (m, 2H); 1.99 (m, 2H); 2.14 (s, 3H); 3.05 (m, 2H); 3.56 (m, 2H); 3.94 (s, 3H); 4.00 (m, 1H); 3.9-4.5 (v br s, 1H); 7.21 (m, 1H); 7.29 (m, 1H); 7.52 (m, 3H); 11.97 (s, 1H)	477 / 479	Example 323

Example	Compound	^{1}H NMR δ	m/z (ES^+)	SM
280	8-Fluoro-4-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)quinoline-2-carboxylic acid	1.86 (m, 2H); 2.03 (m, 2H); 2.14 (s, 3H); 3.06 (m, 2H); 3.59 (m, 2H); 3.87 (s, 3H); 4.01 (m, 1H); 7.56 (m, 3H); 7.80 (m, 1H)	465 / 467	Example 324
281	6-Fluoro-4-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)quinoline-2-carboxylic acid	1.91 (m, 2H); 2.03 (m, 2H); 2.18 (s, 3H); 3.14 (m, 2H); 3.61 (m, 2H); 4.05 (m, 1H); 7.31 (d, 1H, J = 7.5); 7.58 (s, 1H); 7.68 (m, 1H); 7.80 (m, 1H); 8.20 (m, 1H); 12.03 (s, 1H)	465 / 467	Example 325
282	8-Chloro-4-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)quinoline-2-carboxylic acid	1.85 (m, 2H); 2.02 (m, 2H); 2.14 (s, 3H); 3.06 (m, 2H); 3.57 (m, 2H); 3.93 (s, 3H); 3.99 (m, 1H); 7.36 (d, 1H, J = 7.5); 7.55 (s, 1H); 7.58 (m, 1H); 7.93 (m, 2H)	481 / 483	Example 326
283	2-(4-{[(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)oxazole-4-carboxylic acid	1.60 (m, 2H); 1.86 (m, 2H); 2.18 (s, 3H); 3.16 (m, 2H); 3.89 (m, 2H); 4.02 (m, 1H); 7.27 (d, 1H, J = 7.7); 8.22 (s, 1H); 11.99 (s, 1H); 12.72 (br s, 1H)	387 / 389	Example 328

Example 284: 5-(4-{[(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)nicotinamide

The title compound was synthesized by an analogous method to Example 8 starting from 5-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)nicotinic acid (Example 291) and a solution of ammonia in MeOH.

MS (ESP) (MH^+): 396 for $C_{17}H_{19}Cl_2N_5O_2$

^{1}H NMR δ: 1.60-1.73 (m, 2H); 1.89-1.92 (m, 2H); 2.17 (s, 3H); 2.98 (t, 2H); 3.79-3.84 (m, 2H); 3.97 (m, 1H); 7.33 (d, 1H); 7.51 (s, 1H); 7.69 (s, 1H); 8.09 (s, 1H); 8.41-8.44 (m, 2H); 12.04 (s, 1H).

Example 285: 5-(4-{[(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-N-methoxynicotinamide

The title compound was synthesized by an analogous method to Example 8 starting from 5-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)nicotinic acid (Example 291) and methoxylamine hydrochloride.

MS (ESP) (MH^+): 426 for $C_{18}H_{21}Cl_2N_5O_3$

^{1}H NMR δ: 1.59-1.70 (m, 2H); 1.89-1.92 (m, 2H); 2.17 (s, 3H); 2.99 (t, 2H); 3.72 (s, 3H); 3.79-3.84 (m, 2H); 4.00 (m, 1H); 7.25 (d, 1H); 7.56 (s, 1H); 8.27 (s, 1H); 8.47 (d, 1H); 11.85 (s, 1H); 11.96 (s, 1H).

Example 286: 4-(4-{[(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-N-methoxypyridine-2-carboxamide

The title compound was synthesized by an analogous method to Example 8 starting from 4-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyridine-2-carboxylic acid (Example 293) and methoxylamine hydrochloride.

MS (ESP) (MH^+): 426 for $C_{18}H_{21}Cl_2N_5O_3$

^{1}H NMR δ: 1.52-1.62 (m, 2H); 1.87-1.95 (m, 2H); 2.17 (s, 3H); 3.11 (t, 2H); 3.67 (s, 3H); 3.93-3.98 (m, 2H); 4.07 (m, 1H); 7.01 (m, 1H); 7.26 (d, 1H); 7.39 (d, 1H); 8.15 (d, 1H); 11.82 (s, 1H); 11.97 (s, 1H).

Examples 287 - 294

The following examples were prepared by an analogous method to Example 310 starting from the ester and 2 N lithium hydroxide.

Ex	Compound	^{1}H NMR δ	M/z (M+1)	SM
287	3-Bromo-5-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl] amino}piperidin-1-yl)benzoic acid	1.53-1.72 (m, 2H); 1.82-1.95 (m, 2H); 2.17 (s, 3H); 2.97 (t, 2H); 3.71-3.84 (m, 2H); 3.98 (m, 1H); 7.26 (d, 1H); 7.36 (s, 2H); 7.43 (s, 1H); 12.02 (s, 1H); 13.19 (br s, 1H).	474, 476 (M, M+2)	Example 212
288	3-Allyl-5-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl] amino}piperidin-1-yl)benzoic acid	1.53-1.75 (m, 2H); 1.83-1.98 (m, 2H); 2.17 (s, 3H); 2.90 (t, 2H); 3.27-3.44 (m overlapping water, 2H); 3.61-3.78 (m, 2H); 3.95 (m, 1H); 5.00-5.20 (m, 2H); 5.94 (m, 1H); 7.05 (s, 1H); 7.18 (s, 1H); 7.26 (d, 1H); 7.32 (s, 1H); 11.97 (s, 1H); 12.78 (br s, 1H).	436	Example 295
289	3-(4-{[(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-5-(2,3-dihydroxypropyl) benzoic acid	1.60-1.79 (m, 2H); 1.87-2.00 (m, 2H); 2.18 (s, 3H); 2.69-2.84 (m, 1H); 2.99 (t, 2H); 3.21-3.38 (m, 4H); 3.89-4.04 (m, 2H); 7.06-7.46 (m, 4H); 11.57 (s, 1H).	470	Example 296
290	5-(4-{[(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl) isophthalic acid	1.72-1.89 (m, 2H); 2.06-2.13 (m, 2H); 2.21 (s, 3H); 3.00 (t, 2H); 3.62-3.71 (m, 2H); 4.07 (m, 1H); 7.70 (s, 2H); 7.88 (s, 1H).	440	Example 297
291	5-(4-{[(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl) nicotinic acid	1.60-1.71 (m, 2H); 1.89-1.98 (m, 2H); 2.17 (s, 3H); 3.06 (t, 2H); 3.85-3.90 (m, 2H); 4.04 (m, 1H); 7.38 (d, 2H); 7.88 (s, 1H); 8.46 (s, 1H); 8.57 (s, 1H); 12.10 (s, 1H).	397	Example 214

Ex	Compound	^{1}H NMR δ	M/z (M+1)	SM
292	6-(4-{[(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl) pyridine-2-carboxylic acid	1.48-1.63 (m, 2H); 1.86-1.90 (m, 2H); 2.17 (s, 3H); 3.05 (t, 2H); 4.03 (m, 1H); 4.13-4.36 (m, 2H); 7.10 (d, 1H); 7.21-7.29 (m, 2H); 7.67 (m, 1H); 11.96 (s, 1H); 12.65 (br s, 1H).	397	Example 215
293	4-(4-{[(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl) pyridine-2-carboxylic acid	1.55-1.67 (m, 2H); 1.93-1.99 (m, 2H); 2.18 (s, 3H); 3.31-3.39 (m, overlapping water, 2H); 4.13-4.18 (m 3H); 7.15 (d, 1H); 7.41-7.56 (m, 2H); 7.99 (d, 1H); 12.14 (s, 1H).	397	Example 299
294	5-(4-{[(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl) nicotinic acid 1-oxide	1.55-1.70 (m, 2H); 1.80-1.93 (m, 2H); 2.17 (s, 3H); 3.03 (t, 2H); 3.75-3.85 (m, 2H); 4.00 (m, 1H); 7.20-7.33 (m, 2H); 7.90 (s, 1H); 8.17 (s, 1H); 12.01, s, 1H); 13.73 (br s, 1H).	413	Example 300

Examples 295-300

The following compounds were prepared by an analogous method to Example 118 starting from 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid (Intermediate 3) and the intermediates shown in the table below.

Ex	Compound	^{1}H NMR δ	M+1	SM
295	Methyl 3-allyl-5-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl] amino}piperidin-1-yl) benzoic acid	1.60-1.70 (m, 2H); 1.86-1.93 (m, 2H); 2.17 (s, 3H); 2.93 (t, 2H); 3.37 (d, 2H); 3.68-3.73 (m, 2H); 3.82 (s, 3H); 3.96 (m, 1H); 5.05-5.14 (m, 2H); 5.94 (m, 1H); 7.20-7.33 (m, 4H); 11.95 (s, 1H).	450	Intermediate 143

Ex	Compound	^{1}H NMR δ	M+1	SM
296	Methyl 3-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl) carbonyl]amino} piperidin-1-yl)-5-(2,3-dihydroxy propyl)benzoate	1.55-1.71 (m, 2H); 1.88-1.94 (m, 2H); 2.17 (s, 3H); 2.76 (m, 1H); 2.90 (t, 2H); 3.22-3.33 (m, 3H); 3.57-3.70 (m, 4H); 3.81 (s, 3H); 3.92-3.96 (m, 2H); 7.10 (s, 1H); 7.25-7.35 (m, 3H); 11.97 (s, 1H).	484	Intermediate 144
297	Dimethyl 5-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl] amino}piperidin-1-yl)isophthalate	1.60-1.70 (m, 2H); 1.91-1.98 (m, 2H); 2.17 (s, 3H); 3.00 (t, 2H); 3.76-3.81 (m, 2H); 3.87 (s, 6H); 4.00 (m, 1H); 7.25 (d, 1H); 7.71 (s, 2H); 7.87 (s, 1H); 11.95 (s, 1H)	468	Intermediate 145
298	Dimethyl 2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl] amino}piperidin-1-yl)terephthalate	1.65-1.76 (m, 2H); 1.90-1.98 (m, 2H); 2.18 (s, 3H); 2.87 (t, 2H); 3.24-3.28 (m, 2H); 3.85 (s, 3H); 3.87 (s, 3H); 3.91 (m, 1H); 7.29 (d, 1H); 7.53-7.69 (m, 3H); 11.97 (s, 1H).	468	Intermediate 146
299	Methyl 4-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl] amino}piperidin-1-yl)pyridine-2-carboxylate	1.47-1.63 (m, 2H); 1.87-1.92 (m, 2H); 2.17 (s, 3H); 3.13 (t, 2H); 3.85 (s, 3H); 3.95-4.06 (m, 2H); 4.09 (m, 1H); 7.08 (m, 1H); 7.23 (d, 1H); 7.47 (s, 1H); 8.24 (d, 1H); 11.96 (s, 1H).	411	Intermediate 147
300	Methyl 5-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl] amino}piperidin-1-yl)nicotinate 1-oxide	1.50-1.66 (m, 2H); 1.85-1.88 (m, 2H); 2.17 (s, 3H); 3.04 (t, 2H); 3.78-3.83 (m, 2H); 3.87 (s, 3H); 4.00 (m, 1H); 7.23 (d, 1H); 7.35 (s, 1H); 7.93 (s, 1H); 8.18 (s, 1H); 11.96 (s, 1H).	427	Intermediate 148

Example 301: Methyl 1-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)isoquinoline-3-carboxylate

In a sealed high pressure container with a Teflon lining was combined methyl 1-chloroisoquinoline-3-carboxylate (Intermediate 86; 450 mg, 2 mmol), (1.7 g, 4.4 mmol), and K_2CO_3 (1.7 g) in 20 ml tert-butanol. The container was heated at 155 °C with stirring for 3 hours. The solution was concentrated by rotary evaporation and reconstituted with EtOAc. The organic layer was washed 4x with H_2O, and dried over $MgSO_4$. Crude product was purified by flash Si and 100 mg yellow solid collected.

MS (ES): 461 $(M+H)^+$, MS (ES): 459 $(M-H)^-$.

^{1}H NMR δ: 1.89 (m, 2 H) 2.03 (s, 2 H) 2.19 (s, 3 H) 3.06 - 3.21 (m, 2 H) 3.89 (s, 2 H) 4.05 (s, 1 H) 7.33 (s, 1 H) 7.79 (s, 2 H) 8.11 (m, 2 H) 8.19 (s, 1 H) 12.02 (s, 1 H).

Example 302: Methyl 5-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-1,3,4-oxadiazole-2-carboxylate

The title compound was synthesized by an analogous method to Example 42 by coupling methyl 5-{4-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-1,3,4-oxadiazole-2-carboxylate (Intermediate 160) with 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid (Intermediate 3). De-BOC and coupling should be separate steps.

MS (ESP): 402.0 (M+H) for $C_{15}H_{17}Cl_2N_5O_4$

^{1}H NMR δ: 1.57 (m, 2H); 1.86 (d, 2H); 2.11 (s, 3H); 3.02 (m, 2H); 3.82 (s, 3H); 3.84 (d, 2H); 3.96 (m, 1H); 7.19 (d, 1H); 11.91 (s, 1H).

Example 303: 3,4-Dichloro-N-{1-[5-(hydroxymethyl)-1,3,4-oxadiazol-2-yl]piperidin-4-yl}-5-methyl-1H-pyrrole-2-carboxamide

Diisobutylaluminum hydride (0.94 ml, 1 M solution in toluene, 0.94 mmol) was added dropwise to a solution of methyl 5-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3,4-oxadiazole-2-carboxylate (Example 302) (95 mg, 0.24 mmol) in THF (8 ml) at 0 °C. The resultant mixture was allowed to slowly warm to room temperature and was stirred overnight. Potassium sodium tartrate (15 ml, 10% aqueous solution) and EtOAc (100 ml) were added to the reaction mixture and the resultant mixture was stirred vigorously for 1 h. The organic phase was separated, dried over sodium sulfate, filtered and concentrated. The crude residue was purified by preparative reversed-phase HPLC (water/acetonitrile gradient, 10-95%) to yield 45 mg of the title compound.

MS (ESP): 374.0 (M+H) for $C_{14}H_{17}Cl_2N_5O_3$

^{1}H NMR δ: 1.55 (m, 2H); 1.83 (d, 2H); 2.11 (s, 3H); 3.13 (t, 2H); 3.74 (d, 2H); 3.94 (m, 1H); 4.38 (s, 2H); 5.80 (br s, 1H); 7.19 (d, 1H); 11.90 (s, 1H).

Example 304: 5-(4-{[(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3,4-oxadiazole-2-carboxylic acid

The title compound was synthesized by an analogous method to **Example 310** using methyl 5-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3,4-oxadiazole-2-carboxylate (**Example 302**).

MS (ESP): 388.0 (M+H) for $C_{14}H_{15}Cl_2N_5O_4$

^{1}H NMR δ: 1.55 (m, 2H); 1.81 (d, 2H); 2.11 (s, 3H); 3.10 (t, 2H); 3.72 (d, 2H); 3.94 (m, 1H); 7.31 (d, 1H); 6.80-7.40 (br. s, 2H).

Example 305: 3,4-Dichloro-5-methyl-N-[1-(1,3,4-oxadiazol-2-yl)piperidin-4-yl]-1H-pyrrole-2-carboxamide

The title compound was synthesized by an analogous method to **Example 310** using methyl 5-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3,4-oxadiazole-2-carboxylate (**Example 302**) (spontaneous decarboxylation occurred during the hydrolysis).

MS (ESP): 344.2 (M+H) for $C_{13}H_{15}Cl_2N_5O_2$

Example 306: 3,4-Dichloro-5-methyl-*N*-{1-[2-(methylthio)pyrimidin-4-yl]piperidin-4-yl}-1*H*-pyrrole-2-carboxamide

3,4-Dichloro-*N*-[1-(2-chloropyrimidin-4-yl)piperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide (**Example 307**, 200 mg, 0.515 mmol) and sodium thiomethoxide (108.2 mg, 1.545 mmol) were combined in DMF (12 ml) and heated at 90 °C for 1 h. The reaction mixture was cooled to room temperature, diluted with EtOAc and water. The phases were separated, and the aqueous phase was extracted three times with EtOAc. The combined organic portions were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a peach coloured solid (200 mg, 0.499 mmol, 97% yield) that was used without further purification.

MS (ESI): 398.12, 400.05 for $C_{16}H_{19}Cl_2N_5OS$

^{1}H NMR δ: 1.25 (m, 2H); 1.62 (m, 2H); 1.93 (s, 3H); 2.17 (s, 3H); 2.86 (m, 2H); 3.83 (m, 1H); 4.07 (m, 2H); 6.35 (d, 1H); 7.00 (d, 1H); 7.76 (d, 1H); 11.72 (s, 1H)

Example 307: 3,4-Dichloro-*N*-[1-(2-chloropyrimidin-4-yl)piperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide

3,4-Dichloro-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (Intermediate 1, 650 mg, 2.08 mmol), 2,4-dichloropyrimidine (309.7 mg, 2.08 mmol), and Et_3N (0.6 ml, 4.16 mmol) were combined in DMF (12 ml) and heated at 90 °C under nitrogen for 1.5 h. Upon cooling to room temperature, the reaction was diluted with EtOAc and water. The phases were separated, and the aqueous portion was extracted twice with EtOAc. The combined organic portions were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a light brown solid. The crude material was triturated with cold MeOH and filtered to give 458 mg (1.18 mmol, 57%) of the title product.

MS (ES$^-$): 386.09, 388.03, 389.83 for $C_{15}H_{16}Cl_2N_5O$

^{1}H NMR δ: 1.60 (m, 2H); 1.93 (m, 2H); 2.23 (s, 3H); 3.22 (m, 2H); 4.17 (m, 2H); 4.34 (m, 1H); 6.94 (d, 1H); 7.27 (d, 1H); 8.12 (d, 1H); 12.02 (s, 1H)

Example 308: 1-(6-Chloro-4-cyanopyridin-2-yl)piperidin-4-yl 3,4-dichloro-5-methyl-1H-pyrrole-2-carboxylate

3,4-Dichloro-5-methyl-1H-pyrrole-2-carboxylic acid (Intermediate 3, 164 mg, 0.84 mmol) was dissolved in anhydrous THF (3 ml). 2-Chloro-6-(4-hydroxypiperidin-1-yl)isonicotinonitrile (Intermediate 26), 200 mg, 0.84 mmol) was added, then DEAD (133 µl, 0.84 mmol) was added dropwise followed by triphenylphosphine (221 mg, 0.84 mmol). The mixture was stirred at room temperature for 18 h. The mixture was concentrated, filtered and purified by semi-preparative reverse phase HPLC eluting with CH_3CN/water (0.1% TFA). (135 mg).

MS (ES, M+H): 413 for $C_{17}H_{15}Cl_2N_4O_2$

^{1}H NMR δ: 1.63 (m, 2H); 1.80 (m, 2H); 2.08 (s, 3H); 3.70 (m, 4H); 5.21 (m, 1H); 7.14 (s, 1H); 7.32 (s, 1H); 12.12 (s, 1H)

Example 309: 3,4-Dichloro-N-{1-[6-chloro-4-(hydrazinocarbonyl)pyridin-2-yl]piperidin-4-yl}-5-methyl-1H-pyrrole-2-carboxamide

Diisopropylethylamine (0.043 ml, 0.25 mmol), HATU (0.048 g, 0.12 mmol) and HOAT (0.017 g 0.12 mmol) were added to a stirred solution of 2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)isonicotinic acid (**Example 153**; 0.055 g, 0.12 mmol) in DMF (2 ml). The resultant solution was stirred for 5 mins and hydrazine (0.04 ml, 0.12 mmol) was added. The mixture was stirred at room temperature for 14 h, partitioned between water and EtOAc. The layers were separated and the organic layer was washed with water two more times. The organic phase was dried over magnesium sulfate and concentrated to give the title compound (30 mg).

MS (ES) : 445 (MH^+) for $C_{17}H_{19}Cl_3N_6O_2$

Example 310: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-morpholin-4-ylpyrimidine-4-carboxylic acid

Methyl 6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-morpholin-4-ylpyrimidine-4-carboxylate (**Example 9**, 224 mg, 0.45 mmol) was dissolved in MeOH (5 ml). 2 N lithium hydroxide (2 ml) was added and the reaction was stirred at room temperature for 3 h. The mixture was acidified with 1 N HCl and was extracted with EtOAc (3x50 ml), dried over Na_2SO_4 and concentrated in vacuo to provide 200 mg of the title compound.

MS (ESP): 483.4 (M+H) for $C_{20}H_{24}Cl_2N_6O_4$

Example 311: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-2-methoxypyrimidine-4-carboxylic acid

Title compound was synthesized by an analogous method to **Example 312** using methyl 2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)pyrimidine-4-carboxylate (**Example 6**) and sodium methoxide.

MS (ES): 428 (M+1) for $C_{17}H_{19}Cl_2N_5O_4$

^{1}H NMR δ: 1.54 (m, 2H); 1.88 (m, 2H); 2.16 (s, 3H); 3.20 (t, 2H); 3.86 (s, 3H); 4.10 (m, 1H); 4.40 (m, 2H); 7.05 (s, 1H); 7.24 (d, 1H); 11.97 (s, 1H).

Example 312: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-ethoxypyrimidine-4-carboxylic acid

Sodium ethoxide solution (1 ml, 3.0 mmol, 21 wt % in EtOH) was added to a stirred solution of methyl 2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylate (Example 6, 0.40 g, 0.89 mmol) in DMF (1.5 ml). The reaction was stirred overnight, then quenched with water (2 ml) and the EtOH removed under reduced pressures. The resulting aqueous solution was acidified with 1 N HCl (pH ~ 2) and the precipitated product was collected by suction filtration (0.07 g).

MS (ES): 442 (M+1) for $C_{18}H_{21}Cl_2N_5O_4$

^{1}H NMR δ: 1.28 (t, 3H); 1.49 (m, 2H); 1.86 (m, 2H); 2.15 (s, 3H); 3.16 (t, 2H); 4.07 (m, 1H); 4.27 (q, 2H); 4.29 (m, 2H); 6.99 (s, 1H); 7.19 (d, 1H); 11.95 (s, 1H)

Example 313: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-2-[(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]-*N*-methoxypyrimidine-4-carboxamide

The title compound was synthesized by an analogous method to Example 8 starting from 6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-2-[(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]pyrimidine-4-carboxylic acid (Example 314) and methoxylamine hydrochloride.

MS (ES) MH^+: 557 for $C_{23}H_{30}Cl_2N_6O_6$

Example 314: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-2-[(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]pyrimidine-4-carboxylic acid

The title compound was synthesized by an analogous method to Example 154 starting from (2,2-dimethyl-1,3-dioxolan-4-yl) MeOH (commercially available) and sodium hydride, and reacting the alkoxide generated in situ with methyl 2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylate (Example 6).

MS (ES) MH^+: 528 for $C_{22}H_{27}Cl_2N_5O_6$

Example 315: Methyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-methoxypyrimidine-4-carboxylate

The title compound was synthesized by an analogous method to Example 6 starting from 3,4-dichloro-5-methyl-N-piperidin-4-yl-1H-pyrrole-2-carboxamide hydrochloride (Intermediate 1) and methyl 2-chloro-6-methoxypyrimidine-4-carboxylate (Intermediate 88).

MS (ES) MH^+: 442 for $C_{18}H_{21}Cl_2N_5O_4$

Example 316: Methyl 6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-pyrrolidin-1-ylpyrimidine-4-carboxylate

The title compound was synthesized by an analogous method to **Example 9** starting from methyl 2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylate (**Example 6**), pyrrolidine, and TEA.

MS (ES^-): 479.34, 481.34

Example 317: Methyl 6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-piperazin-1-ylpyrimidine-4-carboxylate

The title compound was synthesized by an analogous method to **Example 9** starting from methyl 2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylate (**Example 6**), piperazine, and TEA.

MS (ES^-): 494.60, 496.59

Example 318: Methyl 6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-(4-methylpiperazin-1-yl)pyrimidine-4-carboxylate

The title compound was synthesized by an analogous method to **Example 9** starting from methyl 2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylate (**Example 6**), 1-methylpiperazine, and TEA.

MS (ES^-): 508.61, 510.60

Example 319: 2-(2-Aminoethoxy)-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-*N*-methoxypyrimidine-4-carboxamide

The title compound was synthesized by a method analogous to **Intermediate 70** starting from *tert*-butyl 2-({4-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-[(methoxyamino)carbonyl]pyrimidin-2-yl}oxy)ethylcarbamate (**Example 322**).

MS (ES) MH^+: 486 for $C_{19}H_{25}Cl_2N_7O_4$

Example 320: Methyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylate

3,4-Dichloro-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (Intermediate 1, 0.300 g, 0.961 mmol) was dissolved in NMP (3 ml). TEA (267 µl, 1.922 mmol) was added followed by the addition of methyl 2-bromo-1,3-thiazole-5-carboxylate (0.213 g, 0.961 mmol) at room temperature. Using a Smith Microwave Synthesizer, the mixture was subjected to single-mode microwave at 150 °C for 20 minutes and was partitioned between water and EtOAc. The organic layer was washed with water and combined organic phase was dried over magnesium sulfate and concentrated to give the desired product. (432 mg).

MS (ES): 417 (MH^+) for $C_{16}H_{18}Cl_2N_4O_3S$

^{1}H NMR δ: 1.70 (m, 2H); 1.97 (m, 2H); 2.24 (s, 3H); 3.39 (m, 2H); 3.81 (s, 3H); 4.03 (m, 2H); 4.13 (m, 1H); 7.34 (d, 1H); 7.93 (s, 1H); 12.03 (s, 1H)

Example 321: 3,4-Dichloro-*N*-[1-(5-cyano-1,3-thiazol-2-yl)piperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide

To a solution of 3,4-dichloro-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (Intermediate 1; 0.330 g, 1.058 mmol) in NMP (2 ml) was added TEA (0.150 ml, 1.058 mmol) followed by the addition of 2-bromo-1,3-thiazole-5-carbonitrile (prepared according to F. Campagna et al. *Tet. Lett*, 1977, 21, 1815-1816) (0.200 g, 1.058 mmol) at room temperature. Using a Smith Microwave Synthesizer, the mixture was subjected to single-mode microwave at 150 °C for 20 minutes. The crude mixture was diluted with EtOAc and washed with water several times. The extracts were combined dried over magnesium sulfate and concentrated to give the desired product. (0.450 g).

MS (ES): 384 (MH^+) for $C_{15}H_{15}Cl_2N_5OS$

^{1}H NMR δ: 1.77 (m, 2H); 1.98 (m, 2H); 2.24 (s, 3H); 3.47 (m, 2H); 4.02 (m, 2H); 4.16 (m, 1H); 7.36 (d, 1H); 8.09 (s, 1H); 12.03 (s, 1H)

Example 322: *tert*-Butyl 2-{[4-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-{(methoxyamino)carbonyl]pyrimidin-2-yl]oxy}ethylcarbamate

The title compound was synthesized by an analogous method to Example 8 starting from 2-{2-[(*tert*-butoxycarbonyl)amino]ethoxy}-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-

yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylic acid (Example 154) and methoxylamine hydrochloride.

MS (ES) MH^+: 586 for $C_{24}H_{33}Cl_2N_7O_6$

Examples 323 - 328

The following esters were prepared by an analogous method to Example 134 from 3,4-dichloro-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (Intermediate 1) and the starting materials indicated.

Example	Compound	^{1}H NMR δ	m/z (ES+)	SM
323	Ethyl 8-methoxy-4-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl) quinoline-2-carboxylate		505 / 507	Ethyl 4-chloro-8-methoxyquinoline-2-carboxylate (Intermediate 137)
324	Methyl 8-fluoro-4-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)quinoline-2-carboxylate	1.98 (m, 2H); 2.03 (m, 2H); 2.18 (s, 3H); 3.11 (m, 2H); 3.33 (s, 1H); 3.60 (m, 2H); 3.94 (s, 3H); 4.03 (m, 1H); 7.34 (m, 1H); 7.62 (m, 2H); 7.83 (m, 1H); 12.02 (s, 1H)	479 / 481	Methyl 4-chloro-8-fluoroquinoline-2-carboxylate (Intermediate 138)
325	Methyl 6-fluoro-4-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl) quinoline-2-carboxylate	1.92 (m, 2H); 2.03 (m, 2H); 2.18 (s, 3H); 3.11 (m, 2H); 3.60 (m, 2H); 3.94 (s, 3H); 4.05 (m, 1H); 7.32 (d, 1H, J = 7.5); 7.60 (s, 1H); 7.63 (m, 1H); 7.99 (m, 2H); 12.01 (s, 1H)	495 / 497	Methyl 4-chloro-6-fluoroquinoline-2-carboxylate (Intermediate 140)

Example	Compound	^{1}H NMR δ	m/z (ES+)	SM
326	Methyl 8-chloro-4-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl) quinoline-2-carboxylate	1.92 (m, 2H); 2.03 (m, 2H); 2.18 (s, 3H); 3.11 (m, 2H); 3.60 (m, 2H); 3.94 (s, 3H); 4.05 (m, 1H); 7.32 (d, 1H, J = 7.5); 7.53 (m, 1H); 7.60 (m, 2H); 7.99 (m, 2H); 12.01 (s, 1H)	ES^+ 495 / 497	Methyl 4,8-dichloroquinoline-2-carboxylate (Intermediate 141)
327	Methyl 8-methyl-4-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl) quinoline-2-carboxylate	1.91 (m, 2H); 2.04 (m, 2H); 2.17 (s, 3H); 2.72 (s, 3H); 3.05 (m, 2H); 3.55 (m, 2H); 3.93 (s, 3H); 4.03 (m, 1H); 7.32 (m, 1H); 7.59 (m, 3H); 7.86 (m, 1H); 12.01 (s, 1H)	ES^+ 475 / 477	Methyl 4-chloro-8-methyl quinoline-2-carboxylate (Intermediate 139)
328	Ethyl 2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl) carbonyl]amino} piperidin-1-yl) oxazole-4-carboxylate	1.26 (t, 3H, J = 7.1); 1.60 (m, 2H); 1.88 (m, 2H); 2.18 (s, 3H); 3.17 (m, 2H); 3.90 (m, 2H); 4.02 (m, 1H); 4.24 (q, 2H, J = 7.2); 7.27 (d, 1H, J = 7.9); 8.31 (s, 1H); 11.99 (s, 1H)	415 / 417	Ethyl 2-chloro-oxazole-4-carboxylate (Intermediate 142)

Example 329: 3,4-Dichloro-5-methyl-N-[1-(1,3-thiazol-2-yl)piperidin-4-yl]-1H-pyrrole-2-carboxamide

3,4-Dichloro-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (Intermediate 1; 1 g, 3.2 mmol) was dissolved in NMP (10 ml). Bromothiazole (2.65 g; 16 mmol) was added followed by the addition of *N,N*-diisopropylethylamine (2.75 ml, 16 mmol). Using a Smith Microwave Synthesizer, the mixture was subjected to single-mode microwave at 150 °C for a total of 3 h. The mixture was diluted with EtOAc and washed well with water,

$NaHCO_3$, brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo to give the title compound as a brown solid (692 mg).

MS (ES) MH^+: 361 for $C_{14}H_{16}Cl_2N_4OS$

^1H NMR δ: 1.78 (m, 2H); 1.98 (m, 2H); 2.26 (s, 3H); 3.28 (m, 2H); 3.95 (m, 2H); 4.12 (m, 1H); 6.93 (d, 1H); 7.22 (s, 1H); 7.31 (d, 1H); 12.10 (s, 1H).

Example 330: 1-(6-Chloro-4-cyanopyridin-2-yl)piperidin-4-yl-4-bromo-5-methyl-1H-pyrrole-2-carboxylate

The title compound was prepared in a manner analogous to **Example 308** from 2-chloro-6-(4-hydroxypiperidin-1-yl)isonicotinonitrile (**Intermediate 26**) and 4-bromo-5-methyl-1H-pyrrole-2-carboxylic acid (**Intermediate 18**).

MS (ES)M+H: 425 for $C_{17}H_{16}BrClN_4O$

Example 331: Methyl 2-(4-{[5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-6-chloroisonicotinate

The title compound was prepared in a manner analogous to **Example 18** starting from 5-methyl-1H-pyrrole-2-carboxylic acid (**Intermediate 29**) and methyl 2-(4-aminopiperidin-1-yl)-6-chloroisonicotinate hydrochloride salt (**Intermediate 93**).

MS (ES, M+H): 376 for $C_{18}H_{21}ClN_4O_3$

Example 332: 2-Chloro-6-(4-{[(5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)isonicotinic acid

The title compound was prepared in a manner analogous to **Example 44** starting from methyl 2-(4-{[5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-6-chloroisonicotinate (**Example 331**).

MS (ES, M+H): 362 for $C_{17}H_{19}ClN_4O_3$

Example 333: Methyl 2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl] amino}piperidin-1-yl)isonicotinate

The title compound was prepared in a manner analogous to **Example 18** starting from 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid (**Intermediate 3**) and methyl 2-(4-aminopiperidin-1-yl)-6-chloroisonicotinate hydrochloride salt (**Intermediate 93**).

MS (ES, M+H): 445,447 for $C_{18}H_{19}Cl_3N_4O_3$

Example 334: Methyl 2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-6-(methylsulfinyl)isonicotinate

The title compound was prepared in a manner analogous to Example 6 starting from 3,4-dichloro-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (Intermediate 1) and methyl 2-chloro-6-(methylsulfinyl)isonicotinate (Intermediate 84).

MS (ES, M+H): 473,471 for $C_{19}H_{22}Cl_2N_4O_4S$

Example 335: 6-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-pyrrolidin-1-ylpyrimidine-4-carboxylic acid

The title compound was synthesized by an analogous method to Intermediate 3 starting from methyl 6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-2-pyrrolidin-1-ylpyrimidine-4-carboxylate (Example 316).

MS (ES): 465.3 (M-H) for $C_{20}H_{24}Cl_2N_6O_3$

^{1}H NMR δ: 1.5 (q, 2H); 1.86 (br s, 4H); 2.11 (s, 3H); 3.21 (t, 2H); 3.49 (br s, 4H); 3.6-4.5 (m, 6H); 6.84 (s, 1H); 7.16 (d, 1H); 11.93 (s, 1H).

Example 336: Ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-1,3-thiazole-4-carboxylate

The title compound was prepared in a manner analogous to Example 320 from 3,4-dichloro-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (Intermediate 1) and ethyl 2-bromo-1,3-thiazole-4-carboxylate (commercially available).

MS (ES)M+H: 431,433 for $C_{17}H_{20}Cl_2N_4O_3S$

Example 337: 3,4-Dichloro-*N*-[1-(4-cyano-1,3-thiazol-2-yl)piperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide

The title compound was prepared as described for Example 321 from 3,4-dichloro-5-methyl-*N*-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride (Intermediate 1) and 2-bromo-1,3-thiazole-4-carbonitrile (prepared as described in *J. Am. Chem. Soc.* 1952, *74*, 5799).

MS (ES) (M+H): 384 for $C_{15}H_{15}Cl_2N_5OS$

^{1}H NMR δ: 1.69 -1.77 (m, 2H); 1.98 (dd, 2H); 2.24 (s, 3H); 3.42 (m, 2H); 3.97 (d, 2H); 4.10 - 4.16 (m, 1H); 7.34-7.36 (d, 1H); 8.09 (s, 1H); 12.03 (s, 1H).

Example 338: 4-Bromo-*N*-[1-(4-cyanopyridin-2-yl)piperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide

The title compound was prepared in a manner analogous to **Example 18** from 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid (**Intermediate 3**) and 2-(4-aminopiperidin-1-yl)isonicotinonitrile hydrochloride salt (**Intermediate 208**).

MS (ES): 412 (M+H) for $C_{17}H_{16}Cl_3N_5O$

Example 339: Ethyl 4-[(*tert*-butylamino)carbonyl]-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylate

Example 340: 5-Thiazolecarboxylic acid, 4-cyano-2-[4-[[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino]-1-piperidinyl]-, ethyl ester

A solution of ethyl 2-{4-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}-4-cyano-1,3-thiazole-5-carboxylate (**Intermediate 223**) (1.9 g) and 15 ml TFA in 20 ml DCM was stirred at room temperature overnight. Solvent was removed and the residue was taken up in DCM and washed with aqueous Na_2CO_3 and brine. Drying ($MgSO_4$) and removal of solvent gave 920 mg of a dark brown oil. To a solution of 880 mg (3.1 mmol) of the oil and diisopropylethylamine (0.7 ml, 3.8 mmol) was added 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl chloride (**Intermediate 224**) (800 mg, 3.8 mmol), and the mixture was stirred at room temperature overnight. Additional 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl chloride (100 mg) was added, and stirring was continued for 2 hours. The mixture was diluted with EtOAc and washed with water and brine. Drying ($MgSO_4$) and removal of solvent gave a oil which was chromatographed on silica gel (DCM followed by gradient elution to 5% MeOH in DCM). During TFA deprotection, isobuytlene reaction with the nitrile group was observed- the mixture was carried though. The major material was isolated and chromatographed by reverse phase HPLC (45-65% gradient of CH_3CN in water with 0.1% TFA). Two materials were isolated. The first eluting compound was **Example 339**:

MS (ES): 530.1 $(M+H)^{+1}$, 528.2 $(M-H)^{-1}$

^{1}H NMR δ: 1.22 (t, *J*=7.06Hz, 2H); 1.32 (s, 9H); 1.63 (s, 2H); 1.91 (s, 3H); 2.18 (s, 3H); 3.34 (s, 2H); 4.1 (m, 1H); 3.90 (s, 2H); 4.18 (q, *J*=7.16Hz, 2H); 7.30 (d, *J*=7.54Hz, 1H); 8.01 (s, 1H); 11.99 (s, 1H).

The second eluting compound was **Example 340**:

MS (ES): 456.0 $(M+H)^{+1}$, 454.1 $(M-H)^{-1}$

^{1}H NMR δ: 1.28 (t, *J*=7.06Hz, 3H); 1.55 - 1.75 (m, 2H); 1.82 - 2.02 (m, 2H); 2.18 (s, 3H); 3.33 - 3.52 (m, 2H); 3.85 - 4.02 (m, 2H); 4.04 (s, 1H); 4.30 (q, *J*=7.10Hz, 2H); 7.29 (d, *J*=7.72Hz, 1H); 11.80 - 12.17 (m, 1H).

Example 341: 4-Cyano-2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino} piperidin-1-yl)-1,3-thiazole-5-carboxylic acid

A solution of ethyl 4-[(*tert*-butylamino)carbonyl]-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylate (Example 340; 140 mg, 0.31 mmol) and 2 N LiOH in water (0.93 ml, 1.86 mmol) in 6 ml 1:1 THF:MeOH was heated at 80 °C for 30 min in a microwave reactor. 1 N HCl (1.86 ml) was added and the mixture was diluted with water. Precipitated material was filtered and rinsed well with water. Drying of the precipitate in vacuo gave 105 mg of product.

MS (ES): 428.0 (M+H)

^{1}H NMR δ: 1.67 (s, 1H); 1.80 - 2.04 (m, 2H); 2.18 (s, 3H); 3.33 (s, 2H); 3.89 (s, 2H); 4.06 (d, *J*=5.09Hz, 1H); 7.30 (s, 1H); 12.03 (s, 1H); 13.92 (s, 1H).

Example 342: 4-[(*tert*-Butylamino)carbonyl]-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylic acid

A solution of 5-thiazolecarboxylic acid, 4-cyano-2-[4-[[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino]-1-piperidinyl]-, ethyl ester (Example 339; 186 mg, 0.35 mmol) and 2 N LiOH in water (0.35 ml, 0.7 mmol) in 6 ml MeOH was heated at 80 °C for 30 min in a microwave reactor. 1 N HCl (0.7 ml) was added and the mixture was diluted with water. Precipitated material was filtered, rinsed well with water and dried in vacuo to give 164 mg of product

MS (ES): 502.1 (M+H)

^{1}H NMR δ:1.20 - 1.57 (m, 9H); 1.66 (s, 2H); 1.90 (s, 2H); 2.18 (s, 3H); 3.34 (s, 2H); 4.00 (s, 3H); 7.31 (d, *J*=7.72Hz, 1H); 12.01 (s, 1H); 16.06 (s, 1H).

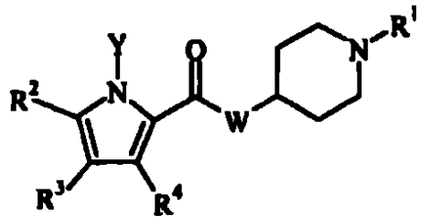
Examples 343-346

The following examples were prepared by the procedure of Example 223 from the starting materials indicated.

Ex.	R	^{1}H NMR δ	M+1	SM
343	2-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid	1.62 (q, 2H); 1.89 (d, 2H); 2.16 (s, 3H); 2.91 (t, 2H); 3.55 (s, 3H); 3.69 (d, 2H); 3.87-4.04 (m, 1H); 7.26 (d, 1H); 11.95 (s, 1H).	417	Ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate (Example 218)
344	3-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)benzoic acid	1.65 (q, 2H); 1.89 (d, 2H); 2.16 (s, 3H); 2.91 (t, 2H); 3.70 (d, 2H); 3.83-4.04 (m, 1H); 7.17-7.27 (m, 2H); 7.27-7.40 (m, 2H); 7.45 (s, 1H); 11.94 (s, 1H).	396	Methyl 3-(4-{[(3,4-dichloro-5-methyl-1 H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)benzoate (Example 211)
345	3-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-5-morpholin-4-ylbenzoic acid	1.63-1.85 (q, 2H); 1.90-2.06 (m, 2H); 2.13 (s, 3H); 3.05-3.23 (m, 6H); 3.59 (d, 2H); 3.71 (bs, 4H); 3.89-4.02 (m, 1H); 6.94 (s, 1H); 7.13 (s, 1H); 7.19 (s, 1H).	481	Methyl 3-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-5-morpholin-4-ylbenzoate (Example 216)
346	3-(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-5-(4-methylpiperazin-1-yl)benzoic acid	1.51-1.73 (m, 2H); 1.80-1.97 (m, 2H); 2.14 (s, 3H); 2.53 (s, 4H); 2.81 (s, 3H); 2.87-3.01 (m, 3H); 3.04-3.24 (m, 2H); 3.39-3.56 (m, 2H); 3.65 (d, 2H); 6.76 (s, 1H); 6.94 (s, 1H); 7.04 (s, 1H).	495	Methyl 3-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-5-(4-methylpiperazin-1-yl)benzoate (Example 217)

Claims

1. A compound of the formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

W is O or NR^5;

Y is hydrogen;

R^1 is selected from R^1a, R^1b, R^1c, R^1d, R^1e and R^1f;

R^1a is a 4 to 7 membered saturated, partially unsaturated or unsaturated heterocyclic ring containing 1, 2, 3, or 4 heteroatoms independently selected from O, S and N (provided that such a ring does not contain O-O or S-S bonds), wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-, a ring sulphur atom may be optionally oxidised to form the S-oxide(s), and a ring nitrogen atom may be optionally oxidised to form the N-oxide, and wherein said ring may be optionally substituted by 1, 2 or 3 substituents independently selected from: nitro, cyano, sulfo, formyl, hydroxyiminomethyl, (2-6C)alkenyl, (2-6C)alkynyl, -CO(1-6C)alkyl, -COO(1-6C)alkyl (optionally substituted with -COO(1-6C)alkyl), trifluoromethyl, $-CONR^6R^7$, $-OCONR^6R^7$, $-N(R^7)COR^6$, $-CONHCH(CO_2R^7)R^6$, halo, hydroxy, carboxy, (1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo, cyano, nitro, -COO(1-6C)alkyl, -OCO(1-4C)alkyl, (1-6C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(1-4C)alkoxy-, (2-4C)alkenyloxy, trifluoromethyl, $-CONR^6R^7$, carboxy, -NHC(O)O(1-4C)alkyl, $-OCONR^6R^7$, $-C(=NOH)(1-4C)alkyl$, $-C(=NOH)NR^6R^7$, $-NHC(=NH)NR^6R^7$, $-NHC(O)NR^6R^7$, -NHC(O)(1-4C)alkyl, -NHC(O)heterocyclyl, -NHC(O)aryl, -NHS(O)p(1-4C)alkyl, -S(O)p(1-4C)alkyl, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$, and heterocyclyl], (3-6C)cycloalkyl (optionally substituted by 1 or 2 substituents selected from (1-6C)alkyl and the optional substituents described for (1-6C)alkyl hereinbefore), -O(1-6C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), -S(O)p(1-4C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), heterocyclyl,

aryl, -NHC(O)O(1-4C)alkyl, -C(=NOR^7)(1-4C)alkyl, -C(=NOR^7)NR^{6}R^7, -S(O)pNR^{6}R^7, -S(O)p(1-4C)alkylCONHR^7, -NR^{7}S(O)pNR^{6}R^7, -NR^{7}S(O)p(1-4C)alkyl, -NR^{7}S(O)p-aryl, -C(O)NHS(O)p(1-4C)alkyl, -C(O)NHS(O)p-aryl, -NR^{6}R^7, -CH$_2$CH(CO$_2$R^6)OH, -(1-4C)alkylCH(NR^{6}R^7)CO$_2$R^6 and -(1-4C)alkylCH(NR^{6}R^7)CO(NR^{6}R^7);

wherein any aryl or heterocyclyl group in any of the preceding values for substituents on R^{1}a may optionally be substituted by 1 or 2 substituents independently selected from (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, hydroxy, (1-4C)alkoxy, halo, cyano, nitro, carboxy, hydroxy(1-4C)alkyl-, (1-4C)alkoxy(1-4C)alkyl-, halo(1-4C)alkyl-, difluoromethyl, trifluoromethyl, trifluoromethoxy, formyl, -CO(1-4C)alkyl, -COO(1-4C)alkyl, -C(O)NH$_2$, -C(O)NH(1-4C)alkyl, -C(O)N[di(1-4C)alkyl], -S(O)$_2$NH$_2$, -S(O)$_2$NH(1-4C)alkyl and -S(O)$_2$N[di(1-4C)alkyl];

R^{1}b is an 8-10 membered bicyclic heterocyclic ring containing 1, 2, 3, or 4 heteroatoms independently selected from O, S and N (provided that such a ring does not contain O-O or S-S bonds), wherein a -CH$_2$- group can optionally be replaced by a -C(O)-, a ring sulphur atom may be optionally oxidised to form the S-oxide(s), and a ring nitrogen atom may be optionally oxidised to form the N-oxide, and wherein said ring may be optionally substituted by 1, 2 or 3 substituents independently selected from the substituents listed for R^{1}a above;

R^{1}c is a phenyl ring, substituted by 1, 2 or 3 substituents independently selected from the substituents listed for R^{1}a above;

R^{1}d is selected from -CH$_2$R^{1}a, -C(O)R^{1}a, -OR^{1}a, S(O)qR^{1}a (wherein q is 1 or 2);

R^{1}e is selected from -CH$_2$R^{1}b, -C(O)R^{1}b, -OR^{1}b, S(O)qR^{1}b (wherein q is 1 or 2);

R^{1}f is selected from -CH$_2$R^{1}c, -C(O)R^{1}c -OR^{1}c, S(O)qR^{1}c (wherein q is 1 or 2);

R^2 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, (2-4C)alkenyl, (2-4C)alkynyl, halo, cyano, fluoromethyl, difluoromethyl and trifluoromethyl;

R^3 is selected from hydrogen, (1-4C)alkyl, cyclopropyl, (2-4C)alkenyl, (2-4C)alkynyl, halo, hydroxy, cyano, fluoromethyl, difluoromethyl trifluoromethyl, -CO(1-6C)alkyl, and (1-6C)alkoxy;

R^4 is selected from hydrogen, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, nitro, hydroxy, halo, cyano, (3-6C)cycloalkyl, -(1-6C)alkyl(3-6C)cycloalkyl, halo(1-4C)alkyl-, difluoromethyl, trifluoromethyl, -CO(1-6C)alkyl, and (1-6C)alkoxy;

R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-4C)alkenyl, (3-6C)cycloalkyl, -(1-4C)alkylC(O)O(1-4C)alkyl, hydroxy, amino, -NH(1-4C)alkyl, -N[di(1-4C)alkyl], (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy,

(1-4C)alkoxy(1-4C)alkoxy(1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl-, (1-4C)alkylthio(1-4C)alkyl-, hydroxy(1-4C)alkyl-, -(1-4C)alkylNH_2, -(1-4C)alkylNH(1-4C)alkyl, -(1-4C)alkylN[di(1-4C)alkyl], and -(1-4C)alkylheterocyclyl;
R^7 is independently at each occurrence selected from hydrogen and (1-6C)alkyl;
or R^6 and R^7 may together with the nitrogen to which they are attached form a 5 or 6-membered heterocyclyl ring, optionally substituted with 1 or 2 substituents independently selected from (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, hydroxy, (1-4C)alkoxy, halo, cyano, nitro, carboxy, hydroxy(1-4C)alkyl-, (1-4C)alkoxy(1-4C)alkyl-, halo(1-4C)alkyl-, difluoromethyl, trifluoromethyl, trifluoromethoxy, formyl, -CO(1-4C)alkyl, -COO(1-4C)alkyl, -C(O)NH_2, -C(O)NH(1-4C)alkyl, -C(O)N[di(1-4C)alkyl], -$S(O)_2NH_2$, -$S(O)_2$NH(1-4C)alkyl, -$S(O)_2$N[di(1-4C)alkyl] and -S(O)p(1-4C)alkyl;
R^5 is selected from hydrogen and (1-4C)alkyl;
p is (independently at each occurrence) 0, 1 or 2.

2. A compound of formula (1) or a pharmaceutically acceptable salt thereof as claimed in claim 1 wherein W is O.

3. A compound of formula (1) or a pharmaceutically acceptable salt thereof as claimed in claim 1 wherein W is NR^5.

4. A compound of formula (1) or a pharmaceutically acceptable salt thereof as claimed in anyone of claims 1-3 wherein R^1 is selected from R^1a, R^1b, R^1c and R^1d; wherein

R^1a is a 5 or 6 membered saturated, partially unsaturated or unsaturated heterocyclic ring containing 1, 2, 3, or 4 heteroatoms independently selected from O, S and N (provided that such a ring does not contain O-O or S-S bonds), wherein a -CH_2- group can optionally be replaced by a -C(O)-, a ring sulphur atom may be optionally oxidised to form the S-oxide(s), and a ring nitrogen atom may be optionally oxidised to form the N-oxide, and wherein said ring may be optionally substituted by 1, 2 or 3 substituents independently selected from: nitro, cyano, sulfo, formyl, hydroxyiminomethyl, (2-6C)alkenyl, -CO(1-6C)alkyl, -COO(1-6C)alkyl trifluoromethyl, -CONR^{6}R^7, -N(R^7)COR^6, halo, hydroxy, carboxy, (1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, -OCO(1-4C)alkyl, (1-6C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(1-4C)alkoxy, (2-4C)alkenyloxy, -NHC(O)O(1-4C)alkyl, -NHC(=NH)NR^{6}R^7, -NHC(O)NR^{6}R^7,

-NHC(O)(1-4C)alkyl, -NHC(O)heterocyclyl, -NHC(O)aryl, -NHS(O)p(1-4C)alkyl, -S(O)p(1-4C)alkyl, -S(O)pNR^{6}R^7, -NHSO$_2$R^6, -NR^{6}R^7, and heterocyclyl], (3-6C)cycloalkyl, -O(1-6C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), -S(O)p(1-4C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), heterocyclyl, -NHC(O)O(1-4C)alkyl, -C(=NOR^7)(1-4C)alkyl, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alkylCONHR^7, -C(O)NHS(O)p(1-4C)alkyl, and -NR^{6}R^7, wherein any aryl or heterocyclyl group in any of the preceding values for substituents on R^{1}a may optionally be substituted by 1 or 2 substituents independently selected from (1-4C)alkyl and carboxy;

R^{1}b is a 10 membered bicyclic heterocyclic ring containing 1, 2 or 4 heteroatoms independently selected from S and N (provided that such a ring does not contain S-S bonds), wherein a -CH$_2$- group can optionally be replaced by a -C(O)-, and wherein said ring may be optionally substituted by 1, 2 or 3 substituents independently selected from the substituents listed for R^{1}a above;

R^{1}c is a phenyl ring, substituted by 1, 2 or 3 substituents independently selected from the substituents listed for R^{1}a above;

R^{1}d is selected from -CH$_2$R^{1}a, and -C(O)R^{1}a.

5. A compound of formula (1) or a pharmaceutically acceptable salt thereof as claimed in anyone of claims 1-4 wherein R^2 is selected from (1-4C)alkyl, halo and cyano.

6. A compound of formula (1) or a pharmaceutically acceptable salt thereof as claimed in anyone of claims 1-5 wherein R^3 is selected from hydrogen, (1-4C)alkyl, halo, cyano and -CO(1-6C)alkyl.

7. A compound of formula (1) or a pharmaceutically acceptable salt thereof as claimed in anyone of claims 1-6 wherein R^4 is selected from hydrogen, (1-4C)alkyl, halo and cyano.

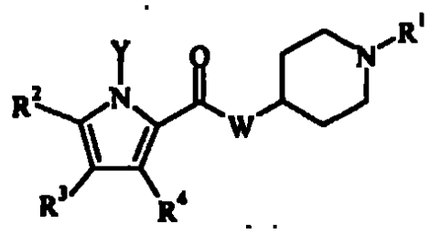
8. A compound of formula (1) or a pharmaceutically acceptable salt thereof as claimed in anyone of claims 1-7 wherein:

R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-4C)alkenyl, (3-6C)cycloalkyl, -(1-4C)alkylC(O)O(1-4C)alkyl, hydroxy, amino, -N[di(1-4C)alkyl], (1-4C)alkoxy and -(1-4C)alkylheterocyclyl;

R^7 is independently at each occurrence selected from hydrogen and (1-6C)alkyl;

or R^6 and R^7 may together with the nitrogen to which they are attached form a 5 or 6-membered heterocyclyl ring, optionally substituted with 1 or 2 substituents independently selected from (1-4C)alkyl.

9. A compound of formula (1) or a pharmaceutically acceptable salt thereof:



(1)

wherein:

R^1 is selected from R^1a, R^1b, R^1c and R^1d; wherein

R^1a is pyridinyl, *N*-oxopyridinyl, pyrimidinyl, thiazolyl, thiadiazolyl, tetrazolyl, imidazolyl, triazinyl, pyrrolidinyl, thienyl, furanyl, oxadiazolyl, isoxazolyl, oxazolyl or pyrrolyl, wherein said R^1a may be optionally substituted by 1, 2 or 3 substituents independently selected from:

nitro, cyano, sulfo, formyl, hydroxyiminomethyl, (2-6C)alkenyl, -CO(1-6C)alkyl, -COO(1-6C)alkyl trifluoromethyl, $-CONR^6R^7$, $-N(R^7)COR^6$, halo, hydroxy, carboxy, (1-6C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, -OCO(1-4C)alkyl, (1-6C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, hydroxy(1-4C)alkoxy, (2-4C)alkenyloxy, -NHC(O)O(1-4C)alkyl, $-NHC(=NH)NR^6R^7$, $-NHC(O)NR^6R^7$, -NHC(O)(1-4C)alkyl, -NHC(O)tetrahydrofuranyl, -NHC(O)phenyl, -NHS(O)p(1-4C)alkyl, -S(O)p(1-4C)alkyl, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$, morpholino, 1,3-dioxo-1,3-dihydro-2H-isoindolyl and 1,3-dioxolanyl], cyclopropyl, -O(1-6C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), -S(O)p(1-4C)alkyl (optionally substituted by 1 or 2 substituents as described for (1-6C)alkyl hereinbefore), tetrazolyl, 2-oxo-1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, morpholino, piperazinyl, pyrrolidinyl, -NHC(O)O(1-4C)alkyl, $-C(=NOR^7)$(1-4C)alkyl, $-C(=NOR^7)NR^6R^7$, -S(O)p(1-4C)alkylCONHR^7, -C(O)NHS(O)p(1-4C)alkyl and $-NR^6R^7$;

wherein any phenyl, tetrahydrofuranyl, morpholino, 1,3-dioxo-1,3-dihydro-2H-isoindolyl, 1,3-dioxolanyl, tetrazolyl, 2-oxo-1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, morpholino,

piperazinyl, pyrrolidinyl, in any of the preceding values for substituents on R^1a may optionally be substituted by 1 or 2 substituents independently selected from (1-4C)alkyl and carboxy;

R^1b is R^1b is quinolinyl, purinyl, benzothiazolyl, indolyl, 4-oxoquinolinyl, 2,7-naphthyridinyl or quinazolinyl, and wherein said R^1b may be optionally substituted by 1, 2 or 3 substituents independently selected from the substituents listed for R^1a above;

R^1c is a phenyl ring, substituted by 1, 2 or 3 substituents independently selected from the substituents listed for R^1a above;

R^1d is selected from $-CH_2R^1a$, and $-C(O)R^1a$;

R^2 is selected from methyl, ethyl, isopropyl, chloro and cyano;

R^3 is selected from hydrogen, methyl, ethyl, chloro, bromo, cyano and -COMe;

R^4 is selected from hydrogen, chloro, methyl, ethyl and cyano;

R^5 is hydrogen or methyl;

R^6 is independently at each occurrence selected from hydrogen, (1-4C)alkyl, (3-4C)alkenyl, cyclopropyl, -(1-4C)alkylC(O)O(1-4C)alkyl, hydroxy, amino, -N[di(1-4C)alkyl], (1-4C)alkoxy and -(1-4C)alkylmorpholino;

R^7 is independently at each occurrence selected from hydrogen and (1-4C)alkyl;

or R^6 and R^7 may together with the nitrogen to which they are attached form piperazinyl or morpholino optionally substituted with 1 or 2 substituents independently selected from (1-4C)alkyl;

p is (independently at each occurrence) 0, 1 or 2.

10. A compound of formula (1) or a pharmaceutically acceptable salt thereof selected from:

2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-*N*-methoxypyrimidine-4-carboxamide;

2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)isonicotinamide;

1-[4-(aminocarbonyl)-6-chloro-2-pyridinyl]-4-piperidinyl 4-bromo-5-methyl-1H-pyrrole-2-carboxylate;

1-{4-[amino(hydroxyimino)methyl]-6-chloro-2-pyridinyl}-4-piperidinyl 3,4-dichloro-5-methyl-1H-pyrrole-2-carboxylate;

2-butoxy-6-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)isonicotinic acid;

2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-6-(2-methoxyethoxy)isonicotinic acid;

2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-*N*-methoxy-6-(methylsulfonyl)isonicotinamide;

2-(butylthio)-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylic acid;

2-(*tert*-butylthio)-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylic acid;

2-*tert*-butyl-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyrimidine-4-carboxylic acid;

4-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)quinoline-2-carboxylic acid;

2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylic acid;

2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-4-carboxylic acid;

6-chloro-4-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)quinoline-2-carboxylic acid;

5-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-N-methoxynicotinamide;

6-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)pyridine-2-carboxylic acid;

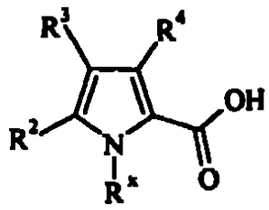
4-[(*tert*-butylamino)carbonyl]-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylic acid;

2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid; and

3-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)benzoic acid.

11. A process for preparing a compound of formula (1) or a pharmaceutically acceptable salt thereof which process (wherein variable groups are, unless otherwise specified, as defined in claim 1) comprises of:

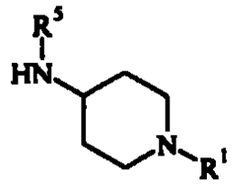
a) for compounds of formula (1) where W is NR^5; reacting an acid of the formula (2a):



(2a)

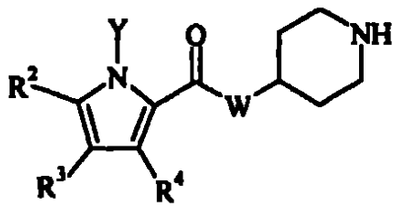
(wherein R^x is hydrogen or a suitable protecting group) or an activated derivative thereof;

with an amine of formula (3a); or



(3a)

b) reacting a compound of formula (4a):



(4a)

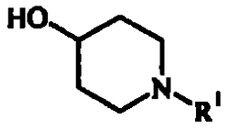
with a compound of formula (5a):

$X\text{-}R^1$

(5a)

wherein X is a displaceable group;

c) for compounds of formula (1) where W is O; reacting an acid of the formula (2a) or an activated derivative thereof, with an alcohol of formula (6a); or



(6a)

and thereafter if necessary:

i) converting a compound of the formula (1) into another compound of the formula (1);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt.

12. A compound of the formula (I), or a pharmaceutically-acceptable salt thereof, as claimed in any one of claims 1-10, for use in a method of treatment of the human or animal body by therapy.

13. A method for producing an antibacterial effect in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically-acceptable salt thereof as claimed in any one of claims 1-10.

14. A method for inhibition of bacterial DNA gyrase in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-10.

15. A method of treating a bacterial infection in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-10.

16. A compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-10 for use as a medicament.

17. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-10 in the manufacture of a medicament for use in the production of an anti-bacterial effect in a warm-blooded animal such as a human being.

18. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-10 in the manufacture of a medicament for use in inhibition of bacterial DNA gyrase in a warm-blooded animal such as a human being.

19. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-10 in the manufacture of a medicament for use in the treatment of a bacterial infection in a warm-blooded animal such as a human being.

20. A compound of formula (I), or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-10 for use in the production of an anti-bacterial effect in a warm-blooded animal such as a human being.

21. A compound of formula (I), or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-10 for use in inhibition of bacterial DNA gyrase in a warm-blooded animal such as a human being.

22. A compound of formula (I), or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-10 for use in the treatment of a bacterial infection in a warm-blooded animal such as a human being.

23. A pharmaceutical composition which comprises a compound of the formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-10, and a pharmaceutically acceptable diluent or carrier.

24. A pharmaceutical composition which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-10, in association with a pharmaceutically acceptable excipient or carrier for use in the production of an anti-bacterial effect in an warm-blooded animal, such as a human being.

25. A pharmaceutical composition which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-10, in association with a pharmaceutically acceptable excipient or carrier for use in inhibition of bacterial DNA gyrase in an warm-blooded animal, such as a human being.

26. A pharmaceutical composition which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-10, in association

with a pharmaceutically acceptable excipient or carrier for use in the treatment of a bacterial infection in an warm-blooded animal, such as a human being.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/003874

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/12 C07D401/14 C07D413/14 C07D417/14 C07D409/14
A61K31/454 A61P31/04

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, BEILSTEIN Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/085886 A (SREENIVAS KANDEPU ; CHUGH Y (IN); NAIR SHEELA C (IN); BERI RUPINDER K) 31 October 2002 (2002-10-31) page 13, line 28 - page 14, line 15; claim 1	1-26
A	EP 0 894 805 A (HOECHST MARION ROUSSEL INC) 3 February 1999 (1999-02-03) page 13, line 40 - line 43; claim 1	1-26

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
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	Seelmann, I

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB2004/003874

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CA 2417799 A1	07-02-2002
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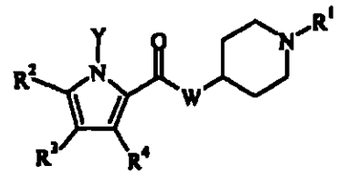
(54) Título: DERIVADOS DEL PIRROL CON ACTIVIDAD ANTIBACTERIANA



(1)

(57) Extracto: Se describen compuestos de Fórmula (I) y sus sales farmacéuticamente aceptables: Fórmula (I) También se describen procesos para su preparación, las composiciones farmacéuticas que los contienen, su utilización como medicamentos y su uso en el tratamiento de infecciones bacterianas.

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Para códigos de dos letras y otras abreviaturas, consulte las "Notas de Guía sobre Códigos y Abreviaturas" que aparece al principio de cada ejemplar regular de la Gaceta de PCT.

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DERIVADOS DEL PIRROL CON ACTIVIDAD ANTIBACTERIANA

La presente invención se relaciona con compuestos que demuestran una actividad antibacteriana, con procesos para su preparación, con composiciones farmacéuticas que los contienen como ingrediente activo, con su utilización como medicamentos y con su uso en la manufactura de medicamentos para ser empleados en el tratamiento de infecciones bacterianas en animales de sangre caliente como los humanos. En particular esta invención se relaciona con compuestos útiles para el tratamiento de infecciones bacterianas en animales de sangre caliente como los humanos, más particularmente con el uso de estos compuestos en la manufactura de medicamentos para su utilización en el tratamiento de infecciones bacterianas en animales de sangre caliente como los humanos.

La comunidad microbiológica internacional continúa expresando una gran preocupación debido a que la evolución de la resistencia a los antibióticos puede resultar en cepas contra las cuales los agentes antibacterianos actualmente disponibles serán ineficaces. En general, los patógenos bacterianos se pueden clasificar como patógenos Gram-positivos o Gram-negativos. Por lo general se considera que los compuestos antibióticos con una actividad efectiva contra los patógenos Gram-positivo y Gram-negativo tienen una actividad de amplio espectro. Los compuestos de la presente invención se consideran efectivos contra los patógenos Gram-positivos y contra ciertos patógenos Gram-negativos.

Los patógenos Gram-positivos, por ejemplo el estafilococo, el enterococo, el estreptococo y la micobacteria, son particularmente importantes debido al desarrollo de unas cepas resistentes que son difíciles de tratar y erradicar de los medios hospitalarios una vez se establecen allí. Ejemplos de estas cepas son *Staphylococcus aureus* resistente a la meticilina (MRSA), estafilococo coagulasa negativo resistente a la meticilina (MRCNS), *Streptococcus pneumoniae* resistente a la penicilina y *Enterococcus faeciu* de resistencia múltiple.

La vancomicina es el antibiótico clínicamente efectivo preferido para el tratamiento de último recurso de estos patógenos Gram-positivos. La vancomicina es una glicopeptida y se asocia a varias toxicidades, incluyendo la nefrotoxicidad. Adicionalmente y lo más importante, es que también se está viendo una resistencia antibacteriana a la vancomicina y a otras glicopeptidas. Esta resistencia está aumentando a un ritmo constante y estos agentes son cada vez menos efectivos para el tratamiento de patógenos Gram-positivos. Ahora también se está percibiendo un aumento de la resistencia a agentes como β-lactamos, quinolonas y macrolidas empleados para el tratamiento de las infecciones del tracto respiratorio superior, igualmente causadas por ciertas cepas Gram negativas incluyendo la *H. influenzae* y *M. catarrhalis*.

En consecuencia, con el objeto de superar la amenaza altamente difundida de unos organismos resistentes a múltiples fármacos, existe una necesidad constante de desarrollar nuevos antibióticos, particularmente aquellos con un mecanismo de acción novedoso y/o conteniendo unos nuevos grupos farmacofóricos.

La girasa del ácido desoxirribonucleico (ADN) es un miembro de la familia de tipo II de las topoisomerasas que controlan el estado topológico del ADN en las células (Champoux, J. J.; 2001. Ann. Rev. Biochem. 70: 369-413). Las topoisomerasas de tipo II emplean la energía libre de la hidrólisis del trifosfato de adenosina (ATP) para alterar la topología del ADN introduciendo unos cortes bicatenarios transientes en el ADN, catalizando el paso de la cepa a través del corte y volviendo a unir el ADN. La ADN girasa es una enzima esencial y conservada en la bacteria y es única entre las topoisomerasas que tiene la capacidad de introducir unas superhélices negativas en el ADN. La enzima consta de dos subunidades codificadas por *gyrA* y *gyrB* que forman un complejo tetramérico A_2B_2. La subunidad de girasa (GyrA) está comprometida en el corte del ADN y en su resellado y contiene un residuo conservado de tirosina que forma el enlace covalente transiente al ADN durante el paso de la hebra. La subunidad B (GyrB) cataliza la hidrólisis del ATP e interactúa con la subunidad A para

trasladar la energía libre de la hidrólisis al cambio de conformación en la enzima permitiendo el paso de la hebra y el resellado del ADN.

Otra topoisomerasa tipo II conservada y esencial en la bacteria, denominada topoisomerasa IV, es esencialmente la responsable de separar los cromosomas bacterianos circulares cerrados y unidos que se producen en la replicación. Esta enzima está estrechamente relacionada con la ADN girasa y su estructura tetramérica es similar y se forma a partir de subunidades homólogas de Gyr A y de Gyr B. La identidad completa de la secuencia entre la girasa y la topoisomerasa IV en diferentes especies bacterianas es alta. Por lo tanto, los compuestos dirigidos a las topoisomerasas bacterianas tipo II tienen el potencial de inhibir dos blancos en las células: la ADN girasa y la topoisomerasa IV; como es el caso de los antibacterianos de quinolona existentes (Maxwell, A. 1997, Trends Microbiol. 5: 102-109).

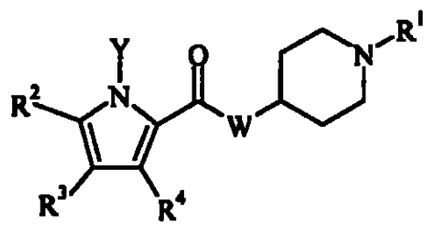
La ADN girasa es un blanco bien validado para los antibacterianos, incluyendo las quinolonas y los cumarinos. Las quinolonas (por ejemplo la ciprofloxacina) son antibacterianos de amplio espectro que inhiben el corte del ADN y la actividad de reunión de la enzima y atrapan la subunidad Gyr A unida mediante covalencia con el ADN (Drlica, K. y X. Zhao, 1997, Microbiol. Molec. Biol. Rev. 61: 377-392). Los miembros de esta clase de antibacterianos también pueden inhibir la topoisomerasa IV y como resultado, el principal blanco de estos compuestos varía entre las especies. Aunque las quinolonas son antibacterianos exitosos, la resistencia generada esencialmente por las mutaciones en el blanco (ADN girasa y topoisomerasa IV) se está convirtiendo en un problema mayor en varios organismos, incluyendo *S. aureus* y *Streptococcus pneumoniae* (Hooper, D. C., 2002, The Lancet Infectious Diseases 2: 530-538). Además, las quinolonas, como una clase química, sufren efectos secundarios tóxicos incluyendo la artropatía lo cual evita su uso en niños (Lipsky, B. A. and Baker, C. A. , 1999, Clin. Infect. Dis. 28: 352-364). Adicionalmente, el potencial de la toxicidad como se predijo por la prolongación del intervalo QT_c ha sido citado como un problema de toxicidad para las quinolonas.

Existen diversos productos naturales conocidos que inhiben la ADN girasa los cuales compiten con el ATP para unir la subunidad GyrB (Maxwell, A. y Lawson, D.M. 2003, Curr. Topics in Med. Chem. 3:283-303). Los cumarinos son productos naturales aislados de *Streptomyces spp.*, cuyos ejemplos son la novobiocina, la clorobiocina y la cumermicina A1. Aunque estos compuestos son unos inhibidores potentes de ADN girasa, su utilidad terapéutica es limitada debido a la toxicidad en las eucariotas y por su deficiente penetración en las bacterias Gram-negativas (Maxwell, A. 1997, Trends Microbiol. 5: 102-109). Otra clase natural de productos de compuestos dirigidos a la subunidad GyrB son las ciclotialidinas, que se aíslan del *Streptomyces filipensis* (Watanabe, J. y colaboradores 1994, J. *Antibiot.* 47: 32-36). A pesar de la potente actividad contra la ADN girasa, la ciclotialidina es un agente antibacteriano deficiente que únicamente muestra una actividad en algunas especies eubacterianas (Nakada, N, 1993, *Antimicrob. Agentes Chemother.* 37:2656-2661).

Los inhibidores sintéticos que se dirigen a la subunidad B de la ADN girasa son conocidos en el arte. Por ejemplo, en la solicitud de patente número WO 99/35155 se describen compuestos que contienen cumarin; en la solicitud de patente número WO 02/060879 se describen compuestos heteroaromáticos 5,6-bicíclicos y en la solicitud de patente WO 01/52845 (patente de Estados Unidos US6,608,087) se describen compuestos de pirazol.

Descubrimos una nueva clase de compuestos que son útiles para inhibir la ADN girasa.

... Por lo tanto, la presente invención dispone un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo;



(1)

donde:

W es O o NR^5;

Y es hidrógeno;

R^1 se selecciona entre R^1a, R^1b, R^1c, R^1d, R^1e y R^1f;

R^1a es un anillo heterocíclico saturado, parcialmente insaturado o insaturado de 4 a 7 miembros que contiene 1, 2, 3 o 4 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga enlaces O-O o S-S), donde un grupo $-CH_2-$ se puede reemplazar opcionalmente por un -C(O)-, un anillo de átomos de sulfuro opcionalmente se puede oxidar para formar el S-óxido (s) y un anillo de átomos de nitrógeno opcionalmente se puede oxidar para formar el N-óxido y donde el citado anillo se puede sustituir opcionalmente por 1, 2 o 3 radicales seleccionados independientemente entre: nitro, ciano, sulfo, formilo, hidroxiiminometilo, (2-6C)alquenilo, (2-6C)alquinilo, -CO(1-6C)alquilo, -COO(1-6C)alquilo (opcionalmente sustituido por -COO(1-6C)alquilo), trifluorometilo, $-CONR^6R^7$, $-OCONR^6R^7$, $-N(R^7)COR^6$, $-CONHCH(CO_2R^7)R^6$, halo, hidroxi, carboxi, (1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, halo, ciano, nitro, -COO(1-6C)alquilo, -OCO((1-4C)alquilo, (1-6C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, hidroxi(1-4C)alcoxi-, (2-4C)alqueniloxi, trifluorometilo, $-CONR^6R^7$, carboxi, -NHC(O)O(1-4C)alquilo, $-OCONR^6R^7$, $-C(=NOH)$(1-4C)alquilo, $-C(=NOH)NR^6R^7$, $-NHC(=NH)NR^6R^7$, $-NHC(O)NR^6R^7$, -NHC(O)(1-4C)alquilo, -NHC(O)heterociclilo, -NHC(O)arilo, -NHS(O)p(1-4C)alquilo, -S(O)p(1-4C)alquilo, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$ y heterociclilo], (3-6C) cicloalquilo (opcionalmente sustituido por 1 o 2 radicales seleccionados entre (1-6C)alquilo y los radicales opcionales descritos para (1-6C)alquilo arriba), -O(1-6C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), -S(O)p(1-4C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), heterociclilo, arilo, -NHC(O)O(1-4C)alquilo, $-C(=NOR^7)$(1-4C)alquilo, $-C(=NOR^7)NR^6R^7$, $-S(O)pNR^6R^7$, $-S(O)p$(1-4C)alquilCONHR^7, -

$NR^7S(O)pNR^6R^7$, $-NR^7S(O)p(1-4C)$alquilo, $-NR^7S(O)p$-arilo, $-C(O)NHS(O)p(1-4C)$alquilo, $-C(O)NHS(O)p$-arilo, $-NR^6R^7$, $-CH_2CH(CO_2R^6)OH$, $-(1-4C)$alquilCH(NR^6R^7) CO_2R^6 y $-(1-4C)$alquilCH$(NR^6R^7)CO(NR^6R^7)$; donde cualquier grupo arilo o heterociclilo en cualquiera de los anteriores valores para los radicales en R^1a puede sustituirse opcionalmente por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, hidroxi, (1-4C)alcoxi, halo, ciano, nitro, carboxi, hidroxi(1-4C)alquil-, (1-4C)alquil(1-4C)alquil-, halo(1-4C)alquil-, difluorometilo, trifluorometilo, trifluorometoxi, formilo, -CO(1-4C)alquilo -COO(1-4C)alquilo, $-C(O)NH_2$, -C(O)NH(1-4C)alquilo, -C(O)N[di(1-4C)alquilo], $-S(O)_2NH_2$, $-S(O)_2$NH(1-4C)alquilo y $-S(O)_2$N[di(1-4C)alquilo];

R^1b es un anillo bicíclico heterocíclico de 8-10 miembros que contiene 1, 2, 3 o 4 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga enlaces O-O o S-S), donde un grupo $-CH_2-$ se puede reemplazar opcionalmente por un -C(O)-, un anillo de átomos de sulfuro opcionalmente se puede oxidar para formar el S-óxido (s) y un anillo de átomos de nitrógeno opcionalmente se puede oxidar para formar el N-óxido y donde el citado anillo se puede sustituir opcionalmente por 1, 2 o 3 radicales seleccionados independientemente entre los radicales enumerados para R^1a arriba;

R^1c es un anillo fenilo, sustituido por 1, 2 o 3 radicales seleccionados independientemente entre los radicales enumerados para R^1a arriba;

R^1d se selecciona entre $-CH_2R^1$a, $-C(O)R^1$a, $-OR^1$a, $S(O)qR^1$a (donde q es 1 o 2);

R^1e se selecciona entre $-CH_2R^1$b, $-C(O)R^1$b, $-OR^1$b, $S(O)qR^1$b (donde q es 1 o 2);

R^1f se selecciona entre $-CH_2R^1$c, $-C(O)R^1$c $-OR^1$c, $S(O)qR^1$c (donde q es 1 o 2);

R^2 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, (2-4C)alquenilo, (2-4C)alquinilo, halo, ciano, fluorometilo, difluorometilo y trifluorometilo;

R^3 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, (2-4C)alquenilo, (2-4C)alquinilo, halo, hidroxi, ciano, fluorometilo, difluorometilo trifluorometilo, -CO(1-6C)alquilo y (1-6C)alcoxi;

R^4 se selecciona entre hidrógeno, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, nitro, hidroxi, halo, ciano, (3-6C)cicloalquilo, -(1-6C)alquil(3-6C) cicloalquilo, halo(1-4C)alquil-, difluorometilo, trifluorometilo, -CO(1-6C)alquilo y (1-6C)alcoxi;

R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-4C)alquenilo, (3-6C)cicloalquilo, -(1-4C)alquilC(O)O(1-4C)alquilo, hidroxi, amino, -NH(1-4C)alquilo, - N[di(1-4C)alquilo], (1-4C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi(1-4C)alcoxi, (1-4C)alcoxi(1-4C)alquil-, (1-4C)alquiltio(1-4C)alquil-, hidroxi(1-4C)alquil-, -(1-4C)alquilNH_2, -(1-4C)alquilNH(1-4C)alquilo, -(1-4C)alquilN[di(1-4C)alquilo] y -(1-4C)alquilheterociclilo;

R^7 se selecciona independientemente en cada caso entre hidrógeno y (1-6C)alquilo;

o R^6 y R^7 pueden junto con el nitrógeno al cual están adheridos formar un anillo heterociclilo de 5 o 6 miembros, opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, hidroxi, (1-4C)alcoxi, halo, ciano, nitro, carboxi, hidroxi(1-4C)alquil-, (1-4C)alcoxi (1-4C)alquil-, halo (1-4C)alquilo, difluorometilo, trifluorometilo, trifluorometoxi, formilo, -CO(1-4C)alquilo, -COO(1-4C)alquilo, -C(O)NH_2, -C(O)NH(1-4C)alquilo, -C(O)N[di(1-4C)alquilo], -$S(O)_2NH_2$, -$S(O)_2$NH(1-4C)alquilo, -$S(O)_2$N[di(1-4C)alquilo] y -S(O)p(1-4C)alquilo;

R^5 se selecciona entre hidrógeno y (1-4C)alquilo;

p es (independientemente en cada caso) 0, 1 o 2.

En otro aspecto de la invención, se dispone un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, donde:

W es O o NR^5;

Y es hidrógeno o metilo;

R^1 se selecciona entre R^1a, R^1b, R^1c, R^1d, R^1e y R^1f;

R^1a es un anillo heterocíclico saturado, parcialmente insaturado o insaturado de 4 a 7 miembros que contiene 1, 2, 3 o 4 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga enlaces O-O o S-S), donde el citado anillo es sustituido por 1, 2 o 3 radicales seleccionados independientemente entre:

nitro, ciano, (2-6C)alquenilo, (2-6C)alquinilo, -CO(1-6C)alquilo, -COO(1-6C)alquilo, -O(1-6C)alquilo, trifluorometilo, -CONR^{6}R^7, -OCONR^{6}R^7, -N(R^7)COR^6, -CONHCH(CO$_2$R^7)R^6, halo, hidroxi, carboxi, (1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, halo, ciano, nitro, -COO(1-6C)alquilo, -O(1-6C)alquilo, trifluorometilo, -CONR^{6}R^7, carboxi, -NHC(O)O(1-4C)alquilo, -C(=NOH) (1-4C)alquilo, -C(=NOH)NR^{6}R^7, -S(O)p(1-4C)alquilo, -S(O)pNR^{6}R^7, -NR^{6}R^7 y heterociclilo {opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, hidroxi, (1-4C)alcoxi, halo, ciano, nitro, carboxi, hidroxi (1-4C)alquilo, (1-4C)alcoxi(1-4C)alquilo, halo(1-4C)alquilo, difluorometilo, trifluorometilo, trifluorometoxi, formilo, -CO(1-4C)alquilo, -COO(1-4C)alquilo, -C(O)NH$_2$, -C(O)NH(1-4C)alquilo, -C(O)N[di(1-4C)alquilo], -S(O)$_2$NH$_2$, -S(O)$_2$NH(1-4C)alquilo, -S(O)$_2$N[di(1-4C)alquilo] y -S(O)p(1-4C)alquil}].

heterociclilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, hidroxi, (1-4C)alcoxi, halo, ciano, nitro, carboxi, hidroxi(1-4C)alquilo, (1-4C)alcoxi (1-4C)alquilo, halo (1-4C)alquilo, difluorometilo, trifluorometilo, trifluorometoxi, formilo, -CO(1-4C)alquilo, -COO(1-4C)alquilo, -C(O)NH$_2$, -C(O)NH(1-4C)alquilo, -C(O)N[di(1-4C)alquilo], -S(O)$_2$NH$_2$, -S(O)$_2$NH(1-4C)alquilo, -S(O)$_2$N[di(1-4C)alquilo] y -S(O)p(1-4C)alquilo], arilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, hidroxi, (1-4C)alcoxi, halo, ciano, nitro, carboxi, hidroxi(1-4C)alquilo, (1-4C)alcoxi(1-4C)alquilo, halo(1-4C)alquilo, difluorometilo, trifluorometilo, trifluorometoxi, formilo, -CO(1-4C)alquilo, -COO(1-4C)alquilo, -

$C(O)NH_2$, -C(O)NH(1-4C)alquilo, -C(O)N[di(1-4C)alquilo], $-S(O)_2NH_2$, -$S(O)_2$NH(1-4C)alquilo, -$S(O)_2$N[di(1-4C)alquilo] y-S(O)p(1-4C)alquilo], -NHC(O)O(1-4C)alquilo, -C(=NOR^7)(1-4C)alquilo, -C(=NOR^7)NR^6R^7, -S(O)p(1-4C)alquilo (opcionalmente sustituido por hidroxi), -S(O)pNR^6R^7, -S(O)p(1-4C)alquilCONHR^7, -NR^7S(O)pNR^6R^7, -NR^7S(O)p(1-4C)alquilo, -NR^7S(O)p-arilo, -C(O)NHS(O)p(1-4C)alquilo, -C(O)NHS(O)p-arilo, -NR^6R^7, -$CH_2CH(CO_2R^6)OH$, -(1-4C)alquilCH(NR^6R^7)CO_2R^6 y -(1-4C)alquilCH(NR^6R^7)CO(NR^6R^7);

R^1b es un anillo bicíclico heterocíclico de 8-10 miembros que contiene 1, 2, 3 o 4 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga enlaces O-O o S-S), donde el citado anillo es sustituido por 1, 2 o 3 radicales seleccionados independientemente entre los radicales enumerados para R^1a arriba;

R^1c es un anillo fenilo, sustituido por 1, 2 o 3 radicales seleccionados independientemente entre los radicales enumerados para R^1a arriba;

R^1d se selecciona entre -CH_2R^1a, -C(O)R^1a, -OR^1a, S(O)qR^1a (donde q es 1 o 2);

R^1e se selecciona entre -CH_2R^1b, -C(O)R^1b, -OR^1b, S(O)qR^1b (donde q es 1 o 2);

R^1f se selecciona entre –CH_2R^1c, -C(O)R^1c -OR^1c, S(O)qR^1c (donde q es 1 o 2);

R^2 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, (2-4C)alquenilo, (2-4C)alquinilo, halo, fluorometilo, difluorometilo y trifluorometilo;

R^3 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, (2-4C)alquenilo, (2-4C)alquinilo, halo, hidroxi, ciano, fluorometilo, difluorometilo trifluorometilo, -CO(1-6C)alquilo y (1-6C)alcoxi;

R^4 se selecciona entre hidrógeno, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, nitro, hidroxi, halo, ciano, (3-6C)cicloalquilo, -(1-6C)alquil(3-6C)cicloalquilo, halo(1-4C)alquilo, difluorometilo, trifluorometilo, -CO(1-6C)alquilo y (1-6C)alcoxi;

R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-6C)cicloalquilo, -(1-4C)alquilC(O)O(1-4C)alquilo, hidroxi, amino, (1-4C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi(1-4C)alcoxi, (1-4C)alcoxi(1-4C)alquilo, (1-4C)alquiltio(1-4C)alquilo, hidroxi(1-4C)alquilo, -(1-4C)alquilNH_2, -(1-4C)alquilNH(1-4C)alquilo, -(1-4C)alquilN[di(1-4C)alquilo] y -(1-4C)alquilheterociclilo;

R^7 se selecciona independientemente en cada caso entre hidrógeno y (1 - 6C)alquilo;

o R^6 y R^7 pueden conjuntamente formar un anillo heterociclilo de 5 o 6 miembros, opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, hidroxi, (1-4C)alcoxi, halo, ciano, nitro, carboxi, hidroxi(1-4C)alquilo, (1-4C)alcoxi(1-4C)alquilo, halo(1-4C)alquilo, difluorometilo, trifluorometilo, trifluorometoxi, formilo, -CO(1-4C)alquilo, -COO(1-4C)alquilo, -C(O)NH_2, -C(O)NH(1-4C)alquilo, -C(O)N[di(1-4C)alquilo], -$S(O)_2NH_2$, -$S(O)_2$NH(1-4C)alquilo, -$S(O)_2$N[di(1-4C)alquilo] y -S(O)p(1-4C)alquilo;

R^5 se selecciona entre hidrógeno y (1-4C)alquilo;

p es (independientemente en cada caso) 0, 1 o 2.

Por lo tanto, la presente invención dispone un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo; donde:

W es O o NR^5;

Y es hidrógeno;

R^1 se selecciona entre R^1a, R^1b, R^1c, R^1d, R^1e y R^1f;

R^1a es un anillo heterocíclico saturado, parcialmente insaturado o insaturado de 4 a 7 miembros que contiene 1, 2, 3 o 4 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga enlaces O-O o S-S), donde el citado anillo es sustituido por 1, 2 o 3 radicales seleccionados independientemente entre:

nitro, ciano, (2-6C)alquenilo, (2-6C)alquinilo, -CO(1-6C)alquilo, -COO(1-6C)alquilo (opcionalmente sustituido por -COO(1-6C)alquilo), trifluorometilo, -$CONR^6R^7$, -$OCONR^6R^7$, -$N(R^7)COR^6$, -$CONHCH(CO_2R^7)R^6$, halo, hidroxi, carboxi, (1-6C)alquilo [opcionalmente

sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, halo, ciano, nitro, -COO(1-6C)alquilo, -OCO(1-4C)alquilo, (1-6C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, hidroxi(1-4C)alcoxi, (2-4C)alqueniloxi, trifluorometilo, -CONR^{6}R^7, carboxi, -NHC(O)O(1-4C)alquilo, -OCONR^{6}R^7, -C(=NOH)(1-4C)alquilo, -C(=NOH)NR^{6}R^7, -S(O)p(1-4C)alquilo, -S(O)pNR^{6}R^7, -NHSO$_2$R^6, -NR^{6}R^7 y heterociclilo], (3-6C)cicloalquilo (opcionalmente sustituido por 1 o 2 radicales seleccionados entre (1-6C)alquilo y los radicales opcionales descritos para (1-6C)alquilo arriba), -O(1-6C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), -S(O)p(1-4C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), heterociclilo, arilo, -NHC(O)O(1-4C)alquilo, -C(=NOR^7)(1-4C)alquilo, -C(=NOR^7)NR^{6}R^7, -S(O)pNR^{6}R^7, -S(O)p(1-4C)alquilCONHR^7, -NR^{7}S(O)pNR^{6}R^7, -NR^{7}S(O)p(1-4C)alquilo, -NR^{7}S(O)p-arilo, -C(O)NHS(O)p(1-4C)alquilo, -C(O)NHS(O)p-arilo, -NR^{6}R^7,-CH$_2$CH(CO$_2$R^6)OH, -(1-4C)alquilCH(NR^{6}R^7)CO$_2$R^6 y -(1-4C)alquilCH(NR^{6}R^7)CO(NR^{6}R^7);

donde cualquier grupo arilo o heterociclilo en cualquiera de los anteriores valores para los radicales en R^{1}a puede sustituirse opcionalmente por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, hidroxi, (1-4C)alcoxi, halo, ciano, nitro, carboxi, hidroxi(1-4C)alquilo, (1-4C)alcoxi(1-4C)alquilo, halo (1-4C)alquilo, difluorometilo, trifluorometilo, trifluorometoxi, formilo, -CO(1-4C)alquilo, -COO(1-4C)alquilo, -C(O)NH$_2$, -C(O)NH(1-4C)alquilo, -C(O)N[di(1-4C)alquilo], -S(O)$_2$NH$_2$, -S(O)$_2$NH(1-4C)alquilo y -S(O)$_2$N[di(1-4C)alquilo];

R^{1}b es un anillo bicíclico heterocíclico de 8-10 miembros que contiene 1, 2, 3 o 4 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga enlaces O-O o S-S), donde el citado anillo es sustituido por 1, 2 o 3 radicales seleccionados independientemente entre los radicales enumerados para R^{1}a arriba;

R^1c es un anillo fenilo, sustituido por 1, 2 o 3 radicales seleccionados independientemente entre los radicales enumerados para R^1a arriba;

R^1d se selecciona entre -CH_2R^1a, -C(O)R^1a, -OR^1a, S(O)qR^1a (donde q es 1 o 2);

R^1e se selecciona entre -CH_2R^1b, -C(O)R^1b, -OR^1b, S(O)qR^1b (donde q es 1 o 2);

R^1f se selecciona entre -CH_2R^1c, -C(O)R^1c-OR^1c, S(O)qR^1c (donde q es 1 o 2);

R^2 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, (2-4C)alquenilo, (2-4C)alquinilo, halo, fluorometilo, difluorometilo y trifluorometilo;

R^3 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, (2-4C)alquenilo, (2-4C)alquinilo, halo, hidroxi, ciano, fluorometilo, difluorometilo trifluorometilo, -CO(1-6C)alquilo y (1-6C)alcoxi;

R^4 se selecciona entre hidrógeno, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, nitro, hidroxi, halo, ciano, (3-6C)cicloalquilo, -(1-6C)alquil(3-6C)cicloalquilo, halo(1-4C)alquilo, difluorometilo, trifluorometilo, -CO(1-6C)alquilo y (1-6C)alcoxi;

R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-4C)alquenilo, (3-6C)cicloalquilo, -(1-4C)alquilC(O)O(1-4C)alquilo, hidroxi, amino, -NH(1-4C)alquilo, -N[di(1-4C)alquilo, (1-4C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi(1-4C)alcoxi, (1-4C)alcoxi(1-4C)alquilo, (1-4C)alquiltio(1-4C)alquilo, hidroxi(1-4C)alquilo, -(1-4C)alquilNH_2, -(1-4C)alquilNH(1-4C)alquilo, -(1-4C)alquilN[di(1-4C)alquilo] y -(1-4C)alquilheterociclilo;

R^7 se selecciona independientemente en cada caso entre hidrógeno y (1-6C)alquilo;

o R^6 y R^7 pueden junto con el nitrógeno al cual están adheridos formar un anillo heterociclilo de 5 o 6 miembros, opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, hidroxi, (1-4C)alcoxi, halo, ciano, nitro, carboxi, hidroxi(1-4C)alquilo, (1-4C)alcoxi (1-4C)alquilo, halo(1-

4C)alquilo, difluorometilo, trifluorometilo, trifluorometoxi, formilo, -CO(1-4C)alquilo, -COO(1-4C)alquilo, $-C(O)NH_2$, -C(O)NH(1-4C)alquilo, -C(O)N[di(1-4C)alquilo], $-S(O)_2NH_2$, $-S(O)_2$NH(1-4C)alquilo, $-S(O)_2$N[di(1-4C)alquilo] y -S(O)p(1-4C)alquilo;

R^5 se selecciona entre hidrógeno y (1-4C)alquilo;

p es (independientemente en cada caso) 0, 1 o 2.

En esta especificación, el término **alquilo** incluye grupos alquilo de cadena recta y de cadena ramificada, pero referencias a grupos alquilo individuales como propilo son específicas únicamente para la versión de cadena recta. Una convención análoga aplica para otros términos genéricos. Salvo si se afirma en contrario, el término alquilo hace referencia en forma ventajosa a cadenas de 1-6 átomos de carbono, preferiblemente de 1-4 átomos de carbono. En esta especificación, los términos **alquenilo, alquinilo** y **cicloalquenilo** incluyen todos los isómeros posicionales y geométricos.

En esta especificación, el término **alcoxi** significa un grupo alquilo como se define arriba enlazado a un átomo de oxígeno.

Cuando se escogen radicales opcionales entre 0, 1, 2 o 3 grupos, se deberá entender que esta definición incluye todos los radicales que se escogen entre uno de los grupos especificados o los radicales que se escogen de dos o más grupos especificados. Una convención análoga aplica para los radicales escogidos entre 0, 1 o 2 grupos; 1, 2 o 3 radicales; y 1 o 2 grupos.

Se entenderá que cuando los radicales contienen dos radicales en una cadena alquilo, cuando los dos están enlazados por un heteroátomo (por ejemplo dos radicales alcoxi), entonces estos dos radicales no son radicales en el mismo átomo de carbono de la cadena alquilo. Se entenderá que no se contemplan compuestos inestables como parte de esta invención.

Siguen unos valores particulares y apropiados para ciertos radicales y grupos a los cuales se hace referencia en esta especificación. Estos valores se pueden emplear cuando sea lo indicado en cualquiera de las definiciones e incorporaciones divulgadas arriba o a continuación. Para evitar dudas,

cada especie citada representa un aspecto particular e independiente de esta invención.

Donde "**R^6 y R^7 pueden junto con el nitrógeno al cual están adheridos formar un anillo heterociclilo de 5 o 6 miembros**" el citado "anillo heterociclilo de 5 o 6-miembros" es un anillo monocíclico saturado, parcialmente saturado o totalmente insaturado, donde uno de los átomos es el átomo de hidrógeno al cual están adheridos R^6 y R^7 y los otros átomos son todos átomos de carbono o son átomos de carbono y 1, 2 o 3 heteroátomos escogidos entre nitrógeno, sulfuro u oxígeno, donde un grupo $-CH_2-$ se puede reemplazar opcionalmente por un -C(O)- y un anillo de átomos de nitrógeno o un anillo de átomos de sulfuro opcionalmente se puede oxidar para formar el N- y/o S-óxido(s). Ejemplos y unos valores apropiados para "R^6 y R^7 pueden junto con el nitrógeno al cual están adheridos formar un anillo heterociclilo de 5 o 6 miembros" son piperazinilo y morfolino.

Ejemplos particulares de "**anillo heterocíclico de 4 a 7 miembros saturado, parcialmente saturado o insaturado que contiene 1, 2, 3 o 4 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga enlaces O-O o S-S), donde un grupo $-CH_2-$ se puede reemplazar opcionalmente por un -C(O)-, un anillo de átomos de sulfuro opcionalmente se puede oxidar para formar el S-óxido(s) y un anillo de átomos de nitrógeno opcionalmente se puede oxidar para formar el N-óxido**" incluyen piridinilo, *N*-oxopiridinilo, pirimidinilo, tiazolilo, tiadiazolilo, tetrazolilo, imidazolilo, triazinilo, pirrolidinilo, tienilo, furanilo, oxadiazolilo, isoxazolilo, oxazolilo y pirrolilo.

Ejemplos particulares de un "**anillo heterocíclico bicíclico de 8-10 miembros que contiene 1, 2, 3 o 4 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga enlaces O-O o S-S), donde un grupo $-CH_2-$ se puede**

reemplazar opcionalmente por un -C(O)-, un anillo de átomos de sulfuro opcionalmente se puede oxidar para formar el S-óxido(s) y un anillo de átomos de nitrógeno opcionalmente se puede oxidar para formar el N-óxido" incluyen quinolinilo, purinilo, benzotiazolilo, indolilo, 4-oxoquinolinilo, 2, 7-naftiridinilo y quinazolinilo.

Heterociclilo es un anillo monocíclico saturado, parcialmente saturado o insaturado opcionalmente sustituido que contiene de 5 a 7 átomos de los cuales 1, 2, 3 o 4 átomos de anillos se escogen entre nitrógeno, sulfuro u oxígeno, que pueden, salvo si se especifica en contrario, estar enlazados al carbono o al nitrógeno, donde un grupo $-CH_2-$ se puede reemplazar opcionalmente por un -C(O)-, un anillo de átomos de sulfuro opcionalmente se puede oxidar para formar el S-óxido(s) y un anillo de átomos de nitrógeno opcionalmente se puede oxidar para formar el N-óxido. Ejemplos y valores apropiados del término heterociclilo son morfolino, morfolinilo, piperidino, piperidilo, piridilo, piridil-N-óxido, piranilo, pirrolilo, imidazolilo, tiazolilo, tienilo, dioxolanilo, tiadiazolilo, piperazinilo, isotiazolidinilo, triazolilo, tetrazolilo, pirrolidinilo, 2-oxazolidinonilo, 5-isoxazolonilo, tiomorfolino, pirrolinilo, homopiperazinilo, 3,5-dioxapiperidinilo, 3-oxopirazolin-5-ilo, tetrahidropiranilo, tetrahidrotiopiranilo, 1-oxotetrahidrotiopiranilo, 1,1-dioxotetrahidrotiopiranilo, pirimidilo, pirazinilo, piridazinilo, pirazolilo, pirazolinilo, isoxazolilo, 4-oxopidridilo, 2-oxopirrolidilo, 4-oxotiazolidilo, furilo, tienilo, oxazolilo, oxadiazolilo, 2-[(5-oxo)-1-oxa-3,4-diazolilo] y 3-[oxa-2,4-diazolilo].

Idealmente el **heterociclilo** es morfolino, morfolinilo, piperidino, piperidilo, piridilo, piranilo, pirrolilo, imidazolilo, tiazolilo, tienilo, tiadiazolilo, piperazinilo, isotiazolidinilo, 1,3,4-triazolilo, tetrazolilo, pirrolidinilo, tiomorfolino, pirrolinilo, homopiperazinilo, 3,5-dioxapiperidinilo, pirimidilo, pirazinilo, piridazinilo, pirazolilo, pirazolinilo, isoxazolilo, 4-oxopidridilo, 2-oxopirrolidilo, 4-oxotiazolidilo, furilo, tienilo, oxazolilo, 1,3,4-oxadiazolilo, 1,2,4-oxadiazolilo 2-[(5-oxo)-1-oxa-3,4-diazolilo] y 3-[oxa-2,4-diazolilo].

Convenientemente el **heterociclilo** es oxazolilo, 1,3,4-oxadiazolilo, 1,2,4-oxadiazolilo, 2-[(5-oxo)-1-oxa-3,4-diazolilo], 3-[oxa-2,4-diazolilo], tetrazolilo, tiazolilo, tiadiazolilo, piridilo, imidazolilo, furilo, tienilo, morfolino, pirimidilo, pirazinilo, piridazinilo, pirazolilo, pirazolinilo y piperazinilo.

Unos radicales opcionales apropiados para el **heterociclilo** como un anillo saturado o parcialmente saturado son, salvo si se define en contrario, 1, 2 o 3 radicales seleccionados independientemente entre halo, ciano, hidroxi, (1-4C)alquilo, (1-4C)alcoxi y (1-4C)alquil$S(O)_b$ (donde b es 0, 1 o 2). Otros radicales apropiados para "heterociclilo" como un anillo saturado o parcialmente saturado son 1, 2 o 3 radicales seleccionados independientemente entre fluoro, cloro, ciano, hidroxi, metilo, etilo, metoxi, metiltio, metilsulfinilo y metilsulfonilo.

Unos radicales apropiados opcionales para el heterociclilo como un anillo insaturado son, salvo si se define en contrario, 1, 2 o 3 radicales seleccionados independientemente entre halo, ciano, nitro, amino, hidroxi, (1-4C)alquilo, (1-4C)alcoxi, (1-4C)alquil$S(O)_b$ (donde b es 0, 1 o 2), *N*-((1-4C)alquil) amino y *N*,*N*-((1-4C)alquil)$_2$amino. Otros radicales apropiados opcionales para el "heterociclilo" como un anillo insaturado son 1, 2 o 3 radicales seleccionados independientemente entre fluoro, cloro, ciano, nitro, amino, metilamino, dimetilamino, hidroxi, metilo, etilo, metoxi, metiltio, metilsulfinilo y metilsulfonilo.

Para evitar dudas, los radicales opcionales en los grupos heterociclilo generalmente son radicales en los átomos de carbono del anillo, pero cuando sea apropiado pueden estar en un átomo N, por ejemplo N-alquilpiridina.

Los ejemplos de **(heterociclil)(1-4C)alquilo** son morfolinometilo, morfolinoetilo, morfolinilmetilo, morfoliniletilo, piperidinometilo, piperidinoetilo, piperidilmetilo, piperidiletilo, imidazolilmetilo, imidazoliletilo, tetrazolilmetilo, tetrazoliletilo, oxazolilmetilo, oxazoliletilo, 1, 3, 4-oxadiazolilmetilo, 1, 2, 4-oxadiazolilmetilo, 1, 2, 4-oxadiazoliletilo,

...

piridilmetilo, piridiletilo, furilmetilo, furiletilo, (tienil)metilo, (tienil)etilo, pirazinilometilo, piraziniloetilo, piperazinilometilo y piperaziniloetil.

Arilo es un anillo de carbono mono o bicíclico parcialmente saturado o insaturado, que contiene 3-12 átomos; donde un grupo $-CH_2-$ se puede reemplazar opcionalmente por un -C(O)-. Particularmente el **arilo** es un anillo monocíclico que contiene 5 o 6 átomos o un anillo bicíclico que contiene 9 o 10 átomos. En otro aspecto, el arilo es un anillo totalmente insaturado. Unos valores apropiados para el **arilo** incluyen ciclopentenilo, ciclohexenilo, fenilo, naftilo, indanilo o 1-oxoindanilo. Ejemplos de **arilo** son fenilo y naftilo opcionalmente sustituidos.

Ejemplos de **arilo ((1-4C))alquilo** son bencilo, fenotilo, naftilmetilo y naftiletil.

Ejemplos de **(1-4C)alquilo** incluyen metilo, etilo, propilo, butilo, tert-butilo e isopropilo; ejemplos de **(1-6C)alquilo** incluyen (1-4C)alquilo, pentilo y hexilo; ejemplos de **(2-4C)alquenilo** incluyen vinilo, propenilo, alilo, but-2-enilo y but-3-enilo; ejemplos de **(3-4C)alquenilo** incluyen propenilo, alilo, but-2-enilo y but-3-enilo; ejemplos de **(2-6C)alquenilo** incluyen (2-4C)alquenilo, pent-2-enilo, pent-3-enilo y hex-5-enilo; ejemplos de **(2-4C)alquinilo** incluyen etinilo, prop-2-inilo, but-2-inilo y but-3-inilo; ejemplos de **(2-6C)alquinilo** incluyen (2-4C)alquinilo, pent-3-inilo y hex-4-inil; ejemplos de **(1-6C)alcoxi y -O(1-6C)alquilo** incluyen metoxi, etoxi, propoxi, iso-propoxi, butoxi, tert-butoxi y pentoxi; ejemplos de **(1-4C)alcoxi** incluyen metoxi, etoxi y propoxi; ejemplos de **(1-4C)alcoxi (1-4C)alquilo** incluyen metoximetilo, etoximetilo, metoxietilo y propoximetilo; ejemplos de **(3-6C)cicloalquilo** incluyen ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo; ejemplos de **-(1-6C)alquil(3-6C)cicloalquilo** incluyen ciclopropilmetilo, ciclopropiletilo, ciclobutilmetilo, ciclopentilmetilo y ciclohexilmetilo; ejemplos de grupos **halo** incluyen fluoro, cloro y bromo; ejemplos de grupos **halo(1-4C)alquilo** incluyen fluorometilo, fluoroetilo, clorometilo, cloroetilo y bromometilo; ejemplos de **hidroxi(1-4C)alquilo** e **hidroxi(1-6C)alquilo** incluyen hidroximetilo, 1-hidroxietilo, 2-hidroxietilo y 3-hidroxipropilo; ejemplos de

(1-4C)alcoxi-(1-4C)alcoxi y **(1-6C)alcoxi-(1-6C)alcoxi** incluyen metoximetoxi, 2-metoxietoxi, 2-etoxietoxi y 3-metoxipropoxi; ejemplos de **(1-4C)alcoxi-(1-4C)alcoxi-(1-4C)alcoxi** incluyen 2-(metoximetoxi) etoxi, 2-(2-metoxietoxi)etoxi; 3-(2-metoxietoxi)propoxi y 2-(2-etoxietoxi)etoxi; ejemplos de **(1-4C)alquilS(O)$_p$-** donde p es 0, 1 o 2 incluyen metiltio, etiltio, metilsulfinilo, etilsulfinilo, metilsulfonilo y etilsulfonilo; ejemplos de **(1-4C)alquiltio(1-4C)alquilo** incluyen metiltioetilo, metiltiometilo, etiltiometilo, propiltiometilo y propiltioetilo; ejemplos de **ciano(1-4C)alquilo** incluyen cianometilo, 1-cianoetilo, 2-cianoetilo y 3-cianopropilo; ejemplos de-**CO(1-4C)alquilo** incluyen metilcarbonilo, etilcarbonilo, propilcarbonilo, isopropilcarbonilo y tert-butilcarbonilo; ejemplos de **-CO(1-6C)alquilo** incluyen **-CO(1-4C)alquilo** y pentilcarbonilo; ejemplos de **-COO(1-4C)alquilo** incluyen metoxicarbonilo, etoxicarbonilo, propoxicarbonilo, isopropoxicarbonilo y tert-butoxicarbonilo; ejemplos de **-COO(1-6C)alquilo** incluyen -COO(1-4C)alquilo y pentoxicarbonilo; ejemplos de **-OCO(1-4C)alquilo** incluyen metilcarboniloxi, etilcarboniloxi, propilcarboniloxi, isopropilcarboniloxi y tert-butilcarboniloxi; ejemplos de **-OCO(1-6C)alquilo** incluyen -OCO(1-4C)alquilo y pentilcarboniloxi; ejemplos de **-(1-4C)alquilCOO(1-4C)alquilo** incluyen metoxicarbonilmetilo, etoxicarbonilmetilo, metoxicarboniletilo, propoxicarbonilmetilo, isopropoxicarbonilmetilo y tert-butoxicarbonilmetilo; ejemplos de **-NH(1-4C)alquilo** incluyen metilamino, etilamino, propilamino y butilamino; ejemplos de **-N[di(1-4C)alquil]** incluyen N, N-dimetilamino, N-metil-N-etilamino, N, N-dietilamino y N, N-dipropilamino; ejemplos de **-(1-4C)alquilNH(1-4C)alquilo** incluyen metilaminometilo, etilaminometilo, metilaminoetilo, propilaminometilo e isopropilaminometilo; ejemplos de **-(1-4C)alquilN[di(1-4C)alquil]** incluyen N,N-dimetilaminometilo, N,N-dimetilaminoetilo, N-metil-N-etilaminometilo y dimetilaminopropilo; ejemplos de **-CONH(1-4C)alquilo** incluyen metilaminocarbonilo, etilaminocarbonilo, propilaminocarbonilo, isopropilaminocarbonilo y tert-butilaminocarbonilo; ejemplos de **-CON[di(1-4C)alquil]** incluyen N-dimetilaminocarbonilo y N-metil-N-

etilaminocarbonilo; ejemplos de **-S(O)$_2$NH(1-4C)alquilo** incluyen N-metilaminosulfonilo y N-etilaminosulfonilo; ejemplos de **-S(O)$_2$N[di(1-4C)alquil]** incluyen N,N-dimetilaminosulfonilo, N,N-dietilaminosulfonilo y N-metil-N-etilaminosulfonilo; ejemplos de **-S(O)p(1-4C)alquilo** incluyen metiltio, metilsulfinilo, metilsulfonilo, etiltio, propiltio, isopropiltio, etilsulfinilo y etilsulfonilo; ejemplos de **-NHC(O)(1-4C)alquilo** incluyen acetilamino y propionilamino; ejemplos de **-NHC(O)heterociclilo** incluyen pirimidin-2-ilcarbonilamino y piperazin-1-ilcarbonilamino; ejemplos de **-NHC(O)arilo** incluyen benzoilamino y naft-3-ilcarbonilamino; ejemplos de **-NHS(O)p(1-4C)alquilo** incluyen mesilamino e isopropilsulfonilamino.

En esta especificación se emplean términos compuestos para describir unos grupos que comprenden más de una funcionalidad como -(1-4C)alquilSO$_2$(1-4C)alquilo. Dichos términos se deberán interpretar de conformidad con el significado adscrito al mismo por una persona con destreza en el arte para cada parte citada del componente. Por ejemplo -(1-4C)alquilSO$_2$(1-4C)alquilo incluye -metilsulfonilmetilo, -metilsulfoniletilo, -etilsulfonilmetilo y -propilsulfonilbutilo.

Un compuesto de fórmula (I) puede formar unas sales ácidas o alcalinas estables y en dichos casos, la administración de un compuesto como una sal puede ser apropiada y las sales farmacéuticamente aceptables se pueden preparar mediante métodos convencionales como aquellos descritos a continuación.

Sales apropiadas farmacéuticamente aceptables incluyen sales de adición de ácido como metanosulfonato, tosilat, α-glicerofosfato, fumarato, clorhidrato, citrato, maleato, tartrato y (menos preferiblemente) hidrobromuro. También se forman sales apropiadas con ácido fosfórico y sulfúrico. En otro aspecto, unas sales apropiadas son sales alcalinas como una sal de metal alcalino por ejemplo sodio, una sal de metal alcalinotérreo por ejemplo calcio o magnesio, una sal orgánica de amina por ejemplo trietilamina, morfolino, N-metilpiperidina, N-etilpiperidina, procaína, dibencilamina, N,N-dibenciletilamina, tris-(2-hidroxietil)amina, N-metilo d-glucamina y amino ácidos como la lisina. Puede haber más de un catión o

anión dependiendo del número de funciones cargadas y de la valencia de los cationes o de los aniones. Una sal farmacéuticamente aceptable preferida es la sal de sodio.

Sin embargo, para facilitar el aislamiento de la sal durante la preparación, las sales que son menos solubles en el solvente escogido se pueden preferir, así sean farmacéuticamente aceptables o no.

En la presente invención, se entenderá que un compuesto de fórmula (I) o una sal del mismo puede mostrar el fenómeno del tauterismo y que los dibujos de las fórmulas en esta especificación únicamente pueden representar una de las formas tautoméricas posibles. Se entenderá que la invención comprende cualquier forma tautomérica que inhibe la ADN girasa y no se debe limitar meramente a una cualquiera de las formas tautoméricas utilizadas en los dibujos de las fórmulas. Los dibujos de las fórmulas en esta especificación únicamente pueden representar una de las formas tautoméricas y se entenderá que la especificación comprenderá todas las formas tautoméricas posibles de los compuestos dibujados y no solamente aquellas formas que se han podido mostrar en forma gráfica en la presente.

Aquellos con destreza en el arte apreciarán que ciertos compuestos de fórmula (I) contienen un carbono sustituido en forma asimétrica y/o un átomo de sulfuro y por lo tanto pueden existir en y aislarse de, formas ópticamente activas y racémicas. Algunos compuestos pueden exhibir polimorfismo. Se entenderá que la presente invención comprende cualquier forma racémica, ópticamente activa, polimórfica o esteroisomérica o mezclas de las mismas, cuya forma posee unas propiedades útiles en la inhibición de ADN girasa. En el arte se sabe muy bien como preparar las formas ópticamente activas (por ejemplo mediante resolución de la forma racémica por medio de unas técnicas de recristalización, por síntesis de unos materiales de partida ópticamente activos, mediante síntesis quiral, por resolución enzimática, por biotransformación o por separación cromatográfica empleando una fase quiral estacionaria) y como determinar

la eficacia de la inhibición de la ADN girasa por medio de unas pruebas estándar descritas abajo.

También se entiende que ciertos compuestos de fórmula (I) y las sales de los mismos pueden existir en forma solvatada e insolvatada como por ejemplo en formas hidratadas. Se entenderá que la invención comprende todas estas formas solvatadas que inhiben la ADN girasa.

Como se anotó arriba, hemos descubierto un rango de compuestos que son buenos inhibidores de la ADN girasa. En general tienen buenas propiedades físicas y/o farmacocinéticas. Los siguientes compuestos poseen unas propiedades farmacéuticas y/o físicas y/o farmacocinéticas preferidas.

Unos compuestos particularmente preferidos de la invención comprenden un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, donde los radicales W y R^1 a R^7 y otros radicales mencionados arriba tienen valores divulgados arriba, o cualquiera de los siguientes valores (que se pueden emplear cuando sea apropiado con cualquiera de las definiciones e incorporaciones divulgadas arriba o a continuación):

En una incorporación de la invención, se disponen unos compuestos de fórmula (I), en una incorporación alterna se disponen unas sales farmacéuticamente aceptables de los compuestos de fórmula (I).

En un aspecto, de la invención, W es O. En otro aspecto, W es NR^5.

En una incorporación, R^1 se selecciona entre R^1a.

En otra incorporación, R1 se selecciona entre R^1b.

En otra incorporación, R^1 se selecciona entre R^1c.

En otra incorporación, R^1 se selecciona entre R^1d.

En otra incorporación, R^1 se selecciona entre R^1e.

En otra incorporación, R^1 se selecciona entre R^1f.

En un aspecto, R^1a es un anillo heterocíclico de 5 miembros que contiene 1, 2, 3 o 4 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga ningún enlace O-O o S-S). En otro aspecto, R^1a es un anillo heterocíclico de 5 miembros que contiene

1, 2 o 3 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga ningún enlace O-O o S-S). En otro aspecto, R^1 a es un anillo heterocíclico de 5 miembros que contiene 1 o 2 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga ningún enlace O-O o S-S). En otro aspecto, R^1a es un anillo heterocíclico de 5 miembros que contiene 1 heteroátomo seleccionado independientemente entre O, S y N.

En un aspecto, R^1a es un anillo heterocíclico de 6 miembros que contiene 1, 2, 3 o 4 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga ningún enlace O-O o S-S). En otro aspecto, R^1a es un anillo heterocíclico de 6 miembros que contiene 1, 2 o 3 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga ningún enlace O-O o S-S). En otro aspecto, R^1a es un anillo heterocíclico de 6 miembros que contiene 1 o 2 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga ningún enlace O-O o S-S). En otro aspecto, R^1a es un anillo heterocíclico de 6 miembros que contiene 1 heteroátomo seleccionado independientemente entre O, S y N.

Unos valores apropiados para R^1a como un anillo heterociclilo de 5 miembros incluyen furilo, tienilo, oxazolilo, isoxazolilo, imidazolilo, tiazolilo, triazolilo, tetrazolilo, 1-oxa-3, 4-diazolilo, 2-oxo-[1-oxa-3,4-diazolilo], oxa-2,4-diazolilo, tia-2,4-diazolilo y pirrolilo.

Unos valores apropiados para R^1a como un anillo heterociclilo de 6 miembros incluyen morfolinilo, tiomorfolinilo, piridilo, pirimidinilo, triazinilo, piperidinilo y piperazinilo.

Unos valores apropiados para R^1a como un anillo heterociclilo de 6 miembros incluyen morfolinilo, tiomorfolinilo, piridilo, piridinonilo (por ejemplo piridin-2(1H)-ona), pirimidinilo, pirimidinonilo (por ejemplo pirimidin-2(1*H*)-ona), triazinilo, piperidinilo y piperazinilo.

Otros valores apropiados para R^1a son imidazolilo, pirimidinilo, piridinilo, tiazolilo, triazinilo, pirrolilo, tiadiazolilo y tetrazolilo.

R^1 a es un anillo heterocíclico saturado, parcialmente insaturado o insaturado de 5 o 6 miembros que contiene 1, 2, 3 o 4 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga enlaces O-O o S-S), donde un grupo $-CH_2-$ se puede reemplazar opcionalmente por un -C(O)-, un anillo de átomos de sulfuro opcionalmente se puede oxidar para formar el S-óxido(s) y un anillo de átomos de nitrógeno opcionalmente se puede oxidar para formar el N-óxido.

R^1a es piridinilo, *N*-oxopiridinilo, pirimidinilo, tiazolilo, tiadiazolilo, tetrazolilo, imidazolilo, triazinilo, pirrolidinilo, tienilo, furanilo, oxadiazolilo, isoxazolilo, oxazolilo o pirrolilo.

R^1a es un anillo heterocíclico saturado, parcialmente insaturado o insaturado de 5 o 6 miembros que contiene 1, 2, 3 o 4 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga enlaces O-O o S-S), donde un grupo $-CH_2-$ se puede reemplazar opcionalmente por un -C(O)-, un anillo de átomos de sulfuro opcionalmente se puede oxidar para formar el S-óxido(s) y un anillo de átomos de nitrógeno opcionalmente se puede oxidar para formar el N-óxido y donde el citado anillo opcionalmente se puede sustituir por 1, 2 o 3 radicales seleccionados independientemente entre: nitro, ciano, sulfo, formilo, hidroxiiminometilo, (2-6C)alquenilo, -CO(1-6C)alquilo, -COO(1-6C)alquilo trifluorometilo, $-CONR^6R^7$, $-N(R^7)COR^6$, halo, hidroxi, carboxi, (1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, -OCO(1-4C)alquilo, (1-6C)alcoxi, (1-4C)alcoxi (1-4C)alcoxi, hidroxi(1-4C)alcoxi, (2-4C)alqueniloxi, -NHC(O)O(1-4C)alquilo, $-NHC(=NH)NR^6R^7$, $-NHC(O)NR^6R^7$, -NHC(O)(1-4C)alquilo, -NHC(O)heterociclilo, -NHC(O)arilo, -NHS(O)p(1-4C)alquilo, -S(O)p(1-4C)alquilo, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$ y heterociclilo], (3-6C) cicloalquilo, -O(1-6C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), -S(O)p(1-4C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), heterociclilo, -NHC(O)O(1-4C)alquilo, $-C(=NOR^7)$(1-

4C)alquilo, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alquilCONHR^7, -C(O)NHS(O)p(1-4C)alquilo y -NR^{6}R^7; donde cualquier grupo arilo o heterociclilo en cualquiera de los anteriores valores para los radicales en R^{1}a puede sustituirse opcionalmente por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo y carboxi.

R^{1}a es piridinilo, *N*-oxopiridinilo, pirimidinilo, tiazolilo, tiadiazolilo, tetrazolilo, imidazolilo, triazinilo, pirrolidinilo, tienilo, furanilo, oxadiazolilo, isoxazolilo, oxazolilo o pirrolilo, donde el citado R^{1}a se puede sustituir opcionalmente por 1, 2 o 3 radicales seleccionados independientemente entre:

nitro, ciano, sulfo, formilo, hidroxiiminometilo, (2-6C)alquenilo, -CO(1-6C)alquilo, -COO(1-6C)alquilo trifluorometilo, -CONR^{6}R^7, -N(R^7)COR^6, halo, hidroxi, carboxi, (1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, -OCO(1-4C)alquilo, (1-6C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, hidroxi(1-4C)alcoxi, (2-4C)alqueniloxi, -NHC(O)O(1-4C)alquilo, -NHC(=NH)NR^{6}R^7, -NHC(O)NR^{6}R^7, -NHC(O)(1-4C)alquilo, -NHC(O)tetrahidrofuranilo, -NHC(O)fenilo, -NHS(O)p(1-4C)alquilo, -S(O)p(1-4C)alquilo, -S(O)pNR^{6}R^7, -NHSO$_2$R^6, -NR^{6}R^7, morfolino, 1,3-dioxo-1,3-dihidro-2H-isoindolilo y 1,3-dioxolanil], ciclopropilo, -O(1-6C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), -S(O)p(1-4C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), tetrazolilo, 2-oxo-1,3,4-oxadiazolilo, 1,2,4-oxadiazolilo, morfolino, piperazinilo, pirrolidinilo, -NHC(O)O(1-4C)alquilo, -C(=NOR^7)(1-4C)alquilo, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alquilCONHR^7, -C(O)NHS(O)p(1-4C)alquilo y -NR^{6}R^7;

donde cualquier fenilo, tetrahidrofuranilo, morfolino, 1,3-dioxo-1,3-dihidro-2H-isoindolilo, 1,3-dioxolanilo, tetrazolilo, 2-oxo- 1, 3, 4-oxadiazolilo, 1,2,4-oxadiazolilo, morfolino, piperazinilo, pirrolidinilo, en cualquiera de los anteriores valores para los radicales en R^{1}a puede sustituirse opcionalmente por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo y carboxi.

En un aspecto, R^1b es un anillo heterocíclico de 8 miembros que contiene 1, 2, 3 o 4 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga ningún enlace O-O o S-S). En otro aspecto, R^1b es un anillo heterocíclico de 8 miembros que contiene 1, 2 o 3 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga ningún enlace O-O o S-S). En otro aspecto, R^1b es un anillo heterocíclico de 8 miembros que contiene 1 o 2 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga ningún enlace O-O o S-S). En otro aspecto, R^1b es un anillo heterocíclico de 8 miembros que contiene 1 heteroátomo seleccionado independientemente entre O, S y N.

En un aspecto, R^1b es un anillo heterocíclico de 9 miembros que contiene 1, 2, 3 o 4 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga ningún enlace O-O o S-S). En otro aspecto, R^1b es un anillo heterocíclico de 9 miembros que contiene 1, 2 o 3 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga ningún enlace O-O o S-S). En otro aspecto, R^1b es un anillo heterocíclico de 9 miembros que contiene 1 o 2 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga ningún enlace O-O o S-S). En otro aspecto, R^1b es un anillo heterocíclico de 9 miembros que contiene 1 heteroátomo seleccionado independientemente entre O, S y N.

En un aspecto, R^1b es un anillo heterocíclico de 10 miembros que contiene 1, 2, 3 o 4 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga ningún enlace O-O o S-S). En otro aspecto, R^1b es un anillo heterocíclico de 10 miembros que contiene 1, 2 o 3 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga ningún enlace O-O o S-S). En otro aspecto, R^1b es un anillo heterocíclico de 10 miembros que contiene 1 o 2 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga ningún enlace O-O o S-S). En otro aspecto,

R^1b es un anillo heterocíclico de 10 miembros que contiene 1 heteroátomo seleccionado independientemente entre O, S y N.

Ejemplos de R^1b como un anillo bicíclico heterocíclico de 8-10 miembros que contiene 1, 2, 3 o 4 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga enlaces O-O o S-S) incluyen, por ejemplo, sistemas bicíclico benzo-fusionados que contienen un anillo heteroarilo de 5- o 6- miembros que contiene un átomo de nitrógeno y opcionalmente 1-3 heteroátomos adicionales escogidos entre oxígeno, sulfuro y nitrógeno. Ejemplos específicos de dichos sistemas de anillos incluyen, por ejemplo, indole, benzofurano, benzotiofeno, benzimidazol, benzotiazol, benzisotiazol, benzoxazol, benzisoxazol, quinolina, quinoxalina, quinazolina, ftalazina, 1,4-benzoxazina y cinolina. Otros ejemplos de dichos sistemas de anillos son isómeros de los ejemplos citados arriba, como isoquinolina e isoindol; se entenderá que las referencias de dichos sistemas de anillos deberán abarcar dichos isómeros.

R^1b es un anillo bicíclico heterocíclico de 10 miembros que contiene 1, 2 o 4 heteroátomos seleccionados independientemente entre S y N (siempre que dicho anillo no contenga enlaces S-S), donde un grupo $-CH_2-$ se puede reemplazar opcionalmente por un -C(O)-.

R^1b es quinolinilo, purinilo, benzotiazolilo, indolilo, 4-oxoquinolinilo, 2,7-naftiridinilo o quinazolinilo.

R^1b es un anillo bicíclico heterocíclico de 10 miembros que contiene 1, 2 o 4 heteroátomos seleccionados independientemente entre S y N (siempre que dicho anillo no contenga enlaces S-S), donde un grupo $-CH_2-$ se puede reemplazar opcionalmente por un -C(O)-, donde el citado anillo se puede sustituir opcionalmente por 1, 2 o 3 radicales seleccionados independientemente entre: nitro, ciano, sulfo, formilo, hidroxiiminometilo, (2-6C)alquenilo, -CO(1-6C)alquilo, -COO(1-6C)alquilo trifluorometilo, $-CONR^6R^7$, $-N(R^7)COR^6$, halo, hidroxi, carboxi, (1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, -OCO(1-4C)alquilo, (1-6C)alcoxi, (1-

4C)alcoxi (1-4C)alcoxi, hidroxi(1-4C)alcoxi, (2-4C)alqueniloxi, -NHC(O)O(1-4C)alquilo, -NHC (=NH)NR^6R^7, -NHC(O)NR^6R^7, -NHC(O)(1-4C)alquilo, -NHC(O)heterociclilo, -NHC(O)arilo, -NHS(O)p(1-4C)alquilo, -S(O)p(1-4C)alquilo, -S(O)pNR^6R^7, -$NHSO_2R^6$, -NR^6R^7 y heterociclilo], (3-6C) cicloalquilo, -O(1-6C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), -S(O)p(1-4C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), heterociclilo, -NHC(O)O(1-4C)alquilo, -C(=NOR^7)(1-4C)alquilo, -C(=NOR^7)NR^6R^7, -S(O)p(1-4C)alquilCONHR^7, -C(O)NHS(O)p(1-4C)alquilo y –NR^6R^7; donde cualquier grupo arilo o heterociclilo en cualquiera de los anteriores valores para los radicales en R^1a puede sustituirse opcionalmente por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo y carboxi.

R^1b es quinolinilo, purinilo, benzotiazolilo, indolilo, 4-oxoquinolinilo, 2,7-naftiridinilo o quinazolinilo donde el citado R^1b se puede sustituir opcionalmente por 1, 2 o 3 radicales seleccionados independientemente entre:

nitro, ciano, sulfo, formilo, hidroxiiminometilo, (2-6C)alquenilo, -CO(1-6C)alquilo, -COO(1-6C)alquilo trifluorometilo, -CONR^{6}R^7, -N(R^7)COR^6, halo, hidroxi, carboxi, (1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, -OCO(1-4C)alquilo, (1-6C)alcoxi, (1-4C)alcoxi (1-4C)alcoxi, hidroxi (1-4C)alcoxi, (2-4C)alqueniloxi, -NHC(O)O(1-4C)alquilo, -NHC(=NH)NR^{6}R^7, -NHC(O)NR^{6}R^7, -NHC(O)(1-4C)alquilo, -NHC(O)tetrahidrofuranilo, -NHC(O)fenilo, -NHS(O)p(1-4C)alquilo, -S(O)p(1-4C)alquilo, -S(O)pNR^{6}R^7, -NHSO$_2$R^6, -NR^{6}R^7, morfolino, 1,3-dioxo-1,3-dihidro-2H-isoindolilo y 1,3-dioxolanil], ciclopropilo, -O(1-6C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), -S(O)p(1-4C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), tetrazolilo, 2-oxo-1,3,4-oxadiazolilo, 1,2,4-oxadiazolilo, morfolino, piperazinilo, pirrolidinilo, -NHC(O)O(1-

4C)alquilo, -C(=NOR^7)(1-4C)alquilo, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alquilCONHR^7, -C(O)NHS(O)p(1-4C)alquilo y -NR^{6}R^7;
donde cualquier fenilo, tetrahidrofuranilo, morfolino, 1,3-dioxo-1,3-dihidro-2H-isoindolilo, 1,3-dioxolanilo, tetrazolilo, 2-oxo-1,3,4-oxadiazolilo, 1,2,4-oxadiazolilo, morfolino, piperazinilo, pirrolidinilo, en cualquiera de los anteriores valores para los radicales en R^{1}a puede sustituirse opcionalmente por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo y carboxi.

Otros ejemplos de R^{1}b como un anillo heterocíclico de 8-10 miembros incluyen sistemas de anillos bicíclicos 5/5-, 5/6 y 6/6 que contienen heteroátomos en ambos anillos. Otros ejemplos de R^{1}b como un anillo heterocíclico de 8-10 miembros incluyen sistemas de anillos bicíclicos heteroarilo por lo menos con un nitrógeno cabeza de puente y opcionalmente 1-3 heteroátomos adicionales seleccionados entre oxígeno, sulfuro y nitrógeno.

Ejemplos específicos de dichos sistemas de anillos incluyen, por ejemplo, purina, naftiridina, pirido[2,3-d]pirimidinilo, pirimido[4,5-d]pirimidinilo, indolicina, quinolicina, indazol, indan-2-ilo, carbazol, pirrolo[1,2-c]pirimidina, pirazolo[3,4-b]piridina, 1H-pirazolo[3,4-d]pirimidina, tiadiazolo[3,4-b]piridina, 1H-imidazo[4,5-b]piridina, azapurina, furazanopirimidinas, cumarín, benzopirano, tiazolo [4,5-d] pirimidina, pirido [2,3-b] pirazin-3(2H)-ona, H-pirimido[5,4-b][1,4] oxazin-7(6H)-ona, 3H-pirrolo[1,2-a]pirrol, pirrolo[2,1-b]tiazol, 1H-imidazo [1,2-a] pirrol, 1H-imidazo[1, 2-a]imidazol, 1H, 3H-pirrolo [l, 2-c]oxazol, 1H-imidazo[1,5-a]pirrol, pirrolo[l,2-b]isoxazol, imidazo [5,1-b]tiazol, imidazo [2,1-b]tiazol, indolicina, imidazo[1,2-a]piridina, imidazo[1,5-a]piridina, pirazol[1,5-a] piridina, pirrolo [1,2-b] piridacina, pirrolo[1,2-c]pirimidina, pirrolo[1,2-a]piracina, pirrolo[1,2-a] pirimidina, pirido[2,1-c]-s-triazol, s-triazol [1,5-a] piridina, imidazo[1, 2-c]pirimidina, imidazo [1,2-a]piracina, imidazo[1,2-a]pirimidina, imidazo[1,5-a]piracina, imidazo[1,5-a]pirimidina, imidazo[1,2-b] -piridacina, s-triazolo[4,3-a]pirimidina, imidazo[5,1-b]oxazol e imidazo [2,1-b]oxazol. Otros ejemplos específicos de dichos

sistemas de anillos incluyen, por ejemplo, [1H]-pirrolo[2,1-c]oxacina, [3H]-oxazolo[3,4-a]piridina, [6H]-pirrolo[2,1-c]oxacina y pirido[2,1-c][1,4]oxacina.

Otros ejemplos específicos de sistemas de anillos bicíclicos 5/5- son imidazooxazol o imidazotiazol, como imidazo[5,1-b]tiazol, imidazo[2,1-b]tiazol, imidazo[5,1-b]oxazol o imidazo[2,1-b] oxazol.

Otros ejemplos de R^1b como un anillo heterocíclico de 8-10 miembros incluyen sistemas de anillos donde uno o los dos anillos está parcial o totalmente saturado, por ejemplo indolina, 1, 3,4, 6,9, 9a-hexahidropirido [2, 1 c][1, 4] oxazin-8-ilo,

1, 2, 3, 5,8, 8a-hexahidroimidazo [1,5a]piridin-7-ilo,

1, 5, 8, 8a-tetrahidrooxazolo [3,4a]piridin-7-ilo,

1, 5,6, 7, 8, 8a-hexahidrooxazolo [3,4a]piridin-7-ilo,

(7aS)[3H,5H]-1,7a-dihidropirrolo[1,2c]oxazol-6-ilo,

(7aS)[5H]-1, 2, 3, 7a-tetrahidropirrolo[1,2c]imidazol-6-ilo,

(7aR)[3H,5H]-1,7a-dihidropirrolo [1,2c] oxazol-6-ilo, [3H, 5H]-pirrolo [1, 2-c]oxazol-6-ilo,

[5H]-2,3-dihidropirrolo[1,2-c]imidazol-6-ilo, [3H,5H]-pirrolo[1,2-c] tiazol-6-ilo,

[3H,5H]-1,7a-dihidropirrolo[1,2-c]tiazol-6-ilo,[5H]-pirrolo[1,2-c]imidazol-6-ilo,

[1H]-3, 4, 8, 8a-tetrahidropirrolo[2,1-c]oxazin-7-ilo,

[3H]-1,5,8,8a-tetrahidrooxazolo[3,4-a]pirid-7-ilo, [3H]-5,8-dihidroxazolo [3,4-a]piridilo y 5,8-dihidroimidazo [1,5-a]pirid-7-ilo.

La nomenclatura empleada es la que se encuentra por ejemplo en "Heterocyclic Compounds (Systems with bridgehead nitrogen)", W.L. Mosby (Interscience Publishers Inc., New York), 1961, Partes 1 y 2.

Otros ejemplos de unos valores apropiados para R^1b se pueden encontrar en Handbook of Heterocyclic Chemistry 2nda Ed por A.R. Katritzky A.F. Pozharskii.

Unos valores apropiados para R^1b son quinolinilo, purinilo, benzotiazolilo e indolilo.

En un aspecto, R^1d se selecciona entre -CH_2R^1a,

En otro aspecto, R^1d se selecciona entre -C(O)R^1a.

En otro aspecto, R^1d se selecciona entre -OR^1a.

En otro aspecto, R^1d se selecciona entre S(O)qR^1a (donde q es 1 o 2).

R^1d se selecciona entre -CH_2R^1a o-C(O) R^1a.

En un aspecto, R^1e se selecciona entre -CH_2R^1b.

En otro aspecto, R^1e se selecciona entre -C(O)R^1b.

En otro aspecto, R^1e se selecciona entre -OR^1b.

En otro aspecto R^1e se selecciona entre S(O)qR^1b (donde q es 1 o 2).

En un aspecto, R^1f se selecciona entre -CH_2R^1c.

En otro aspecto, R^1f se selecciona entre -C(O)R^1c.

En otro aspecto, R^1f se selecciona entre -OR^1c.

En otro aspecto R^1f se selecciona entre S(O)qR^1c (donde q es 1 o 2).

En un aspecto, R^1 contiene un radical seleccionado entre los radicales opcionales enumerados en cualquier aspecto o incorporación arriba o a continuación. En otro aspecto, R^1contiene dos radicales seleccionados independientemente entre los radicales opcionales enumerados en cualquier aspecto o incorporación arriba o a continuación. En otro aspecto, R^1 no se sustituye.

En un aspecto, los radicales opcionales para R^1 (donde R^1 se selecciona entre R^1a, R^1b, R^1c, R^1d, R^1e y R^1d) se seleccionan entre nitro, ciano, (2-6C)alquenilo, (2-6C)alquinilo, -CO(1-6C)alquilo, -COO(1-6C)alquilo, -O(1-6C)alquilo, trifluorometilo, -CONR^{6}R^7, -OCONR^{6}R^7, -N(R^7)COR^6, -CONHCH(CO$_2$R^7)R^6, halo, hidroxi, carboxi, (1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, halo, ciano, nitro, -COO(1-6C)alquilo, -O(1-6C)alquilo, trifluorometilo, -CONR^{6}R^7, carboxi, -NHC(O)O(1-4C)alquilo, -C(=NOH)(1-4C)alquilo, -C (=NOH)NR^{6}R^7, -S(O)p(1-4C)alquilo, -S(O)pNR^{6}R^7 y - NR^{6}R^7],

heterociclilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, hidroxi, (1-4C)alcoxi, halo, ciano, nitro, carboxi, hidroxi(1-4C)alquilo, (1-4C)alcoxi(1-4C)alquilo, halo(1-

4C)alquilo, difluorometilo, trifluorometilo, trifluorometoxi, (1-4C)alquilcarbonilo, (1-4C)alcoxicarbonilo, -C(O)NH_2, -C(O)NH(1-4C)alquilo, -C(O)N[di(1-4C)alquilo], -$S(O)_2NH_2$, -$S(O)_2$NH(1-4C)alquilo, -$S(O)_2$N[di(1-4C)alquil] y -S(O)p(1-4C)alquilo], arilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, hidroxi, (1-4C)alcoxi, halo, ciano, nitro, carboxi, hidroxi(1-4C)alquilo, (1-4C)alcoxi(1-4C)alquilo, halo(1-4C)alquilo, difluorometilo, trifluorometilo, trifluorometoxi, (1-4C)alquilcarbonilo, (1-4C)alcoxicarbonilo, -C(O)NH_2, -C(O)NH(1-4C)alquilo, -C(O)N[di(1-4C)alquilo], -$S(O)_2NH_2$, -$S(O)_2$NH(1-4C)alquilo, -$S(O)_2$N[di(1-4C)alquil] y -S(O)p(1-4C)alquil),

arilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, hidroxi, (1-4C)alcoxi, halo, ciano, nitro, carboxi, hidroxi(1-4C)alquilo, (1-4C)alcoxi(1-4C)alquilo, halo(1-4C)alquilo, difluorometilo, trifluorometilo, trifluorometoxi, (1-4C)alquilcarbonilo, (1-4C)alcoxicarbonilo, -C(O)NH_2, -C(O)NH(1-4C)alquilo, -C(O)N[di(1-4C)alquilo], -$S(O)_2NH_2$, -$S(O)_2$NH(1-4C)alquilo, -$S(O)_2$N[di(1-4C)alquil] y

-S(O)p(1-4C)alquil],

-NHC(O)O(1-4C)alquilo, -C(=NOR^7)(1-4C)alquilo, -C(=NOR^7)NR^6R^7, -S(O)p(1-4C)alquilo (opcionalmente sustituido por hidroxi), -S(O)pNR^6R^7, -S(O)p(1-4C)alquilCONHR^7, -NR^7S(O)pNR^6R^7, -NR^7S(O)p(1-4C)alquilo; -NR^7S(O)p-arilo, -C(O)NHS(O)p(1-4C)alquilo, -C(O)NHS(O)p-arilo, -NR^6R^7, -$CH_2CH(CO_2R^6)OH$, -(1-4C)alquilCH(NR^6R^7)CO_2R^6 y -(1-4C)alquilCH(NR^6R^7)CO(NR^6R^7).

En otro aspecto, los radicales opcionales para R^1 (donde R^1 se selecciona entre R^1a, R^1b, R^1c, R^1d, R^1e y R^1d) se seleccionan entre

nitro, ciano, (2-6C)alquenilo, (2-6C)alquinilo, -CO(1-6C)alquilo, -COO(1-6C)alquilo, -O(1-6C)alquilo, trifluorometilo, -CONR^6R^7, -OCONR^6R^7, -$N(R^7)COR^6$, -CONHCH(CO_2R^7)R^6, halo, hidroxi, carboxi,

(1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, halo, -COO(1-6C)alquilo, -O(1-

6C)alquilo, trifluorometilo, -CONR^{6}R^7, -NHC(O)O(1-4C)alquilo, -C(=NOH)(1-4C)alquilo, -C(=NOH)NR^{6}R^7, -S(O)p(1-4C)alquilo, -S(O)pNR^{6}R^7 y - NR^{6}R^7],

heterociclilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, hidroxi, (1-4C)alcoxi, halo, ciano, nitro, carboxi, hidroxi(1-4C)alquilo, halo(1-4C)alquilo, difluorometilo, trifluorometilo, trifluorometoxi, (1-4C)alquilcarbonilo, (1-4C)alcoxicarbonilo, -C(O)NH$_2$, -C(O)NH(1-4C)alquilo, -C(O)N[di(1-4C)alquilo], -S(O)$_2$NH$_2$, -S(O)$_2$NH(1-4C)alquilo, -S(O)$_2$N[di(1-4C)alquil] y -S(O)p(1-4C)alquilo], arilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, hidroxi, (1-4C)alcoxi, halo, ciano, nitro, carboxi, hidroxi(1-4C)alquilo, halo(1-4C)alquilo, difluorometilo, trifluorometilo, trifluorometoxi, (1-4C)alquilcarbonilo, (1-4C)alcoxicarbonilo, -C(O)NH$_2$, -C(O)NH(1-4C)alquilo, -C(O)N[di(1-4C)alquilo], -S(O)$_2$NH$_2$, -S(O)$_2$NH(1-4C)alquilo, -S(O)$_2$N[di(1-4C)alquil] y -S(O)p(1-4C)alquilo], -NHC(O)O(1-4C)alquilo, -C(=NOR^7)(1-4C)alquilo, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alquilo (opcionalmente sustituido por hidroxi), -S(O)pNR^{6}R^7, -S(O)p(1-4C)alquilCONHR^7, -NR^{7}S(O)pNR^{6}R^7, -NR^{7}S(O)p(1-4C)alquilo, -NR^{7}S(O)p-arilo, -C(O)NHS(O)p(1-4C)alquilo, -C(O)NHS(O)p-arilo y -NR^{6}R^7.

En otro aspecto, los radicales opcionales para R^1 (donde R^1 se selecciona entre R^{1}a, R^{1}b, R^{1}c, R^{1}d, R^{1}e y R^{1}d) se seleccionan entre

nitro, ciano, -CO(1-6C)alquilo, -COO(1-6C)alquilo, -O(1-6C)alquilo, trifluorometilo, -CONR^{6}R^7, -OCONR^{6}R^7, -N(R^7)COR^6, -CONHCH(CO$_2$R^7)R^6, halo, hidroxi, carboxi, (1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, halo, -COO(1-6C)alquilo, -O(1-6C)alquilo, trifluorometilo, -CONR^{6}R^7, -S(O)p(1-4C)alquilo, -S(O)pNR^{6}R^7 y - NR^{6}R^7],

heterociclilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, hidroxi, (1-4C)alcoxi, halo, ciano, nitro, carboxi, halo(1-4C)alquilo, difluorometilo, trifluorometilo y

trifluorometoxi], arilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, hidroxi, (1-4C)alcoxi, halo, ciano, nitro, carboxi, halo(1-4C)alquilo, difluorometilo, trifluorometilo y trifluorometoxi],
-NHC(O)O(1-4C)alquilo, -C(=NOR^7)(1-4C)alquilo, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alquilo (opcionalmente sustituido por hidroxi), -S(O)pNR^{6}R^7, -S(O)p(1-4C)alquilCONHR^7, -NR^{7}S(O)pNR^{6}R^7, -NR^{7}S(O)p(1-4C)alquilo, -NR^{7}S(O)p-arilo, -C(O)NHS(O)p(1-4C)alquilo, -C(O)NHS(O)p-arilo y -NR^{6}R^7.

En otro aspecto, los radicales opcionales para R^1 (donde R^1 se selecciona entre R^{1}a, R^{1}b, R^{1}c, R^{1}d, R^{1}e y R^{1}d) se seleccionan entre
nitro, ciano, -CO(1-6C)alquilo, -COO(1-6C)alquilo, -O(1-6C)alquilo, trifluorometilo, -CONR^{6}R^7, -OCONR^{6}R^7, -N(R^7)COR^6, -CONHCH(CO$_2$R^7)R^6, halo, hidroxi, carboxi, (1-6C)alquilo, heterociclilo, arilo, -NHC(O)O(1-4C)alquilo, -C(=NOR^7)(1-4C)alquil, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alquilo (opcionalmente sustituido por hidroxi), -S(O)pNR^{6}R^7, -S(O)p(1-4C)alquilCONHR^7, -NR^{7}S(O)pNR^{6}R^7, -NR^{7}S(O)p(1-4C)alquilo, -NR^{7}S(O)p-arilo, -C(O)NHS(O)p(1-4C)alquilo, -C(O)NHS(O)p-arilo y -NR^{6}R^7.

En otro aspecto, los radicales opcionales para R^1 (donde R^1 se selecciona entre R^{1}a, R^{1}b, R^{1}c, R^{1}d, R^{1}e y R^{1}d) se seleccionan entre
nitro, ciano, -CO(1-6C)alquilo, -COO(1-6C)alquilo, -O(1-6C)alquilo, trifluorometilo, -CONR^{6}R^7, -OCONR^{6}R^7, -N(R^7)COR^6, halo, hidroxi, carboxi, (1-6C)alquilo, heterociclilo, arilo, -NHC(O)O(1-4C)alquilo, -C(=NOR^7)(1-4C)alquilo, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alquilo (opcionalmente sustituido por hidroxi), -S(O)pNR^{6}R^7, -S(O)p(1-4C)alquilCONHR^7, -NR^{7}S(O)pNR^{6}R^7, -NR^{7}S(O)p(1-4C)alquilo, -NR^{7}S(O)p-arilo y -NR^{6}R^7.

En otro aspecto, los radicales opcionales para R^1 (donde R^1 se selecciona entre R^{1}a, R^{1}b, R^{1}c, R^{1}d, R^{1}e y R^{1}d) se seleccionan entre
nitro, ciano, -CO(1-4C)alquilo, -COO(1-4C)alquilo, -O(1-4C)alquilo, trifluorometilo, -CONR^{6}R^7, -N(R^7)COR^6, fluoro, cloro, bromo, hidroxi,

carboxi, (1-4C)alquilo, heterociclilo, -NHC(O)O(1-4C)alquilo, -C(=NOR^7)(1-4C)alquilo, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alquilo (opcionalmente sustituido por hidroxi), -S(O)p(1-4C)alquilCONHR y -NR^{6}R^7.

En otro aspecto, los radicales opcionales para R^1 (donde R^1 se selecciona entre R^{1}a, R^{1}b, R^{1}c, R^{1}d, R^{1}e y R^{1}d) se seleccionan entre
nitro, ciano, -CO(1-6C)alquilo, -COO(1-6C)alquilo (opcionalmente sustituido por -COO(1-4C)alquilo), trifluorometilo, -CONR^{6}R^7, -OCONR^{6}R^7, -N(R^7)COR^6, -CONHCH(CO$_2$R^7)R^6, halo, hidroxi, carboxi, (1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, halo, ciano, nitro, -COO(1-6C)alquilo, -OCO(1-4C)alquilo, (1-6C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, hidroxi(1-4C)alcoxi, (2-4C)alqueniloxi, trifluorometilo, -CONR^{6}R^7, carboxi, -NHC(O)O(1-4C)alquilo, -OCONR^{6}R, -C(=NOH)(1-4C)alquilo, -C(=NOH)NR^{6}R^7, -S(O)p(1-4C)alquilo, -S(O)pNR^{6}R^7, -NHSO$_2$R^6, -NR^{6}R^7 y heterociclilo],
(3-6C) cicloalquilo (opcionalmente sustituido por 1 o 2 radicales seleccionados entre (1-6C)alquilo y los radicales opcionales descritos para (1-6C)alquilo arriba), -O(1-6C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), -S(O)p(1-4C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), heterociclilo, -NHC(O)O(1-4C)alquilo, -C(=NOR^7)(1-4C)alquilo, -C(=NOR^7)NR^{6}R^7, -S(O)pNR^{6}R^7, -NR^{7}S(O)p(1-4C)alquilo, -NR^{7}S(O)p-arilo, - C(O)NHS(O)p(1-4C)alquilo, -C(O)NHS(O)p-arilo y -NR^{6}R^7;
donde cualquier grupo heterociclilo o arilo en cualquiera de los anteriores valores para los radicales en R^{1}a puede sustituirse opcionalmente por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, hidroxi, (1-4C)alcoxi, halo, ciano, nitro, carboxi, hidroxi(1-4C)alquilo, (1-4C)alcoxi(1-4C)alquilo, halo(1-4C)alquilo, difluorometilo, trifluorometilo, trifluorometoxi, formilo, -CO(1-4C)alquilo, -COO(1-4C)alquilo, -

$C(O)NH_2$, -C(O)NH(1-4C)alquilo, -C(O)N[di(1-4C)alquilo], $-S(O)_2NH_2$, -$S(O)_2$NH(1-4C)alquilo y -$S(O)_2$N[di(1-4C)alquil].

En otro aspecto, los radicales opcionales para R^1 (donde R^1 se selecciona entre R^1a, R^1b, R^1c, R^1d, R^1e y R^1d) se seleccionan entre
nitro, ciano, -CO(1-6C)alquilo, -COO(1-6C)alquilo (opcionalmente sustituido por -COO(1-4C)alquilo), trifluorometilo, $-CONR^6R^7$, $-OCONR^6R^7$, $-N(R^7)COR^6$, $-CONHCH(CO_2R^7)R^6$, halo, carboxi, (1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, halo, ciano, nitro, -COO(1-6C)alquilo, -OCO(1-4C)alquilo, (1-6C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, hidroxi(1-4C)alcoxi, (2-4C)alqueniloxi, trifluorometilo, $-CONR^6R^7$, carboxi, $-NHC(O)O$(1-4C)alquilo, $-OCONR^6R^7$, -C(=NOH)(1-4C)alquilo, $-C(=NOH)NR^6R^7$, -S(O)p(1-4C)alquilo, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$ y heterociclilo],
(3-6C)cicloalquilo (opcionalmente sustituido por 1 o 2 radicales seleccionados entre (1-6C)alquilo y los radicales opcionales descritos para (1-6C)alquilo arriba), -O(1-6C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), -S(O)p(1-4C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), heterociclilo, $-NHC(O)O$(1-4C)alquilo, $-C(=NOR^7)$(1-4C)alquilo, $-C(=NOR^7)NR^6R^7$, $-S(O)pNR^6R^7$, $-NR^7S(O)p$(1-4C)alquilo, -C(O)NHS(O)p(1-4C)alquilo y $-NR^6R^7$;
donde cualquier grupo heterociclilo o arilo en cualquiera de los anteriores valores para los radicales en R^1a puede sustituirse opcionalmente por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, (1-4C)alcoxi, halo, ciano, nitro, carboxi, hidroxi(1-4C)alquilo, (1-4C)alcoxi(1-4C)alquilo, halo(1-4C)alquilo, difluorometilo, trifluorometilo y trifluorometoxi.

En otro aspecto, los radicales opcionales para R^1 (donde R^1 se selecciona entre R^1a, R^1b, R^1c, R^1d, R^1e y R^1d) se seleccionan entre
nitro, ciano, -CO(1-6C)alquilo, -COO(1-6C)alquilo (opcionalmente sustituido por -COO(1-4C)alquilo), trifluorometilo, $-CONR^6R^7$, -

$OCONR^6R^7$, $-N(R^7)COR^6$, halo, carboxi, (1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, halo, -COO(1-6C)alquilo, -OCO(1-4C)alquilo, (1-6C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, hidroxi(1-4C)alcoxi, (2-4C)alqueniloxi, trifluorometilo, $-CONR^6R^7$, carboxi, -NHC(O)O(1-4C)alquilo, $-OCONR^6R^7$, -C(=NOH)(1-4C)alquilo, $-C(=NOH)NR^6R^7$, -S(O)p(1-4C)alquilo, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$ y heterociclilo], (3-6C)cicloalquilo (opcionalmente sustituido por 1 o 2 radicales seleccionados entre (1-6C)alquilo y los radicales opcionales descritos para (1-6C)alquilo arriba), -O(1-6C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), -S(O)p(1-4C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), heterociclilo, -NHC(O)O(1-4C)alquilo, $-C(=NOR^7)$(1-4C)alquilo, $-C(=NOR^7)NR^6R^7$, $-S(O)pNR^6R^7$, $-NR^7S(O)p$(1-4C)alquilo, -C(O)NHS(O)p(1-4C)alquilo y NR^6R^7;

donde cualquier grupo heterociclilo o arilo en cualquiera de los anteriores valores para los radicales en R^1a puede sustituirse opcionalmente por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, (1-4C)alcoxi, halo, ciano, nitro, carboxi, halo(1-4C)alquilo, difluorometilo, trifluorometilo y trifluorometoxi.

En otro aspecto, los radicales opcionales para R^1 (donde R^1 se selecciona entre R^1a, R^1b, R^1c, R^1d, R^1e y R^1d) se seleccionan entre nitro, ciano, sulfo, formilo, hidroxiiminometilo, (2-6C)alquenilo, -CO(1-6C)alquilo, -COO(1-6C)alquilo trifluorometilo, $-CONR^6R^7$, $-N(R^7)COR^6$, halo, hidroxi, carboxi, (1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, -OCO(1-4C)alquilo, (1-6C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, hidroxi(1-4C)alcoxi, (2-4C)alqueniloxi, -NHC(O)O(1-4C)alquilo, $-NHC(=NH)NR^6R^7$, $-NHC(O)NR^6R^7$, - NHC(O)(1-4C)alquilo, -NHC(O)heterociclilo, -NHC(O)arilo, -NHS(O)p(1-4C)alquilo, -S(O)p(1-4C)alquilo, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$ y heterociclilo], (3-6C)cicloalquilo, -O(1-6C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-

6C)alquilo arriba), -S(O)p(1-4C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), heterociclilo, -NHC(O)O(1-4C)alquilo, -C(=NOR^7)(1-4C)alquilo, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alquilCONHR^7, -C(O)NHS(O)p(1-4C)alquilo y -NR^{6}R^7; donde cualquier grupo arilo o heterociclilo en cualquiera de los anteriores valores para los radicales en R^{1}a puede sustituirse opcionalmente por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo y carboxi.

En otro aspecto, los radicales opcionales para R^1 (donde R^1 se selecciona entre R^{1}a, R^{1}b, R^{1}c, R^{1}d, R^{1}e y R^{1}d) se seleccionan entre nitro, ciano, sulfo, formilo, hidroxiiminometilo, (2-6C)alquenilo, -CO(1-6C)alquilo, -COO(1-6C)alquilo trifluorometilo, -CONR^{6}R^7, -N(R^7)COR^6, halo, hidroxi, carboxi, (1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, -OCO(1-4C)alquilo, (1-6C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, hidroxi(1-4C)alcoxi, (2-4C)alqueniloxi, -NHC(O)O(1-4C)alquilo, -NHC (=NH)NR^{6}R^7, -NHC(O)NR^{6}R^7, - NHC(O) (1-4C)alquilo, -NHC(O) tetrahidrofuranilo, -NHC(O)fenilo, -NHS(O)p(1-4C)alquilo, -S(O)p(1-4C)alquilo, -S(O)pNR^{6}R^7, -NHSO$_2$R^6, -NR^{6}R^7, morfolino, 1,3-dioxo-1,3-dihidro-2H-isoindolilo y 1,3-dioxolanil], ciclopropilo, -O(1-6C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), -S(O)p(1-4C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), tetrazolilo, 2-oxo-1,3,4-oxadiazolilo, 1,2,4-oxadiazolilo, morfolino, piperazinilo, pirrolidinilo, -NHC(O)O(1-4C)alquilo, -C(=NOR^7)(1-4C)alquilo, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alquilCONHR^7, -C(O)NHS(O)p(1-4C)alquilo y -NR^{6}R^7; donde cualquier fenilo, tetrahidrofuranilo, morfolino, 1,3-oxo-1,3-dihidro-2H-isoindolilo, 1,3-dioxolanilo, tetrazolilo, 2-oxo-1,3,4-oxadiazolilo, 1,2,4-oxadiazolilo, morfolino, piperazinilo, pirrolidinilo, en cualquiera de los anteriores valores para los radicales en R^1 a puede sustituirse opcionalmente por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo y carboxi.

En otro aspecto, R^1 es sustituido por 2 radicales; donde un radical se selecciona entre carboxi, $-CONHSO_2Me$ y $-CONHR^6$ (donde R^6 se selecciona entre cualquiera de los valores enumerados en cualquier aspecto o incorporación arriba o a continuación) y donde el otro radical se selecciona entre

(1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, halo, ciano, nitro, -COO(1-6C)alquilo, -OCO(1-4C)alquilo, (1-6C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, hidroxi(1-4C)alcoxi, (2-4C)alqueniloxi, trifluorometilo, $-CONR^6R^7$, carboxi, $-NHC(O)O$(1-4C)alquilo, $-OCONR^6R^7$, $-C(=NOH)$(1-4C)alquilo, $-C(=NOH)NR^6R^7$, -S(O)p(1-4C)alquilo, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$ y heterociclilo], -O(1-6C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba) y -S(O)p(1-4C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), donde R^6 y R^7 se seleccionan entre cualquiera de los valores enumerados en cualquier aspecto o incorporación arriba o a continuación.

En otro aspecto, R^1 es sustituido por 2 radicales; donde un radical se selecciona entre carboxi, $-CONHSO_2Me$ y $-CONHR^6$ (donde R^6 se selecciona entre -OMe, hidrógeno, amino y 3-4C alquenil); y donde el otro radical se selecciona entre (1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, halo, ciano, nitro, -COO(1-6C)alquilo, -OCO(1-4C)alquilo, (1-6C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, hidroxi(1-4C)alcoxi, (2-4C)alqueniloxi, trifluorometilo, $-CONR^6R^7$, carboxi, $-NHC(O)O$(1-4C)alquilo, $-OCONR^6R^7$, $-C(=NOH)$(1-4C)alquilo, $-C(=NOH)NR^6R^7$, -S(O)p(1-4C)alquilo, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$ y heterociclilo], -O(1-6C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba) y -S(O)p(1-4)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), donde R^6 y R^7 se seleccionan entre cualquiera de los valores enumerados en cualquier aspecto o incorporación arriba o a continuación.

En otro aspecto, R^1 es sustituido por 2 radicales; donde un radical se selecciona entre carboxi, -$CONHSO_2Me$ y -$CONHR^6$ (donde R^6 se selecciona entre -OMe, hidrógeno, amino, (3-4C alquenilo y -SO_2Me); y donde el otro radical se selecciona entre

(1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, halo, ciano, nitro, -COO(1-6C)alquilo, -OCO(1-4C)alquilo, (1-6C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, hidroxi(1-4C)alcoxi, (2-4C)alqueniloxi, trifluorometilo, -$CONR^6R^7$, carboxi, -$NHC(O)O$(1-4C)alquilo, -$OCONR^6R^7$, -C(=NOH)(1-4C)alquilo, -$C(=NOH)NR^6R^7$, -S(O)p(1-4C)alquilo, -$S(O)pNR^6R^7$, -$NHSO_2R^6$, -NR^6R^7 y heterociclilo], -O(1 -6C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1 -6C)alquilo arriba) y -S(O)p(1-4C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), donde R^6 se selecciona entre hidrógeno y (1-4C)alquilo y R^7 es hidrógeno o metilo, o donde R^6 y R^7 juntos forman una piperidina, un morfolino o un anillo de piperacina, anillo este que se puede sustituir opcionalmente con metilo sobre un átomo de carbono o de nitrógeno disponible (siempre que un átomo de nitrógeno no se cuaternice por lo anterior) y un átomo de carbono opcionalmente se puede oxidar para formar un grupo carbonilo.

R^1 se selecciona entre R^1a, R^1b, R^1c y R^1d; donde

R^1a es un anillo heterocíclico saturado, parcialmente insaturado o insaturado de 5 o 6 miembros que contiene 1, 2, 3 o 4 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga enlaces O-O o S-S), donde un grupo -CH_2- se puede reemplazar opcionalmente por un -C(O)-, un anillo de átomos de sulfuro opcionalmente se puede oxidar para formar el S-óxido(s) y un anillo de átomos de nitrógeno opcionalmente se puede oxidar para formar el N-óxido y donde el citado anillo se puede sustituir opcionalmente por 1, 2 o 3 radicales seleccionados independientemente entre:

nitro, ciano, sulfo, formilo, hidroxiiminometilo, (2-6C)alquenilo, -CO(1-6C)alquilo, -COO(1-6C)alquilo trifluorometilo, -$CONR^6R^7$, -$N(R^7)COR^6$,

halo, hidroxi, carboxi, (1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, -OCO(1-4C)alquilo, (1-6C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, hidroxi(1-4C)alcoxi, (2-4C)alqueniloxi, -NHC(O)O(1-4C)alquilo, -NHC(=NH)NR^6R^7, -$NHC(O)NR^6R^7$, -NHC(O)(1-4C)alquilo, -NHC(O)heterociclilo, -NHC(O)arilo, -NHS(O)p(1-4C)alquilo, -S(O)p(1-4C)alquilo, -$S(O)pNR^6R^7$, -$NHSO_2R^6$, -NR^6R^7 y heterociclilo], (3-6C)cicloalquilo, -O(1-6C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba) -S(O)p(1-4C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), heterociclilo, -NHC(O)O(1-4C)alquilo, -$C(=NOR^7)$(1-4C)alquilo, -$C(=NOR^7)NR^6R^7$, -S(O)p(1-4C)alquilCONHR^7, -C(O)NHS(O)p(1-4C)alquilo y -NR^6R^7, donde cualquier grupo arilo o heterociclilo en cualquiera de los anteriores valores para los radicales en R^1a puede sustituirse opcionalmente por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo y carboxi;

R^1b es un anillo bicíclico heterocíclico de 10 miembros que contiene 1, 2 o 4 heteroátomos seleccionados independientemente entre S y N (siempre que dicho anillo no contenga enlaces S-S), donde un grupo -CH_2- se puede reemplazar opcionalmente por un -C(O)- y donde el citado anillo se puede sustituir opcionalmente por 1, 2 o 3 radicales seleccionados independientemente entre los radicales enumerados para R^1a arriba;

R^1c es un anillo fenilo, sustituido por 1, 2 o 3 radicales seleccionados independientemente entre los radicales enumerados para R^1a arriba;

R^1d se selecciona entre -CH_2R^1a y -$C(O)R^1$a.

R^1 se selecciona entre R^1a, R^1b, R^1c y R^1d; donde

R^1a es piridinilo, *N*-oxopiridinilo, pirimidinilo, tiazolilo, tiadiazolilo, tetrazolilo, imidazolilo, triazinilo, pirrolidinilo, tienilo, furanilo, oxadiazolilo, isoxazolilo, oxazolilo o pirrolilo, donde el citado R^1a se puede sustituir opcionalmente por 1, 2 o 3 radicales seleccionados independientemente entre:

nitro, ciano, sulfo, formilo, hidroxiiminometilo, (2-6C)alquenilo, -CO(1-6C)alquilo, -COO(1-6C)alquilo trifluorometilo, -$CONR^6R^7$, -$N(R^7)COR^6$,

halo, hidroxi, carboxi, (1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, -OCO(1-4C)alquilo, (1-6C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, hidroxi(1-4C)alcoxi, (2-4C)alqueniloxi, -NHC(O)O(1-4C)alquilo, -NHC(=NH)NR^6R^7, -$NHC(O)NR^6R^7$, -NHC(O)(1-4C)alquilo, -NHC(O)tetrahidrofuranilo, -NHC(O)fenilo, -NHS(O)p(1-4C)alquilo, -S(O)p(1-4C)alquilo, -$S(O)pNR^6R^7$, -$NHSO_2R^6$, -NR^6R^7, morfolino, 1,3-dioxo-1,3-dihidro-2H-isoindolilo y 1,3-dioxolanil], ciclopropilo, -O(1-6C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), -S(O)p(1-4C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), tetrazolilo, 2-oxo-1,3,4-oxadiazolilo, 1,2,4-oxadiazolilo, morfolino, piperazinilo, pirrolidinilo, -NHC(O)O(1-4C)alquilo, -$C(=NOR^7)$(1-4C)alquilo, -$C(=NOR^7)NR^6R^7$, -S(O)p(1-4C)alquilCONHR^7, -C(O)NHS(O)p(1-4C)alquilo y -NR^6R^7;

donde cualquier fenilo, tetrahidrofuranilo, morfolino, 1,3-dioxo-1,3-dihidro-2H-isoindolilo, 1,3-dioxolanilo, tetrazolilo, 2-oxo-1,3,4-oxadiazolilo, 1,2,4-oxadiazolilo, morfolino, piperazinilo, pirrolidinilo, en cualquiera de los anteriores valores para los radicales en R^1a puede sustituirse opcionalmente por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo y carboxi;

R^1b es R^1b es quinolinilo, purinilo, benzotiazolilo, indolilo, 4-oxoquinolinilo, 2,7-naftiridinilo o quinazolinilo y donde el citado R^1b se puede sustituir opcionalmente por 1, 2 o 3 radicales seleccionados independientemente entre los radicales enumerados para R^1a arriba;

R^1c es un anillo fenilo, sustituido por 1, 2 o 3 radicales seleccionados independientemente entre los radicales enumerados para R^1a arriba;

R^1d se selecciona entre -CH_2R^1a y -C(O)R^1a.

En un aspecto, R^2 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, fluorometilo, difluorometilo y trifluorometilo.

En otro aspecto, R^2 se selecciona entre (1-4C)alquilo, ciclopropilo, halo y trifluorometilo.

En otro aspecto, R^2 se selecciona entre (1-4C)alquilo, halo y trifluorometilo.

En otro aspecto, R^2 se selecciona entre (1-4C)alquilo, cloro y bromo.

En otro aspecto, R^2 se selecciona entre (1-4C)alquilo, halo y ciano.

En otro aspecto R^2 se selecciona entre metilo, etilo, isopropilo y cloro.

En otro aspecto, R^2 se selecciona entre metilo, etilo, isopropilo, cloro y ciano.

En un aspecto, R^3 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, ciano, fluorometilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo.

En otro aspecto, R^3 se selecciona entre hidrógeno, (1-4C)alquilo, halo, ciano, trifluorometilo y -CO(1-4C)alquilo.

En otro aspecto, R^3 se selecciona entre hidrógeno, (1-4C)alquilo, halo, ciano, trifluorometilo y -COMe.

En otro aspecto, R^3 se selecciona entre hidrógeno, (1-4C)alquilo, halo, ciano y -CO(1-6C)alquilo.

En otro aspecto, R^3 se selecciona entre hidrógeno, metilo, etilo, cloro, bromo, ciano, trifluorometilo y -COMe.

En otro aspecto R^3 se selecciona entre hidrógeno, metilo, etilo, cloro, bromo, ciano y -COMe.

En un aspecto, R^4 se selecciona entre hidrógeno, (1-4C)alquilo, nitro, hidroxi, halo, ciano, halo(1-4C)alquilo, difluorometilo, trifluorometilo, -CO(1-4C)alquilo y (1-4C)alcoxi.

En otro aspecto, R^4 se selecciona entre hidrógeno, (1-4C)alquilo, halo, ciano, halo(1-4C)alquilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo.

En otro aspecto, R^4 se selecciona entre hidrógeno, (1-4C)alquilo, halo, ciano, fluorometilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo.

En otro aspecto, R^4 se selecciona entre hidrógeno, (1-4C)alquilo, halo, ciano, trifluorometilo y -COMe.

En otro aspecto, R^4 se selecciona entre hidrógeno, (1-4C)alquilo, halo y ciano.

En otro aspecto, R^4 se selecciona entre hidrógeno, metilo, etilo, cloro, bromo, ciano y -COMe.

En otro aspecto R^4 se selecciona entre hidrógenó, metilo, etilo, cloro, bromo y ciano.

En otro aspecto, R^4 se selecciona entre hidrógeno, cloro, metilo, etilo y ciano.

Un valor preferido de R^4 como halo (1-4C)alquilo es fluorometilo.

En un aspecto, R^5 es hidrógeno o metilo.

En un aspecto, R^5 es hidrógeno. En otro aspecto, R^5 es metilo.

En un aspecto, R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-6C)cicloalquilo, -(1-4C)alquilC(O)O(1-4C)alquilo, hidroxi, amino, -NH(1-4C)alquilo, -(N[di(1-4C)alquilo], (1-4C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, (1-4C)alcoxi(1-4C)alquilo, hidroxi(1-4C)alquilo, -(1-4C)alquilNH_2, -(1-4C)alquilNH(1-4C)alquilo, -(1-4C)alquilN[di(1-4C)alquilo] y -(1-4C)alquilheterociclilo.

En otro aspecto, R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-4C)alquenilo, (3-6C)cicloalquilo, -(1-4C)alquilC(O)O(1-4C)alquilo, hidroxi, amino, -NH(1-4C)alquilo, -(N[di(1-4C)alquilo], (1-4C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, (1-4C)alcoxi(1-4C)alquilo, hidroxi(1-4C)alquilo, -(1-4C)alquilNH_2, -(1-4C)alquilNH(1-4C)alquilo, -(1-4C)alquilN[di(1-4C)alquilo] y -(1-4C)alquilheterociclilo.

En otro aspecto, R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-6C)cicloalquilo, -(1-4C)alquilC(O)O(1-4C)alquilo, hidroxi, amino, -NH(1-4C)alquilo, -(N[di(1-4C)alquilo], (1-4C)alcoxi, (1-4C)alcoxi(1-4C)alquilo, hidroxi(1-4C)alquilo y -(1-4C)alquilheterociclilo.

En otro aspecto, R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-4C)alquenilo, (3-6C)cicloalquilo, -(1-4C)alquilC(O)O(1-4C)alquilo, hidroxi, amino, -NH(1-4C)alquilo, -(N[di(1-4C)alquilo], (1-4C)alcoxi, (1-4C)alcoxi(1-4C)alquilo, hidroxi(1-4C)alquilo y -(1-4C)alquilheterociclilo.

En otro aspecto, R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, ciclopropilo, -(1-4C)alquilC(O)O(1-4C)alquilo, amino, -NHMe, $-NMe_2$, (1-4C)alcoxi y -(1-4C)alquilheterociclilo.

En otro aspecto, R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-4C)alquenilo, ciclopropilo, -(1-4C)alquilC(O)O(1-4C)alquilo, amino, -NHMe, $-NMe_2$, (1-4C)alcoxi y -(1-4C)alquilheterociclilo.

En otro aspecto, R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, ciclopropilo, -(1-4C)alquilC(O)OMe, amino, -NHMe, $-NMe_2$, (1-4C)alcoxi y -(1-4C)alquilheterociclilo.

En otro aspecto, R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, alilo, ciclopropilo, -(1-4C)alquilC(O)OMe, amino, -NHMe, $-NMe_2$, (1-4C)alcoxi y -(1-4C)alquilheterociclilo.

Cuando R^6 es -(1-4C)alquilheterociclilo, el grupo heterociclilo se selecciona preferiblemente entre morfolinilo, piperidinilo, piperazinilo, tiomorfolinilo y tetrahidropiranilo. Dicho grupo heterociclilo opcionalmente se puede sustituir con un grupo metilo.

R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-4C)alquenilo, (3-6C)cicloalquilo, -(1-4C)alquilC(O)O(1-4C)alquilo, hidroxi, amino, -N[di(1-4C)alquilo], (1-4C)alcoxi y -(1-4C)alquilheterociclilo.

R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-4C)alquenilo, ciclopropilo, -(1-4C)alquilC(O)O(1-4C)alquilo, hidroxi, amino, -N[di(1-4C)alquilo], (1-4C)alcoxi y -(1-4C)alquilmorfolino.

En otro aspecto, R^6 y R^7 junto con el nitrógeno al cual están adheridos forman un anillo heterociclilo de 5 miembros, opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, hidroxi, (1-4C)alcoxi, halo, ciano, nitro, carboxi, hidroxi(1-4C)alquilo, (1-4C)alcoxi(1-4C)alquilo, halo(1-4C)alquilo, difluorometilo, trifluorometilo, trifluorometoxi, formilo, (1-

4C)alquilcarbonilo, (1-4C)alcoxicarbonilo, -C(O)NH_2, -C(O)NH(1-4C)alquilo, -C(O)N[di(1-4C)alquilo], -$S(O)_2NH_2$, -$S(O)_2$NH(1-4C)alquilo, -$S(O)_2$N[di(1-4C)alquil] y -S(O)p(1-4C)alquilo.

En otro aspecto, R^6 y R^7 junto con el nitrógeno al cual están adheridos forman un anillo heterociclilo de 5 miembros, opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, hidroxi, (1-4C)alcoxi, halo, ciano, nitro, carboxi, hidroxi(1-4C)alquilo, (1-4C)alcoxi(1-4C)alquilo, halo(1-4C)alquilo, difluorometilo, trifluorometilo y trifluorometoxi.

En otro aspecto, R^6 y R^7 junto con el nitrógeno al cual están adheridos forman un anillo heterociclilo de 5 miembros, opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, hidroxi, (1-4C)alcoxi, halo, ciano, nitro y carboxi.

En otro aspecto, R^6 y R^7 junto con el nitrógeno al cual están adheridos forman un anillo heterociclilo de 5 miembros, opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo y halo.

En otro aspecto, R^6 y R^7 junto con el nitrógeno al cual están adheridos forman un anillo heterociclilo de 5 miembros, opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre formilo, (1-4C)alquilcarbonilo, (1-4C)alcoxicarbonilo, -C(O)NH_2, -C(O)NH(1-4C)alquilo, -C(O)N[di(1-4C)alquilo], -$S(O)_2NH_2$, -$S(O)_2$NH(1-4C)alquilo, -$S(O)_2$N[di(1-4C)alquil] y -S(O)p(1-4C)alquilo.

En otro aspecto, R^6 y R^7 junto con el nitrógeno al cual están adheridos forman un anillo heterociclilo de 6 miembros, opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, hidroxi, (1-4C)alcoxi, halo, ciano, nitro, carboxi, hidroxi(1-4C)alquilo, (1-4C)alcoxi(1-4C)alquilo, halo (1-4C)alquilo, difluorometilo, trifluorometilo, trifluorometoxi, formilo, (1-4C)alquilcarbonilo, (1-4C)alcoxicarbonilo, -C(O)NH_2, -C(O)NH(1-4C)alquilo, -C(O)N[di(1-4C)alquilo], -$S(O)_2NH_2$, -$S(O)_2$NH(1-4C)alquilo, -$S(O)_2$N[di(1-4C)alquil] y -S(O)p(1-4C)alquilo.

En otro aspecto, R^6 y R^7 junto con el nitrógeno al cual están adheridos forman un anillo heterociclilo de 6 miembros, opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, hidroxi, (1-4C)alcoxi, halo, ciano, nitro, carboxi, hidroxi(1-4C)alquilo, (1-4C)alcoxi(1-4C)alquilo, halo (1-4C)alquilo, difluorometilo, trifluorometilo y trifluorometoxi.

En otro aspecto, R^6 y R^7 junto con el nitrógeno al cual están adheridos forman un anillo heterociclilo de 6 miembros, opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, hidroxi, (1-4C)alcoxi, halo, ciano, nitro y carboxi.

En otro aspecto, R^6 y R^7 junto con el nitrógeno al cual están adheridos forman un anillo heterociclilo de 6 miembros, opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo y halo.

En otro aspecto, R^6 y R^7 junto con el nitrógeno al cual están adheridos forman un anillo heterociclilo de 6 miembros, opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre formilo, (1-4C)alquilcarbonilo, (1-4C)alcoxicarbonilo, $-C(O)NH_2$, -C(O)NH(1-4C)alquilo, -C(O)N[di(1-4C)alquilo], $-S(O)_2NH_2$, $-S(O)_2NH$(1-4C)alquilo, $-S(O)_2N$[di(1-4C)alquil] y -S(O)p(1-4C)alquilo.

Cuando R^6 y R^7 junto con el nitrógeno al cual están adheridos forman un anillo heterociclilo de 5 miembros, unos valores apropiados para dicho anillo son pirrolidina, pirazol, pirrol, tetrazol, imidazol, imidazolina y triazol. Otros valores apropiados son los anillos citados arriba donde un átomo de carbono en el anillo se oxida para formar un grupo carbonilo, como 2-pirrolidona.

Cuando R^6 y R^7 junto con el nitrógeno al cual están adheridos forman un anillo heterociclilo de 6 miembros, unos valores apropiados para dicho anillo son morfolinilo, piperidinilo, piperazinilo, tiomorfolinilo y tetrahidropiridinilo. Otros valores apropiados son los anillos citados arriba donde un átomo de carbono en el anillo se oxida para formar un grupo carbonilo, como 2-piperidinona, 2-piperazinona y 2-tetrahidropiridona.

R^6 y R^7 pueden junto con el nitrógeno al cual están adheridos formar un anillo heterociclilo de 5 o 6 miembros, opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo.

R^6 y R^7 pueden junto con el nitrógeno al cual están adheridos formar piperazinilo o morfolino opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo.

En un aspecto, R^7 se selecciona independientemente en cada caso entre hidrógeno y (1-4C)alquilo.

En otro aspecto de la invención, R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-4C)alquenilo, (3-6C)cicloalquilo, -(1-4C)alquilC(O)O(1-4C)alquilo, hidroxi, amino, -N[di(1-4C)alquilo], (1-4C)alcoxi y -(1-4C)alquilheterociclilo;

R^7 se selecciona independientemente en cada caso entre hidrógeno y (1-6C)alquilo;

o R^6 y R^7 pueden junto con el nitrógeno al cual están adheridos formar un anillo heterociclilo de 5 o 6 miembros, opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo.

En una incorporación se dispone un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, donde:

Y es H;

W es O;

R^1 se selecciona entre R^1a y R^1b;

R^2 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, fluorometilo, difluorometilo y trifluorometilo;

R^3 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, ciano, fluorometilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo;

R^4 se selecciona entre hidrógeno, (1-4C)alquilo, halo, ciano, halo(1-4C)alquilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo;

R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-6C) cicloalquilo, -(1-4C)alquilC(O)O(1-4C)alquilo, hidroxi, amino, -NH(1-4C)alquilo, -(N[di(1-4C)alquilo], (1-4C)alcoxi, (1-4C)alcoxi(1-4C)alquilo, hidroxi(1-4C)alquilo y -(1-4C)alquilheterociclilo;

R^7 se selecciona independientemente en cada caso entre hidrógeno y (1-4C)alquilo.

En otra incorporación se dispone un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, donde:

Y es H;

W es O;

R^1 se selecciona entre R^1a y R^1b, opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre nitro, ciano, -CO(1-6C)alquilo, -COO(1-6C)alquilo, -COO(1-6C)alquilo (opcionalmente sustituido por -COO(1-4C)alquilo), trifluorometilo, $-CONR^6R^7$, $-OCONR^6R^7$, $-N(R^7)COR^6$, $-CONHCH(CO_2R^7)R^6$, halo, hidroxi, carboxi, (1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, halo, ciano, nitro, -COO(1-6C)alquilo, -OCO(1-4C)alquilo, (1-6C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, hidroxi(1-4C)alcoxi, (2-4C)alqueniloxi, trifluorometilo, $-CONR^6R^7$, carboxi, -NHC(O)O(1-4C)alquilo, $-OCONR^6R^7$, -C(=NOH)(1-4C)alquilo, $-C(=NOH)NR^6R^7$, -S(O)p(1-4C)alquilo, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$ y heterociclilo], (3-6C) cicloalquilo (opcionalmente sustituido por 1 o 2 radicales seleccionados entre (1-6C)alquilo y los radicales opcionales descritos para (1-6C)alquilo arriba), -O(1-6C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), -S(O)p(1-4C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), heterociclilo, -NHC(O)O(1-4C)alquilo, $-C(=NOR^7)$(1-4C)alquilo, $-C(=NOR^7)NR^6R^7$, $-S(O)pNR^6R^7$, $-NR^7S(O)p$(1-4C)alquilo, $-NR^7S(O)p$-arilo,

-C(O)NHS(O)p(1-4C)alquilo, -C(O)NHS(O)p-arilo y $-NR^6R^7$;

donde cualquier grupo heterociclilo o arilo en cualquiera de los anteriores valores para los radicales en R^1a puede sustituirse opcionalmente por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, hidroxi, (1-4C)alcoxi, halo, ciano, nitro, carboxi, hidroxi(1-4C)alquilo, (1-4C)alcoxi(1-4C)alquilo, halo(1-4C)alquilo, difluorometilo, trifluorometilo, trifluorometoxi, formilo, -CO(1-4C)alquilo, -COO(1-4C)alquilo, -

$C(O)NH_2$, -C(O)NH(1-4C)alquilo, -C(O)N[di(1-4C)alquilo], $-S(O)_2NH_2$, $-S(O)_2NH$(1-4C)alquilo y $-S(O)_2N$[di(1-4C)alquilo];

R^2 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, fluorometilo, difluorometilo y trifluorometilo;

R^3 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, ciano, fluorometilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo;

R^4 se selecciona entre hidrógeno, (1-4C)alquilo, halo, ciano, halo(1-4C)alquilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo;

R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-4C)alquenilo,

(3-6C)cicloalquilo, -(1-4C)alquilC(O)O(1-4C)alquilo, hidroxi, amino, -NH(1-4C)alquilo, -(N[di(1-4C)alquilo], (1-4C)alcoxi, (1-4C)alcoxi(1-4C)alquilo, hidroxi(1-4C)alquilo y -(1-4C)alquilheterociclilo;

R^7 se selecciona independientemente en cada caso entre hidrógeno y (1-4C)alquilo; y p es (independientemente en cada caso) 0, 1 o 2.

En otra incorporación se dispone un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, donde:

Y es H;

W es O;

R^1 se selecciona entre R^1a y R^1b, opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre nitro, ciano, -CO(1-6C)alquilo, -COO(1-6C)alquilo, -O(1-6C)alquilo, trifluorometilo, $-CONR^6R^7$, $-OCONR^6R^7$, $-N(R^7)COR^6$, $-CONHCH(CO_2R^7)R^6$, halo, hidroxi, carboxi, (1-6C)alquilo, heterociclilo, arilo, -NHC(O)O(1-4C)alquilo, $-C(=NOR^7)$(1-4C)alquilo, $-C(=NOR^7)NR^6R^7$, -S(O)p(1-4C)alquilo (opcionalmente sustituido por hidroxi), $-S(O)pNR^6R^7$, -S(O)p(1-4C)alquilCONHR^7, $-NR^7S(O)pNR^6R^7$, $-NR^7S(O)p$(1-4C)alquilo, $-NR^7S(O)p$-arilo, -C(O)NHS(O)p(1-4C)alquilo, -C(O)NHS(O)p-arilo y $-NR^6R^7$;

R^2 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, fluorometilo, difluorometilo y trifluorometilo;

R^3 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, ciano, fluorometilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo;
R^4 se selecciona entre hidrógeno, (1-4C)alquilo, halo, ciano, halo(1-4C)alquilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo;
R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-6C)cicloalquilo, -(1-4C)alquilC(O)O(1-4C)alquilo, hidroxi, amino, -NH(1-4C)alquilo, -(N[di(1-4C)alquilo], (1-4C)alcoxi, (1-4C)alcoxi(1-4C)alquilo, hidroxi(1-4C)alquilo y -(1-4C)alquilheterociclilo;
R^7 se selecciona independientemente en cada caso entre hidrógeno y (1-4C)alquilo; y p es (independientemente en cada caso) 0, 1 o 2.

En otra incorporación se dispone un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, donde:
Y es H;
W es O;
R^1 se selecciona entre R^1a y R^1b, opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre nitro, ciano, -CO(1-6C)alquilo, -COO(1-6C)alquilo (opcionalmente sustituido por -COO(1-4C)alquilo), trifluorometilo, $-CONR^6R^7$, $-OCONR^6R^7$, $-N(R^7)COR^6$, halo, carboxi, (1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, halo, -COO(1-6C)alquilo, -OCO(1-4C)alquilo, (1-6C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, hidroxi(1-4C)alcoxi, (2-4C)alqueniloxi, trifluorometilo, $-CONR^6R^7$, carboxi, $-NHC(O)O(1-4C)alquilo$, $-OCONR^6R^7$, $-C(=NOH)(1-4C)alquilo$, $-C(=NOH)NR^6R^7$, $-S(O)p(1-4C)alquilo$, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$ y heterociclilo], (3-6C)cicloalquilo (opcionalmente sustituido por 1 o 2 radicales seleccionados entre (1-6C)alquilo y los radicales opcionales descritos para (1-6C)alquilo arriba), -O(1-6C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), $-S(O)p(1-4C)alquilo$ (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), heterociclilo, $-NHC(O)O(1-4C)alquilo$, $-C(=NOR^7)(1-4C)alquilo$, $-C(=NOR^7)NR^6R^7$, $-S(O)pNR^6R^7$, $-NR^7S(O)p(1-4C)alquilo$, $-C(O)NHS(O)p(1-4C)alquilo$ y $-NR^6R^7$;

donde cualquier grupo heterociclilo o arilo en cualquiera de los anteriores valores para los radicales en R^1a puede sustituirse opcionalmente por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, (1-4C)alcoxi, halo, ciano, nitro, carboxi, halo(1-4C)alquilo, difluorometilo, trifluorometilo y trifluorometoxi;

R^2 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, fluorometilo, difluorometilo y trifluorometilo;

R^3 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, ciano, fluorometilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo;

R^4 se selecciona entre hidrógeno, (1-4C)alquilo, halo, ciano, halo(1-4C)alquilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo;

R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-4C)alquenilo, (3-6C) cicloalquilo, -(1-4C)alquilC(O)O(1-4C)alquilo, hidroxi, amino, -NH(1-4C)alquilo, -(N[di(1-4C)alquilo], (1-4C)alcoxi, (1-4C)alcoxi(1-4C)alquilo, hidroxi(1-4C)alquilo y -(1-4C)alquilheterociclilo;

R^7 se selecciona independientemente en cada caso entre hidrógeno y (1-4C)alquilo; y p es (independientemente en cada caso) 0, 1 o 2.

En otra incorporación se dispone un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, donde:

Y es H;

W es O;

R^1 se selecciona entre R^1a y R^1b, opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre nitro, ciano, -CO(1-4C)alquilo, -COO(1-4C)alquilo, -O(1-4C)alquilo, trifluorometilo, -$CONR^6R^7$, -$N(R^7)COR^6$, fluoro, cloro, bromo, hidroxi, carboxi, (1-4C)alquilo, heterociclilo, -NHC(O)O(1-4C)alquilo, -$C(=NOR^7)$(1-4C)alquilo, -$C(=NOR^7)NR^6R^7$, -S(O)p(1-4C)alquilo (opcionalmente sustituido por hidroxi), -S(O)p(1-4C)alquilCONHR^7 y -NR^6R^7;

R^2 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, fluorometilo, difluorometilo y trifluorometilo;

R^3 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, ciano, fluorometilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo;

R^4 se selecciona entre hidrógeno, (1-4C)alquilo, halo, ciano, fluorometilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo;

R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-6C)cicloalquilo, -(1-4C)alquilC(O)O(1-4C)alquilo, hidroxi, amino, -NH(1-4C)alquilo, -(N[di(1-4C)alquilo], (1-4C)alcoxi, (1-4C)alcoxi(1-4C)alquilo, hidroxi(1-4C)alquilo y -(1-4C)alquilheterociclilo;

R^7 se selecciona independientemente en cada caso entre hidrógeno y (1-4C)alquilo; y p es (independientemente en cada caso) 0, 1 o 2.

En otra incorporación se dispone un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, donde:

Y es H;

W es O;

R^1 se selecciona entre imidazolilo, pirimidinilo, piridinilo, tiazolilo, triazinilo, pirrolilo, tiadiazolilo, tetrazolilo, quinolinilo, purinilo, benzotiazolilo e indolilo; opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre nitro, ciano, -CO(1-4C)alquilo, -COO(1-4C)alquilo, -O(1-4C)alquilo, trifluorometilo, $-CONR^6R^7$, $-N(R^7)COR^6$, fluoro, cloro, bromo, hidroxi, carboxi, (1-4C)alquilo, heterociclilo, -NHC(O)O(1-4C)alquilo, $-C(=NOR^7)$(1-4C)alquilo, $-C(=NOR^7)NR^6R^7$, -S(O)p(1-4C)alquilo (opcionalmente sustituido por hidroxi), -S(O)p(1-4C)alquil$CONHR^7$ y $-NR^6R^7$;

R^2 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, fluorometilo, difluorometilo y trifluorometilo;

R^3 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, ciano, fluorometilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo;

R^4 se selecciona entre hidrógeno, (1-4C)alquilo, halo, ciano, fluorometilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo;

R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-6C)cicloalquilo, -(1-4C)alquilC(O)O(1-4C)alquilo, hidroxi,

amino, -NH(1-4C)alquilo, -(N[di(1-4C)alquilo], (1-4C)alcoxi, (1-4C)alcoxi(1-4C)alquilo, hidroxi(1-4C)alquilo y -(1-4C)alquilheterociclilo;
R^7 se selecciona independientemente en cada caso entre hidrógeno y (1-4C)alquilo; y p es (independientemente en cada caso) 0, 1 o 2.

En otra incorporación se dispone un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, donde:
Y es H;
W es O;
R^1 se selecciona entre imidazolilo, pirimidinilo, piridinilo, tiazolilo, triazinilo, pirrolilo, tiadiazolilo, tetrazolilo, quinolinilo, purinilo, benzotiazolilo e indolilo; opcionalmente sustituido por 2 radicales; donde un radical se selecciona entre carboxi, $-CONHSO_2Me$ y $-CONHR^6$ y donde el otro radical se selecciona entre
(1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, halo, ciano, nitro, -COO(1-6C)alquilo, -OCO(1-4C)alquilo, (1-6C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, hidroxi(1-4C)alcoxi, (2-4C)alqueniloxi, trifluorometilo, $-CONR^6R^7$, carboxi, -NHC(O)O(1-4C)alquilo, $-OCONR^6R^7$, -C(=NOH)(1-4C)alquilo, $-C(=NOH)NR^6R^7$, -S(O)p(1-4C)alquilo, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$ y heterociclilo], -O(1-6C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba) y -S(O)p(1-4C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba);
R^2 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, fluorometilo, difluorometilo y trifluorometilo;
R^3 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, ciano, fluorometilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo;
R^4 se selecciona entre hidrógeno, (1-4C)alquilo, halo, ciano, fluorometilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo;
R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-4C)alquenilo, (3-6C)cicloalquilo, -(1-4C)alquilC(O)O(1-4C)alquilo, hidroxi, amino, -NH(1-4C)alquilo, -(N[di(1-4C)alquilo], (1-

4C)alcoxi, (1-4C)alcoxi(1-4C)alquilo, hidroxi(1-4C)alquilo y -(1-4C)alquilheterociclilo;

R^7 se selecciona independientemente en cada caso entre hidrógeno y (1-4C)alquilo; y p es (independientemente en cada caso) 0, 1 o 2.

En otra incorporación se dispone un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, donde:

Y es H;

W es O;

R^1 se selecciona entre imidazolilo, pirimidinilo, piridinilo, tiazolilo, triazinilo, pirrolilo, tiadiazolilo, tetrazolilo, quinolinilo, purinilo, benzotiazolilo e indolilo; opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre nitro, ciano, -CO(1-4C)alquilo, -COO(1-4C)alquilo, -O(1-4C)alquilo, trifluorometilo, $-CONR^6R^7$, $-N(R^7)COR^6$, fluoro, cloro, bromo, hidroxi, carboxi, (1-4C)alquilo, heterociclilo, -NHC(O)O(1-4C)alquilo, $-C(=NOR^7)$(1-4C)alquilo, $-C(=NOR^7)NR^6R^7$, -S(O)p(1-4C)alquilo (opcionalmente sustituido por hidroxi), -S(O)p(1-4C)alquilCONHR^7 y $-NR^6R^7$;

R^2 se selecciona entre (1-4C)alquilo, cloro y bromo;

R^3 se selecciona entre hidrógeno, metilo, etilo, cloro, bromo, ciano, trifluorometilo y -COMe;

R^4 se selecciona entre hidrógeno, metilo, etilo, cloro, bromo, ciano y -COMe;

R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, ciclopropilo, -(1-4C)alquilC(O)OMe, amino, -NHMe, $-NMe_2$, (1-4C)alcoxi y -(1-4C)alquilheterociclilo;

R^7 se selecciona independientemente en cada caso entre hidrógeno y (1-4C)alquilo; y

p es (independientemente en cada caso) 0, 1 o 2.

En otra incorporación se dispone un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, donde:

Y es H;

W es O;

R^1 se selecciona entre imidazolilo, pirimidinilo, piridinilo, tiazolilo, triazinilo, pirrolilo, tiadiazolilo, tetrazolilo, quinolinilo, purinilo, benzotiazolilo e indolilo; opcionalmente sustituido por 2 radicales; donde un radical se selecciona entre carboxi, $-CONHSO_2Me$ y $-CONHR^6$ (donde R^6 se selecciona entre -OMe, hidrógeno, amino y 3-4C alquenilo); y donde el otro radical se selecciona entre

(1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, halo, ciano, nitro, -COO(1-6C)alquilo, -OCO(1-4C)alquilo, (1-6C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, hidroxi(1-4C)alcoxi, (2-4C)alqueniloxi, trifluorometilo, $-CONR^6R^7$, carboxi, $-NHC(O)O$(1-4C)alquilo, $-OCONR^6R^7$, $-C(=NOH)$(1-4C)alquilo, $-C(=NOH)NR^6R^7$, -S(O)p(1-4C)alquilo, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$ y heterociclilo], -O(1-6C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba) y -S(O)p(1-4C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba);

R^2 se selecciona entre (1-4C)alquilo, cloro y bromo;

R^3 se selecciona entre hidrógeno, metilo, etilo, cloro, bromo, ciano, trifluorometilo y -COMe;

R^4 se selecciona entre hidrógeno, metilo, etilo, cloro, bromo, ciano y -COMe;

R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, alilo, ciclopropilo, -(1-4C)alquilC(O)OMe, amino, -NHMe, $-NMe_2$, (1-4C)alcoxi y -(1-4C)alquilheterociclilo;

R^7 se selecciona independientemente en cada caso entre hidrógeno y (1-4C)alquilo; y p es (independientemente en cada caso) 0, 1 o 2.

En otra incorporación se dispone un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, donde:

Y es H;

W es O;

R^1 se selecciona entre imidazolilo, pirimidinilo, piridinilo, tiazolilo, triazinilo, pirrolilo, tiadiazolilo, tetrazolilo, quinolinilo, purinilo,

benzotiazolilo e indolilo; opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre nitro, ciano, -CO(1-4C)alquilo, -COO(1-4C)alquilo, -O(1-4C)alquilo, trifluorometilo, -CONR^{6}R^7, fluoro, cloro, bromo, hidroxi, carboxi, (1-4C)alquilo, heterociclilo, -NHC(O)O(1-4C)alquilo, -C(=NOH)NR^{6}R^7, -S(O)p(1-4C)alquilo (opcionalmente sustituido por hidroxi), -S(O)p(1-4C)alquilCONHMe y -NR^{6}R^7;

R^2 se selecciona entre (1-4C)alquilo, cloro y bromo;

R^3 se selecciona entre hidrógeno, metilo, etilo, cloro, bromo, ciano, trifluorometilo y -COMe;

R^4 se selecciona entre hidrógeno, metilo, etilo, cloro, bromo, ciano y -COMe;

R^6 y R^7 juntos forman un anillo heterociclilo de 5 o 6 miembros, opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, hidroxi, (1-4C)alcoxi, halo, ciano, nitro, carboxi, hidroxi(1-4C)alquilo, (1-4C)alcoxi(1-4C)alquilo, halo (1-4C)alquilo, difluorometilo, trifluorometilo y trifluorometoxi; y p es (independientemente en cada caso) 0, 1 o 2.

En una incorporación se dispone un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, donde:

Y es H;

W es NR^5;

R^1 se selecciona entre R^{1}a y R^{1}b;

R^2 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, fluorometilo, difluorometilo y trifluorometilo;

R^3 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, ciano, fluorometilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo.

R^4 se selecciona entre hidrógeno, (1-4C)alquilo, halo, ciano, halo(1-4C)alquilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo;

R^5 es hidrógeno o metilo;

R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-6C) cicloalquilo, -(1-4C)alquilC(O)O(1-4C)alquilo, hidroxi,

amino, -NH(1-4C)alquilo, -(N[di(1-4C)alquilo], (1-4C)alcoxi, (1-4C)alcoxi(1-4C)alquilo, hidroxi(1-4C)alquilo y -(1-4C)alquilheterociclilo;
R^7 se selecciona independientemente en cada caso entre hidrógeno y (1-4C)alquilo.

En otra incorporación se dispone un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, donde:
Y es H;
W es NR^5;
R^1 se selecciona entre R^1a y R^1b, opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre nitro, ciano, -CO(1-6C)alquilo, -COO(1-6C)alquilo, -COO(1-6C)alquilo (opcionalmente sustituido por -COO(1-4C)alquilo), trifluorometilo, $-CONR^6R^7$, $-OCONR^6R^7$, $-N(R^7)COR^6$, $-CONHCH(CO_2R^7)R^6$, halo, hidroxi, carboxi,
(1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, halo, ciano, nitro, -COO(1-6C)alquilo, -OCO(1-4C)alquilo, (1-6C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, hidroxi(1-4C)alcoxi, (2-4C)alqueniloxi, trifluorometilo, $-CONR^6R^7$, carboxi, $-NHC(O)O$(1-4C)alquilo, $-OCONR^6R^7$, -C(=NOH)(1-4C)alquilo, $-C(=NOH)NR^6R^7$, -S(O)p(1-4C)alquilo, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$ y heterociclilo], (3-6C) cicloalquilo (opcionalmente sustituido por 1 o 2 radicales seleccionados entre (1-6C)alquilo y los radicales opcionales descritos para (1-6C)alquilo arriba), -O(1-6C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), -S(O)p(1-4C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), heterociclilo, $-NHC(O)O$(1-4C)alquilo, $-C(=NOR^7)$(1-4C)alquilo, $-C(=NOR^7)NR^6R^7$, $-S(O)pNR^6R^7$, $-NR^7S(O)p$(1-4C)alquilo, $-NR^7S(O)p$-arilo, -C(O)NHS(O)p(1-4C)alquilo, -C(O)NHS(O)p-arilo y $-NR^6R^7$;
donde cualquier grupo heterociclilo o arilo en cualquiera de los anteriores valores para los radicales en R^1a puede sustituirse opcionalmente por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, hidroxi, (1-4C)alcoxi, halo, ciano, nitro, carboxi, hidroxi(1-4C)alquilo, (1-

4C)alcoxi(1-4C)alquilo, halo(1-4C)alquilo, difluorometilo, trifluorometilo, trifluorometoxi, formilo, -CO(1-4C)alquilo, -COO(1-4C)alquilo, -C(O)NH_2, -C(O)NH(1-4C)alquilo, -C(O)N[di(1-4C)alquilo], -$S(O)_2NH_2$, -$S(O)_2$NH(1-4C)alquilo y -$S(O)_2$N[di(1-4C)alquilo];

R^2 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, fluorometilo, difluorometilo y trifluorometilo;

R^3 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, ciano, fluorometilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo;

R^4 se selecciona entre hidrógeno, (1-4C)alquilo, halo, ciano, halo (1-4C)alquilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo;

R^5 es hidrógeno o metilo;

R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-4C)alquenilo, (3-6C)cicloalquilo, -(1-4C)alquilC(O)O(1-4C)alquilo, hidroxi, amino, -NH(1-4C)alquilo, -(N[di(1-4C)alquilo], (1-4C)alcoxi, (1-4C)alcoxi(1-4C)alquilo, hidroxi(1-4C)alquilo y -(1-4C)alquilheterociclilo;

R^7 se selecciona independientemente en cada caso entre hidrógeno y (1-4C)alquilo; y p es (independientemente en cada caso) 0, 1 o 2.

En otra incorporación se dispone un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, donde:

Y es H;

W es NR^5;

R^1 se selecciona entre R^1a y R^1b, opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre nitro, ciano, -CO(1-6C)alquilo, -COO(1-6C)alquilo, -O(1-6C)alquilo, trifluorometilo, -CONR^{6}R^7, -OCONR^{6}R^7, -N(R^7)COR^6, -CONHCH(CO$_2$R^7)R^6, halo, hidroxi, carboxi, (1-6C)alquilo, heterociclilo, arilo, -NHC(O)O(1-4C)alquilo, -C(=NOR^7)(1-4C)alquilo, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alquilo (opcionalmente sustituido por hidroxi), -S(O)pNR^{6}R^7, -S(O)p(1-4C)alquilCONHR^7, -NR^{7}S(O)pNR^{6}R^7, -NR^{7}S(O)p(1-4C)alquilo, -NR^{7}S(O)p-arilo, -C(O)NHS(O)p(1-4C)alquilo, -C(O)NHS(O)p-arilo y -NR^{6}R^7;

R^2 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, fluorometilo, difluorometilo y trifluorometilo;

R^3 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, ciano, fluorometilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo.

R^4 se selecciona entre hidrógeno, (1-4C)alquilo, halo, ciano, halo(1-4C)alquilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo;

R^5 es hidrógeno o metilo;

R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-6C)cicloalquilo, -(1-4C)alquilC(O)O(1-4C)alquilo, hidroxi, amino, -NH(1-4C)alquilo, -(N[di(1-4C)alquilo], (1-4C)alcoxi, (1-4C)alcoxi(1-4C)alquilo, hidroxi(1-4C)alquilo y -(1-4C)alquilheterociclilo;

R^7 se selecciona independientemente en cada caso entre hidrógeno y (1-4C)alquilo; y p es (independientemente en cada caso) 0, 1 o 2.

En otra incorporación se dispone un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, donde:

Y es H;

W es NR^5;

R^1 se selecciona entre R^1a y R^1b, opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre nitro, ciano, -CO(1-6C)alquilo, -COO(1-6C)alquilo (opcionalmente sustituido por -COO(1-4C)alquilo), trifluorometilo, $-CONR^6R^7$, $-OCONR^6R^7$, $-N(R^7)COR^6$, halo, carboxi, (1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, halo, -COO(1-6C)alquilo, -OCO(1-4C)alquilo, (1-6C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, hidroxi(1-4C)alcoxi, (2-4C)alqueniloxi, trifluorometilo, $-CONR^6R^7$, carboxi, $-NHC(O)O(1-4C)alquilo$, $-OCONR^6R^7$, $-C(=NOH)(1-4C)alquilo$, $-C(=NOH)NR^6R^7$, $-S(O)p(1-4C)alquilo$, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$ y heterociclilo], (3-6C)cicloalquilo (opcionalmente sustituido por 1 o 2 radicales seleccionados entre (1-6C)alquilo y los radicales opcionales descritos para (1-6C)alquilo arriba), -O(1-6C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), $-S(O)p(1-4C)alquilo$ (opcionalmente sustituido por 1 o 2 radicales como se

describió para (1-6C)alquilo arriba), heterociclilo, -NHC(O)O(1-4C)alquilo, -C(=NOR^7)(1-4C)alquilo, -C(=NOR^7)NR^{6}R^7, -S(O)pNR^{6}R^7, -NR^{7}S(O)p(1-4C)alquilo, -C(O)NHS(O)p(1-4C)alquilo y NR^{6}R^7;

donde cualquier grupo heterociclilo o arilo en cualquiera de los anteriores valores para los radicales en R^{1}a puede sustituirse opcionalmente por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, (1-4C)alcoxi, halo, ciano, nitro, carboxi, halo(1-4C)alquilo, difluorometilo, trifluorometilo y trifluorometoxi;

R^2 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, fluorometilo, difluorometilo y trifluorometilo;

R^3 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, ciano, fluorometilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo;

R^4 se selecciona entre hidrógeno, (1-4C)alquilo, halo, ciano, halo(1-4C)alquilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo;

R^5 es hidrógeno o metilo;

R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-4C)alquenilo, (3-6C)cicloalquilo, -(1-4C)alquilC(O)O(1-4C)alquilo, hidroxi, amino, -NH(1-4C)alquilo, -(N[di(1-4C)alquilo], (1-4C)alcoxi, (1-4C)alcoxi(1-4C)alquilo, hidroxi(1-4C)alquilo y -(1-4C)alquilheterociclilo;

R^7 se selecciona independientemente en cada caso entre hidrógeno y (1-4C)alquilo; y p es (independientemente en cada caso) 0, 1 o 2.

En otra incorporación se dispone un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, donde:

Y es H;

W es NR^5;

R^1 se selecciona entre R^{1}a y R^{1}b, opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre nitro, ciano, -CO(1-4C)alquilo, -COO(1-4C)alquilo, -O(1-4C)alquilo, trifluorometilo, -CONR^{6}R^7, -N(R^7)COR^6, fluoro, cloro, bromo, hidroxi, carboxi, (1-4C)alquilo, heterociclilo, -NHC(O)O(1-4C)alquilo, -C(=NOR^7)(1-

4C)alquilo, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alquilo (opcionalmente sustituido por hidroxi), -S(O)p(1-4C)alquilCONHR^7 y -NR^{6}R^7;

R^2 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, fluorometilo, difluorometilo y trifluorometilo;

R^3 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, ciano, fluorometilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo.

R^4 se selecciona entre hidrógeno, (1-4C)alquilo, halo, ciano, fluorometilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo;

R^5 es hidrógeno o metilo;

R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-6C)cicloalquilo, -(1-4C)alquilC(O)O(1-4C)alquilo, hidroxi, amino, -NH(1-4C)alquilo, -(N[di(1-4C)alquilo], (1-4C)alcoxi, (1-4C)alcoxi(1-4C)alquilo, hidroxi(1-4C)alquilo y -(1-4C)alquilheterociclilo;

R^7 se selecciona independientemente en cada caso entre hidrógeno y (1-4C)alquilo; y p es (independientemente en cada caso) 0, 1 o 2.

En otra incorporación se dispone un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, donde:

Y es H;

W es NR^5;

R^1 se selecciona entre imidazolilo, pirimidinilo, piridinilo, tiazolilo, triazinilo, pirrolilo, tiadiazolilo, tetrazolilo, quinolinilo, purinilo, benzotiazolilo e indolilo; opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre nitro, ciano, -CO(1-4C)alquilo, -COO(1-4C)alquilo, -O(1-4C)alquilo, trifluorometilo, -CONR^{6}R^7, -N(R^7)COR^6, fluoro, cloro, bromo, hidroxi, carboxi, (1-4C)alquilo, heterociclilo, -NHC(O)O(1-4C)alquilo, -C(=NOR^7)(1-4C)alquilo, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alquilo (opcionalmente sustituido por hidroxi), -S(O)p(1-4C)alquilCONHR^7 y -NR^{6}R^7;

R^2 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, fluorometilo, difluorometilo y trifluorometilo;

R^3 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, ciano, fluorometilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo.

R^4 se selecciona entre hidrógeno, (1-4C)alquilo, halo, ciano, fluorometilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo;

R^5 es hidrógeno o metilo;

R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-6C)cicloalquilo, -(1-4C)alquilC(O)O(1-4C)alquilo, hidroxi, amino, -NH(1-4C)alquilo, -(N[di(1-4C)alquilo], (1-4C)alcoxi, (1-4C)alcoxi(1-4C)alquilo, hidroxi(1-4C)alquilo y -(1-4C)alquilheterociclilo;

R^7 se selecciona independientemente en cada caso entre hidrógeno y (1-4C)alquilo; y p es (independientemente en cada caso) 0, 1 o 2.

En otra incorporación se dispone un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, donde:

Y es H;

W es NR^5;

R^1 se selecciona entre imidazolilo, pirimidinilo, piridinilo, tiazolilo, triazinilo, pirrolilo, tiadiazolilo, tetrazolilo, quinolinilo, purinilo, benzotiazolilo e indolilo; opcionalmente sustituido por 2 radicales; donde un radical se selecciona entre carboxi, $-CONHSO_2Me$ y $-CONHR^6$ y donde el otro radical se selecciona entre

(1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, halo, ciano, nitro, -COO(1-6C)alquilo, -OCO(1-4C)alquilo, (1-6C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, hidroxi(1-4C)alcoxi, (2-4C)alqueniloxi, trifluorometilo, $-CONR^6R^7$, carboxi, -NHC(O)O(1-4C)alquilo, $-OCONR^6R^7$, -C(=NOH)(1-4C)alquilo, $-C(=NOH)NR^6R^7$, -S(O)p(1-4C)alquilo, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$ y heterociclilo], -O(1-6C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba) y -S(O)p(1-4C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba);

R^2 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, fluorometilo, difluorometilo y trifluorometilo;

R^3 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, halo, ciano, fluorometilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo.

R^4 se selecciona entre hidrógeno, (1-4C)alquilo, halo, ciano, fluorometilo, difluorometilo, trifluorometilo y -CO(1-4C)alquilo;

R^5 es hidrógeno o metilo;

R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-4C)alquenilo, (3-6C)cicloalquilo, -(1-4C)alquilC(O)O(1-4C)alquilo, hidroxi, amino, -NH(1-4C)alquilo, -(N[di(1-4C)alquilo], (1-4C)alcoxi, (1-4C)alcoxi(1-4C)alquilo, hidroxi(1-4C)alquilo y -(1-4C)alquilheterociclilo;

R^7 se selecciona independientemente en cada caso entre hidrógeno y (1-4C)alquilo; y p es (independientemente en cada caso) 0, 1 o 2.

En otra incorporación se dispone un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, donde:

Y es H;

W es NR^1;

R^1 se selecciona entre imidazolilo, pirimidinilo, piridinilo, tiazolilo, triazinilo, pirrolilo, tiadiazolilo, tetrazolilo, quinolinilo, purinilo, benzotiazolilo e indolilo; opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre nitro, ciano, -CO(1-4C)alquilo, -COO(1-4C)alquilo, -O(1-4C)alquilo, trifluorometilo, $-CONR^6R^7$, $-N(R^7)COR^6$, fluoro, cloro, bromo, hidroxi, carboxi, (1-4C)alquilo, heterociclilo, -NHC(O)O(1-4C)alquilo, $-C(=NOR^7)$(1-4C)alquilo, $-C(=NOR^7)NR^6R^7$, -S(O)p(1-4C)alquilo (opcionalmente sustituido por hidroxi), -S(O)p(1-4C)alquilCONHR^7 y $-NR^6R^7$;

R^2 se selecciona entre (1-4C)alquilo, cloro y bromo;

R^3 se selecciona entre hidrógeno, metilo, etilo, cloro, bromo, ciano, trifluorometilo y -COMe;

R^4 se selecciona entre hidrógeno, metilo, etilo, cloro, bromo, ciano y -COMe;

R^5 es hidrógeno o metilo;

R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, ciclopropilo, -(1-4C)alquilC(O)OMe, amino, -NHMe, $-NMe_2$, (1-4C)alcoxi y -(1-4C)alquilheterociclilo;

R^7 se selecciona independientemente en cada caso entre hidrógeno y (1-4C)alquilo; y p es (independientemente en cada caso) 0, 1 o 2.

En otra incorporación se dispone un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, donde:

Y es H;

W es NR^5;

R^1 se selecciona entre imidazolilo, pirimidinilo, piridinilo, tiazolilo, triazinilo, pirrolilo, tiadiazolilo, tetrazolilo, quinolinilo, purinilo, benzotiazolilo e indolilo; opcionalmente sustituido por 2 radicales; donde un radical se selecciona entre carboxi, $-CONHSO_2Me$ y $-CONHR^6$ (donde R^6 se selecciona entre -OMe, hidrógeno, amino y 3-4C alquenilo); y donde el otro radical se selecciona entre

(1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, halo, ciano, nitro, -COO(1-6C)alquilo, -OCO(1-4C)alquilo, (1-6C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, hidroxi(1-4C)alcoxi, (2-4C)alqueniloxi, trifluorometilo, $-CONR^6R^7$, carboxi, $-NHC(O)O$(1-4C)alquilo, $-OCONR^6R^7$, $-C(=NOH)$(1-4C)alquilo, $-C(=NOH)NR^6R^7$, $-S(O)p$(1-4C)alquilo, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$ y heterociclilo], -O(1-6C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba) y -S(O)p(1-4C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba);

R^2 se selecciona entre (1-4C)alquilo, cloro y bromo;

R^3 se selecciona entre hidrógeno, metilo, etilo, cloro, bromo, ciano, trifluorometilo y -COMe;

R^4 se selecciona entre hidrógeno, metilo, etilo, cloro, bromo, ciano y -COMe;

R^5 es hidrógeno o metilo;

R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, alilo, ciclopropilo, -(1-4C)alquilC(O)OMe, amino, -NHMe, $-NMe_2$, (1-4C)alcoxi y -(1-4C)alquilheterociclilo;

R^7 se selecciona independientemente en cada caso entre hidrógeno y (1-4C)alquilo; y p es (independientemente en cada caso) 0, 1 o 2.

En otra incorporación se dispone un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, donde:

Y es H;

W es NR^5;

R^1 se selecciona entre imidazolilo, pirimidinilo, piridinilo, tiazolilo, triazinilo, pirrolilo, tiadiazolilo, tetrazolilo, quinolinilo, purinilo, benzotiazolilo e indolilo; opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre nitro, ciano, -CO(1-4C)alquilo, -COO(1-4C)alquilo, -O(1-4C)alquilo, trifluorometilo, $-CONR^6R^7$, $-N(R^7)COR^6$, fluoro, cloro, bromo, hidroxi, carboxi, (1-4C)alquilo, heterociclilo, -NHC(O)O(1-4C)alquilo, $-C(=NOR^7)$(1-4C)alquilo, $-C(=NOR^7)NR^6R^7$, -S(O)p(1-4C)alquilo (opcionalmente sustituido por hidroxi), -S(O)p(1-4C)alquilCONHR^7 y $-NR^6R^7$;

R^2 se selecciona entre (1-4C)alquilo, cloro y bromo;

R^3 se selecciona entre hidrógeno, metilo, etilo, cloro, bromo, ciano, trifluorometilo y -COMe;

R^4 se selecciona entre hidrógeno, metilo, etilo, cloro, bromo, ciano y -COMe;

R^5 es hidrógeno o metilo;

R^6 y R^7 junto con el nitrógeno al cual están adheridos forman un anillo heterociclilo de 5 o 6 miembros, opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, hidroxi, (1-4C)alcoxi, halo, ciano, nitro, carboxi, hidroxi(1-4C)alquilo, (1-4C)alcoxi(1-4C)alquilo, halo (1-4C)alquilo, difluorometilo, trifluorometilo y trifluorometoxi; y p es (independientemente en cada caso) 0, 1 o 2.

En una incorporación de la invención se dispone un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, donde:

R^1 se selecciona entre R^1a, R^1b, R^1c y R^1d; donde

R^1a es un anillo heterocíclico saturado, parcialmente insaturado o insaturado de 5 o 6 miembros que contiene 1, 2, 3 o 4 heteroátomos

seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga enlaces O-O o S-S), donde un grupo -CH_2- se puede reemplazar opcionalmente por un -C(O)-, un anillo de átomos de sulfuro opcionalmente se puede oxidar para formar el S-óxido(s) y un anillo de átomos de nitrógeno opcionalmente se puede oxidar para formar el N-óxido y donde el citado anillo se puede sustituir opcionalmente por 1, 2 o 3 radicales seleccionados independientemente entre: nitro, ciano, sulfo, formilo, hidroxiiminometilo, (2-6C)alquenilo, -CO(1-6C)alquilo, -COO(1-6C)alquilo trifluorometilo, -$CONR^6R^7$, -$N(R^7)COR^6$, halo, hidroxi, carboxi, (1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, -OCO(1-4C)alquilo, (1-6C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, hidroxi(1-4C)alcoxi, (2-4C)alqueniloxi, -NHC(O)O(1-4C)alquilo, -$NHC(=NH)NR^6R^7$, -$NHC(O)NR^6R^7$, -NHC(O)(1-4C)alquilo, -NHC(O)heterociclilo, -NHC(O)arilo, -NHS(O)p(1-4C)alquilo, -S(O)p(1-4C)alquilo, -$S(O)pNR^6R^7$, -$NHSO_2R^6$, -NR^6R^7 y heterociclilo], (3-6C) cicloalquilo, -O(1-6C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), -S(O)p(1-4C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), heterociclilo, -NHC(O)O(1-4C)alquilo, -$C(=NOR^7)$(1-4C)alquilo, -$C(=NOR^7)NR^6R^7$, -S(O)p(1-4C)alquilCONHR^7, -C(O)NHS(O)p(1-4C)alquilo y –NR^6R^7, donde cualquier grupo arilo o heterociclilo en cualquiera de los anteriores valores para los radicales en R^1a puede sustituirse opcionalmente por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo y carboxi.

R^1b es un anillo bicíclico heterocíclico de 10 miembros que contiene 1, 2 o 4 heteroátomos seleccionados independientemente entre S y N (siempre que dicho anillo no contenga enlaces S-S), donde un grupo -CH_2- se puede reemplazar opcionalmente por un -C(O)- y donde el citado anillo se puede sustituir opcionalmente por 1, 2 o 3 radicales seleccionados independientemente entre los radicales enumerados para R^1a arriba;

R^1c es un anillo fenilo, sustituido por 1, 2 o 3 radicales seleccionados independientemente entre los radicales enumerados para R^1a arriba;

R^1d se selecciona entre -CH_2R^1a y -C(O)R^1a;

R^2 se selecciona entre (1-4C)alquilo, halo y ciano

R^3 se selecciona entre hidrógeno, (1-4C)alquilo, halo, ciano y –CO(1-6C)alquilo;

R^4 se selecciona entre hidrógeno, (1-4C)alquilo, halo y ciano;

R^5 se selecciona entre hidrógeno y (1-4C)alquilo;

R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-4C)alquenilo, (3-6C)cicloalquilo, -(1-4C)alquilC(O)O(1-4C)alquilo, hidroxi, amino, -(N[di(1-4C)alquilo], (1-4C)alcoxi y -(1-4C)alquilheterociclilo.

R^7 se selecciona independientemente en cada caso entre hidrógeno y (1-4C)alquilo;

o R^6 y R^7 pueden junto con el nitrógeno al cual están adheridos formar un anillo heterociclilo de 5 o 6 miembros, opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo; y

p es (independientemente en cada caso) 0, 1 o 2.

En una incorporación de la invención se dispone un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, donde:

R^1 se selecciona entre R^1a, Rb, R^1c y R^1d; donde

R^1a es piridinilo, *N*-oxopiridinilo, pirimidinilo, tiazolilo, tiadiazolilo, tetrazolilo, imidazolilo, triazinilo, pirrolidinilo, tienilo, furanilo, oxadiazolilo, isoxazolilo, oxazolilo o pirrolilo, donde el citado R^1a se puede sustituir opcionalmente por 1, 2 o 3 radicales seleccionados independientemente entre:

nitro, ciano, sulfo, formilo, hidroxiiminometilo, (2-6C)alquenilo, -CO(1-6C)alquilo, -COO(1-6C)alquilo trifluorometilo, -CONR^{6}R^7, -N(R^7)COR^6, halo, hidroxi, carboxi, (1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, -OCO(1-4C)alquilo, (1-6C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, hidroxi(1-4C)alcoxi, (2-4C)alqueniloxi, -NHC(O)O(1-4C)alquilo, -NHC(=NH)NR^{6}R^7, -NHC(O)NR^{6}R^7, -NHC(O)(1-4C)alquilo, -NHC(O)tetrahidrofuranilo, -NHC(O) fenilo, -NHS(O)p(1-4C)alquilo, -S(O)p(1-4C)alquilo, -

S(O)pNR^{6}R^7, -NHSO$_2$R^6, -NR^{6}R^7, morfolino, 1,3-oxo-1,3-dihidro-2H-isoindolilo y 1,3-dioxolanil], ciclopropilo, -O(1-6C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), -S(O)p(1-4C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), tetrazolilo, 2-oxo-1,3,4-oxadiazolilo, 1,2,4-oxadiazolilo, morfolino, piperazinilo, pirrolidinilo, -NHC(O)O(1-4C)alquilo, -C(=NOR^7)(1-4C)alquilo, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alquilCONHR^7, -C(O)NHS(O)p(1-4C)alquilo y -NR^{6}R^7;

donde cualquier fenilo, tetrahidrofuranilo, morfolino, 1,3-dioxo-1,3-dihidro-2H-isoindolilo,1,3-dioxolanilo, tetrazolilo, 2-oxo-1,3,4-oxadiazolilo, 1,2,4-oxadiazolilo, morfolino, piperazinilo, pirrolidinilo, en cualquiera de los anteriores valores para los radicales en R^{1}a puede sustituirse opcionalmente por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo y carboxi;

R^{1}b es R^{1}b es quinolinilo, purinilo, benzotiazolilo, indolilo, 4-oxoquinolinilo, 2,7-naftiridinilo o quinazolinilo y donde el citado R^{1}b se puede sustituir opcionalmente por 1, 2 o 3 radicales seleccionados independientemente entre los radicales enumerados para R^{1}a arriba;

R^{1}c es un anillo fenilo, sustituido por 1, 2 o 3 radicales seleccionados independientemente entre los radicales enumerados para R^{1}a arriba;

R^{1}d se selecciona entre -CH$_2$R^{1}a y -C(O)R^{1}a;

R^2 se selecciona entre metilo, etilo, isopropilo, cloro y ciano;

R^3 se selecciona entre hidrógeno, metilo, etilo, cloro, bromo, ciano y -COMe;

R^4 se selecciona entre hidrógeno, cloro, metilo, etilo y ciano;

R^5 es hidrógeno o metilo;

R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-4C)alquenilo, ciclopropilo, -(1-4C)alquilC(O)O(1-4C)alquilo, hidroxi, amino, -N[di(1-4C)alquilo], (1-4C)alcoxi y -(1-4C)alquilmorfolino;

R^7 se selecciona independientemente en cada caso entre hidrógeno y (1-4C)alquilo;

o R^6 y R^7 pueden junto con el nitrógeno al cual están adheridos formar un piperazinilo o un morfolino opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo;
p es (independientemente en cada caso) 0, 1 o 2.

Los compuestos preferidos de la invención son los compuestos de los ejemplos, cada uno de los cuales provee otro aspecto independiente de la invención. En otros aspectos, la presente invención también comprende dos o más compuestos cualquiera de los Ejemplos.

Los Ejemplos particulares son los Ejemplos 11, 20, 109, 114, 140, 141, 151, 176, 181, 208, 225, 227, 228, 278, 285, 292, 342, 343 y 344 o una sal farmacéuticamente aceptable de los mismos.

Proceso

En otro aspecto, la presente invención dispone un proceso para preparar un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo.

Si no se encuentran disponibles en el comercio, los materiales de partida requeridos para los procedimientos como los descritos arriba se pueden preparar mediante unos procedimientos que se seleccionan entre unas técnicas estándar de la química orgánica que son análogas a la síntesis de compuestos conocidos y de estructura similar, o por técnicas que son análogas al procedimiento descrito arriba o a los procedimientos descritos en los ejemplos.

Se anota que muchos de los materiales de partida para los métodos sintéticos como se describen arriba están disponibles en el comercio y/o están ampliamente reportados en la literatura científica, o se pueden preparar a partir de unos compuestos disponibles en el comercio empleando adaptaciones de los procesos reportados en la literatura científica. Igualmente se remite el lector a Advanced Organic Chemistry, 4ta Edición, por Jerry March, publicado por John Wiley & Sons 1992, para una guía general sobre las condiciones de reacción y los reactivos.

Igualmente se apreciará que en algunas de las reacciones citadas en la presente, puede ser necesario/deseable proteger cualquier grupo sensible en

los compuestos. Las instancias en las cuales la protección sea necesaria o deseable son conocidas por aquellos con destreza en el arte, como lo son los métodos de protección apropiados. Se pueden emplear unos grupos de protección convencionales de conformidad con la práctica estándar (con fines ilustrativos consultar T.W. Greene, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991).

Ejemplos de un grupo de protección apropiado para un grupo hidroxi son por ejemplo, un grupo acilo, por ejemplo un grupo alcanol como acetilo, un grupo aroilo, por ejemplo benzoilo, un grupo sililo como trimetilsililo o un grupo arilmetilo, por ejemplo bencilo. Las condiciones de desprotección para los grupos de protección citados arriba necesariamente van a variar de acuerdo con el grupo de protección escogido. Así, por ejemplo, un grupo acilo como un alcanol o un grupo aroilo se puede extraer, por ejemplo, mediante hidrólisis con una base apropiada como un hidróxido de metal alcalino, por ejemplo litio o hidróxido de sodio. Alternativamente se puede extraer un grupo sililo como trimetilsililo, por ejemplo, por fluoruro o mediante ácido acuoso; o un grupo arilmetilo como un grupo bencilo se puede extraer, por ejemplo, mediante hidrogenación en presencia de un catalizador como paladio sobre carbono.

Un grupo de protección apropiado para un grupo amino, por ejemplo R^x de fórmula (2a) abajo, es por ejemplo, un grupo acilo, por ejemplo un grupo alcanol como acetil, un grupo alcoxicarbonilo, por ejemplo un grupo metoxicarbonilo, etoxicarbonilo o *t*-butoxicarbonilo, un grupo arilmetoxicarbonilo, por ejemplo benciloxicarbonilo, o un grupo aroilo, por ejemplo benzoilo. Las condiciones de desprotección para los grupos de protección anteriores necesariamente varían según el grupo de protección elegido. Así por ejemplo, un grupo acilo como un alcanoilo o un grupo alcoxicarbonilo o un grupo aroilo se puede extraer por ejemplo, mediante hidrólisis con una base apropiada como un hidróxido de metal alcalino, por ejemplo litio o hidróxido de sodio. Alternativamente se puede extraer un grupo acilo como un grupo *t*-butoxicarbonilo, por ejemplo mediante el

tratamiento con un ácido apropiado como el ácido clorhídrico, sulfúrico o fosfórico o el ácido trifluoroacético y se puede extraer un grupo arilmetoxicarbonilo como un grupo benciloxicarbonilo, por ejemplo, mediante la hidrogenación sobre un catalizador como paladio sobre carbono, o mediante el tratamiento con un ácido de Lewis por ejemplo boron tris (trifluoroacetato). Un grupo de protección alterno y apropiado para un grupo de amino primario es por ejemplo un grupo ftaloilo que se puede extraer mediante el tratamiento con una alquilamina, por ejemplo dimetilaminopropilamina o 2-hidroxietilamina o con hidrazina.

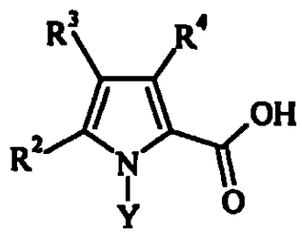
Los grupos de protección se pueden extraer en cualquier etapa que sea conveniente en la síntesis empleando unas técnicas convencionales bien conocidas en el arte de la química, o se pueden extraer durante un paso posterior de la reacción o preparación.

Un químico orgánico con destrezas podrá emplear y adaptar la información contenida y referenciada en las referencias citadas arriba y en los ejemplos de las mismas y en los ejemplos de la presente para obtener los materiales y productos de partida necesarios.

Por lo tanto, la presente invención también dispone que los compuestos de fórmula (I) y las sales farmacéuticamente aceptables de los mismos, se pueden preparar por medio de un proceso como sigue (donde las variables son como se define arriba, salvo si se especifica en contrario):

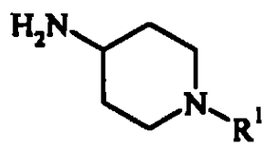
Otro aspecto de la presente invención dispone un proceso para preparar un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo proceso este (donde R^2,R^3,R^4 son, salvo si se especifica en contrario, como se define en la fórmula (I)) que comprende:

a) hacer reaccionar un ácido de fórmula (2):



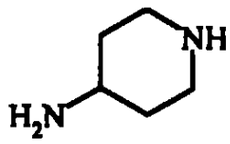
(2)

(donde Y es H o un grupo de protección apropiado) o un derivado activado del mismo; con una amina de fórmula (3); o



(3)

b) hacer reaccionar un ácido de fórmula (2) o un derivado activado del mismo, con una amina de fórmula (4) (protegido en forma apropiada en el nitrógeno de piperidina), extraer el grupo de protección, seguido por la reacción con un compuesto de fórmula (5);

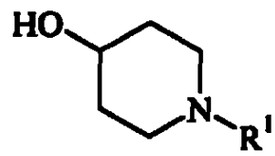


(4)

(5)

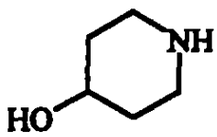
donde X es un grupo desplazable; o

c) hacer reaccionar un ácido de fórmula (2) o un derivado activado del mismo, con un alcohol de fórmula (6); o



(6)

d) hacer reaccionar un ácido de fórmula (2) o un derivado activado del mismo, con un alcohol de fórmula (7) (protegido en forma apropiada en el nitrógeno de piperidina), extraer el grupo de protección, seguido por la reacción con un compuesto de fórmula (8);



(7)

(8)

donde X es un grupo desplazable; y posteriormente, en caso de ser necesario:

i) convertir un compuesto de fórmula (I) en otro compuesto de fórmula (I);

ii) extraer cualquier grupo de protección;

iii) formar una sal farmacéuticamente aceptable.

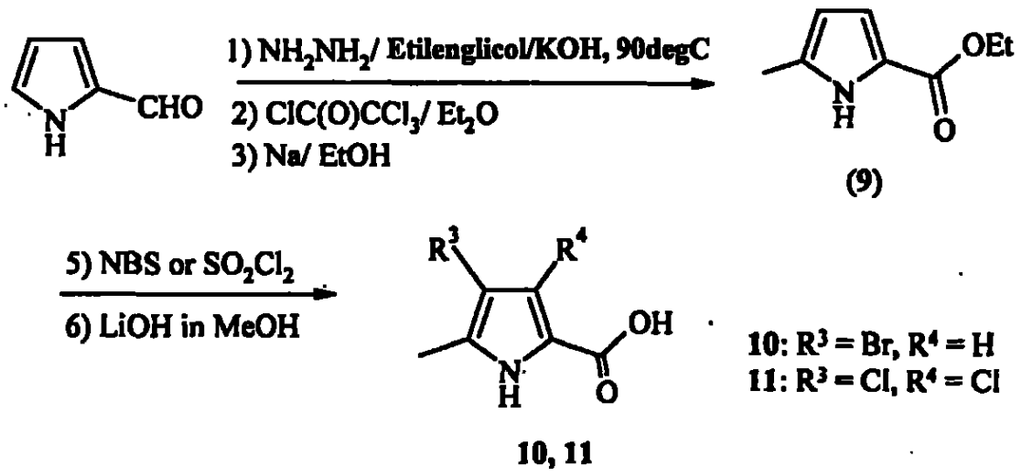
X es un grupo desplazable, unos valores apropiados para X son por ejemplo, un grupo cloro, bromo o iodo.

Las condiciones específicas de reacción para la anterior reacción son las siguientes.

Los ácidos de fórmula (2) y las aminas de fórmula (3) o de fórmula (4) se pueden acoplar en presencia de un reactivo de acople apropiado. Se pueden utilizar unos reactivos de peptida estándar de acople conocidos en el arte, o por ejemplo HATU, clorhidrato de carbonildiimidazol, 1-etil-3-(3-dimetilaminopropil)carbodi-imida (EDCI) y diciclohexil-carbodiimida (DCCI), opcionalmente en presencia de un catalizador como 1-hidroxi-7-azabenzotriazol, HOAT, dimetilaminopiridina o 4-pirrolidinopiridina, opcionalmente en presencia de una base por ejemplo trietilamina, di-isopropiletilamina, piridina, o 2,6-di-alquil-piridinas como 2,6-lutidina o 2,6-di-tert-butilpiridina. Unos solventes apropiados incluyen dimetilacetamida, diclorometano, N-metilpirrolidona, tetrahidrofurano y dimetilformamida. La reacción de acople se puede realizar en forma conveniente a una temperatura en el rango de 0 °C a 40 °C.

Unos derivados de los ácidos de fórmula (2) activados en forma apropiada incluyen ésteres activos, por ejemplo pentafluorofenilo ésteres, hálidos ácidos, por ejemplo cloruros ácidos y fluoruros ácidos. La reacción de esta clase de compuestos con aminas es bien conocida en el arte, por ejemplo se pueden hacer reaccionar en presencia de una base, como aquellas descritas arriba y en un solvente apropiado, como aquellos descritos arriba. La reacción se puede realizar en forma conveniente a una temperatura en el rango de 0°C a 40°C.

Se puede preparar un compuesto de fórmula (2) mediante la funcionalización de un compuesto de pirrol sustituido que se encuentra disponible en el comercio o son compuestos conocidos o se preparan por medio de unos procesos conocidos en el arte, por ejemplo por procesos como los que se muestran en el Esquema 1 para Y = H.



Esquema 1

Por ejemplo, se pueden preparar compuestos de fórmula (10) (R^3 es Br y R^4 es H) mediante la bromación de un compuesto de fórmula (9) con un agente de bromación como N-bromosuccinimida y otros reactivos de bromación conocidos en el arte, en un solvente orgánico inerte y clorado como diclorometano o 1,2-dicloroetano, seguido por el tratamiento con una base acuosa como hidróxido de sodio acuoso.

Por ejemplo, se pueden preparar compuestos de fórmula (11) (R^3 y R^4 son ambos cloro) mediante la clorinación de un compuesto de fórmula (9) con un agente de clorinación como cloruro de sulfurilo y otros reactivos de clorinación conocidos en el arte en un solvente orgánico inerte clorado como tetracloruro de carbono, diclorometano o 1,2-dicloroetano seguido por el tratamiento con una base acuosa, como hidróxido acuoso de litio en metanol.

Alternativamente se puede emplear dietiléter en vez del solvente clorado. El compuesto mono clorado se puede formar de manera similar.

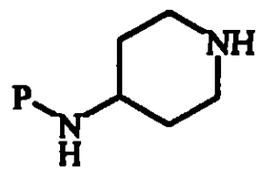
Convenientemente, se emplea el tetracloruro de carbono (CCl_4) como un solvente puesto que el compuesto (11) se precipita de la mezcla de la

reacción. El proceso de conversión del compuesto (9) al compuesto (11) empleando cloruro de sulfuro en tetracloruro de carbono es novedoso y además forma otro aspecto independiente de la invención.

Igualmente se puede preparar el compuesto (9) por medio de un procedimiento de una sola preparación siguiendo el procedimiento descrito en Curran, T. P.; Keaney, M. T., ***J Org Chem*** 1996, 61 (25), 9068.

Los compuestos de fórmula (2) que contienen otros grupos funcionales se pueden preparar mediante unos procesos análogos a aquellos ilustrados en el Esquema I arriba, o por medio de unos procesos conocidos en el arte (consultar por ejemplo Heterocyclic Chemistry, 4ta Ed., J. A. Joule y K. Mills, Blackwell Science; Heterocyclic Chemistry, T. L. Gilchrist, Adison Wesley Longman, 1997) o por medio de unos procesos ilustrados en los ejemplos a continuación.

Se preparan los compuestos de fórmula (3) mediante unos procesos conocidos en el arte y se pueden obtener acoplando un compuesto de fórmula (4) (debidamente protegido en el nitrógeno de la amina como se muestra abajo, fórmula (4-P)) con un compuesto de fórmula (5).



(4-P)

Por lo tanto una persona con destreza en el arte reconoce que con el fin de formar el compuesto de fórmula (I):

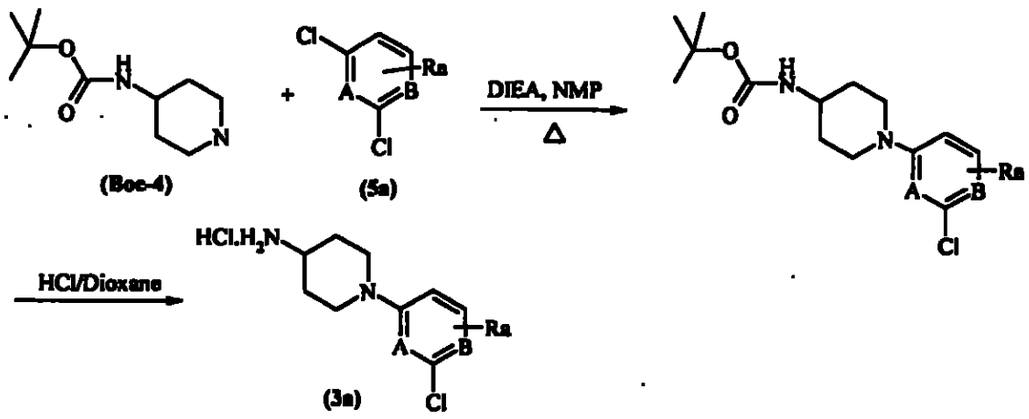
Se hacen reaccionar conjuntamente unas versiones debidamente protegidas de los compuestos de fórmula (4) y (5) para formar un compuesto de fórmula (3) el cual entonces (una vez se desprotege, de ser necesario) se acopla al compuesto de fórmula (2);

o una versión debidamente protegida del compuesto de fórmula (4) se acopla al compuesto de fórmula (2) y luego (una vez se desprotege, en caso de ser necesario) se hace reaccionar con el compuesto de fórmula (5).

Los compuestos de fórmula (4) están disponibles en el comercio, o se conocen en el arte, o se pueden fabricar mediante procesos conocidos en el arte.

Los compuestos de fórmula (5) están disponibles en el comercio, o se conocen en el arte, o se pueden fabricar mediante procesos conocidos en el arte.

Por ejemplo cuando el compuesto de fórmula (5) (X = Cl) es un compuesto de fórmula (5a), se puede acoplar con el (4) como se muestra en el Esquema 2 (donde el grupo de protección P del grupo amina es un grupo Boc).



Esquema 2

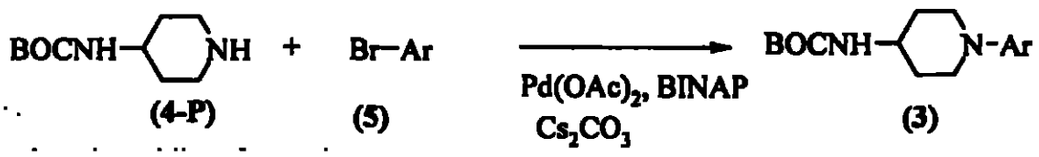
A y B se seleccionan entre carbono y nitrógeno, por lo tanto un compuesto de fórmula (5a) puede ser un derivado de fenilo, piridina o pirimidina.

Ra es un radical de un anillo que cae en la definición de la fórmula (I).

Se pueden manufacturar compuestos de fórmula (3) donde R^1 es otro heterociclo, por ejemplo triazina, tiazol y tiadiazol mediante procesos análogos.

Unos grupos de protección apropiados para la reacción de acople que se muestra arriba son por ejemplo grupos de protección Boc (tert-butoxicarbonilo) u otros grupos de protección apropiados que se conocen en el arte o que se citaron arriba.

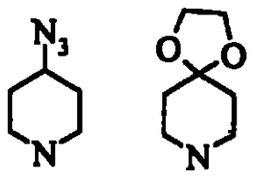
Se pueden fabricar unos compuestos de fórmula (3) donde R^1 es fenilo, o un heterociclo como por ejemplo furano, tiofeno o piridina, acoplando una versión protegida de un compuesto de fórmula (4) (es decir un compuesto de fórmula (4-P)) con un compuesto apropiado de fórmula (5), por ejemplo donde X es halo como Br, empleando una reacción de aminación catalizada por paladio conocida en el arte. (Consultar por ejemplo Hartwig, J.F.; *Angew. Chem. Int.* Ed, **1998**, 37, 2046-2067, *Topics in Chemistry*, 219, **2002**, Alex R. Muci; Stefen L. Buchwald; Artis Klapars y colaboradores. *J. Am. Chem. Soc*, **2001**, 123, 7727-7729). Este proceso se ilustra en el siguiente Esquema.



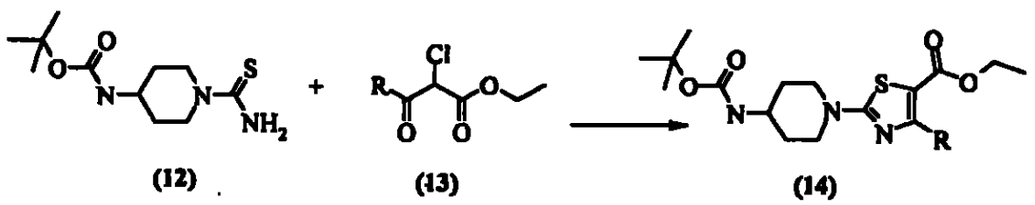
(4-P) (5) (3)

Ar = fenilo, piridina, furano, tiofeno tolueno 100oC

Alternativamente, se puede emplear un precursor de un compuesto de fórmula (4), por ejemplo, derivados de azida o acetal como los que se muestran abajo.



También se pueden preparar compuestos de fórmula (3) donde R^1 es otro heterociclo, por ejemplo tiazol, mediante una reacción de ciclización de un derivado apropiado (N- protegido) de un compuesto de fórmula (4). Este proceso se ilustra en el Esquema abajo para R^1 es tiazol, donde se hace reaccionar un derivado de tioúrea de un compuesto de fórmula (12) con un derivado de halodicarbonilo (13) (donde R es un radical opcional en R^1 como se definió arriba) para obtener el compuesto N-protegido de fórmula (14). Apropiadamente, dicha reacción se puede efectuar en un solvente de alcohol como metanol o etanol, a temperaturas elevadas. El grupo de N-protección (un grupo BOC en el esquema ilustrativo abajo) se puede entonces extraer bajo unas condiciones apropiadas conocidas en el arte.



(12) (13) (14)

La reacción de un compuesto de fórmula (2) con un compuesto de fórmula (6) (proceso c) o un compuesto de fórmula (7) (proceso d) arriba se puede efectuar por ejemplo empleando unos reactivos de acople como trifenilfosfina y dietilazodicarboxilato (DEAD), u otros reactivos bien conocidos en el arte para estimular la formación de enlaces de ésteres.

Se puede formar un compuesto de fórmula (6) mediante la reacción de un compuesto de fórmula (7) con un compuesto de fórmula (8) como se describe arriba.

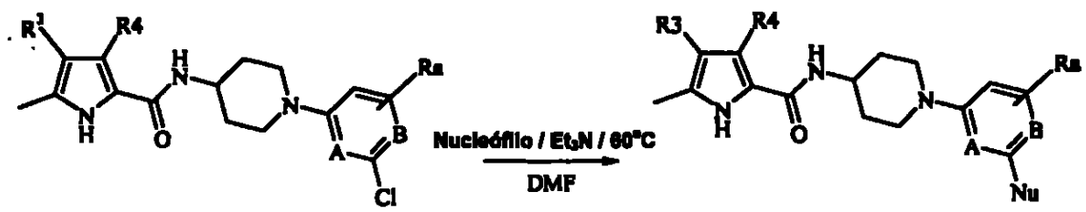
Donde un compuesto de fórmula (8) es X-R^1d, X-R^1e o X-R^1f (donde R^1d a R^1f son como se define arriba y contienen un grupo CH_2), se puede efectuar un acople apropiado de un compuesto de fórmula (4) o (7) (protegido según lo apropiado) empleando una reacción de reducción de amina, empleando un reactivo como triacetoxiborohidruro sódico, por ejemplo como se muestra en el Esquema 3 para R^1d:

(4)

P es un grupo de protección

Esquema 3

Los compuestos de fórmula (I) se pueden combinar con nucleófilos (por ejemplo R-SH y R-OH y R-NH_2) de acuerdo con el Esquema 4 para formar otros compuestos de fórmula 1:



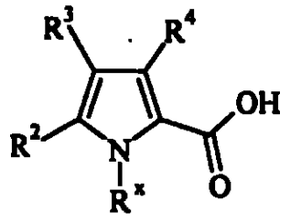
Esquema 4

Ra es un radical de un anillo que cae en la definición de la fórmula (I).

Alternativamente, donde B en el Esquema 4 arriba es carbono, la reacción equivalente se puede desarrollar donde el nucleófilo es ROH, en presencia de metales alcalinos como sodio o potasio, bajo condiciones de reflujo.

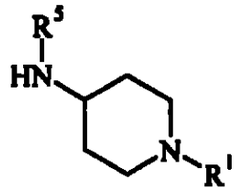
En otro aspecto de la invención, se dispone un proceso para preparar un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, proceso este (donde los grupos variables son, salvo si se especifica en contrario, como se define en la fórmula (I)) comprende:

a). para compuestos de fórmula (I) donde W es NR^5; hacer reaccionar un ácido de fórmula (2a):



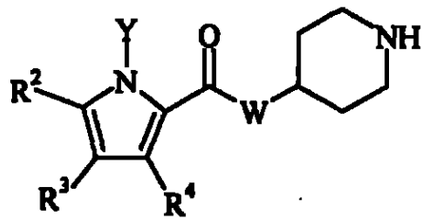
(2a)

(donde R^x es hidrógeno o un grupo de protección apropiado) o un derivado activado del mismo; con una amina de fórmula (3a); o



(3a)

b) hacer reaccionar un compuesto de fórmula (4a):



(4a)

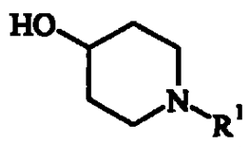
con un compuesto de fórmula (5a):

$$X\text{-}R^1$$

(5a)

donde X es un grupo desplazable;

c) para compuestos de fórmula (I) donde W es O; hacer reaccionar un ácido de fórmula (2a) o un derivado activado del mismo, con un alcohol de fórmula (6a); o



(6a)

y posteriormente, de ser necesario:

i) convertir un compuesto de fórmula (I) en otro compuesto de fórmula (I);

ii) extraer cualquier grupo de protección;

iii) formar una sal farmacéuticamente aceptable.

X es un grupo desplazable, unos valores apropiados para X son por ejemplo, un grupo cloro, bromo o iodo.

Las condiciones para el proceso y los esquemas genéricos para la síntesis de los intermedios se dan en la presente más arriba.

Se apreciará que se pueden introducir algunos de los diferentes radicales de un anillo en los compuestos de la presente invención, por ejemplo los radicales en el anillo R^1, ilustrados como Ra en los Esquemas arriba, mediante una sustitución aromática estándar o por unas reacciones generadas por unas modificaciones convencionales funcionales de los

grupos bien sea antes o inmediatamente después de los procesos citados arriba, y como tal se incluyen en el aspecto del proceso de la invención. Los reactivos empleados para introducir dichos radicales en los anillos están disponibles en el comercio o se fabrican mediante unos procesos conocidos en el arte. Alternativamente, los materiales de partida donde R^1 ya está sustituido pueden estar disponibles en el comercio.

La introducción de los radicales en el anillo de R^1 puede convertir un compuesto de fórmula (I) en otro compuesto de fórmula (I). Dichas reacciones y modificaciones incluyen, por ejemplo, la introducción de un radical mediante una reacción de sustitución aromática, la reducción de radicales, la alquilación de los radicales, la oxidación de los radicales, la esterificación de los radicales, la amidación de los radicales, la formación de anillos heteroarilos. Los reactivos y las condiciones de reacción para dichos procedimientos son muy conocidos en el arte de la química. Ejemplos particulares de la reacción de sustitución aromática incluyen la introducción de alcóxidos, reacciones de diazotización seguidas por la introducción de un grupo tiol, un grupo alcohol, un grupo halógeno. Ejemplos de modificaciones incluyen; oxidación de alquiltio a alquilsulfinilo o alquilsulfonilo.

La extracción de cualquier grupo de protección y la formación de una sal farmacéuticamente aceptable son parte de las destrezas de un químico orgánico común empleando unas técnicas estándar. Arriba se agregó mayor información sobre estos pasos.

Cuando se requiere una forma ópticamente activa de un compuesto de la invención, se puede obtener mediante uno de los procesos descritos arriba empleando un material de partida ópticamente activo (formado por ejemplo, por la inducción asimétrica de un paso de reacción apropiado), o mediante la resolución de una forma racémica del compuesto o intermedio empleando un procedimiento estándar, o por medio de una separación cromatográfica de los diastereoisómeros (cuando se producen). Las técnicas enzimáticas también pueden ser útiles para la preparación de unos compuestos y/o intermedios ópticamente activos.

De forma similar, cuando se requiere un regioisómero puro de un compuesto de la invención se puede obtener siguiendo uno de los procedimientos descritos arriba empleando un regioisómero puro como material de partida, o mediante la resolución de una mezcla de los regioisómeros o intermedios utilizando un procedimiento estándar.

De acuerdo con otra característica de la invención, se dispone un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo para su utilización en un método para el tratamiento del cuerpo humano o animal mediante terapia.

Encontramos que los compuestos de la presente invención inhiben la ADN girasa bacterial y por lo tanto son de interés por sus efectos antibacteriales.

De acuerdo con otra característica de la presente invención, se dispone un método para producir un efecto antibacterial en un animal de sangre caliente, como el hombre, que requiera el citado tratamiento, que comprende administrar al citado animal una cantidad efectiva de un compuesto de la presente invención, o una sal farmacéuticamente aceptable del mismo.

De acuerdo con otra característica de la invención, se dispone un método para la inhibición de la ADN girasa bacterial en un animal de sangre caliente, como un ser humano, que requiera el citado tratamiento que comprende administrar al citado animal una cantidad efectiva de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo como se define arriba.

De acuerdo con otra característica de la invención, se dispone un método para tratar una infección bacterial en un animal de sangre caliente, como un ser humano, que requiera el citado tratamiento que comprende administrar al citado animal una cantidad efectiva de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo como se define arriba.

Otra característica de la presente invención es un compuesto de fórmula (I) y sales farmacéuticamente aceptables del mismo para su

utilización como un medicamento. En forma apropiada, el medicamento es un agente antibacterial.

Convenientemente este es un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, para su utilización como un medicamento para producir un efecto antibacterial en un animal de sangre caliente como un ser humano.

Convenientemente este es un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, para su utilización como un medicamento para inhibir la ADN girasa bacterial en un animal de sangre caliente, como un ser humano.

Particularmente este es un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, para su utilización como un medicamento para tratar una infección bacterial en un animal de sangre caliente como un ser humano.

De acuerdo con otro aspecto de la invención, se dispone la utilización de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo en la manufactura de un medicamento para su utilización en la producción de un efecto antibacterial en un animal de sangre caliente como un ser humano.

De acuerdo con otro aspecto de la invención, se dispone la utilización de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo en la manufactura de un medicamento para su utilización en la inhibición de la ADN girasa bacterial en un animal de sangre caliente como un ser humano.

Por lo tanto de acuerdo con otro aspecto de la invención, se dispone la utilización de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo en la manufactura de un medicamento para su utilización en el tratamiento de una infección bacterial en un animal de sangre caliente como un ser humano.

De acuerdo con otro aspecto de la invención, se dispone un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo para su

utilización en la producción de un efecto antibacterial en un animal de sangre caliente como un ser humano.

De acuerdo con otro aspecto de la invención, se dispone un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo para su utilización en la inhibición de la ADN girasa bacterial en un animal de sangre caliente como un ser humano.

Por lo tanto de acuerdo con otro aspecto de la invención, se dispone un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo para su utilización en el tratamiento de una infección bacterial en un animal de sangre caliente como un ser humano.

Con el fin de utilizar un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, (a continuación en esta sección relacionada con la composición farmacéutica "un compuesto de esta invención") para el tratamiento terapéutico (incluyendo el profiláctico) de los mamíferos incluyendo los humanos, en particular en el tratamiento de infecciones, normalmente se formula de acuerdo con la práctica farmacéutica estándar como una composición farmacéutica.

Por lo tanto en otro aspecto, la presente invención dispone una composición farmacéutica que comprende un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo y un diluyente o excipiente farmacéuticamente aceptable.

De acuerdo con otro aspecto de la invención, se dispone una composición farmacéutica que comprende un compuesto de fórmula (I) como se define arriba o una sal farmacéuticamente aceptable del mismo, en asocio con un diluyente o excipiente farmacéuticamente aceptable para su utilización en la inhibición de ADN girasa bacterial en un animal de sangre caliente, como un ser humano.

De acuerdo con otro aspecto de la invención, se dispone una composición farmacéutica que comprende un compuesto de fórmula (I) como se define arriba o una sal farmacéuticamente aceptable del mismo, en asocio con un diluyente o excipiente farmacéuticamente aceptable para su

utilización en el tratamiento de una infección bacterial en un animal de sangre caliente, como un ser humano.

Las composiciones de la invención pueden ser en una forma apropiada para uso oral (por ejemplo como tabletas, pastillas, cápsulas blandas o duras, suspensiones acuosas o aceitosas, emulsiones, polvos dispersables o gránulos, jarabes o elíxires), para uso tópico (por ejemplo como cremas, ungüentos, geles, o soluciones acuosas o aceitosas o suspensiones), para administración mediante inhalación (por ejemplo como un polvo divido en partículas muy finas o un aerosol líquido), para administración mediante insuflación (por ejemplo como un polvo dividido en partículas muy finas) o para administración parenteral (por ejemplo como una solución estéril acuosa o aceitosa para dosis intravenosas, subcutáneas, intramusculares o como un supositorio para dosis rectales).

Las composiciones de la invención se pueden obtener mediante unos procedimientos convencionales, empleando unos excipientes farmacéuticos convencionales, bien conocidos en el arte. Por lo tanto, las composiciones que se van a administrar en forma oral pueden contener por ejemplo, uno o varios agentes colorantes, edulcorantes, saborizantes y/o conservantes.

Unos excipientes apropiados y farmacéuticamente aceptables para una formulación en tabletas incluyen, por ejemplo, unos diluyentes inertes como lactosa, carbonato de sodio, fosfato de calcio o carbonato de calcio; unos agentes de granulado y desintegración como almidón de maíz o ácido algénico; agentes aglutinantes como almidón; agentes lubricantes como estearato de magnesio, ácido esteárico o talco; agentes conservantes como etilo o propilo p-hidroxibenzoato y anti-oxidantes, como ácido ascórbico. Las formulaciones en tabletas pueden estar recubiertas o sin recubrir bien sea para modificar su desintegración y posterior absorción del ingrediente activo en el tracto gastrointestinal; o para mejorar su estabilidad y/o presentación, en cualquiera de los casos, empleando unos agentes de recubrimiento convencionales y unos procedimientos bien conocidos en el arte.

Las composiciones para uso oral pueden ser en forma de cápsulas de gelatina dura donde el ingrediente activo se mezcla con un diluyente sólido inerte, por ejemplo, carbonato de calcio, fosfato de calcio o caolín; o como una cápsula de gelatina blanda donde el ingrediente activo se mezcla con agua o un aceite como aceite de maní, parafina líquida o aceite de oliva.

Generalmente las suspensiones acuosas contienen el ingrediente activo en forma de polvo muy fino junto con uno o varios agentes de suspensión como carboximetilcelulosa sódica, metilcelulosa, hidroxipropilmetilcelulosa, alginato sódico, polivinil-pirrolidona, goma de tragacanto y goma de acacia; agentes de dispersión o hidratación como lecitina o productos de condensación como un óxido de alquileno con ácidos grasos (por ejemplo estearato de polioxetileno), o productos de condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo heptadecaetilenoxicetanol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y un hexitol como monooleato de polioxietileno sorbitano, o productos de condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo heptadecaetilenoxicetanol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y un hexitol como monooleato de polioxietileno sorbitano, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo monooleato de sorbitano polietileno. Las suspensiones acuosas también pueden contener uno o varios conservantes (como etilo o propilo p-hidroxibenzoato, anti-oxidantes (como ácido ascórbico), agentes colorantes, agentes saborizantes, y/o agentes edulcorantes (como sacarosa, sacarina o aspartame).

Se pueden formular suspensiones aceitosas mediante la suspensión del ingrediente activo en un aceite vegetal (como aceite de arachis, aceite de oliva, aceite de ajonjolí o aceite de coco) o en un aceite mineral (como parafina líquida). Las suspensiones aceitosas también pueden contener un agente espesante como cera de abeja, parafina dura o cetilo alcohol. Se pueden agregar agentes edulcorantes como los descritos arriba y agentes

saborizantes para obtener una preparación agradable al paladar. Estas composiciones se pueden conservar mediante la adición de un anti-oxidante como el ácido ascórbico.

Los polvos dispersables y los gránulos apropiados para la preparación de una suspensión acuosa mediante la adición de agua por lo general contienen el ingrediente activo junto con otro agente dispersante o hidratante, el agente de suspensión y uno o varios conservantes. Unos agentes de dispersión o hidratación y de suspensión apropiados se ejemplifican por aquellos ya citados arriba. También se pueden encontrar presentes unos excipientes como agentes edulcorantes, saborizantes y colorantes.

Las composiciones farmacéuticas de la invención también pueden ser en forma de emulsiones de aceite en agua. La fase aceitosa puede ser un aceite vegetal, como aceite de oliva o de arachis, un aceite mineral como por ejemplo una parafina líquida o una combinación de cualquiera de estos. Unos agentes emulsificantes apropiados pueden ser por ejemplo, gomas naturales como la goma de acacia o la goma de tragacanto, unas fosfatidas naturales como la soya, la lecitina, un éster, o unos ésteres parciales derivados de ácidos grasos y anhídridos de hexitol (por ejemplo monooleato de sorbitano) y productos de condensación de los citados ésteres parciales con óxido de etileno como monooleato de polioxietileno sorbitano. Las emulsiones también pueden contener agentes edulcorantes, saborizantes y conservantes.

Se pueden formular jarabes y elíxires con agentes edulcorantes como glicerol, propilenglicol, sorbitol, aspartame o sacarosa y también pueden contener un agente demulcente, conservante, saborizante y/o colorante.

Las composiciones farmacéuticas también pueden ser en forma de una solución inyectable estéril acuosa o aceitosa que se puede formular de acuerdo con unos procedimientos conocidos empleando uno o varios de los agentes de dispersión o de hidratación apropiados y unos agentes de suspensión, que ya fueron citados arriba. Una preparación inyectable estéril también puede ser una solución inyectable estéril o una suspensión en un

diluyente o solvente no tóxico y aceptable para uso parenteral, por ejemplo una solución en 1,3-butanediol.

Las composiciones para la administración mediante inhalación pueden ser en forma de un aerosol presurizado convencional dispuesto para dispensar el ingrediente activo como un aerosol que contiene unas gotículas sólidas o líquidas finamente divididas. Se pueden utilizar unos aerosoles propulsores convencionales como unos hidrocarburos fluorados volátiles o hidrocarbonos y el dispositivo del aerosol está dispuesto en forma conveniente para dispensar una cantidad medida del ingrediente activo.

Para mayor información sobre formulación, se remite el lector al Capítulo 25.2 del Volumen 5 de Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

La cantidad de ingrediente activo que se combina con uno o varios excipientes para producir una sola forma de dosis necesariamente deberá variar dependiendo del anfitrión tratado y de la vía de administración en particular. Por ejemplo, una formulación para una administración oral a los humanos generalmente va a contener por ejemplo, de 0.5 mg a 2 g de agente activo combinado con una cantidad apropiada y conveniente de excipientes que puede variar de alrededor de 5 a alrededor de 98 por ciento por peso de la composición total. Las formas de unidad de dosis generalmente van a contener alrededor de 1 mg a alrededor de 500 mg de un ingrediente activo. Para mayor información sobre Vías de Administración y Regímenes de Dosis, se remite el lector al Capítulo 25.3 en el Volumen 5 de Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

Además de los compuestos de la presente invención, la composición farmacéutica de esta invención también puede contener o se puede co-administrar (en forma simultánea, secuencial o separada) con uno o varios fármacos conocidos seleccionados entre otros agentes antibacteriales clínicamente útiles (por ejemplo, macrolidas, quinolonas, β-lactamos o aminoglicosidas) y/u otros agentes antiinfecciosos (por ejemplo, un antimicótico, triazol o amfotericina). Estos pueden incluir carbapenemos,

por ejemplo meropenemo o imipenemo, para ampliar la efectividad terapéutica. Los compuestos de esta invención también pueden contener o se pueden co-administrar con productos proteicos bactericidas/incrementadores de la permeabilidad (BPI) o unos inhibidores de la bomba de eflujo para mejorar la actividad contra las bacterias gram negativas y las bacterias resistentes a los agentes antimicrobianos.

Como se anotó arriba, el tamaño de la dosis requerida para el tratamiento terapéutico o profiláctico de una enfermedad en particular necesariamente deberá variar de acuerdo con el anfitrión tratado, la vía de administración y la gravedad de la enfermedad que se está tratando. Preferiblemente se utiliza una dosis diaria en el rango de 1-50 mg/kg. Sin embargo la dosis diaria necesariamente deberá variar dependiendo del anfitrión tratado, la vía de administración en particular que se emplee y la gravedad de la enfermedad que se está tratando. Por lo tanto, el facultativo tratante quien está tratando una enfermedad en particular puede determinar una dosis óptima.

Además de su uso en la medicina terapéutica, los compuestos de fórmula (I) y sus sales farmacéuticamente aceptables también son útiles como herramientas farmacológicas para el desarrollo y la estandarización de sistemas de pruebas *in-vitro* e *in-vivo* para la evaluación de los efectos de los inhibidores de la ADN girasa en animales de laboratorio como gatos, perros, conejos, monos, ratas y ratones, como parte de la investigación en busca de nuevos agentes terapéuticos.

En lo anterior, también aplican las composiciones farmacéuticas, las características de los procesos, del método, de la utilización y de la manufactura de medicamentos y las incorporaciones alternas y preferidas de los compuestos de la invención aquí descritos.

Métodos de Prueba de la Potencia de la Enzima

Se hicieron pruebas con los compuestos para examinar la inhibición de la actividad GyrB ATPase empleando un análisis de detección de fosfato de molibdato/malaquita de amonio de base verde (Lanzetta, P. A., L. J.

Alvarez, P. S. Reinach y O. A. Candia, 1979, 100: 95-97). Los análisis se efectuaron en placas de múltiples pozos en reacciones de 100µl que contenían: 50 mM solución amortiguadora TRIS pH 7.5, 75 mM acetato de amonio, 5.5 mM cloruro de magnesio, 0.5 mM ácido etilendiaminatotraacético, glicerol al 5%, 1 mM 1,4-Ditio-DL-treitol, 200 nM albúmina de suero bovino, l6 µg/ml ADN de esperma de salmón cizallado, 4 nM *E. coli* GyrA, 4 nM *E.coli* GyrB, 250 µM ATP y combinado en dimetilsulfóxido. Las reacciones se extinguieron con 150 µL de reactivo molibdato/malaquita de amonio de detección verde que contenía 1.2 mM clorhidrato de malaquita verde, 8.5 mM molibdato tetrahidrato de amonio y 1 M ácido clorhídrico. Las placas se leyeron en un lector de placas de absorción a 625 nm y se calcularon los valores porcentuales de la inhibición empleando dimetilsulfóxido (2%)- que contenía reacciones como 0% inhibición y novobiocina- que contenía (2 µM) reacciones como 100% para los controles de inhibición. La potencia del compuesto se basó en mediciones $1C_{50}$ determinadas a partir de las reacciones efectuadas en presencia de 10 concentraciones diferentes del compuesto.

Los compuestos de los Ejemplos generalmente tienen un $1C_{50}$ de < 20 µg/ml.

Métodos de Prueba de la Susceptibilidad Bacterial

Se ensayaron los compuestos para conocer su actividad antimicrobial mediante pruebas en medios líquidos. Los compuestos se disolvieron en dimetilsulfóxido y se ensayaron en 10 diluciones de duplicación en los análisis de susceptibilidad. Los organismos empleados en el análisis se cultivaron durante la noche en un medio de agar apropiado y luego se suspendieron en un medio líquido apropiado para el crecimiento del organismo. La suspensión fue 0.5 McFarland y nuevamente se efectuó una dilución 1 en 10 en el mismo medio líquido para preparar la suspensión final del organismo en 100 µL. Las placas se incubaron bajo condiciones apropiadas a 37 grados C durante 24 hrs antes de la lectura. La Concentración Inhibidora Mínima (MIC) se determinó como la

concentración más baja del fármaco que pudiera reducir el crecimiento en un 80% o más.

El **Ejemplo 130** tuvo una MIC de 2µg/ml frente a *Streptococcus pneumoniae.*

Ahora bien, la invención se ilustra, pero no se limita, por los siguientes Ejemplos en los cuales, salvo si se expresa en contrario:-

(i) las evaporaciones se efectuaron mediante una evaporación rotatoria al vacío y los procedimientos de preparación se efectuaron después de la extracción de los sólidos residuales mediante filtración; (ii) las operaciones se efectuaron a temperatura ambiente, típicamente en el rango de 18-26 °C y sin excluir el aire, salvo si se expresa en contrario, o salvo si una persona con destrezas trabajaría bajo una atmósfera inerte; (iii) se empleó la cromatografía en columna (mediante procedimiento instantáneo) para purificar los compuestos y se realizó sobre sílice Merck Kieselgel (Art. 9385) salvo si se anota en contrario;

(iv) los rendimientos únicamente se dan para efectos ilustrativos y no son necesariamente el máximo alcanzable;

(v) la estructura de los productos finales de la invención generalmente se confirmó mediante NMR y técnicas de masa espectral [generalmente el espectro de la resonancia magnética de protones se determinó en DMSO-d_6 salvo si se expresa que se empleó un espectrómetro Bruker DRX-300 operando a una fuerza de campo de 300 MHz. Los cambios químicos se reportan en partes por millón campo abajo del tetrametisilano como un estándar interno (escala δ) y por lo tanto se muestran las multiplicidades: s, singlete; d, doblete; AB o dd, doblete de dobletes; dt, doblete de tripletes; dm, doblete de multipletes; t, triplete, m, multiplete; br, amplio; bombardeo rápido de átomos (FAB) por lo general los datos del espectro de masa se obtuvieron empleando un espectrómetro Platform (suministrado por Micromass) operado bajo electrorociado cuando fuera lo apropiado, se recolectaron datos de iones positivos o de iones negativos] o empleando Agilent 1100 series LC/MSD equipados con Sedex 75ELSD, operados bajo el modo APCI y cuando fuera lo apropiado, se recolectaron datos de iones

positivos o de iones negativos; se determinaron las rotaciones ópticas a 589 nm a 20°C para soluciones 7.6 mM en metanol empleando un polarímetro Perkin Elmer 341; HPLC DE FASE INVERSA efectuada empleando un Paquete YMC ODS-AQ(100x20 mmID, tamaño de partícula S-5µ, tamaño de poro 12 nm)

(vi) cada intermedio se purificó hasta alcanzar el estándar requerido para la siguiente etapa y se caracterizó con suficientes detalles para confirmar que la estructura asignada estaba correcta; se evaluó la pureza por medio de HPLC, TLC, o NMR y la identidad se determinó a través de una espectroscopia infrarroja (IR), espectroscopia de masa o espectroscopia NMR según lo apropiado;

(vii) donde se podrán utilizar las siguientes abreviaturas: -DMF es N, N-dimetilformamida; DMA es N, N-dimetilacetamida; TLC es cromatografía en capa delgada; HPLC cromatografía líquida de alta presión; MPLC es cromatografía líquida de presión media; DMSO es dimetilsulfóxido; $CDCl_3$ es cloroformo deuterado; MS espectroscopia de masa; ESP (o ES) es electrorociado; EI impacto de electrón; Cl es ionización química; APCI es ionización química presión atmosférica; EtOAc es acetato de etilo; MeOH es metanol; DEAD es dietilazodicarboxilato; DIEA isdiisopropiletilamina; mCPBA es ácido meta-cloroperoxibenzoico; TFA es ácido trifluoroacético; HATU es N-[(dimetilamino)-1H, 2,3-triazolo[4,5-b-]piridin-1-ilmetilen]-N-metilmetanaminio hexafluorofosfato N-óxido; HOAT es 1-hidroxi-7-azabenzotriazol; EDC es 1-(3-dimetilaminopropil)-3-etilcarbodiimida clorhidrato; TEA es trietilamina; NMP es N-metilpirrolidinona; Pd (dba) es bis(dibencilidinaacetona) paladio; Dppf es 1,1'bis(difenilfosfina)ferroceno; THF es tetrahidrofurano; EtOH es etanol; LCMS es cromatografía líquida/espectrometría de masa; DBU es 1,8-diazabiciclo[5.4.0]undec-7-eno; DCM es diclorometano;

(viii) las temperaturas se citan en °C;

(ix) Smith Microwave Synthesizer hace referencia a un equipo que utiliza la energía de microondas para calendar las reacciones orgánicas en un periodo de tiempo corto; se empleó de conformidad con las instrucciones del

fabricante y se obtuvo en Personal Chemistry Uppsala AB; y destilación (x) Kugelrohr hace referencia a una porción de equipo que destila los líquidos y calienta los compuestos sensibles empleando una temperatura de horno de baño de aire; se empleó de conformidad con las instrucciones del fabricante y se obtuvo en Buchi, Suiza o Aldrich,
Milwaukee, USA.

Intermedio 1: 3,4-Dicloro-5-metil-N-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida

Se trató *tert*-butilo 4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino} piperidina-1-carboxilato (**Intermedio 2**, 1.978 g, 5.257 mol) con 4 M HCl en dioxano (20ml) y la reacción se revolvió a temperatura ambiente durante 1.5 h. La mezcla de la reacción se concentró bajo presión reducida para producir el material deseado como un sólido rosado (1.61 g, rendimiento del 98%).

MS (ES-): 274.08, 276.08 para $C_{11}H_{15}Cl_2N_3O$

^{1}H NMR δ: 1.71 (m, 2H); 1.95 (m, 2H); 2.18 (s, 3H); 2.99 (m, 2H); 3.27 (m, 2H); 3.99 (m, 1H); 7.64 (d, 1H); 8.67 (brs, 1H); 12.16 (s, 1H)

Intermedio 2: *tert*-Butilo 4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidina-1-carboxilato

Se combinó 3,4-dicloro-5-metil-1*H*-pirrol-2-ácido carboxílico (**Intermedio 3**, 3.0 g, 0.016 mol), *tert*-butilo 4-aminopiperidina-1-carboxilato (3.1 g, 0.016 mol) y Et_3N (2.2 ml, 0.032 mol) en DMF (20ml) y se revolvió bajo N_2 durante 5 minutos. Se agregó HATU (6.47 g, 0.017 mol) en una porción y la reacción se revolvió a temperatura ambiente durante 5h. La mezcla de la reacción se diluyó con EtOAc y H_2O. La fase orgánica se lavó con 1 N HCl y las porciones acuosas combinadas se extrajeron una vez con EtOAc. Las porciones orgánicas combinadas se lavaron secuencialmente con $NaHCO_3$ saturado y NaCl saturado, se lavaron sobre $MgSO_4$, se filtraron y se concentraron bajo presión reducida para producir un sólido marrón. La

mayor parte del material crudo se aisló mediante trituración con EtOAc/hexanos para producir un sólido casi blanco. El material restante se sometió a cromatografía sobre sílice, levigado con 3:1, 2:1 y 1:1 EtOAc/hexanos para producir un sólido marrón claro que se trituró con EtOAc, se recolectó y se combinó con el otro material triturado para producir un total de 1.978 g del producto deseado.

MS (ES⁻): 374.33, 376.34 para $C_{16}H_{23}Cl_2N_3O_3$

^{1}H NMR δ: 1.16 (s, 9H); 1.20 (m, 2H); 1.53 (m, 2H); 1.93 (s, 3H); 2.65 (m, 2H); 3.65 (m, 3H); 6.97 (d, 1H); 11.72 (s, 1H)

Intermedio 3: 3,4-Dicloro-5-metil-1*H*-pirrol-2-ácido carboxílico

Se disolvió etil 3,4-dicloro-5-metil-1*H*-pirrol-2-carboxilato (**Intermedio 4**, 7.765 g, 0.03496 mol) en MeOH (80 ml) y DCM (10ml) y lentamente se agregó a 70°C solución de 2N LiOH (105 ml, 0.21 mol). Después de 2 h, la mezcla de la reacción se enfrió a temperatura ambiente y luego en un baño de hielo, seguido por una acidificación con 2N HCl. La mezcla se revolvió a 0° C durante 1 h y un sólido púrpura se filtró, se lavó con agua y se liofilizó durante la noche para producir 4.314 g (0.0222 mol, rendimiento 64%) del producto deseado.

MS (ES⁻): 192.13, 194.13 para $C_6H_5Cl_2NO_2$

^{1}H NMR δ: 2.17 (s, 3H)

Intermedio 4: Etil 3,4-dicloro-5-metil-1*H*-pirrol-2-carboxilato

Una solución de etil 5-metil-1*H*-pirrol-2-carboxilato (**Intermedio 20**) (7.00 g, 0.0457 mol) en tetraclorometano (30ml) se enfrió a 0° C bajo nitrógeno. El septo de caucho utilizado en el aparato se perforó con una aguja y luego se agregó SO_2Cl_2 (7.8ml, 0.096 mol) en forma de goteo durante 25 minutos. En 1 hr, la mezcla de la reacción había formado una lechada. El sólido se recolectó mediante filtración por succión, se lavó con tetraclorometano frío y se secó al vacío durante la noche para producir el producto del título como un sólido de color durazno (7.84 g, 0.0353 mol, rendimiento del 77%).

MS (ES⁻): 222.00, 224.00 para $C_8H_9Cl_2NO_2$

^{1}H NMR δ: 1.34-1.40 (t, 3H); 2.28 (s, 3H); 4.32-4.38 (m, 2H)

Intermedio 5: Etil 4-metoxi-3-oxobutanoato

El compuesto del título se preparó en forma análoga a la del Intermedio **123** comenzando a partir de 2,2-dimetil-1,3-dioxano-4,6-diona y cloruro de metoxiacetilo.

MS (APCl) MH+:161, 162 para $C_7H_{12}O_{14}$

^{1}H NMR($CDCl_3$) δ: 1.12-1.26 (t, 3H); 3.26 (s, 3H); 3.51 (s, 2H); 4.03-4.16 (brs, 4H).

Intermedio 6: Etil 2-cloro-4-metoxi-3-oxobutanoato

El compuesto del título se preparó en forma análoga a la del Intermedio **124** comenzando a partir de etil 4-metoxi-3-oxobutanoato (Intermedio **5**) y cloruro de sulfurilo.

MS (APCI) MH^+: 193,195 para $C_7H_{11}ClO_4$

^{1}H NMR($CDCl_3$) δ: 1.10-1.12 (t, 3H); 3.22 (s, 3H); 3.22 (s, 3H); 4.22-4.25 (s, 2H); 4.08-4.19 (q, 2H); 4.48 (s, 1H)

Intermedio 7: *N*-(2,6-Dicloropirimidin-4-il)acetamida

Se llevó a reflujo 4-amino-2,6-dicloropirimidina (500 mg, 3.05 mmol) en anhídrido acético (10ml) durante 3 h. Una vez se enfrió a temperatura ambiente, la mezcla de la reacción se enfrió en un baño de hielo y se alcalinizó a un pH 8 con $NaHCO_3$ acuoso al 10%. Las fases se separaron y la porción acuosa se extrajo dos veces con EtOAc. Las porciones orgánicas combinadas se lavaron sobre Na_2SO_4, se filtraron y se concentraron para producir un sólido casi blanco (503.7 mg, 2.44 mmol, rendimiento del 80%).

MS (ES$^-$): 204.08, 206.08 para $C_6H_5Cl_2N_3O$

^{1}H NMR δ: 2.15 (s,3H); 8.07 (s, 1H); 11.56 (brs, 1H)

Intermedio 8:4-Cloro-5-metil-1*H*-pirrol-2-ácido carboxílico

Se calentó hidróxido de litio (2 M, 4 ml) a 50 °C y se le agregó una solución de etil 4-cloro-5- metil-1*H*-pirrol-2-carboxilato (**Intermedio 9**, 0.30 g, 1. 60 mmol) en MeOH. La reacción se calentó a 80°C y se revolvió durante dos horas. El MeOH se extrajo y la solución acuosa se enfrió a 0°C y se acidificó con HCl al 30%. El producto precipitado (0.23 g, 92%) se filtró y se secó.

MS (ES): 160(M+l) para $C_6H_6ClNO_2$

^{1}H NMR($CDCl_3$) δ: 2.25 (s, 3H); 6.85 (s, 1H); 8.98 (brs, 1H)

Intermedio 9: Etil 4-cloro-5-metil-1*H*-pirrol-2-carboxilato

Se agregó N-clorosuccinimida (0.67 g, 5.08 mmol) a una solución de etil 5-metil-1*H*-pirrol-2-carboxilato (**Intermedio 20**) (0.65 g, 4.23 mmol) en cloroformo (20ml). La reacción se calentó a 40 °C y se revolvió durante 4 horas, luego se vertió en un vaso de precipitados que contenía 2 N NaOH (20ml) a 0 °C. Las capas se separaron y la capa acuosa se extrajo con cloroformo (x3). Los extractos orgánicos combinados se lavaron sobre sulfato de magnesio y se concentraron. El sólido resultante casi blanco se purificó mediante cromatografía instantánea (hexanos/EtOAc, 16: 1) para producir el producto del título como un sólido blanco (0.3 g, 38%).

MS(ES): 188(M+1) para $C_8H_{10}ClNO_2$

^{1}H NMR ($CDCl_3$) δ: 1,34 (t, 3H); 2.27 (s, 3H); 4.30 (q, 2H); 6.76 (s, 1H); 9.07 (brs, 1H)

Intermedio 10:4-Bromo-5-etil-1*H*-pirrol-2-ácido carboxílico

Este intermedio se sintetizó a partir de etil 4-bromo-5-etil-1*H*-pirrol-2-carboxilato (**Intermedio 11**) mediante un método análogo al del Intermedio 8.

MS (ES): 218 (M+l) para $C_7H_8BrN_2$

^{1}H NMR ($CDCl_3$) δ: 1.11 (t, 3H); 2.54 (q, 2H); 6.67 (s, 1H); 11.94 (brs, 1H); 12.38 (s, 1H)

Intermedio 11: Etil 4-bromo-5-etil-1*H*-pirrol-2-carboxilato

Se agregó N-bromosuccinimida (5.86 g, 0.033 mol) a una solución de etil 5-etil-1*H*-pirrol- 2-carboxilato (**Intermedio 12**,5. 0 g, 0.03 mol) en DCM (85 ml) a 0 °C y la reacción se revolvió durante 30 minutos luego se vertió en un vaso de precipitados frío que contenía 2 N NaOH (50 ml). Las capas se separaron y la capa acuosa se extrajo con DCM (x3). Los extractos orgánicos combinados se lavaron con agua y solución salina, se lavaron sobre sulfato de magnesio y se concentraron. El sólido marrón oscuro resultante se purificó mediante cromatografía instantánea (hexanos/ EtOAc, 10:1) para producir el producto del título como un sólido blanco (5.0 g, 68%).

MS(ES): 247(M+1) para $C_9H_{12}BrNO_2$

^{1}H NMR($CDCl_3$) δ: 1.04 (t, 3H); 1.14 (t, 3H); 2.46 (q, 2H); 4.10 (q, 2H); 6.64 (s, 1H); 8.68 (brs, 1H)

Intermedio 12: Etil 5-etil-1*H*-pirrol-2-carboxilato

Se agregó EtOH absoluto (6ml) a una solución al 21 % por peso de etóxido de sodio en EtOH (0.33ml, 1. 05 mmol) seguido por la adición en porciones de 2, 2, 2-tricloro-1-(5-etil-1H-pirrol-2-il)etanona (*J. Chem. Soc. Perkin Trans 1*, 1996,03) (2.1 g, 8.75 mmol) bajo nitrógeno. La solución resultante amarilla se revolvió a temperatura ambiente durante 30 minutos. Luego la reacción se concentró para producir un aceite color naranja claro. Se agregó ácido clorhídrico (3 M, 2.5ml) y dietiléter (8ml) al aceite y las capas se separaron. La capa acuosa se extrajo con dietiléter (x2) y los extractos orgánicos combinados se lavaron con solución saturada de bicarbonato de sodio y solución salina, se lavaron sobre sulfato de magnesio y se concentraron para producir el producto deseado como un sólido blanco (1.27 g, 86%).

MS (ES): 168 (M+1) para $C_9H_{13}NO_2$

^{1}H NMR($CDCl_3$) δ: 1.18 (t, 3H); 1.27 (t,3H); 2.59 (q, 2H); 4.23 (q, 2H); 5.89 (s, 1H); 6.64 (s, 1H); 8.68 (brs, 1H)

Intermedio 13:4-Ciano-5-metil-1H-pirrol-2-ácido carboxílico

Se calentó hidróxido de litio (2 N, 2ml) a 40 °C y se agregó una solución de etil 4-ciano-5- metil-1*H*-pirrol-2-carboxilato (**Intermedio 14**, 0.16 g) en 2 ml de MeOH. La temperatura de la reacción se incrementó gradualmente a 90 °C y la reacción se revolvió a esa temperatura durante 2 horas. Luego se extrajo el MeOH y la solución acuosa restante se enfrió a 0 °C y se acidificó con 3 M HCl (pH ~ 2). La solución acídica se extrajo con EtOAc, los extractos orgánicos combinados se lavaron sobre sulfato de magnesio y se concentraron para producir un sólido marrón (0.07 g, crudo).
MS (ES): 151(M+1) para $C_7H_6N_2O_2$
^{1}H NMR δ: 2.33 (s, 3H); 7.01 (s, 1H); 12.47 (s, 1H)

Intermedio 14: Etil 4-ciano-5-metil-1*H*-pirrol-2-carboxilato

Se disolvió etil 4-formilo-5-metil-1*H*-pirrol-2-carboxilato (**Intermedio 15**, 0.2 g, 1.1 mmol) y clorhidrato de hidroxilamina (0.08 g, 1.1 mmol) en EtOH (10ml) y se llevó a reflujo durante 1.5 horas. La mezcla se concentró al vacío para producir un sólido amarillo, el cual se disolvió en DMF (5ml) antes de la adición de $SOCl_2$ (0.35ml) a 0 °C. El solvente se extrajo al vacío una vez se completó la reacción y el residuo se distribuyó entre agua y EtOAc. Las capas se separaron y la capa acuosa se extrajo con EtOAc dos veces. Los extractos orgánicos combinados se lavaron sobre $MgSO_4$ y se concentraron para producir un sólido marrón (0.16 g, crudo).
MS (ES): 179 (M+1) para $C_9H_{10}N_2O_2$

Intermedio 15: Etil 4-formilo-5-metil-1H-pirrol-2-carboxilato

Se agregó trimetoximetano (1.18ml, 10.78 mmol) a una solución de etil 5-metil-1*H*- pirrol-2-carboxilato (**Intermedio 20**) (0.5 g, 3.26 mmol) (2.5ml) a 0 °C. La reacción se revolvió a esa temperatura durante 10 mins luego se extinguió con agua fría (20 ml).
Las capas se separaron y la capa acuosa se extrajo con EtOAc. Los extractos orgánicos combinados se lavaron sobre sulfato de magnesio y se concentraron para producir un sólido amarillo el cual se purificó mediante cromatografía instantánea (10% a 20 % EtOAc en hexanos, 0.25 g).

MS (ES): 182 (M+l) para $C_9H_{11}NO_3$

^{1}H NMR ($CDCl_3$) δ: 1.37 (t, 3H); 2.61 (s, 3H); 4.34 (q, 2H); 7.24 (s, 1H); 9.51 (brs, 1H); 9.88 (s, 1H).

Intermedio 16: tert-Butilo 1-[4-(aminocarbonil)-6-cloropiridin-2-ilpiperidin-4- ilcarbamato

Se disolvió tert-butilo piperidin-4-ilcarbamato (500 mg, 2.62mmol), en N, N'- dimetilacetamida anhidro (4 ml). Se agregó 2,6-dicloroisonicotinamida (522 mg, 2.62 mmol), seguido por N, N-dimetilisopropiletilamina (465 µl, 2.62mmol). Empleando un Smith Microwave Synthesizer, la mezcla se sometió a microondas unimodal a 150 °C durante 20 minutos. Se agregó H_2O (50ml) y EtOAc (100 ml), la capa de EtOAc se lavó (4 x 50ml), se lavó sobre Na_2SO_4 y se concentró al vacío para producir el producto del título como un sólido marrón. (760 mg).

MS (ES, M+H): 355 para $C_{16}H_{23}ClN_4O_3$

^{1}H NMR δ: 1.42 (m, 2H); 1.53 (s, 9H); 1.94 (m, 2H); 3.12 (m, 2H); 3.45 (s, 1H); 3.70 (m, 1H);4.34 (m, 2H); 7.07 (s, 1H); 7.26 (s, 1H); 7.81 (s, 1H); 8.49 (s, 1H).

Intermedio 17: Pentafluorofenilo 4-bromo-5-metil-1-H-pirrol-2-carboxilato

Se disolvió 4-bromo-5-metil-lH-pirrol-2-ácido carboxílico (**Intermedio 18**, 2.16 g, 10.59 mmol) y THF (10 ml). Se agregó pentafluorofenol y EDC (2.03 g, 10.59 mmol) y la mezcla se revolvió a temperatura ambiente durante 6 h. El solvente se extrajo al vacío y se agregó EtOAc (50ml). La fase orgánica se lavó con agua, Na_2CO_3 al 10% (2 x 25ml), agua (50ml) y solución salina (50ml), se lavó sobre Na_2SO_4 y se concentró al vacío para producir el compuesto del título como un sólido casi blanco (2.23 g).

MS(ESI, M+H): 368,371 para $C_{12}H_5BrF_5NO_2$

^{1}H NMR δ: 2.39 (s, 3H); 7.46 (d, 1H); 12.06 (s, 1H)

^{19}F NMR δ: -151.5 a -192. 7ppm

Intermedio 18:4-Bromo-5-metil-lH-Pirrol-2-ácido carboxílico

Se disolvió etil 4-bromo-5-metil-1H-pirrol-2-carboxilato (**Intermedio 19**,16.5 g, 71.09 mmol) en THF anhidro (100 ml) y se agregó a una solución precalentada de 2 N hidróxido de litio (500 ml) a 70 °C. La mezcla se calentó a 70 °C durante 4 h y El solvente se extrajo al vacío y la solución acuosa cruda se enfrió en un baño de hielo y lentamente se acidificó con 3 N HCl. El producto precipitado se extrajo con EtOAc (3x100 ml), los extractos orgánicos se lavaron con agua, solución salina y se secaron con Na_2SO_4, se trataron con carbón decolorante durante 1 h, se filtraron sobre célite y se concentraron al vacío. El sólido marrón se filtró y se lavó bien con n-hexanos y se secó al vacío. (13 g).

MS(APCl. M+H): 205 para $C_6H_6BrNO_2$

^{1}H NMR δ: 2.27 (s, 3H); 6.74 (d, 1H); 12.06 (s, 1H); 12.57 (s, 1H).

Intermedio 19: Etil 4-bromo-5-metil-1H-pirrol-2-carboxilato

Se disolvió etil 5-metil-1H-pirrol-2-carboxilato (**Intermedio 20**, 12.3 g, 0.803 mmol) en DCM anhidro y se enfrió a-5°C. Se agregó N-bromosuccinimida (14.23 g; 0.0803 mmol) y la reacción se revolvió durante 10 min y luego se vertió sobre 2 N hidróxido de sodio helado (500 ml). La solución marrón se extrajo con EtOAc (2 x 150 ml), los extractos orgánicos combinados se lavaron con agua, solución salina y se lavaron sobre Na_2SO_4, luego se concentraron al vacío para producir un sólido marrón el cual se secó al vacío. (16.5 g).

MS (ES, M+H): 233 para $C_8H_{10}BrNO_2$

^{1}H NMR δ: 1.32 (t, 3H); 2.1 (s, 3H); 4.371 (q, 2H); 6.23 (d, 1H); 11.54 (s, 1H).

Intermedio 20: Etil 5-metil-lH-pirrol-2-carboxilato

Se disolvió sodio (2.79 g, 0.121 mmol) en EtOH anhidro (100 ml), luego se agregó 2,2,2-tricloro-1-(5-metil-1H-pirrol-2-il)etanona (**Intermedio 21**, 22.5 g, 0.099 mmol) en porciones pequeñas. La solución marrón oscuro se revolvió a temperatura ambiente durante 30 minutos luego se concentró al

vacío hasta obtener un volumen pequeño. La mezcla se enfrió en un baño de hielo y lentamente se agregó 3N HCl, luego se extrajo con (3 x 100 ml). Los extractos de éter se lavaron con $NaHCO_3$ al 10%, agua y solución salina, se lavaron sobre Na_2SO_4 y se concentraron al vacío para producir el compuesto del título como un sólido marrón. (15.04 g).

^{1}H NMR δ: 1. 32 (t, 3H); 2.1 (s, 3H); 4.371 (q, 2H); 5.96 (dd, 1H); 6.78 (dd, 1H); 11.67 (s, 1H).

En un procedimiento alterno, se sintetizó etil 5-metil-1H-pirrol-2-carboxilato (**Intermedio 20**) en un recipiente de acuerdo con Curran, T. P.; Keaney, M. T., J *Org Chem* 1996, 61 (25), 9068.

Intermedio 21: 2,2,2-Tricloro-1-(5-metil-lH-pirrol-2-il)etanona

Se agregó 2-metil-1H-pirrol (**Intermedio 22**,10 g, 0.123 mmol) a dietiléter anhidro (30ml) en forma de goteo durante 1 h a una solución agitada de cloruro de triacetil (29 g, 0.16 mmol) en Et_2O anhidro (100ml). La mezcla se revolvió durante una 1 hora más y luego lentamente se agregó K_2CO_3 (10 g/30ml) a través de un embudo de goteo. La fase orgánica se lavó sobre Na_2SO_4 y se trató con carbón decolorante (3 g) durante 30 minutos a temperatura ambiente. La solución resultante púrpura se concentró y se trituró con n-hexanos para producir el compuesto del título como un sólido púrpura. (16.72 g).

^{1}H NMR($CDCl_3$) δ: 2.36 (s, 3H); 6.04 (dd, 1H); 7.45 (dd, 1H); 10.344 (s, 1H).

Intermedio 22: 2-Metil-1H-pirrol

Se agregó hidróxido de potasio (50 g, 0.89 mmol) a una solución de etilenglicol (750 ml) y 1H-pirrol-2-carbaldehído (50g, 0.53 mmol). Lentamente se agregó hidrato de hidrazina (37 ml, 0.745 mmol) durante 15 minutos. La mezcla de la reacción se llevó a reflujo a 90°C durante 90 minutos. La mezcla se enfrió a temperatura ambiente y se agregó agua fría (250ml).

La mezcla acuosa se extrajo con DCM (250 ml). La fase orgánica se lavó con agua (250 ml), se lavó sobre Na_2SO_4 y se concentró al vacío. La destilación Kugelrohr produjo el compuesto del título como un líquido transparente e incoloro (29.75 g).

^{1}H NMR δ: 2.1 (s, 3H); 5.77 (s, 1H); 5.9 (dd, 1H); 6.25 (dd, 1H); 10.54 (s, 1H).

Intermedio 23: Metil 2-{4-[(tert-butoxicarbonil)amino]piperidin-1-il}-6-cloroisonicotinato

Se disolvió tert-butilo piperidin-4-ilcarbamato (972 mg, 4.85 mmol), en NMP anhidro (5 ml). Se agregó metil 2,6-dicloroisonicotinato (**Intermedio 24**, 1 g, 4.85 mmol) seguido por TEA (675 µl, 4.85mmol). La mezcla se calentó bajo condiciones de microondas a 150 °C durante 10 minutos. Se agregó agua (50 ml) y EtOAc (100ml), la fase acuosa se trató con NaCl sólido y se extrajo con EtOAc (4 x 100 ml). La capa de EtOAc se secó, se concentró al vacío y se purificó mediante cromatografía instantánea levigado con hexano: EtOAc (4: 1) para producir el producto del título como un sólido casi blanco. (1.4 g).

MS (ES, M+H): 370 para $C_{17}H_{24}ClN_3O_4$

^{1}H NMR δ: 1.38 (m, 2H); 1.49 (s, 9H); 1.93 (m, 2H); 2.29 (m, 1H); 3.17 (m, 2H); 3.48 (s, 1H); 3.94 (s, 3H); 4.38 (m, 2H); 7.02 (s, 1H); 7.31 (s, 1H); 7.81 (s, 1H); 8.49 (s, 1H)

Intermedio 24: Metil 2,6-dicloroisonicotinato

Se suspendió 2,6-ácido dicloroisonicotínico (5 g, 26.04 mmol) en tolueno anhidro (75 ml). Se agregó cloruro de tionilo (19 ml, 260.4 mmol) y la mezcla se calentó a reflujo durante 4 h. Se extrajo el excedente del cloruro del tionilo y del solvente al vacío. Se agregó MeOH anhidro (25 ml) y la reacción se revolvió durante 4 h más. Los solventes se extrajeron al vacío para producir un sólido de color blanco el cual se secó al vacío (4.8 g).

MS (APCL M+H): 206 para $C_7H_5Cl_2NO_2$

^{1}H NMR δ: 4.10 (s, 3H); 8.15 (s, 2H).

Intermedio 25: Etil 4-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-3-oxobutanoato

El compuesto del título se preparó en forma análoga a la del Intermedio **123** comenzando a partir de 2,2-dimetil-1,3-dioxano-4,6-diona y (1,3-dioxo-1,3-dihidro-2H-isoindol-2-il) cloruro de acetilo.

MS (APCI) MH^+: 276, 277 para $C_{14}H_{13}NO_5$

^{1}H NMR ($CDCl_3$) δ: 1.18-1.22 (t, 3H); 3.85 (s, 2H); 4.10-4.13 (q, 2H); 4.71 (s, 2H); 7.89-7.93 (brs, 4H).

Intermedio 26:2-Cloro-6-(4-hidroxipiperidin-1-il) isonicotinonitrilo

Se disolvió 2,6- dicloroisoniconitrilo (200 mg, 1.15 mmol) y 4-hidroxipiperidina (117 mg, 1.15 mmol) en NMP (3 ml). Se agregó TEA (160µl, 1.15 mmol). Empleando un Smith Microwave Synthesizer, la mezcla se sometió a microondas unimodal a 150°C durante 20 minutos. La mezcla marrón se extrajo con EtOAc y se lavó con agua (3 x 15 ml). La fase orgánica se lavó sobre Na_2SO_4 y se concentró al vacío. (250 mg).

MS (ES, M+H): 238 para $C_{11}H_{12}ClN_3O$

Intermedio 27: 3-Ciano-5-etil-1H-pirrol-2-ácido carboxílico metil éster

Se disolvió 3-ciano-5-etil-1 H-pirrol-2-ácido carboxílico (**Intermedio 31**) (500 mg) en THF anhidro (5 ml) y se enfrió a 0°C. Se agregó (Trimetilsilil) diazometano/éter (2 ml). La mezcla se revolvió a temperatura ambiente bajo gas nitrógeno durante 1 h. El solvente se extrajo al vacío y se agregó MeOH. La mezcla se revolvió durante 15 min más, El solvente se extrajo al vacío y el sólido se secó al vacío para producir el compuesto del título (580 mg).

MS (ES) MH^+: 177 para $C_9H_{10}N_2O_2$

Intermedio 28: 3-Ciano-5-metil-1H-pirrol-2-ácido carboxílico metil éster

El compuesto del título se preparó mediante un procedimiento análogo al del **Intermedio 27** comenzando a partir de 3-ciano-5-metil-1H-pirrol-2-ácido carboxílico (**Intermedio 32**).
MS (ES) MH^+: 164 para $C_8H_8N_2O_2$

Intermedio 29: 5-Metil-1H-pirrol-2-ácido carboxílico

El compuesto del título se sintetizó mediante un método análogo al del Intermedio **18** comenzando a partir de etil 5-metil-1H-pirrol-2-carboxilato (**Intermedio 20**).
MS (ES): 250 (MH) dímer para $C_6H_7NO_2$
^{1}H NMR δ: 2.24 (s, 3H); 5.92 (s, 1H); 6.68 (s, 1H); 11.55 (s, 1H); 12.05 (s, 1H)

Intermedio 30:5-Etil-1H-pirrol-3-carbonitrilo

Se agregó lodoetano (3.99 g, 25.61 mmol) a una solución de 1-isocianometanosulfonil-4-metil-benceno (5g, 25.61 mmol) en THF anhidro (20 ml). La mezcla se enfrió a -78°C y se agregó potasio tert-butóxido (31 ml de 1 M solución en THF, 31 mmol) en forma de goteo durante 15 minutos. La mezcla se calentó a temperatura ambiente durante 1 h. Se agregó agua (50 ml) y la solución se extrajo con dietiléter y se lavó sobre Na_2SO_4 y se evaporó hasta el secado. El material marrón aceitoso resultante se empleó sin purificación. El 1-(1-Isociano-propano-1-sulfonil)-4-metil-benceno (4.29 g, 19.05 mmol) resultante y el acrilonitrilo (1. 26ml, 19.05 mmol) se revolvieron en THF anhidro (20ml). La mezcla se enfrió a 0°C y se agregó potasio tert-butóxido en THF (38.1ml, 38.1 mmol) en forma de goteo.

La mezcla se calentó a reflujo durante 2 h luego se dejó a temperatura ambiente durante la noche y después se concentró al vacío. Se agregó EtOAc (30 ml) al sólido marrón y la mezcla se revolvió a temperatura ambiente durante unas pocas horas, se filtró y el sólido se lavó bien con EtOAc. La solución EtOAc se concentró al vacío y se purificó mediante

cromatografía instantánea levigado con una mezcla de EtOAc/n-hexanos: 3:2 para obtener el compuesto del título. (0.856 g).

MS (APCI, M+): 119,121 para $C_7H_8N_2$

^{1}H NMR ($CDCl_3$) δ: 1.43 (m, 3H); 2.79 (m, 2H); 6.24 (s, 1H); 7.35 (s, 1H); 8.91 (s, 1H).

Intermedio 31: 3-Ciano-5-etil-1H-pirrol-2-ácido carboxílico

Se agregó nitrato de plata (1.41 g, 8.3 mmol) en agua (100 ml) a una solución de 5-etil-2-formilo-lH-pirrol-3-carbonitrilo (**Intermedio 58**) (819 mg, 5.53 mmol) en 1 N hidróxido de sodio (100 ml) en la oscuridad. La mezcla se calentó a 100°C en la oscuridad durante 1 h. La mezcla de la reacción se enfrió a temperatura ambiente y se acidificó con ácido nítrico acuoso al 65%. La solución amarillo/marrón se extrajo con EtOAc, se lavó sobre sulfato de sodio y se concentró al vacío para producir el compuesto del título (600 mg).

^{1}H NMR δ: 1.03 (m, 3H); 2.37 (m, 2H); 6.39 (d, 1H); 8.03 (brs, 1H); 12.45 (s, 1H).

Intermedio 32:3-Ciano-5-metil-1H-pirrol-2-ácido carboxílico

El compuesto del título se preparó mediante un procedimiento análogo al del **Intermedio 31** comenzando a partir de 5-metil-2-formilo-1H-pirrol-3-carbonitrilo (preparación: *J. Med. Chem.* 1998,41 (6) 808- 820).

^{1}H NMR δ: 2.26 (s, 3H); 6.46 (d, 1H); 12.58 (s, 1H); 13.47 (brs, 1H).

Intermedio 33:4-Bromo-3-ciano-5-etil-1H-pirrol-2-ácido carboxílico

Se agregó N-bromosuccinimida (289 mg, 1.63 mmol) a una solución fría de 3-ciano-5-etil-1H-pirrol-2-ácido carboxílico metil éster (**Intermedio 27**; 290 mg, 1.63 mmol) en DCM anhidro a 0°C. La mezcla se revolvió a 0°C durante 30 minutos. La mezcla se vertió sobre una solución fría de 2 N hidróxido de sodio (15 ml) y se extrajo con DCM. Los extractos combinados se lavaron con agua (2 x 15 ml), se lavaron sobre sulfato de sodio y se concentraron al vacío para producir pequeñas cantidades del

compuesto del título. La fase acuosa se acidificó, se extrajo con EtOAc, se concentró al vacío para producir el compuesto del título como un sólido marrón cremoso (240 mg).

^{1}H NMR δ: 1.03 (m, 3H); 3.46 (m, 2H); 13.16 (s, 1H); 13.82 (brs, 1H).

Intermedio 34:4-Bromo-3-ciano-5-metil-1H-pirrol-2-ácido carboxílico

El compuesto del título se preparó mediante un procedimiento análogo al del **Intermedio 33** comenzando a partir de 3-ciano-5-metil-1H-pirrol-2-ácido carboxílico metil éster (**Intermedio 28**).

^{1}H NMR δ: 2.03 (m, 3H); 13.05 (s, 1H).

Intermedio 35: Etil 2-cloro-4-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-3-oxobutanoato

El compuesto del título se preparó en forma análoga a la del Intermedio **124** comenzando a partir de etil 4-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-3-oxobutanoato (**Intermedio 25**) y cloruro de sulfurilo.

MS (APCI) MH^+: 313 para $C_{14}H_{12}ClNO_5$

^{1}H NMR($CDCl_3$) δ: 1.24-1.33 (t, 3H); 4.20-4.28 (q, 2H); 4.43 (q, 2H); 4.88 (s, 2H); 5.07 (s, 1H); 5.76 (s, 1H); 6.0 (s, 1H); 7.88-7.96 (brs, 6H).

Intermedio 36: Etil 2-(4-aminopiperidin-1-il)-4-(metoximetil)-1,3-tiazol-5-clorhidrato de carboxilato

El compuesto del título se preparó en forma análoga a la del Intermedio **126** comenzando a partir de *tert-Butil* [1-(aminocarbonotioil)piperidin-4-il] carbamato (**Intermedio 125**) y etil 2-cloro-4-metoxi-3-oxobutanoato (**Intermedio 6**).

MS (ES) (M+H): 300, 301 para $C_{13}H_{22}ClN_3O_3S$

Intermedio 37:4-Bromo-5-isopropil-1H-pirrol-2-ácido carboxílico

Se sintetizó el **Intermedio 37** de acuerdo con Elder, T y colaboradores. *Synth. Commun.* 1989,19 (5 & 6) 763-767 y las referencias del mismo; Kelly, TR y colaboradores. *Tetrahedron.* **1984**, 40 (22) 4569.

Intermedio 38:tert-Butil[1-(3-nitropiridin-2-il)piperidin-4-ilo carbamato

Se agregó TEA anhidro (0.76ml, 5.49 mmol) a piperidin-4-il-ácido carbámico tert-butilo éster (1 g, 5 mmol) y 2-cloro-3-nitro-piridina (0.791 g, 5 mmol) en NMP anhidro (3ml). Empleando un Smith Microwave Synthesizer, la mezcla se sometió a microondas unimodal a 150°C durante 10 minutos. La solución marrón se distribuyó entre EtOAc y agua y la fase orgánica se lavó varias veces con agua, se lavó sobre sulfato de sodio y se concentró al vacío para producir el compuesto del título como un sólido amarillo (1.35 g).

MS (ES): 323 (MH^+) para $C_{15}H_{22}N_4O_4$

^{1}H NMR δ: 1.37 (s, 9H); 1.48 (m, 2H); 1.96 (m, 2H); 3.18 (m, 2H); 3.7(m, 1H); 3.86 (m, 2H); 7.05 (m, 2H); 8.33 (m, 2H)

Intermedio 39: 1-(3-Nitroniridin-2-il)piperidin-4-amina sal de clorhidrato

Se agregó una solución de 4 N ácido clorhídrico en dioxano (10ml) a tert-Butil [1-(3-nitropiridin-2-il)piperidin-4-il]carbamato (**Intermedio 38**; 1.3 g, 4.2mmol). La mezcla se revolvió a temperatura ambiente durante 1 h bajo gas nitrógeno. El solvente se extrajo al vacío para producir el compuesto del título como un polvo amarillo (500 mg).

MS (APCI): MH^+ 222 para $C_{11}H_{15}N_3O_2$

^{1}H NMR δ: 1.76 (m, 2H); 2.10 (m, 2H); 3.18 (m, 2H); 3.82 (m, 12H); 3.3. 83 (m, 2H); 7.02 (m, 1H); 8.39 (m, 1H); 8.48 (m, 1H); 9.32 (b, 2H)

Intermedio 40: 2,6-Dicloro-N-(2-morfolin-4-il-etil)-isonicotinamida

Se agregó HATU (989 mg, 2.6 mmol), HOAT (354 mg, 2.6 mmol) y DIEA (907 µl, 5.21 mmol) a una solución agitada de 2,6-ácido dicloroisonicotínico (500 mg, 2.60 mmol) en DMA anhidro (4 ml). La mezcla se revolvió durante 10 minutos después de lo cual se agregó 2-morfolin-4-il-etilamina (420 µl, 2.86 mmol). La mezcla se revolvió a

temperatura ambiente durante 12 h y la mezcla se distribuyó entre EtOAc y agua. La capa de EtOAc se lavó bien con agua, se lavó sobre sulfato de sodio y se concentró al vacío para producir el compuesto del título como un aceite (830 mg).

MS (ES) MH^+: 304

Intermedio 41:2-(2,6-Dicloro-piridin-4-ilsulfanil)-N-metil-acetamida

Se enfrió 2,6-dicloro-piridin-4-ilamina (1 g, 6.13 mmol) en ácido clorhídrico concentrado (5ml) a 0°C. Lentamente se agregó nitrito de sodio (465 mg, 6.75 mmol) en agua (10 ml) mientras se conservaba la temperatura por debajo de 5°C. La mezcla se revolvió a baja temperatura durante 20 minutos. Lentamente se agregó N-metilmercaptoacetamida (645 mg, 6.13 mmol), se revolvió a baja temperatura durante 10 minutos y se calentó a 90°C durante 1 h. La solución amarilla se enfrió y se extrajo con EtOAc, se lavó con agua, se secó al vacío y se purificó mediante cromatografía en sílice levigado con una mezcla de EtOAc/hexano para producir el compuesto del título (855 mg).

^{1}H NMR δ: 2.55 (s, 3H); 3.94 (s, 2H); 7.55 (s, 2H)

Intermedio 42: tert-Butil {1-[4-(aminocarbonil)-6-cianonpiridin-2-il]piperidin-4-il}carbamato

Se colocó tert-Butil {1-[4-(aminocarbonil)-6-cloropiridin-2-il]piperidin-4-il} carbamato (**Intermedio 16**) (100 mg, 0.282mmol), cianuro de cobre (101 mg, 1.13 mmol), Pd(dba) (103 mg, 0.11 mmol) y Dppf (250 mg, 0.45 mmol) en dioxano anhidro (5ml) bajo argón. La mezcla se calentó a 100°C durante 5 h, luego se diluyó con EtOAc (20ml) y se filtró mediante célite. La mezcla se lavó con bicarbonato de sodio (2 x 20 ml), solución salina (20ml), se lavó sobre sulfato de sodio y se concentró al vacío. El residuo marrón se purificó mediante cromatografía instantánea levigado con una mezcla de DCM y MeOH para producir el compuesto del título como un sólido marrón (61 mg).

MS (ES): 346 (MH+) para $C_{17}H_{23}N_5O_3$

^{1}H NMR δ: 1.27 (m, 2H); 1.38 (s, 9H); 1.78 (m, 2H); 3.03 (m, 2H); 3.52 (m, 1H); 4.24 (m, 2H); 7.79 (s, 1H); 8.22 (s, 1H).

Intermedio 43: Tiofeno-2-ácido carboxílico-2-cloro-piridinil-3-ilo éster

Se agregó TEA (1.2ml, 8.49 mmol) a 2-cloro-3-piridinol (1 g, 7.72 mmol) y 2-cloruro de tiofenocarbonilo (1.13 g, 7.72 mmol) en tolueno anhidro (10 ml). La mezcla se calentó a 100°C durante 25 minutos. El solvente se extrajo al vacío (x1) y la mezcla se distribuyó entre EtOAc y agua, se lavó con agua, se lavó sobre sulfato de sodio y se secó al vacío para producir un aceite el cual se trituró con n-hexanos para producir el compuesto del título como un sólido casi blanco (1.85 g).

^{1}H NMR δ: 7.42 (m, 1H); 7.70 (m, 1H); 8.09 (m, 1H); 8.14 (m, 1H); 8.26 (m, 1H); 8.52 (m, 1H).

Intermedio 44: N-[6-Cloro-2-(metiltio)pirimidin-4-il]lacetamida

Se agregó anhidro acético (10.4 ml, 0.11 mol) a 6-cloro-2-(metiltio) pirimidin-4-amina (2.5 g, 0.01 mol) y la mezcla de la reacción se llevó a reflujo a 135 °C durante 5 hr. La mezcla de la reacción se enfrió a temperatura ambiente y se alcalinizó a un pH 7 con una solución saturada de bicarbonato de sodio (20ml). La mezcla se distribuyó entre EtOAc y agua, la capa orgánica se lavó con agua y solución salina, se lavó sobre $MgSO_4$ y se concentró para producir el compuesto del título (2.62 g).

MS (ES): 218 (MH^+) para $C_7H_8ClNO_3S$

Intermedio 45: tert-Butilo 1-[6-amino-2-(metiltio)pirimidin-4-il]piperidin-4-ilcarbamato

Se agregó TEA (0.243ml, 1.74 mmol) y 6-cloro-2-(metiltio)pirimidin-4-amina (0.309 g, 1.74 mmol) a una solución de tert-butilo piperidin-4-ilcarbamato (0.35 g, 1.74 mmol) en NMP (4ml). Empleando un Smith Microwave Synthesizer, la mezcla se sometió a microondas unimodal a 150 °C durante 90 minutos. La mezcla se distribuyó entre agua y EtOAc (x2) y

se lavó con agua. La fase orgánica se lavó sobre sulfato de magnesio y se concentró para producir el compuesto del título (0.294 g).
MS (ES) (MH^+): 340 para $C_{16}H_{26}N_4O_2S$

Intermedio 46: 6-(4-Aminopiperidin-1-il)-2-(metiltio)pirimidin-4-amina clorhidrato

Se agregó 4 N cloruro de hidrógeno en dioxano (3ml) a tert-butilo 1-[6-amino-2-(metiltio)pirimidin-4-il]piperidin-4-ilcarbamato (**Intermedio 45**, 0.29 mg 0.86 mmol). La mezcla se revolvió a temperatura ambiente durante 90 minutos. El solvente se extrajo al vacío para obtener el compuesto del título (238 mg).
MS (ES) (MH^+): 240 para $C_{10}H_{17}N_5S$

Intermedio 47: 2,6-Dicloro-N-metoxi-N-metilisonicotinamida

Se agregó HATU (1.97 g, 5.20mmol), HOAT (707 mg, 5.20 mmol) y DIEA (1.77 ml, 10.5 mmol) a 2,6-ácido dicloroisonicotínico (1 g, 5.20 mmol) (5 ml). La mezcla se revolvió durante 5 minutos, luego se agregó N-metilo clorhidrato de metoxilamina (507 mg, 5.20 mmol) en una porción seguido por DIEA (800 µl, 5.2mmol). La reacción se revolvió durante 30 minutos, luego el producto crudo se distribuyó entre EtOAc (50ml) y agua (50ml) y el nivel orgánico se lavó con agua (3 x 50ml). La fase orgánica se lavó sobre sulfato de sodio y se concentró al vacío. El producto crudo se purificó mediante cromatografía instantánea levigado con EtOAc: n-hexanos (2:3) para obtener el compuesto del título (1.12 g).

MS (APC1, M+H): 235 para $C_8H_8Cl_2N_2O_2$
^{1}H NMR δ: 3.29 (s, 3H); 3. 61 (s, 3H); 7.77 (s, 2H)

Intermedio 48: 1-(2,6-Dicloropiridin-4-il)etanona

Se enfrió 2,6-dicloro-N-metoxi-N-metilisonicotinamida (**Intermedio 47**, 780 mg, 3.3 mmol) en dietiléter anhidro (13ml) a -78 °C. Se agregó metilitio (1.6 M solución en dietiléter (5.2ml, 8.3 mmol) en forma de goteo.

La mezcla se revolvió a -78 °C durante 1 h y se extinguió con una solución de cloruro de amonio, seguido por un calentamiento hasta alcanzar la temperatura ambiente. La mezcla de la reacción se diluyó con agua (20ml) y se extrajo con dietiléter (2 x 30 ml), se lavó sobre sulfato de sodio y se concentró al vacío para producir el compuesto del título (575 mg).

MS (APCI, M+H): 191 para $C_7H_5Cl_2O$

^{1}H NMR δ: 2.66 (s, 3H); 7.96 (s, 2H)

Intermedio 49: tert-Butilo 1-[6-cloro-4-(hidrazinacarbonil)piridin-2-il]piperidin-4- ilcarbamato

Se agregó hidrazina (0.55 ml 17.0 mmol) a una solución de metil 2-{4-[(tert-butoxicarbonil)amino]piperidin-1-il}-6-cloroisonicotinato (**Intermedio 23**, 0.15 g, 0.40 mmol) en isopropanol (3 ml). La mezcla se revolvió a temperatura ambiente durante la noche luego el isopropanol se extrajo al vacío para producir el producto del título (130 mg).

MS(ES, MH): 370, 368 para $C_{17}H_{25}Cl_2N_4O_3$

Intermedio 50: tert-Butilo 1-[6-cloro-4-(5-oxo-2,5-dihidro-1,3,4-oxadiazol-2-il)piridin-2-il]piperidin-4-ilcarbamato

Se agregó N, N'-carbonildiimidazol (0.12 g, 0.82 mmol) a una solución de tert-butilo 1-[6-cloro-4-(hidrazinacarbonil)piridin-2-il]piperidin-4-ilcarbamato (**Intermedio 49**, 0.15 g, 0.41 mmol) en DMF (3 ml). La mezcla se revolvió a temperatura ambiente durante la noche y se purificó mediante HPLC de semi preparación levigado con mezclas de CH_3CN/H_2O (TFA al 0.1%) para obtener el compuesto del título (0.125 g).

MS (ES, MH): 396, 394 para $C_{18}H_{23}ClN_4O_4$

Intermedio 51: 5-[2-(4-Aminopiperidin-1-il)-6-cloropiridin-4-il]-1,3,4-oxadiazol-2(5*H*)-ona clorhidrato

Se agregó 4 N ácido clorhídrico en dioxano (3ml) a tert-butilo 1-[6-cloro-4-(5-oxo-2,5-dihidro-1,3,4-oxadiazol-2-il)piridin-2-il]piperidin-4-ilcarbamato (**Intermedio 50**, 0.12 mg, 0.32mmol). La mezcla se revolvió a temperatura

ambiente durante 45 min, luego se concentró al vacío para obtener el compuesto del título (100 mg).

MS (ES, MH): 296, 294 para $C_{13}H_{15}ClN_4O_2$

Intermedio 52: *tert*-Butilo 4-{[(4-bromo-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidina-1-carboxilato

El compuesto del título se sintetizó mediante un método análogo al del Intermedio **2**, comenzando a partir de 4-bromo-5-metil-1H-pirrol-2-ácido carboxílico (**Intermedio 18**).

MS (ESP): 386.1 (M+H) para $C_{16}H_{24}BrN_3O_3$

^{1}H NMR δ: 1.34 (m, 2H); 1.41 (s, 9H); 1.74 (d, 2H); 2.13 (s, 3H); 2.84 (m, 2H); 3.92 (m, 3H); 6.81 (s, 1H); 7.75 (d, 1H); 11.67 (s, 1H).

Intermedio 53: tert-Butilo 1-(6-cloro-4-cianopiridin-2-il)piperidin-4-ilcarbamato

Se agregó TEA (0.20 ml, 1.44 mmol) y 2,6-dicloroisonicotinonitrilo (0.25 g, 1.44 mmol) a una solución de tert-butilo piperidin-4-ilcarbamato (0.28 g, 1.44 mmol) en NMP (2 ml). Empleando un Smith Microwave Synthesizer, la mezcla se sometió a microondas unimodal a 150 °C durante 10 minutos. La mezcla cruda se distribuyó entre agua y EtOAc y se lavó (x2) con agua. Los extractos se combinaron, se lavaron sobre $MgSO_4$ y se concentraron para producir el compuesto del título (400 mg).

MS (ES): 337 (MH^+) para $C_{17}H_{22}ClN_3O_2$

Intermedio 54: tert-Butilo 1-{4-[amino(hidroxiimino)metil]-6-cloropiridin-2-il}piperidin-4-ilcarbamato

Se agregó TEA (0.24ml, 1.78 mmol) a una solución de tert-butilo 1-(6-cloro-4-cianopiridin-2-il)piperidin-4-ilcarbamato (**Intermedio 53**, 0.4 g, 1.19 mmol) en MeOH (2 ml), seguido por la adición de clorhidrato de hidroxilamina (0.82 g, 1.19mmol). La mezcla se llevó a reflujo durante 4 h, luego El solvente se extrajo al vacío para producir el producto deseado. (410 mg).

MS (ES): 370 (MH^+) para $C_{17}H_{25}ClN_4O_3$

Intermedio 55: tert-Butilo 1-[6-cloro-4-(1,2,4-oxadiazol-3-il)piridin-2-il]piperidin-4-ilcarbamato

Se agregó trifluoréterato de boro (0.1ml) a una solución de tert-butilo 1-{4-[amino(hidroxiimino)metil]-6-cloropiridin-2-il}piperidin-4-ilcarbamato (**Intermedio 54**) (0.254 g, 0.69 mmol) en 1,1,1-trietoxietano (1.5ml) a temperatura ambiente. La mezcla se llevó a reflujo durante 10 minutos. La mezcla se purificó mediante cromatografía instantánea en gel de sílice levigado con (n-hexanos:EtOAc; 70:30) para obtener el compuesto del título (50 mg).

MS (ES): 380 (MH^+) para $C_{18}H_{23}ClN_4O_3$

Intermedio 56: 1-[6-Cloro-4-(1,2,4-oxadiazol-3-il)piridin-2-il] piperidin-4-amina clorhidrato

Se disolvió tert-butilo 1-[6-cloro-4-(1,2,4-oxadiazol-3-il)piridin-2-il]piperidin-4-ilcarbamato (**Intermedio 55**) (50 mg 0.13 mmol) en 4 N HCl en dioxano (2 ml). La mezcla se revolvió a temperatura ambiente durante 2 h. El solvente se concentró al vacío para obtener el compuesto crudo del título el cual se utilizó sin una purificación posterior (74 mg).

MS (ES): 280 (MH^+) para $C_{13}H_{15}ClN_4O$

Intermedio 57: 4-Bromo-5-metil-*N*-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida

El compuesto del título se sintetizó mediante un método análogo al del Intermedio 1, comenzando a partir de *tert*-butilo 4-{[(4-bromo-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidina-1-carboxilato (**Intermedio 52**).

MS (ESP): 286.1 (M+H) para $C_{11}H_{16}BrN_3O$

^{1}H NMR δ: 1.36 (m, 2H); 1.74 (d, 2H); 2. 13 (s, 3H); 2.83 (m, 2H); 3.85-4.05 (m, 3H); 6.81 (s, 1H); 7.75 (d, 1H); 11.66 (s, 1H).

Intermedio 58: 5-Etil-2-formilo-1H-pirrol-3-carbonitrilo

Se agregó $POCl_3$ (3.3ml, 35.67 mmol) a 1,2-dicloroetano (4 ml), luego muy lentamente se agregó DMF anhidro (2.75ml, 35.67 mmol). La mezcla se revolvió a temperatura ambiente durante ~10 minutos. Se agregó 5 -etil-1H-pirrol-3-carbonitrilo (**Intermedio 30**, 856 mg, 7.13 mmol) en 1,2-dicloroetano (2ml) en forma de goteo y la mezcla se calentó a 80 °C durante ~30 minutos. La mezcla se enfrió a temperatura ambiente y se agregó acetato de sodio (2.5 g/5 ml) y la mezcla se revolvió durante 1 h. La emulsión marrón/negro se extrajo con DCM (4 x 50ml). La fase orgánica combinada se lavó con agua (2 x 50ml) se lavó sobre Na_2SO_4 y se concentró al vacío para producir el compuesto del título. (819 mg).
^{1}H NMR ($CDCl_3$) δ; 1.52 (m, 3H); 2.81 (m, 2H); 6.46 (s, 1H); 9.65 (s, 1H); 9.96 (s, 1H).

Intermedio 59: Etil 4,5-cloro-1H-pirrol-2-carboxilato

El compuesto del título se preparó en forma análoga a la del Intermedio **20** comenzando a partir de 2,2,2-tricloro-1-(4,5-dicloro-1H-pirrol-2-il)etanona **(Intermedio 60).**

MS (ES): MH^- 207, 209 para $C_7H_7Cl_2NO_2$

Intermedio 60: 2,2,2-Tricloro-1-(4,5-dicloro-1H-pirrol-2-il)etanona

Se agregó una solución de cloruro de sulfurilo (11.3ml, 0.14 mol) en éter (5ml) a 0 °C a una solución de 2,2,2-tricloro-1-(1H-pirrol-2-il) etanona (15.0 g, 0.07 mol) en dietiléter (10 ml). Se permitió que la mezcla se revolviera a temperatura ambiente durante la noche. El solvente se extrajo al vacío. La mezcla cruda se distribuyó entre éter y K_2CO_3 acuoso al 10%. La fase orgánica se concentró al vacío y se purificó mediante cromatografía instantánea en sílice gradiente de levigado (EtOAc al 2-5% en hexano) para producir el compuesto del título (17.0 g).
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.42 (d, 1H); 13.85 (s, 1H)

Intermedio 61: 4,5-Dicloro-1H-pirrol-2-ácido carboxílico

Se agregó una solución de hidróxido de litio en agua (2N, 0.80 ml, 0.16 mol) a una solución agitada de una mezcla de etil 4,5-dicloro-1H-pirrol-2-carboxilato (**Intermedio 59**; 7.0 g, 0.033 mol) en THF (15 ml) a temperatura ambiente. La mezcla se revolvió a 50 °C durante 8 h por 2 días. La mezcla de la reacción se acidificó con una solución de HCl al 10% hasta un pH ~ 2 y se distribuyó entre EtOAc y agua. La capa orgánica se lavó sobre $MgSO_4$ y se concentró al vacío para producir el compuesto del título (4.0 g).

MS (ES): MH^- 178 para $C_5H_3Cl_2NO_2$

^1H NMR (500 MHz) δ:: 7.06 (s, 1H); 12.43 (s, 1H); 13.43 (s, 1H)

Intermedio 62: 2-Cloro-6-(4-hidroxipiperidin-1-il)isonicotinamida

El compuesto del título se preparó en forma análoga a la del Intermedio **26** comenzando a partir de 2,6-dicloroisonicotinamida y 4-hidroxipiperidina (ambos disponibles en el comercio).

MS(LCMS): 255

Intermedio 63: 2-Cloro-6-[4-(metilamino)piperidin-1-il] isonicotinonitrilo

Se agregó 2,6-dicloroisoniconitrilo (1.28 g, 7.38 mmol) y DIEA (3.85ml) a piperidin-4-ona (1 g, 7.38 mmol) en DMA anhidro (8 ml). Empleando un Smith Microwave Synthesizer, la mezcla se sometió a microondas unimodal a 150 °C durante 20 minutos en dos lotes. Los lotes se combinaron y se diluyeron con EtOAc (100ml) y se lavaron con agua (3 x 50ml). La fase orgánica se lavó sobre Na_2SO_4 y se concentró al vacío para producir un sólido marrón correspondiente [LCMS indicó la masa esperada (236)] a 2-cloro-6-(4-oxopiperidin-1-il) isonicotinonitrilo (1.58 g).

Se agregó metilamina (2.65 ml, 5.3 mmol) a una solución de 2-cloro-6-(4-oxopiperidin-1-il) isonicotinonitrilo (**Intermedio 26**; 500 mg, 2.12 mmol) en THF anhidro (4 ml). La mezcla se revolvió durante 30 minutos y se agregó triacetoxiborohidruro sódico (674 mg, 3.18 mmol). La mezcla se revolvió a temperatura ambiente durante 18 h, luego se concentró al vacío,

se diluyó con EtOAc y se lavó con 1 N NaOH, agua y solución salina. La fase orgánica se lavó sobre Na_2SO_4 luego se concentró al vacío para producir un aceite marrón el cual se secó al vacío para producir el compuesto del título (507 mg).

MS (ES): 251 para $C_{12}H_{15}ClN_4$

^{1}H NMR δ: 1.21 (m, 2H); 1.90 (m, 2H); 2.32 (s, 3H); 2.61 (m, 1H); 3.12 (m, 2H); 4.14 (m, 2H); 7.10 (s, 1H); 7.39 (s, 1H)

Intermedio 64: 1-[6-Cloro-4-(1*H*-tetrazol-5-il)piridin-2-il]-*N*-metilpiperidin-4-amina

Se agregó azida de sodio (131 mg, 2.02 mmol) y NH_4Cl (108 mg, 2.02 mmol) a una solución de 2-cloro-6-[4-(metilamino)piperidin-1-il] isonicotinonitrilo (**Intermedio 63**, 507 mg, 2.02 mmol) en DMF anhidro (3 ml). La mezcla se calentó a 120 °C bajo gas nitrógeno durante 1 h cuando la LCMS mostró la masa esperada. La mezcla se filtró y se purificó mediante HPLC de semi preparación levigado con acetonitrilo/agua (TFA al 0.1 %) y el compuesto del título se concentró al vacío para producir un sólido marrón higroscópico (220 mg).

MS (ES): (MH^+) 294 para $C_{12}H_{16}ClN_7$

Intermedio 65: 1-[6-Cloro-4-(1-metil-1*H*-tetrazol-5-il)piridin-2-il]-*N*-metilpiperidin-4-amina

Se agregó azida de sodio (225 mg, 3.47 mmol) y cloruro de amonio (186 mg, 3.47 mmol) a una solución de 2,6-dicloroisoniconitrilo (500 mg, 2.89 mmol) en DMF anhidro (3ml). La mezcla se calentó a 120 °C bajo gas nitrógeno durante 1 h. La mezcla se enfrió a temperatura ambiente y se agregó K_2CO_3 (798 mg, 5.78 mmol). La mezcla resultante se revolvió durante 30 minutos después de lo cual se agregó iodometano (270 µl, 4.33 mmol). La mezcla se revolvió a temperatura ambiente durante 18 h, se diluyó con EtOAc y se lavó con agua y solución salina. La fase orgánica se lavó sobre Na_2SO_4 y se concentró al vacío para producir un sólido marrón 2,6-dicloro-4-(2-metil-2H-tetrazol-5-il)-piridina (486 mg).

Se agregó tert-butilo piperidin-4-ilcarbamato (87 mg, 0.44 mmol) y DIEA (76µl, 0.44 mmol) a una solución de 2,6-dicloro-4-(2-metil-2H-tetrazol-5-il)-piridina (100 mg, 0.44 mmol) en NMP anhidro (2 ml). Empleando un Smith Microwave Synthesizer, la mezcla se sometió a microondas unimodal a 150 °C durante 15 minutos, se diluyó con EtOAc (25ml) y se lavó con agua (4 x 25ml). La fase orgánica se lavó sobre Na_2SO_4 y se concentró al vacío para producir un sólido marrón. Esta muestra se trató con 4 N HCl/dioxano (8 ml) durante 45 minutos. El solvente se extrajo bajo presión reducida y el material se secó al vacío.

MS (ES): MH^+ 294, para $C_{12}H_{16}ClN_7O$

Intermedio 66: tert-Butil [1-(6-cloropiridin-2-il)piperidin-4-il]carbamato

Se agregó TEA (0.13ml, 0.99 mmol) y 2, 6-dicloropiridina (0.14 g, 0.99 mmol) a una solución de tert-butilo piperidin-4-ilcarbamato (0.20 g, 0.99 mmol) en NMP (2ml) a temperatura ambiente. Empleando un Smith Microwave Synthesizer, la mezcla se sometió a microondas unimodal a 150°C durante 30 minutos. La mezcla se diluyó con EtOAc y se lavó con agua tres veces. La fase orgánica se lavó sobre sulfato de magnesio y se concentró para producir el compuesto del título. (300 mg).

MS (ES): 337 (MH^+) para $C_{17}H_{22}ClN_3O_2$

Intermedio 67: 2-Bromo-5-(etiltio)-1,3,4-tiadiazol

Se agregó *tert*-butilo nitrito (2.20 ml, 1.91 g, 18.50 mmol) en forma de goteo a una mezcla de bromuro de cobre (II) (3.32 g, 14.86 mmol) en acetonitrilo (30ml). Se agregó una solución de 5-(etiltio)-1,3,4- tiadiazol-2 amina (2.00 g, 12.40 mmol) en acetonitrilo (66 ml) y la mezcla se calentó a 65°C. Después de aproximadamente tres horas, la mezcla se enfrió, se diluyó con agua y se extrajo con éter. La fase orgánica se secó ($MgSO_4$) y se concentró al vacío. El material crudo se purificó mediante cromatografía instantánea utilizando EtOAc/hexanos al 10% para producir 2.15g del producto del título.

MS (ESP): 226 (MH^+) para $C_4H_5BrN_2S_2$

Intermedio 68: tert-Butil {1-[6-(acetilamino)-2-(metiltio) pirimidin-4-il}piperidin-4-il]carbamato

Se agregó TEA (0.32ml, 2.28 mmol) y N-[6-cloro-2-(metiltio)pirimidin-4-il] acetamida (**Intermedio 44**, 0.50 g, 2.28 mmol) a una solución de tert-butilo piperidin-4-ilcarbamato (0.46 g, 2.28 mmol) en NMP (2ml) a temperatura ambiente. Empleando un Smith Microwave Synthesizer, la mezcla se sometió a microondas unimodal a 150 °C durante 10 minutos. La mezcla se distribuyó entre agua y EtOAc. Las capas se separaron y la capa orgánica se lavó con agua dos veces más. La fase orgánica se lavó sobre sulfato de magnesio y se concentró para producir el compuesto del título (816 mg).

MS (ES): 381 (MH^+) para $C_{18}H_{28}N_4O_3S$

Intermedio 69: N-[6-(4-Aminopiperidin-1-il)-2-(metiltio) pirimidin-4-il]acetamida clorhidrato

Se disolvió tert-butil{1-[6-(acetilamino)-2-(metiltio)pirimidin-4-il]piperidin-4-il} carbamato (**Intermedio 68**) (816 mg, 2.15 mmol) en 4 N HCl/Dioxano (10 ml). La mezcla se revolvió a temperatura ambiente durante 2 h. Se extrajo el excedente de 4 N HCl/Dioxano mediante concentración al vacío para producir el compuesto del título como un sólido de color amarillo fuerte. (790 mg).

MS (ES): 281 (MH^+) para $C_{13}H_{20}N_4OS$

Intermedio 70: 2-(4-Aminopiperidin-1-il)-6-cloroisonicotinamida sal de clorhidrato

Se agregó una solución 4 N HCl/Dioxano (6 ml) a tert-butilo 1-[4-(aminocarbonil)-6-cloropiridin-2-il]piperidin-4-ilcarbamato (**Intermedio 16**, 100 mg, 0.282 mmol). La mezcla se revolvió a temperatura ambiente durante 90 minutos. El solvente se extrajo al vacío y se agregó el dietiléter anhidro (25 ml). El solvente se extrajo al vacío y el sólido amarillo claro

resultante se secó al vacío durante varias horas para producir el compuesto del título como un sólido casi blanco (87 mg).

MS ES: 255 para $C_{11}H_{15}ClN_4O$

^{1}H NMR δ: 1.56 (m, 2H); 2.08 (m, 2H); 2.35 (m, 2H); 3.27 (m, 1H); 4.35 (m, 2H); 7.00 (s, 1H); 7.21 (s, 1H); 7.68 (s, 1H); 7.90 (s, 1H); 8,20 (b, 3H).

Intermedio 71: 4-Cloro-5-etil-1*H*-pirrol-2-ácido carboxílico

El compuesto del título se sintetizó a partir de etil 4-cloro-5-etil-1*H*-pirrol-2-carboxilato **(Intermedio 72)** mediante un método análogo al del Intermedio **8**.

MS (ESP): 172.1 (M-H) para $C_7H_8ClNO_2$

Intermedio 72: Etil 4-cloro-5-etil-1*H*-pirrol-2-carboxilato

El compuesto del título se sintetizó a partir de etil 5-etil-1*H*-pirrol-2-carboxilato **(Intermedio 12)** mediante un método análogo al del Intermedio **9**.

MS (ESP): 200.1 (M-H) para $C_9H_{12}ClNO_2$

Intermedio 73: 3,4-Dicloro-5-etil-1*H*-pirrol-2-ácido carboxílico

El compuesto del título se sintetizó a partir de etil 3,4-dicloro-5-etil-1*H*-pirrol-2-carboxilato **(Intermedio 74)** mediante un método análogo al del Intermedio **8**.

MS (ESP): 208.1 (M+H) para $C_7H_7Cl_2NO_2$

Intermedio 74: Etil 3,4-dicloro-5-etil-1*H*-pirrol-2-carboxilato

El compuesto del título se sintetizó a partir de etil 5-etil-1*H*-pirrol-2-carboxilato **(Intermedio 12)** mediante un método análogo al del Intermedio **4**.

MS (ESP): 234.1 (M-H) para $C_9H_{11}C_{12}NO_2$

Intermedio 75: 4-Cloro-3,5-dimetil-1H-pirrol-2-ácido carboxílico

El compuesto del título se sintetizó a partir de etil 4-cloro-3,5-dimetil-1*H*-pirrol-2-carboxilato (**Intermedio 76**) mediante un método análogo al del Intermedio **8**.

MS (ESP): 172 (M-H) para $C_7H_8ClNO_2$

Intermedio 76: Etil 4-cloro-3,5-dimetil-1*H*-pirrol-2-carboxilato

El compuesto del título se sintetizó a partir de etil 3,5-dimetil-1H-pirrol-2-carboxilato (disponible en el comercio) mediante un método análogo al del Intermedio **9**.

MS (ESP): 200 (M-H) para $C_9H_{12}ClNO_2$

Intermedio 77: Etil 2-(4-aminopiperidin-1-il)-4-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]-1,3-tiazol-5-clorhidrato de carboxilato

El compuesto del título se preparó en forma análoga a la del Intermedio **126** comenzando a partir de *tert*-Butil [1-(aminocarbonotioil)piperidin-4-il] carbamato (**Intermedio 125**) y etil 2-cloro-4-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-3-oxobutanoato (**Intermedio 35**).

MS (ES) $(M+H)^+$: 416 para $C_{20}H_{23}ClN_4O_4S$

Intermedios 78-80

Los siguientes compuestos se prepararon en una forma análoga a la del Intermedio **126** comenzando a partir de *tert*-Butil [1-(aminocarbonotioil) piperidin-4-il]carbamato (**Intermedio 125**) y los materiales de partida enumerados.

Intermedio	Compuesto	M/Z	MP
Intermedio 78	Etil 2-(4-aminopiperidin-1-il)-4-(trifluorometil)-1, 3-tiazol-5-carboxilato sal de clorhidrato	323	Etil 2-cloro-4,4,4-trifluoro-3-oxobutanoato (disponible en el comercio)

Intermedio 79	Etil 2-(4-aminopiperidin-1-il)-4-(metoximetil)-1,3-tiazol-5-clorhidrato de carboxilato	300, 301	Etil 2-cloro-metoxi-3-oxobutanoato **(Intermedio 6)**
Intermedio 80	Etil 2-(4-aminopiperidin-1-il)-4-butil-1, 3-tiazol-5-carboxilato sal de clorhidrato	311	Etil 2-bromo-3-oxoheptanoato **(Intermedio 85)**

Intermedio 81: 2-(4-Aminopiperidin-1-il)-1,3-tiazol-5-clorhidrato de carboxamida

El compuesto del título se sintetizó a partir de *tert*-butilo 1-[5-(aminocarbonil)-1,3-tiazol-2-il]piperidin-4-ilcarbamato **(Intermedio 82)** mediante un método análogo al del Intermedio 1.

MS (ESP): 227 (M+H) para $C_9F_{14}N_4OS$

Intermedio 82: *tert*-Butilo 1-[5-(aminocarbonil)-1,3-tiazol-2-il]piperidin-4-ilcarbamato

El compuesto del título se sintetizó mediante un método análogo al del Intermedio **38** mediante el acoplamiento de *tert*-butilpiperidin-4-ilcarbamato (disponible en el comercio) con 2-bromo-1,3-tiazol-5-carboxamida (*J. Am. Chem. Soc.* **1952**, *74*, 5799).

MS (ESP): 327 (M+H) para $C_{14}H_{22}N_4O_3S$

Intermedio 83: Metil 2-cloro-6-(metiltio) isonicotinato

Se disolvió metil 2,6-dicloroisonicotinato (300 mg, 1.45 mmol) en DMF anhidro.

Se agregó tiometóxido sódico (102 mg, 1.45 mmol) y la mezcla se revolvió a temperatura ambiente durante 4 h. La mezcla se diluyó con EtOAc y se lavó con agua (x3), solución salina (x1) y se lavó sobre sulfato de sodio y se

concentró al vacío para obtener el compuesto del título (294 mg).
MS (ES) (M+H): 218 para $C_8H_8ClNO_2S$
^{1}H NMR δ: 2.73 (s, 3H); 4.04 (t, 3H); 7.64 (s, 1H); 7.79 (s, 1H)

Intermedio 84: Metil 2-cloro-6-(metilsulfinil)isonicotinato

Se disolvió metil 2-cloro-6-(metiltio)isonicotinato (**Intermedio 83**; 290 mg), en DCM anhidro (5 ml). Se agregó mCPBA (345 mg) y la mezcla se revolvió a temperatura ambiente durante 90 minutos. La mezcla se diluyó con EtOAc y se lavó con agua, trisulfato de sodio al 10%, agua, solución salina y se lavó sobre sulfato de sodio. La mezcla se concentró al vacío y se purificó mediante cromatografía instantánea levigado con EtOAc: Hexano (7:3) para obtener el compuesto del título (129 mg).
MS (ES) (M+H): 224 para $C_8H_8ClNO_3S$
^{1}H NMR δ: 2.97 (s, 3H); 4.04 (s, 3H); 8.06 (s, 1H); 8.29 (s, 1H)

Intermedio 85: Etil 2-bromo-3-oxoheptanoato

Se disolvió etil 3-oxoheptanoato (**Intermedio 94**; 5g, 29.03 mmol) en anh. CH_3CN (75mol) y se enfrió a 0°C. Se agregó $CuBr_2$, seguido por la adición de (hidroxi(tosiloxi)iodo)benceno(Reactivo de Koser). La mezcla se calentó a temperatura ambiente durante 1 h, después de lo cual la reacción se extinguió con agua (100ml). La solución azul se extrajo con DCM y la fase orgánica combinada se lavó bien con agua, solución salina y se lavó sobre Na_2SO_4 y se concentró al vacío. El material crudo se purificó mediante cromatografía instantánea levigado con un gradiente de 10%-50% Hexano/EtOAc, seguido por la destilación de Kugelrohr produciendo el compuesto del título (3.5g).
^{1}H NMR δ: 0.75-0.93 (m, 3H); 1.13-1.25 (m, 5H); 1.38-1.64 (m, 2H); 2.43-2.50 (m, 2H); 3.5- 3.69 (s, 2H); 5.54 (s, 1H).

Intermedio 86: 4-{(3,4-Dicloro-5-metil-1H-pirrol-2-il) carbonil] amino}trifluoroacetato de piperidinio

A una solución de tert-butilo 4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino}piperidina-1-carboxilato (**Intermedio 2**, 2.9 g, 7.7 mmol) en 15 ml DCM se agregó 15 ml TFA. La solución se revolvió a temperatura ambiente durante 30 minutos antes de retirar El solvente mediante evaporación bajo presión reducida. Se obtuvo un producto sólido oscuro con un rendimiento cuantitativo.

^{1}H NMR δ: 1.61-1.76 (m, 2H); 1. 91 - 2.03 (m, 2H); 2.18 (s, 3H); 2.96-3.10 (m, 2H); 3.30 (m, 2H); 4.01 (m, 1H); 11.98 (s, 1H).

Intermedio 87: 3,4-Dicloro-5-metil-N-(1-nitrosopiperidin-4-il)-1H-pirrol-2-carboxamida

Se agregó una solución de $NaNO_2$ (1.7 g, 24.6 mmol) en 20 ml de agua a una solución de 4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino} trifluoroacetato de piperidinio (**Intermedio 86**; 4 g, 10.3 mmol) y 400 µl de ácido acético en 60 ml de 1:1 EtOH-H_2O. La mezcla se calentó a 90 °C durante 1 hora. Después de enfriarla a temperatura ambiente, se agregó 200 ml de agua. Mediante filtración se recolectaron unos sólidos blancos y se secaron al vacío (2.8 g).

MS (APCI): 305 $(M+H)^+$ para $C_{11}H_{14}Cl_2N_4O_2$

^{1}H NMR δ: 1.31-1.54 (m, 1H); 1.63-1.80 (m, 1H); 1.80-1.98 (m, 1H); 1.96-2.16 (m, 1H); 2.18 (s, 3H); 2.85-3.16 (m, 1H); 3.76-4.05 (m, 1H); 4.07-4.33 (m, 1H); 4.49-4.81 (m, 2H); 7.33 (d, J=7.72 Hz, 1H); 12.00 (s, 1H).

Intermedio 88: Metil 2-cloro-6-metoxipirimidina-4-carboxilato

Lentamente se agregó 0.5 M solución de metóxido sódico en MeOH a una solución de metil 2,6-dicloropirimidina-4-carboxilato (0.30 g, 1.45 mmol) en MeOH (2 ml). Se formó un producto precipitado blanco el cual se revolvió durante otros 15 minutos. El producto se recolectó mediante filtración (0.20 g).

MS (ES) MH^+: 203 para $C_7H_7ClN_2O_3$

^{1}H NMR δ: 3.90 (s, 3H); 4.01 (s, 3H); 7.44 (s, 1H)

Intermedio 89: N-(1-Aminopiperidin-4-il)-3,4-dicloro-5-metil-1H-pirrol-2-carboxamida

Se agregó una solución de $TiCl_3$ al 20% (36ml, 27 mmol) en agua a una solución de 3,4-dicloro-5-metil-N-(1-nitrosopiperidin-4-il)-1H-pirrol-2-carboxamida (**Intermedio 87**, 2.8 g, 9.2 mmol) en 60 ml de MeOH. La mezcla se calentó a 70 °C durante 1 hora. Se agregó Na_2CO_3 acuoso para acidificar la mezcla, la cual se filtró mediante célite enjuagando con MeOH hasta que no se levigó más material. El producto filtrado se concentró y la solución acuosa residual se saturó con NaCl antes de extraerla 6 veces con DCM. Las capas orgánicas combinadas se secaron ($MgSO_4$) y El solvente se extrajo para producir un producto como un sólido beige.

MS (ES): 291 $(M+H)^+$.

^{1}H NMR δ: 1.43-1.70 (m, 2H); 1.76 (s, 2H); 2.03-2.36 (m, 5H); 2.83 (s, 2H); 3.18-3.54 (m, 2H); 3.68 (s, 1H); 7.11 (d, J=7.54 Hz, 1H); 11.95 (s, 1H).

Intermedio 90: 3,4-Dicloro-5-metil-N-piperidin-4-il-1H-pirrol-2-carboxamida

Se suspendió 4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino}trifluoroacetato de piperidinio (**Intermedio 86**, 6.07 g) en agua (100ml). A lo anterior se agregó 100 ml de $CHCl_3$: isopropanol (3:1) y Na_2CO_3 (50ml) sat.. La porción orgánica se separó y la porción acuosa se lavó con 100 ml porciones de $CHCl_3$: isopropanol (3:1) cinco veces. Las porciones orgánicas se combinaron, se secaron con $MgSO_4$ y se concentraron a un sólido amarillo (2.73 g, 64%).

^{1}H NMR δ: 1.22-1.53 (m, 2H); 1.76 (dd, J=12.34, 3.11 Hz, 2H); 2.17 (s, 3H); 2.50-2.62 (m, 2H); 2.81-3.02 (m, 2H); 3.62-3.97 (m, 1H); 7.11 (d, J=7.72 Hz, 1H).

Intermedio 91: Metil N-ciano-4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino}piperidina-1-carbimidotioato

Se calentó una solución de 3,4-dicloro-5-metil-N-piperidin-4-il-1H-pirrol-2-carboxamida (**Intermedio 90**, 2.73 g, 10 mmol) y dimetilo cianoditioimidocarbonato (1.61 g, 10 mmol) en dicloroetano a reflujo durante 5 horas. La mezcla de la reacción se concentró a un aceite naranja el cual se purificó mediante cromatografía instantánea en gel de sílice (gradiente de elución de DCM al 100% a MeOH en DCM al 5%). Se combinaron fracciones puras para producir el compuesto del título en 2.25 g (61%).

MS (ES): $374(M+H)^+$

^{1}H NMR δ: 1.53-1.67 (m, 2H); 1.93 (dd, J=13.56, 3.01 Hz, 2H); 2.18 (s, 3H); 2.67-2.75 (m, 3H); 3.31-3.44 (m, 2H); 4.03-4.16 (m, 1H); 4.33 (d, J=13.75 Hz, 2H); 7.32 (d, J=7.72 Hz, 1H); 12.06 (s, 1H).

Intermedio 92: 2,6-Dioxo-1,2,3,6-tetrahidropirimidina-4-carbaldehído monohidrato

El compuesto del título (9.53 g) se preparó de acuerdo con el procedimiento de Johnson y colaboradores (Johnson, Treat B.; Schroeder, Elmer F. *J. Am. Chem.* Soc. **1931**, 53, 1989-1994).

^{1}H NMR δ: 6.75 (brs, 2H); 9.60 (s, 1H); 10.61 (s, 1H); 10.99 (s, 1H)

Intermedio 93: Metil 2-(4-aminopiperidin-1-il)-6-cloroisonicotinato sal de clorhidrato

Se disolvió metil 2-{4-[(tert-butoxicarbonil)amino]piperidin-1-il}-6-cloroisonicotinato (**Intermedio 23**,1.81 g, 4.9 mmol) en 4 N HCl/dioxano (200 ml). La mezcla se revolvió a temperatura ambiente durante 2 h. El solvente se extrajo al vacío para producir el compuesto del título (1.5 g).

MS (LCMS): 269

Intermedio 94: Etil 3-oxoheptanoato

El compuesto del título se preparó en forma análoga a la del Intermedio **123** a partir de cloruro de valerilo y 2,2-dimetil-1,3-dioxano-4,6-diona (ambos disponibles en el comercio).

^{1}H NMR δ: 0.7-0.96 (m, 3H); 1.06-1.31 (m,5H); 1.36-1.58 (m, 2H); 2.43-2.50 (m, 2H); 3.5- 3.69 (s, 2H); 3.99-4.22 (m, 2H).

Intermedio 95: N-[1-(Aminocarbonotioil)piperidin-4-il]-3,4-dicloro-5-metil-1H-pirrol-2-carboxamida

El compuesto del título se preparó mediante un procedimiento análogo al del **Intermedio 125** comenzando a partir de 3,4-dicloro-5-metil-N-piperidin-4-il-1 H-pirrol-2-carboxamida (**Intermedio 90**, 0.5 g, 2 mmol). El producto se concentró a un sólido el cual se purificó en una columna de sílice instantánea (gradiente de elución de MeOH 0-5 % en DCM durante 30 min). La purificación produjo un sólido blanco (0.22g).

^{1}H NMR δ: 1.41-1.56 (m, 2H); 1.80 (dd, J=12.81, 3.20 Hz, 2H); 2.17 (s, 3H); 3.08-3.22 (m, 2H); 3.96-4.11 (m, 1H); 4.43 (d, J=15.07 Hz, 2H); 7.27 (d, J=7.72 Hz, 1H); 7.32-7.47 (m, 2H); 11.96 (s, 1H).

Intermedio 96: Metil 2-cloro-6-(etiltio)pirimidina-4-carboxilato

Se agregó una solución de etanotiol (0.30 g, 4.8 mmol) en THF (1 ml) en forma de goteo a una solución de metil 2,6-dicloropirimidina-4-carboxilato (1 g, 4.8 mmol), THF (8 ml) y TEA (0.49 g, 4.8 mmol) a 0 °C bajo nitrógeno. La mezcla se revolvió durante 2 h y lentamente se calentó a temperatura ambiente. La mezcla se diluyó con EtOAc (50 ml) y agua (10 ml). La capa orgánica se separó, se lavó sobre sulfato de sodio, se filtró y se concentró al vacío para obtener el compuesto del título (1.1 g).

MS (ESP): 431 (M+H) para $C_8H_9ClN_2O_2S$

^{1}H NMR δ: 1.38 (t, 3H); 3.29 (q, 2H); 3.96 (s, 3H); 7.97 (s, 1H).

Intermedio 97:4-Cloro-2-butil-6-metilpirimidina

Utilizando el procedimiento de Papet, Anne-Lure y colaboradores, (*Synthesis* 1993 (5), 478-481) se preparó el compuesto del título (1.28 g) a partir de 2-butil-6-metilpirimidin-4-ol (**Intermedio 98**,4 g, 32.85mmol).

MS (ES) (M+H): 184 para $C_9H_{13}ClN_2$

^{1}H NMR δ: 1.10 (m, 3H); 1.57 (m, 2H); 1.80 (m, 2H); 2.37 (s, 3H); 2.99 (m, 2H); 6.67 (s, 1H)

Intermedio 98:2-Butil-6-metilpirimidin-4-ol

Se trató clorhidrato de pentanimidamida (3.2 g) (preparado de acuerdo con Garigipati, R. S.; *Tetrahedron Lett* 1990, 31 (14), 1969) con acetoacetato de etil (3.05 g) en un procedimiento modificado utilizando sodio (1.62 g) en EtOH anhidro (50 ml) como base (como se describe en Salimbeni, Aldo; y colaboradores, *J. Med. Chem.* (1995), 38 (24), 4806-20) produciendo el compuesto del título (4.04 g).

MS (ES) (M+H): 166 para $C_9H_{14}N_2O$

^{1}H NMR δ: 0.80 (m, 3H); 1.31 (m, 2H); 1.63 (m, 2H); 2.25 (s, 3H); 2.41 (m, 2H); 6.29 (s, 1H)

Intermedio 99: *tert*-Butil[(2-butil-6-metilpirimidin-4-il)piperidin-4-il]carbamato

Preparado en una forma análoga a la del Intermedio **38** comenzando a partir de 4-cloro-2-butil-6-metilpirimidina (**Intermedio 97**) y *tert*-butilo piperidin-4-ilcarbamato.

MS (ES) (M+H): 349 para $C_{19}H_{32}N_4O_2$

^{1}H NMR δ: 0.93 (m, 3H); 1.33 (m, 2H); 1.45 (s, 9H);1.70 (m, 2H); 1.82 (m, 2H); 2.02 (m, 1H); 2.25 (s, 3H); 2.61 (m, 4H); 3.03 (m, 2H); 3.39 (m, 2H); 3.66 (m, 1H); 4.20 (m, 2H); 6.58 (s, 1H); 6.93 (d, 1H); 6.29.

Intermedio 100: 6-{4-[(*tert*-Butoxicarbonil)aminolpiperidin-1-il}-2-butilpirimidina- 4-ácido carboxílico

Se disolvió *tert*-Butil [1-(2-butil-6-metilpirimidin-4-il)piperidin-4-il]carbamato (1.08 g) (**Intermedio 99**) en piridina anhidra (25 ml). Se agregó dióxido de selenio (1.72 g) y la mezcla se calentó a 120 °C durante 4 h. La solución negra se diluyó con agua (40 ml), se filtró sobre un lecho de célite. El producto filtrado se acidificó con 1 N HCl y se extrajo con EtOAc, se lavó bien con agua, se lavó sobre sulfato de sodio y se concentró

al vacío. El material crudo se purificó mediante cromatografía instantánea levigado con triclorometano/MeOH/hidróxido de amonio (9:1:1) para obtener el compuesto del título (241 mg).

MS (ES) (M+H): 378 para $C_{19}H_{30}N_4O_4$

^{1}H NMR δ: 0.74 (t, 3H); 1.12 (m, 4H); 1.20 (s,9H); 1.49 (m, 2H); 1.65 (m, 2H); 2.54 (m, 1H); 2.9 (m, 2H); 3.45 (m, 2H); 4.18 (m, 2H); 6.69 (d, 1H); 6.82 (s, 1H)

Se prepararon los Intermedios 101 a 109 mediante el siguiente método general:

Se combinaron los materiales de partida 4-(*N*-BOC amino)-piperidina (1.00 equivalente, 5.00 mmol), acetato de paladio (II) (0.10 equiv), BINAP (*rac*-2,2'-bis(difenilfosfinio)-1,1'-binaftilo, 0.10 equiv), carbonato de caesio (1.40 equiv) y arilo hálido que aparecen en la siguiente tabla (1.00 equiv) Se retiró el gas de los sólidos y se colocaron bajo argón. Se agregó tolueno (10ml) y la mezcla se revolvió a 100 °C durante aproximadamente 16 h. La mezcla se filtró y el producto filtrado se concentró al vacío. El producto crudo se purificó mediante cromatografía en columna instantánea de gel de sílice. Los materiales de partida arilo hálido que aparecen en la siguiente tabla para los **Intermedios 101 a 109** están disponibles en el comercio, excepto el metil 6-bromopiridina-2-carboxilato (**Intermedio 158**) y el metil 5-bromotiofeno-2-carboxilato (**Intermedio 159**) los cuales se formaron mediante la esterificación de ácidos disponibles en el comercio.

Intermedio 101: Metil 5-{4-[(tert-butoxicarbonil)amino]piperidin-1-il}tiofeno-2-carboxilato

Intermedio 102: Metil 5-{4-[(tert-butoxicarbonil)amino]piperidin-1-il}-2-furoato

Intermedio 103: Metil 3-{4-[(tert-butoxicarbonil)amino]piperidin-1-il}benzoato

Intermedio 104: Metil 3-bromo-5-{4-[(*tert*-butoxicarbonil) amino]piperidin-1-il}benzoato

Intermedio 105: Etil 5-{4-[(*tert*-butoxicarbonil)amino]piperidin-1-il}nicotinato

Intermedio 106: Metil 5-{4-[(*tert*-butoxicarbonil)amino]piperidin-1-il}nicotinato

Intermedio 107: Metil 6-{4-[(*tert*-butoxicarbonil)amino]piperidin-1-il}piridina-2-carboxilato

Intermedio 108: Metil 3-{4-[(*tert*-butoxicarbonil)amino]piperidin-1-il}-5-morfolin-4-ilbenzoato

Intermedio 109: Metil 3-{4-[(*tert*-butoxicarbonil)amino]piperidin-1-il}-5-(4-metilpiperazin-1-il)benzoato

Intermedio	Material de Partida Arilo Hálido	^{1}H NMR δ	m/z
101	Metil 5-bromotiofeno-2-carboxilato (Intermedio 159)	1.38 (s, 9H); 1.43-1.53 (m, 2H); 1.78-1.81 (m, 2H); 3.00 (t, 2H); 3.45 (m, 1H); 3.55-3.60 (m, 2H); 3.70 (s, 3H); 6.17 (d, 1H); 6.90 (d, 1H); 7.49 (d, 1H).	341
102	Metil 5-bromo-2- furoato	1.32-1.43 (m, 11H); 1.75-1.77 (m, 2H); 2.91 (t, 2H); 3.42 (m, 1H); 3.61-3.65 (m, 2H); 3.68 (s, 3H); 5.43 (d, 1H); 6.89 (d, 1H); 7.21 (d, 1H).	325
103	Metil 3-bromobenzoato	1.38 (s, 9H); 1.42-1.51 (m, 2H); 1.78-1.82 (m, 2H); 2.77 (t, 2H); 3.40 (m, superpuesto con agua, 1H); 3.65-3.70 (m, 2H); 3.82 (s, 3H); 6.86 (d, 1H); 7.22 (m,	335

Intermedio	Material de Partida Arilo Hálido	^{1}H NMR δ	m/z
		1H); 7.33 (d, 2H); 7.43 (br s, 1H).	
104	Metil 3,5-dibromobenzoato	1.38 (s, 9H); 1.43-1.48 (m, 2H); 1.76-1.79 (m, 2H); 2.84 (t, 2H); 3.43 (m, 1H); 3.70- 3.74 (m, 2H); 3.83 (s, 3H); 6.85 (d, 1H); 7. 35 (br s, 2H); 7. 39 (s, 1H).	413 415
105	Etil 5-bromonicotinato	1.33 (t, 3H); 1.39 (s, 9H); 1.43-1.52 (m, 2H); 1.79-1.83 (m, 2H); 2.86 (t, 2H); 3.39 (m, 1H); 3.75-3.79 (m, 2H); 4.33 (q, 2H); 6.88 (d, 1H); 7.65 (m, 1H); 8.45 (m, 1H); 8.53 (m, 1H).	350
106	Metil 5-bromonicotinato	1.26-1.34 (m, 2H); 1.38 (s, 9H); 1.76-1.80 (m, 2H); 2.91 (t, 2H); 3.49 (m, 1H); 3.82 (s, 3H); 4.25-4.30 (m, 2H); 6.84 (d, 1H); 7.07 (d, 1H); 7.26 (d, 1H); 7.65 (t, 1H).	336
107	Metil 6-bromopiridina-2-carboxilato (Intermedio 158)	1.26-1.34 (m, 2H); 1.39 (s, 9H); 1.76-1.80 (m, 2H); 2.91 (t, 2H); 3.50 (m, 1H); 3.82 (s, 3H); 4.26-4.30 (m, 2H); 6.85 (d, 1H); 7.08 (d, 1H); 7.26 (d, 1H); 7.65 (t, 1H)	336

Intermedio	Material de Partida Arilo Hálido	^{1}H NMR δ	m/z
108	Metil 3-bromo-5-{4-[(tert-butoxi carbonil)amino]piperidin-1-il} benzoato (**Intermedio 104**)	1.32-1.52 (m, 11H); 1.77 (d, 2H); 2.72 (t, 2H); 3.02-3.15 (m, 4H); 3.31 (s, 3H); 3.34-3.47 (m, 1H); 3.64 (d, 2H); 3.58-3.74 (m, 4H); 3.79 (s, 3H); 6.70 (s, 1H); 6.84 (d, 1H); 6.89 (s, 1H); 6.93 (s, 1H).	420
109	Metil 3-bromo-5-{4-[(tert-butoxi carbonil)amino]piperidin-1-il} enzoato (**Intermedio 104**)	1.32-1.53 (m, 11H); 1.77 (d, 2H); 2.21 (s, 3H); 2.37-2.47 (m, 4H); 2.72 (t, 2H); 3.07-3.20 (m, 4H); 3.35-3.41 (m, 1H); 3.64 (d, 2H); 3.79 (s, 3H); 6.69 (s, 1H); 6.85 (d, 1H); 6.91 (d, 2H).	433

Los Intermedios 110 a 118 se fabricaron mediante la desprotección de los **Intermedios 101 a 109** por medio del tratamiento con un exceso de 4 N HCl en THF, un procedimiento análogo a aquel empleado en el **Intermedio 46.** El material crudo resultante se utilizó sin una purificación posterior.

Intermedio 110: Metil 5-(4-aminopiperidin-1-il)tiofeno-2-clorhidrato de carboxilato

MS (APCI) (MH^+): 241 para $C_{11}H_{16}N_2O_2S$; SM: **Intermedio 101**

Intermedio 111: Metil 5-(4-aminopiperidin-1-il)-2-clorhidrato de furoato

MS (ES) (MH^+): 225 para $C_{11}H_{16}N_2O_3$; SM: **Intermedio 102**

Intermedio 112: Metil 3-(4-aminopiperidin-1-il)clorhidrato de benzoato

MS (ES) (MH^+): 235 para $C_{13}H_{18}N_2O_2$; SM: **Intermedio 103**

Intermedio 113: Metil 3-(4-aminopiperidin-1-il)-5-bromoclorhidrato de benzoato

MS (ESP) (M, MH^{+2}): 313, 315 para $C_{13}H_{17}BrN_2O_2$; SM: **Intermedio 104**

Intermedio 114: Etil 5-(4-aminopiperidin-1-il)clorhidrato de nicotinato

MS (ESP) (MH^+): 250 para $C_{13}H_{19}N_3O_2$; SM: **Intermedio 105**

Intermedio 115: Metil 5-(4-aminopiperidin-1-il)clorhidrato de nicotinato

MS (ESP) (MH^+): 236 para $C_{12}H_{17}N_3O_2$; SM: **Intermedio 106**

Intermedio 116: Metil 6-(4-aminopiperidin-1-il)piridina-2-clorhidrato de carboxilato

MS (ESP) (MH^+): 236 para $C_{12}H_{17}N_3O_2$; SM: **Intermedio 107**

Intermedio 117: Metil 3-(4-aminopiperidin-1-il)-5-morfolin-4-ilclorhidrato de benzoato

MS (ESP): 320 (MH^+) para $C_{17}H_{25}N_3O_3$; SM: **Intermedio 108**

Intermedio 118: Metil 3-(4-aminopiperidin-1-il)-5-(4-metilpiperazin-1-il)clorhidrato de benzoato

MS (ESP): 333 (MH^+) para $C_{18}H_{28}N_4O_2$; SM: **Intermedio 109**

Intermedio 119: Etil 3-bromoisoxazol-5-carboxilato

Se disolvió dibromoformaldoxima (407 mg, 2.07 mmol) (preparado con el procedimiento de JC Rohloff, y colaboradores, Tetrahedron Lett 1992, 33:3113-6) y propiolato de etil (311 mg, 3.17 mmol) en 10 ml EtOH acuoso al 50%. Mientras se revolvía, se agregó una solución de 243 mg (2.43 mmol) de bicarbonato de potasio en 5 ml de agua en forma de goteo durante 1 h. La solución resultante se revolvió durante otras 4 h, se diluyó con 25 ml de agua y se extrajo con cloroformo (3 x 25 ml). El extracto orgánico combinado se lavó sobre sulfato de sodio y se concentró al vacío hasta obtener un aceite incoloro, 345 mg (rendimiento 78%) como una mezcla 7:1 de los carboxilatos 5- y 4-.

^1H NMR ($CDCl_3$) δ: 1.34 (t, 3H, J = 7.16Hz), 4.30 & 4.37 (2q, 2H, J = 7.16 Hz), 6.92 & 8.81 (2s, 1H, proporción 7:1).

Intermedio 120: 3-Bromoisoxazol-5-ácido carboxílico

Se revolvió una solución de 442 mg (2.0 mmol) de etil 3-bromoisoxazol-5-carboxilato (**Intermedio 119**) y 5.0 ml de 1 N hidróxido de sodio en 10 ml de MeOH a temperatura ambiente durante 5 h, luego se acidificó con 6.0 ml de 1 N ácido clorhídrico, se diluyó con 25 ml de agua y se extrajo con EtOAc (3 x 25ml). El extracto orgánico combinado se lavó sobre sulfato de magnesio y se concentró al vacío para producir el compuesto del título como un sólido blanco (310 mg).

MS. 0.30 (ES^-) 189.99/191.99/193.17; $C_4H_2BrNO_3$ 191.97

^{1}H NMR δ: 7.46 (s, 1H)

Intermedio 121: Metil 6-aminopiridina-2-carboxilato

Se disolvió 6-aminopiridina-2-ácido carboxílico (5.0 g, 36 mmol) en 50 ml de MeOH. A lo anterior se agregó cloruro de acetil (9.0 ml, 126 mmol) en 50 ml de MeOH. La reacción se calentó a reflujo durante la noche. Se concentró hasta obtener un aceite naranja y se partió con EtOAc y agua. Las porciones orgánicas se lavaron con solución salina, se secaron ($MgSO_4$) y se concentraron hasta obtener un sólido amarillo.

^{1}H NMR δ: 3.79 (s, 3H); 6.32 (s, 2H); 6.64 (d, J=8.29 Hz, 1H); 7.18 (d, J=7.35 Hz, 1H); 7.51 (dd, J=8.29, 7.35 Hz, 1H).

Intermedio 122: Metil 6-aminopiridina-2-carboxilato 1-óxido clorhidrato

Se disolvió metil 6-aminopiridina-2-carboxilato (**Intermedio 121**, 3.3 g, 22 mmol) en acetona y a lo anterior se agregó una solución de mCPBA (5.9 g, 23.5 mmol) en acetona. Después de revolver durante la noche, se extrajo la acetona y el residuo se suspendió en 3 N HCl. El producto precipitado se retiró por filtración para producir la sal de HCl (3.57 g, 87%).

MS (ES): 169 $(M+H)^+$.

^{1}H NMR δ: 3.91 (s, 3H); 7.20 (dd, J=7.25, 1.60 Hz, 1H); 7.39 (dd, J=8.85, 1.70 Hz, 1H); 7.82 (dd, J=8.95, 7. 25 Hz, 1H).

Intermedio 123: Etil 4-(2-metoxietoxi)-3-oxobutanoato

Se suspendió 2,2-dimetil-1,3-dioxano-4,6-diona (1.72 g) en piridina anhidra (20 ml) y se enfrió a 0°C. Se agregó (2-metoxietoxi) cloruro de acetil (2 g) lentamente. La mezcla se revolvió a temperatura ambiente durante 3 h. La mezcla se vertió sobre 2 N HCl (30ml) y se extrajo con DCM (x3). La fase orgánica combinada se lavó con agua, solución salina, se lavó sobre sulfato de sodio y se concentró al vacío. El aceite naranja se disolvió en EtOH (20ml) y se llevó a reflujo durante 7 h. El solvente se extrajo al vacío y el aceite marrón se destiló por Kugelrohr produciendo el compuesto del título como un aceite incoloro (1.55 g).

MS (ES) (M+H): 204 para $C_9H_{16}O_5$

^{1}H NMR ($CDCl_3$) δ: 1.58 (m, 2H); 1.92 (m, 2H); 2.18 (s, 3H); 2.80 (s, 3H); 3.18 (m, 2H); 3.76 (s, 3H); 4.12 (m, 1H); 4.29 (m, 2H); 7.08 (s, 1H); 7.22 (d, 1H); 7.34 (s, 1H); 11.96 (s, 1H); 12.17 (s, 1H)

Intermedio 124: Etil 2-cloro-4-(2-metoxietoxi)-3-oxobutanoato

Se disolvió etil 4-(2-metoxietoxi)-3-oxobutanoato (**Intermedio 123**) (0.5 g) en DCM anhidro (5 ml). Se agregó cloruro de sulfurilo (430 mg) en forma de goteo a temperatura ambiente.

La mezcla se revolvió durante 6 h. La mezcla cruda se diluyó con EtOAc (50ml) y se lavó bien con agua y solución salina, se lavó sobre sulfato de sodio y se concentró al vacío para obtener el compuesto del título como un aceite naranja claro (414 mg).

MS(ES) (M+H): 238 para $C_9H_{15}ClO_5$

^{1}H NMR($CDCl_3$) δ: 1.70 (m, 3H); 3.70 (s, 3H); 4.18 (m, 4H); 4.62 (m, 2H); 4.71(s, 1H)

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Intermedio 125: *tert*-Butil [1-(aminocarbonotioil)piperidin-4-il]carbamato

Se disolvió tert-butilo piperidin-4-ilcarbamato (5.5 g) en DCM anhidro (75 ml). Se agregó H-fluoren-9-ilmetilo isotiocianatidocarbonato (Fmoc isotiocianato; 7.75 g) en porciones pequeñas a temperatura ambiente después de lo cual se formó un producto precipitado blanco. La mezcla se

revolvió a temperatura ambiente durante 90 min. El solvente se extrajo al vacío y la mezcla cruda se trató con piperidina al 10% en MeOH (100ml) durante 12 h. La mezcla se concentró al vacío y se trituró con n-hexanos. El material cristalino blanco se filtró y se lavó bien con n-hexanos y se secó al vacío para obtener el compuesto del título (6.55 g).

MS (ES) (M+H): 260 para $C_{12}H_{21}N_3O_2S$

^{1}H NMR δ: 1.24 (m, 2H); 1.38 (s, 9H); 1.67 (m, 2H); 2.99 (m, 2H); 3.33 (m, 1H); 4.15 (m, 2H); 6.52 (d, 1H); 7.72 (s, 2H).

Intermedio 126: Etil 2-(4-aminopiperidin-1-il)-4-[(2-metoxietoxi)metil]-1,3- tiazol-5-clorhidrato de carboxilato

Se disolvió *tert*-butil[1-(aminocarbonotioil)piperidin-4-il]carbamato (**Intermedio 125**, 400 mg) en EtOH anhidro (5 ml). Se agregó etil 2-cloro-4-(2-metoxietoxi)-3-oxobutanoato (**Intermedio 124**,368 mg) y la mezcla se calentó a 90 °C durante 18 h. Se detectó una extracción parcial del grupo Boc. Se extrajo El solvente al vacío y el material seco se trató con 4 N HCl/dioxano durante 2 h. Se extrajo El solvente al vacío para producir un sólido marrón/amarillo el cual se secó para obtener el compuesto del título que se utilizó sin una purificación posterior (508 mg).

MS (ES) (M+H): 343 para $C_{15}H_{24}ClN_3O_4S$

Intermedio 127: Metil 6-azidopiridina-2-carboxilato 1-óxido

Se disolvió metil 6-aminopiridina-2-carboxilato 1-óxido clorhidrato (**Intermedio 122**, 3. 34 g, 16 mmol) en HCl al 10% (acuoso) y se enfrió a 5°C. Se agregó una solución acuosa de $NaNO_2$ (1.5 g, 21 mmol) en forma de goteo manteniendo la temperatura por debajo de 5°C. Después de revolver durante 15 minutos se agregó una solución acuosa de NaN_3 (1.4 g, 21 mmol) en forma de goteo manteniendo la temperatura por debajo de 5°C. La reacción se revolvió a 5 °C durante 30 minutos y lentamente se calentó a temperatura ambiente. El producto se extrajo con DCM y luego la capa acuosa se alcalinizó (con NaOH al 50% para obtener un pH 13) y luego se extrajo de nuevo con DCM.

El secado ($MgSO_4$) y la extracción del solvente produjo un aceite amarillo (2.6 g, 82%).

^{1}H NMR δ: 3.89 (s, 3H); 7.61 (dd, 1H); 7.78 (dd, J=8.85, 1.70 Hz, 1H); 8.02 (dd, J=8.95, 7.25 Hz, 1H).

Intermedio 128: Metil5-ciano-1-hidroxi-1H-pirrol-2-carboxilato

Una solución de metil 6-azidopiridina-2-carboxilato 1-óxido (**Intermedio 127**, 2.6 g, 13 mmol) en isopropanol se burbujeó con nitrógeno durante 20 minutos seguido por calentamiento hasta reflujo durante 16 horas. La solución se concentró hasta obtener un aceite rojo (2.55 g, 99%).

^{1}H NMR δ: 3.81 (s, 3H); 6.75 (d, J=4.90 Hz, 1H); 6.87 (d, J=4.90 Hz, 1H).

Intermedio 129: Metil 5-ciano-1H-pirrol-2-carboxilato

Se agregó una solución de $TiCl_3$ al 20% (25ml, 32 mmol) en agua a una solución de metil 5-ciano-1-hidroxi-1H-pirrol-2-carboxilato (**Intermedio 128**, 2.55 g, 15 mmol) en MeOH.

La reacción se calentó hasta una temperatura externa de 70°C durante 3 horas. La mezcla de la reacción se concentró para extraer MeOH y el residuo se partió con EtOAc y agua.

La porción orgánica se secó con $MgSO_4$ y se concentró hasta obtener un aceite naranja.

^{1}H NMR δ: 3.79-3.87 (m, 3H); 6.88 (dd, J=3.86, 2.35 Hz, 1H); 7.02 (dd, J=3.77, 2.07 Hz, 1H); 13.42 (s, 1H).

Intermedio 130: Metil 3,4-dicloro-5-ciano-1H-Pirrol-2-carboxilato

Se disolvió metil 5-ciano-1H-pirrol-2-carboxilato (**Intermedio 129**, 0.95 g, 6.3 mmol) en DCM anhidro y se enfrió a 0°C. Se agregó TEA en forma de goteo y se revolvió durante varios minutos seguido por la adición en forma de goteo de SO_2Cl_2. La reacción se revolvió durante 20 minutos a 0 °C antes de calentarla a temperatura ambiente. La mezcla de la reacción se diluyó con agua y se extrajo. La porción orgánica se secó con $MgSO_4$ y se concentró hasta obtener un sólido amarillo (1.32 g, 96%).

^{1}H NMR δ: 3.80-3.91 (m, 3H); 14.25 (s, 1H).

Intermedio 131: 3,4-Dicloro-5-ciano-1H-pirrol-2-ácido carboxílico

El compuesto del título se preparó mediante un procedimiento análogo al del **Intermedio 3** comenzando a partir de metil 3,4-dicloro-5-ciano-1H-pirrol-2-carboxilato (**Intermedio 130**).

^{1}H NMR δ: 14.02 (s, 1H).

Intermedio 132: 3,4-Dicloro-5-ciano-1H-pirrol-2-carbonilo cloruro

Se disolvió 3,4-dicloro-5-ciano-1H-pirrol-2-ácido carboxílico (**Intermedio 131**, 0.9 g, 0.2 mmol) en un excedente de cloruro de tionilo (5 ml) y se calentó a reflujo durante 30 minutos. La mezcla de la reacción se concentró y el residuo se disolvió en THF y se concentró (x2). El sólido (0.82 g, 89%) se bombeó hasta secarlo y se almacenó bajo argón.

^{1}H NMR($CDCl_3$): 12. 39 (s, 1H).

Intermedio 133: Metil 2-{4-[(tert-butoxicarbonil)amino]piperidin-1-il}-1,3-tiazol- 5-carboxilato

Se suspendió tert-butilo piperidin-4-ilcarbamato (4.5 g, 22 mmol), metil 2-bromo-1,3-tiazol-5- carboxilato (5.0 g, 22 mmol) y diisopropiletilamina (3.8 ml, 22 mmol) en DMF anhidro y se calentó hasta alcanzar una temperatura externa de 130 °C durante 1.5 horas. Se extrajo el DMF y el sólido se partió con EtOAc y agua. Los extractos orgánicos combinados se lavaron con solución salina, se secaron con $MgSO_4$ y se concentraron hasta obtener un sólido amarillo (7.05 g, 94%).

^{1}H NMR δ: 1.34-1.41 (m, 9H); 1.41-1.47 (m, 2H); 1.82 (dd, J=12.81, 2.83 Hz, 2H); 3.15- 3.28 (m, 2H); 3.54 (s, 1H); 3.74 (s, 3H); 3.83-3.95 (m, 2H); 6.93 (d, J=7.72 Hz, 1H); 7.85 (s, 1H).

Intermedio 134: Metil 2-(4-aminopiperidin-1-il)-1,3-tiazol-5-carboxilato

Se disolvió etil 2-{4-[(tert-butoxicarbonil)amino]piperidin-1-il}-1,3-tiazol-5-carboxilato (**Intermedio 133**,6. 92 g, 20 mmol) en un excedente de 4 M

HCl en dioxano. Después de varios minutos se formó un producto precipitado blanco y la reacción se completó después de 1 hora. El producto precipitado se retiró por filtración, se lavó con éter y se secó, produciendo la sal di-HCl, monohidrato 6.03 g, 96%). Luego el sólido se disolvió en $NaHCO_3$ sat, se colocó en el extractor continuo con DCM durante la noche. La porción orgánica se secó con $MgSO_4$ y se concentró hasta obtener un sólido blanco (3.84 g, 83%).

^{1}H NMR δ: 1.19-1.33 (m, 2H); 1.57 (s, 2H); 1 70-1.83 (m, 2H); 2.76-2.89 (m, 1H); 3.12- 3.25 (m, 2H); 3.74 (s, 3H); 3.87 (dt, J=13.09,3.72 Hz, 2H); 7.84 (s, 1H).

Intermedio 135: Metil 4-{4-[(tert-butoxicarbonil)amino]piperidin-1-il}quinolina-2carboxilato

El compuesto del título se preparó mediante un procedimiento análogo al del **Intermedio 133** comenzando con metil 4-cloroquinolina-2-carboxilato (WO 9505378). El producto se purificó en una columna instantánea de gel de sílice (0 → 5% MeOH en DCM) seguido por la recristalización de EtOAc.

^{1}H NMR δ: 1.37-1.44 (m, 9H); 1.63-1.78 (m, 2H);1.93 (s, 1H); 1.98 (d, J=7.54 Hz, 1H); 2.96 (t, J=11.11 Hz, 2H); 3.56 (d,J=12.25 Hz, 3H); 3.93 (s, 3H); 7.03 (d, J=7.54 Hz, 1H); 7.52 (s, 1H); 7.64-7.74 (m, 1H); 7.80 (td, J=7.63, 1.32 Hz, 1H); 7.99 (d, J=7.91 Hz, 1H); 8.07 (d, J=7.54 Hz, 1H).

Intermedio 136: Metil 4-(4-aminopiperidin-1-il)quinolina-2-clorhidrato de carboxilato

El compuesto del título se preparó mediante un procedimiento análogo al del **Intermedio 134** comenzando a partir de metil 4-{4-[(tert-butoxicarbonil)amino]piperidin-1-il}quinolina-2-carboxilato (**Intermedio 135**). El producto se obtuvo como la sal monoclorhidrato.

^{1}H NMR δ: 1.89 (d, J=10.17 Hz, 2H); 2.19 (s, 2H); 3.45-3.60 (m, 3H); 4.05 (s, 3H); 4.24 (d, J=13.00 Hz, 2H); 7.59 (s, 1H); 7.75 (t, J=7.63 Hz, 1H);

7.97-8.05 (m, 1H); 8.12 (d, J=8.48 Hz, 1H); 8.34 (d, J=8.48 Hz, 1H); 8.60 (s, 2H).

Intermedios 137-142

Las siguientes quinolinas se prepararon empleando el método de FR Alexandre, y colaboradores, Tetrahedron 2003, 59: 1413

Intermedio 137: Etil 4-cloro-8-metoxiquinolina-2-carboxilato

Intermedio 138: Metil 4-cloro-8-fluoroquinolina-2-carboxilato

Intermedio 139: Metil 4-cloro-8-metilquinolina-2-carboxilato

Intermedio 140: Metil 4-cloro-6-fluoroquinolina-2-carboxilato

Intermedio 141: Metil 4,8-dicloroquinolina-2-carboxilato

Intermedio 142: Etil 2-cloro-oxazol-4-carboxilato

Bajo una atmósfera de nitrógeno, se agregó 1.70ml (14.3 mmol) de nitrito de tert-butilo a una suspensión de 1.65 g (12.3 mmol) de cloruro de cobre (II) en 50 ml de acetonitrilo. La suspensión resultante se calentó a 75°C, luego se agregó 1.60 g (10.2 mmol) de etil 2-aminooxazol-4carboxilato (G Crank & MJ Foulis, J Med Chem 1971, 14: 1075-1077) en porciones durante 20 min (evolución de gas). Después de revolver durante otros 30 min, se dejó que la reacción se enfriara a temperatura ambiente, se diluyó con 50 ml de EtOAc y se extrajo con agua (2 x 25 ml). La capa orgánica se lavó sobre $MgSO_4$ y se concentró al vacío hasta obtener un sólido oscuro aceitoso.

La cromatografía instantánea a través de un gel de sílice neutro empleando una mezcla de hexano y EtOAc 3:1 produjo 1.27 g (71 %) del compuesto del título, el cual se cristalizó del hexano como agujas blancas.

m/z (ES+): 176/177.

^{1}H NMR ($CDCl_3$) δ: 1.47(t, 3H, J = 7.16); 4.48 (q, 2H, J = 7.16); 6.92 & 8.28 (s, 1H).

Intermedios 143 a 148

Los siguientes compuestos en la tabla abajo se fabricaron mediante la desprotección de los **Intermedios 149** a **154** con el tratamiento de un excedente de 4 N HCl en THF, un procedimiento análogo a aquel empleado en el **Intermedio 46**. El material crudo resultante se utilizó sin una purificación posterior.

Intermedio	Compuesto	MS (ESP)(MH^+)	MP
Intermedio 143	Metil 3-alil-5-(4-aminopiperidin-1-il) clorhidrato de benzoato	275 para $C_{16}H_{22}N_2O_2$	**Intermedio 149**
Intermedio 144	Metil 3-(4-aminopiperidin-1-il)-5-(2,3-dihidroxipropil)-clorhidrato de benzoato	309 para $C_{16}H_{24}N_2O_4$	**Intermedio 150**
Intermedio 145	Dimetil 5-(4-aminopiperidin-1-il) clorhidrato de isoftalato	293 para $C_{15}H_{20}N_2O_4$	**Intermedio 151**
Intermedio 146	Dimetil 2-(4-aminopiperidin-1-il) clorhidrato de isoftalato	293 para $C_{15}H_{20}N_2O_4$	**Intermedio 152**
Intermedio 147	Metil 4-(4-aminopiperidin-1-il) piridina-2-clorhidrato de carboxilato	236 para $C_{12}H_{17}N_3O_2$	**Intermedio 153**
Intermedio 148	Metil 5-(4-aminopiperidin-1-il) nicotinato 1-óxido clorhidrato	252 para $C_{12}H_{17}N_3O_3$	**Intermedio 154**

Intermedio 149: Metil 3-alil-5-{4-[(tert-butoxicarbonil)amino] piperidin-1-il}benzoato

Se pesó metil 3-bromo-5-{4-[(tert-butoxicarbonil)amino]piperidin-1-il} benzoato (**Intermedio 104**, 300 mg, 0.73 mmol), tris (dibencilidinaacetona)dipaladio (O) (26 mg, 0.03mmol), trifurilfosfina (14 mg, 0.06 mmol) en un matraz y se colocó bajo argón.

Se agregó NMP (3 ml), seguido por la adición de aliltributilo tin (0.25 ml, 0.80 mmol). La mezcla se revolvió a 100°C. Después de 64 h, la mezcla se diluyó con EtOAc y se lavó secuencialmente con agua seguido por solución salina. La fase orgánica se lavó sobre $MgSO_4$ y se concentró hasta el secado. El material crudo se purificó mediante cromatografía en gel de sílice utilizando EtOAc/hexanos al 25% para producir 174 mg del producto del título.

MS (ESP) (MH^+): 375 para $C_{21}H_{30}N_2O_4$

^{1}H NMR δ: 1.38 (s, 9H); 1.42-1.51 (m, 2H); 1.78-1.81 (m, 2H); 2.76 (t, 2H); 3.34-3.40 (m agua superpuesta, 3H); 3.64-3.68 (m, 2H); 3.81 (S, 3H); 5.04-5.13 (m, 2H); 5.94 (m, 1H); 6.86 (d, 1H); 7.05 (s, 1H); 7.17 (s, 1H); 7.28 (s, 1H).

Intermedio 150: Metil 3-{4-[(tert-butoxicarbonil)amino]piperidin-1-il}-5-(2,3-dihidroxipropil)benzoato

El compuesto del título se preparó a partir de metil 3-alil-5-{4-[(tert-butoxicarbonil)amino]piperidin-1-il}benzoato (**Intermedio 149**) y la mezcla β utilizando el método descrito en J. Org. Chem.1992, 57, 2768.

MS (ESP) (MH^+): 409 para $C_{21}H_{32}N_2O_6$

^{1}H NMR($CDCl_3$) δ: 1.47 (s, 9H); 1.51-1.55 (m agua superpuesto, 2H);1.89 (t, 1H); 2.05-2.09 (m, 3H); 2.71-2.80 (m, 2H); 2.82-2.92 (m, 2H); 3.53 (m, 1H); 3.65-3.75 (m, 4H); 3.90 (s, 3H); 3.97(m, 1H); 4.48 (m, 1H); 6.98 (s, 1H); 7.38 (s, 1H); 7.48 (s, 1H).

Intermedios 151 a 154

Los siguientes compuestos se prepararon mediante el siguiente método general: Se combinó la 4-(N-BOC amino)-piperidina (1.00 equivalente, 5.00 mmol), acetato de paladio (II) (0. 10 equiv), BINAP (rac-2,2'-

bis(difenilfosfinio)-l,l'-binaftilo, 0.10 equiv), carbonato de caesio (1.40 equiv) y arilo hálido (1.00 equiv). Se eliminó el gas de los sólidos y se colocaron bajo argón. Se agregó tolueno (10 ml) y la mezcla se revolvió a 100 °C durante aproximadamente 16 h. La mezcla se filtró y el producto filtrado se concentró al vacío. El producto crudo se purificó mediante cromatografía en columna instantánea de gel de sílice.

Intermedio	Compuesto	^{1}H NMR δ	M+l	MP
Intermedio 151	Dimetil 5-(4- tert-butoxi carbonilamino piperidin-1- il) isoftalato	1.37 (s, 9H); 1.42-1.50 (m, 2H); 1.76-1.87 (m, 2H); 2.85 (t, 2H); 3.45 (br s, 1H superpuesto con pico de agua); 3.66-3.79 (m, 2H); 3.85 (s, 6H); 6.84 (m, 1H); 7.66 (s, 2H); 7.85 (s, 1H).	393	Dimetil 5-bromo isoftalato
Intermedio 152	Dimetil 2-(4-tert-butoxi carbonilamino piperidin-1-il) tereftalato	1.46 (s, 9H); 1.54-1.67 (m, 2H); 2.03-2.07 (m, 2H); 2.88 (t, 2H); 3.28-3.33 (m, 2H); 3.61 (m, 1H); 3.91 (s, 3H); 3.93 (s, 3H); 4.50 (m, 1H); 7.60-7.74 (m, 3H)	393	Dimetil 2-bromo tereftalato
Intermedio 153	Metil 4-(4-tert-butoxi carbonilamino piperidin-1-il) piridina-2-carboxilato	1.45 (s, 9H); 1.89 (br s, 1H); 2.00-2.04 (m, 3H); 3.07 (t, 2H); 3.72 (m, 1H); 3.76-3.92 (m, 2H); 3.97(s, 3H); 4.51 (br s, 1H); 6.76 (m, 1H); 7.55 (d, 1H); 8.34 (d, 1H).	336	**Intermedio 155**
Intermedio	Metil 5- (4-	1.46 (s, 9H); 1.51-1.56	352	**Intermedio**

154	tert-butoxi carbonilamino piperidin-1-il) nicotinato 1-óxido	(m, 2H); 2.05-2.10 (m, 2H); 2.99(t, 2H); 3.65-3.69 (m, 2H); 3.95 (s, 3H); 4.48 (m, 1H); 7.42 (s, 1H); 8.00 (s, 1H); 8.35 (s, 1H).		156

Intermedio 155: Metil 4-iodopiridina-2-carboxilato

Este se preparó a partir del respectivo ácido carboxílico como se describe bajo **Intermedios 101-109.**

MS (ESP) (MH^+): 264 para $C_7H_6INO_2$

Intermedio 156: Metil 5-bromonicotinato-1-óxido

Se agregó una solución de mCPBA (70%, 4.46 g, 18.11 mmol) en DCM (100 ml) a una solución de metil 5-bromonicotinato (3.11 g, 15.09 mmol) en DCM (100 ml). Después de revolver a temperatura ambiente durante varias horas, se agregó más mCPBA (6.6 g, 26.77 mmol) (en porciones) para llevar la reacción a que se completara. Después de 4 días, la mezcla de la reacción se lavó secuencialmente con una solución saturada de bicarbonato de sodio seguido por agua. La fase orgánica se lavó sobre $MgSO_4$ y se concentró hasta el secado. El material crudo se purificó mediante cromatografía en gel de sílice utilizando EtOAc/hexanos al 50 % a EtOAc al 100% para producir 1.16 g del producto del título.

MS (ESP) (M^+, MH^{2+}): 232, 234 para $C_7H_6BrNO_3$

^1H NMR δ: 3.89 (s, 3H); 7.95 (s, 1H); 8.52 (s, 1H); 8.85 (s, 1H).

Intermedio 157: Metilo [2-({4-[(tert-butoxicarbonil)amino] piperidin-1-il}carbonil)hidrazina](oxo)acetato

Se agregó una solución de tert-butilo piperidin-4-ilcarbamato (disponible en el comercio) (1.0 g, 5.0 mmol), TEA (2.0 g, 20 mmol) y DCM (30 ml) en forma de goteo a fosgeno (20 %) en tolueno (disponible en el comercio) (10 ml, ~ 20 mmol) a 0°C. Se permitió que lentamente la mezcla resultante se

calentara a temperatura ambiente mientras se revolvía durante la noche. La mezcla se filtró para extraer el material sólido y el producto filtrado se concentró bajo presión reducida para producir el cloruro de carbamoilo (1.2 g). Se combinó el cloruro de carbamoilo crudo (1.2 g, 5.0 mmol), TEA (0.70 ml, 5.0 mmol), metilo hidracina (oxo)acetato (0.59 g, 5 mmol, referencia: J. Med. Pharm. Chem. 1961, vol. 4, (2), p. 259) y THF (20 ml) y se calentó a 60 °C durante 24 h. La mezcla se enfrió a temperatura ambiente y se concentró bajo presión reducida. El residuo crudo se purificó mediante cromatografía en columna instantánea (DCM/acetona, 5:1 proporción con MeOH al 1%) para producir 462 mg del compuesto del título.

MS (ESP): 345. 1 (M+H) para $C_{14}H_{24}N_4O_6$

^{1}H NMR δ: 1.03 (m, 2H); 1.44 (s, 9H); 1.73 (d, 2H); 2.85 (t, 2H); 3.45 (m, 1H); 3.85 (s, 3H); 3.92 (d, 2H); 6.94 (d, 1H); 8.72 (s, 1H); 10.48 (s, 1H).

Intermedio 158: Metil 6-bromopiridina-2-carboxilato

Se suspendió 6-ácido bromopicolínico(411 mg, 2.03 mmol) en MeOH anhidro (6 ml). Se agregó ácido sulfúrico (0.3 ml) concentrado a la solución resultante, se revolvió a temperatura ambiente durante aproximadamente 3 h. Se agregó EtOAc, seguido por una solución saturada de bicarbonato de sodio. Las fases se separaron y la fase orgánica se lavó con agua, se lavó sobre $MgSO_4$ y se concentró hasta el secado. El éster crudo (313 mg) se utilizó sin una purificación posterior.

MS (ESP) (M, MH^{+2}) 216, 218 para $C_7H_6NO_2$

Intermedio 159: Metil 5-bromotiofeno-2-carboxilato

Este se fabricó a partir del respectivo ácido carboxílico como se describe en el Intermedio 158.

MS (APCI) (M, MH^{+2}) 221, 223 para $C_6H_5BrO_2S$

Intermedio 160: Metil 5-{4-[(tert-butoxicarbonil)amino]piperidin-1-il}-1,3,4-oxadiazol-2-carboxilato

Intermedio	Compuesto	M/Z	^{1}H NMR	MP
Intermedio 163	4-Cloro-2-ciclopropil-6-metilpirimidina	168	0.83 (m, 2H); 0.93 (m, 2H); 2.03 (m, 1H); 2.29 (s, 3H); 7.21 (s, 1H)	2-ciclopropil-6-metilpirimidin-4-ol **(Intermedio 161)**
Intermedio 164	4-Cloro-2-isopropil-6-metilpirimidina	170	1.27 (d, 6H); 2.49 (s, 3H); 3.17 (q, 1H); 7.50 (s, 1H)	2-isopropil-6-metilpirimidin-4-ol (disponible en el comercio)
Intermedio 165	2-*tert*-Butil-4-cloro-6-metilo piridina	184	1.48 (s, 9H); 2.49 (s, 3H); 6.98 (s, 1H)	2-*tert*-Butil-6-metilpirimidin-4-ol **(Intermedio 162)**

Intermedios 166-168

Los siguientes compuestos se prepararon en una forma análoga a la del Intermedio **99** comenzando a partir de *tert*-butilo piperidin-4-ilcarbamato y los MPs enumerados.

Intermedio	Compuesto	M/Z	^{1}H NMR	MP
Intermedio 166	*tert*-Butil[1-(2-ciclopropil-6-metilpirimidin-4-il) piperidin-4-il] carbamato	332		4-Cloro-2-ciclopropil-6-metilpirimidina **(Intermedio 163)**
Intermedio 167	*tert*-Butil [1-(2- isopropil-6-metilpirimidin-4-il) piperidin-4-il] carbamato	334	1.23 (d, 6H); 1.4 (s, 9H); 2.26 (s, 3H); 3.20 (q, 1H); 3.09 (m, 2H); 3.43 (m, 2H); 3.67 (m, 3H); 4.46 (m, 2H);	4-Cloro-2-isopropil-6-metilpirimidina **(Intermedio 164)**

			6.56 (s, 1H); 7.1 (d, 1H)	
Intermedio 168	*tert*-Butil [1-(2- *tert*-butil-6-metilpirimidin-4-il) piperidin-4-il]carbamato	349	1.33 (s, 9H); 1.44-1.51(s, 9H); 1.89 (m, 2H); 2.35 (s, 3H); 3.09 (m, 2H); 3.43 (s, 2H); 3.67 (m, 1H); 4.46 (m, 2H); 6.64 (s, 1H); 6. 9 (d, 1H)	2-tert-Butil-4-cloro-6-metilpirimidina **(Intermedio 165)**

Intermedios 169-171

Los siguientes compuestos se prepararon en una forma análoga a la del Intermedio **100** comenzando a partir de los MPs enumerados.

Intermedio	**Compuesto**	**M/Z**	**MP**
Intermedio 169	6-{4-[(*tert* Butoxicarbonil) amino]piperidin-1-il}-2-ciclopropilpirimidina-4-ácido carboxílico	363	*tert*-Butil [1-(2-ciclopropil-6-metilpirimidin-4-il)piperidin-4-il]carbamato **(Intermedio 166)**
Intermedio 170	6-{4-[(*tert*-Butoxicarbonil) amino]piperidin-1-il}-2-isopropilpirimidina-4-ácido carboxílico	364	*tert*-Butil [1-(2-isopropil-6-metilpirimidin-4-il)piperidin-4-il]carbamato

Intermedio 171	6-{4-[(*tert*-Butoxicarbonil) amino]piperidin-1-il}-2-*tert*-butilpirimidina-4-ácido carboxílico	378	*tert*-Butil [1-(2-*tert*-butil-6-metilpirimidin-4-il)piperidin-4-il]carbamato **(Intermedio 168)**

Intermedios 172-174

Los siguientes compuestos se prepararon en una forma análoga a la del Intermedio **70** comenzando a partir de los MPs enumerados.

Intermedio	Compuesto	M/Z	MP
Intermedio 172	6-(4-Aminopiperidin-1-il)-2- ciclopropilpirimidina-4-ácido carboxílico sal de clorhidrato	263	6-{4-[(*tert*-butoxicarbonil)amino] piperidin-1-il}-2-ciclopropilpirimidina-4-ácido carboxílico **(Intermedio 169)**
Intermedio 173	6-(4-Aminopiperidin-1-il)-2- isopropilpirimidina-4-ácido carboxílico sal de clorhidrato	264	6-{4-[(tert-butoxicarbonil) amino]piperidin-1-il}-2-isopropilpirimidina-4-ácido carboxílico **(Intermedio 170)**
Intermedio 174	6-(4-Aminopiperidin-1-il)-2-tert-butilpirimidina-4-ácido carboxílico sal de clorhidrato	278	6-{4-[(tert-butoxicarbonil) amino]piperidin-1-il}-2-tert- butilpirimidina-4-

			ácido carboxílico **(Intermedio 171)**

Intermedios 175-195

Los siguientes compuestos se prepararon en una forma análoga a la del Intermedio **16** comenzando a partir de tert-butilo piperidin-4-ilcarbamato y los materiales de partida de haloheteroarilo enumerados abajo (disponibles en el comercio salvo si se expresa en contrario).

Intermedio	**Compuesto**	**M/Z**	**MP**
Intermedio 175	Etil 2- {4-[(*tert*-butoxicarbonil)amino] piperidin-1-il}-3-ciano-6-metilisonicotinato	409	etil 2-cloro-3-ciano-6-metilisonicotinato
Intermedio 176	*tert*-Butil [1-(3-cianopiridin-2-il)piperidin-4-il]carbamato	303	2-cloronicotinonitrilo
Intermedio 177	*tert*-Butil (1-quinolin-2-ilpiperidin-4-il)carbamato	328	2-cloroquinolina
Intermedio 178	*tert*-Butil [1-(6-metoxi-3-nitro piridin-2-il)piperidin-4-il]carbamato	353	2-cloro-6-metoxi-3-nitropiridina
Intermedio 179	*tert*-Butil [1-(4-acetil-6-cloropiridin-2-il) piperidin-4-il}carbamato	353	1-(2,6-Dicloropiridin-4-il)etanona **(Intermedio 48)**
Intermedio 180	*tert*-Butil {1-[6-(trifluorometil)piridin-2-il]piperidin-4-il}carbamato	346	2-cloro-6-trifluorometil)piridina
Intermedio 181	*tert*-Butil {1-[3-(aminocarbonil)-6-(trifluorometil)piridin-2-il]piperidin-4-il}carbamato	391	2-cloro-6-(trifluorometil) nicotinamida

Intermedio	Compuesto	M/Z	MP
Intermedio 182	*tert*-Butil {1-[3-ciano-6-(trifluorometil)piridin-2-il]piperidin-4-il}carbamato	371	2-cloro-6-(trifluorometil) nicotinonitrilo
Intermedio 183	*tert*-Butil [1-(3-cloropiridin-2-il)piperidin-4-il]carbamato	313	2,3-dicloropiridina
Intermedio 184	*tert*-Butil [1-(4-cianopiridin-2-il)piperidin-4-il] carbamato	303	2-cloroisonicolino nitrito
Intermedio 185	*tert*-Butil {1-[5-(trifluorometil)piridin-2-il}piperidin-4-il}carbamato	347	2-cloro-5-(trifluorometil) piridina
Intermedio 186	*tert*-Butil {1-[5-(aminocarbonil)piridin-2-il]piperidin-4-il}carbamato	321	6-cloronicotinamida
Intermedio 187	*tert*-Butil [1-(6-bromopiridin-2-il)piperidin-4-il]carbamato	357	2,6-dibromopiridina
Intermedio 188	6-{4-[(*tert*-Butoxicarbonil) amino]piperidin-1-il}-2-ácido cloronicotínico	357	2,6-diácido cloronicotínico
Intermedio 189	*tert*-Butil (1-pirimidin-2-ilpiperidin-4-il)carbamato	278	2-cloropirimidina
Intermedio 190	Metil 2-{4-[(*tert*-butoxicarbonil)amino] piperidin-1-il}-6-metilpirimidina-4-carboxilato	349	metil 2-cloro-6-metilpirimidina-4-carboxilato
Intermedio 191	*tert*-Butil [1-(7*H*-purin-6-il) piperidin-4-il]carbamato	318	6-cloro-7H-purina
Intermedio 192	Metil 6-{4-[*tert*-butoxicarbonil)amino]	270	metil 2,6-dicloropirimidina-4-

Intermedio	Compuesto	M/Z	MP
	piperidin-1-il}-2-cloropirimidina-4-carboxilato		carboxilato
Intermedio 193	*tert*-Butil [1-(6-cloro-4-{[(2-morfolin-4-iletil) amino]carbonil}piridin-2-il)piperidin-4-il]carbamato	468	2,6-Dicloro-N-(2-morfolin-4-il-etil)-isonicotinamida **(Intermedio 40)**
Intermedio 194	*tert*-Butil [1-(6-cloro-4-{[(3-morfolin-4-ilpropil) amino]carbonil}piridin-2-il)piperidin-4-il]carbamato	481	2,6-Dicloro-N-(3-morfolin-4-il-propil)-isonicotinamida **(Intermedio 196)**
Intermedio 195	*tert*-Butil [1-(6-cloro-4-{[2-(metilamino)-2-oxoetil]tio}piridin-2-il) piperidin-4-il]carbamato	415	2-(2,6-Dicloro-piridin-4-ilsulfanil)-N-metil-acetamida **(Intermedio 41)**

Intermedio 196: 2,6-Dicloro-N-(3-morfolin-4-il-propil)-isonicotinamida

El compuesto del título se preparó mediante el procedimiento del **Intermedio 40** a partir de 3-morfolin-4-il-propan-1-amina y 2,6-ácido dicloroisonicotínico (ambos disponibles en el comercio).

MS (ES) (M+H): 318 para $C_{13}H_{17}Cl_2N_3O_2$

Intermedios 197-220

Los siguientes compuestos se prepararon en una forma análoga a la del Intermedio 70 a partir de los MPs enumerados a continuación. El material crudo resultante se utilizó sin una purificación posterior.

Intermedio	Compuesto	M/Z	MP
Intermedio 197	1-[2-(4-Aminopiperidin-1-	253	*tert*-Butil [1-(4-acetil-6-cloropiridin-2-il) piperidin-4-

Intermedio	Compuesto	M/Z	MP
	il)-6-cloropiridin-4-il)etanona sal de clorhidrato		il]carbamato **(Intermedio 179)**
Intermedio 198	2-(4-Aminopiperidin-1-il)-6-cianoisonicotinamida sal de clorhidrato	246	tert-Butil {1 -[4-(aminocarbonil)-6-cianopiridin-2-il] piperidin-4-il}carbamato **(Intermedio 42)**
Intermedio 199	Etil 2-(4-aminopiperidin-1-il)-3-ciano-6-metilisonicotinato sal de clorhidrato	308	etil 2-{4-[(*tert*-butoxicarbonil)amino] piperidin-1-il}-3-ciano-6-metilisonicotinato **(Intermedio 175)**
Intermedio 200	2-(4-Aminopiperidin-1-il)nicotinonitrilo sal de clorhidrato	202	*tert*-Butil [1-(3-cianopiridin-2-il) piperidin-4-il]carbamato **(Intermedio 176)**
Intermedio 201	1-Quinolin-2-ilpiperidin-4-amina sal de clorhidrato	228	*tert*-Butil (1-quinolin-2-ilpiperidin-4-il) carbamato **(Intermedio 177)**
Intermedio 202	1 -(6-Metoxi-3-nitropiridin-2-il) piperidin-4-amina sal de clorhidrato	253	*tert*-Butil [1-(6-metoxi-3-nitropiridin-2-il)piperidin-4-il]carbamato **(Intermedio 178)**
Intermedio 203	2-(4-Aminopiperidin-1-il)-6-cloroisonicotinonitrilo sal de clorhidrato	237	tert-Butilo 1-(6-cloro-4-cianopiridin-2-il) piperidin-4-ilcarbamato **(Intermedio 53)**
Intermedio 204	1-[6-(Trifluorometil) piridin-2-il]piperidin-	246	*tert*-Butil {1-[6-(trifluorometil)piridin-2-

Intermedio	Compuesto	M/Z	MP
	4-amina sal de clorhidrato		il]piperidin-4-il} carbamato **(Intermedio 180)**
Intermedio 205	2-(4-Aminopiperidin-1-il)-6-(trifluorometil) nicotinamida sal de clorhidrato	291	*tert*-Butil {1-[3-(aminocarbonil)-6-(trifluorometil)piridin-2-il]piperidin-4-il} carbamato **(Intermedio 181)**
Intermedio 206	2-(4-Aminopiperidin-1-il)-6-(trifluorometil) nicotinonitrilo sal de clorhidrato	271	*tert*-Butil {1-[3-ciano-6-(trifluorometil)piridin-2-il] piperidin-4-il}carbamato **(Intermedio 182)**
Intermedio 207	1 -(3-Cloropiridin-2-il)piperidin-4-amina sal de clorhidrato	213	*tert*-Butil [1-(3-cloropiridin-2-il)piperidin-4-il]carbamato **(Intermedio 183)**
Intermedio 208	2-(4-Aminopiperidin-1-il)isonicotinonitrilo sal de clorhidrato	202	*tert*-Butil [1-(4-cianopiridin-2-il)piperidin-4-il]carbamato **(Intermedio 184)**
Intermedio 209	1-[5-Trifluorometil) piridin-2il]piperidin-4-amina sal de clorhidrato	247	*tert*-Butil {1-[5-(trifluorometil) piridin-2-il]piperidin-4-il} carbamato **(Intermedio 185)**
Intermedio 210	6-(4-Aminopiperidin-1-il)nicotinamida sal de clorhidrato	221	*tert*-Butil {1-[5-(aminocarbonil) piridin-2-il]piperidin-4-il} carbamato **(Intermedio 186)**
Intermedio 211	1 -(6-Bromopiridin-2-il)piperidin-4-amina sal de clorhidrato	257	*tert*-Butil [1-(6-bromopiridin-2-il)piperidin-4-il]carbamato **(Intermedio 187)**

Intermedio	Compuesto	M/Z	MP
Intermedio 212	[1-(6-Cloropiridin-2-il)piperidin-4-il] amina sal de clorhidrato	213	*tert*-Butil [1-(6-cloropiridin-2-il)piperidin-4-il]carbamato **(Intermedio 66)**
Intermedio 213	6-(4-Aminopiperidin-1-il)-2-ácido cloronicotínico sal de clorhidrato	257	6-{4-[*tert*-butoxicarbonil) amino]piperidin-1-il}-2-ácido cloronicotínico **(Intermedio 188)**
Intermedio 214	1 -Pirimidin-2-ilpiperidin-4-amina sal de clorhidrato	278	*tert*-Butil (1-pirimidin-2-ilpiperidin-4-il)carbamato **(Intermedio 189)**
Intermedio 215	Metil 2-(4-aminopiperidin-1-il)-6-metilpirimidina-4-Carboxilato sal de clorhidrato	249	metil 2-{4-[(*tert*-butoxicarbonil)amino]piperidin-1-il}-6-metilpirimidina-4-carboxilato **(Intermedio 190)**
Intermedio 216	1 -(7*H*-Purin-6-il) piperidin-4-amina sal de clorhidrato	218	*tert*-Butil [1-(7*H*-purin-6-il) piperidin-4-il]carbamato **(Intermedio 191)**
Intermedio 217	Metil 6-(4-aminopiperidin-1-il)-2-cloropirimidina-4-Carboxilato sal de clorhidrato	270	metil 6-{4-[(*tert*-butoxicarbonil) amino]piperidin-1-il}-2-cloropirimidina-4-carboxilato **(Intermedio 192)**
Intermedio 218	2-(4-Aminopiperidin-1-il)-6-cloro-*N*-(2-morfolin-4-iletil) isonicotinamida sal de clorhidrato	368	*tert*-Butil [1-(6-cloro-4-{1-[(2-morfolin-4-iletil)amino] carbonil}piridin-2-il)piperidin-4-il]carbamato **(Intermedio 193)**

Intermedio	Compuesto	M/Z	MP
Intermedio 219	2-(4-Aminopiperidin-1-il)-6-cloro-*N*-(3-morfolin-4-ilpropil) isonicotinamida sal de clorhidrato	381	*tert*-Butil [1-(6-cloro-4-{[(3-morfolin-4-ilpropil)amino] carbonil}piridin-2-il)piperidin-4-il]carbamato **(Intermedio 194)**
Intermedio 220	2-{ [2-(4-Aminopiperidin-1-il)-6-cloropiridin-4-il] tio}-*N*-metilacetamida sal de clorhidrato	315	*tert*-Butil [1-(6-cloro-4-{[2-(metilamino)-2-oxoetil]tio} piridin-2-il)piperidin-4-il] carbamato **(Intermedio 195)**

Intermedio 221: Etil 2,4-dibromo-1,3-tiazol-5-carboxilato

Lentamente se agregó una solución de 14 ml de 1.6 N *n*-butilitio en hexano a una solución de diisopropilamina (3.1 ml, 22 mmol) en 80 ml THF, se enfrió en un baño de hielo seco/acetona bajo una atmósfera inerte. La solución se calentó a 0 °C y se volvió a enfriar a -70°C. Se agregó una solución de 2,5-dibromotiazol en 20 ml THF y la mezcla se revolvió durante 30 min antes de agregar etilcloroformato (2.1 ml, 22mmol). Después de calentarla a temperatura ambiente, la mezcla se extinguió con $NaHCO_3$ acuoso y se diluyó con EtOAc. El EtOAc se separó y se lavó con água y solución salina. El secado ($MgSO_4$) y la extracción del solvente produjo un aceite que se purificó mediante cromatografía (1:1 hexanos-DCM seguido por gradiente de elución de DCM al 100%) para producir 4.5 g de producto como un aceite que se solidificó lentamente.

MS (ES): 316 (M+H)

^{1}H NMR ($CDCl_3$) δ: 1.4 (t, 3H); 4.4 (q, 2H).

Intermedio 222: Etil 4-bromo-2-{4-[(*tert*-butoxicarbonil)amino] piperidin-1-il}-1,3-tiazol-5-carboxilato

Se calentó una solución de etil 2,4-dibromo-1,3-tiazol-5-carboxilato (**Intermedio 221**) (4.5 g, 14.3mmol), ácido carbámico, 4-piperidinil-, 1,1-dimetiletiléster (2.86 g, 14.3mmol) y diisopropiletilamina (2.6ml, 14.5 mmol) en 45ml dioxano a 100 °C durante 4 horas. La mezcla se distribuyó entre EtOAc y agua. El EtOAc se separó y se lavó con solución salina. El secado ($MgSO_4$) y la extracción del solvente produjo un aceite que se sometió a cromatografía sobre gel de sílice (1:1 hexanos-DCM seguido por gradiente de elución DCM al 100% y después MeOH al 8% en DCM) para producir 2.1 gm de producto.

MS (ES): 378, 380 (M+H)

^{1}H NMR δ: 1.24 (t, *J*=7.06Hz, 3H); 1.33-1.47 (m, 11H); 1.80 (s, 2H); 3.13-3.31 (m, 2H); 3.54 (s, 1H); 3.83 (s, 2H); 4.19 (q, *J*=7.10Hz, 2H); 6.95 (d, *J*=7.91 Hz, 1H)

Intermedio 223: Etil 2-{4-[(*tert*-butoxicarbonil)amino]piperidin-1-il}-4-ciano-1,3-tiazol-5-carboxilato

Se calentó una solución de etil 4-bromo-2-{4-[(*tert*-butoxicarbonil)amino]piperidin-1-il}-1,3-tiazol-5-carboxilato (**Intermedio 222**) (1.3 g, 2.9 mmol), $Zn(CN)_2$ (250 mg, 2.2 mmol), tris(dibencilidinaaceetona) dipaladio(0) (125 mg, 0.13 mmol) y 1,1'- bis (difenilfosfino) ferroceno (151 mg, 13 mmol) en 20ml DMF bajo argón a 130 °C durante 1 hora en un reactor de microondas. El solvente se extrajo y el residuo se absorbió en EtOAc y se lavó con agua y solución salina. El secado ($MgSO_4$) y la extracción del solvente produjo un aceite que se sometió a cromatografía sobre gel de sílice (DCM seguido por gradiente de elusión de MeOH al 5% en DCM) para producir 1.9 g de producto como un sólido amarillo.

^{1}H NMR δ: 1.28 (t, *J*=7. 06Hz, 3H); 1.31-1.52 (m, 11 H); 1.72-1.95 (m, 2H); 3.19-3.33 (m, 2H); 3.54 (s, 1H); 3.89 (d, *J*=13.19Hz, 2H); 4.29 (q, *J*=7. 16Hz, 2H); 6.95 (s, 1H).

Intermedio 224 3,4-Dicloro-5-metil-1*H*-pirrol-2-carbonilo cloruro

Se calentó una solución de 3,4-dicloro-5-metil-1*H*-pirrol-2-ácido carboxílico (**Intermedio 3**) en 50 ml $SOCl_2$ a reflujo durante 30 min. El solvente se extrajo y el residuo se secó al vacío.

^{1}H NMR ($CDCl_3$) δ: 9.0 (s, 1H); 2.4 (s, 3H).

Ejemplos

Ejemplo 1: *tert*-Butil 2-[(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)metil]-1-metil-1*H*-imidazol-4-ilcarbamato

Se revolvió una mezcla de 3,4-dicloro-5-metil-*N*-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 1**,243 mg, 0.777 mmol) y *tert*-butil 2-formilo-1-metil-1*H*-imidazol-4-ilcarbamato (W003/002567) (175 mg, 0.777 mmol) en THF (15 ml) a temperatura ambiente durante 10 minutos. Después se añadió triacetoxiborohidruro sódico (494 mg, 2.33 mmol) en dos porciones y la mezcla de la reacción se revolvió a temperatura ambiente durante 16 horas. La mezcla de la reacción se diluyó con EtOAc y Na_2CO_3 acuoso al 10%. La capa acuosa se extrajo con EtOAc, las porciones orgánicas combinadas se lavaron con solución salina, se lavaron sobre Na_2SO_4, se filtraron y se concentraron bajo presión reducida para producir 398 mg de un sólido amarillo pálido, 100 mg de los cuales se disolvieron en DMSO y se purificó mediante HPLC de preparación empleando un gradiente de 20-95% CH_3CN/H_2O (TFA al 0.1 %) para producir la sal de TFA del compuesto del título.

MS (ES^-): 483.30, 485.37 para $C_{21}H_{30}Cl_2N_6O_3$

^{1}H NMR δ: 1.55 (s, 9H); 1.95 (m, 2H); 2.09 (s, 3H); 2.32 (s, 3H); 3.18 (m, 2H); 3.43 (m, 2H); 3.67 (s, 3H); 3.93 (m, 1H); 4.38 (s, 2H); 7.36 (d, 1H); 7.99 (s, 1H); 11.89 (brs, 1H).

Ejemplo 2: 3,4-Dicloro-5-metil-*N*-{1-[2-(metilsulfonil)pirimidin-4-il]piperidin-4-il}-1*H*-pirrol-2-carboxamida

Se trató una suspensión de 3,4-dicloro-5-metil-*N*-{1-[2-(metiltio)pirimidin-4-il]piperidin-4-il}-1*H*-pirrol-2-carboxamida (**Ejemplo 306**,200 mg, 0.5

mmol) en DCM anhidro (8 ml) con mCPBA al 70% (250 mg, 1 mmol). La solución resultante se revolvió bajo nitrógeno durante 1 h, luego se diluyó con DCM y se lavó con solución acuosa de $NaHCO_3$ al 10%. La porción acuosa se extrajo una vez con DCM y las porciones orgánicas combinadas se lavaron con solución salina, se lavaron sobre Na_2SO_4, se filtraron y se concentraron bajo presión reducida para producir 215 mg de un sólido casi blanco. El material crudo se purificó mediante HPLC de preparación empleando un gradiente de 20-60% acetonitrilo/agua (TFA al 0.1 %) para producir la sal de TFA del compuesto del título (103.1 mg).

MS(ES⁻): 430.11, 432.11 para $C_{16}H_{19}Cl_2N_5O_3S$

^{1}H NMR δ: 1.29 (m, 2H); 1.66 (m, 2H); 1.92 (s, 3H); 2.94 (m, 2H); 3.04 (s, 3H); 3.21 (m, 2H); 3.84 (m, 1H); 6.87 (d, 1H); 7.02 (d, 1H); 8.07 (d, 1H); 11.73 (s, 1H).

Ejemplo 3: 3,4-Dicloro-5-metil-*N*-{1-[2-(metilsulfinil)pirimidin-4-il]piperidin-4- il}-1*H*-pirrol-2-carboxamida

Se trató una suspensión de 3,4-dicloro-5-metil-*N*-{1-[2-(metiltio)pirimidin-4-il]piperidin-4-il}-1*H*-pirrol-2-carboxamida (**Ejemplo 306**, 114.6 mg, 0.2863 mmol) en DCM anhidro (5 ml) a 0 °C con mCPBA al 70% (77.6 mg, 0.314 mmol). La reacción se revolvió a 0 °C durante 30 minutos y luego se extinguió con solución acuosa de Na_2SO_3 al 10%. Las fases se separaron y la porción acuosa se extrajo con DCM. Las porciones orgánicas combinadas se lavaron con solución acuosa diluida de Na_2CO_3 y solución salina, se lavaron sobre Na_2SO_4, se filtraron y se concentraron bajo presión reducida para producir un aceite amarillo pálido que se purificó mediante HPLC de preparación empleando un gradiente de 20-60% CH_3CN/H_2O (TFA al 0.1 %) para producir la sal de TFA del compuesto del título (67.0 mg).

MS (ES⁻): 414.15, 416.15 para $C_{16}H_{19}C_{12}N_5O_2S$

^{1}H NMR δ: 1.43 (m, 2H); 1.81 (m, 2H); 2.07 (s, 3H); 2.69 (s, 3H); 3.06 (m, 2H); 4.02 (m, 2H); 4.22 (m, 1H); 6.85 (d, 1H); 7.16 (d, 1H); 7.81 (d, 1H); 11.87 (s, 1H).

Ejemplo 4: *N*-[1-(6-Amino-2-cloropirimidin-4-il)piperidin-4-il]-3,4-dicloro-5-metil-1*H*-pirrol-2-carboxamida

Se combinó 3,4-dicloro-5-metil-*N*-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 1**, 500 mg, 1.6 mmol), 4-amino-2,6-dicloropirimidina (262 mg, 1.6 mmol) y Et_3N (0.45 ml, 3.2 mmol) en DMF (15 ml) y se calentó a 100 °C bajo nitrógeno durante 1 h. Una vez se enfrió a temperatura ambiente, la reacción se diluyó con EtOAc y agua. La fase acuosa se extrajo dos veces con EtOAc y las porciones orgánicas combinadas se lavaron con solución salina, se lavaron sobre Na_2SO_4, se filtraron y se concentraron bajo presión reducida para producir un aceite marrón. Se agregó aproximadamente 1ml DMF al aceite, seguido por una adición lenta de agua. La trituración resultó en un sólido marrón claro (212 mg) que se recolectó mediante filtración. Se purificó 66 mg de este material crudo mediante HPLC de preparación empleando un gradiente de 20-60% CH_3CN/H_2O (TFA al 0.1 %) para producir la sal de TFA del compuesto del título (21 mg).

MS(ES$^-$): 401.12, 403.13, 405.13 para $C_{15}H_{17}Cl_3N_6O$

^{1}H NMR δ: 1.38 (m, 2H); 1.76 (m, 2H); 2.10 (s, 3H); 2.97 (m, 2H); 3.94 (m, 1H); 4.35(m, 2H); 5.66 (s, 2H); 6.68 (m, 1H); 7.12 (d, 1H); 11.89(s, 1H).

Ejemplo 5: *N*-{1-[6-(Acetilamino)-2-cloropirimidin-4-il]piperidin-4-il}-3,4-dicloro-5-metil-1*H*-pirrol-2-carboxamida

Se combinó 3,4-dicloro-5-metil-*N*-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 1**,280 mg, 0.896 mmol), *N*-(2,6-dicloropirimidin-4-il)acetamida (**Intermedio 7**, 184.5 mg, 0.896mmol) y TEA (0.25ml, 1.79 mmol) en DMF (6 ml) y se calentó a 100°C bajo nitrógeno durante 1 h. Una vez se enfrió a temperatura ambiente, la reacción se diluyó con EtOAc y agua. Las fases se separaron y la porción acuosa se extrajo dos veces con EtOAc. Las porciones orgánicas combinadas se lavaron con solución salina, se lavaron sobre Na_2SO_4, se filtraron y se concentraron bajo presión

reducida para producir un líquido marrón (todavía había presencia de DMF), el cual se trituró con agua. El sólido marrón claro resultante (76 mg) se purificó mediante HPLC de preparación empleando un gradiente de 20-60% CH_3CN/H_2O (TFA al 0.1 %) para producir la sal de TFA del compuesto del título (20 mg).

MS ES⁻: 445.14, 447.14, 448.14 para $C_{17}H_{19}C_{13}N_6O_2$

^{1}H NMR δ: 1.45 (m, 2H); 1.82 (m, 2H); 2.01 (s, 3H); 2.11 (s, 3H); 3.09 (m, 2H); 4.04 (m, 2H); 4.22 (m, 1H); 7.15 (d, 1H); 7.30 (s, 1H); 10.67 (s, 1H); 11.90 (s, 1H)

Ejemplo 6: Metil 2-cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)pirimidina-4-carboxilato

Se agregó una solución de metil 2,3-dicloropirimidina-6-carboxilato (disponible en el comercio) (0.95 g, 4.6 mmol) en DMF (5 ml) en forma de goteo a una solución de 3,4-dicloro-5-metil-N-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 1**, 0.43 g, 4.6 mmol) y TEA (0.92 g, 9.2 mmol) en DMF (10 ml) bajo nitrógeno. La mezcla resultante se revolvió durante 1 h a temperatura ambiente. Se agregó agua (50 ml) a la mezcla de la reacción agitada y el material que se precipitó se recolectó y se lavó con agua/acetonitrilo (1:1, 15 ml) para producir 1.9 g del compuesto del título. Se purificó una muestra analítica mediante HPLC de fase inversa (agua/acetonitrilo, gradiente 20-95%).

MS (ESP): 446.3 (M+H) para $C_{17}H_{18}Cl_3N_5O_3$

^{1}H NMR δ: 1.73-1.83 (m, 2H); 2.14 (d, 2H); 2.39 (s, 3H); 3.40-3.52 (m, 2H); 4.09 (s, 3H); 4.30-4.45 (m, 2H); 4.60-4.80 (m, 1H); 7.46 (d, 1H); 7.60 (s, 1H); 12.2 (s, 1H).

Ejemplo 7: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)-2-(metiltio)pirimidina-4-ácido carboxílico

Se agregó tiometóxido sódico (0.275 g, 3.94 mmol) a una solución de metil 2-cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)pirimidina-4-carboxilato (**Ejemplo 6**,0.44 g, 0.99

mmol) en DMF (3 ml) bajo nitrógeno. La mezcla resultante se revolvió a temperatura ambiente durante 18 h. La reacción se extinguió mediante la adición de agua (5 ml) y 1 N HCl (5 ml), luego se diluyó con EtOAc (100ml) y la fase orgánica se separó. La fase acuosa se extrajo con EtOAc (30 ml) y las capas orgánicas combinadas se lavaron con solución salina, se lavaron sobre Na_2SO_4, se filtraron y se concentraron al vacío.

El residuo crudo se purificó mediante HPLC de preparación de fase inversa (agua/acetonitrilo, gradiente 10-95%) para producir 275 mg del compuesto del título.

MS (ESP): 444.3 (M+H) para $C_{17}H_{19}Cl_2N_5O_3S$

^{1}H NMR δ: 1.40-1.60 (m, 2H); 1.80 (d, 2H); 2.06 (s, 3H); 2.39 (s, 3H); 3.09 (t, 2H); 4.0-4.15 (m, 1H); 4.10-4.50 (m, 2H); 5.50-6.50 (br s, 1H); 6.90 (s, 1H); 7.11 (d, 1H); 11.85 (s, 1H).

Ejemplo 8:6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il) carbonil] amino}piperidin-1-il)-*N*-metoxi-2-(metiltio)pirimidina-4-carboxamida

Se agregó HATU (197 mg, 0.52 mmol) a una solución de TEA (0.14 ml, 1.0 mmol), 6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino} piperidin-1-il)-2-(metiltio)pirimidina-4-ácido carboxílico (**Ejemplo 7**, 230 mg, 0.52 mmol) y clorhidrato de metoxilamina (43 mg, 0.52 mmol) en DMF (3 ml) bajo nitrógeno. La mezcla resultante se revolvió durante la noche a temperatura ambiente, luego se diluyó con EtOAc (50 ml) y agua (10 ml) y la fase orgánica se separó. La fase orgánica se lavó con 1 N HCl (5 ml), solución saturada de $NaHCO_3$ (5 ml) y solución salina (5 ml). Las capas acuosas se extrajeron en forma inversa con EtOAc (25 ml). Las capas orgánicas combinadas se lavaron sobre Na_2SO_4, se filtraron y se concentraron al vacío para producir 400 mg de producto crudo, el cual se purificó por medio de HPLC de preparación de fase inversa (agua/acetonitrilo, gradiente 20-95%) para producir 200 mg del compuesto del título.

MS (ESP): 473.3 (M+H) para $C_{18}H_{22}Cl_2N_6O_3S$

^{1}H NMR δ: 1.42-1.52 (m, 2H); 1.80-1.88 (m, 2H); 2.10 (s, 3H); 2.44 (s, 3H); 3.16 (t, 2H); 3.61 (s, 3H); 4.00-4.14 (m, 1H); 4.20-4.50 (m, 2H); 6.94 (s; 1H); 7.16 (d, 1H); 11.70 (s, 1H); 11.90 (s, 1H).

Ejemplo 9: Metil 6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-ilo carbonil]amino}piperidin-1-il)-2-morfolin-4-ilpirimidina-4-carboxilato

Se revolvió una solución de metil 2-cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2- il)carbonil]amino}piperidin-1-il)pirimidina-4-carboxilato (**Ejemplo 6**, 300 mg, 0.67 mmol), morfolino (58 mg, 0.67 mmol) y TEA (0.09ml, 0.67 mmol) en DMF (3 ml) a 60 °C bajo nitrógeno durante 4 horas. La mezcla se enfrió a temperatura ambiente y se diluyó con EtOAc (75 ml) y agua (10 ml). La capa orgánica se separó, se lavó sobre Na_2SO_4, se filtró y se concentró al vacío para producir 320 mg del compuesto del título. Una muestra analítica se purificó mediante HPLC de fase inversa (agua/acetonitrilo, gradiente 20- 95%).

MS (ESP): 497.4 (M+H) para $C_{21}H_{26}Cl_2N_6O_4$

^{1}H NMR δ: 1.40-1.58 (m, 2H); 1.81 (d, 2H); 2.10 (s, 3H); 3.06 (t, 2H); 3.58 (br s, 8H); 3.75 (s, 3H); 3.95-4.10 (m, 1H); 4.15-4.40 (m, 2H); 6.65 (s, 1H); 7.16 (d, 1H); 11.90(s, 1H).

Ejemplo 10: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)-*N*-metoxi-2-(metilsulfonil) pirimidina-4-carboxamida

Se agregó mCPBA (70%, 104 mg, 0.42 mmol) a una suspensión de 6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-*N*-metoxi-2-(metiltio) pirimidina- 4-carboxamida (**Ejemplo 8**, 100 mg, 0.21 mmol) en DCM (15 ml) y la mezcla resultante se revolvió durante 3 h. La mezcla de la reacción se diluyó con DCM (50 ml), se lavó con solución saturada de Na_2CO_3 (10 ml), se lavó sobre Na_2SO_4, se filtró y se concentró al vacío. El residuo se purificó mediante HPLC de fase inversa (agua/acetonitrilo, gradiente 15- 95%).

MS (ESP): 505.3 (M+H) para $C_{18}H_{22}Cl_2N_6O_5S$

^{1}H NMR δ: 1.45-1.62 (m, 2H); 1.88 (d, 2H); 2.11 (s, 3H); 3.15-3.35 (m, 2H); 3.33 (s, 3H); 3.66 (s, 3H); 4.02-4.18 (m, 2H); 4.45-4.70 (m, 1H); 7.18 (d, 1H); 7.40 (s, 1H); 11.91 (s, 1H); 11.98 (s, 1H).

Ejemplo 11: 2-Cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-N-metoxipirimidina-4-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 8** comenzando a partir de 2-cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)pirimidina-4-ácido carboxílico (**Ejemplo 32**) y clorhidrato de metoxilamina.

MS (ESP): 461.2 (M+H) para $C_{17}H_{19}Cl_3N_6O_3$

^{1}H NMR δ: 1.45-1.59 (m, 2H); 1.89 (d, 2H); 2.15 (s, 3H); 3.12-3.30 (m, 2H); 3.65 (s, 3H); 4.04-4.17 (m, 2H); 4.35-4.62 (m, 1H); 7.20 (d, 1H); 7.26 (s, 1H); 11.95 (s, 2H).

Ejemplo 12: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)-*N*-metoxi-2-morfolin-4-ilpirimidina-4-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 8** comenzando a partir de 6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)-2-morfolin-4-ilpirimidina-4-ácido carboxílico (**Ejemplo 310**) y clorhidrato de metoxilamina.

MS (ESP): 512.4 (M+H) para $C_{21}H_{27}Cl_2N_7O_4$

^{1}H NMR δ: 1.40-1.65 (m, 2H); 1.81 (d, 2H); 2.10 (s, 3H); 3.03 (t, 2H); 3.50-3.70 (m, 8H); 3.62 (s, 3H); 3.90-4.10 (m, 1H); 4.15-4.32 (m, 2H); 6.57 (s, 1H); 7.15 (d, 1H); 11.61 (s, 1H); 11.90 (s, 1H).

Ejemplo 13:2-Cloro-6-(4-{[(3.4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-*N*-(2-morfolin-4-iletil)pirimidina-4-carboxamida

Se revolvió una solución de metil2-cloro-6-(4-{[(3, 4-dicloro-5-metil-1H-pirrol-2- il) carbonil]amino} piperidin-1-il) pirimidina-4-carboxilato (Ejemplo 6:380 mg, 0.85 mmol),2-morfolin-4-iletanamina (222 mg, 1.70 mmol) y TEA (0.12ml, 0.85 mmol) en DMF (3 ml) a 60 °C bajo nitrógeno durante 18 horas. La mezcla se enfrió a temperatura ambiente y se diluyó con EtOAc (75 ml) y agua (10 ml). La capa orgánica se separó, se lavó sobre Na_2SO_4, se filtró y se concentró al vacío. La purificación por medio de HPLC de fase inversa (agua/acetonitrilo, gradiente 5-95%) produjo 110 mg del compuesto del título.

MS (ESP): 544.5 (M+H) para $C_{22}H_{28}Cl_3N_7O_3$

^{1}H NMR δ: 1.40-1.55 (m, 2H); 1.88 (d, 2H); 2.11 (s, 3H); 2.95-3.30 (m, 6H); 3.40-3.65 (m, 6H); 3.70-4.50 (m, 5H); 7.18 (d, 1H); 7.26 (s, 1H); 8.86 (t, 1H); 11.94 (s, 1H).

Ejemplo 14: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)-2-(metilsulfonil)pirimidina-4-ácido carboxílico

Se agregó mCPBA (70%, 164 mg, 0.67 mmol) a una suspensión de 6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-2-(metiltio)pirimidina-4-ácido carboxílico (**Ejemplo 7**, 151 mg, 0.34 mmol) en DCM (15ml) a 0 °C y la mezcla resultante se revolvió durante 3 h. La mezcla se dejó calentar lentamente hasta llegar a la temperatura ambiente durante el periodo de 3 h. La mezcla de la reacción se diluyó con DCM (50 ml), se lavó sobre Na_2SO_4, se filtró y se concentró al vacío. El residuo se purificó mediante HPLC de fase inversa (agua/acetonitrilo, gradiente 5-95%) para producir 32 mg del compuesto del título.

MS (ESP): 476.1 (M+H) para $C_{17}H_{19}Cl_2N_5O_5S$

^{1}H NMR δ: 1.45-1.59 (m, 2H); 1.89 (d, 2H); 2.11 (s, 3H); 3.10-3.30 (m, 2H); 3.27 (s, 3H); 4.00-4.15 (m, 2H); 4.48-4.70 (m, 1H); 7.18 (d, 1H); 7.46 (s, 1H); 11.92 (s, 1H); 13.80 (s, 1H).

Ejemplo 15: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)-*N*-metoxi-2-(metilsulfinil) pirimidina-4-carboxamida

Se agregó mCPBA (70%, 86 mg, 0.35 mmol) a una suspensión de 6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)-*N*-metoxi-2-(metiltio)pirimidina-4-carboxamida (**Ejemplo 8**, 166 mg, 0.35 mmol) en DCM (12 ml) a 0 °C y la mezcla resultante se revolvió durante 2 h. La mezcla de la reacción se diluyó con DCM (50 ml), se lavó con solución de Na_2SO_3 (5%, 10 ml), se lavó sobre Na_2SO_4, se filtró y se concentró al vacío.

La purificación por medio de HPLC de fase inversa (agua/acetonitrilo, gradiente 10-95%) produjo 45 mg del producto del título.

MS (ESP): 489.1 (M+H) para $C_{18}H_{22}Cl_2N_6O_4S$

^{1}H NMR δ: 1.40-1.60 (m, 2H); 1.88 (d, 2H); 2.11 (s, 3H); 2.84 (s, 3H); 3.21 (t, 2H); 3.64 (s, 3H); 4.00-4.15 (m, 2H); 4.40-4.80 (m, 1H); 7.18 (d, 1H); 7. 25 (s, 1H); 11.91 (s, 2H).

Ejemplo 16:6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il) carbonil] amino}piperidin-1-il)-2-[(2-hidroxietil)tio]pirimidina-4-ácido carboxílico

Se revolvió una suspensión de metil 2-cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)pirimidina-4-carboxilato (**Ejemplo 6**, 150 mg, 0.34 mmol), 2-mercaptoetanol (31 mg, 0.40 mmol) y carbonato de potasio (139 mg, 1.01 mmol) en DMF (3 ml) a 65 °C bajo nitrógeno durante 3 horas. La mezcla se enfrió a temperatura ambiente y se diluyó con EtOAc (75 ml) y 1 N HCl (3 ml). La capa orgánica se separó, se lavó sobre Na_2SO_4, se filtró y se concentró al vacío. La purificación del residuo por medio de HPLC de fase inversa (agua/acetonitrilo, gradiente 10-95%) produjo 39 mg del compuesto del título.

MS (ESP): 474.2 (M+H) para $C_{18}H_{21}Cl_2N_5O_4S$

^{1}H NMR δ: 1.40-1.55 (m, 2H); 1.83 (d, 2H); 2.11 (s, 3H); 3.07-3.20 (m, 4H); 3.52-3.62 (m, 2H); 4.00-4.40 (m, 5H); 7.00 (s, 1H); 7.16 (d, 1H); 11.90 (s, 1H).

Ejemplo 17: Metil 6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)-2-[(2-hidroxietil)tiolpirimidina-4-carboxilato

El compuesto del título también se aisló del **Ejemplo 16.**

MS(ESP): 488.2 (M+H) para $C_{19}H_{23}Cl_2N_5O_4S$

^{1}H NMR δ: 1.40-1.55 (m, 2H); 1.84 (d, 2H); 2.11 (s, 3H); 3.05-3.22 (m, 4H); 3.56 (t, 2H); 4.00-4.40 (m, 4H); 7.00 (s, 1H); 7.16 (d, 1H); 11.91 (s, 1H).

Ejemplo 18: 2-Cloro-6-(4-{[(4-cloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)isonicotinamida

Se agregó diisopropiletilamina (0.34ml, 2.0 mmol), EDC (0.121 g, 0.63 mmol) y HOAT (0.086 g, 0.63 mmol) a una solución agitada de 4-cloro-5-metil-1*H*-pirrol-2-ácido carboxílico (**Intermedio 8**, 0.1 g, 0.63 mmol) en DMF (2 ml) a temperatura ambiente. La solución resultante se revolvió durante 15 mins luego se agregó una solución de 2-(4-aminopiperidin-1-il)-6-clorhidrato de cloroisonicotinamida (**Intermedio 70**, 0.19 g, 0.75 mmol) en 3 ml de DMF. La reacción se concentró después de 2 horas y el residuo se distribuyó entre agua y EtOAc. La capa acuosa se extrajo con EtOAc (x2), las capas orgánicas combinadas se lavaron con 1 N HCl, agua y solución salina, luego se lavaron sobre sulfato de magnesio y se concentraron al vacío. El residuo se purificó mediante cromatografía de fase inversa (agua/acetonitrilo, gradiente 20-95%) para producir el producto del título como un sólido blanco.

MS(ES): 396 (M+1) para $C_{17}H_{19}Cl_2N_5O_2$

^{1}H NMR δ: 1.46 (m, 2H); 1.82 (m, 2H); 2.13 (s, 3H); 3.04 (t, 2H); 4.03 (m, 1H); 4.25 (m, 2H); 6.74 (s, 1H); 6.97 (s, 1H); 7.19 (s, 1H); 7.69 (m, 2H); 8.15 (s, 1H); 11.59 (brs, 1H)

Ejemplo 19: 2-(4-{[(4-Bromo-5-etil-1*H*-pirrol-2-il)carbonil]amino} piperidin-1-il)-6-cloroisonicotinamida

Se agregó diisopropiletilamina (0.28ml, 1.64mmol), EDC (0.088 g, 0.46 mmol) y HOAT (0.063 g, 0.46 mmol) a una solución agitada de 4-bromo-5-etil-1*H*-pirrol-2-ácido carboxílico (**Intermedio 10**, 0.1 g, 0.46 mmol) en DMF (1.5 ml) a temperatura ambiente. La solución resultante se revolvió durante 30 mins y se agregó una solución de 2-(4-aminopiperidin-1-il)-6-clorhidrato de cloroisonicotinamida (**Intermedio 70**, 0.14 g, 0.55 mmol) en 3 ml de DMF. La reacción se revolvió durante la noche, luego se concentró al vacío y el residuo se distribuyó entre agua y EtOAc. La capa acuosa se extrajo con EtOAc (x2) y los extractos orgánicos combinados se lavaron con 1 N HCl, agua y solución salina, se lavaron sobre $MgSO_4$ y se concentraron al vacío. El residuo se purificó mediante cromatografía de fase inversa para producir el producto deseado como un sólido blanco.
MS (ES): 456 (M+1) para $C_{18}H_{21}BrClN_5O_2$
^{1}H NMR δ: 1.09 (t, 3H); 1.47 (m, 2H); 1.82 (m, 2H); 3.04 (t, 2H); 3.30 (q, 2H); 4.03 (m, H); 4.25 (m, 2H); 6.79 (s, 1H); 6.97 (s, 1H); 7.19 (s, 1H); 7.69 (s, 1H); 7.76 (d, 1H); 8.15 (s, 1H); 11.64 (brs, 1H)

Ejemplo 20: 2-Cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)isonicotinamida

Se agregó diisopropiletilamina (0.063ml, 0.37 mmol), EDC (0.095 g, 0.31 mmol) y HOAT (0.042 g, 0.31 mmol) a una solución agitada de 3,4-dicloro-5-metil-1*H*-pirrol-2-ácido carboxílico (**Intermedio 3**, 0.060 g, 0. 31 mmol) en DMF (1.0 ml) a temperatura ambiente.
La solución resultante se revolvió durante 30 mins y se agregó una solución de 2-(4-aminopiperidin-1-il)-6-clorhidrato de cloroisonicotinamida (**Intermedio 70**, 0.096 g, 0.37 mmol) en 1 ml de DMF. La reacción se revolvió durante la noche, luego se concentró al vacío y el residuo se distribuyó entre agua y EtOAc. La capa acuosa se extrajo con EtOAc (x2) y los extractos orgánicos combinados se lavaron con 1 N HCl, agua y

solución salina, se lavaron sobre $MgSO_4$ y se concentraron al vacío. El residuo se purificó mediante cromatografía de fase inversa para producir el producto deseado como un sólido blanco (40 mg).

MS (ES): 431 (M+1) para $C_{17}H_{18}Cl_3N_5O_2$

^{1}H NMR δ: 1.56 (m, 2H); 1.88 (m, 2H); 2.17 (s, 3H); 3.11 (t, 2H); 4.10 (m, 1H); 4.25 (m, 2H); 6.97 (s, 1H); 7.18 (s, 1H); 7.23 (d, 1H); 7.69 (s, 1H); 8. 14 (s, 1H); 11.95 (s, 1H)

Ejemplo 21: 2-Cloro-6-(4-{[(4-ciano-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)isonicotinamida

Se agregó diisopropiletilamina (0.1ml, 0.56 mmol), EDC (0.09 g, 0.46 mmol) y HOAT (0.064 g, 0.46 mmol) a una solución agitada de 4-ciano-5-metil-1*H*-pirrol-2-ácido carboxílico (**Intermedio 13**, 0.07 g, 0.47 mmol) en DMF (1.5 ml) a temperatura ambiente. La solución resultante se revolvió durante 30 mins y se agregó una solución de 2-(4-aminopiperidin-1-il)-6-clorhidrato de cloroisonicotinamida (**Intermedio 70**, 0.16 g, 0.56 mmol) en 1 ml de DMF. La reacción se revolvió durante la noche, luego se concentró al vacío y el residuo se distribuyó entre agua y EtOAc. La capa acuosa se extrajo con EtOAc y los extractos orgánicos combinados se lavaron (x2) con 1 N HCl, agua y solución salina, se lavaron sobre $MgSO_4$ y se concentraron al vacío. El residuo se purificó mediante cromatografía de fase inversa para producir el producto deseado como un sólido blanco (13 mg).

MS (ES): 387(M+1) para $C_{18}H_{19}ClN_6O_2$

^{1}H NMR δ: 1.48 (m, 2H); 1.84 (m, 2H); 2.31 (s, 3H); 3.05 (t, 2H); 4.04 (m, 1H); 4.26 (m, 2H); 6.98 (s, 1H); 7.03 (s, 1H); 7.19 (s, 1H); 7.69 (s, 1H); 7.98 (d, 1H); 8.15 (s, 1H); 12.23 (s, 1H)

Ejemplo 22: 2-Cloro-6-(4-{[(4-cloro-5-etil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)isonicotinamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 18** mediante el acoplamiento de 2-(4-aminopiperidin-1-il)-6-

clorhidrato de cloroisonicotinamida (**Intermedio 70**) con 4-cloro-5-etil-1*H*-pirrol-2-ácido carboxílico (**Intermedio 71**).

MS (ES): 410 (M+1) para $C_{18}H_{21}Cl_2N_5O_2$

^{1}H NMR δ: 1.10 (t, 3H); 1.45 (m, 2H); 1.83 (m, 2H); 2.54 (q, 2H); 3.04 (t, 2H); 4.03 (m, 1H); 4.27 (m, 2H); 6.73 (d, 1H); 6.97 (s, 1H); 7.19 (s, 1H); 7.69 (s, 1H); 7.76 (d, 1H); 8.15 (s, 1H); 11.57 (s, 1H)

Ejemplo 23: 2-Cloro-6-(4-{[(3,5-dimetil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1il)isonicotinamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 18** utilizando 2-(4-aminopiperidin-1-il)-6-clorhidrato de cloroisonicotinamida (**Intermedio 70**) y 3,5-dimetil-1*H*-pirrol-2-ácido carboxílico (disponible en el comercio).

MS (ES)::: 476 (M+1) para $C_{18}H_{22}ClN_5O_2$

^{1}H NMR δ: 1.46 (m, 2H); 1.87 (m, 2H); 2.13 (s, 3H); 2.19 (s, 3H); 3.09 (t, 2H); 4.03 (m, 1H); 4.23 (m, 2H); 5.63 (s, 1H); 6.97 (s, 1H); 7.00 (d, 1H); 7.19 (s, 1H); 7.69 (s, 1H); 8.15 (s, 1H); 10.69 (s, 1H)

Ejemplo 24:2-Cloro-6-(4-{[(3,4-dicloro-5-etil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)isonicotinamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 18** mediante el acoplamiento de 2-(4-aminopiperidin-1-il)-6-clorhidrato de cloroisonicotinamida (**Intermedio 70**) con 3,4-dicloro-5-etil-1*H*-pirrol-2-ácido carboxílico (**Intermedio 73**).

MS (ES): 446 (M+1) para $C_{18}H_{20}Cl_2N_5O_2$

^{1}H NMR δ: 1.12 (t, 3H); 1.56 (m, 2H); 1.87 (m, 2H); 2.56 (q, 2H); 3.11 (t, 2H); 4.06 (m, 1H); 4.24 (m, 2H); 6.97 (s, 1H); 7.18 (s, 1H); 7.25 (d, 1H); 7.69 (s, 1H); 8.14 (s, 1H); 11.92 (s, 1H)

Ejemplo 25:2-Cloro-6-(4-{[(3-etil-4,5-dimetil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)ison icotinamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 18** mediante el acoplamiento de 2-(4-aminopiperidin-1-il)-6-clorhidrato de cloroisonicotinamida (**Intermedio 70**) con 3-etil-4,5-dimetil-1*H*-pirrol-2-ácido carboxílico (disponible en el comercio).

MS (ES): 404 (M+1) para $C_{20}H_{26}Cl_3N_5O_2$

^{1}H NMR δ: 0.97 (t, 3H); 1.43 (m, 2H); 1.82 (s, 3H); 1.90 (m, 2H); 2.08 (s, 3H); 2.65 (q, 2H); 3.07 (t, 2H); 3.99 (m, 1H); 4.22 (m, 2H); 6.96 (s, 1H); 7.06 (d, 1H); 7.18 (s, 1H); 7.68 (s, 1H); 8.14 (s, 1H); 10.48 (s, 1H)

Ejemplo 26:2-Cloro-6-(4-{[(3,4-dietil-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)isonicotinamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo** 18 mediante el acoplamiento de 2-(4-aminopiperidin-1-il)-6-clorhidrato de cloroisonicotinamida (**Intermedio 70**) con 3,4 dietil-5-metil-1*H*-pirrol-2-ácido carboxílico (disponible en el comercio).

MS (ES): 418 (M+l) para $C_{21}H_{28}ClN_5O_2$

^{1}H NMR δ: 0.94- 1.04 (m, 6H); 1.43 (m, 2H); 1.90 (m, 2H); 2.08 (s, 3H); 2.28 (q, 2H); 2.63 (q, 2H); 3.07 (t, 2H); 4.08 (m, 1H); 4.20 (m, 2H); 6.96 (s, 1H); 7.07 (d, 1H); 7.18 (s, 1H); 7.66 (s, 1H); 8.14 (s, 1H); 10.51 (s, 1H)

Ejemplo 27: 2-Cloro-6-(4-{[(4-cloro-3,5-dimetil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)isonicotinamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 18** mediante el acoplamiento de 2-(4-aminopiperidin-1-il)-6-clorhidrato de cloroisonicotinamida (**Intermedio 70**) con 4-cloro-3,5-dimetil-1*H*-pirrol-2-ácido carboxílico (**Intermedio 75**).

MS (ES): 408 (M-1) para $C_{18}H_{21}Cl_2N_5O_2$

^{1}H NMR δ: 1.47 (m, 2H); 1.87 (m, 2H); 2.13 (s, 3H); 2.16 (s, 3H); 3.10 (t, 2H); 4.00 (m, 1H); 4.21 (m, 2H); 6.96 (s, 1H); 7.18 (s, 1H); 7.20 (d, 1H); 7.68 (s, 1H); 8.14 (s, 1H); 11.17 (s, 1H)

Ejemplo 28: 2-Cloro-6-(4-{[(4-ciano-3,5-dimetil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)isonicotinamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 18** mediante el acoplamiento de 2-(4-aminopiperidin-1-il)-6-clorhidrato de cloroisonicotinamida (**Intermedio 70**) con 4-ciano-3,5-dimetil-1H-pirrol-2-ácido carboxílico (disponible en el comercio).

MS (ES): 399 (M-1) para $C_{19}H_{21}ClN_6O_2$

^{1}H NMR δ: 1.48 (m, 2H); 1.86 (m, 2H); 2.25 (s, 3H); 2.28 (s, 3H); 3.08 (t, 2H); 4.01 (m, 1H); 4.21 (m, 2H); 6.96 (s, 1H); 7.18 (s, 1H); 7.40 (d, 1H); 7.68 (s, 1H); 8.13 (s, 1H); 11.77 (s, 1H)

Ejemplo 29: 2-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1il)-1,3-tiazol-5-carboxamida

Se agregó diisopropiletilamina (0.19ml, 1.12 mmol), EDC (0.098 g, 0.51 mmol) y HOAT (0.070 g, 0.51 mmol) a una solución agitada de 3,4-dicloro-5-metil-1H-pirrol-2ácido carboxílico (**Intermedio 3**, 0.1 g, 0.51 mmol) en DMF (1.5 ml) a temperatura ambiente.

La solución resultante se revolvió durante 30 mins y se agregó 2-(4-aminopiperidin-1-il)-1,3-tiazol-5-clorhidrato de carboxamida (**Intermedio 81**; 0.163 g, 0.62 mmol). La reacción se revolvió a temperatura ambiente durante la noche bajo nitrógeno. La reacción se revolvió durante la noche, luego se concentró al vacío y el residuo se distribuyó entre agua y EtOAc.

La capa acuosa se extrajo con EtOAc y los extractos orgánicos combinados se lavaron con 1 N HCl, agua y solución salina, se lavaron sobre $MgSO_4$ y se concentraron al vacío. El residuo se purificó mediante cromatografía de fase inversa (agua/acetonitrilo, gradiente 20-95%) para producir el producto deseado como un sólido blanco (50 mg).

MS (ES): 402 (M+l) para $C_{15}H_{17}Cl_2N_5O_2S$

^{1}H NMR δ: 1.58 (m, 2H); 1.82 (m, 2H); 2.11 (s, 3H); 3.17 (t, 2H); 3.81 (m, 2H); 3.97 (m, 1H); 7.07(brs, 1H); 7.20 (d, 1H); 7.61 (brs, 1H); 7.71 (s, 1H); 11.90 (s, 1H)

Ejemplo 30:2-(4-{[(3,4-Dicloro-5-etil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)-1,3-tiazol-5-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 29** mediante el acoplamiento de 3,4-dicloro-5-etil-1*H*-pirrol-2-ácido carboxílico (**Intermedio 73**) con 2-(4-aminopiperidin-1-il)-1,3-tiazol-5-clorhidrato de carboxamida (**Intermedio 81**).

MS (ES): 416 (M+1) para $C_{16}H_{19}Cl_2N_5O_2S$

^{1}H NMR δ: 1.11 (t, 3H); 1.66 (m, 2H); 1.89 (m, 2H); 2.56 (q, 2H); 3.24 (t, 2H); 3.81 (m, 2H); 4.06 (m, 1H); 7.14 (brs, 1H); 7.31 (d, 1H); 7.71 (brs, 1H); 7.78 (s, 1H); 11.94 (s, 1H)

Ejemplo 31:6-(4-{[(4-Bromo-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)-2-cloropirimidina-4-ácido carboxílico

Se calentó hidróxido de litio (2 M, 4 ml) a 40 °C y se agregó una solución de metil 6-(4-{[(4-bromo-5-metil-1*H*-pirrol-2-il)carbonil]amino} piperidin-1-il)-2-cloropirimidina-4-carboxilato (**Ejemplo 73**, 0.180 g, 0.394 mmol) en MeOH. La reacción se revolvió a 40 °C durante 30 mins. El MeOH se extrajo y la solución acuosa se enfrió a 0 °C y se acidificó con 6 M HCl. La solución acídica se extrajo con EtOAc, se lavó sobre $MgSO_4$ y se concentró para producir un sólido rosado (0.15 g, 86%). Una muestra analítica se purificó mediante HPLC de fase inversa (acetonitrilo/agua (TFA al 0.1 %), 20-95%).

MS (ES): 443 (M+1) para $C_{16}H_{17}BrClN_5O_3$

^{1}H NMR δ: 1.45 (m, 2H); 1.88 (m, 2H); 2.12 (s, 3H); 3.17 (m, 2H); 3.81 (m, 2H); 4.06 (m, 1H); 6.79 (s, 1H); 7.37 (s, 1H); 7.76 (d, 1H); 11.67 (s, 1H)

Ejemplo 32:2-Cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)pirimidina-4-ácido carboxílico

El compuesto del título se sintetizó a partir de metil 2-cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il) pirimidina-4-carboxilato (**Ejemplo 6**) mediante un método análogo al del **Ejemplo 31**.

MS (ES): 432 (M+1) para $C_{16}H_{16}Cl_3N_5O_3$

^{1}H NMR δ: 1.57 (m, 2H); 1.91 (m, 2H); 2.17 (s, 3H); 3.21 (m, 2H); 4.11 (m, 1H); 4.36 (m, 2H); 7.22 (d, 1H); 7.33 (s, 1H); 11.96 (s, 1H)

Ejemplo 33: 6-(4-{[(4-Bromo-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-2-cloro-*N*-metoxipirimidina-4-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 8** mediante el acoplamiento de 6-(4-{[(4-bromo-5-metil-1*H*-pirrol-2-il)carbonil]amino} piperidin-1-il)-2-cloropirimidina-4-ácido carboxílico (**Ejemplo 31**) con clorhidrato de metoxilamina (disponible en el comercio).

MS ES: 473 (M+1) para $C_{17}H_{20}BrClN_6O_3$

^{1}H NMR δ: 1.43 (m, 2H); 1.85 (m, 2H); 2.10 (s, 3H); 3.24 (m, 2H); 3.16 (t, 3H); 4.06 (m, 1H); 4.71 (m, 2H); 6.79 (s, 1H); 7.26 (s, 1H); 7.74 (d, 1H); 11.65 (s, 1H);11.94 (s, 1H)

Ejemplo 34: 6-(4-{[(4-Bromo-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-*N*-metoxi-2-(metiltio) pirimidina-4-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 8** mediante el acoplamiento de 6-(4-{[(4-bromo-5-metil-1*H*-pirrol-2-il)carbonil]amino} piperidin-1-il)-2-(metiltio)pirimidina-4-ácido carboxílico (**Ejemplo 35**) con clorhidrato de metoxilamina (disponible en el comercio).

MS (ES): 484 (M+1) para $C_{18}H_{23}BrN_6O_3S$

^{1}H NMR δ: 1.38 (m, 2H); 1.84 (m, 2H); 2.11 (s, 3H); 2.50 (s, 3H); 3.10 (t, 2H); 3.67 (s, 3H); 4.03 (m, 1H); 4.37 (m, 2H); 6.78 (s, 1H); 6.95 (s, 1H); 7.74 (d, 1H); 11.66 (s, 1H); 11.75 (s, 1H)

Ejemplo 35: 6-(4-{[(4-Bromo-5-metil-1*H*-pirrol-2-

il)carbonil]amino}piperidin-1-il)-2-(metiltio)pirimidina-4-ácido carboxílico

El compuesto del título se sintetizó a partir de metil 6-(4-{[(4-bromo-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-2-cloropirimidina-4-carboxiliato (**Ejemplo 73**) mediante un método análogo al del **Ejemplo 7**.

MS ES: 455 (M+1) para $C_{17}H_{20}BrN_5O_3S$

^{1}H NMR δ: 1.44 (m, 2H); 1.86 (m, 2H); 2.12 (s, 3H); 2.46 (s, 3H); 3.12 (t, 2H); 4.06 (m, 1H); 4.36 (m, 2H); 6.79 (s, 1H); 7.06 (s, 1H); 7.75 (d, 1H); 11.67 (s, 1H); 11.66 (s, 1H)

Ejemplo 36:6-(4-{[(4-Bromo-5-metil-1*H*-pirrol-2-il) carbonil]amino} piperidin-1-il)-2-cloropirimidina-4-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 8** mediante el acoplamiento de 6-(4-{[(4-bromo-5-metil-1*H*-pirrol-2-il)carbonil]amino} piperidin-1-il)-2-cloropirimidina-4-ácido carboxílico (**Ejemplo 31**) con 2 M amoniaco en MeOH.

MS (ES): 443 (M+1) para $C_{16}H_{18}BrClN_6O_2$

^{1}H NMR δ: 1.45 (m, 2H); 1.90 (m, 2H); 2.12 (s, 3H); 3.18 (t, 2H); 4.06 (m, 1H); 4.39 (m, 2H); 6.79 (s, 1H); 7.30 (s, 1H); 7.79 (d, 1H); 7.83 (s, 1H); 7.95 (s, 1H); 11.68 (s, 1H)

Ejemplo 37: 2-Cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)pirimidina-4-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 8** mediante el acoplamiento de 2-cloro-6-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil] amino}piperidin-1-il)pirimidina-4-ácido carboxílico (**Ejemplo 32**) con 2 M amoniaco en MeOH.

MS (ES): 431 (M+1) para $C_{16}H_{17}Ci_3N_6O_2$

^{1}H NMR δ: 1.56 (m, 2H); 1.90 (m, 2H); 2.16 (s, 3H); 3.30 (t, 2H); 4.12(m, 1H); 4.36 (m, 2H); 7.23 (d, 1H); 7.30 (s, 1H); 7.82 (s, 1H); 7.94 (s, 1H); 11.97 (s, 1H)

Ejemplo 38: 6-(4-{[(4-Bromo-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-2-(metiltio)pirimidina-4-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 8** mediante el acoplamiento de 6-(4-{[(4-bromo-5-metil-1*H*-pirrol-2-il)carbonil]amino} piperidin-1-il)-2-(metiltio) pirimidina-4-ácido carboxílico (**Ejemplo 35**) con 2 M amoniaco en MeOH (disponible en el comercio).

MS (ES): 454 (M+1) para $C_{17}H_{21}BrN_6O_2S$

^{1}H NMR δ: 1.43 (m, 2H); 1.88 (m, 2H); 2.12 (s, 3H); 2.46 (s, 3H); 3.11 (t, 2H); 4.04 (m, 1H); 4.45 (brs, 2H); 6.78 (s, 1H); 7.04 (s, 1H); 7.74 (s, 2H); 7.93 (s, 1H); 11.67 (s, 1H).

Ejemplo 39: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)-*N*,2-dimetoxipirimidina-4-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 8** comenzando a partir de 6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)-2-metoxipirimidina-4-ácido carboxílico (**Ejemplo 311**) y clorhidrato de metoxilamina.

MS (ES): 457 (M+1) para $C_{18}H_{22}Cl_2N_6O_4$

^{1}H NMR δ: 1.52 (m, 2H); 1.88 (m, 2H); 2.16 (s, 3H); 3.17 (t, 2H); 3.67 (s, 3H); 3.87 (s, 3H); 4.09 (m, 1H); 4.32 (m, 2H); 6.96 (s, 1H); 7.22 (d, 1H); 11.81 (s, 1H); 11.96 (s, 1H)

Ejemplo 40: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-2-etoxi-*N*-metoxipirimidina-4-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 8** comenzando a partir de 6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-2etoxipirimidina-4-ácido carboxílico (**Ejemplo 312**) y clorhidrato de metoxilamina.

MS (ES):: 471 (M+1) para $C_{19}H_{24}Cl_2N_6O_4$

^{1}H NMR δ: 1.28 (t, 3H); 1.52 (m, 2H); 1.88 (m, 2H); 2.16 (s, 3H); 3.16 (t, 2H); 3.66 (s, 3H); 4.09 (m, 1H); 4.32 (m, 2H); 4.32 (q, 2H); 6.95 (s, 1H); 7.22 (d, 1H); 11.80 (s, 1H); 11.96 (s, 1H)

Ejemplo 41: 3,4-Dicloro-*N*-[1-(4-cloro-6-metoxi-1,3,5-triazin-2-il) piperidin-4-il]-5-metil-1*H*-pirrol-2-carboxamida

Se agregó una solución de 2,4-dicloro-6-metoxi-1,3,5-triazina (disponible en el comercio) (0.05 g, 0.32 mmol) en DMF (0.5 ml) a una solución de 3,4-dicloro-5-metil-*N*-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 1**, 0.1 g, 0.32 mmol) y TEA (0.06 g, 0.64 mmol) en DMF (1.5 ml). La mezcla resultante se revolvió durante 1 h a temperatura ambiente, luego se diluyó con agua y se extrajo con EtOAc. Durante la preparación acuosa, una parte del producto se precipitó y se recolectó mediante filtración por succión. El extracto orgánico se lavó sobre sulfato de magnesio, se filtró y se concentró para producir el producto deseado con pequeñas cantidades de impurezas.

MS(ESP): 419 (M+1) para $C_{15}H_{17}Cl_3N_6O_2$

^{1}H NMR δ: 1.54 (m, 2H); 1.90 (m, 2H); 2.16 (s, 3H); 3.10 (t, 2H); 3.88 (t, 3H); 4.08 (m, 1H); 4.45 (t, 2H); 7.25 (d, 1H); 12.01 (s, 1H).

Ejemplo 42: 2-(4-{[(4-Bromo-5-metil-1H-pirrol-2-il)carbonil]amino} piperidin-1-il)-6-cloroisonicotinamida

Se agregó 4N HCl/dioxano solución (10ml) a tert-butilo 1-[4-(aminocarbonil)-6-cloropiridin-2-il]piperidin-4-ilcarbamato (**Intermedio 16**, 100 mg, 0.282 mmol). La mezcla se revolvió a temperatura ambiente durante 90 minutos. El solvente se extrajo al vacío y se agregó el dietiléter anhidro (25 ml). El solvente se extrajo al vacío y el sólido marrón claro resultante se secó al vacío durante varias horas. LCMS indicó un producto puro 2-(4-aminopiperidin-1-il)-6-cloroisonicotinamida sal de clorhidrato (MS M+H: 255). Se agregó pentafluorofenilo 4-bromo-5-metil-1H-pirrol-2-carboxilato (**Intermedio 17**) (104 mg, 0.282 mmol) y N,N-diisopropilo etilamin (98 µl, 0.564 mmol) a 2-(4-aminopiperidin-1-il)-6-

cloroisonicotinamida sal de clorhidrato (82 mg, 0.282 mmol) en DMA anhidro (4ml). La mezcla se revolvió a temperatura ambiente durante 18 h y se filtró y se purificó mediante HPLC de semi preparación utilizando CH_3CN/H_2O (TFA al 0.1 %) para producir el compuesto del título (28 mg).
MS (ES, M+H): 442 para $C_{17}H_{19}ClN_5O_2$
^{1}H NMR δ: 1.25 (m, 2H); 1.62 (m, 2H); 1.93 (s, 3H); 2.83 (m, 2H); 3.88 (m, 1H); 4.29 (m, 2H); 6.64 (d, 1H); 6.8 (s, 1H); 6.99 (s, 1H); 7.47 (s, 1H); 7.78 (s, 1H); 7.96 (s, 1H); 11.54 (s, 1H).

Ejemplo 43: Metil 2-(4-{[(4-bromo-5-metil-1H-pirrol-2-il)carbonil]amino}piperidin-1-il)-6-cloroisonicotinato

Se agregó pentafluorofenilo 4-bromo-5-metil-1H-pirrol-2-carboxilato (**Intermedio 17**, 1.81 g, 4.90 mmol) y TEA (682 µl, 4.9 mmol) a metil 2-(4-aminopiperidin-1-il)-6-cloroisonicotinato sal de clorhidrato (**Intermedio 93**; 1.5 g, 4.90 mmol) en DMA anhidro (10ml). La mezcla se revolvió a temperatura ambiente durante 18 h luego se distribuyó entre EtOAc y agua. La capa orgánica se lavó con agua, se lavó sobre Na_2SO_4 y se concentró al vacío. El material sólido se purificó mediante cromatografía instantánea levigado con EtOAc/n-hexanos mezcla (7:3) para producir el compuesto del título como un sólido marrón (1.7 g).
MS (ES, M+H): 456 para $C_{18}H_2BrClN_4O_3$
^{1}H NMR δ: 1.39 (m, 2H); 1.82 (m, 2H); 2.11 (s, 3H); 3.00 (m, 2H); 3.86 (s, 3H); 3.99 (m, 1H); 4.23 (d, 2H); 6.80 (d, 1H); 6.96 (s, 1H); 7.21 (s, 1H); 7.73 (d, 1H); 11.26 (s, 1H)

Ejemplo 44: 2-(4-{[(4-Bromo-5-metil-1H-pirrol-2-il)carbonil]amino}piperidin-1-il)-6-ácido cloroisonicotínico

Se disolvió metil 2-(4-{[(4-bromo-5-metil-1H-pirrol-2-il)carbonil]amino}piperidin-1-il)-6-cloroisonicotinato (Ejemplo 43,1. 7 g, 3.72 mmol) en THF (10 ml). Se agregó 2N hidróxido de litio (10ml) y la reacción se revolvió a temperatura ambiente durante 3 h. La mezcla se acidificó con 1 N HCl y

se extrajo con EtOAc (3x50 ml), se lavó sobre Na_2SO_4 y se concentró al vacío.

MS (ES M+H): 442 para $C_{17}H_{18}BrN_4O_3$

^{1}H NMR δ: 1.29 (m, 2H); 1.72 (m, 2H); 2.04 (s, 3H); 2.91 (m, 2H); 3.89(m, 1H); 4.13 (d, 2H); 6.70 (d, 1H); 6.84 (s, 1H); 7.10 (s, 1H); 7.65 (d, 1H); 11.26 (s, 1H)

Ejemplo 45: 2-(4-[{(4-Bromo-5-metil-1H-pirrol-2-il)carbonil]amino} piperidin-1-il)-6-cloro-N-metoxiisonicotinamida

Se revolvió 2-(4-{[(4-bromo-5-metil-1H-pirrol-2-il)carbonil]amino}piperidin-1-il)-6- ácido cloroisonicotínico (**Ejemplo 44**, 150 mg, 0.34 mmol); HATU, (129 mg, 0.34 mmol); HOAT (46.25 mg; 0.34 mmol); N,N-diisopropilo etilamin (116 µl, 0.68 mmol) en DMF anhidro (3ml) durante 30 minutos. Se agregó clorhidrato de metoxilamina (28.4 mg, 0.340mmol), N,N-diisopropilo etilamina (58 µl, 0.340 mmol). La mezcla se revolvió a temperatura ambiente durante 18 h y la mezcla cruda se filtró, luego se purificó mediante HPLC de semi preparación de fase inversa levigado con CH_3CN/H_2O (TFA al 0.1 %). (23 mg).

MS (ES, M+H): 472 para $C_{18}H_{21}BrClN_5O_3$

^{1}H NMR δ: 1.36 (m, 2H); 1.78 (m, 2H); 2.08 (s, 3H); 2.96 (m, 2H); 3.66 (s, 3H); 3.96 (m, 1H); 4.17 (d, 2H); 6.76 (d, 1H); 6.82 (s, 1H); 7.02 (s, 1H); 7.71 (d, 1H); 11.63 (s, 1H); 11.92 (s, 1H)

Ejemplo 46: 3,4-Dicloro-N-(1-{6-cloro-4-[(1E)-N-hidroxietanimidoil] piridin-2-il}piperidin-4-il)-5-metil-1H-pirrol-2-carboxamida

Se disolvió N-[1-(4-acetil-6-cloropiridin-2-il)piperidin-4-il]-3,4-dicloro-5-metil-1H-pirrol-2-carboxamida (Ejemplo 115) (49 mg, 0.114 mmol) en EtOH (2 ml). Se agregó piridina (74 µl, 0.913 mmol) seguido por clorhidrato de hidroxilamina (63.4 mg, 0.913 mmol). La mezcla se revolvió a temperatura ambiente durante la noche. El producto se purificó mediante mediante HPLC de semi preparación de fase inversa levigado con CH_3CN/H_2O (0.1% TEA). (28 mg).

MS (ES, M+H): 446 para $C_{18}H_{20}Cl_3N_5O_2$

^{1}H NMR δ: 146 (m, 2H); 1.83 (s, 3H); 2.10 (s, 3H); 2.15 (s, 3H); 3.02 (m, 2H); 3.99 (m, 1H); 4.17 (d, 2H); 6.83 (s, 1H); 6.91 (s, 1H); 7.20 (s, 1H); 11.65 (s, 1H); 11.93 (s, 1H)

Ejemplo 47: N-(1-{4-[Amino(hidroxiimino)metil]-6-cloro-2-piridinil}-4-piperidinil)-3,4-dicloro-5-metil-1H-pirrol-2-carboxamida

Se disolvió 3,4-dicloro-N-[1-(6-cloro-4-cianopiridin-2-il) piperidin-4-il]-5-metil-1H-pirrol-2-carboxamida (**Ejemplo 95**; 150 mg, 0.362 mmol) en MeOH (5 ml) y se agregó TEA (100 µl, 0.724 mmol). Se agregó clorhidrato de hidroxilamina (25.2 mg, 0.362 mmol) y la mezcla se llevó a reflujo durante 1 h. El solvente se extrajo al vacío y el producto precipitado resultante se disolvió en DMSO y se purificó mediante HPLC de semi preparación de fase inversa levigado con CH_3CN/H_2O (TFA al 0.1 %). (80 mg).

MS (ES, M+H): 447 para $C_{17}H_{19}Cl_3N_6O_2$

^{1}H NMR δ: 1.35 (m, 2H); 1.73 (m, 2H); 2.06 (s, 3H); 2.94 (m, 2H); 3.89 (m, 1H); 4.07 (d, 2H); 6.04 (brm, 2H); 6.78 (s, 1H); 6.95 (s, 1H); 7.13 (d, 1H); 9.98 (s, 1H); 11.85 (s, 1H)

Ejemplo 48: 1-[6-Cloro-4-(1H-tetrazol-5-il)piridin-2-il]piperidin-4-ilo 3, 4-dicloro-5-metil-1H-pirrol-2-carboxilato

Se disolvió 1-(6-cloro-4-cianopiridin-2-il)piperidin-4-ilo 3,4-dicloro-5-metil-1H-pirrol-2-carboxilato (**Ejemplo 308**, 64 mg, 0.154 mmol), azida de sodio (12 mg, 0. 185 mmol) y cloruro de amonio (8.3 mg, 0.154 mmol) en DMF anhidro (2 ml) y la mezcla se calentó a 120 °C durante 8 h. La mezcla se filtró y se purificó mediante HPLC de semi preparación de fase inversa levigado con CH_3CN/H_2O (TFA al 0.1 %) (48 mg).

MS (ES, M+H): 456 para $C_{17}H_{16}Cl_3N_7O_2$

^{1}H NMR δ: 1.67 (m, 2H); 1.91 (m, 2H); 2.16 (s, 3H); 3.66 (m, 2H); 3.79 (m, 2H); 5.19 (m, 1H); 7.17 (s, 1H); 7.39 (s, 1H); 12.24 (s, 1H)

Ejemplo 49: 3,4-Dicloro-5-metil-*N*-[1-(1-metil-5-nitro-1*H*-imidazol-2-il)piperidin-4-il]-1H-pirrol-2-carboxamida

Se agregó TEA (0.26 ml, 1.86 mmol) a una mezcla de 2-bromo-1-metil-5-nitro-1*H*-imidazol (G.B. Barlin, *J. Chem. Soc. B*, **1967**, 641; 126 mg, 0.61 mmol,) y 3,4-dicloro-5-metil-*N*-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 1**), 191 mg, 0.61 mmol) en 1-metil-2-pirrolidinona (1.5ml). Empleando un Smith Microwave Synthesizer, la mezcla se sometió a microondas unimodal a 150 °C durante 30 min. Se agregó EtOAc y la solución se lavó con agua (2X). La fase orgánica se separó, se lavó sobre $MgSO_4$ y se concentró al vacío. El material crudo se purificó mediante cromatografía en gel de sílice utilizando 50% EtOAc/hexanos para producir 158 mg del producto del título.

MS (ESP): 401 (MH^+) para $C_{15}H_{18}Cl_2N_6O_3$

^{1}H-NMR δ: 1.73-1.86 (m, 2H); 1.97-2.01 (m, 2H); 2.25 (s, 3H); 3.18 (t, 2H); 3.56-3.64 (m, 2H); 3.71 (s, 3H); 4.08 (m, 1H); 7.34 (d, 1H); 8.02 (s, 1H); 12.19 (s, 1H).

Ejemplo 50: 3,4-Dicloro-5-metil-*N*-[1-(1-metil-4-nitro-1*H*-imidazol-2-il)piperidin-4-il]-1*H*-pirrol-2-carboxamida

Empleando un procedimiento similar a aquel empleado en el **Ejemplo 52**, se obtuvieron 30 mg del producto del título comenzando a partir de 2-bromo-1-metil-4-nitro-1*H*-imidazol (G. B. Barlin, *J. Chem. Soc. B*, **1967**, 641).

MS (ESP): 401(MH^+) para $C_{15}H_{18}Cl_2N_6O_3$

^{1}H-NMR δ: 1.76-1.86 (m, 2H); 1.98-2.01 (m, 2H); 2.26 (s, 3H); 3.02 (t, 2H); 3.42-3.52 (m agua superpuesta, 2H); 3.65 (s, 3H); 4.03 (m, 1H); 7.35 (d, 1H); 8.28 (s, 1H); 12.06 (s, 1H).

Ejemplo 51: 1-*tert*-Butil 2-metil (2*S*)-4-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)pirrolidina-1,2-dicarboxilato

Se revolvió *N*-BOC-*trans*-4-hidroxi-L-prolina metiléster (0.20 g, 0.81mM) y 3,4-dicloro-5-metil-*N*-piperidin-4-il-1*H*-pirrol-2-carboxamida (base libre

del **Intermedio 1**), 0.16 g, 0.81 mM) en 1,2-dicloroetano (3.5 ml). Se agregó triacetoxiborohidruro sódico (0.24 g, 1.1 mM) seguido por ácido acético (0.05ml). La reacción se revolvió bajo nitrógeno a temperatura ambiente durante la noche, luego se diluyó con éter y se lavó con 1 N hidróxido de sodio. La fase orgánica se lavó con solución salina, se lavó sobre $MgSO_4$ y se concentró para producir un aceite de color naranja. El aceite se sometió a cromatografía utilizando EtOAc para producir el producto deseado como un sólido amarillo claro.

MS (ESP): 503 (MH^+) para $C_{22}H_{32}Cl_2N_4O_5$

^{1}H-NMR ($CDCl_3$) δ: 1.39 y 1.45 (2s, 9H, rotámeros); 1.71-1.92 (m, 1H); 1.92-2.10 (m, 2H); 2.10-2.34 (m, 5H); 2.41-2.61 (m, 1H); 2.67-2.94 (m, 3H); 3.21 (t, 1H); 3.71 (s, 3H); 3.81-4.01 (m, 2H); 4.19-4.31 (m, 1H); 6.58 (d, 1H); 9.59 (brs, 1H).

Ejemplo 52: Metil 4-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)-L-prolinato

Se revolvió 1-*tert*-butil 2-metil (2*S*)-4-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)pirrolidina-1,2-dicarboxilato (**Ejemplo 51**, 0.16 g, 0.32 mM) en 4 N cloruro de hidrógeno en dioxano (4.0 ml) a temperatura ambiente durante veinte minutos. La mezcla naranja se concentró, luego se disolvió en una cantidad pequeña de MeOH/DCM, se diluyó con DCM y se lavó con bicarbonato de sodio. La capa orgánica se lavó sobre $MgSO_4$, se filtró y se concentró para producir un sólido de color naranja (0.130 g).

MS (ESP): 403 (MH^+) para $C_{17}H_{24}Cl_2N_4O_3$

^{1}H-NMR ($CDCl_3$) δ: 1.51-1.70 (m, 2H); 1.70-1.82(m, 1H); 1.89-2.04 (m, 2H); 2.18-2.34 (m, 5H); 2.36-2.48 (m, 1H); 2.77-3.01 (m, 4H); 3.07-3.20 (m, 1H); 3.72 (s, 3H); 3.77-3.95 (m, 2H).

Ejemplo 53: 4-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)-L-prolina

Se calentó una 2 N solución de hidróxido de litio a 70 °C. Se agregó metil 4-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-L-prolinato (**Ejemplo 52**, 0.081 g, 0.20 mM) en acetonitrilo (1.1ml) y agua (0.4ml) a la solución y se revolvió a 70 °C durante diez minutos, luego a temperatura ambiente durante veinte minutos. Se agregó 1 N cloruro de hidrógeno y se extrajo una impureza menor utilizando EtOAc. La capa acuosa se liofilizó para producir un sólido de color naranja que se purificó mediante HPLC levigando CH_3CN/H_2O (TFA al 0.1 %). Se recolectaron unas fracciones relevantes, se concentraron y se liofilizaron para producir el producto deseado como un sólido de color naranja claro (0.039 g).

MS (ESP): 389 (MH^+) para $C_{16}H_{22}Cl_2N_4O_3$

^{1}H-NMR (D_2O) δ: 1.80-2.02 (m, 2H); 2.11-2.33 (m, 6H); 2.85-3.04 (m, 1H); 3.15-3.41 (m, 2H); 3.48-3.73 (m, 3H); 3.92 (t, 1H); 4.04-4.20 (m, 2H); 4.27 (t, 1H).

Ejemplo 54: 4-Bromo-5-metil-*N*-[1-(3-nitro-2-piridinil)-4-piperidinil]-1H-pirrol-2-carboxamida

Se agregó 1-(3-nitropiridin-2-il)piperidin-4-amina sal de clorhidrato (**Intermedio 39**) (41 mg, 1.35 mmol) y TEA (37 µl, 1.35 mmol) a pentafluorofenilo 4-bromo-5-metil-1H-pirrol-2-carboxilato (**Intermedio 17**): (50 mg, 1.35 mmol) en DMA anhidro (1 ml). La mezcla se revolvió a temperatura ambiente durante la noche. La mezcla cruda se filtró y se purificó mediante HPLC de semi preparación utilizando CH_3CN/H_2O (TFA al 0.1 %) para producir el compuesto del título como un sólido amarillo (26 mg).

MS (ES) MH^+: 410 para $C_{16}H_{18}Br\,N_5O_3$

^{1}H NMR δ: 1.25 (m, 2H); 1.53 (m, 2H); 1.79 (s, 3H); 2.82 (m, 2H); 3.43 (m, 2H); 3.74 (m, 1H); 6.4 (d, 1H); 6.83 (m, 1H); 7.58(d, 1H); 7.96 (d, 1H); 8.16 (d, 1H); 11.39 (s, 1H).

Ejemplos 55-69

Los siguientes compuestos se sintetizaron mediante un método análogo al del **Ejemplo 54** comenzando a partir de pentafluorofenilo 4-bromo-5-metil-1H-pirrol-2-carboxilato (**Intermedio 17**) y los materiales de partida descritos en la siguiente tabla.

Ejemplos 55-69:

Ejemplo 55: Etil 2-(4-{[(4-bromo-5-metil-1H-pirrol-2-il)carbonil] amino}-1-piperidinil)-3-ciano-6-metilisonicotinato

Ejemplo 56: 4-Bromo-N-[1-(3-ciano-2-piridinil)-4-piperidinil]-5-metil-1H-pirrol-2-carboxamida

Ejemplo 57: 4-Bromo-5-metil-N-[1-(2-quinolinil)-4-piperidinil]-1H-pirrol-2-carboxamida

Ejemplo 58: 4-Bromo-N-[1-(6-metoxi-3-nitro-2-piridinil)-4-piperidinil]-5-metil-1H-pirrol-2-carboxamida

Ejemplo 59: 4-Bromo-N-[1-(6-cloro-4-ciano-2-piridinil)-4-piperidinil]-5-metil-1H-pirrol-2-carboxamida

Ejemplo 60: 4-Bromo-5-metil-N-{1-[6-(trifluorometil)-2-piridinil]-4-piperidinil}-1H-pirrol-2-carboxamida

Ejemplo 61: 2-(4-{[(4-Bromo-5-metil-1H-pirrol-2-il)carbonil] amino}-1-piperidinil)-6-(trifluorometil)nicotinamida

Ejemplo 62: 4-Bromo-N-{1-[3-ciano-6-(trifluorometil)-2-piridinil]-4-piperidinil}-5-metil-1H-pirrol-2-carboxamida

Ejemplo 63: 4-Bromo-N-[1-(3-cloro-2-piridinil)-4-piperidinil]-5-metil-1H-pirrol-2-carboxamida

Ejemplo 64: 4-Bromo-N-[1-(4-ciano-2-piridinil)-4-piperidinil]-5-metil-1H-pirrol-2- carboxamida

Ejemplo 65: 4-Bromo-5-metil-N-{1-[5-(trifluorometil)piridin-2-il]piperidin-4-il}-1H-pirrol-2-carboxamida

Ejemplo 66: 6-(4-{[(4-Bromo-5-metil-1H-pirrol-2-il)carbonil]amino}-1-piperidinil)nicotinamida

Ejemplo 67: 4-Bromo-N-[1-(6-bromopiridin-2-il)piperidin-4-il]-5-metil-1H-pirrol-2-carboxamida

Ejemplo 68: 4-Bromo-N-[1-(6-cloro-2-piridinil)-4-piperidinil]-5-metil-1H-pirrol-2-carboxamida

Ejemplo 69: 6-(4-{[(4-Bromo-5-metil-1H-pirrol-2-il)carbonil] amino}-1-piperidinil)2-ácido cloronicotínico

Ejemplo	^{1}H NMR δ	*m/z*	MP
55	1.5 (t, 3H); 1.8 (m, 2H); 2.1 (m, 2H); 2.3 (s, 3H); 2.6 (s, 3H); 3.3 (m, 2H); 4.2 (m, 1H); 4.4 (m, 2H); 4.6 (m, 2H); 7.0 (d, 1H); 7.4 (s, 1H); 11.6 (s, 1H).	474	Etil 2-(4-aminopiperidin-1-il)-3-ciano-6-metilisonicotinato sal de clorhidrato **(Intermedio 199)**
56	1.5 (m, 2H); 1.8 (m, 2H); 2.1 (s, 3H); 3.1 (m, 2H); 3.3 (m, 2H); 3.9 (m, 1H); 4.41 (m, 2H); 6.8(d, 1H); 6.9 (d, 1H); 7.8 (d, 1H); 8.0 (d, 1H); 8.4 (d, 1H); 11.6 (s, 1H).	388	2-(4-Aminopiperidin-1-il)nicotinonitrilo sal de clorhidrato **(Intermedio 200)**
57	1.4 (m, 2H); 1.8 (m, 2H); 2.0 (s, 3H); 3.1 (m, 2H); 2.9 (m, 2H); 4.0 (m, 1H); 4.4 (m, 2H); 6.6 (d, 1H); 7.3 (m, 1H); 7.8 (brm, 4H); 8.2 (m, 1H); 8.4 (d, 1H); 11.6 (s, 1H).	415	1 -Quinolin-2-ilpiperidin-4-amina sal de clorhidrato **(Intermedio 201)**
58	1.5 (m, 2H); 1.8 (m, 2H); 2.0 (s, 3H); 3.0 (m, 2H); 3.7 (m, 2H); 3.8 (s, 3H); 3.9 (m, 1H); 6.2 (d, 1H); 6.7 (s, 1H); 6.9 (d, 1H); 8.2 (d, 1H); 11.6(s, 1H).	440	1-(6-Metoxi-3-nitropiridin-2-il) piperidin-4-amina sal de clorhidrato **(Intermedio 202)**
59	1.30 (m, 2H); 1.7 (m, 2H); 1.93 (s, 3H); 2.83 (m, 2H); 3.88 (m, 1H); 4.29 (m, 2H); 6.64 (d, 1H); 6.8 (s,	420	2-(4-Aminopiperidiri-1 -il)-6-cloroisonicotinonitrilo

Ejemplo	^{1}H NMR δ	*m/z*	MP
	1H); 6.99 (s, 1H); 7.27 (s, 1H); 7.7 (d, 1H); 11.54 (s, 1H).		sal de clorhidrato **(Intermedio 203)**
60	1.29 (m, 2H); 1.70 (m, 2H); 1.97 (s, 3H); 2.86 (m, 2H); 3.89 (m, 1H); 4.13 (m, 2H); 6.92 (s, 1H); 7.09 (d, 1H); 7.61 (m, 2H); 11.58 (s, 1H).	433	1 -[6-(Trifluorometil) piridin-2-il]piperidin-4-amina sal de clorhidrato **(Intermedio 204)**
61	1.43 (m, 2H); 1.72 (m, 2H); 2.03 (s, 3H); 2.91 (m, 2H); 3.75 (m, 3H); 6.70 (s, 1H); 7.08 (s, 1H); 7.61 (d, 1H); 7.75 (d, 2H); 7.91 (m, 1H); 11.54 (s, 1H).	476	2-(4-Aminopiperidin-1 -il)-6-(trifluorometil) nicotinamida sal de clorhidrato **(Intermedio 205)**
62	1.43 (m, 2H); 1.78 (m, 2H); 1.99 (s, 3H); 2.96 (m, 2H); 3.91 (m, 1H); 4.22 (m, 1H); 6.63 (s, 1H); 7.16 (d, 1H); 7.66 (d, 1H); 8.24 (d, 1H); 11.50 (s, 1H).	458	2-(4-Aminopiperidin-1 -il)-6-(trifluorometil) nicotinonitrilo sal de clorhidrato **(Intermedio 206)**
63	1.58 (m, 2H); 1.76 (m, 2H); 2.00 (s, 3H); 2.2.71 (m, 2H); 3.61 (d, 2H); 3.84 (m, 1H); 6.75 (s, 1H); 6.91 (s, 1H); 7.66 (m, 1H); 8.03 (m, 1H); 11.55 (s, 1H).	399	1-(3-Cloropiridin-2-il) piperidin-4-amina sal de clorhidrato **(Intermedio 207)**
64	1.17 (m, 2H); 1.62 (m, 2H); 1.97 (s, 3H); 2.95 (m, 2H); 3.84 (m, 1H); 4.19 (d, 2H); 6.64 (d, 1H); 7.09 (d, 1H); 7.4 (s, 1H); 7.8 (d, 1H); 8.34 (d, 1H); 11.68 (s, 1H).	389	2-(4-Aminopiperidin-1-il) isonicotinonitrilo sal de clorhidrato **(Intermedio 208)**
65	1.45 (m, 2H); 1.85 (m, 2H); 2.10 (s, 3H); 2.35 (s, 3H); 2.97 (m, 2H); 3.82 (s, 3H); 4.10 (m, 1H); 4.7 (d, 2H); 6.85 (s, 1H); 7.56 (s, 1H);		1-[5-(Trifluorometil) piridin-2-il]piperidin-4-amina sal de clorhidrato **(Intermedio 209)**

Ejemplo	^{1}H NMR δ	*m/z*	MP
	7.85 (d, 1H); 11.68 (s, 1H).		
66	1.35 (m, 2H); 1.77 (m, 2H); 2.10 (s, 3H); 3.10 (m, 2H); 4.12 (m, 1H); 4.45 (d, 2H); 6.82 (brs, 1H); 7.18 (d, 1H); 7.71 (s, 1H); 7.92 (s, 1H); 7.99 (dd 1H); 8.58 (d, 1H); 11.69(s, 1H).	406	6-(4-Aminopiperidin-1 -il)nicotinamida sal de clorhidrato **(Intermedio 210)**
67	1.13 (m, 2H); 1.53 (m, 2H); 1.87 (s, 3H); 2.67 (m, 2H); 3.70 (m, 1H); 3.92 (d, 2H); 6.50 (d, 1H); 6.60 (d, 1H); 6.67 (d, 1H); 7.17 (dd, 1H); 7.49 (d, 1H); 11.40 (s, 1H).	443	1-(6-Bromopiridin-2-il) piperidin-4-amina sal de clorhidrato **(Intermedio 211)**
68	1.28 (m, 2H); 1.68 (m, 2H); 2.02 (s, 3H); 2.83 (m, 2H); 3.87 (m, 1H); 4.09 (d, 2H); 6.52 (d, 1H); 6.70 (m, 2H); 7.41 (m, 1H); 7.63 (d, 1H); 11.52 (s, 1H)	399	[1-(6-Cloropiridin-2-il) piperidin-4-il]amina sal de clorhidrato **(Intermedio 212)**
69	1.27 (m, 2H); 1.72 (m, 2H); 2.01 (s, 3H); 2.94 (m, 2H); 3.90 (m, 1H); 4.18 (d, 2H); 6.69 (s, 1H); 6.76 (d, 1H); 7.65 (d, 1H); 7.88 (d, 1H); 11.55 (s, 1H); 12.53 (s, 1H).	443	6-(4-Aminopiperidin-1-il)-2-ácido cloronicotínico sal de clorhidrato **(Intermedio 213)**

Ejemplos 70-73

Los siguientes compuestos se sintetizaron mediante un método análogo al del **Ejemplo 54** utilizando pentafluorofenilo 4-bromo-5-metil-1H-pirrol-2-

carboxilato (**Intermedio 17**) y los materiales de partida descritos en la siguiente tabla.

Ejemplo 70: 4-Bromo-5-metil-N-[1-(2-pirimidinil)-4-piperidinil]-1H-pirrol-2-carboxamida

Ejemplo 71: Metil 2-(4-{[(4-bromo-5-metil-1H-pirrol-2-il) carbonil]amino}-1-piperidinil)-6-metil-4-pirimidinacarboxilato

Ejemplo 72: 4-Bromo-5-metil-N-[1-(7H-purin-6-il)piperidin-4-il]-1H-pirrol-2-carboxamida

Ejemplo 73: Metil 6-(4-{[(4-bromo-5-metil-1H-pirrol-2-il) carbonil]amino}-1-piperidinil)-2-cloro-4-pirimidinacarboxilato

Ejemplo	^{1}H NMR δ	*m/z*	MP
70	1.17 (m, 2H); 1.62 (m, 2H); 1.97 (s, 3H); 2.95 (m, 2H); 3.84 (m, 1H); 4.19 (d, 2H); 6.64 (d, 1H); 7.09 (d, 1H); 7.4(s, 1H); 7.8 (d, 1H); 8.34 (d, 1H); 11.68(s, 1H).	365	1-Pirimidin-2-ilpiperidin-4-amina sal de clorhidrato **(Intermedio 214)**
71	1.45 (m, 2H); 1.85 (m, 2H); 2.10 (s, 3H); 2.35 (s, 3H); 2.97 (m, 2H); 3.82 (s, 3H); 4.10 (m, 1H); 4.7 (d, 2H); 6.85 (s, 1H); 7.56 (s, 1H); 7.85 (d, 1H); 11.68 (s, 1H).	438	Metil 2-(4-aminopiperidin-1-il)-6-metilpirimidina-4-carboxilato sal de clorhidrato **(Intermedio 215)**
72	1.29 (m, 2H); 1.77 (m, 2H); 2.05 (s, 3H); 3.99 (m, 1H); 4.96 (m, 2H); 6.60 (d, 1H); 7.55 (s, 1H); 7.96 (d, 1H); 8.13 (d, 1H); 8.86 (brs, 2H); 11.46 (s, 1H); 12.76 (brs, 1H)	406	1-(7*H*-Purin-6-il) piperidin-4-amina sal de clorhidrato **(Intermedio 216)**

Ejemplo	^{1}H NMR δ	*m/z*	MP
73	1.21 (m, 2H); 1.71 (m, 2H); 1.91 (s, 3H); 2.97 (m, 2H); 3.30 (m, 2H); 3.67 (s, 3H); 3.92 (m, 1H); 6.49 (s, 1H); 7.16 (s, 1H); 7.53 (d, 1H); 11.46 (s, 1H)	458	Metil 6-(4-aminopiperidin-1-il)-2-cloropirimidina-4-carboxilato sal de clorhidrato (**Intermedio 217**)

Ejemplos 74-85

Los siguientes compuestos se sintetizaron mediante un método análogo al del **Ejemplo 45**, comenzando a partir de 2-(4-{[(4-bromo-5-metil-1H-pirrol-2-il) carbonil]amino}piperidin-1-il)-6-ácido cloroisonicotínico (**Ejemplo 44**) y las aminas disponibles en el comercio descritos en la siguiente tabla.

Ejemplo 74: 2-(4-{[(4-Bromo-5-metil-1H-pirrol-2-il)carbonil] amino}-1-piperidinil)-6-cloro-N-ciclopropilisonicotinamida

Ejemplo 75: 2-(4-{[(4-Bromo-5-metil-1H-pirrol-2-il)carbonil] amino}-1-piperidinil)-6-cloro-N-metilisonicotinamida

Ejemplo 76: Metil 2-{[2-(4-{[(4-bromo-5-metil-1H-pirrol-2-il)carbonil] amino}-1-piperidinil)-6-cloroisonicotinoil]amino}acetato

Ejemplo 77: 2-(4-{[(4-Bromo-5-metil-1H-pirrol-2-il)carbonil] amino}-1-piperidinil)-6-cloro-N-hidroxiisonicotinamida

Ejemplo 78: 4-Bromo-N-{1-[6-cloro-4-(hidrazinacarbonil)-2-piridinil]-4-piperidinil}-5-metil-1H-pirrol-2-carboxamida

Ejemplo 79: 4-Bromo-N-(1-{6-cloro-4-[(4-metil-1-piperazinilo) carbonil]-2-piridinil}-4-piperidinil)-5-metil-1H-pirrol-2-carboxamida

Ejemplo 80: 4-Bromo-N-(1-{6-cloro-4-[(2,2-dimetilhidrazina) carbonil]-2-piridinil}-4-piperidinil)-5-metil-1H-pirrol-2-carboxamida

Ejemplo 81: 4-Bromo-N-{1-[6-cloro-4-(4-morfolinilcarbonil)-2-piridinil]-4-piperidinil}-5-metil-1H-pirrol-2-carboxamida

Ejemplo 82: 2-(4-{[(4-Bromo-5-metil-1H-pirrol-2-il)carbonil] amino}-1-piperidinil)-6-cloro-N,N-dimetilisonicotinamida

Ejemplo 83: 2-(4-{[(4-Bromo-5-metil-1H-pirrol-2-il)carbonil] amino}-1-piperidinil)-6-cloro-N-metoxi-N-metilisonicotinamida

Ejemplo 84: 2-(4-{[(4-Bromo-5-metil-1H-pirrol-2-il)carbonil] amino}-1-piperidinil)-6-cloro-N-[3-(4-morfolinil)propil]isonicotinamida

Ejemplo 85: 2-(4-{[(4-Bromo-5-metil-1H-pirrol-2-il)carbonil]amino}-1-piperidinil)-6-cloro-N-[2-(4-morfolinil)etil]isonicotinamida

Ejemplo	Amina	^{1}H NMR δ	m/z
74	Ciclopropilamina	0.28 (m, 2H); 0.40 (m, 2H); 0.97 (m, 2H); 1.6 (m, 2H); 1.87 (s, 3H); 2.51 (m, 1H); 2.69 (m, 2H); 3.60 (m, 1H); 4.18 (d, 2H); 3.69 (s, 1H); 3.91 (d, 2H); 6.43 (s, 1H); 6.58 (s, 1H); 6.78 (s, 1H); 7.36 (d, 1H); 8.21 (d, 1H); 11.26 (s, 1H)	482
75	Metilamina	1.59 (m, 2H); 2.01 (m, 2H); 2.32 (s, 3H); 2.96 (m, 1H); 3.27 (m, 2H); 4.18 (m, 1H); 4.41 (d, 2H); 6.99 (d, 1H); 7.12 (s, 2H); 7.33 (s, 1H); 7.92 (d, 1H); 8.79 (d, 1H); 11.81 (s, 1H)	456
76	Amino-ácido acético metil éster. HCl	1.56 (m, 2H); 1.91 (m, 2H); 2.15 (s, 3H); 3.14 (m, 2H); 3.41 (s, 3H); 3.69 (m, 1H); 4.08 (m, 2H); 4.4 (m, 2H); 6.85 (m, 1H); 7.07 (s, 1H); 7.94 (d, 1H); 11.81 (s, 1H)	512
77	Hidroxilamina. HCl	1.27 (m, 2H); 1.7 (m, 2H); 2.03 (s, 3H); 2.84 (m, 2H); 3.88 (m, 1H); 4.07 (d, 2H); 6.68 (d, 1H); 6.76 (s, 1H); 6.93 (s, 1H); 7.60 (d, 1H); 9.12 (d, 1H); 11.27 (s, 1H); 11.47 (s, 1H).	457

Ejemplo	Amina	^{1}H NMR δ	m/z
78	Hidrazina	1.29 (m, 2H); 1.71 (m, 2H); 2.03 (s, 3H); 2.89 (m, 2H); 2.69 (m, 2H); 3.87 (m, 1H); 4.13 (d, 2H); 5.48 (brm, 2H); 6.69 (d, 1H); 6.84 (s, 1H); 7.05 (s, 1H); 7.64 (d, 1H); 9.95 (d, 1H); 11.55 (s, 1H)	456
79	1-metil-piperazina	1.35 (m, 2H); 1.78 (m, 2H); 2.09 (s, 3H); 2.75 (s, 3H); 2.96 (m, 4H); 3.95 (m, 1H); 4.17 (d, 2H); 4.41 (m, 1H); 6.61 (d, 1H); 6.76 (m, 2H); 7.72 (d, 1H); 11.60 (s, 1H)	525
80	N,N-dimetil hidrazina	1.36 (m, 2H); 1.78 (m, 2H); 2.09 (s, 3H); 2.54 (s, 6H); 2.94 (m, 2H); 3.31 (m, 2H); 4.10 (m, 1H); 4.33 (d, 2H); 6.76 (d, 1H); 6.85 (s, 1H); 7.03 (s, 1H); 7.71 (d, 1H); 9.55, (s, 1H); 11.62 (s, 1H)	485
81	morfolino	1.32 (m, 2H); 1.75 (m, 2H); 2.07 (s, 3H); 2.92 (m, 2H); 3.12 (m, 2H); 3.22 (m, 2H); 3.30 (m, 2H); 3.47 (m, 4H); 3.94 (m, 1H); 4.05 (m, 1H); 4.16 (m, 2H); 6.57 (s, 1H); 6.74 (m, 2H); 7.67 (d, 1H); 11.60 (s, 1H)	512
82	dimetilamina	1.51 (m, 2H); 192 (m, 2H); 2.26 (s, 3H); 3.01 (s, 3H); 3.09 (s, 3H); (m, 2H); 3.15 (m, 21H); 3.44 (d, 4H); 4.10 (m, 1H); 4.36 (d, 2H); 6.73 (s, 1H); 6.93 (d, 2H); 7.87 (d, 1H); 11.78 (s, 1H)	468
83	O, N-Dimetil-hidroxilamina	1.35 (m, 2H); 1.76 (m, 2H); 2.11 (s, 3H); 2.95 (m, 2H); 3.20 (s, 3H); 3.56 (s, 3H); 3.95 (m, 1H); 4.19 (d, 2H); 6.67 (s, 1H); 6.77 (s, 1H); 6.88 (s, 1H); 7.71 (d, 1H); 11.64 (s, 1H)	486

Ejemplo	Amina	^{1}H NMR δ	m/z
84	3-Morfolin-4-il-propilamina	1.33 (m, 2H); 1.70 (m, 4H); 2.08 (s, 3H); 2.94 (m, 4H); 3.24 (m, 2H); 3.38 (m, 2H); 3.51 (m, 6H); 3.87 (m, 2H); 4.12 (m, 1H); 6.74 (s, 1H); 6.91 (s, 1H); 7.04 (s, 1H); 7.61 (s, 1H); 8.66 (d, 1H); 11.51 (s, 1H).	569
85	2-Morfolin-4-il-etilamina	1.24 (m, 2H); 1.66 (m, 2H); 2.05 (s, 3H); 2.93 (m, 4H); 3.24 (m, 2H); 3.4 (m, 8H); 3.79 (m, 2H); 4.13 (m, 1H); 6.71 (s, 1H); 6.88 (s, 1H); 7.04 (s IH); 7.66 (d, 1H); 8.78 (m, 1H); 11.58 (s, 1H).	555

Ejemplos 86-88

Los siguientes ejemplos se sintetizaron mediante un método análogo al del **Ejemplo** 48 a partir de los materiales de partida descritos en la siguiente tabla.

Ejemplo 86: 4-Bromo-5-metil-N-{1-[4-(1H-1,2,3,4-tetrazol-5-il)-2-piridinil]-4-piperidinil}-1H-pirrol-2-carboxamida

Ejemplo 87: 4-Bromo-N-{1-[6-cloro-4-(1H-1,2,3,4-tetrazol-5-il)-2-piridinil]-4-piperidinil}-5-metil-1H-pirrol-2-carboxamida

Ejemplo 88: 3,4-Dicloro-N-{1-[6-cloro-4-(1H-1,2,3,4-tetrazol-5-il)-2-piridinil]-4-piperidinil}-5-metil-1H-pirrol-2-carboxamida

Ejemplo	^{1}H NMR δ	m/z	MP
86	1.30 (m, 2H); 1.7 (m, 2H); 1.93 (s, 3H); 2.83 (m, 2H); 3.88 (m, 1H); 4.29 (m, 2H); 6.64 (d, 1H); 6.8 (s, 1H); 6.99 (s, 1H); 7.27 (s, 1H); 7.7 (d, 1H); 11.54 (s, 1H).	433	4-Bromo-N-[1-(4-ciano-2-piridinil)-4-piperidinil]-5-metil-1H-pirrol-2-carboxamida (**Ejemplo 64**)

87	1.24 (m, 2H); 1.66 (m, 2H); 1.99 (s, 3H); 2.88 (m, 2H); 3.84 (m, 1H); 4.08 (d, 1H); 6.55 (s, 1H); 6.96 (s, 1H); 7.16 (s, 1H); 7.53 (d, 1H); 11.28 (s, 1H).	467	4-Bromo-N-[1-(6-cloro-4-ciano-2-piridinil)-4-piperidinil]-5-metil-1H-pirrol-2-carboxamida (**Ejemplo 59**)
88	1.32 (m, 2H); 1.71 (m, 2H); 2.04 (s, 3H); 2.97 (m, 2H); 3.88 (m, 1H); 4.13 (d, 2H); 6.97 (s, 1H); 7.15 (d, 1H); 7.29 (s, 1H); 11.58 (s, 1H).	457	3,4-Dicloro-*N*-[1-(6-cloro-4-cianopiridin-2-il) piperidin-4-il]-5-metil-1*H*-pirrol-2-carboxamida (**Ejemplo 95**)

Ejemplos 89-95

Los siguientes compuestos se prepararon de acuerdo con el método del **Ejemplo 18**, mediante el acoplamiento del derivado de la amina de tert-butilo 1-[4-(aminocarbonil)-6-cloropiridin-2-il]piperidin-4-ilcarbamato (**Intermedio 16**) con el respectivo ácido carboxílico descrito en la siguiente tabla.

Ejemplo 89: 2-(4-{[(4-Acetil-3-ciano-5-metil-1H-pirrol-2-il)carbonil] amino}-1-piperidinil)-6-cloroisonicotinamida

Ejemplo 90: 2-Cloro-6-(4-{[(3-ciano-5-etil-1H-pirrol-2-il)carbonil] amino}-1-piperidinil)isonicotinamida

Ejemplo 91: 2-(4-{[(4-Bromo-3-ciano-5-etil-1H-pirrol-2-il)carbonil] amino}-1-piperidinil)-6-cloroisonicotinamida

Ejemplo 92: 2-(4-{[(4-Bromo-3-ciano-5-metil-1H-pirrol-2-il)carbonil]amino}-1-piperidinil)-6-cloroisonicotinamida

Ejemplo 93: 2-Cloro-6-(4-{[(3-ciano-5-metil-1H-pirrol-2-il) carbonil] amino}-1-piperidinil)isonicotinamida

Ejemplo 94: 2-Cloro-6-(4-{[(5-metil-1H-pirrol-2-il)carbonil] amino}-1-piperidinil) isonicotinamida

Ejemplo	Ácido	^{1}H NMR δ	m/z

Ejemplo	Ácido	^{1}H NMR δ	m/z
89	4-Acetil-3-ciano-5-metil-1H-pirrol-2-ácido carboxílico (disponible en el comercio)	1.36 (m, 2H); 1.79 (m, 2H); 2.32 (s, 6H); 2.89 (m, 2H); 3.88 (m, 1H); 4.12 (m, 2H); 6.86 (s, 1H); 7.07 (s, 1H); 7.47 (s, 1H); 7.92 (m, 2H); 12.36 (s, 1H)	429
90	3-Ciano-5-etil-1H-pirrol-2-ácido carboxílico **(Intermedio 31)**	0.96 (t, 3H); 1.29 (m, 2H); 1.70 (m, 2H); 2.90 (m, 2H); 3.14 (m, 2H); 3.81 (m, 1H); 4.02 (d, 2H); 6.14 (s, 1H); 6.77 (s, 1H); 6.96 (s, 1H); 7.50 (s, 1H); 7.65 (m, 1H); 11.70 (s, 1H).	401
91	4-Bromo-3-ciano-5-etil-1H-pirrol-2-ácido carboxílico **(Intermedio 33)**	1.14 (t, 3H); 1.51 (m, 2H); 1.89 (m, 2H); 2.61 (m, 2H); 3.12 (m, 2H); 4.22 (m, 3H); 6.93 (s, 1H); 7.17 (s, 1H); 7.69 (s, 1H); 8.05 (s, 1H); 8.17 (m, 1H); 12.39 (s, 1H).	481
92	4-Bromo-3-ciano-5-metil-1H-pirrol-2-ácido carboxílico **(Intermedio 34)**	1.15 (m, 2H); 1.60 (m, 2H); 1.88 (m, 3H); 2.72 (m, 2H); 3.70 (m, 1H); 3.91 (m, 2H); 6.59 (s, 1H); 6.89 (s, 1H); 7.33 (s, 1H); 7.65 (d, 1H); 7.85 (m, 1H); 12.06 (s, 1H).	467
93	3-Ciano-5-metil-H-pirrol-2-ácido carboxílico **(Intermedio 32)**	1.31 (m, 2H); 1.74 (m, 2H); 2.07 (s, 3H); 2.96 (m, 2H); 3.89 (m, 1H); 4.07 (d, 2H); 6.09 (s, 1H); 6.78 (d, 1H); 7.00 (s, 1H); 7.58 (s, 1H); 7.71 (s, 1H); 7.99 (s, 1H); 11.88 (s, 1H).	389
94	5-Metil-1H-pirrol-2-ácido carboxílico **(Intermedio 29)**	1.33 (m, 2H); 1.70 (m, 2H); 2.09 (s, 3H); 2.88 (m, 2H); 3.95 (m, 1H); 4.18 (m, 2H); 5.70 (s, 1H); 6.49 (d, 1H); 6.88 (s, 1H); 7.14 (s, 1H); 7.49 (m, 2H); 8.05 (s, 1H); 11.03 (s, 1H).	362

Ejemplo 95: 3,4-Dicloro-*N*-[1-(6-cloro-4-cianopiridin-2-il) piperidin-4-il]-5-metil-1*H*-pirrol-2-carboxamida

El compuesto del título se preparó a partir de 3,4-dicloro-5-metil-1*H*-pirrol-2-ácido carboxílico (**Intermedio 3**) y 2-(4-aminopiperidin-1-il)-6-cloroisonicotinonitrilo sal de clorhidrato (**Intermedio 203**) en una forma análoga a la del **Ejemplo 18.**

MS (ES, M+H): 411, 413 para $C_{17}H_{16}Cl_3N_5O$

Ejemplos 96 y 97

Los siguientes compuestos se prepararon mediante un método análogo al del **Ejemplo 18** utilizando 1-(3-nitropiridin-2-il)piperidin-4-amina sal de clorhidrato (**Intermedio 39**) como un material de partida.

Ejemplo 96: 4,5-Dicloro-N-[1-(3-nitro-2-piridinil)-4-piperidinil]-1H-pirrol-2-carboxamida

Ejemplo 97: 4-Bromo-5-isopropil-N-[1-(3-nitro-2-piridinil)-4-piperidinil]-1H-pirrol-2-carboxamida

Ejemplo	Ácido	^{1}H NMR δ	m/z
96	4,5, Dicloro-1H-pirrol-2-ácido carboxílico (**Intermedio 61**)	1.55 (m, 2H); 1.92 (m, 2H); 3.2 (m, 2H); 3.82 (m, 2H); 4.1 (m, 1H); 6.8 (d, 1H); 6.95 (m, 1H); 8.1 (d, 1H); 8.3 (d, 1H); 8.5 (d, 1H); 11.39 (s, 1H).	386
97	4-Bromo-5-isopropil-1H-pirrol-2-ácido carboxílico (**Intermedio 37**)	1.33 (m, 6H); 1.71 (m, 2H); 2.03 (m, 2H); 3.26 (m, 3H); 3.89 (m, 2H); 4.18 (m, 1H); 6.9 (d, 1H); 7.01 (q, 1H); 8.09 (d, 1H); 8.40 (dd, 1H); 8.63 (dd, 1H); 11.77 (s, 1H)	435

Ejemplo 98: 3,4-Dicloro-N-[1-(6-cloro-2-piridinil)-4-piperidinil]-5-metil-1H-pirrol-2-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 42** comenzando a partir de [1-(6-cloropiridin-2-il)piperidin-4-il]amina sal de clorhidrato (**Intermedio 212**; 1 mmol) y 3,4-dicloro-5-metil-1H-pirrol-2-ácido carboxílico (**Intermedio 3**, 1 mmol).

MS (ES): 410 (MH^+) para $C_{16}H_{17}Cl_3N_4O$

^{1}H NMR δ: 1.38 (m, 2H); 1.76 (m, 2H); 2.10 (s, 3H); 2.94 (m, 2H); 3.92 (m, 1H); 4.10 (m, 2H); 6.57 (d, 1H); 6.71 (d, 1H); 7.08 (d, 1H); 7.42 (m, 1H); 11.71 (s, 1H).

Ejemplo 99: 2-Cloro-6-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino}-1-piperidinil)-N-[2-(4-morfolinil)etil] isonicotinamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 18** a partir de 2-(4-aminopiperidin-1-il)-6-cloro-*N*-(2-morfolin-4-iletil) isonicotinamida sal de clorhidrato (**Intermedio 218**) y 3,4-dicloro-5-metil-1H-pirrol-2-ácido carboxílico (**Intermedio 3**).

MS (ES): 543 (MH^+) para $C_{23}H_{29}Cl_3N_6O_3$

^{1}H NMR δ: 1.42 (m, 2H); 1.86 (m, 2H); 2.13 (s, 3H); 3.04 (m, 4H); 3.22 (m, 2H); 3.40 (m, 8H); 3.93 (m, 3H); 4.13 (m, 2H); 3.96 (m, 2H); 6.89 (s, 1H); 7.09 (s, 1H); 7.21 (d, 1H); 8.76 (d, 1H); 11.84 (s, 1H).

Ejemplo 100: 2-Cloro-6-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino}-1-piperidinil)-N-[3-(4-morfolinil)propil] isonicotinamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 99** comenzando a partir de 2-(4-aminopiperidin-1-il)-6-cloro-*N*-(3-morfolin-4-ilpropil)isonicotinamida sal de clorhidrato (**Intermedio 219**) y 3,4-dicloro-5-metil-1H-pirrol-2-ácido carboxílico (**Intermedio 3**).

MS (ES): 559 (MH^+) para $C_{24}H_{31}Cl_3N_6O_3$

^{1}H NMR δ: 1.28 (m, 2H); 1.69 (m, 4H); 1.92 (s, 3H); 2.76 (m, 6H); 3.05 (m, 2H); 3.21 (m, 2H); 3.37 (d, 2H); 3.72 (m, 3H); 3.96 (m, 2H); 6.61 (s, 1H); 6.87 (s, 1H); 7.00 (s, 1H); 8.49 (d, 1H); 11.63 (s, 1H).

Ejemplo 101: 3,4-Dicloro-*N*-[1-(6-cloro-4-{[2-(metilamino)-2-oxoetil]sulfanil}-2-piridinil)-4-piperidinil]-5-metil-1*H*-pirrol-2-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 18** comenzando a partir de 2-{[2-(4-aminopiperidin-1-il)-6-cloropiridin-4-il]tio}-*N*-metilacetamida sal de clorhidrato (**Intermedio 220**) y 3,4-dicloro-5-metil-1H-pirrol-2-ácido carboxílico (**Intermedio 3**).

MS (ES): 492 (MH^+) para $C_{19}H_{22}Cl_3N_5O_2S$

^{1}H NMR δ: 1.41 (m, 2H); 1.79 (m, 2H); 2.11 (s, 3H); 2.54 (s, 3H); 2.92 (m, 2H); 3.64 (s, 2H); 3.89 (m, 2H); 4.12 (m, 1H); 6.51 (s, 1H); 6.59 (s, 1H); 7.11 (s, 1H); 8.08 (m, 1H); 11.90 (s, 1H).

Ejemplo 102: 4-Bromo-N-[1-(6-cloro-4-{[2-(metilamino)-2-oxoetil]sulfanil}-2-piridinil)-4-piperidinil]-5-metil-1H-pirrol-2-carboxamida

El compuesto del título se preparó mediante un método análogo al del **Ejemplo 18** comenzando a partir de 2-{[2-(4-aminopiperidin-1-il)-6-cloropiridin-4-il]tio}-*N*-metilacetamida sal de clorhidrato (**Intermedio 220**) y 4-bromo-5-metil-1H-pirrol-2-ácido carboxílico (**Intermedio 18**).

MS (ES): 502 (MH^+) para $C_{19}H_{23}BrClN_5O_2S$

^{1}H NMR δ: 1.33 (m, 2H); 1.70 (m, 2H); 2.07 (s, 3H); 2.41 (s, 3H); 2.58 (m, 2H); 3.64 (s, 2H); 3.89 (m, 2H); 4.17 (m, 1H); 6.42 (s, 1H); 6.62 (s, 1H); 6.71 (s, 1H); 7.67 (s 1H); 7.97 (m, 1H); 11.51 (s, 1H).

Ejemplo 103: 2-Ciano-6-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino}-1-piperidinil)isonicotinamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 18** comenzando a partir de 2-(4-aminopiperidin-1-il)-6-cianoisonicotinamida sal de clorhidrato (**Intermedio 198**) y 3,4-dicloro-5-metil-1*H*-pirrol-2-ácido carboxílico (**Intermedio 3**).

MS (ES): 423 (MH^+) para $C_{18}H_{18}Cl_2N_5O_2$

^{1}H NMR δ: 1.36 (m, 2H); 1.64 (m, 2H); 2.01 (s, 3H); 2.17 (m, 2H); 2.90 (m, 2H); 4.08 (m, 2H); 4.32 (m, 3H); 7.05 (d, 1H); 7.67(s, 1H); 8.06 (s, 1H); 11.73 (s, 1H).

Ejemplo 104: 2-(4-{[(4-Bromo-5-metil-1*H*-pirrol-2-il)carbonil] amino}-1-piperidinil)-3-hidroxi-1-piridiniumolato

Se agregó TEA anhidro (0.23ml, 1.65 mmol) a piperidin-4-il-ácido carbámico tert-butilo éster (300 mg, 1.65 mmol) y tiofeno-2-ácido carboxílico-2-cloro-piridinil-3-ilo éster (**Intermedio 43**, 119 mg, 0.5 mmol) en NMP anhidro (2 ml). La mezcla se calentó en una botella de presión a 165°C durante 18 h. La solución marrón se distribuyó entre EtOAc y agua y la fase orgánica se lavó varias veces con agua, se lavó sobre sulfato de sodio y se concentró al vacío para producir 2-{4-[(*tert*-butoxicarbonil)amino]piperidin-1-il}piridin-3-ilo tiofeno-2-carboxilato (170 mg, LCMS:420). Este compuesto se trató con 4 N ácido clorhídrico en dioxano durante 45 minutos, el solvente se extrajo al vacío y se secó para producir 2-(4-amino]piperidin-1-il)piridin-3-iltiofeno-2-carboxilato como un sólido blanco. El sólido blanco (0.421 mmol) se disolvió en NMP anhidro (3 ml) y se agregó pentafluorofenilo 4-bromo-5-metil-1H-pirrol-2-carboxilato (**Intermedio 17**) (75 mg, 0.21 mmol) seguido por TEA (64 µl, 0.46mmol). La mezcla se revolvió a temperatura ambiente durante 18 h y la mezcla cruda se filtró y se purificó mediante HPLC de semi preparación levigado con CH_3CN/H_2O (TFA al 0.1 %) para producir el compuesto del título (30 mg) (oxidación e hidrólisis espontáneas para que se produjera el compuesto del título).

MS (ES): 398 (MH^+) para $C_{16}H_{19}BrN_4O3$

^{1}H NMR δ: 1.29 (m, 2H); 1.47 (m, 2H); 1.82 (s, 3H); 3.72 (m, 1H); 3.90 (m, 2H); 6.47 (d, 1H); 6.78 (m, 1H); 7.07 (m, 1H); 7.42 (d, 1H); 7.57 (d, 1H); 9.16 (m, 3H); 11.32 (s, 1H).

Ejemplo 105: 4-Bromo-N-[1-(6-metoxi-2-piridinil)-4-Piperidinil]-5-metil-1H-pirrol-2-carboxamida

Se disolvió tert-butil [1-(6-cloropiridin-2-il)piperidin-4-il]carbamato (**Intermedio 66**) (300 mg, 0.99 mmol) en 0.5 M solución de metóxido sódico en MeOH (9 ml, 4.45 mmol) a temperatura ambiente y la mezcla se llevó a reflujo durante 72 h. El solvente se extrajo al vacío, se extrajo con EtOAc luego se lavó con agua. La fase orgánica se concentró al vacío y se trató con 4 N ácido clorhídrico en dioxano (10ml) durante 2 h. El solvente se extrajo al vacío y se secó para extraer el excedente de ácido clorhídrico. El sólido se disolvió en NMP (3ml) y se agregó pentafluorofenilo 4-bromo-5-metil-1H-pirrol-2-carboxilato (**Intermedio 17**) (80 mg, 0.216 mmol) y TEA (137µl, 0.9 mmol). La mezcla se revolvió a temperatura ambiente durante 2 h y la mezcla se purificó mediante HPLC de semi preparación empleando un gradiente de 15-95% CH_3CN/H_2O (TFA al 0.1 %) para producir el compuesto del título (23 mg).

MS (ES): 395 (MH^+) para $C_{17}H_{21}BrN_4O_2$

^{1}H NMR δ: 1.31 (m, 2H); 1.67 (m, 2H); 2.03 (s, 3H); 2.78 (m, 2H); 3.67 (s, 3H); 3.87 (m, 1H); 4.10 (d, 2H); 5.97 (d, 1H); 6.24 (d, 1H); 6.77 (d, 1H); 7.32 (t, 1H); 7.63 (d, 1H); 11.54 (s, 1H)

Ejemplo 106: 4-Bromo-N-{1-[6-cloro-4-(5-oxo-2,5-dihidro-1,3,4-oxadiazol-2-il)piridin-2-il]piperidin-4-il-5-metil-1H-pirrol-2-carboxamida

Se agregó TEA (0.10 ml, 0.70 mmol) y 5-[2-(4-aminopiperidin-1-il)-6-cloropiridin-4-il]-1,3,4-oxadiazol-2(5H)-ona clorhidrato (**Intermedio 51**, 0.10 g, 0.33 mmol) a una solución de pentafluorofenilo 4-bromo-5-metil-1H-pirrol-2-carboxilato (**Intermedio 17**) (0.12 g, 0.33 mmol) en DMA (2ml). La mezcla se revolvió a temperatura ambiente durante la noche y se purificó mediante HPLC de semi preparación levigado con mezclas de agua/acetonitrilo y TFA para producir el compuesto del título (18 mg).

MS (ES): 480 (MH^+) para $C_{18}H_{18}ClBrN_6O_3$

^{1}H NMR δ: 1.42 (m, 2H); 1.84 (m, 2H); 2.16 (s, 3H); 3.05 (m, 2H); 4.02(m, 1H); 4.29 (d, 2H); 6.84 (d, 1H); 6.93 (s, 1H); 7.11 (s, 1H); 7.79 (d, 1H); 11.70 (s, 1H); 12.96 (s, 1H)

Ejemplo 107: 4-Bromo-N-{1-[(4-bromo-5-metil-1H-pirrol-2-il) carbonil]-4-piperidinil-5-metil-1H-pirrol-2-carboxamida

Se obtuvo el compuesto del título como un sub-producto durante la síntesis del Ejemplo 44 (69 mg).

MS (ES): 471 (MH^+) para $C_{17}H_{20}Br_2N_4O_2$

^{1}H NMR δ: 1.34 (m, 2H); 1.74 (m, 2H); 1.93 (s, 3H); 2.02 (s, 3H); 2.84 (m, 2H); 3.93 (m, 1H); 4.26 (d, 2H); 6.40 (d, 1H); 6.78 (d, 1H); 7.73 (d, 1H); 11.48 (s, 1H)

Ejemplo 108: 3,4-Dicloro-N-{1-[6-cloro-4-(5-oxo-4,5-dihidro-1,3,4-oxadiazol-2-il)-2-piridinil]-4-piperidinil}-5-metil-1*H*-pirrol-2-carboxamida

Se agregó N, N'-carbonildimidazol (0.021 g, 0.13 mmol) a una solución agitada de 3,4-dicloro-N-{1-[6-cloro-4-(hidrazinacarbonil)piridin-2-il]piperidin-4-il}-5-metil-1H-pirrol-2-carboxamida (**Ejemplo 309**) (30 mg, 0.06 mmol) en DMF (2 ml). La mezcla se revolvió a temperatura ambiente durante 6 h. La mezcla se filtró y se purificó mediante HPLC de semi preparación levigado con mezclas de CH_3CN/H_2O (TFA al 0.1 %) para producir el compuesto del título (15 mg).

MS (ES): 471 (MH^+) para $C_{18}H_{17}Cl_3N_6O_3$

^{1}H NMR δ: 1.47 (m, 2H); 1.84 (m, 2H); 2.15 (m, 3H); 3.06 (m, 2H); 4.01 (m, 1H); 4.18 (d, 2H); 6.87 (s, 1H); 7.02 (s, 1H); 7.20 (d, 1H); 11.91 (s, 1H); 12.87 (s, 1H).

Ejemplo 109: 1-[4-(Aminocarbonil-6-cloro-2-piridinil]-4-piperidinilo 4-bromo-5-metil-1H-pirrol-2-carboxilato

Se revolvió 2-cloro-6-(4-hidroxipiperidin-1-il)isonicotinamida (**Intermedio 62**; 123 mg, 0.48 mmol), 4-bromo-5-metil-1H-pirrol-2-ácido carboxílico (**Intermedio 18**) (98 mg, 0.48 mmol) y trifenilfosfina (138 mg, 0.53 mmol) en THF anhidro y se enfrió a 0 °C. Se agregó DEAD (83 µl, 0.53 mmol) y la mezcla se revolvió a temperatura ambiente durante 18 h. La mezcla se

filtró, se diluyó con EtOAc y se lavó con agua y se lavó sobre sulfato de sodio y se concentró al vacío. El producto crudo se purificó mediante cromatografía instantánea levigado con EtOAc/hexano (4:1) para obtener el compuesto del título (11 mg).

MS (ES): 441 (MH^+) para $C_{17}H_{18}BrClN_4O_3$

^{1}H NMR δ: 1.69 (m, 2H); 1.97 (m, 2H); 2.24 (s, 3H); 3.58 (m, 2H); 3.91 (m, 2H); 5.18 (m, 1H); 6.86 (d, 1H); 7.03 (s, 1H); 7.25 (s, 1H); 7.73 (d, 1H); 8.17 (s, 1H); 12.08 (s, 1H)

Ejemplo 110: 1-[6-Cloro-4-(1H-tetrazol-5-il)piridin-2-ilpiperidin-4-ilo 4-bromo-5-metil-1H-pirrol-2-carboxilato

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 48** comenzando a partir de 1-(6-cloro-4-cianopiridin-2-il)piperidin-4-il-4-bromo-5-metil-1H-pirrol-2-carboxilato (**Ejemplo 330**).

MS (ES): 468 (MH^+) para $C_{17}H_{17}BrClN_7O_2$

^{1}H NMR δ: 1.69 (m, 2H); 1.97 (m, 2H); 2.24 (s, 3H); 3.58 (m, 2H); 3.91 (m, 2H); 5.18 (m, 1H); 6.86 (d, 1H); 7.03 (s, 1H); 7.25 (s, 1H); 7.73 (d, 1H); 8.17 (s, 1H); 12.08 (s, 1H)

Ejemplo 111: 3,4-Dicloro-N-{1-[6-cloro-4-(1,2,4-oxadiazol-3-il)-2-piridinil}-4-piperidinil}-5-metil-1H-pirrol-2-carboxamida

Se agregó diisopropiletilamina (0.04ml, 0.46 mmol), HOAT (0.03 g, 0.23 mmol) y HATU (0.08 g, 0.23 mmol) a una solución agitada de 3,4-dicloro-5-metil-1H-pirrol-2-ácido carboxílico (**Intermedio 3**, 0.04 g, 0.23 mmol) en DMF (2ml) a temperatura ambiente. La solución resultante se revolvió durante 5 minutos y se agregó 1-[6-cloro-4-(1,2,4-oxadiazol-3-il) piridin-2-il] piperidin-4-amina clorhidrato (**Intermedio 56**) (0.074 g, 0.23 mmol). La mezcla se revolvió a temperatura ambiente durante 1 h y se filtró y se purificó mediante HPLC de semi preparación levigado con mezclas de CH_3CN/H_2O (TFA al 0.1 %) para producir el compuesto del título (100 mg).

MS (ES): 457 (MH^+) para $C_{18}H_{17}Cl_3N_6O_2$

^{1}H NMR δ: 1.50 (m, 2H); 1.84 (m, 2H); 2.13 (s, 3H); 3.09 (m, 2H); 4.04 (m, 1H); 4.20 (d, 2H); 7.08 (s, 1H); 7.20 (d, 1H); 7.28 (s, 1H); 9.80 (s, 1H); 11.91 (s, 1H)

Ejemplo 112: 1-[6-Cloro-4-(1,2,4-oxadiazol-3-il)-2-piridinil]-4-piperidinilo 3,4-dicloro-5-metil-1H-pirrol-2-carboxilato

Se agregó BF_3Et_2O (0.1 mol) a una solución de 1-{4-[amino (hidroxiimino) metil-6-cloropiridin-2-il}piperidin-4-ilo 3,4-dicloro-5-metil-1H-pirrol-2-carboxilato (**Ejemplo 114**) (0.07 g, 0.15 mmol) en 1,1,1-trietoxietano (1.0ml) a temperatura ambiente. La mezcla se revolvió a temperatura ambiente durante 1 h. La mezcla se purificó mediante HPLC de semi preparación levigado con mezclas de CH_3CN/H_2O (TFA al 0.1 %) para producir el compuesto del título (21 mg).

MS (ES): 458 (MH^+) para $C_{18}H_{16}Cl_3N_5O_3$

^{1}H NMR δ: 1.66 (m, 2H); 1.90 (m, 2H); 2.17 (s, 3H); 3.67 (m, 2H); 3.79 (m, 2H); 5.18 (m, 1H); 7.09 (s, 1H); 7.31 (s, 1H); 9.80 (s, 1H); 12.23 (s, 1H)

Ejemplo 113: 2-Cloro-6-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino}-1-piperidinil)-N-metoxiisonicotinamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 45** comenzando a partir de 2-cloro-6-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino}piperidin-1-il)ácido isonicotínico (**Ejemplo 153**) y clorhidrato de metoxilamina.

MS (ES): 462 (MH^+) para $C_{18}H_{20}Cl_3N_5O_3$

^{1}H NMR δ: 1.46 (m, 2H); 1.84 (m, 2H); 2.15 (s, 3H); 3.05 (m, 2H); 3.68 (s, 3H); 4.00 (m, 1H); 4.16 (d, 2H); 6.82 (s, 1H); 7.04 (s, 1H); 7.19 (d, 1H); 11.91 (s, 1H)

Ejemplo 114: 1-4-[Amino(hidroxiimino)metil]-6-cloro-2-piridinil}-4-piperidinilo 3,4-dicloro-5-metil-1H-pirrol-2-carboxilato

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 47** a partir de 1-(6-cloro-4-cianopiridin-2-il)piperidin-4-ilo 3,4-dicloro-5-metil-1H-pirrol-2-carboxilato (**Ejemplo 308**).

MS (ES): 446 (MH^+) para $C_{17}H_{18}Cl_3N_5O_3$

^{1}H NMR δ: 1.48 (m, 2H); 1.72 (m, 2H); 2.04 (s, 3H); 3.43 (m, 2H); 3.60 (d, 2H); 5.01 (m, 1H); 6.72 (s, 1H); 6.90 (s, 1H); 7.35 (s, 2H); 9.91 (s, 1H); 12.09 (s, 1H)

Ejemplo 115: N-[1-(4-Acetil-6-cloro-2-piridinil)-4-piperidinil]-3,4-dicloro-5-metil-1H-pirrol-2-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del Ejemplo **18** comenzando a partir de 1-[2-(4-aminopiperidin-1-il)-6-cloropiridin-4-il] etanona sal de clorhidrato (**Intermedio 197**) y 3,4-dicloro-5-metil-1H-pirrol-2-ácido carboxílico (**Intermedio 3**).

MS (ES): 431 (MH^+) para $C_{18}H_{19}Cl_3N_4O_2$

^{1}H NMR δ: 1.46 (m, 2H); 1.84 (m, 2H); 2.14 (s, 3H); 2.55 (s, 3H); 3.05 (m, 2H); 4.00 (m, 1H); 4.21 (d, 2H); 6.94 (s, 1H); 7.18 (s, 1H); 7.21 (s, 1H); 11.91 (s, 1H)

Ejemplo 116: N-[1-(4-Acetil-6-cloro-2-piridinil)-4-piperidinil]-4-bromo-5-metil-1H-pirrol-2-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 42** comenzando a partir de 1-1-[2-(4-aminopiperidin-1-il)-6-cloropiridin-4-il] etanona sal de clorhidrato (**Intermedio 197**) y 4-bromo-5-metil-1H-pirrol-2-ácido carboxílico (**Intermedio 18**).

MS (ES): 441 (MH^+) para $C_{18}H_{20}BrClN_5O_2$

^{1}H NMR δ: 1.38 (m, 2H); 1.80 (m, 2H); 2.11 (s, 3H); 2.57 (s, 3H); 2.99 (m, 2H); 3.97 (m, 1H); 4.26 (d, 2H); 6.78 (s, 1H); 6.94 (s, 1H); 7.18 (s, 1H); 7.73 (d. 1H); 11.64 (s, 1H)

Ejemplo 117: 2-Cloro-N-metoxi-6-(4-{[(5-metil-1H-pirrol-2-il)carbonil]amino}-1-piperidinil)isonicotinamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 45** comenzando a partir de 2-cloro-6-(4-{[(5-metil-1H-pirrol-2-il)carbonil] amino} piperidin-1-il)ácido isonicotínico (**Ejemplo 332**) y clorhidrato de metoxilamina.

MS (ES): 392 (MH^+) para $C_{18}H_{22}BrClN_5O_3$

^{1}H NMR δ: 1.36 (m, 2H); 1.76 (m, 2H); 2.12 (s, 3H); 2.96 (m, 2H); 3.66 (s, 3H); 3.96 (m, 1H); 4.20 (m, 2H); 5.72 (s, 3H); 6.59 (s, 1H); 6.81 (s, 1H); 7.03 (s, 1H); 7.56 (d 1H); 11.11 (s, 1H); 11.92 (s, 1H)

Ejemplo 118: N-{1-[6-Amino-2-(metilsulfanil)-4-pirimidinil]-4-piperidinil}-3,4-dicloro-5-metil-1H-pirrol-2-carboxamida

Se agregó diisopropiletilamina (0.21ml, 1.25 mmol) y HATU (0.239 g, 0.63 mmol) a una solución agitada de 3,4-dicloro-5-metil-1H-pirrol-2-ácido carboxílico (**Intermedio 3**) (0.122 g, 0.63 mmol) en DMF (2 ml). La solución resultante se revolvió durante 5 minutos, se agregó 6-(4-amino-piperidin-1-il)-2-(metiltio)pirimidin-4-amina clorhidrato (**Intermedio 46**) (0.2 g, 0.63 mmol) y la mezcla se revolvió a temperatura ambiente durante 18 h. La mezcla cruda se filtró y se purificó mediante HPLC de semi preparación levigado con CH_3CN/H_2O (TFA al 0.1 %) para producir el producto del título (42 mg).

MS (ES): 417 (MH^+) para $C_{16}H_{20}Cl_2N_6OS$

^{1}H NMR δ: 1.22 (m, 2H); 1.61 (m, 2H); 1.92 (s, 3H); 2.84 (m, 2H); 3.78 (m 4H); 5.25 (s, 1H); 5.52 (s, 1H); 6.50 (m, 2H); 11.72 (s, 1H)

Ejemplo 119: N-{1-[6-(Acetilamino)-2-(metilsulfanil)-4-pirimidinil]-4-piperidinil}-3,4-dicloro-5-metil-1H-pirrol-2-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 118** comenzando a partir de N-[6-(4-aminopiperidin-1-il)-2-(metiltio)pirimidin-4-il]acetamida clorhidrato (**Intermedio 69**) y 3,4-dicloro-5-metil-1H-pirrol-2-ácido carboxílico (**Intermedio 3**).

MS (ES): 456 (MH^+) para $C_{16}H_{20}Cl_2N_6OS$

^{1}H NMR δ: 1.39 (m, 2H); 1.78 (m, 2H); 1.99 (s, 3H); 2.10 (s, 3H); 2.36 (s, 3H); 2.99 (m, 2H); 3.95 (m, 1H); 4.23 (m, 2H); 7.09 (s, 1H); 7.15 (d, 1H); 7.50 (q, 1H); 8.46 (dd, 1H); 10.31 (s, 1H); 11.88(s, 1H)

Ejemplo 120: N-{1-[6-(Acetilamino)-2-(metilsulfinil)-4-pirimidinil]-4-piperidinil}-3,4-dicloro-5-metil-1H-pirrol-2-carboxamida

Se agregó mCPBA (0.11 g, 0.133 mmol) a una solución agitada de N-{1-[6-(acetilamino)-2-(metiltio)pirimidin-4-il]piperidin-4-il}-3,4-dicloro-5-metil-1H-pirrol-2-carboxamida (**Ejemplo 119**), 0.15 g, 0.33 mmol) en DCM (2 ml). La mezcla se revolvió a temperatura ambiente durante 3 hr y se purificó mediante HPLC de semi preparación levigado con CH_3CN/H_2O (0.1 % TEA) para obtener el compuesto del título (5 mg).

MS (ES): 473 (MH^+) para $C_{18}H_{22}Cl_2N_6O_3S$

^{1}H NMR δ: 1.42 (m, 2H); 1.86 (m, 2H); 2.06 (s, 3H); 2.13 (s, 3H); 2.76 (s, 3H); 4.02 (m, 4H); 7.21 (d, 1H); 7.42 (s, 1H); 10.81 (s, 1H); 11.94 (s, 1H)

Ejemplo 121: N-{1-[6-(Acetilamino)-2-(metilsulfonil)pirimidin-4-il] piperidin-4-il}-3,4-dicloro-5-metil-1H-pirrol-2-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 120** comenzando a partir de N-{1-[6-(acetilamino)-2-(metilsulfinil)-4-pirimidinil]-4-piperidinil}-3,4-dicloro-5-metil-1H-pirrol-2-carboxamida (**Ejemplo 120**).

MS (ES): 489 (MH^+) para $C_{18}H_{22}Cl_2N_6O_4S$

^{1}H NMR δ: 1.48 (m, 2H); 1.87 (m, 2H); 2.08 (s, 3H); 2.14 (s, 3H); 3.13-3.26 (m, 2H); 3.29 (s, 3H); 4.04 (m, 2H); 4.18 (m, 1H); 7.20 (d, 1H); 7.51 (s, 1H); 10.89 (s, 1H); 11.93 (s, 1H)

Ejemplo 122: 4-Bromo-5-metil-N-{1-[(1-metil-1*H*-imidazol-2-il) metil]piperidin-4-il}-1*H*-pirrol-2-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 1** mediante el acoplamiento de 4-bromo-5-metil-*N*-piperidin-4-il-

1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 57**) con 1-metil-1*H*-imidazol-2-carbaldehído (disponible en el comercio).

MS (ESP): 380.1 (M+H) para $C_{16}H_{22}BrN_5O$

^{1}H NMR δ: 1.45 (m, 2H); 1.72 (d, 2H); 2.04 (m, 2H); 2.12 (s, 3H); 2.75 (d, 2H); 3.50 (s, 2H); 3.65 (s, 3H); 3.72 (m, 1H); 6.74 (s, 1H); 6.81 (s, 1H); 7.00 (s, 1H); 7.69 (d, 1H); 11.62 (s, 1H).

Ejemplo 123: Etil 2-(4-{[(4-bromo-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)-1,3-tiazol-4-carboxilato

Se combinó 4-bromo-5-metil-*N*-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 57**, 0.41 g, 1.27 mmol), bicarbonato de sodio (0.42 g, 1.78 mmol) y etil 2-bromo-1,3tiazol-4-carboxilato (0.30 g, 1.27 mmol) en DMF (5ml) bajo nitrógeno y se calentó a 50 °C durante 18 h. La mezcla se enfrió a temperatura ambiente y se diluyó con EtOAc (75 ml) y agua (10 ml). La capa orgánica se separó, se lavó sobre sulfato de sodio, se filtró y se concentró al vacío. La purificación mediante cromatografía instantánea (MeOH/DCM, 10%) produjo 275 mg del compuesto del título.

MS (ESP): 439.2 (M-H) para $C_{17}H_{21}BrN_4O_3S$

^{1}H NMR δ: 1.28 (t, 3H); 1.56 (m, 2H); 1.87 (d, 2H); 2.14 (s, 3H); 3.18 (t, 2H); 3.81-4.10 (m, 3H); 4.24 (q, 2H); 6.83 (s, 1H); 7.71 (s, 1H); 7.81 (d, 1H); 11.54 (s, 1H).

Ejemplo 124: 4-Bromo-5-metil-*N*-[1-(1,3-tiazol-2-il)piperidin-4-il]-1*H*-pirrol-2-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 123** mediante el acoplamiento de 4-bromo-5-metil-*N*-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 57**) con 2-bromo-1,3-tiazol (disponible en el comercio).

MS (ESP): 369.1 (M+H) para $C_{14}H_{17}BrN_4OS$

^{1}H NMR δ: 1.57 (m, 2H); 1.86 (d, 2H); 2.14 (s, 3H); 3.16 (t, 2H); 3.87-4.10 (m, 3H); 6.82 (s, 1H); 6.86 (s, 1H); 7.19 (s, 1H); 7.81 (d, 1H); 11.68 (s, 1H).

Ejemplo 125: *N*-[1-(1,3-Benzotiazol-2-il)piperidin-4-il]-4-bromo-5-metil-1*H*-pirrol-2-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 123** mediante el acoplamiento de 4-bromo-5-metil-*N*-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 57**) con 2-bromo-1,3-benzotiazol (disponible en el comercio).

MS (ESP): 419.1 (M+H) para $C_{18}H_{19}BrN_4OS$

^{1}H NMR δ: 1.58 (q, 2H); 1.91 (d, 2H); 2.14 (s, 3H); 3.31 (t, 2H); 3.95-4.15 (m, 3H); 6.82 (s, 1H); 7.07 (t, 1H); 7.28 (t, 1H); 7.47 (d, 1H); 7.76-7. 82 (m, 2H); 11.70 (s, 1H).

Ejemplo 126: Etil 5-(4-{[(4-bromo-5-metil-1*H*-pirrol-2-il)carbonil] amino} piperidin-1-il)-1,3,4-tiadiazol-2-carboxilato

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 123** mediante el acoplamiento de 4-bromo-5-metil-*N*-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 57**) con 5-cloro-[1,3,4]tiadiazol-2-ácido carboxílico éster (Demaree, P y colaboradores *Can. J. Chem* **1977**, 55(2) 243-50).

MS (ESP): 442.0 (M+H) para $C_{16}H_{20}BrN_5O_3S$

^{1}H NMR δ: 1.32 (t, 3H); 1.58 (m, 2H); 1.92 (d, 2H); 2.14 (s, 3H); 3.41 (t, 2H); 3.85-4.10 (m, 3H); 4.36 (q, 2H); 6.82 (s, 1H); 7.82 (d, 1H); 11.70 (s, 1H).

Ejemplo 127: 2-(4-{[(4-Bromo-5-metil-1*H*-pirrol-2-il) carbonil]amino} piperidin-1-il)-1,3-tiazol-5-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 123** mediante el acoplamiento de 4-bromo-5-metil-*N*-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 57**) con 2-bromo-1,3-tiazol-5-carboxamida (*J. Am. Chem. Soc.* **1952**, 74, 5799).

MS (ESP): 412.0 (M+H) para $C_{15}H_{18}BrN_5O_2S$

^{1}H NMR δ: 1.54 (m, 2H); 1.86 (d, 2H); 2.14 (s, 3H); 3.21 (t, 2H); 3.87-4.10 (m, 3H); 6.82 (s, 1H); 7.16 (s, 1H); 7.64 (s, 1H); 7.79 (s, 1H); 7.81 (d, 1H); 11.69 (s, 1H).

Ejemplo 128: 5-(4-{[(4-Bromo-5-metil-1*H*-pirrol-2-il) carbonil]amino} piperidin-1-il)-1,3,4-tiadiazol-2-ácido carboxílico

El compuesto del título se sintetizó a partir de etil 5-(4-{[(4-bromo-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-1,3,4-tiadiazol-2-carboxilato (**Ejemplo 126**) mediante un método análogo al del **Ejemplo 31**.

MS (ESP): 414.0 (M+H) para $C_{14}H_{16}BrN_5O_3S$

^{1}H NMR δ: 1.58 (m, 2H); 1.87 (d, 2H); 2.14 (s, 3H); 3.28 (t, 2H); 3.88 (d, 2H); 4.01 (m, 1H); 6.82 (s, 1H); 7.84 (d, 1H); 8.82 (s, 1H); 11.71 (s, 1H).

Ejemplo 129: 2-(4-{[(4-Bromo-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)-1,3-tiazol-4-ácido carboxílico

El compuesto del título se sintetizó a partir de etil 2-(4-{[(4-bromo-5-metil-1*H*-pirrol-2il)carbonil]amino}piperidin-1-il)-1,3-tiazol-4-carboxilato (**Ejemplo 123**) mediante un método análogo al del **Ejemplo 31**.

MS (ESP): 413.0 (M+H) para $C_{15}H_{17}BrN_4O_3S$

^{1}H NMR δ: 1.56 (m, 2H); 1.86 (d, 2H); 2.14 (s, 3H); 3.17 (t, 2H); 3.90 (d, 2H); 4.00 (m, 1H); 6.83 (s, 1H); 7.64 (s, 1H); 7.85 (d, 1H); 8.20 (s, 1H); 11.72 (s, 1H).

Ejemplo 130: 4-Bromo-*N*-[1-(4-ciano-1,3-tiazol-2-il)piperidin-4-il]-5-metil-1*H*-pirrol-2-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 123** mediante el acoplamiento de 4-bromo-5-metil-*N*-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 57**) con 2-bromo-1,3-tiazol-4-carbonitrilo (*Tetrahedron Lett.* **1977**, *18 (21)*, 1813).

MS (ESP): 394.0 (M+H) para $C_{15}H_{16}BrN_5OS$

^{1}H NMR δ: 1.56 (m, 2H); 1.88 (d, 2H); 2.14 (s, 3H); 3.24 (t, 2H); 3.89 (d, 2H); 4.02 (m, 1H); 6.82 (s, 1H); 7.81 (d, 1H); 7.98 (s, 1H); 11.69 (s, 1H).

Ejemplo 131: 4-Bromo-5-metil-*N*-[1-(1-metil-1*H*-tetrazol-5-il) piperidin-4-il]-1*H*-pirrol-2-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 123** mediante el acoplamiento de 4-bromo-5-metil-*N*-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 57**) con 5-bromo-1-metil-1*H*-tetrazol (*Can. J. Chem.* **1971**, *49*, 2139).

MS (ESP): 368.0 (M+H) para $C_{13}H_{18}BrN_7O$

^{1}H NMR δ: 1.66 (m, 2H); 1.85 (d, 2H); 2.14 (s, 3H); 3.10 (t, 2H); 3.64 (d, 2H); 3.89 (s, 3H); 3.99 (m, 1H); 6.85 (s, 1H); 7.84 (d, 1H); 11.68 (s, 1H).

Ejemplo 132: 4-Bromo-*N*-(1-(5-ciano-1,3-tiazol-2-il)piperidin-4-il]-5-metil-1*H*-pirrol-2-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 123** mediante el acoplamiento de 4-bromo-5-metil-*N*-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 57**) con 2-bromo-1,3-tiazol-5-carbonitrilo (*Tetrahedron Lett.* **1977**, *21*, 1813).

MS (ESP): 394.0 (M+H) para $C_{15}H_{16}BrN_5OS$

^{1}H NMR δ: 1.56 (m, 2H); 1.90 (d, 2H); 2.14 (s, 3H); 3.35 (t, 2H); 3.97 (d, 2H); 4.05 (m, 1H); 6.82 (s, 1H); 7.82 (d, 1H); 8.04 (s, 1H); 11.70 (s, 1H).

Ejemplo 133: 2-(4-{[(4-Bromo-5-metil-1*H*-pirrol-2-il)carbonil] amino} piperidin-1-il)-1,3-tiazol-4-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 123** mediante el acoplamiento de 4-bromo-5-metil-*N*-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 57**) con 2-bromo-1,3-tiazol-4-carboxamida (*J. Am. Chem. Soc.* **1952**, *74*, 5799).

MS (ESP): 412.0 (M+H) para $C_{15}H_{18}BrN_5O_2S$

^{1}H NMR δ: 1.57 (m, 2H); 1.86 (d, 2H); 2.14 (s, 3H); 3.18 (t, 2H); 3.90-4.10 (m, 3H); 6.82 (s, 1H); 7.39 (s, 1H); 7.40 (s, 1H); 7.46 (s, 1H); 7.81 (d, 1H); 11.68 (s, 1H).

Ejemplo 134: Metil 6-cloro-4-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)quinolina-2-carboxilato

Se calentó una solución de 3,4-dicloro-5-metil-*N*-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 1**; 59 mg, 0.21mmol), metil 4, 6-dicloroquinolina-2-carboxilato (FR Alexandre, y colaboradores, Tetrahedron 2003, 59: 1413; 57 mg 0.22 mmol) y diisopropiletilamina (0.10 ml) en DMF (2.0ml) en un reactor de microondas a 180 °C durante 30 minutos. La reacción se diluyó con 50 ml de EtOAc, luego se extrajo con 25 ml de 1 N NaOH, 2 x 25 ml de agua, se lavó sobre $MgSO_4$ anhidro y se concentró al vacío. El sólido crudo se sometió a cromatografía instantánea a través de un gel de sílice neutro utilizando EtOAc como la fase móvil para producir 37 mg del compuesto del título; la cristalización del MeOH produjo un sólido blanco.

MS (ES+): 494.95/496.95/498.90 para $C_{22}H_{21}Cl_3N_4O_3$

^{1}H NMR δ: 1.85 (m, 2H); 1.954 (m, 2H); 2.10 (s, 3H); 2.98 (m, 2H); 3.49 (m, 2H); 3.85 (s, 3H); 3.97 (m, 1H); 7.24 (d, 1H, J = 7. 91); 7.50 (s, 1H); 7.75 (m, 1H); 7.87 (s, 1H); 8.02 (d, 1H, J = 9.04); 11.93 (s, 1H).

Ejemplo 135: 4-Bromo-5-metil-*N*-(1-{[4-(trifluorometil)-1*H*-indol-2-il]carbonil}piperidin-4-il)-1*H*-pirrol-2-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Intermedio 2** mediante el acoplamiento de 4-bromo-5-metil-*N*-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 57**) con 4-(trifluorometil)-1*H*-indole-2-ácido carboxílico (*J. Am. Chem. Soc.* **1957**, 79, 1745).

MS (ESP): 497.0 (M+H) para $C_{21}H_{20}BrF_3N_4O_2$

^{1}H NMR δ: 1.50 (q, 2H); 1.93 (d, 2H); 2.14 (s, 3H); 3.23 (m, 2H); 4.07 (m, 1H); 4.40 (m, 2H); 6.77 (s, 1H); 6.83 (s, 1H); 7.37 (t, 1H); 7.46 (d, 1H); 7.74 (d, 1H); 7.83 (d, 1H); 11.70 (s, 1H); 12.23 (s, 1H).

Ejemplo 136: 4-Bromo-*N*-{1-[6-cloro-4-(1H-1,2,3,4-tetraazol-5-il)-2-piridinil]-4-piperidinil}-N,5-dimetil-1*H*-pirrol-2-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 18** comenzando a partir de 1-[6-cloro-4-(1*H*-tetrazol-5-il)piridin-2-il]-*N*-metilpiperidin-4-amina (**Intermedio 64**) y pentafluorofenilo 4-bromo-5-metil-1H-pirrol-2-carboxilato (**Intermedio 17**).

MS (ES): 481 (M+H) para $C_{18}H_{20}BrIN_8O$

^{1}H NMR δ: 1.54 (m, 4H); 2.04 (s, 3H); 2.72 (s, 3H); 2.95 (t, 2H); 4.21 (d, 2H); 4.46 (t, 1H); 6.30 (s, 1H); 7.01 (s, 1H); 7.17 (s, 1H); 11.29 (s, 1H).

Ejemplo 137: 4-Bromo-N-{1-[6-cloro-4-(2-metil-2H-1,2,3,4-tetraazol-5-il)-2-piridinil]-4-piperidinil}-5-metil-1H-pirrol-2-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 42** comenzando a partir de 1-[6-cloro-4-(1-metil-1*H*-tetrazol-5-il)piridin-2-il]-*N*-metilpiperidin-4-amina (**Intermedio 65**) y pentafluorofenilo 4-bromo-5-metil-1*H*-pirrol-2-carboxilato (**Intermedio 17**).

MS (ES): 481 (M+H) para $C_{18}H_{20}BrClN_8O$

^{1}H NMR δ: 1.49 (m, 2H); 1.87 (m, 2H); 2.14 (s, 3H); 3.11 (m, 2H); 4.06 (m, 1H); 4.31 (m, 2H); 4.34 (s, 3H); 6.82 (s, 1H); 7.07 (s, 1H); 7.16 (s, 1H); 7.78 (d, 1H); 11.68 (s, 1H).

Ejemplo 138: Etil 2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino}piperidin-1-il)-4-(hidroximetil)-1,3-tiazol-5-carboxilato

Se disolvió etil 2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino} piperidin-1-il)-4-(metoximetil)-1,3-tiazol-5-carboxilato (**Ejemplo 276**; 50 mg; 0.105 mmol) en DCM anhidro y se enfrió a -78 °C. Se agregó 1 M tribromuro de boro/DCM (105 µl; 0.105 mmol) en forma de goteo. La mezcla se revolvió a -78 °C durante 15 min, luego a temperatura ambiente durante 4 h. La mezcla se diluyó con DCM, se lavó con agua y se lavó sobre Na_2SO_4. La fase orgánica se concentró al vacío produciendo el compuesto del título (20 mg).

MS (ES) MH+: 461 para $C_{18}H_{22}Cl_2N_4O_4S$

^{1}H NMR δ: 1.16-1.19 (t, 3H); 1.56-1.61 (brs, 2H); 1.84-1.87 (d, 2H); 2.11 (s, 3H); 3.24 (t, 2H); 3.88 (d, 2H); 4.00 (brs, 1H); 4.11-4.13 (q, 2H); 4.55 (s, 1H); 7.21-7.23 (d, 1H); 11.91 (s, 1H).

Ejemplo 139: 2-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)-6-[2-(dimetilamino)etoxi]ácido isonicotínico

Se combinó sodio (155 mg, 6.74 mmol) y 2-(dimetilamino) etanol (0.677ml, 6.74 mmol) en DMF (1.5ml). Se agregó metil 2-cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il) isonicotinato (**Ejemplo 333**; 200 mg, 0.449 mmol). La mezcla de la reacción se llevó a reflujo durante la noche, luego se llevó a temperatura ambiente y se acidificó con HCl al 10%. La mezcla de la reacción se distribuyó entre EtOAc y agua. La capa orgánica se lavó con agua, luego con solución salina, se lavó sobre sulfato de sodio y se concentró para producir el producto deseado. El producto crudo se purificó mediante HPLC de fase inversa levigado con mezclas de agua/acetonitrilo/TFA para obtener el producto deseado (60 mg).

MS (ES): 484 (MH^+) para $C_{21}H_{27}Cl_2N_5O_4$

^{1}H NMR δ: 1.57 (m, 2H); 1.88 (m, 2H); 2.17 (s, 3H); 2.85 (s, 6H); 3.09 (m, 2H); 4.07 (m, 1H); 4.24 (m, 2H); 4.55 (m, 2H); 6.46 (s, 1H); 6.83 (s, 1H); 7.20 (d, 1H); 9.52 (brs, 1H); 11.98 (s, 1H); 13.41 (brs, 1H)

Ejemplos 140-147

Los siguientes compuestos se sintetizaron mediante un método análogo al del **Ejemplo 139**, comenzando a partir de metil 2-cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)isonicotinato (**Ejemplo 333**) y los alcoholes disponibles en el comercio descritos en la siguiente tabla.

Ejemplo 140: 2-Butoxi-6-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino}piperidin-1-il)ácido isonicotínico

Ejemplo 141: 2-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il) carbonil] amino}piperidin-1-il)-6-(2-metoxietoxi)ácido isonicotínico

Ejemplo 142: 2-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-6-(2-hidroxietoxi)ácido isonicotínico

Ejemplo 143: 2-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-6-[2-(2-hidroxietoxi)etoxi]ácido isonicotínico

Ejemplo 144: 2-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-6-[2-(2-metoxietoxi)etoxi]ácido isonicotínico

Ejemplo 145: 2-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino} piperidin-1-il)-6-(2-isopronoxietoxi)ácido isonicotínico

Ejemplo 146: 2-[2-(Aliloxi)etoxi]-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)ácido isonicotínico

Ejemplo 147: 2-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-6-(2-morfolin-4-iletoxi)ácido isonicotínico

Ejemplos	Alcohol	^{1}H NMR δ	m/z
140	butan-1-ol	0.94 (t, 3H); 1.44 (m, 2H); 1.61 (m, 2H); 1.76 (m, 2H); 1.95 (m, 2H); 2.22 (s, 3H); 3.15 (m, 2H); 4.05 (m, 1H); 4.24 (m, 2H); 6.38 (s, 1H); 6.76 (s, 1H); 7.23 (d, 1H); 11.98 (s, 1H); 13.31 (brs, 1H)	469
141	2-metoxi etanol	1.38 (m, 2H); 1.67 (m, 2H); 1.98 (s, 3H); 2.84 (m, 2H); 3.10 (s, 3H); 3.45 (m, 2H); 3.85 (m, 2H); 3.99 (m, 2H); 4.17 (m, 2H); 6.19 (s, 1H); 6.57 (s, 1H); 7.02 (d, 1H); 11.76 (s, 1H); 13.12 (s, 1H).	471
142	etilenglicol	1.56 (m, 2H); 1.60 (m, 2H); 2.17 (s, 3H); 2.57 (m, 2H); 3.69 (m, 2H); 4.04 (m, 1H); 4.24 (m, 4H); 6.38 (s, 1H); 6.75 (s, 1H); 7.21 (d, 1H); 11.96 (s, 1H); 13.31 (brs, 1H)	457

Ejemplos	Alcohol	^{1}H NMR δ	m/z
143	2,2'-oxidietanol	1.63 (m, 2H); 1.93 (m, 2H); 2.24 (s, 3H); 3.13 (m, 2H); 3.53 (m, 4H); 3.79 (m, 2H); 4.07 (m, 1H); 4.25 (m, 2H); 4.39 (m, 2H); 6.45 (s, 1H); 6.82 (s, 1H); 7.27 (d, 1H); 12.02 (s, 1H); 13.38 (brs, 1H).	501
144	2-(2-metoxi etoxi)etanol	1.56 (m. 2H); 1.85 (m, 2H); 2.16 (s, 3H); 3.06 (m, 2H); 3.23 (s, 3H); 3.45 (m, 2H); 3.54 (m, 2H); 3.71 (m, 2H); 4.03 (m, 1H); 4.18 (m, 2H); 6.37 (s, 1H); 6.75 (s, 1H); 7.20 (d, 1H); 11.95 (s, 1H); 13.31 (brs, 1H).	499
145	2-isopropoxi etanol	1.31 (m, 6H); 1.79 (m, 2H); 2.08 (m, 2H); 2.40 (s, 3H); 3.29 (m, 2H); 3.79 (q, 1H); 3.90 (m, 2H); 4.26 (m, 1H); 4.45 (m, 2H); 4.53 (m, 2H); 6.60 (s, 1H); 6.98 (s, 1H); 7.43 (d, 1H); 12.18 (s, 1H); 13.54 (brs, 1H).	515
146	2-(alquiloxi) etanol	1.67 (m, 2H); 1.96 (m, 2H); 2.28 (s, 3H); 3.17 (m, 2H); 3.81 (t, 2H); 4.09 (m, 2H); 4.11 (m, 1H); 4.29 (m, 2H); 4.46 (m, 2H); 5.26 (dd, 1H); 5.34 (dd, 1H); 5.98 (m, 1H); 6.49 (s, 1H); 6.86 (s, 1H); 7.43 (d, 1H); 12.06 (s, 1H); 13.41 (brs, 1H).	497
147	2-morfolin-4-iletanol	1.54 (m, 2H); 1.65 (m, 1H); 1.87 (m, 2H); 2.19 (s, 3H); 2.46 (m, 4H); 2.67 (m, 2H); 2.99 (m, 1H); 3.05 (m, 2H); 3.57 (m, 4H); 4.04 (m, 1H); 4.18 (m, 2H); 4.33 (m, 2H); 6.36 (s, 1H); 6.75	526

Ejemplos	Alcohol	^{1}H NMR δ	m/z
		(s, 1H); 7.37 (d, 1H).	

Ejemplo 148: 2-*tert*-Butoxi-2-oxoetil 2-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-6-(2-metoxietoxi)isonicotinato

Se agregó *tert*-butil cloroacetato (28 mg, 0.190 mmol) a una solución de 2-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-6-(2-metoxietoxi)ácido isonicotínico (60 mg, 0.127 mmol) (**Ejemplo141**) en DMF (2 ml), seguido por la adición de fluoruro de caesio (47 mg, 0.313 mmol). La mezcla resultante se revolvió a temperatura ambiente durante 24 hr. La mezcla se filtró y se purificó por medio de HPLC levigado con mezclas de agua/acetonitrilo/TFA para obtener el producto deseado (20 mg).

MS (ES): 585 (MH^+) para $C_{26}H_{34}Cl_2N_4O_7$

^{1}H NMR δ: 0.96 (s, 9H); 1.37 (m, 2H); 1.67 (m, 2H); 1.97 (s, 3H); 2.85(m, 2H); 3.09 (s, 3H); 3.44 (m, 2H); 3.84 (m, 1H); 3.99 (m, 2H); 4.14 (m, 3H); 5.73 (s, 1H); 6.16 (s, 1H); 6.55 (s, 1H); 7.00 (d, 1H); 11.75 (s, 1H).

Ejemplo 149: 2-(4- {[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino} piperidin-1-il)-6-12-(dimetilamino)etoxil-*N*-metoxiisonicotinamida

El compuesto del título se preparó como se describe para el **Ejemplo 8** a partir de 2-(4-{[(3,4-dicloro-5-metil-1 *H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-6-[2-(dimetilamino)etoxi]ácido isonicotínico (**Ejemplo 139**) ácido y O-metilclorhidrato de hidroxilamina.

MS (ES): 513 (MH^+) para $C_{22}H_{30}Cl_2N_6O_4$

^{1}H NMR δ: 1.56 (m, 2H); 1.88 (m, 2H); 2.17 (s, 3H); 2.85 (s, 6H); 3.08 (m, 2H); 3.70 (s, 3H); 4.19 (m, 1H); 4.52 (d, 2H); 4.54 (m, 2H); 6.34 (s, 1H); 6.69 (s, 1H); 7.20 (d, 1H); 11.85 (s, 1H); 11.98 (s, 1H).

Ejemplo 150: 2-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-6-[2-(propioniloxi) etoxi]ácido isonicotínico

Se disolvió 2-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-6-(2-hidroxietoxi)ácido isonicotínico (**Ejemplo 142**) (199 mg, 0.435 mmol) en DCM (3 ml). Se agregó cloruro de propanoilo (37.83 µl, 0.435 mmol) en forma de goteo y la mezcla resultante se revolvió a temperatura ambiente durante 2.5 h. La mezcla se diluyó con EtOAc y se lavó con agua. La fase acuosa se extrajo con EtOAc y la fase orgánica combinada se lavó sobre sulfato de sodio y se concentró al vacío para producir el producto deseado. El producto crudo se disolvió en DMSO y se purificó mediante HPLC de fase inversa, levigado con mezclas de agua/acetonitrilo/TFA para obtener el producto deseado (35 mg).

MS (ES): 513 (MH^+) para $C_{22}H_{26}C_{12}N_4O_6$

^{1}H NMR δ: 1.01 (t, 3H); 1.57 (m, 2H); 1.87 (m, 2H); 2.17 (s, 3H); 2.31 (m, 2H); 3.07 (m, 2H); 4.05 (m, 1H); 4.23 (m, 2H); 4.33 (m, 2H); 4.44 (m, 2H); 6.40 (s, 1H); 6.79 (s, 1H); 7.43 (d, 1H); 12.17 (s, 1H); 13.62 (m, 1H).

Ejemplo 151: 2-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-*N*-metoxi-6-(metilsulfonil)isonicotinamida

Se disolvió 2-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-*N*-metoxi-6-(metilsulfinil)isonicotinamida (**Ejemplo 152**) (90 mg, 0.185 mmol) en DCM anhidro (5 ml). Se agregó mCPBA (32 mg, 0185 mmol) y la mezcla se revolvió a temperatura ambiente durante 12 h. La mezcla cruda se diluyó y se lavó con trisulfato de sodio al 10%, agua, solución salina y se lavó sobre sulfato de sodio y se

concentró al vacío. El aceite marrón se purificó mediante cromatografía instantánea levigado con acetonitrilo/agua (TFA al 0.1 %) para producir el compuesto del título (11 mg).

MS (ES) (M+H): 504 para $C_{19}H_{23}Cl_2N_5O_5S$

^{1}H NMR δ: 1.53 (m, 2H); 1.83 (m, 2H); 2.03 (s, 3H); 2.97 (m, 2H); 3.12 (s, 3H); 3.62 (s, 3H); 4.07 (m, 1H); 4.28 (m, 2H); 7.16 (d, 1H); 7.30 (s, 2H); 11.87 (s, 1H); 12.05 (s, 1H).

Ejemplo 152: 2-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il) carbonilamino}piperidin-1-il)-*N*-metoxi-6-(metilsulfinil) isonicotinamida

Se disolvió metil 2-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino} piperidin-1-il)-6-(metilsulfinil)isonicotinato (**Ejemplo 334**; 200 mg, 0.422 mmol) en THF anhidro (5 ml) y se trató con 2 N hidróxido de litio (10 ml) revolviéndolo durante 45 minutos. La mezcla se enfrió en un baño de hielo y se acidificó con 1 N HCl. La solución acuosa se extrajo con EtOAc. La fase orgánica se lavó con agua, se lavó sobre sulfato de sodio y se concentró al vacío para producir el derivado del ácido como un sólido marrón (LCMS mostró un pico de 459). Este ácido (95 mg, 0.207 mmol) se trató con clorhidrato de metoxiamina (17.3 mg, 0.207 mmol) en una forma análoga a la del **Ejemplo 8** para obtener el compuesto del título. (30 mg).

MS (ES) (M+H): 488 para $C_{19}H_{23}Cl_2N_5O_4S$

^{1}H NMR δ: 1.58 (m, 2H); 1.92 (m, 2H); 2.18 (s, 3H); 2.80(s, 3H); 3.18 (m, 2H); 3.76 (s, 3H); 4.12 (m, 1H); 4.29 (m, 2H); 7.08 (s, 1H); 7.22 (d, 1H); 7.34 (s, 1H); 11.96 (s, 1H); 12.17 (s, 1H)

Ejemplo 153: 2-Cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)ácido isonicotínico

El compuesto del título se preparó en forma análoga al **Ejemplo 44** a partir de metil 2-cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)isonicotinato (**Ejemplo 333**).

MS (ES) (M+H): 431 para $C_{17}H_{17}Cl_3N_4O_3$

^{1}H NMR δ: 1.64 (m, 2H); 2.00 (m, 2H); 2.46 (s, 3H); 3.46 (m, 2H); 4.40 (m, 1H); 4.55 (m, 2H); 7.21 (s, 1H); 7.27 (s, 1H); 7.59 (d, 1H); 12.13 (s, 1H); 14.06 (brs, 1H).

Ejemplo 154: 2-{2-[(*tert*-Butoxicarbonil)amino]etoxi}-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il) pirimidina-4-ácido carboxílico

Se agregó hidruro de sodio (0.097 g, 4.02 mmol) a una solución agitada de *tert*-butil 2-hidroxietilcarbamato (0.62 ml, 4.02 mmol) en THF a 0 °C bajo una atmósfera de nitrógeno. Esta mezcla se revolvió durante 15 minutos a 0°C y se calentó a temperatura ambiente. Se agregó metil 2-cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il) pirimidina-4-carboxilato (**Ejemplo 6**, 0.30 g, 0.67 mmol) a la mezcla de la reacción y la mezcla resultante se revolvió durante la noche. La reacción se extinguió con agua (10 ml) y el THF se extrajo bajo presión reducida. La solución acuosa se acidificó con 1 N HCl y se extrajo con EtOAc. El extracto combinado se lavó con agua y solución salina, se lavó sobre sulfato de magnesio, se filtró y se concentró para producir un aceite marrón el cual se purificó mediante HPLC de semi preparación de fase invertida levigado con acetonitrilo/agua (TFA al 0.1 %).

MS (ES) MH^+: 557 para $C_{23}H_{30}Cl_2N_6O_6$

^{1}H NMR δ: 1.36 (s, 9H); 1.53 (m, 2H); 1.89 (m, 2H); 2.16 (s, 3H); 3.20 (m, 2H); 3.27 (m, 2H); 4.09 (m, 1H); 4.24 (t, 2H); 4.53 (brs, 2H); 7.00 (t, 1H); 7.05 (s, 1H); 7.23 (d, 1H); 11.96 (s, 1H).

Ejemplo 155-162

Los siguientes compuestos se sintetizaron mediante un método análogo al del **Ejemplo 154** comenzando a partir de alcoholes disponibles en el comercio e hidruro de sodio y haciendo reaccionar el alcóxido generado in situ con metil 2-cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-

il)carbonil]amino}piperidin-1-il) pirimidina-4-carboxilato (**Ejemplo 6**). Los alcoholes disponibles en el comercio se describen en la siguiente tabla.

Ejemplo 155: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-2-(2-metoxietoxi)pirimidina-4-ácido carboxílico

Ejemplo 156: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-2-[2-(metiltio)etoxi]pirimidina-4-ácido carboxílico

Ejemplo 157: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-2-(2-morfolin-4-iletoxi)pirimidina-4-ácido carboxílico

Ejemplo 158: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-2-(2-hidroxietoxi)pirimidina-4-ácido carboxílico

Ejemplo 159: 2-Butoxi-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il) pirimidina-4-ácido carboxílico

Ejemplo 160: 2-(2-Aminoetoxi)-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]aminopiperidin-1-il)pirimidina-4-ácido carboxílico

Ejemplo 161: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-2-[2-(dimetilamino)etoxi] pirimidina-4-ácido carboxílico

Ejemplo 162: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-2-[3-(dimetilamino)propoxi] pirimidina-4-ácido carboxílico

Ejemplo	Alcohol	^{1}H NMR δ	m/z
155	2-metoxi etanol	1.54 (m, 2H); 1.88 (m, 2H); 2.16 (s, 3H); 3.18 (m, 2H); 3.28 (s, 3H); 3.62 (t, 2H); 4.08 (brs, 1H); 4.33 (m, 2H); 4.37 (t, 2H); 7.03 (s, 1H); 7.22 (d, 1H); 11.96 (s, 1H).	472

Ejemplo	Alcohol	^{1}H NMR δ	m/z
156	2-(metiltio) etanol	1.53 (m, 2H); 1.89 (m, 2H); 2.13 (s, 3H); 2.16 (s, 3H); 2.82 (t, 2H); 3.19 (t, 2H); 4.09 (brs, 1H); 4.35 (m, 2H); 4.42 (t, 2H); 7.04 (s, 1H); 7.23 (d, 1H); 11.96 (s, 1H).	488
157	2-morfolin-4-iletanol	1.52 (m, 2H); 1.95 (m, 2H); 2.16 (s, 3H); 3.20 (t, 2H); 3.56 (brs, 2H); 3.73 (brs, 2H); 3.94 (brs, 2H); 4.09 (brs, 2H); 4.35 (brs, 3H); 4.61 (brs, 4H); 7.10 (s, 1H); 7.25 (d, 1H); 12.01 (s, 1H).	527
158	etilenglicol	1.52 (m, 2H); 1.87 (m, 2H); 2.15 (s, 3H); 3.17 (t, 2H); 3.66 (t, 2H); 4.07 (m, 1H); 4.26 (t, 2H); 4.35 (brs, 2H); 7.02 (s, 1H); 7.21 (d, 1H); 11.95 (s, 1H).	458
159	butan-1-ol	0.92 (t, 3H); 1.39 (m, 2H); 1.53 (m, 2H); 1.67 (m, 2H); 1.80 (m, 2H); 2.16 (s, 3H); 3.22 (m, 2H); 4.10 (m, 2H); 4.28 (t, 2H); 4.45 (brs, 1H); 7.05 (s, 1H); 7.23 (d, 1H); 11.97(s, 1H)	470
160	3-(dimetilamino) propan-1-ol	1.52 (m, 2H); 1.89 (m, 2H); 2.02 (m, 2H); 2.16 (s, 3H); 2.80 (s, 3H); 2.81 (s, 3H); 3.18 (m, 4H); 4.09 (m, 1H); 4.31 (t, 2H); 4.58 (m, 2H); 7.05 (s, 1H); 7.21 (d, 1H); 9.36(brs, 1H); 11.98 (s, 1H).	499

Ejemplo	Alcohol	^{1}H NMR δ	m/z
161	2-aminoetanol	1.53 (m, 2H); 1.91 (m, 2H); 2.17 (s, 3H); 3.21 (m, 4H); 4.13 (m, 1H); 4.35 (brs, 2H); 4.43 (t, 2H); 7.10 (s, 1H); 7.22 (d, 1H); 7.96 (brs, 2H); 11.98 (s, 1H).	457
162	2-(dimetilamino) etanol	1.52 (m, 2H); 1.92 (m, 2H); 2.16 (s, 3H); 2.85 (s, 6H); 3.21 (t, 2H); 3.49 (brs, 2H); 4.10 (m, 1H); 4.33 (brs, 2H); 4.58 (m, 2H); 7.11 (s, 1H); 7.23 (d, 1H); 9.88 (brs, 1H); 11.99 (s, 1H).	485

Ejemplo 163:6-(4-[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)-2-[2-(metilsulfonil) etoxi]pirimidina-4-ácido carboxílico

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 14** comenzando a partir de 6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)-2-[2-(metiltio)etoxi]pirimidina-4-ácido carboxílico (**Ejemplo 156**).

MS(ES) MH^+: 520 para $C_{19}H_{23}Cl_2N_5O_6S$

^{1}H NMR δ: 1.54 (m, 2H); 1.88 (m, 2H); 2.16 (s, 3H); 3.00 (s, 3H); 3.14 (t, 2H); 3.55 (m, 2H); 4.03 (m, 1H); 4.28 (m, 2H); 4.55 (t, 2H); 7.01 (s, 1H); 7.16 (d, 1H); 11.90 (s, 1H).

Ejemplos 164-168

Los siguientes compuestos se sintetizaron mediante un método análogo al del **Ejemplo 8** comenzando a partir de los respectivos derivados del ácido carboxílico y clorhidrato de metoxilamina. Los derivados del ácido carboxílico de partida se describen en la siguiente tabla.

Ejemplo 164: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)-*N*-metoxi-2-(2-metoxietoxi) pirimidina-4-carboxamida

Ejemplo 165: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino} piperidin-1-il)-*N*-metoxi-2-12-(metiltio) etoxi]pirimidina-4-carboxamida

Ejemplo 166: 2-Butoxi-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-*N*-metoxipirimidina-4-carboxamida

Ejemplo 167: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)-2-12-(dimetilamino)etoxil-*N*-metoxipirimidina-4-carboxamida

Ejemplo 168: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-2-(2-hidroxietoxi)-*N*-metoxipirimidina-4-carboxamida

Ejemplo	SM	^{1}H NMR δ	m/z
164	6-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino}piperidin-1-il)-2-(2-metoxietoxi) pirimidina-4-ácido carboxílico (Ejemplo 155)	1.52 (m, 2H); 1.88 (m, 2H); 2.16 (s, 3H); 3.21 (t, 2H); 3.28 (s,3H); 3.61 (t, 2H); 3.66 (s, 3H); 4.08 (m, 1H); 4.33 (m, 2H); 4.41 (t, 2H); 6.96 (s, lH); 7.22 (d, 1H); 11.84 (brs, 1H); 11.96 (s, 1H).	501
165	6-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino}piperidin-1-il)-2-[2-(metiltio) etoxi]pirimidina-4-carboxílico (Ejemplo 156)	1.52 (m, 2H); 1.88 (m, 2H); 2.13 (s, 3H); 2.16 (s, 3H); 2.81 (t, 2H); 3.17 (t, 2H); 3.67 (s, 3H); 4.08 (m, 1H); 4.31 (m, 2H); 4.44 (t, 2H); 6.97 (s, 1H); 7.22 (d, 1H); 11.84 (brs, 1H); 11.96 (s, 1H).	517

Ejemplo	SM	^{1}H NMR δ	m/z
166	2-butoxi-6-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil] amino}piperidin-1-il) pirimidina-4-ácido carboxílico (**Ejemplo 159**)	0.92 (t, 3H); 1.40 (m, 2H); 1.51 (m, 2H); 1.66 (m, 2H); 1.88 (m, 2H); 2.16 (s,3H); 3.17 (t, 2H); 3.66 (t, 3H); 4.08 (m, 1H); 4.27 (t, 2H); 4.38 (brs, 2H); 6.95 (s, 1H); 7.22 (d, 1H); 11.81 (brs, 1H); 11.96 (s, 1H)	499
167	6-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino} piperidin-1-il)-2-[2-(dimetilamino)etoxi] pirimidina-4-ácido carboxílico (**Ejemplo 161**)	1.50 (m, 2H); 1.89 (m, 2H); 2.16 (s, 3H); 2.83 (s, 3H); 2.85 (s, 3H); 3.19 (t, 2H); 3.69 (s, 3H); 4.08 (m, 1H); 4.31 (m, 2H); 4.65 (t, 2H); 7.03 (s, 1H); 7.20 (d, 1H); 11.85 (s, 1H); 11.97 (s, 1H); 2H enterrado debajo del pico del agua	514
168	6-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino} piperidin-1 -il)-2-(2-hidroxietoxi)pirimidina-4-ácido carboxílico (**Ejemplo 158**)	1.52 (m, 2H); 1.88 (m, 2H); 2.16 (s, 3H); 3.17 (t, 2H); 3.67 (s, 3H); 3.68 (t, 2H); 4.10 (m, 1H); 4.30 (t, 2H); 4.35 (m, 2H); 6.96 (s, 1H); 7.21 (d, 1H); 11.81 (s, 1H); 11.95 (s, 1H)	487

Ejemplo 169: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)-2-(2,3-dihidroxipropoxi)-*N*-metoxipirimidina-4-carboxamida

Se disolvió 6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-2-[(2,2-dimetil-1,3-dioxolan-4-il)metoxi]-*N*-metoxipirimidina-4-carboxamida (**Ejemplo 313**; 0.60 g, 1.08 mmol) en

THF/agua (4: 1; 2.5ml) y se enfrió a 0° C. Se agregó TFA (0.1 ml) a la solución la cual se calentó lentamente hasta llegar a la temperatura ambiente y se revolvió durante la noche. La mezcla se neutralizó con hidróxido de amonio concentrado y el THF se extrajo al vacío. La mezcla se diluyó con agua (4 ml), se extrajo con DCM y las capas orgánicas se lavaron sobre sulfato de magnesio. La mezcla se concentró al vacío y el producto crudo se purificó mediante cromatografía de fase inversa levigado con acetonitrilo/agua (0. 1 % TFA) (33 mg).

MS (ES) MH^+: 517 para $C_{20}H_{26}Cl_2N_6O_6$

^{1}H NMR δ: 1.52 (m, 2H); 1.88 (m, 2H); 2.16 (s, 3H); 3.18 (t, 2H); 3.43 (d, 2H); 3.67 (s, 3H); 4.08 (m, 1H); 4.17 (m, 2H); 4.30 (m, 2H); 4.35 (m, 1H); 6.96 (s, 1H); 7.22 (d, 1H); 11.81 (s, 1H); 11.96 (s, 1H).

Ejemplo 170: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-*N*-metoxi-2-[2-(metilsulfonil) etoxi]pirimidina-4-carboxamida

Se suspendió 6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-*N*-metoxi-2-[2-(metiltio)etoxi]pirimidina-4-carboxamida (**Ejemplo 165**, 0.10 g, 0.19 mmol) en DCM (5 ml) y se enfrió a 0°C. Se agregó mCPBA (0.067 g, 0.387 mmol, 70 %), luego la reacción se calentó a temperatura ambiente y se revolvió durante 4 h. Se agregó una cantidad equivalente de mCPBA y la mezcla se revolvió durante la noche. Se agregó una solución de sulfito de sodio (5 %, 3 ml) y las capas se separaron. La fase acuosa se extrajo con EtOAc y el extracto orgánico combinado se lavó sobre sulfato de magnesio y se concentró para producir un sólido blanco el cual se purificó mediante cromatografía de fase inversa levigado con (20 % a 75 % acetonitrilo en agua, TFA al 0.1 %) produciendo el compuesto del título (44 mg).

MS (ES) MH^+: 549 para $C_{20}H_{26}Cl_2N_6O_6S$

^{1}H NMR δ: 1.52 (m, 2H); 1.88 (m, 2H); 2.15 (s, 3H); 3.05 (s, 3H); 3.18 (t, 2H); 3.60 (t, 2H); 3.67 (s, 3H); 4.10 (m, 1H); 4.32 (m, 2H); 4.64 (t, 2H); 7.00 (s, 1H); 7.21 (d, 1H); 11.86 (s, 1H); 11.95 (s, 1H).

Ejemplo 171: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il) carbonil] amino}piperidin-1-il)-*N*-metoxi-2-{2-[(metilsulfonil) amino]etoxi}pirimidina-4-carboxamida

Se agregó metano sulfonilo cloruro (0.032 ml, 0.412 mmol) en forma de goteo a una solución de 2-(2-aminoetoxi)-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-*N*-metoxipirimidina-4-carboxamida (**Ejemplo 319**, 0.20 g, 0.412 mmol), TEA (0.11 ml, 0.824 mmol) y DMF (3 ml) a 0°C. La reacción se revolvió durante 15 minutos a 0 °C luego se extinguió con agua. La fase acuosa se extrajo con EtOAc, se lavó con solución saturada de bicarbonato de sodio, agua y solución salina. Se lavó sobre sulfato de magnesio y se concentró para producir un sólido marrón, el cual se purificó mediante HPLC de fase inversa (30% a 35% acetonitrilo en agua, TFA al 0.1 %) produciendo el compuesto del título (70 mg).

MS (ES) MH^+: 564 para $C_{20}H_{27}Cl_2N_7O_6S$

^{1}H NMR δ: 1.52 (m, 2H); 1.88 (m, 2H); 2.16 (s, 3H); 2.93 (s, 3H); 3.18 (t, 2H); 3.29 (m, 2H); 3.67 (s, 3H); 4.20(m, 1H); 4.32 (m, 2H); 4.34 (t, 2H); 6.98 (s, 1H); 7.23 (m, 2H); 11.82 (s, 1H); 11.97 (s, 1H).

Ejemplo 172: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il) carbonil] amino}piperidin-1-il)-*N*-metoxi-2-oxo-2,3-dihidropirimidina-4-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 8** comenzando a partir de 6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)-2-oxo-2,3dihidropirimidina-4-ácido carboxílico (**Ejemplo 173**) y clorhidrato de metoxilamina.

MS (ES) MH^+: 443 para $C_{17}H_{20}Cl_2N_6O_4$

^{1}H NMR δ: 1.54 (m, 2H); 1.90 (m, 2H); 2.17 (s, 3H); 3.25 (m, 2H); 3.71 (s, 3H); 4.10 (m, 2H); 4.39 (br s, 1H); 6.55 (s, 1H); 7.24 (d, 1H); 11.97 (s, 1H); 12.11 (s, 1H);I H por debajo del pico del agua.

Ejemplo 173: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)-2-oxo-2,3-dihidropirimidina-4-ácido carboxílico

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 154** comenzando a partir de 2-furilmetanol (disponible en el comercio) e hidruro de sodio y haciendo reaccionar el alcóxido generado in situ con metil 2-cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il) pirimidina-4-carboxilato (**Ejemplo 6**). La purificación del material crudo por medio de HPLC de fase inversa resultó en la hidrólisis del producto deseado para formar el compuesto del título.

MS (ES) MH^+; 414 para $C_{16}H_{17}Cl_2N_5O_4$

^{1}H NMR δ: 1.54 (m, 2H); 1.90 (m, 2H); 2.16 (s, 3H); 3.26 (m, 2H); 3.71 (s, 3H); 4.09 (m, 2H); 4.49 (br s, 1H); 6.68 (s, 1H); 7.24 (d, 1H); 11.97 (s, 1H); 1H sepultado debajo del pico de agua.

Ejemplo 174: 2-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino} piperidin-1-il)-6-metoxipirimidina-4-ácido carboxílico

Se calentó hidróxido de litio (2M, 4 ml) a 40 °C y se agregó una solución de metil 2-(4-{[(3,4-dicloro-5-metil-lH-pirrol-2-il)carbonil]amino} piperidin-1-il)-6-metoxipirimidina-4- carboxilato (**Ejemplo 315**, 0.30 g, 0.68 mmol) en MeOH. La temperatura de la reacción se incrementó a 60 °C y se revolvió a esa temperatura durante 3 h. Se extrajo el MeOH, la solución acuosa se enfrió a 0 °C y luego se acidificó con 1 N HCI. El producto precipitado se recolectó mediante filtración por succión y se lavó con EtOAc para producir el compuesto del título (0.13 g).

MS(ES) MH^+: 428 para $C_{17}H_{19}Cl_2N_5O_4$

^{1}H NMR δ: 1.54 (m, 2H); 1.90 (m, 2H); 2.17 (s, 3H); 3.24 (t, 2H); 3.89 (s, 3H); 4.04 (m, 1H); 4.49 (d, 2H); 6.50 (s, 1H); 7.22 (d, 1H); 11.97 (s, 1H); 13.23 (s, 1H).

Ejemplo 175: 2-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)-*N*,6-dimetoxipirimidina-4-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 8** comenzando a partir de 2-(4-[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)-6-metoxipirimidina-4-ácido carboxílico (**Ejemplo 174**) y clorhidrato de metoxilamina.

MS (ES) MH^+: 457 para $C_{18}H_{22}Cl_2N_6O_4$

^{1}H NMR δ: 1.51 (m, 2H); 1.87 (m, 2H); 2.16 (s, 3H); 3.11 (t, 2H); 3.69 (s, 3H); 3.86 (s, 3H); 4.06 (m, 1H); 4.67 (brs, 2H); 6.45 (s, 1H); 7.20 (d, 1H); 11.83 (s, 1H); 11.96 (s, 1H).

Ejemplo 176: 2-(Butiltio)-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)pirimidina-4-ácido carboxílico

Se enfrió una suspensión de hidruro de sodio (239.5 mg, 9.98 mmol) en THF (5 ml) a 0 °C y se trató con una solución de 1-butanetiol (1.0 g, 0.011 mol) en THF (5 ml). Se permitió que lentamente la mezcla de la reacción se calentara hasta llegar a la temperatura ambiente. La concentración bajo presión reducida produjo un sólido blanco (1.02 g), el cual se presumió que era la sal de sodio del tiol. Se combinó metil 2-cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)pirimidina-4-carboxilato (**Ejemplo 6**) (500 mg, 1.12 mmol) y la sal de sodio del tiol (627 mg, 5.6 mmol) en DMF (12 ml) y se calentó a 90 °C bajo nitrógeno durante 1 h. Una vez se enfrió a temperatura ambiente, la solución de la reacción se diluyó con EtOAc y agua y luego se acidificó con 1 N HCl. La porción acuosa se extrajo con EtOAc y las porciones orgánicas combinadas se lavaron sobre sulfato de sodio, se filtraron y se concentraron bajo presión reducida para producir un aceite marrón. Una parte del material crudo se purificó mediante HPLC de preparación empleando un gradiente de 20-60% acetonitrilo/agua (TFA al 0.1 %) para producir la sal de TFA del compuesto del título (50 mg).

MS (ES^+): 486.22, 488.22

^{1}H NMR δ: 0.83 (t, 3H); 1.32 (m, 2H); 1.4 (m, 2H); 1.58 (m, 2H); 1.81 (m, 2H); 2.10 (s, 3H); 3.0 (t, 2H); 3.14 (m, 2H); 4.04 (m, 2H); 4.27 (m, 1H); 6.98 (s, 1H); 7.16 (d, 1H); 11.90 (s, 1H); ácido carboxílico protón no visible

Ejemplos 177-181

Los siguientes compuestos se sintetizaron mediante un método análogo al del **Ejemplo 176** a partir de tioles e hidruro de sodio disponibles en el comercio haciendo reaccionar la sal de sodio generada in situ con metil 2-cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il) pirimidina-4-carboxilato (**Ejemplo 6**). Los respectivos tioles se describen en la siguiente tabla.

Ejemplo 177: 2-({2-[(*tert*-Butoxicarbonil)amino]etil}tio)-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il) pirimidina-4-ácido carboxílico

Ejemplo 178: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil] aminol} piperidin-1-il)-2-[(2,3-dihidroxipropil)tio]pirimidina-4-ácido carboxílico

Ejemplo 179: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino} piperidin-1-il)-2-(isobutiltio)pirimidina-4-ácido carboxílico

Ejemplo 180: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)-2-(isopropiltio)pirimidina-4-ácido carboxílico

Ejemplo 181: 2-(*tert*-Butiltio)-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)pirimidina-4-ácido carboxílico

Ejemplo	Material de partida	^{1}H NMR δ	m/z
177	tert-butilo N-(2-mercaptoetil) carbamato	1.25 (m, 2H); 1.30 (s, 9H); 1.49 (m, 2H); 1.83 (m, 2H); 2.11 (s, 3H); 3.03 (m, 2H); 3.18 (m, 2H); 4.05 (m, 2H); 4.27 (m, 1H); 6.99 (s, 1H); 7.0 (t, 1H); 7.15 (d, 1H); 1.91 (s, 1H); ácido carboxílico protón no visible	571

Ejemplo	Material de partida	^{1}H NMR δ	m/z
178	3-mercapto-1,2-propanodiol	1.48 (m, 2H); 1.82 (m, 2H); 2.10 (s, 3H); 2.91 (d, 2H); 2.96 (d, 2H); 3.14 (m, 2H); 3.6 (m, 1H); 4.03 (m, 2H); 4.29 (m, 1H); 7.00 (s, 1H); 7.15 (d, 1H); 11.90 (s, 1H); ácido carboxílico protón no visible	504
179	2-metil-1-propanotiol	0.90 (d, 6H); 1.46 (m, 2H); 1.84 (m, 2H); 2.11 (s, 3H); 2.91 (d, 2H); 3.15 (m, 2H); 3.7-4.3 (multipletes superpuestos, 4H); 7.00 (s, 1H); 7.17 (d, 1H); 11.90 (s, 1H); ácido carboxílico protón no visible	484
180	2-propanotiol	1.28 (d, 6H); 1.49 (m, 2H); 1.82 (m, 2H); 2.10 (s, 3H); 3.14 (m, 2H); 3.77 (m, 1H); 4.04 (m, 2H); 4.28 (m, 1H); 6.99 (s, 1H); 7.18 (d, 1H); 11.93 (s, 1H); ácido carboxílico protón no visible	472
181	tert-butilo mercaptan	1.43 (m, 4H); 1.50 (s, 9H); 1.82 (m, 2H); 2.10 (s, 3H); 3.11 (m, 2H); 4.05 (m, 2H); 4.24 (m, 1H); 6.98 (s, 1H); 7.16 (d, 1H); 11.90 (s, 1H); ácido carboxílico protón no visible.	484

Ejemplos 182-185

Los siguientes compuestos se sintetizaron mediante un método análogo al del **Ejemplo 8** mediante el acoplamiento de los ácidos en la siguiente tabla con clorhidrato de metoxilamina.

Ejemplo 182: *tert*-Butil 2-({4-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-6-[(metoxiamino)carbonil]pirimidin-2-il}tio)etilcarbamato

Ejemplo 183: 2-(Butiltio)-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-*N*-metoxipirimidina-4-carboxamida

Ejemplo 184: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-2-(isopropiltio)-*N*-metoxipirimidina-4-carboxamida

Ejemplo 185: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonilamino}piperidin-1-il)-2-[(2-hidroxietil)tio]-*N*-metoxipirimidina-4-carboxamida

Ejemplo	Ácido	^{1}H NMR δ	m/z
182	2-({2-[(tert-butoxicarbonil) amino]etil}tio)-6-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil] amino}piperidin-1-il) pirimidina-4-ácido carboxílico (**Ejemplo 177**)	1.38 (m, 2H); 1.46 (s, 9H); 1.60 (m, 2H); 1.94 (m, 2H); 2.23 (s, 3H); 3.1 (m, 2H); 3.24 (m, 2H); 4.15 (m, 2H); 4.39 (m, 1H); 7.11 (s, 1H); 7.3 (triplete y doblete superpuesto, 2H); 11.85 (s, 1H); 12.03 (s, 1H)	600
183	2-(butiltio)-6-(4-{[(3,4-dicloro-5-meti1H-pirrol-2-il)carbonil]amino} piperidin-1-il)pirimidina-4-ácido carboxílico (**Ejemplo 176**)	0.81 (t, 3H); 1.33 (m, 2H); 1.5 (m, 2H); 1.57 (m, 2H); 1.81 (m, 2H); 2.10 (s, 3H); 3.01 (t, 2H); 3.15(m, 2H); 3.61 (s, 3H); 4.05 (m, 2H); 4.21 (m, 1H); 6.92 (s, 1H); 7.18 (d, 1H); 11.68 (s, 1H); 11.90 (s, 1H)	513

Ejemplo	Ácido	^{1}H NMR δ	m/z
184	6-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino}piperidin-1-il)-2-(isopropiltio) pirimidina-4-ácido carboxílico (**Ejemplo 180**)	1.27 (d, 6H); 1.48 (m, 2H); 1.81 (m, 2H); 2.10 (s, 3H); 3.12 (m, 2H); 3.88 (m, 1H); 4.03 (m, 2H); 4.27 (m, 1H); 6.92 (s, 1H); 7.15 (d, 1H); 11.68 (brs, 1H); 11.90 (s, 1H)	501
185	6-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino}piperidin-1-il)-2-[(2-hidroxietil)tio] pirimidina-4-ácido carboxílico (**Ejemplo 16**)	1.44 (m, 2H); 1.82 (m, 2H); 2.11 (s, 3H); 3.1-3.16 (triplete y multiplete superpuesto, 4H); 3,55 (t, 2H); 4.02 (m, 2H); 4.26 (m, 1H); 6.94 (s, 1H); 7.15 (d, 1H); 11.67 (s, 1H); 11.90 (s, 1H)	501

Ejemplos 186-189

Los siguientes compuestos se sintetizaron mediante un método análogo al del **Ejemplo 10** mediante la oxidación de los tioéteres en la tabla arriba con mCPBA.

Ejemplo 186: *tert*-Butil 2-({4-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-6-[(metoxiamino)carbonil]pirimidin-2-il}sulfonil) etilcarbamato

Ejemplo 187: 2-Butilsulfonil)-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-*N*-metoxipirimidina-4-carboxamida

Ejemplo 188: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)-2-(isopropilsulfonil)-*N*-metoxipirimidina-4-carboxamida

Ejemplo	Material de partida	^{1}H NMR δ	m/z
186	Ejemplo 182	1.11 (t, 2H); 1.30 (s, 9H); 1.53 (m, 2H); 1.88 (m, 2H); 2.11 (s, 3H); 3.22 (m, 2H); 3.71 (m, 2H); 4.08 (m, 2H); 4.58 (m, 1H); 6.97(t, 1H); 7.17 (d, 1H); 7.41 (s, 1H); 11.89 (s, 1H); 11.92 (s, 1H)	634
187	Ejemplo 183	0.81 (t, 3H); 1.37 (m, 2H); 1.55 (m, 2H); 1.86 (m, 2H); 2.11 (s, 3H); 3.2 (m, 2H); 3.6 (m, 2H); 3.66 (s, 3H); 4.08 (m, 2H); 4.55 (m, 1H); 7.17 (d, 1H); 7.39 (s, 1H); 11.91 (s, 1H); 11.97 (s, 1H)	545
188	Ejemplo 184	1.16 (d, 6H); 1.53 (m, 2H); 1.87 (m, 2H); 2.11 (s, 3H); 3.24 (m, 2H); 3.66 (s, 3H); 4.08 (m, 2H); 4.25 (m, 1H); 4.55 (m, 1H); 7.17 (d, 1H); 7.39 (s, 1H); 11.91 (s, 1H); 11.95 (s, 1H)	531
189	Ejemplo 185	1.49 (m, 2H); 1.87 (m, 2H); 2.11 (s, 3H); 3.23 (m, 2H); 3.66 (s, 3H); 3.76 (t, 2H); 4.08 (m, 2H); 4.60 (m, 1H); 7.17 (d, 1H); 7.38 (s, 1H); 11.67 (s, 1H); 11.91 (s, 1H); 11.96 (s, 1H)	535

Ejemplo 190: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)-2-(isopropiltio)pirimidina-4-carboxamida

Se combinó 6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-2-(isopropiltio)pirimidina-4-ácido carboxílico (**Ejemplo 180**; 200 mg, 0.423mmol), solución de amoniaco (2

M en MeOH, 0.43ml, 0.846 mmol), TEA (0.06ml, 0.423mmol) y HATU (161 mg, 0.42 mmol) en DMF (3 ml) y se revolvió a temperatura ambiente durante 1 h. La reacción se diluyó con EtOAc y agua y la porción orgánica se lavó secuencialmente con 1 N HCl, bicarbonato de sodio saturado y solución salina. La porción orgánica se lavó sobre sulfato de sodio, se filtró y se concentró para producir un sólido casi blanco (312 mg). El material crudo se purificó mediante HPLC de preparación empleando un gradiente de 40-70% acetonitrilo/agua (TFA al 0.1 %) durante 14 minutos para producir el compuesto del título como un sólido blanco.

MS (ES⁻): 469.06, 471.18

^{1}H NMR δ: 1.27 (d, 6H); 1.49 (m, 2H); 1.82 (m, 2H); 2.10 (s, 3H); 3.12 (m, 2H); 3.86 (m, 3H); 4.04 (m, 2H); 4.25 (m, 1H); 6.97 (s, 1H); 7.15 (d, 1H); 7.68 (s, 1H); 7.78 (s, 1H); 11.90 (s, 1H).

Ejemplo 191: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)-*N*-metoxi-2-pirrolidin-1-ilpirimidina-4-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 8** comenzando a partir de 6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)-2-pirrolidin-1-ilpirimidina-4-ácido carboxílico (**Ejemplo 335**) y clorhidrato de metoxilamina.

MS (ES⁻): 494.67, 496.66

^{1}H NMR δ: 1.49 (m, 2H); 1.85 (m, 6H); 2.11 (s, 3H); 3.17 (m, 2H); 3.67 (s, 3H); 3.7 (m, 4H); 4.04 (m, 2H); 4.28 (m, 1H); 6.67 (s, 1H); 7.17 (d, 1H); 11.86 (s, 1H); 11.91 (s, 1H)

Ejemplo 192: 3,4-Dicloro-*N*-{1-[2-cloro-6-(hidrazinacarbonil) pirimidin-4-il]piperidin-4-il}-5-metil-1*H*-pirrol-2-carboxamida

Se combinó metil 2-cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil} piperidin-1il)pirimidina-4-carboxilato (**Ejemplo 6**) (500 mg, 1.12 mmol), hidrazina (0.035ml, 1.12 mmol) y TEA (0.16ml, 1.12 mmol) en DMF (3 ml) y se revolvió a temperatura ambiente. En 1.5 h, se había

formado un precipitado blanco. La reacción se revolvió durante otros 30 minutos y luego el producto precipitado se recolectó mediante filtración por succión para producir 377 mg del compuesto del título. Se purificaron 100 mg del material crudo mediante HPLC de preparación, empleando un gradiente de 40-70% acetonitrilo/agua (TFA al 0.1 %) durante 14 minutos para producir 23 mg del compuesto del título.

MS (ES⁻): 446.21, 448.20

^{1}H NMR δ: 1.47 (m, 2H); 1.84 (m, 2H); 2.11 (s, 3H); 3.1 (m, 2H); 4.06 (m, 2H); 4.35 (m, 2H); 4.77 (m, 1H); 7.16 (d, 1H); 7.18 (s, 1H); 9.85 (m, 1H); 11.91 (s, 1H)

Ejemplo 193: *N*-Alil-2-cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2il)carbonil]amino}piperidin-1-il)pirimidina-4-carboxamida

Se trató metil 2-cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)pirimidina-4-carboxilato (**Ejemplo 6**) (100 mg, 0.224 mmol) en THF anhidro (3 ml) con alilamina (0.025 ml, 0.336mmol), sodio *tert*-butóxido (32.29 mg, 0. 336 mmol), $Pd(Dppf)_2Cl_2$- DCM complejo (9.14 mg, 0.0112 mmol) y Dppf (18.61 mg, 0.0336 mmol). La reacción se calentó a 80 °C durante 2 h. La mezcla de la reacción se filtró mediante célite y el producto filtrado se concentró para producir un sólido de color óxido. El material crudo se purificó mediante HPLC de preparación, empleando un gradiente de 35-75% acetonitrilo/agua (TFA al 0.1 %) para producir 12 mg de un sólido marrón pálido.

MS (ES⁻): 471. 47

^{1}H NMR δ: 1.47 (m, 2H); 1.84 (m, 2H); 2.11 (s, 3H); 3.18 (m, 2H); 3.79 (t, 2H); 4.02 (m, 2H); 4.3 (m, 1H); 5.02 (t, 2H); 5.8 (m, 1H); 7.16 (d, 1H); 7.24 (s, 1H); 8.7 (t, 1H); 11.91 (s, 1H)

Ejemplo 194: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il) carbonil] amino}piperidin-1-il)-2-piperazin-1-ilpirimidina-4-ácido carboxílico

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 310** comenzando a partir de metil 6-(4-{[(3,4-dicloro-5-metil-1*H*-

pirrol-2-il)carbonil]amino}piperidin-1-il)-2-piperazin-1-ilpirimidina-4-carboxilato (**Ejemplo 317**) y 2 N hidróxido de litio.

MS (ES⁻): 480.29, 482.28

^{1}H NMR δ: 1.41 (m, 2H); 1.81 (m, 2H); 2.11 (s, 3H); 3.08 (m, 4H); 3.75 (m, 4H); 4.01 (m, 2H); 4.23 (m, 2H); 4.48 (m, 1H); 6.68 (s, 1H); 7.14 (d, 1H); 8.71 (m, 1H); 11.92 (s, 1H); ácido carboxílico protón no visible

Ejemplo 195: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il) carbonil] amino}piperidin-1-il)-*N*-metoxi-2-piperazin-1-ilpirimidina-4-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 8** comenzando a partir de 6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)-2-piperazin-1-ilpirimidina-4-ácido carboxílico (**Ejemplo 194**) y clorhidrato de metoxilamina.

MS (ES⁻): 509.70, 511.67

^{1}H NMR δ: 1.41 (m, 2H); 1.81 (m, 2H); 2.11 (s, 3H); 3.06 (m, 4H); 3.63 (s, 3H); 3.75-4.0 (multipletes superpuestos, 6H); 4.23 (m, 2H); 4.55 (m, 1H); 6.62 (s, 1H); 7.15 (d, 1H); 8.75 (m, 1H); 11.69 (s, 1H); 11.93 (s, 1H)

Ejemplo 196: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il) carbonil] amino}piperidin-1-il)-2-(4-metilpiperazin-1-il)pirimidina-4-ácido carboxílico

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 310** comenzando a partir de metil 6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-2-(4-metilpiperazin-1-il)pirimidina-4-carboxilato (**Ejemplo 318**) y 2 N hidróxido de litio.

MS (ES⁻):: 494.31, 496.3

^{1}H NMR δ: 1.44 (m, 2H); 1: 83 (m, 2H); 2.11 (s, 3H); ~2.4 (s, 3H); 3.17 (m, 4H); 3.6-4.1 (multipletes superpuestos, 8H); 4.38 (m, 1H); 7.15 (d, 1H); 7.27 (s, 1H); 11.91 (s, 1H)

Ejemplo 197: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il) carbonil] amino}piperidin-1-il)-*N*-metoxi-2-(4-metilpiperazin-1-il)pirimidina-4-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 8** comenzando a partir de 6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino} piperidin-1-il)-2-(4-metilpiperazin-1-il)pirimidina-4-ácido carboxílico (**Ejemplo 196**) y clorhidrato de metoxilamina.

MS (ES$^-$): 523.72, 525.65

^{1}H NMR δ: 1.44 (m, 2H); 1.81 (m, 2H); 2.11 (s, 3H); 2.76 (s, 3H); 2.94 (m, 2H); 3.06 (m, 2H); 3.39(m, 2H); 3.63 (s, 3H); 3.9 (m, 2H); 4.23 (m, 2H); 4.55 (m, 1H); 4.77 (m, 2H); 6.64 (s, 1H); 7.13 (d, 1H); 7.27 (s, 1H); 11.71 (s, 1H); 11.92 (s, 1H)

Ejemplo 198: 2-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)-6-(etilsulfonil)-*N*-metoxipirimidina-4-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 10** comenzando a partir de 2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil] amino}piperidin-1-il)-6-(etiltio)-*N*-metoxipirimidina-4-carboxamida (**Ejemplo 203**) y mCPBA.

MS (ES$^-$): 517.62, 519.61

^{1}H NMR δ: 1.13 (t, 3H); 1.44 (m, 2H); 1.85 (m, 2H); 2.11 (s, 3H); 3.14 (m, 2H); 3.41 (q, 2H); 3.67 (s, 3H); 4.05 (m, 2H); 4.77 (m, 1H); 7.15 (d,lH); 7.34 (s, 1H); 11.92 (s, 1H); 12.16 (s, 1H)

Ejemplo 199: 3,4-Dicloro-*N*-[1-(2-cloro-6-cianopirimidin-4-il) piperidin-4-il]-5-metil-1*H*-pirrol-2-carboxamida

Se preparó una solución matriz de trimetilsililo polifosfato (preparada de acuerdo con Yokoyama, Masataka; Yoshida, Sayaka; Imamoto, Tsuneo. *Synthesis*, **1982**, 7, 591-592) combinando P_2O_5 (10 g) y hexametildisiloxano (25ml) en tolueno anhidro (50ml) y calentando la mezcla a 80 °C hasta que se convirtió en una solución transparente (alrededor de 45 minutos). Se

trató 2-cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino} piperidin-1-il) pirimidina-4-carboxamida (**Ejemplo 37**, 2.1 g, 4.8 mmol) con trimetilsililo polifosfato (80ml) y la reacción se calentó a 80 °C durante 5 h, después de lo cual la reacción se había completado más o menos en un 50%. No había evidencia de una reacción posterior después de agregar más trimetilsililo polifosfato y se permitió que la reacción se revolviera durante otros 2.5 días más. Una vez se enfrió a temperatura ambiente, la reacción se concentró bajo presión reducida hasta que se extrajo la mayor parte del solvente. El líquido restante se trituró con EtOAc y agua para formar un precipitado marrón, el cual era en gran parte el precursor de la amina. La mezcla se filtró y el producto filtrado se concentró bajo presión reducida para producir el compuesto del título como un sólido amarillo. Se purificó alrededor de 20 mg mediante HPLC de preparación, empleando un gradiente de 35-75% acetonitrilo/agua (TFA al 0.1 %), mientras que el resto se continuó sin una purificación posterior.

MS (ES^-): 436.17, 438.16

^{1}H NMR δ: 1.51 (m, 2H); 1.9 (m, 2H); 2.12 (s, 3H); 3.28 (m, 2H); 4.06 (m, 2H); 4.43 (m, 1H); 7.16 (d, 1H); 7.64 (s, 1H); 11.93 (s, 1H)

Ejemplo 200: *N*-(1{6[(Z)-Amino(hidroxiimino)metil]-2-cloropirimidin-4-il}piperidin-4-il)-3,4-dicloro-5-metil-1*H*-pirrol-2-carboxamida

Se combinó 3,4-dicloro-*N*-[1-(2-cloro-6-cianopirimidin-4-il)piperidin-4-il]-5-metil-1*H*-pirrol-2-carboxamida (**Ejemplo 199**, 150 mg, 0.36mmol), clorhidrato de hidroxilamina (25 mg, 0.36 mmol) y TEA (0.05ml, 0.36 mmol) en MeOH (5 ml) y la reacción se calentó a 80 °C durante 2 h. La reacción se diluyó con EtOAc y se lavó con agua. La porción acuosa se extrajo con EtOAc y las porciones orgánicas combinadas se secaron (sulfato de sodio), se filtraron y se concentraron para producir un sólido amarillo pálido. El material crudo se purificó mediante HPLC de preparación, empleando un gradiente de 35-75% acetonitrilo/agua (TFA al 0.1 %) para producir 53 mg del compuesto del título.

MS (ES^+): 446.06, 448.05

^{1}H NMR δ: 1.50 (m, 2H); 1.84 (m, 2H); 2. 11 (s, 3H); 3. 16 (m, 2H); 4.06 (m, 2H); 4.21 (m, 1H); 7.08 (s, 1H); 7.16 (d, 1H); 10.36 (brs, 1H); 11.91 (s, 1H)

Ejemplo 201: Metil 2-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)-6-(etiltio)pirimidina-4-carboxilato

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 9** mediante el acoplamiento de metil 2-cloro-6-(etiltio)pirimidina-4-carboxilato (**Intermedio 96**) con 3,4-dicloro-5-metil-*N*-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 1**).

MS (ESP): 472.56 (M+H) para $C_{19}H_{23}Cl_2N_5O_3S$

^{1}H NMR δ: 1.31 (t, 3H); 1.52 (m, 2H); 1.90 (d, 2H); 2.17 (s, 3H); 3.05-3.25 (m, 4H); 3.83 (s, 3H); 4.10 (m, 1H); 4.57 (d, 2H); 6.95 (s, 1H); 7.25 (d, 1H); 12.0 (s, 1H).

Ejemplo 202: 2-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il) carbonil] amino}piperidin-1-il)-6-(etiltio)pirimidina-4-ácido carboxílico

El compuesto del título se sintetizó a partir de metil 2-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-6-(etiltio) pirimidina-4-carboxilato (**Ejemplo 201**) mediante un método análogo al del **Ejemplo 31**.

MS (ESP): 458.2 (M+H) para $C_{18}H_{21}Cl_2N_5O_3S$

^{1}H NMR δ 1.25 (t, 3H); 1.50 (m, 2H); 1.85 (d, 2H); 2.11 (s, 3H); 3.03-3.20 (m, 4H); 4.05 (m, 1H); 4.20 (br s, 1H); 4.54 (d, 2H); 6.86 (s, 1H); 7.14 (d, 1H); 11.90 (s, 1H).

Ejemplo 203: 2-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)-6-(etiltio)-*N*-metoxipirimidina-4-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 8** comenzando a partir de 2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil] amino}piperidin-1-il)-6-(etiltio)pirimidina-4-ácido carboxílico (**Ejemplo 202**) y clorhidrato de metoxilamina.

MS (ESP): 487.5 (M+H) para $C_{19}H_{24}Cl_2N_6O_3S$

^{1}H NMR δ: 1.24 (t, 3H); 1.46 (m, 2H); 1.82 (d, 2H); 2.11 (s, 3H); 3.02-3.11 (m, 4H); 3.62 (s, 3H); 4.05 (m, 1H); 4.60 (d, 2H); 6.83 (s, 1H); 7.14 (d, 1H); 11.83 (s, 1H); 11.90 (s, 1H).

Ejemplo 204: 2-Cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-*N*-(metilsulfonil)pirimidina-4-carboxamida

Se agregó una solución de metanosulfonamida (40 mg, 0.44 mmol) y DMF (0.5ml) a una suspensión de hidruro de sodio (95%) (11 mg, 0.44 mmol) y DMF (0.5ml) bajo nitrógeno.

La mezcla se revolvió durante 20 minutos a temperatura ambiente. Se agregó una solución de metil 2-cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)pirimidina-4carboxilato (**Ejemplo 6**, 47 mg, 0.11 mmol) en DMF (1 ml) en forma de goteo a la mezcla durante 5 minutos. La mezcla se revolvió durante 1 h a temperatura ambiente y durante 3 h a 60 °C. La mezcla se enfrió a temperatura ambiente y se concentró bajo presión reducida.

El residuo crudo se purificó mediante HPLC de preparación de fase inversa (agua/acetonitrilo, gradiente 10-90%) para obtener el compuesto del título (14 mg).

MS (ESP): 507.3 (M-H) para $C_{17}H_{19}Cl_3N_6O_4S$

^{1}H NMR δ: 1.49 (m, 2H); 1.86 (d, 2H); 2.11 (s, 3H); 3.20 (m, 2H); 3.29 (s, 3H); 4.05 (m, 2H); 4.45 (m, 1H); 4.60-4.80 (br s, 1H); 7.17 (d, 1H); 7.30 (s, 1H); 11.91 (s, 1H).

Ejemplo 205: 2-Butil-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)pirimidina-4-ácido carboxílico

Se trató (6-{4-[(*tert*-Butoxicarbonil)amino]piperidin-1-il}-2-butilpirimidina-4-ácido carboxílico) (**Intermedio 100**) con 4 N HCl/dioxano como se describió para el **Intermedio 70**.

La sal de clorhidrato resultante, 6-(4-aminopiperidin-1-il)-2-butilpirimidina-4-ácido carboxílico sal de clorhidrato se acopló con 3,4-dicloro-5-metil-1*H*-

pirrol-2-ácido carboxílico (**Intermedio 3**) en una forma análoga a la del **Ejemplo 29** para producir el compuesto del título.

MS (ES) (M+H): 454 para $C_{20}H_{25}Cl_2N_5O_3$

^{1}H NMR δ: 0.95 (t, 3H); 1.36 (m, 2H); 1.56 (m, 2H); 1.71 (m, 2H); 1.96 (m, 2H); 2.15 (s, 3H); 2.80 (m, 2H); 3.36 (b, 2H); 4.18 (m, 1H); 4.52 (m, 2H); 7.15 (s, 1H); 7.29 (d, 1H); 12.01 (s, 1H)

Ejemplos 206-208

Los siguientes compuestos se sintetizaron mediante un método análogo al del **Ejemplo 29** a partir de 3,4-dicloro-5-metil-1*H*-pirrol-2-ácido carboxílico (**Intermedio 3**) y los materiales de partida indicados.

Ejemplo 206: 2-Ciclopropil-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)pirimidina-4-ácido carboxílico

Ejemplo 207: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil]aminopiperidin-1-il)-2-isopropilpirimidina-4-ácido carboxílico

Ejemplo 208: 2-*tert*-Butil-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)pirimidina-4-ácido carboxílico

Ejemplo	Material de partida	^{1}H NMR δ	m/z
206	6-(4-aminopiperidin-1-il)-2 ciclopropilo pirimidina-4-ácido carboxílico clorhidrato (**Intermedio 172**)	1.22 (m, 4H); 1.65 (m, 2H); 2.00 (m, 2H); 2.71 (s, 3H); 3.36 (m, 4H); 3.93 (m, 2H); 4.12 (m, 1H); 7.25 (d, 1H); 7.35 (s, 1H); 11.97 (s, 1H)	438
207	6-(4-aminopiperidin-1-il)-2-isopropilo pirimidina-4-ácido carboxílico clorhidrato (**Intermedio 173**)	1.29 (d, 6H); 1.68 (m, 2H); 2.02 (m, 2H); 2.22 (s, 3H); 3.31 (m, 1H); 3.54 (m, 2H); 4.26 (m, 2H); 4.21 (m, 1H); 7.27 (d, 1H); 7.43 (s, 1H); 12.12 (s, 1H)	440

Ejemplo	Material de partida	^{1}H NMR δ	m/z
208	6-(4-aminopiperidin-1-il)-2-tert-butilo pirimidina-4-ácido carboxílico clorhidrato (**Intermedio 174**)	1.29 (s, 9H); 1.58 (m, 2H); 1.93 (m, 2H); 2.11 (s,3H); 3.32 (m, 2H); 4.17 (m, 2H); 4.21 (m, 1H); 7.06 (s, 1H); 7.18 (d, 1H); 12.02 (s, 1H)	454

Ejemplo 209-217

Los siguientes compuestos se prepararon mediante un método análogo a N-{1- [6-amino-2-(metilsulfanil)-4-pirimidinil]-4-piperidinil}-3,4-dicloro-5-metil-1H-pirrol-2-carboxamida (**Ejemplo 118**) comenzando a partir de 3,4-dicloro-5-metil-1*H*-pirrol-2-ácido carboxílico (**Intermedio 3**) y los intermedios que se muestran en la siguiente tabla.

Ejemplo 209: Metil 5-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)tiofeno-2-carboxilato

Ejemplo 210: Metil 5-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-2-furoato

Ejemplo 211: Metil 3-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)benzoato

Ejemplo 212: Metil 3-bromo-5-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)benzoato

Ejemplo 213: Etil 5-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)nicotinato

Ejemplo 214: Metil 5-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)nicotinato

Ejemplo 215: Metil 6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)piridina-2-carboxilato

Ejemplo 216: Metil 3-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-5-morfolin-4-ilbenzoato

Ejemplo 217: Metil 3-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)benzoato

Ejemplo	Material de partida	^{1}H NMR δ	m/z
209	Intermedio 110	1.65-1.78 (m, 2H); 1.91-1.95 (m, 2H); 2.20 (s, 3H); 3.11-3.19 (m, 2H); 3.62-3.67 (m, 2H); 3.74 (s, 3H); 4.01 (m, 1H); 6.24 (d, 1H); 7.30(d, 1H); 7.54 (d, 1H); 11.98 (s, 1H).	416
210	Intermedio 111	1.56-1.67 (m, 2H); 1.87-1.96 (m, 2H); 2.18 (s, 3H); 3.04 (t, 2H); 3.67-3.71 (m, 5H); 3.98 (m, 1H); 5.5 (d, 1H); 7.25-7.29 (m, 2H); 11.96 s, 1H).	400
211	Intermedio 112	1.61-1.71 (m, 2H); 1.90-1.94 (m, 2H); 2.18 (s, 3H); 2.94 (t, 2H); 3.70-3.75 (m, 2H); 3.84 (s, 3H); 3.96 (m, 1H); 7.23-7.70 (m, 5H); 11.96 (s, 1H).	410
212	Intermedio 113	1.57-1.68 (m, 2H); 1.87-1.91 (m, 2H); 2.18 (s, 3H); 2.99 (t, 2H); 3.76-3.80 (m, 2H); 3.85 (s, 3H); 3.98 (m, 1H); 7.25 (d, 1H); 7.38-7.43 (m, 3H); 11.96 (s, 1H).	489
213	Intermedio 114	1.33 (t, 3H); 1.57-1.73 (m, 2H); 2.08-2.12 (m, 2H); 2.20 (s, 3H); 2.94-3.03 (m, 2H); 3.62-3.66 (m, 2H); 4.09 (m, 1H); 4.32 (q, 2H); 6.52 (d, 1H); 7.70 (s, 1H); 8.39 (s, 1H); 8.60 (s, 1H); 9.26 (s, 1H).	425
214	Intermedio 115	1.59-1.72 (m, 2H); 1.90-1.93 (m, 2H); 2.18 (s, 3H); 3.00 (t, 2H); 3.80-3.85 (m, 2H); 3.87 (s, 3H); 3.99 (m, 1H); 7.25 (d, 1H); 7.70 (s, 1H); 8.46 (S, 1H); 8.57 (s, 1H); 11.96 (s, 1H).	411

Ejemplo	Material de partida	^{1}H NMR δ	m/z
215	Intermedio 116	1.48-1.59 (m, 2H); 1.87-1.90 (m, 2H); 2.17 (s, 3H); 3.05 (t, 2H); 3.83 (s, 3H); 4.05 (m, 1H); 4.27-4.32 (m, 2H); 7.12 (d, 1H); 7.22 (d, 1H); 7.28 (d, 1H); 7.68 (t, 1H); 12.09 (s, 1H).	411
216	Intermedio 117	1.63 (m, 2H); 1.88 (d, 2H); 2.16 (s, 3H); 2.88 (t, 2H); 3.04-3.19 (m, 4H); 3.62-3.76 (m, 6H); 3.80 (s, 3H); 3.86-3.99 (m, 1H); 6.74 (s, 1H); 6.91 (s, 1H); 6.98 (s, 1H); 7.22 (d, 1H); 11.94 (s, 1H).	495
217	Intermedio 118	1.53-1.73 (q, 2H); 1.89 (d, 2H); 2.17 (s, 3H); 2.30-2.47 (m, 2H); 2.57-2.80 (m, 4H); 2.88 (t, 3H); 3.04-3.25 (m, 4H); 3.69 (d, 2H); 3.80 (s, 3H); 3.85-4.03 (m, 1H); 6.74 (s, 1H); 6.92 (s, 1H); 6.97 (s, 1H); 7.22 (d, 1H); 11.94 (s, 1H).	508

Ejemplo 218: Etil 2-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)-4-metil-1,3-tiazol-5-carboxilato

Se revolvió 3,4-dicloro-5-metil-*N*-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 1**; 0.500 g, 2.00 mmol), etil 2-bromo-4-metil-1,3-tiazol-5-carboxilato (0.625 g, 2.00 mmol) y bicarbonato de sodio (0.336 g, 2.00 mmol) en DMF (5 ml). La reacción se calentó a 50 °C durante la noche. La solución se diluyó mediante la adición de agua y las capas resultantes se separaron. La capa acuosa se extrajo con EtOAc (3x) y la capa orgánica se combinó, se lavó sobre sulfato de magnesio anhidro, se filtró y se concentró. Se agregó hexano al material crudo y el producto precipitado se filtró y se enjuagó con EtOAc para producir el compuesto del título como un sólido beige (0.273 g).

MS (ESP): 445(MH^+) para $C_{18}H_{22}Cl_2N_4O_3$

^{1}H NMR ($CDCl_3$) δ: 1.32 (t, 3H); 1.62-1.72 (m, 2H); 2.12 (dd, 2H); 2.27 (s, 3H); 2.55 (s, 3H); 3.27 (dt, 2H); 4. 11 (d, 2H); 4.13-4.33 (m, 3H); 6.57 (d,H); 9.41 (brs, 1H).

Ejemplos 219 y 220

El siguiente ejemplo se preparó por medio del procedimiento general del **Ejemplo 218** utilizando 3,4-dicloro-5-metil-*N*-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 1**) y el respectivo hálido.

Ejemplo 219: Etil 5-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)-1,3,4-tiadiazol-2-carboxilato

Ejemplo 220: 3,4-Dicloro-*N*-{1-[5-(etiltio)-1,3,4-tiadiazol-2-il]piperidin-4-il}-5-metil-1*H*-pirrol-carboxamida

Ejemplo	Hálido	^{1}H NMR δ	m/z
219	etil 5-cloro-1,3,4-tiadiazol-2-carboxilato	1.29 (t, 3H); 1.73 (m, 2H); 1,93 (d, 2H); 2.16 (s, 3H); 3.31-3.45 (escondido por un pico de H_2O, 2H); 3.99 (d, 2H); 4.00-4.16 (m, 1H); 4.34 (q, 2H); 7.28 (d, 1H); 11.95 (brs, 1H).	418'
220	2-bromo-5-(etiltio)-1,3,4-tiadiazol (**Intermedio 67**)	1.29 (t, 3H); 1.66 (m, 2H); 1.88 (d, 2H); 2.16 (s, 3H); 3.09-3.28 (superpuesto con pico de H_2O 2H); 3.77 (d, 2H); 3.91-4.14 (m, 1H); 7.27 (d, 1H); 11.93 (brs, 1H).	420

Ejemplos 221 y 222:

Derivados de sulfóxido y sulfona de 3,4-Dicloro-*N*-{1-[5-(etiltio)-1,3,4-tiadiazol-2-il]piperidin-4-il-5-metil-1*H*-pirrol-2-carboxamida

Se revolvió 3,4-dicloro-*N*-{1-[5-(etiltio)-1,3,4-tiadiazol-2-il]piperidin-4-il}-5-metil-1*H*-pirrol- 2-carboxamida (**Ejemplo 220**; 2.873 g, 6.80 mmol) en DCM (42 ml) y se enfrió a -15 °C. Se agregó mCPBA (2.51 g, 10.2 mmol) y la mezcla de la reacción se revolvió a -15 °C durante una hora, luego se

calentó a temperatura ambiente. La mezcla amarilla se lavó con tiosulfato de sodio al 5% (3x), bicarbonato de sodio al 50 % (1x) y solución salina (1x), se lavó sobre sulfato de magnesio anhidro, se filtró y se concentró para producir una mezcla de productos. Luego el sólido amarillo se purificó mediante HPLC de semi preparación (acetonitrilo/agua solución amortiguadora (20:80 → 95:5) para producir pico 1 como el sulfóxido (0.040 g) y pico 2 como la sulfona (0.025 g).

Ejemplo 221: 3,4-Dicloro-*N*-{1-[5-(etilsulfinil)-1,3,4-tiadiazol-2-il]piperidin-4-il}-5-metil-1*H*-pirrol-2-carboxamida

MS (ESP): 436 (MH^+) para $C_{15}H_{19}Cl_2N_5O_2S_2$

^{1}H NMR δ: 1.17 (t, 3H); 1.69 (m, 2H); 1.92 (dd, 2H); 2.17 (s, 3H); 3.07-3.25 (m, 2H); 3.36-3.54 (m, 2H); 3.82-3.98 (m, 2H); 3.98-4.14 (m, 1H); 7.28 (d, 1H); 11.96 (s, 1H).

Ejemplo 222: 3,4-Dicloro-*N*-{1-[5-(etilsulfonil)-1,3,4-tiadiazol-2-il]piperidin-4-il-5-metil-1*H*-pirrol-2-carboxamida

MS (ESP): 452 (MH^+) para $C_{15}H_{19}Cl_2N_5O_3S_2$

^{1}H NMR δ: 1.23 (t, 3H); 1.70 (m, 2H); 1.93 (dd, 2H); 2.17 (s, 3H); 3.44 (t, 2H); 3.55 (q, 2H); 3.93 (d, 2H); 4.01-4.19 (brs, 1H); 7.28 (d, 1H); 11.97 (s, 1H).

Ejemplo 223: 5-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-1,3,4-tiadiazol-2-ácido carboxílico

Se revolvió etil 5-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino} piperidin-1-il)-1,3,4- tiadiazol-2-carboxilato (**Ejemplo 219**; 0.530 g, 1.2 mmol) e hidróxido de litio (0.117 g, 4.9 mmol) en dioxano (5 ml) y agua (0.5ml) y se calentó a 50 °C durante treinta minutos. La solución se acidificó (pH 4) utilizando 1 N HCl resultando en un producto precipitado. Los sólidos se recolectaron y se purificaron utilizando HPLC de semi preparación para producir el compuesto del título (0.025 g).

MS (ESP): 404 (MH^+) para $C_{14}H_{15}Cl_2N_5O_3S$

^{1}H NMR δ: 1.62 (d, 2H); 1.86 (d, 2H): 2.16 (s, 3H); 3.11-3.27 (m, 2H); 3.78 (d, 2H); 3.93-4.08 (m, 1H); 7.55 (d, 1H).

Ejemplo 224: 3,4-Dicloro-5-metil-*N*-[1-(1,3,4-tiadiazol-2-il) piperidin-4-il]-1*H*-pirrol-2-carboxamida

Se revolvió 5-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-1,3,4- tiadiazol-2-ácido carboxílico (**Ejemplo 223**; 0.250 g, 0.60 mmol) en 10 mM acetato de amonio (pH 8) (15ml) y acetonitrilo (15ml) durante la noche. La mezcla se concentró, luego el residuo se revolvió en acetonitrilo y se filtró. El sólido se disolvió en DMSO y se purificó utilizando HPLC de semi preparación (acetato de amonio: agua/ acetonitrilo al 10% (20:80-95:5)) para producir el compuesto del título como un sólido blanco (0.092 g).

MS (ESP): 360 (MH^+) para $C_{13}H_{15}Cl_2N_5OS$

^{1}H NMR δ: 1.56-1.71 (m, 2H); 1.87 (d, 1H); 2.14 (s, 3H); 3.11-3.51 (superpuesto con H_2O pico, 2H); 3.84 (d, 2H); 3.89-4.09 (m, 1H); 7.97 (brs, 1H); 8.79 (s, 1H).

Ejemplo 225: 4-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino} piperidin- 1-il)quinolina-2-ácido carboxílico

Se suspendió *tert*-butil4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino} piperidina-1-carboxilato (**Intermedio 2**) (280 mg, 0.74 mmol) en 5 ml de 4.0 M HCl en dioxano y se revolvió durante 2 h, luego se evaporó al vacío para producir un sólido marrón, el cual se disolvió en 20 ml de DMF. Se agregó 4-bromoquinolina-2-ácido carboxílico (188 mg, 0.74 mmol) (preparado mediante el procedimiento de Y Kato, y colaboradores, Tetrahedron Lett 2001, 42:4849-51) y bicarbonato de sodio (554 mg, 6.6 mmol) y la solución resultante se calentó bajo una atmósfera de nitrógeno y se agitó durante 20 h. Una vez se enfrió a temperatura ambiente, la reacción se diluyó con 25 ml de agua, el pH se ajustó a 4 utilizando HCl concentrado, se filtró y el producto filtrado se extrajo con cloroformo (2 x 25ml). El extracto orgánico combinado se lavó sobre

sulfato de sodio y se concentró al vacío hasta obtener un sólido amarillo, el cual se suspendió en 10 ml de MeOH y se recolectó mediante filtración por succión, para obtener el compuesto del título como un sólido amarillo (64 mg).

m.p. 254-256 °C.

MS (ES): 448.10/450.10 (MH^+) para $C_{21}H_{20}Cl_2N_4O_3$

^{1}H NMR δ: 1.73 (m, 2H); 1.85 (m, 2H); 2.30 (s, 3H); 3.03 (m, 2H); 3.0-3.5 (br m, 1H); 3.55 (m, 2H); 3.94 (m, 1H); 7.13 (m, 1H); 7.35 (s, 1H); 7.47 (m, 1H); 7.85 (m, 1H); 7.97 (m, 1H); 11.82 (s, 1H).

Ejemplo 226: 3-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)isoxazol-5-ácido carboxílico

El compuesto del título se preparó mediante el procedimiento descrito en el **Ejemplo 1** a partir de 182 mg (0.5 mmol) de 3,4-dicloro-5-metil-*N*-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 1**) y 103 mg (0.54 mmol) de 3-bromoisoxazol-5-ácido carboxílico (**Intermedio 120**), para obtener el compuesto del título como un sólido blanco, (65 mg).

m.p. 232-234°C (EtOAc).

MS(ES) 343.19/345.24 (M-CO_2) MW 387.23 para $C_{15}H_{16}Cl_2N_4O_4$

^{1}H NMR δ: 1.52 (m, 2H); 1.88 (m, 2H); 2.22 (s,3H); 2.91 (m, 1H); 3.20 (m, 2H); 3.68 (m, 1H); 4.06 (m, 1H); 4.11 (d, 1H, J = 6.0 Hz); 4.26 (m, 1H); 7.29 (d, I H, J = 6.0 Hz); 12.03 (s, 1H).

Ejemplo 227: 2-(4- [(3,4-Dicloro-5-metil-1*H*-pirrol-2-il) carbonilamino} piperidin- 1-il)-1,3-tiazol-5-ácido carboxílico

Se disolvió metil 2-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino} piperidin-1-il)-1,3-tiazol-5-carboxilato (**Ejemplo 320**, 250 mg, 0.60 mmol) en THF (3 ml). Se agregó 2 N hidróxido de litio solución en agua (3 ml, 6.00 mmol) y la mezcla se llevó a reflujo durante 1 hr. La mezcla se enfrió a temperatura ambiente y se acidificó con una solución de HCl al 10%. La mezcla se extrajo con EtOAc y la capa orgánica se lavó con agua dos veces, se lavó sobre sulfato de sodio y se

concentró para producir el producto deseado. El material crudo se disolvió en DMF y se purificó mediante HPLC de semi preparación de fase invertida levigado con acetonitrilo/agua (TFA al 0.1 %). Se recolectaron las fracciones deseadas y se concentraron produciendo el compuesto del título (28 mg).

MS (ES): 403 (MH^+) para $C_{15}H_{16}Cl_2N_4O_3S$

^{1}H NMR δ: 1.73 (m, 2H); 1.99 (m, 2H); 2.22 (s, 3H); 3.36 (m, 2H); 3.57 (m, 2H); 4.14 (m, 1H); 7.27 (d, 1H); 7.77 (s, 1H); 11.97 (s, 1H); 12.64 (s, 1H).

Ejemplo 228: 2-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-1,3-tiazol-4-ácido carboxílico

El compuesto del título se preparó en forma análoga al **Ejemplo 227** a partir de etil 2-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino} piperidin-1-il)-1,3-tiazol-4-carboxilato (**Ejemplo 336**).

MS (ES): 403 (MH^+) para $C_{15}H_{16}Cl_2N_4O_3S$

^{1}H NMR δ: 1.44 (m, 2H); 1.66 (m, 2H); 1.95 (s, 3H); 2.93 (m, 2H); 3.62 (m, 2H); 3.80 (m, 1H); 7.04 (d, 1H); 7.40 (s, 1H); 11.74 (s, 1H).

Ejemplo 229: 2-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-*N*-metoxi-1,3-tiazol-5-carboxamida

Se hizo reaccionar 2-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino} piperidin-1-il)-1,3-tiazol-5-ácido carboxílico (**Ejemplo 227**, 100 mg, 0.25 mmol) con clorhidrato de metoxilamina de acuerdo con el procedimiento descrito en el **Ejemplo 8** para obtener el compuesto del título (30 mg).

MS (ES): 432 (MH^+) para $C_{16}H_{19}Cl_2N_5O_3S$

^{1}H NMR δ: 1.54 (m, 2H); 1.78 (m, 2H); 2.07 (s, 3H); 3.24 (m, 2H); 3.57 (brs, 4H); 3.86 (m, 2H); 4.02 (m, 1H); 7.16 (d, 1H); 7.62 (s, 1H); 11.47 (s, 1H); 11.86 (s, 1H).

Ejemplo 230: 2-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)-*N*-metoxi-1,3-tiazol-4-carboxamida

Se preparó en una forma análoga al **Ejemplo 229** comenzando a partir de 2-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-1,3-tiazol-4-ácido carboxílico (**Ejemplo 228**).

MS (ES): 432 (MH^+) para $C_{16}H_{19}Cl_2N_5O_3S$

^{1}H NMR δ: 1.54 (m, 2H); 1.76 (m, 2H); 2.05 (s, 3H); 3.04 (m, 2H); 3.54 (s, 3H); 3.79 (m, 2H); 3.93 (m, 1H); 7.15 (d, 1H); 7.32 (s, 1H); 11.24 (s, 1H); 11.84 (s, 1H).

Ejemplo 231: 3,4-Dicloro-*N*-[5-(hidrazinacarbonil)-1,3-tiazol-2-il]piperidin-4-il}-5-metil-1*H*-pirrol-2-carboxamida

Se disolvió 2-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino} piperidin-1-il)-1,3-tiazol-5-ácido carboxílico (**Ejemplo 227**, 100 mg, 0.240 mmol) en DMF (1 ml) e hidrazina (500 µL, 16.0 mmol). La mezcla se revolvió a temperatura ambiente durante 2 h. La mezcla se filtró y se purificó mediante HPLC de semi preparación de fase invertida levigado con acetonitrilo/agua (TFA al 0.1 %)(36 mg).

MS (ES): 417 (MH^+) para $C_{15}H_{18}Cl_2N_6O_2S$

^{1}H NMR δ: 1.62 (m, 2H); 1.89 (m, 2H); 2.17 (s, 3H); 3.29 (m, 2H); 3.47 (m, 2H); 3.89 (m, 2H); 4.04 (m, 1H); 7.26 (d, 1H); 7.80 (s, 1H); 9.92 (brs, 1H); 11.97 (s, 1H)

Ejemplo 232: 2-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)-*N*-(metilsulfonil)-1,3-tiazol-5-carboxamida

Se suspendió 2-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-1,3-tiazol-5-ácido carboxílico (**Ejemplo 227**; 0.160 g, 0.397 mmol) en tolueno (3ml) y se agregó cloruro de tionilo (0.288 ml, 3.97 mmol) en forma de goteo a temperatura ambiente. La solución se llevó a reflujo durante 1 h. El excedente de cloruro de tionilo y de tolueno se extrajo al vacío.

El producto precipitado formado se disolvió en dioxano y se agregó metano sulfonamida (0.075 g, 0.794 mmol). La mezcla se revolvió a 100 °C durante 0.5 h después de lo cual se agregó DBU (0. 119 ml, 0.794 mmol). La mezcla se revolvió durante 1 h más a temperatura ambiente, se acidificó con una solución de HCl al 10%. La mezcla se extrajo con EtOAc y se lavó con agua. La capa orgánica se lavó sobre sulfato de sodio y se concentró al vacío. La mezcla cruda se disolvió en DMSO y se purificó mediante HPLC de fase inversa levigado con acetonitrilo/agua (0. 1% TFA) para obtener el producto deseado. (15 mg).

MS (ES): 480 (MH^+) para $C_{16}H_{19}Cl_2N_5O_4S_2$

^{1}H NMRδ: 1.58 (m, 2H); 1.90 (m, 2H); 2.18 (s, 3H); 3.32 (m, 5H); 3.94 (m, 2H); 4.09 (m, 1H); 7.30 (d, 1H); 8. 13 (s, 1H); 11.92 (brs, 1H); 11.98 (s, 1H)

Ejemplo 233: 3,4-Dicloro-5-metil-*N*-{1-[5-(1*H*-tetrazol-5-il)-1,3-tiazol-2-il]piperidin-4-il}-1*H*-pirrol-2-carboxamida

A una solución de 3,4-dicloro-*N*-[1-(5-ciano-1,3-tiazol-2-il)piperidin-4-il]-5-metil-1*H*-pirrol-2-carboxamida (**Ejemplo 321**, 0.100 g, 0.26 mmol) en DMF (3ml) se agregó azida de sodio (0.169 g, 2.60 mmol) seguido por la adición de cloruro de amonio (0.139 g, 2.60 mmol) a temperatura ambiente. La reacción se revolvió a 120 °C durante 3 hrs. La mezcla de la reacción se enfrió a temperatura ambiente, se filtró y se purificó mediante HPLC de fase inversa levigado con acetonitrilo/agua (TFA al 0.1 %) (0.025 g).

MS (ES): 427 (MH^+) para $C_{15}H_{16}Cl_2N_8OS$

^{1}H NMR δ: 1.60 (m, 2H); 1.86 (m, 2H); 2.11 (s, 3H); 3.27 (m, 2H); 3.88 (m, 2H); 4.01 (m, 1H); 7.36 (d, 1H); 7.79 (s, 1H); 11.91 (s, 1H)

Ejemplo 234: 3,4-Dicloro-5-metil-*N*-{1-[5-(1*H*-tetrazol-5-il)-1,3-tiazol-2-il]piperidin-4-il}-1*H*-pirrol-2-carboxamida

El compuesto del título se preparó en forma análoga al **Ejemplo 233** a partir de 3, 4-dicloro-*N*-[1-(4-ciano-1,3-tiazol-2-il)piperidin-4-il]-5-metil-1*H*-pirrol-2-carboxamida (**Ejemplo 337**).

MS (ES): 427 (MH^+) para $C_{15}H_{16}Cl_2N_8OS$

^{1}H NMR δ: 1.61 (m, 2H)); 1.86 (m, 2H); 2.11 (s, 3H); 3.20 (m, 2H); 3.90 (m, 2H); 4.00 (m, 1H); 7.23 (d, 1H); 7.59 (s, 1H); 11.92 (s, 1H)

Ejemplo 235: *N*-(1-{4-[(Z)-Amino(hidroxiimino)metil]-1,3-tiazol-2-il}piperidin-4-il)-3,4-dicloro-5-metil-1*H*-pirrol-2-carboxamida

A una solución de 3,4-dicloro-*N*-[1-(5-ciano-1,3-tiazol-2-il)piperidin-4-il]-5-metil-1*H*-pirrol-2-carboxamida (**Ejemplo 321**, 0.100 g, 0.26 mmol) en MeOH (2ml) se agregó TEA (50 µL, 0.26 mmol) seguido por la adición de clorhidrato de hidroxilamina (0.0182 g, 0.26 mmol) y se trató como se describe en el **Ejemplo 47** para obtener el compuesto del título (0.049 g).

MS (ES): 417(MH^+) para $C_{15}H_{18}Cl_2N_6O_2S$

^{1}H NMR δ: 1.63 (m, 2H); 1.91 (m, 2H); 2.17 (s, 3H); 3.32 (m, 2H); 3.89 (m, 2H); 4.07 (m, 1H); 7.27 (d, 1H); 7.88 (s, 1H); 10.46 (s, 1H); 11.98 (s, 1H)

Ejemplo 236: *N*-(1-{4-[(E)-Amino(hidroxiimino)metil]-1,3-tiazol-2-il}piperidin-4-il)-3,4-dicloro-5-metil-1*H*-pirrol-2-carboxamida

Se preparó en una forma análoga al **Ejemplo 235** a partir de 3,4-dicloro-*N*-[1-(4-ciano-1,3-tiazol-2-il)piperidin-4-il]-5-metil-1*H*-pirrol-2-carboxamida (**Ejemplo 337**).

MS(ES): 417 (MH^+) para $C_{15}H_{18}Cl_2N_6O_2S$

^{1}H NMR δ: 1.62 (m, 2H); 1.90 (m, 2H); 2.18 (s, 3H); 3.23 (m, 2H); 3.94 (m, 2H); 4.07 (m, 1H); 7.29 (d, 1H); 7.82 (s, 1H); 8.84 (brs, 2H); 11.11 (s, 1H); 12.00 (s, 1H)

Ejemplo 237: 2-(4-{[(3, 4-Dicloro-5-metil-1H-pirrol-2-il) carbonil] amino}piperidin-1-il)-4-(hidroximetil)-1,3-tiazol-5-ácido carboxílico

El compuesto del título se preparó en forma análoga al Ejemplo 31 a partir de etil 2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino} piperidin-1-il)-4-(hidroximetil)-1,3-tiazol-5-carboxilato (**Ejemplo 138**).

MS (ES) MH^+: 433 para $C_{16}H_{18}Cl_2N_4O_4S$

^{1}H NMR δ: 1.59-1.67 (m, 1H); 1.89-1.93 (d, 2H); 2.18 (s, 3H); 3.23-3.29 (t, 2H); 2.18 (s, 3H); 3.23-3.29 (t, 2H); 3.91 (d, 2H); 4.07 (brs, 1H); 4.58 (s, 2H); 7.28-7.30 (d, 1H); 11.98 (s, 1H).

Ejemplo 238: 2-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)-4-[(2-metoxietoxi)metil]-1,3-tiazol-5-ácido carboxílico

Se preparó en forma análoga a la del **Ejemplo 129** comenzando a partir de etil 2-(4-aminopiperidin-1-il)-4-[(2-metoxietoxi)metil]-1,3-tiazol-5-clorhidrato de carboxilato (**Intermedio 126**) y 3,4-dicloro-5-metil-1*H*-pirrol-2-ácido carboxílico (**Intermedio 3**). El producto éster se sometió a hidrólisis utilizando LiOH/THF a 65 °C.

MS (ES) (M+H): 493 para $C_{19}H_{24}Cl_2N_4O_5S$

^{1}H NMR δ: 1.71 (m, 2H); 1.91 (m, 2H); 2.17 (s, 3H); 3.22 (s, 3H); 3.44 (b, 2H)); 3.57 (m, 2H); 3.80 (m, 1H); 3.94 (m, 2H); 4.07-4.29 (m, 2H); 4.52 (m, 2H); 7.15 (s, 1H); 7.30 (d, 1H); 12.03 (s, 1H)

Ejemplos 239-241

Los siguientes compuestos se prepararon en una forma análoga al **Ejemplo 238** utilizando 3,4- dicloro-5-metil-1*H*-pirrol-2-ácido carboxílico (**Intermedio 3**) y los materiales de partida descritos en la siguiente tabla.

Ejemplo 239: 2-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrolil)carbonil] amino}piperidin-1-il)-4-(trifluorometil)-1,3-tiazol-5-ácido carboxílico

Ejemplo 240: 4-Butil-2-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il) carbonil] amino}piperidin-1-il)-1,3-tiazol-5-ácido carboxílico

Ejemplo 241: 2-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)-4-(metoximetil)-1,3-tiazol-5-ácido carboxílico

Ejemplo	SM	^{1}H NMR δ	m/z

Ejemplo	SM	^{1}H NMR δ	m/z
239	Etil 2-(4-aminopiperidin-1-il)-4-(trifluorometil)-1,3-tiazol-5-carboxilato sal de clorhidrato (**Intermedio 78**)	1.71 (m, 2H); 1.90 (m, 2H); 2.15 (s, 3H); 3.06 (b, 2H); 3.93 (m, 2H); 4.12 (m, 1H); 7.40 (d, 1H); 11.33 (s, 1H); 13.43 (b, 1H).	471
240	Etil 2-(4-aminopiperidin-1-il)-4-(metoximetil)-1,3-tiazol-5-clorhidrato de carboxilato (**Intermedio 79**)	1.42 (m, 2H); 1.67 (m, 2H); 1.95 (s, 3H); 3.09 (m, 5H); 3.67 (m, 2H); 3.82 (m, 1H); 4.34 (s, 2H); 7.08 (d, 1H); 11.74 (s, 1H); 12.54 (s, 1H)	447, 451
241	Etil 2-(4-aminopiperidin-1-il)-4-butil-1,3-tiazol-5-carboxilato sal de clorhidrato (**Intermedio 80**)	1.29 (s, 9H); 1.58 (m, 2H); 1.93 (m, 2H); 2.11 (s, 3H); 3.32 (m, 2H); 4.17 (m, 2H); 4.21 (m. 1H); 7.06 (s, 1H); 7.18 (d, 1H), 12.02 (s, 1H)	459

Ejemplo 242: 4-[(Acetiloxi)metil]-2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino}piperidin-1-il)-1,3-tiazol-5-ácido carboxílico

Se disolvió 2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino}piperidin-1-il)-4-(hidroximetil)-1,3-tiazol-5-ácido carboxílico (**Ejemplo 237**; 100 mg, 0.23 mmol) en piridina (2ml) y se enfrió a 0°C. Se agregó anhidro acético (21.8 µl, 0.230 mmol) y la mezcla se revolvió a temperatura ambiente durante 1 h. La mezcla se diluyó con EtOAc y se lavó con agua. La fase orgánica se lavó sobre Na_2SO_4 y se concentró al vacío para producir el compuesto del título (40 mg).

MS (ES) MH+: 477 para $C_{18}H_{20}Cl_2N_4O_5S$

^{1}H NMR δ: 1.60-1.63 (m, 2H); 1.86-1.91 (m, 4H); 2.03 (s, 2H); 2.18 (s, 3H); 3.16-3.24 (t, 2H); 3.83-3.87 (d, 2H); 4.02-4.03 (s, 1H); 5.25 (d, 1H).

Ejemplo 243: 4-[(Butiriloxi)metil]-2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino}piperidin-1-il)-1,3-tiazol-5-ácido carboxílico

El compuesto del título se preparó en forma análoga al **Ejemplo 242** a partir de 2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino} piperidin-1-il)-4-(hidroximetil)-1,3-tiazol-5-ácido carboxílico (**Ejemplo 237**) y anhidro butanoico.

MS (ES) MH+: 503 para $C_{20}H_{24}Cl_2N_4O_5S$

^{1}H NMR δ: 0.88-0.92 (t, 3H); 1.54-1.59 (m, 2H); 1.61-1.67 (m, 2H); 1.89-1.92 (d, 2H); 2.18 (s, 3H); 2.30-2.33 (t, 2H); 3.25-3.31 (t, 2H); 3.89-3.92 (d, 2H); 4.07 (m, 1H); 4.58 (s, 2H); 5.3 (s, 2H); 7.27-7.29 (d, 1H); 11.98 (s, 1H); 12.84 (s, 1H).

Ejemplo 244: 4-{[(2-Carboxibenzoilo)amino]metil}-2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino}piperidin-1-il)-1,3-tiazol-5-ácido carboxílico

Se agregó etil 2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino) piperidin-1-il)-4-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]-1,3-tiazol-5-carboxilato (**Ejemplo 277**; 194 mg, 0.32 mmol) en THF anhidro (2ml) 2 N LiOH (0.82 ml). La mezcla se revolvió a temperatura ambiente durante 4 h. La mezcla se acidificó para obtener un pH 3 y el producto precipitado que se formó se diluyó con agua y se extrajo con EtOAc, se lavó sobre Na_2SO_4 y se concentró al vacío para producir el compuesto del título (160 mg).

MS (ES) MH+: 580 para $C_{24}H_{23}Cl_2N_5O_6S$

^{1}H NMR δ: 1.71-1.73 (d, 2H); 1.96-1.99 (d, 2H); 2.23 (s, 3H); 3.23 (s, 1H); 3.31-3.37 (brs, 3H); 4.01-4.03 (d, 2H); 4.13 (m, 1H); 4.67 (s, 2H); 7.37-7.39 (d, 1H); 7.54-7.69 (m, 3H); 7.76-7.78 (d, 1H); 12.06 (s, 1H); 12.88 (s, 1H).

Ejemplo 245: 2-(4-{[(3,4-Dicloro-5-metil-1H-pirrol-2-il)carbonil] amino}piperidin-1-il)-4-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il) metil]-1,3-tiazol-5-ácido carboxílico

Se revolvió 4-{[(2-carboxibenzoilo)amino]metil}-2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino}piperidin-1-il)-1,3-tiazol-5-ácido carboxílico (**Ejemplo 244**; 100 mg; 0.17 mmol) con 4 NHCl/Dioxano (3ml) a temperatura ambiente durante 8 h. La mezcla se concentró al vacío y el sólido resultante se purificó mediante HPLC de fase inversa levigado con mezclas de solución amortiguadora agua/acetonitrilo/acetato de amonio produciendo el compuesto del título (31 mg).

MS(ES) MH+: 564 para $C_{24}H_{21}Cl_2N_5O_5$

^{1}H NMR δ: 1.55-1.60 (m, 2H); 1.79-1.81 (d, 2H); 2.29 (s, 3H); 3.03-3.08 (t, 2H); 3.61-3.64 (d, 2H); 3.98-3.99 (m, 1H); 5.13 (s, 2H); 7.88-7.89 (d, 1H); 7.94-8.01 (m, 4H).

Ejemplo 246: Etil 4-(aminometil)-2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino}piperidin-1-il)-1,3-tiazol-5-carboxilato

Se agregó etil 2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino} piperidin-1-il)-4-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]-1,3-tiazol-5-carboxilato (**Ejemplo 277**; 1.43 g, 2.42 mmol) en EtOH (10ml) hidrato de hidrazina (0.174 ml; 3.63 mmol) y se llevó a reflujo durante 14 h. La mezcla de la reacción se enfrió a temperatura ambiente y se concentró al vacío, se diluyó con DCM y se acidificó con HCl al 10%, se lavó con H_2O. El producto precipitado se filtró y se secó al vacío para producir el compuesto del título (600 mg).

MS (ES) MH+: 461 para $C_{18}H_{23}Cl_2N_5O_3S$

Ejemplo 247: 4-(Aminometil)-2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino}piperidin-1-il-1,3-tiazol-5-ácido carboxílico

El compuesto del título se preparó en forma análoga al **Ejemplo 31** a partir de etil 4-(aminometil)-2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino}piperidin-1-il)-1,3-tiazol-5-carboxilato (**Ejemplo 246**) y LiOH/ THF.

MS (ES) MH+: 434 para $C_{16}H_{19}Cl_2N_5O_3S$

^{1}H NMR δ: 1.42-1.57 (d, 2H); 1.63 (s, 6H); 1.75-1.83 (d, 2H); 2.10 (s, 3H); 3.03-3.10 (t, 2H); 3.74-3.79 (m, 4H); 3.93 (m, 1H); 8.22 (d, 1H); 9.32 (brs, 1H).

Ejemplo 248: 4-({[Amino(imino)metil]amino}metil)-2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino}piperidin-1-il)-1,3-tiazol-5-ácido carboxílico

Se disolvió etil 4-(aminometil)-2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino}piperidin-1-il)-1,3-tiazol-5-carboxilato (**Ejemplo 246**) (300 mg, 0.652 mmol) en NMP (2 ml). Se agregó di-tert-butil [(Z)-1H-pirazol-1-ilmetililiden] biscarbamato (1.01 g, 3.26 mmol) y la mezcla se revolvió a 50°C durante 18 h (LCMS: 702, 705). Se agregó 4 N HCl/Dioxano (10 ml) y la mezcla se calentó a 50 °C durante 5 h. El solvente se extrajo al vacío y el material residual se diluyó con EtOAc, se lavó con bicarbonato de sodio. La capa orgánica se filtró y se lavó sobre Na_2SO_4 y se concentró al vacío para producir el etiléster (320 mg): (LCMS: 502, 505). Se disolvió etiléster (185 mg, 0.3 mmol) en THF (3 ml) y 2 N LiOH (1.84 ml, 3.6 mmol) se calentó a 50 °C durante 4 h. El solvente se extrajo al vacío y el material residual se acidificó hasta obtener el pH 3. El producto precipitado se filtró, se lavó con agua, se extrajo con EtOAc, se lavó sobre Na_2SO_4 y se concentró al vacío produciendo el compuesto del título (47 mg).

MS(ES) MH+: 434 para $C_{17}H_{21}Cl_2N_7O_3S$

^{1}H NMR δ: 1.61 (m, 2H); 1.88 (m, 2H); 2.15 (s, 3H); 3.14 (t, 2H); 3.82-3.84 (d, 2H); 4.00 (brs, 1H); 4.40 (s, 2H); 6.60 (s, 2H); 7.33 (d, 1H); 8.12 (s, 1H); 12.09 (s, 1H).

Ejemplo 249: 2-(4-{[(3,4-Dicloro-5-metil-1H-pirrol-2-il)carbonil] amino}piperidin-1-il)-4-{[(metilsulfonil)aminometil}-1,3-tiazol-5-ácido carboxílico

Se disolvió etil 4-(aminometil)-2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino}piperidin-1-il)-1,3-tiazol-5-carboxilato (**Ejemplo 246**; 312 mg, 0.677 mmol) en DCM y lentamente se agregó cloruro de

metanosulfonilo (65 µl; 0.844 mmol). La reacción se revolvió a temperatura ambiente durante 16 h, se diluyó con DCM, se lavó bien con agua, se lavó sobre Na_2SO_4 y se concentró al vacío para producir el compuesto del título como un aceite espeso marrón claro (350 mg) -(LCMS (ES) MH+: 538). El producto etiloéster se hidrolizó con hidróxido de litio/THF en una forma análoga a la del **Ejemplo 31** para producir el compuesto del título (30mg).

MS (ES) MH+: 512 para $C_{17}H_{21}Cl_2N_5O_5S_2$

^{1}H NMR δ: 1.51-1.60 (q, 2H); 1.82-1.85 (m, 2H); 2.11 (s, 3H); 2.79 (s, 3H); 3.14-3.21 (t, 2H); 3.83-3.86 (d, 2H); 4.00 (s, 1H); 4.40 (s, 2H); 7.29 (d, 1H); 12.00 (s, 1H).

Ejemplo 250: 4-({[(tert-Butilamino)carbonil]amino}metil)-2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino}piperidin-1-il)-1,3-tiazol-5-ácido carboxílico

Se disolvió etil 4-(aminometil)-2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino}piperidin-1-il)-1,3-tiazol-5-carboxilato (**Ejemplo 246**; 200 mg; 0.424 mmol) en DCM (4ml). Se agregó tert-butilo isocianato (130 mg; 1.28 mmol) y la mezcla se revolvió a temperatura ambiente durante 1 h. El solvente se extrajo al vacío y el éster (215 mg), LCMS: 561 se trató con LiOH/THF en una forma análoga a la del **Ejemplo 31** para producir el compuesto del título (290 mg).

MS (ES) MH+: 533 para $C_{21}H_{28}Cl_2N_6O_4S$

^{1}H NMR δ: 1.21 (s, 9H); 1.60-1.68 (m, 2H); 1.90-1.93 (m, 2H); 2.18 (s, 3H); 3.25-3.28 (m, 2H); 3.95-3.98 (d, 2H); 4.05-4.10 (m, 1H); 4.34 (s, 2H); 5.92 (s, 1H); 6.06 (s, 1H); 7.49-7.51 (d, 1H).

Ejemplo 251: 2-(4-{[(3,4-Dicloro-5-metil-1H-pirrol-2-il)carbonil] amino}piperidin-1-il)-4-({[(etilamino)carbonil]amino}metil)-1,3-tiazol-5-ácido carboxílico

El compuesto del título se preparó en forma análoga al **Ejemplo 250** a partir de etil 4-(aminometil)-2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)

carbonil]amino}piperidin-1-il)-1,3-tiazol-5-carboxilato (**Ejemplo 246**) y etilo isocianato.

MS (ES) MH+: 506 para $C_{19}H_{24}Cl_2N_6O_4S$

^{1}H NMR δ: 0.95-1.00 (t, 3H); 1.60-1.69 (m, 2H); 1.91 (m, 2H); 2.18 (s, 3H); 2.97-3.04 (q, 2H); 3.20-3.24 (t, 2H); 3.90-3.94 (d, 2H); 4.05-4.06 (m, 1H); 4.34 (s, 2H); 6.13 (brs, 1H); 6.42 (brs, 1H); 7.41-7.44 (d, 1H).

Ejemplo 252: 4-[(Butirilamino)metil]-2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino}piperidin-1-il)-1,3-tiazol-5-ácido carboxílico

El compuesto del título se preparó en forma análoga al **Ejemplo 242** a partir de 4-(aminometil)-2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino}piperidin-1-il)-1,3-tiazol-5-ácido carboxílico (**Ejemplo 247**) y anhidro butanoico.

MS (ES) MH+: 504 para $C_{20}H_{25}Cl_2N_5O_4S$

^{1}H NMR δ: 0.77-0.81 (t, 3H); 1.40-1.48 (m, 2H); 1.53-1.59 (m, 2H); 1.82-1.85 (d, 2H); 2.00-2.04 (t, 2H); 2.11 (s, 3H); 3.16-3.20 (t, 2H); 3.84-3.87 (d, 2H); 3.97-4.02 (m, 1H); 4.37-4.38 (d, 2H); 7.26-7.28(d, 1H); 8.02 (s, 1H); 11.98 (brs, 1H); 12.64 (brs, 1H).

Ejemplo 253: 2-(4-{[(3,4-Dicloro-5-metil-1H-pirrol-2-il)carbonil] amino}piperidin-1-il)-4-{[(tetrahidrofuran-3-ilcarbonil)amino] metil}-1,3-tiazol-5-ácido carboxílico

Se disolvió etil 4-(aminometil)-2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil] amino}piperidin-1-il)-1,3-tiazol-5-carboxilato (**Ejemplo 246**; 200 mg; 0.434 mmol) en DMF anhidro (2ml). Se agregó HATU 165 mg; 0.434 mmol) seguido por diisopropiletilamina (149 µl, 0.868 mmol). La mezcla de la reacción se revolvió durante 10 minutos y tetrahidrofuran-3-ácido carboxílico (50 mg; 0.434 mmol) y la reacción se revolvió a temperatura ambiente durante 2.5 h. La mezcla se diluyó con EtOAc, se lavó bien con agua, se lavó sobre Na_2SO_4 y se concentró al vacío para producir el compuesto del título como un sólido casi blanco (220 mg)- (LCMS (ES) MH+: 558,561). El producto etiléster se hidrolizó con hidróxido de

litio/THF en una forma análoga a la del **Ejemplo 31** para producir el compuesto del título (25 mg).

MS (ES) MH+: 533 para $C_{21}H_{25}Cl_2N_5O_5S$

^{1}H NMR δ: 1.68 (m, 2H); 1.92-1.97 (m, 3H); 2.00-2.07 (m, 2H); 2.25 (s, 3H); 2.97-3.07 (m, 1H); 3.22-3.30 (m, 2H); 3.66-3.72 (m, 2H); 3.74-3.79 (m, 1H); 3.86-3.94 (m, 2H); 4.08 (m, 1H); 4.47-4.49 (d, 1H); 7.59-7.62 (d, 1H); 9.05 (s, 1H)

Ejemplo 254: 2-(4-{[(3,4-Dicloro-5-metil-1H-pirrol-2-il) carbonil] amino}piperidin-1-il)-1,3-tiazol-5-ácido sulfónico

Se disolvió 3,4-dicloro-5-metil-N-[1-(1,3-tiazol-2-il) piperidin-4-il]-1H-pirrol-2-carboxamida (**Ejemplo 329**; 692 mg, 1.93 mmol) en DCM anhidro. Lentamente se agregó ácido clorosulfónico (513 µl, 7.7 mmol) y la mezcla se calentó a 60 °C durante 2 h. La mezcla se enfrió a 0 °C y se agregó agua, ocasionando la separación de un sólido marrón. Este se filtró y se lavó bien con agua, se secó al vacío para producir el compuesto del título (393 mg).

MS (ES) MH+: 441 para $C_{14}H_{16}Cl_2N_4O_4S_2$

^{1}H NMR δ: 1.83 (m, 2H); 2.06 (m, 2H); 2.28 (s, 3H); 3.46 (m, 2H); 3.94 (m, 3H); 7.10 (s, 1H); 7.41 (d, 1H); 12.19 (s, 1H)

Ejemplo 255: N-{-[5-(Aminosulfonil)-1,3-tiazol-2-il]piperidin-4-il}-3, 4-dicloro-5-metil-1H-pirrol-2-carboxamida

Se agregó 0.5 M amoniaco/dioxano (10 ml, 5 mmol) a 2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino}piperidin-1-il)-1,3-tiazol-5-ácido sulfónico (**Ejemplo 254**; 100 mg, 0.226 mmol) en una botella de presión. La mezcla se revolvió a temperatura ambiente durante 4 h.

El excedente del solvente se extrajo al vacío y el sólido marrón se secó al vacío para producir el compuesto del título (56 mg).

MS(ES) MH+: 438 para $C_{14}H_{16}Cl_2N_4O_4S_2$

^{1}H NMR δ: 1.75 (m, 2H); 1.92 (m, 2H); 2.18 (s, 3H); 3.27 (m, 2H); 3.86(m, 2H); 4.10 (m, 1H); 7.01 (s, 1H); 7.14 (d, 1H); 7.34 (s, 2H); 12.07 (s, 1H)

Ejemplo 256: 3,4-Dicloro-N-{1-[5-(hidroximetil)-1,3,4-tiadiazol-2-il][piperidin-4-il}-5-metil-1H-pirrol-2-carboxamida

Se enfrió una solución de etil 5-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil] amino}piperidin-1-il)-1,3,4-tiadiazol-2-carboxilato (**Ejemplo 219**, 280 mg, 0.65 mmol) en THF (5ml) a 0 °C y se trató con hidruro de diisobutilaluminio (1.3ml, 1.95 mmol) en forma de goteo durante 5 min. La reacción se mantuvo en el baño de hielo y lentamente se dejó calentar a temperatura ambiente mientras se revolvía durante la noche. LC-MS indicó que la reacción estaba completa. La reacción se extinguió con sal de Rochelle acuosa y la mezcla resultante se diluyó con EtOAc (10 ml) y se revolvió vigorosamente durante 2 h. Las capas se separaron y la porción acuosa se extrajo con EtOAc. Las porciones orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron para producir un aceite de color naranja pálido. El material crudo se purificó mediante HPLC de preparación (35-75%CH_3CN/H_2O, TFA al 0.1 %, 14 min.) para producir 17 mg del compuesto del título.

MS (ES^+): 390.07 para $C_{14}H_{17}Cl_2N_5O_2S$

^{1}H NMR δ: 1.6 (m, 2H); 1.82 (m, 2H); 2.11 (s, 3H); 3.21 (t, 2H); 3.96 (m, 3H); 7.2 (d, 1H); 11. 9 (s, 1H)

Ejemplo 257: 3-Quinolinaácido carboxílico, 1-[4-[[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino]-1-piperidinil]-1,4-dihidro-4-oxo-,etiléster

Se revolvió una solución de N-(l-aminopiperidin-4-il)-3, 4-dicloro-5-metil-1H-pirrol-2-carboxamida (**Intermedio 89**, 400 mg, 1.4 mmol) y etil (2Z)-3-etoxi-2-(2-fluorobenzoilo) acrilato (WO 2000040561 A1, 370 mg, 1.4 mmol) en 20 ml de EtOH a temperatura ambiente durante 2 horas. Después de la dilución con 100 ml agua, los sólidos se filtraron y se secaron al vacío. Los sólidos se suspendieron en 20 ml dioxano que contenía DBU (300 µl) y la mezcla se calentó en un reactor de microondas a 120 °C durante 3 horas. El solvente se extrajo y el residuo se disolvió en EtOAc antes de lavarlo con agua y solución salina. Luego se procedió con el secado ($MgSO_4$) y la

extracción del solvente mediante trituración con EtOAc caliente produjo 160 mg de producto como un sólido blanco.

MS ES: 491.0 $(M+H)^+$, MS (ES): 489.2 $(M-H)^-$.

^{1}H NMR δ: 1.31 (t, J=7.16 Hz, 3H); 1.78-2.12 (m, 4H); 2.14-2.30 (m, 3H); 3.12 (s, 2H); 3.34-3.50 (m, 2H); 4.05 (s, 1H); 4.14-4.37 (m, 2H); 7.26 (d, J=7.72 Hz, 1H); 7.49 (t, J=7.54 Hz, 1H); 7.71-7.95 (m, 1H); 8.07-8.31 (m, 2H); 8.97 (s, 1H); 12.04 (s, 1H).

Ejemplo 258: 1-(4-{[(3,4-Dicloro-5-metil-1H-pirrol-2-il)carbonil]amino}piperidin-1-il)-4-oxo-1,4-dihidroquinolina-3-ácido carboxílico

Se calentó una suspensión de 3-quinolinaácido carboxílico, 1-[4-[[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino]-1-piperidinil]-1,4-dihidro-4-oxo-, etiléster (**Ejemplo 257**, 67 mg, 0.14 mmol) en 5ml MeOH y 150 µl (0.15 mmol) de 1 N NaOH acuoso a 80 °C durante 40 min en un reactor de microondas. Se agregó una solución acuosa 1 N HCl (150 µl) produciendo una masa de producto precipitado sólido. La mezcla se absorbió en agua caliente y el material insoluble se filtró para obtener 19 mg de producto como un sólido blanco.

MS ES: 463 $(M+H)^+$, MS (ES): 461 $(M-H)^-$.

^{1}H NMR δ: 2.03 (s, 4H); 2.19 (s, 3H); 3.18 (s, 2H); 3.53 (s, 2H); 4.09 (s, 1H); 7.25(s, 1H); 7.69 (s, 1H); 8.01 (s, 1H); 8.39 (s, 2H); 9.37 (s, 1H); 11.82-12.44 (m, 1H); 15.25 (s, 1H).

Ejemplo 259: 3, 4-Dicloro-N-[1-(3-formilo-1H-pirrol-1-il)piperidin-4-il]-5-metil-1H-pirrol-2-carboxamida

Se calentó una mezcla de *N*-(1-aminopiperidin-4-il)-3,4-dicloro-5-metil-1*H*-pirrol-2-carboxamida (**Intermedio 89**; 67 mg, 0.14 mmol), 2,5-dimetoxitetrahidrofuran-3-carbaldehído (100 µl 4.2 mg) y acetato de sodio (0.35 g, 4.1 mmol) en 30 ml ácido acético a 70 ° durante 2 horas. El solvente se extrajo y el residuo se distribuyó entre EtOAc y Na_2CO_3 acuoso. El material insoluble se extrajo mediante filtración con tierra diatomita y enjuagando con EtOAc. El EtOAc del producto filtrado se separó y se lavó

con agua y solución salina. El secado ($MgSO_4$) y la extracción del solvente produjo un sólido marrón que se purificó mediante cromatografía de fase normal (100% DCM con gradiente de elución a MeOH al 2% en DCM) para producir un material que se trituró con éter para obtener 110 mg de un sólido blanco.

MS (ES): 369 $(M+H)^+$, MS (ES): 367.2 $(M-H)^-$.

^{1}H NMR δ: 1.65-1.89 (m, 2H); 1.90-2.11 (m, 2H); 2.18 (s, 3H); 3.15 (dd, J=7.06, 3.30 Hz, 4H); 3.92 (s, 1H); 6.44 (dd, J=3.01, 1.88 Hz, 1H); 7.15-7.27 (m, 1H); 7.31 (d, J=7.72 Hz, 1H); 7.89 (t, J=1.88 Hz, 1H); 9.62 (s, 1H); 12.00 (s, 1H).

Ejemplo 260: 3,4-Dicloro-N-(1-{3-[(E)-(hidroxiimino)metil]-1H-pirrol-1-il}piperidin-4-il)-5-metil-1h-pirrol-2-carboxamida

Se calentó una solución de 3,4-dicloro-N-[1-(3-formilo-1H-pirrol-1-il) piperidin-4-il]-5-metil-1H-pirrol-2-carboxamida (**Ejemplo 259**, 151 mg, 0.41 mmol) e hidroxilamina acuosa al 50% (55 µl, 0.83 mmol) en 5 ml EtOH a 80 °C durante 30 min. La mezcla se diluyó con EtOAc y se lavó con solución salina. El secado ($MgSO_4$) y la extracción del solvente produjo un sólido que se purificó mediante HPLC de fase inversa (30-55% gradiente CH_3CN en agua con TFA al 0.1 %) para producir el producto como una mezcla de isómeros geométricos.

MS (ES): 384 $(M+H)^+$, MS (ES): 282 $(M-H)^-$.

^{1}H NMR δ: 1.78 (m, 1H); 1.94 (m, 2H); 2.2 (s, 3H); 2.95-3.24 (m, 4H); 3.91 (m, 1H); 6.1-6.3 (2d, 1H); 6.9 y 7.1 (2s, 1H); 7.16 (s, 1H); 7.22-7.41 (m, 1H); 7.6 y 7.9 (2s, 1H); 10.9 y 10.4 (2s, 1H); 12.00 (s, 1H).

Ejemplo 261: 1-(4-{[(3,4-Dicloro-5-metil-1H-pirrol-2-il)carbonil] amino}piperidin-1-il)-1H-pirrol-3-ácido carboxílico

Se combinaron soluciones de 3, 4-dicloro-N-[1-(3-formilo-1H-pirrol-1-il)piperidin-4-il]-5-metil-1H-pirrol-2-carboxamida (**Ejemplo 259**, 90 mg, 0.24 mmol) en 10 ml acetona y $KMNO_4$ (39 mg, 0.24 mmol) en 3 ml de agua y se revolvieron a temperatura ambiente durante la noche.

Debido a una conversión incompleta, se agregaron soluciones de $KMnO_4$ (15 y 20 mg) en 3 ml agua a intervalos de 5 horas. La mezcla se extinguió con $NaHSO_3$ acuoso y se distribuyó entre EtOAc y agua. El EtOAc se separó y se lavó con solución salina. El secado ($MgSO_4$) y la extracción del solvente produjeron el producto como un sólido blanco.

MS (ES): 384 $(M+H)^+$, MS (ES): 282 $(M-H)^-$.

^{1}H NMR δ: 1.79 (d, J=3.58 Hz, 2H); 1.86-2.04 (m, 2H); 2.18 (s, 3H); 3.11 (d, J=3.39 Hz, 4H); 3.77-4.05 (m, 1H); 6.22-6.42 (m, 1H); 7.05 (t, J=2.45 Hz, 1H); 7.31 (d, J=7.72 Hz, 1H); 7.58 (s, 1H); 11.96 (d, J=31.65 Hz, 2H).

Ejemplo 262: 1-(4-{[(3,4-Dicloro-5-metil-1H-pirrol-2-il)carbonil] amino}piperidin-1-il) isoquinolina-3-ácido carboxílico

En una mezcla de 20 ml THF, 5 ml H_2O y 1 ml NaOH (aq) 50 peso % se disolvió metil 1-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil] amino}piperidin-1-il)isoquinolina-3-carboxilato (**Ejemplo 301**; 70 mg). La solución se revolvió a 80 °C durante 1 hr. La solución se enfrió a temperatura ambiente, se diluyó con EtOAc y se acidificó con HCl (aq) diluido. La fracción de EtOAc se aisló, y en ese momento se precipitó un sólido blanco de la solución. El sólido se recolectó mediante filtración y se lavó con acetonitrilo para producir 50 mg un sólido blanco.

MS (ES): 447 $(M+H)^+$.

^{1}H NMR δ: 1.90 (s, 2H); 1.98-2.12 (m, 2H); 2.19 (s, 3H); 3.14 (m, 2H); 3.82 (m, 2H); 4.04 (s, 1H; 7.31 (m, 1H); 7.77 (m, 2H); 8.06-8.21 (m, 2H); 12.02 (s, 1H); 12.79 (s, 1H).

Ejemplo 263: 1-(4-{[(3,4-Dicloro-5-metil-1H-pirrol-2-il)carbonil] amino}piperidin-1-il)-4-metoxiisoquinolina-3-ácido carboxílico

En un envase sellado de alta presión con un recubrimiento de teflón, se combinó etil 1-cloro-4-metoxiisoquinolina-3-carboxilato (EP 650961 A1; 390 mg, 1.55 mmol), 4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino} trifluoroacetato de piperidinio (**Intermedio 86**; 1.7 g, 4.4 mmol) y K_2CO_3 (2.2 g) en 20 ml tert-butanol. El envase se calentó a

170 °C y se revolvió durante 8 horas. La solución se concentró mediante evaporación rotatoria y se reconstituyó con EtOAc. La capa orgánica se lavó 4x con H_2O y se lavó sobre $MgSO_4$. Etil 1-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino}piperidin-1-il)-4-metoxiisoquinolina-3-carboxilato crudo se purificó mediante Si de fase inversa produciendo 20 mg del éster intermedio. Luego el etiléster se hidrolizó como en el **Ejemplo 262** para producir 13.5 mg de un producto final como un sólido blanco.

MS (ES): 477 $(M+H)^+$, MS (ES): 475 $(M-H)^-$.

^{1}H NMR δ: 1.81-1.97 (m, 2H); 2.01 (s, 2H); 2.14-2.26 (m, 3H); 3.06 (t, J=11.30 Hz, 2H); 3.71 (m, 2H); 3.93 (s, 3H); 4.03 (s, 1H); 7.40 (m, 1H); 7.73-7.89 (m, 2H); 8.10-8.22 (m, 2H); 12.12 (s, 1H).

Ejemplo 264: Etil 1-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino}piperidin-1-il)-2,7-naftiridina-3-carboxilato

En un envase sellado de alta presión con un recubrimiento de teflón, se combinó etil 1-cloro-2,7-naftiridina-3-carboxilato (280 mg, 1.18 mmol), 4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino}trifluoroacetato de piperidinio (**Intermedio 86**; 957 mg) y K_2CO_3 (1.25 g) en 15 ml tert-butanol. El envase se calentó a 170 °C y se revolvió durante 8 horas.

La solución se concentró mediante evaporación rotatoria y se reconstituyó con EtOAc. La capa orgánica se lavó 4x con H_2O y se lavó sobre $MgSO_4$. El producto se purificó en Si de fase inversa para producir 36 mg de un sólido blanco.

MS (ES): 476 $(M+H)^+$.

^{1}H NMR δ: 1.82-1.95 (m, 2H); 1.99-2.11 (m, 2H); 2.14-2.22 (m, 3H); 3.23-3.33 (m, 2H); 3.98-4.14 (m, 2H); 4.37 (m, 1H); 7.33 (d, J=7.54 Hz, 1H); 7.97 (d, J=5.28 Hz, 1H); 8.05 (s, 1H); 8.75 (d, J=5.28 Hz, 1H); 9.41 (s, 1H); 12.01 (s, 1H).

Ejemplo 265: 1-(4-{[(3,4-Dicloro-5-metil-1H-pirrol-2-il)carbonil] amino}piperidin-1-il)-2,7-naftiridina-3-ácido carboxílico

Como se describió para la síntesis del **Ejemplo 262**, se hidrolizó etil 1-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino}piperidin-1-il)-2,7-naftiridina -3-carboxilato (**Ejemplo 264**; 30 mg) para producir 9.1 mg de un sólido amarillo.

MS (ES): 448 $(M+H)^+$, MS (ES): 446 $(M-H)^-$.

^{1}H NMR δ: 1.80 - 1.94 (m, 2H); 1.98 - 2.12 (m, 2H); 2.19 (s, 3H); 3.24 - 3.36 (m, 2H); 4.07 (d, J=13.57 Hz, 3H); 7.31 (d, J=8.29 Hz, 1H); 7.95-8.09 (m, 2H); 8.73 (d, J=5.28 Hz, 1H; 9.43 (s, 1H); 12.02 (s, 1H).

Ejemplo 266: Etil 4-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino}piperidin-1-il)quinazolina-2-carboxilato

Como se describió para la síntesis del **Ejemplo 264**, se combinó etil 4-cloroquinazolina-2-carboxilato (690 mg), 4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino}trifluoroacetato de piperidinio (**Intermedio 86**; 1.7 g) y K_2CO_3 (1.7 g) en 20 ml tert-butanol para producir 662 mg de un sólido gris.

MS (ES): 476 $(M+H)^+$.

^{1}H NMR δ: 1.34 (t, J=7.16 Hz, 3H); 1.79 (m, 2H); 2.01 (s, 2H); 2.18 (s, 3H); 4.17 (s, 1H); 4.33-4.46 (m, 4H); 7.33 (d, J=7.54 Hz, 1H); 7.68 (d, J=6.03 Hz, 1H); 7.88 - 7.98 (m, 1H); 8.06 (d, J=9.04 Hz, 1H); 12.03 (s, 1H).

Ejemplo 267: 4-(4-{[(3,4-Dicloro-5-metil-1H-pirrol-2-il)carbonil] amino}piperidin-1-il)quinazolina-2-ácido carboxílico

Como se describió para la síntesis del **Ejemplo 262**, se hidrolizó etil 4-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino}piperidin-1-il)quinazolina-2-carboxilato (**Ejemplo 266**; 100 mg) para producir 32 mg de un sólido blanco.

MS (ES): 448 $(M+H)^+$, MS (ES): 446 $(M-H)^-$.

^{1}H NMR δ: 1.60 - 1.75 (m, 2H); 1.75 - 1.90 (m, 2H); 2.15 - 2.24 (s, 3H); 3.70 - 3.86 (m, 2H); 4.23 (m, 1H); 4.53 (m, 2H); 7.41 (d, J=7.54 Hz, 1H); 7.69 (t, J=7. 16 Hz, 1H); 7.92 - 8.04 (m, 2H); 8.10 (d, J=8.29 Hz, 1H); 12.11 (s, 1H).

Ejemplo 268: Metil 4-amino-2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino}piperidin-1-il)-1,3-tiazol-5-carboxilato

Se revolvió una suspensión de metil N-ciano-4-{[(3,4-dicloro-5-metil-1H-pirrol-2- il)carbonil]amino}piperidin-1-carbimidotioato (**Intermedio 91**, 1.78 g, 4.8 mmol) y metilo mercaptoacetato (0.43ml, 4.8 mmol) con TEA (1.2 ml, 8.6 mmol) en MeOH a temperatura ambiente durante la noche. La mezcla de la reacción se concentró a 50% por volumen, el producto precipitado se retiró por filtración y el sólido se lavó con MeOH y se secó.

MS (ES): 432 $(M+H)^+$.

^{1}H NMR δ: 1.54-1.69 (m, 2H); 1.90 (dd, J=12. 62, 2.83 Hz, 2H); 2.18 (s, 3H); 3.16 - 3.31 (m, 2H); 3.61 (s, 3H); 3.87 (d, J=14.69 Hz, 2H); 3.99-4.14 (m, 1H); 6.84 (s, 2H); 7.29 (d, J=7.91 Hz, 1H); 11.98 (s, 1H).

Ejemplo 269: 3,4-Dicloro-N-[1-(5-ciano-4-metoxi-1,3-tiazol-2-il) piperidin-4-il]-5-metil-1H-pirrol-2-carboxamida

Se calentó una suspensión de N-[1-(aminocarbonotioil) piperidin-4-il]-3, 4-dicloro-5-metil-1H- pirrol-2-carboxamida (**Intermedio 95**, 0.22 g, 0.7 mmol) y tert-butilo cloro (ciano) acetato (0.12 g, 0.7 mmol) en MeOH a 80 °C en el reactor del microondas durante 40 minutos. El producto se precipitó y se retiró por filtración.

MS (ES): 414 $(M+H)^+$.

^{1}H NMR δ: 1.57 - 1.72 (m, 2H); 1.93 (dd, J=12.81, 3.01 Hz, 2H); 2.18 (s, 3H); 3.28 - 3.43 (m, 2H); 3.80 - 3.94 (m, 2H); 3.97 (s, 3H); 4.01- 4.15 (m, 1H); 7.31 (d, J=7.72 Hz, 1H); 12.00 (s, 1H).

Ejemplo 270: 3,4-Dicloro-N-[1-(5-ciano-4-hidroxi-1,3-tiazol-2-il) piperidin-4-il]-5- metil-1H-pirrol-2-carboxamida

Se agregó lodotrimetilsilano (0.02ml, 0.13 mmol) a una suspensión de 3,4-dicloro-N-[1-(5-ciano-4-metoxi-1,3-tiazol-2-il)piperidin-4-il]-5-metil-1H-pirrol-2-carboxamida (**Ejemplo 269**, 0.04 g, 0.1 mmol) en DCM:$CHCl_3$ (1:1). Después de revolver durante una hora la reacción estaba completa. La distribución con EtOAc y agua, el secado de la porción orgánica con $MgSO_4$ y la concentración produjeron un aceite amarillo el cual después de triturarlo con éter, produjo a un sólido amarillo.

MS (ES): 400 $(M+H)^+$.

^{1}H NMR δ: 1.65 (s, 2H); 1.84 - 1.95 (m, 2H); 2.08 - 2.20 (m, 3H); 3.77 - 3.90 (m, 2H); 4.09 (s, 2H); 4.41 (s, 1H); 7.25 - 7.39 (m, 1H); 12.00 (d, J=5.84 Hz, 1H); 12.48 (s, 1H).

Ejemplo 271: Metil 2-(4-{[(3,4-dicloro-5-ciano-1H-pirrol-2-il) carbonil]amino}piperidin-1-il)-1,3-tiazol-5-carboxilato

Se agregó TEA (0.06ml, 0.5 mmol) a una solución de metil 2-(4-aminopiperidin-1-il)-1,3-tiazol-5-carboxilato (**Intermedio 134**, 0.1 g, 0.5 mmol)) en THF anhidro. A lo anterior se agregó 3,4-dicloro-5-ciano-1H-pirrol-2-carbonilo cloruro (**Intermedio 132**, 0.1 g, 0.5 mmol) como una solución en THF anhidro. Después de revolver durante 15 minutos, se extrajo el THF. El producto se partió con EtOAc y agua. La porción orgánica se secó con $MgSO_4$ y se concentró hasta obtener un aceite amarillo. La trituración con éter seguido por filtración produjo un sólido de color tostado.

MS (ES): 428 $(M+H)^+$

^{1}H NMR δ: 1.65 (s, 2H); 1.87 (s, 2H); 3.09 (s, 1H); 3.25 - 3.40 (m, 2H); 3.75 (s, 3H); 3.95 (d, J=13.75 Hz, 2H); 7.87 (s, 2H).

Ejemplo 272: 2-(4-{[(3,4-Dicloro-5-ciano-1H-pirrol-2-il) carbonil] amino}piperidin-1-il)-1,3-tiazol-5-ácido carboxílico

El compuesto del título se preparó mediante un procedimiento análogo al del **Intermedio 3** comenzando a partir de metil 2-(4-{[(3,4-dicloro-5-ciano-1H-pirrol-2-il) carbonil]amino}piperidin-1-il)-1,3-tiazol-5-carboxilato

(Ejemplo 271). La mezcla de la reacción se concentró para extraer el MeOH. Se agregó agua y se ajustó el pH a 4 con $NaHCO_3$. El producto se extrajo con $CHCl_3$: isopropanol (3:1). El secado ($MgSO_4$) y la extracción del solvente produjeron un sólido blanco. Se secó en una pistola de secado a 75 °C al vacío.

MS (ES): 414 $(M+H)^+$.

^{1}H NMR δ: 1.66 (s, 2H); 1.91 (s, 2H); 3.36 (s, 2H); 3.94 (d, J=13.38 Hz, 2H); 4.09 (s, 1H); 7.76 - 7.91 (m, 1H); 8.04 (d, J=7.72 Hz, 1H); 12.64 (s, 1H); 13.86 (s, 1H).

Ejemplo 273: Metil4-(4-{[(3,4-dicloro-5-ciano-1H-pirrol-2-il) carbonil] amino}piperidin-1-il)quinolina-2-carboxilato

El compuesto del título se preparó mediante un procedimiento análogo al del **Ejemplo 271** comenzando a partir de 3,4-dicloro-5-ciano-1H-pirrol-2-carbonilo cloruro (**Intermedio 132**) y metil 4-(4-aminopiperidin-1-il)quinolina-2-clorhidrato de carboxilato (**Intermedio 136**).

^{1}H NMR δ: 1.95 (d, J=15.82 Hz, 2H); 2.99 - 3.14 (m, 2H); 3.38 (q, J=6.97 Hz, 2H); 3.54 - 3.69 (m, 2H); 3.94 (s, 4H); 7.55 (s, 1H); 7.69 (t, J=7.63 Hz, 1H); 7.76 - 7.86 (m, 1H); 7.96 - 8.11 (m, 2H).

Ejemplo 274: 4-(4-{[(3,4-Dicloro-5-ciano-1H-pirrol-2-il) carbonil] amino}piperidin-1-il)quinolina-2-ácido carboxílico

El compuesto del título se preparó mediante un procedimiento análogo al del **Intermedio 3** comenzando con metil 4-(4-{[(3,4-dicloro-5-ciano-1H-pirrol-2-il)carbonil]amino}piperidin-1-il)quinolina-2-carboxilato (**Ejemplo 273**) y siguiendo el procedimiento de preparación del **Ejemplo 272**.

MS(ES) $(M+H)^+$: 458

^{1}H NMR δ: 1.93 (s, 2H); 2.05 (s, 2H); 3.27 (s, 2H); 3.77 (s, 2H); 4.12 (s, 1H); 7.56 (s, 1H; 7.69 (s, 1H); 7.85 (s, 1H); 8.05 (s, 1H); 8.18 (d, J=8.67 Hz, 2H).

Ejemplo 275: N-Metoxi 8-fluoro-4-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino}piperidin-1-il)quinolina-2-carboxamida

El compuesto del título se preparó a partir de 8-fluoro-4-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino}piperidin-1-il)quinolina-2-ácido carboxílico (**Ejemplo 280**) y O-metilclorhidrato de hidroxilamina mediante el procedimiento descrito para el **Ejemplo 8.**

MS (ES+): 494/496 para $C_{22}H_{22}Cl_2FN_5O_3$

^{1}H NMR δ: 1.88 (m, 2H); 2.06 (m, 2H); 2.17 (s, 3H); 2.98 (m, 2H); 3.50 (m, 2H)); 3.69 (s, 3H); 4.04 (m, 1H); 7.42 (m, 2H); 7.59 (s, 1H); 7.72 (m, 1H); 8.13 (s, 2H)

Ejemplo 276: Etil 2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino}piperidin-1-il)-4-(metoximetil)-1,3-tiazol-5-carboxilato

El compuesto del título se preparó a partir de 3, 4-dicloro-5-metil-1*H*-pirrol-2-ácido carboxílico (**Intermedio 3**) y etil 2-(4-aminopiperidin-1-il)-4-(metoximetil)-1,3-tiazol-5-clorhidrato de carboxilato (**Intermedio 36**) en una forma análoga a la del **Ejemplo 29.**

MS (ES) (M+H): 474 para $C_{19}H_{24}Cl_2N_4O_4S$

Ejemplo 277: Etil 2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino}piperidin-1-il)-4-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]-1,3-tiazol-5- carboxilato

El compuesto del título se preparó a partir de 3,4-dicloro-5-metil-1*H*-pirrol-2-ácido carboxílico (**Intermedio 3**) y etil 2-(4-aminopiperidin-1-il)-4-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]-1,3-tiazol-5-clorhidrato de carboxilato (**Intermedio 77**) en una forma análoga a la del **Ejemplo 29.**

MS (ES) (M+H): 593 para $C_{26}H_{25}Cl_2N_5O_5S$

Ejemplo 278: 6-Cloro-4-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino}piperidin-1-il)quinolina-2-ácido carboxílico

Se disolvió metil 6-cloro-4-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil] amino}piperidin-1-il)quinolina-2-carboxilato (**Ejemplo 134**; 20

mg) en 6 ml de 2:1 THF/MeOH, se agregó 0.20 ml de 1 N NaOH y la solución resultante se revolvió a temperatura ambiente durante 20 h. Después de la neutralización con 0.25 ml de1 N HCl, la reacción se diluyó con 5 ml de agua y se filtró. El sólido se lavó con agua y se secó al vacío, produciendo 18.4 mg de un sólido granulado amarillo claro.

MS (ES+): 480.94/482.94/484.94 para $C_{21}H_{19}Cl_3N_4O_3$

^{1}H NMR δ: 1.81 (m, 2H); 1.94 (m, 2H); 2.09 (s, 3H); 3.07 (m, 2H); 3.25 (s, 1H); 3.50 (m, 2H); 4.00 (m, 1H); 7.23 (d, 1H, J = 7.54); 7.48 (s, 1H); 7.74 (d, 1H, J = 9.04); 7.88 (s, 1H); 8.02 (d, 1H, J = 9.04); 11.93 (s, 1H).

Ejemplos 279-283

Los siguientes compuestos se prepararon mediante un método análogo al del **Ejemplo 278**.

Ejemplo	Compuesto	^{1}H NMR δ	m/z (ES^+)	MP
279	8-Metoxi-4-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil] amino}piperidin-1-il) quinolina-2-ácido carboxílico	1.86 (m, 2H); 1.99 (m, 2H); 2.14(s, 3H); 3.05 (m, 2H); 3.56 (m, 2H); 3.94 (s, 3H); 4.00 (m, 1H); 3.9-4.5 (v br s, 1H); 7.21 (m, 1H); 7.29 (m, 1H); 7.52 (m, 3H); 11.97 (s, 1H)	477/ 479	Ejemplo 323
280	8-Fluoro-4-(4-{[(3.4-dicloro-5-metil-1H-pirrol-2-il)carbonil] amino}piperidin-1-il) quinolina-2-ácido carboxílico	1.86 (m, 2H); 2.03 (m, 2H); 2.14 (s, 3H); 3.06 (m, 2H); 3.59 (m, 2H); 3.87 (s, 3H); 4.01 (m, 1H); 736 (m, 3H); 7.80 (m, 1H)	465/ 467	Ejemplo 324

Ejemplo	Compuesto	^{1}H NMR δ	m/z (ES^+)	MP
281	6-Fluoro-4-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil] amino}piperidin-1-il) quinolina-2-ácido carboxílico	1.91 (m, 2H); 2.03 (m, 2H); 2.18 (s, 3H); 3.14 (m, 2H)); 3.61 (m, 2H); 4.05 (m, 1H); 731 (d, 1H, J=7.5); 7.58 (s, 1H); 7.68 (m, 1H); 7.80 (m, 1H); 8.20 (m, 1H); 12.03 (s, 1H)	465/ 467	Ejemplo 325
282	8-Cloro-4-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil] amino}piperidin-1-il) quinolina-2-ácido carboxílico	1.85 (m, 2H); 2.02 (m, 2H); 2.14 (s, 3H); 3.06 (m, 2H); 3.57 (m, 2H); 3.93 (s, 3H); 3.99 (m, 1H); 7.36 (d, 1H, J = 7.5); 7.55 (s, 1H); 7.58 (m, 1H); 7.93 (m, 2H)	481/ 483	Ejemplo 326
283	2-(4-{[(3,4-Dicloro-5-metil-1H-pirrol-2-il)carbonil]amino} piperidin-1-il)oxazol-4-ácido carboxílico	1.60 (m, 2H); 1.86 (m, 2H); 2.18 (s, 3H); 3.16 (m.2H); 3.89 (m, 2H); 4.02 (m, 1H); 7.27 (d, 1H, J = 7.7); 8.22 (s, 1H); 11.99 (s, 1H); 12.72 (br s, 1H)	387/ 389	Ejemplo 328

Ejemplo 284: 5-(4-{[(3,4-Dicloro-5-metil-1H-pirrol-2-il)carbonil] amino}piperidin-1-il)nicotinamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 8** comenzando a partir de 5-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil] amino}piperidin-1-il)ácido nicotínico (**Ejemplo 291**) y una solución de amoniaco en MeOH.

MS (ESP) (MH+): 396 para $C_{17}H_{19}Cl_2N_5O_2$

^{1}H NMR δ: 1.60-1.73 (m, 2H); 1.89-1.92 (m, 2H); 2.17 (s, 3H); 2.98 (t, 2H); 3.79-3.84 (m, 2H); 3.97(m, 1H); 7.33 (d, 1H); 7.51 (s, 1H); 7.69 (s, 1H); 8.09 (s, 1H); 8.41-8.44 (m, 2H); 12.04 (s, 1H).

Ejemplo 285: 5-(4-{[(3, 4-Dicloro-5-metil-1H-pirrol-2-il)carbonil] amino}piperidin-1-il]-N-metoxinicotinamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 8** comenzando a partir de 5-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil] amino}piperidin-1-il) ácido nicotínico (**Ejemplo 291**) y clorhidrato de metoxilamina.

MS (ESP) (MH^+): 426 para $C_{18}H_{21}Cl_2N_5O_3$

^{1}H NMR δ: 1.59-1.70 (m, 2H); 1.89-1.92 (m, 2H); 2.17 (s, 3H); 2.99 (t, 2H); 3.72 (s, 3H); 3.79-3.84 (m, 2H); 4.00 (m, 1H); 7.25 (d, 1H); 7.56 (s, 1H); 8.27 (s, 1H); 8.47 (d, 1H); 11.85 (s, 1H); 11.96 (s, 1H).

Ejemplo 286: 4-(4-{[(3,4-Dicloro-5-metil-1H-pirrol-2-il) carbonil] amino}piperidin-1-il)-N-metoxipiridina-2-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 8** comenzando a partir de 4-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil] amino}piperidin-1-il)piridina-2-ácido carboxílico (**Ejemplo 293**) y clorhidrato de metoxilamina.

MS (ESP) (MH^+): 426 para $C_{18}H_{21}Cl_2N_5O_3$

^{1}H NMR δ: 1.52-1.62 (m, 2H); 1.87-1.95 (m, 2H); 2.17 (s, 3H); 3.11 (t, 2H); 3.67 (s, 3H); 3.93-3.98 (m, 2H); 4.07 (m, 1H); 7.01 (m, 1H); 7.26 (d, 1H); 7.39 (d, 1H); 8.15 (d, 1H); 11.82 (s, 1H); 11.97 (s, 1H).

Ejemplos 287-294

Los siguientes ejemplos se prepararon mediante un método análogo al del **Ejemplo 310** comenzando a partir del éster y 2 N hidróxido de litio.

Ejemplo	Compuesto	^{1}H NMR δ	m/z (M+1)	MP
287	3-Bromo-5-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil) amino}piperidin-1-il) ácido benzoico	1.53-1.72 (m, 2H); 1.82-1.95 (m, 2H); 2.17 (s, 3H); 2.97 (t, 2H); 3.71-3.84 (m, 2H); 3.98 (m, 1H); 7.26 (d, 1H); 7.36 (s, 2H); 7.43 (s, 1H); 12.02 (s, 1H); 13.19 (br s, 1H).	474, 476 (M, M+2)	Ejemplo 212
288	3-Alil-5-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil] amino}piperidin-1-il) ácido benzoico	1.53-1.75 (m, 2H); 1.83-1.98 (m, 2H); 2.17 (s, 3H); 2.90 (t, 2H); 3.27-3.44 (m agua superpuesta, 2H); 3.61-3.78 (m, 2H)); 3.95 (m, 1H); 5.00-5.20 (m, 2H)); 5.94 (m, 1H); 7.05 (s, 1H); 7.18 (s, 1H); 7.26 (d, 1H); 7.32 (s, 1H); 11.97 (s, 1H); 12.78 (brs, 1H).	436	Ejemplo 295
289	3-(4-{[(3,4-Dicloro-5-metil-1H-pirrol-2-il)carbonil]amino} piperidin-1-il)-5-(2,3-dihidroxipropil) ácido benzoico	1.60-1.79 (m, 2H); 1.87-2.00 (m, 2H); 2.18 (s, 3H); 2.69-2.84 (m, 1H); 2.99 (t, 2H); 3.21-3.38 (m, 4H); 3.89-4.04 (m, 2H); 7.06-7.46 (m, 4H); 11.57 (s, 1H).	470	Ejemplo 296

Ejemplo	Compuesto	^{1}H NMR δ	m/z (M+1)	MP
290	5-(4-{[(3.4-Dicloro-5-metil-1H-pirrol-2-il)carbonil]amino} piperidin-1-il) ácido isoftálico	1.72-1.89 (m, 2H); 2.06-2.13 (m, 2H); 2.221 (s, 3H); 3.00 (t, 2H); 3.62-3.71 (m, 2H); 4.07 (m, 1H); 7.70 (s, 2H); 7.88 (s, 1H).	440	Ejemplo 297
291	5-(4-{[(3,4-Dicloro-5-metil-1H-pirrol-2-il)carbonil]amino} piperidin-1-il) ácido nicotínico	1.60-1.71 (m, 2H); 1.89-1.98 (m, 2H); 2.17 (s, 3H); 3.06 (t, 2H); 3.85-3.90 (m, 2H); 4.04 (m, 1H); 7.38 (d, 2H); 7.88 (s, 1H); 8.46 (s, 1H); 8.57 (s, 1H); 12.10(s, 1H).	397	Ejemplo 214
292	6-(4-{[(3,4-Dicloro. 5-metil-1H-pirrol-2-il)carbonil]amino} piperidin-1-il) piridina-2-ácido carboxílico	1.48-1.63 (m, 2H); 1.86-1.90 (m, 2H); 2.17 (s, 3H); 3.05 (t, 2H); 4.03 (m, 1H); 4.13-4.18 (m, 2H); 7.10 (d, 1H); 7.21-7.29 (m, 2H); 7.67 (m, 1H); 11.96 (s, 1H), 12.65 (br s, 1H).	397	Ejemplo 215

Ejemplo	Compuesto	^{1}H NMR δ	m/z (M+1)	MP
293	4-(4-{[(3,4-Dicloro-5-metil-1H-pirrol-2-il)carbonil)amino} piperidin-1-il) piridina-2-ácido carboxílico	1.55-1.67 (m, 2H); 1.93-1.99 (m, 2H); 2.18 (s, 3H); 3.31-3.39 (m, agua superpuesta, 2H); 4.13-4.18 (m, 3H); 7.15 (d, 1H); 7.41-7.56 (m, 2H); 7.99 (d, 1H); 12.14 (s, 1H).	397	Ejemplo 299
294	5-(4-{[(3,4-Dicloro-5-metil-1H-pirrol-2-il)carbonil]amino} piperidin-1-il) ácido nicotínico 1-óxido	1.55-1.70 (m, 2H); 1.80-1.93 (m, 2H); 2.17 (s, 3H); 3.03 (t, 2H); 3.75-3.85 (m, 2H); 4.00 (m, 1H); 7.20-7 33 (m, 2H); 7.90 (s, 1H); 8.17 (s, 1H); 12.01, s, 1H); 13.73 (br s, 1H).	413	Ejemplo 300

Ejemplos 295-300

Los siguientes compuestos se prepararon mediante un método análogo al del **Ejemplo 118** comenzando a partir de 3, 4-dicloro-5-metil-1*H*-pirrol-2-ácido carboxílico (**Intermedio 3**) y los intermedios que se muestran en la siguiente tabla.

Ejemplo	Compuesto	^{1}H NMR δ	M+1	MP

Ejemplo	Compuesto	^{1}H NMR δ	M+1	MP
295	Metil 3-alil-5-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino} piperidin-1-il) ácido benzoico	1.60-1.70 (m, 2H); 1.86-1.93 (m, 2H); 2.17 (s, 3H), 2.93 (t, 2H); 3.37 (d, 2H); 3.68-3.73 (m, 2H); 3.82 (s, 3H); 3.96 (m, 1H), 5.05-5.14 (m. 2H); 5.94 (m, 1H); 7.20-7.33 (m, 4H); 11.95 (s, 1H)	450	**Intermedio 143**
296	Metil 3-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino} piperidin-1-il)-5-(2,3-dihidroxi propil)benzoato	1.55-1.71 (m, 2H); 1.88-1.94 (m, 2H); 2.17 (s, 3H); 2.76 (m, 1H); 2.90 (t, 2H); 3.22-333 (m, 3H); 3.57-3.70 (m, 4H); 3.81 (s, 3H); 3.92-3.96 (m, 2H); 7.10 (s, 1H); 7.25-7.35 (m, 3H); 11.97 (s, 1H).	484	**Intermedio 144**
297	Dimetil 5-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil] amino}piperidin-1-il)isoftalato	1.60-1.70 (m, 2H); 1.91-1.98 (m, 2H)); 2.17(s, 3H); 3.00 (t, 2H)); 3.76-3.81 (m, 2H); 3.87 (s, 6H); 4.00 (m, 1H); 7.25 (d, 1H); 7.71 (s, 2H); 7.87 (s, 1H); 11.95 (s, 1H)	468	**Intermedio 145**

Ejemplo	Compuesto	^{1}H NMR δ	M+1	MP
298	Dimetil 2-(4-{[(3,4-dicloro-5-metil-1 H-pirrol-2-il)carbonil] amino}piperidin-1-il)tereftalato	1.65-1.76(m, 2H); 1.90-1.98 (m, 2H); 2.18 (s, 3H); 2.87 (t, 2H); 3.24-3.28 (m, 2H); 3.85 (s, 3H); 3.87 (s, 3H); 3.91 (m, 1H): 7.29(d. 1H): 7.53-7.69 (m, 3H); 11.97 (s, 1H).	468	**Intermedio 145**
299	Metil 4-(4-{[3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino} piperidin-1-il) piridina-2-carboxilato	1.47-1.63 (m, 2H); 1.87-1.92 (m, 2H); 2.17 (s, 3H); 3.13 (t, 2H); 3.85 (s, 3H); 3.95-4.06 (m, 2H); 4.09 (m, 1H); 7.08 (m, 1H); 7.23 (d, 1H); 7.47 (s, 1H); 8.24 (d, 1H); 11.96 (s, 1H).	411	**Intermedio 147**
300	Metil 5-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino} piperidin-1-il) nicotinato 1-óxido	1.50-1.66 (m, 2H); 1.85-1.88 (m, 2H); 2.17 (s, 3H); 3.04 (t, 2H); 3.78-3.83 (m, 2H); 3.87 (s, 3H); 4.00 (m, 1H); 7.23 (d, 1H); 7.35 (s, 1H); 7.93 (s, 1H); 8.18(s, 1H); 11.96(s, 1H).	427	**Intermedio 148**

Ejemplo 301: Metil 1-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino}piperidin-1-il)isoquinolina-3-carboxilato

En un envase sellado de alta presión con un recubrimiento de teflón, se combinó metil 1-cloroisoquinolina-3-carboxilato (**Intermedio 86**; 450 mg, 2 mmol), (1.7 g, 4.4mmol) y K_2CO_3 (1.7 g) en 20 ml tert-butanol. El

envase se calentó a 155 °C y se revolvió durante 3 horas. La solución se concentró mediante evaporación rotatoria y se reconstituyó con EtOAc.
La capa orgánica se lavó 4x con H_2O y se lavó sobre $MgSO_4$. El producto crudo se purificó mediante Si instantánea y se recolectaron 100 mg de un sólido amarillo.
MS(ES): 461 $(M+H)^+$, MS (ES): 459 $(M-H)^-$.
^{1}H NMR δ: 1.89 (m, 2H) 2.03 (s, 2 H) 2.19 (s, 3H) 3.06 - 3.21 (m, 2H) 3.89 (s, 2 H) 4.05 (s, 1H) 7.33 (s, 1H) 7.79 (s, 2 H) 8.11 (m, 2H) 8.19 (s, 1H) 12.02 (s, 1H).

Ejemplo 302: Metil 5-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino}piperidin-1-il)-1,3,4-oxadiazol-2-carboxilato

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 42** mediante el acoplamiento de metil 5-{4-[(tert-butoxicarbonil)amino]piperidin-1-il}-1,3,4-oxadiazol-2-carboxilato (**Intermedio 160**) con 3,4-dicloro-5-metil-1*H*-pirrol-2-ácido carboxílico (**Intermedio 3**). De-BOC y el acople deben ser pasos separados.
MS (ESP): 402.0 (M+H) para $C_{15}H_{17}Cl_2N_5O_4$
^{1}H NMR δ: 1.57 (m, 2H); 1.86 (d, 2H); 2.11 (s, 3H); 3.02 (m, 2H); 3.82 (s, 3H); 3.84 (d, 2H); 3.96 (m, 1H); 7.19 (d, 1H); 11.91 (s, 1H).

Ejemplo 303: 3,4-Dicloro-N-{1-[5-(hidroximetil)-1,3,4-oxadiazol-2-il]piperidin-4-il}-5-metil-1H-pirrol-2-carboxamida

Se agregó hidruro de diisobutilaluminio (0.94 ml, 1 M solución en tolueno, 0.94 mmol) en forma de goteo a una solución de metil 5-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino}piperidin-1-il)-1,3,4-oxadiazol-2-carboxilato (**Ejemplo 302**) (95 mg, 0.24 mmol) en THF (8 ml) a 0 °C. La mezcla resultante se dejó calentar lentamente hasta llegar a la temperatura ambiente y se revolvió durante la noche. Se agregó tartrato de potasio sódico (15ml, solución acuosa al 10%) y EtOAc (100 ml) a la mezcla de la reacción y la mezcla resultante se revolvió vigorosamente durante 1 h. La fase orgánica se separó, se lavó sobre sulfato de sodio, se filtró y se

concentró. El residuo crudo se purificó mediante HPLC de preparación de fase inversa (agua/acetonitrilo, gradiente 10-95%) para producir 45 mg del compuesto del título.

MS (ESP): 374.0 (M+H) para $C_{14}H_{17}Cl_2N_5O_3$

^{1}H NMR δ: 1.55 (m, 2H); 1.83 (d, 2H); 2.11 (s, 3H); 3.13 (t, 2H); 3.74 (d, 2H); 3.94 (m, 1H); 4.38 (s, 2H); 5.80 (br s, 1H); 7.19 (d, 1H); 11.90 (s, 1H).

Ejemplo 304: 5-(4-{[(3,4-Dicloro-5-metil-1H-pirrol-2-il)carbonil] amino}piperidin-1-il)-1,3,4-oxadiazol-2-ácido carboxílico

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 310** utilizando metil 5-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil] amino}piperidin-1-il)-1,3,4-oxadiazol-2-carboxilato (**Ejemplo 302**).

MS (ESP): 388.0 (M+H) para $C_{14}H_{15}Cl_2N_5O_4$

^{1}H NMR δ: 1.55 (m, 2H); 1.81 (d, 2H); 2.11 (s, 3H); 3.10 (t, 2H); 3.72 (d, 2H); 3.94 (m, 1H); 7.31 (d, 1H); 6.80-7.40 (br. s, 2H).

Ejemplo 305: 3,4-Dicloro-5-metil-N-[1-(1,3,4-oxadiazol-2-il) piperidin-4-il]-1H-pirrol-2-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 310** utilizando metil 5-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil] amino}piperidin-1-il)-1,3,4-oxadiazol-2-carboxilato (**Ejemplo 302**) (ocurrió una descarboxilación espontánea durante la hidrólisis).

MS (ESP): 344.2 (M+H) para $C_{13}H_{15}Cl_2N_5O_2$

Ejemplo 306: 3,4-Dicloro-5-metil-*N*-{1-[2-(metiltio)pirimidin-4-il]piperidin-4-il}-1*H*-pirrol-2-carboxamida

Se combinó 3,4-dicloro-*N*-[1-(2-cloropirimidin-4-il)piperidin-4-il]-5-metil-1*H*-pirrol-2-carboxamida (**Ejemplo 307**, 200 mg, 0.515 mmol) y tiometóxido sódico (108.2 mg, 1.545 mmol) en DMF (12ml) y se calentó a 90 °C durante 1 h. La mezcla de la reacción se enfrió a temperatura ambiente, se diluyó con EtOAc y agua. Las fases se separaron y la fase

acuosa se extrajo tres veces con EtOAc. Las porciones orgánicas combinadas se lavaron con solución salina, se secaron sobre Na_2SO_4, se filtraron y se concentraron bajo presión reducida para producir un sólido de color durazno (200 mg, 0.499 mmol, rendimiento del 97%) que se utilizó sin una purificación posterior.

MS(ES⁻): 398.12, 400.05 para $C_{16}H_{19}Cl_2N_5OS$

^{1}H NMR δ: 1.25 (m, 2H); 1.62 (m, 2H); 1.93 (s, 3H); 2.17 (s, 3H); 2.86 (m, 2H); 3.83 (m, 1H); 4.07 (m, 2H); 6.35 (d, 1H); 7.00 (d, 1H); 7.76 (d, 1H); 11.72 (s, 1H)

Ejemplo 307: 3,4-Dicloro-*N*-[1-(2-cloropirimidin-4-il)piperidin-4-il]-5-metil-1H pirrol-2-carboxamida

Se combinó 3,4-dicloro-5-metil-*N*-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 1**, 650 mg, 2.08 mmol), 2,4-dicloropirimidina (309.7 mg, 2.08 mmol) y Et_3N (0.6 ml, 4.16 mmol) en DMF (12 ml) y se calentó a 90 °C bajo nitrógeno durante 1.5 h. Una vez se enfrió a temperatura ambiente, la reacción se diluyó con EtOAc y agua.

Las fases se separaron y la porción acuosa se extrajo dos veces con EtOAc. Las porciones orgánicas combinadas se lavaron con solución salina, se lavaron sobre Na_2SO_4, se filtraron y se concentraron bajo presión reducida para producir un sólido marrón claro. El material crudo se trituró con MeOH frío y se filtró para producir 458 mg (1.18 mmol, 57%) del producto del título.

MS(ES⁻): 386.09, 388.03, 389.83 para $C_{15}H_{16}Cl_3N_5O$

^{1}H NMR δ: 1.60 (m, 2H); 1.93 (m, 2H); 2.23 (s, 3H); 3.22 (m, 2H); 4.17 (m, 2H); 4.34 (m, 1H); 6.94 (d, 1H); 7.27 (d, 1H); 8.12 (d, 1H); 12.02 (s, 1H)

Ejemplo 308: 1-(6-Cloro-4-cianopiridin-2-il)piperidin-4-ilo 3,4-dicloro-5-metil-1H-pirrol-2-carboxilato

Se disolvió 3,4-dicloro-5-metil-1H-pirrol-2-ácido carboxílico (**Intermedio 3**, 164 mg, 0.84 mmol) en THF anhidro (3 ml). Se agregó 2-cloro-6-(4-

hidroxipiperidin-1-il)isonicotinonitrilo (**Intermedio 26**), 200 mg, 0.84 mmol), luego se agregó DEAD (133 µl, 0.84 mmol) en forma de goteo seguido por trifenilfosfina (221 mg, 0.84mmol). La mezcla se revolvió a temperatura ambiente durante 18 h. La mezcla se concentró, se filtró y se purificó mediante HPLC de semi preparación de fase invertida levigado con CH_3CN/agua (TFA al 0.1 %).

(135 mg).

MS (ES, M+H): 413 para $C_{17}H_{15}Cl_3N_4O_2$

^{1}H NMR δ: 1.63 (m, 2H); 1.80 (m, 2H); 2.08 (s, 3H); 3.70 (m, 4H); 5.21 (m, 1H); 7.14 (s, 1H); 7.32 (s, 1H); 12.12 (s, 1H)

Ejemplo 309: 3,4-Dicloro-N-{1-[6-cloro-4-(hidrazinacarbonil) piridin-2-il]piperidin-4-il}-5-metil-1H-pirrol-2-carboxamida

Se agregó diisopropiletilamina (0.043 ml, 0.25 mmol), HATU (0.048 g, 0.12 mmol) y HOAT (0.017 g 0.12 mmol) a una solución agitada de 2-cloro-6-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino} piperidin-1-il) ácido isonicotínico (**Ejemplo 153**; 0.055 g, 0.12 mmol) en DMF (2ml). La solución resultante se revolvió durante 5 mins y se agregó hidrazina (0.04 ml, 0.12 mmol). La mezcla se revolvió a temperatura ambiente durante 14 h, se distribuyó entre agua y EtOAc. Las capas se separaron y la capa orgánica se lavó con agua dos veces más. La fase orgánica se lavó sobre sulfato de magnesio y se concentró para producir el compuesto del título (30 mg).

MS (ES): 445 (MH^+) para $C_{17}H_{19}Cl_3N_6O_2$

Ejemplo 310: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)-2-morfolin-4-ilpirimidina-4-ácido carboxílico

Se disolvió metil 6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino} piperidin-1-il)-2-morfolin-4-ilpirimidina-4-carboxilato (**Ejemplo 9**, 224 mg, 0.45 mmol) en MeOH (5 ml). Se agregó 2 N hidróxido de litio (2 ml) y la reacción se revolvió a temperatura ambiente durante 3 h. La mezcla se acidificó con 1 N HCl y se extrajo con EtOAc

(3x50 ml), se lavó sobre Na_2SO_4 y se concentró al vacío para producir 200 mg del compuesto del título.

MS (ESP): 483.4 (M+H) para $C_{20}H_{24}Cl_2N_6O_4$

Ejemplo 311: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)-2-metoxipirimidina-4-ácido carboxílico

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 312** utilizando metil 2-cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il) pirimidina-4-carboxilato (**Ejemplo 6**) y metóxido sódico.

MS (ES): 428 (M+1) para $C_{17}H_{19}Cl_2N_5O_4$

^{1}H NMR δ: 1.54 (m, 2H); 1.88 (m, 2H); 2.16 (s, 3H); 3.20 (t, 2H); 3.86 (s, 3H); 4.10 (m, 1H); 4.40 (m, 2H); 7.05 (s, 1H); 7.24 (d, 1H); 11.97(s, 1H).

Ejemplo 312: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il) carbonil] amino}piperidin-1-il)-2-etoxipirimidina-4-ácido carboxílico

Se agregó solución de etóxido de sodio (1 ml, 3.0 mmol, 21 peso % en EtOH) a una solución agitada de metil 2-cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)pirimidina-4-carboxilato (**Ejemplo 6**, 0.40 g, 0.89 mmol) en DMF (1.5 ml). La reacción se revolvió durante la noche, luego se extinguió con agua (2 ml) y se extrajo el EtOH bajo presiones reducidas. La solución acuosa resultante se acidificó con 1 N HCl (pH ~ 2) y el producto precipitado se recolectó mediante filtración por succión (0.07 g).

MS (ES): 442 (M+1) para $C_{18}H_{21}Cl_2N_5O_4$

^{1}H NMR δ: 1.28 (t, 3H); 1.49 (m, 2H); 1.86 (m, 2H); 2.15 (s, 3H); 3.16 (t, 2H); 4.07 (m, 1H); 4.27 (q, 2H); 4.29 (m, 2H); 6.99 (s, 1H); 7.19 (d, 1H); 11.95 (s, 1H)

Ejemplo 313: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)-2-[(2,2-dimetil-1,3-dioxolan-4-il)metoxi]-*N*-metoxipirimidina-4-carboxamida

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 8** comenzando a partir de 6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino} piperidin-1-il)-2-[(2,2-dimetil-1,3-dioxolan-4-il) metoxi] pirimidina-4-ácido carboxílico (**Ejemplo 314**) y clorhidrato de metoxilamina.

MS (ES) MH+: 557 para $C_{23}H_{30}Cl_2N_6O_6$

Ejemplo 314: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino} piperidin-1-il)-2-[(2,2-dimetil-1,3-dioxolan-4-il) metoxi] pirimidina-4- ácido carboxílico

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 154** comenzando a partir de (2,2-dimetil-1,3-dioxolan-4-il) MeOH (disponible en el comercio) e hidruro de sodio y haciendo reaccionar el alcóxido generado in situ con metil 2-cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)pirimidina-4-carboxilato (**Ejemplo 6**).

MS (ES) MH^+: 528 para $C_{22}H_{27}Cl_2N_5O_6$

Ejemplo 315: Metil 2-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)-6-metoxipirimidina-4-carboxilato

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 6** comenzando a partir de 3,4-dicloro-5-metil-N-piperidin-4-il-1H-pirrol-2-clorhidrato de carboxamida (**Intermedio 1**) y metil 2-cloro-6-metoxipirimidina-4-carboxilato (**Intermedio 88**).

MS (ES) MH^+: 442 para $C_{18}H_{21}Cl_2N_5O_4$

Ejemplo 316: Metil 6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2- il) carbonil]amino}piperidin-1-il)-2-pirrolidin-1-ilpirimidina-4- carboxilato

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 9** comenzando a partir de metil 2-cloro-6-(4-{[(3,4-dicloro-5-

metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il) pirimidina-4-carboxilato (Ejemplo 6), pirrolidina y TEA.
MS (ES⁻): 479.34, 481.34

Ejemplo 317: Metil 6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)-2-piperazin-1-ilpirimidina-4-carboxilato

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 9** comenzando a partir de metil 2-cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)pirimidina-4-carboxilato (**Ejemplo 6**), piperazina y TEA.
MS(ES⁻): 494.60, 496.59

Ejemplo 318: Metil 6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)-2-(4-metilpiperazin-1-il)pirimidina-4-carboxilato

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 9** comenzando a partir de metil 2-cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)pirimidina-4-carboxilato (**Ejemplo 6**), 1-metilpiperazina y TEA.
MS (ES⁻): 508.61, 510.60

Ejemplo 319: 2-(2-Aminoetoxi)-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-*N*-metoxipirimidina-4-carboxamida

El compuesto del título se sintetizó por medio de un método análogo al del **Intermedio 70** comenzando a partir de *tert*-butil 2-({4-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-6-[(metoxiamino) carbonil]pirimidin-2-il}oxi) etilcarbamato (**Ejemplo 322**).
MS (ES) MH^+: 486 para $C_{19}H_{25}Cl_2N_7O_4$

Ejemplo 320: Metil 2-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino}piperidin-1-il)-1,3-tiazol-5-carboxilato

Se disolvió 3,4-dicloro-5-metil-N-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 1**, 0.300 g, 0.961 mmol) en NMP (3ml). Se agregó TEA (267 µl, 1.922 mmol) seguido por la adición de metil 2-bromo-1,3-tiazol-5-carboxilato (0.213 g, 0.961 mmol) a temperatura ambiente. Empleando un Smith Microwave Synthesizer, la mezcla se sometió a microondas unimodal a 150 °C durante 20 minutos y se distribuyó entre agua y EtOAc. La capa orgánica se lavó con agua y la fase orgánica combinada se lavó sobre sulfato de magnesio y se concentró para producir el producto deseado. (432 mg).

MS (ES): 417 (MH^+) para $C_{16}H_{18}Cl_2N_4O_3S$

^{1}H NMR δ: 1.70 (m, 2H); 1.97 (m, 2H); 2.24 (s, 3H); 3.39 (m, 2H); 3.81 (s, 3H); 4.03 (m, 2H); 4.13 (m, 1H); 7.34 (d, 1H); 7.93 (s, 1H); 12.03 (s, 1H)

Ejemplo 321: 3,4-Dicloro-N-[1-(5-ciano-1,3-tiazol-2-il) piperidin-4-il-5-metil-1H-pirrol-2-carboxamida

A una solución de 3,4-dicloro-5-metil-*N*-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 1**; 0.330 g, 1.058 mmol) en NMP (2 ml) se agregó TEA (0.150 ml, 1.058 mmol) seguido por la adición de 2-bromo-1,3-tiazol-5-carbonitrilo (preparado de acuerdo con F. Campagna y colaboradores. *Tet. Lett*, 1977, 21, 1815-1816) (0.200 g, 1.058 mmol) a temperatura ambiente. Empleando un Smith Microwave Synthesizer, la mezcla se sometió a microondas unimodal a 150 °C durante 20 minutos. La mezcla cruda se diluyó con EtOAc y se lavó con agua varias veces. Los extractos se combinaron, se lavaron sobre sulfato de magnesio y se concentraron para producir el producto deseado. (0.450 g).

MS (ES): 384 (MH^+) para $C_{15},H_{15}Cl_2N_5OS$

^{1}H NMR δ: 1.77 (m, 2H); 1.98 (m, 2H); 2.24 (s, 3H); 3.47 (m, 2H); 4.02 (m, 2H); 4.16 (m, 1H); 7.36 (d, 1H); 8.09 (s, 1H); 12.03 (s, 1H)

Ejemplo 322: *tert*-Butil 2-({4-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2il)carbonil]amino}piperidin-1-il)-6-[(metoxiamino)carbonil] pirimidin-2-il}oxi)etilcarbamato

El compuesto del título se sintetizó mediante un método análogo al del **Ejemplo 8** comenzando a partir de 2-{2-[(*tert*-butoxicarbonil)amino]etoxil-6-(4-{[(3,4-dicloro-5-metil- 1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il) pirimidina-4-ácido carboxílico (**Ejemplo 154**) y clorhidrato de metoxilamina.

MS (ES) MH^+: 586 para $C_{24}H_{33}Cl_2N_7O_6$

Ejemplos 323-328

Los siguientes ésteres se prepararon mediante un método análogo al del **Ejemplo 134** a partir de 3,4-dicloro-5-metil-*N*-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 1**) y los materiales de partida indicados.

Ejemplo	Compuesto	^{1}H NMR δ	m/z (ES+)	MP
323	Etilo 8-metoxi-4-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino}piperidin-1-il) quinolina-2-carboxilato		505 / 507	Etil 4-cloro-8-metoxiquinolina-2-carboxilato (**Intermedio 137**)
324	Metilo 8-fluoro-4-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino} piperidin-1-il) quinolina-2-carboxilato	1.98 (m, 2H); 2.03 (m, 2H); 2.18(s, 3H); 3.11 (m, 2H); 3.33(s, 1H); 3.60 (m, 2H); 3.94 (s, 3H); 4.03 (m, 1H);	479 / 481	Metil 4-cloro-8-fluoroquinolina-2-carboxilato (**Intermedio 138**)

Ejemplo	Compuesto	^{1}H NMR δ	m/z (ES+)	MP
		7.34 (m, 1H); 7.62 (m, 2H); 7.83 (m, 1H); 12.02 (s, 1H)		
325	Metil 6-fluoro-4-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino} piperidin-1-il) quinolina-2-carboxilato	1.92 (m, 2H); 2.03 (m, 2H); 2.18 (s, 3H); 3.11 (m, 2H); 3.60(m, 2H); 3.94 (s, 3H); 4.05 (m, 1H); 732 (d, 1H,J=7.5); 7.60 (s, 1H); 7.63 (m, 1H); 7.99 (m, 2H); 12.01 (s, 1H)	495 / 497	Metil 4-cloro-6-fluoroquinolina-2-carboxilato **(Intermedio 140)**
326	Metilo 8-cloro-4-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino} piperidin-1-il) quinolina-2-carboxilato	1.92 (m, 2H); 2.03 (m, 2H); 2.18 (s, 3H); 3.11 (m, 2H); 3.60 (m, 2H); 3.94 (s, 3H); 4.05 (m, 1H); 7.32 (d, 1H, J=7.5); 7.53 (m, 1H);	ES^+ 475 / 497	Metil 4,8-dicloroquinolina-2-carboxilato **(Intermedio 141)**

Ejemplo	Compuesto	^{1}H NMR δ	m/z (ES+)	MP
		7.60 (m, 2H); 7.99 (m, 2H); 12.01 (s, 1H)		
327	Metilo 8-metil-4-(4-{[(3,4-dicloro-5-metil-il) carbonil]amino} piperidin-1-il) quinolina-2-carboxilato	1.91 (m, 2H); 2.04 (m, 2H); 2.17 (s, 3H); 2.72 (s, 3H); 3.05 (m, 2H); 3.55 (m, 2H); 3.93 (s, 3H); 4.03 (m, 1H); 7.32 (m, 1H); 7.59 (m, 3H); 7.86 (m, 1H); 12.01 (s, 1H)	ES^+ 475 / 477	Metil 4-cloro-8-metilo quinolina-2-carboxilato **(Intermedio 139)**
328	Etil 2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil)amino} piperidin-1-il) oxazol-4-carboxilato	1.26 (t, 3H, J = 7.1); 1.60 (m, 2H); 1.88 (m, 2H); 2.18 (s, 3H); 3.17 (m, 2H); 3.90 (m, 2H); 4.02 (m, 1H); 4.24 (q, 2H, J=7.9); 8.31 (s, 1H); 11.99 (s, 1H)	415 / 417	Etil 2-cloro-oxazol-4 carboxilato **(Intermedio 142)**

Ejemplo 329: 3, 4-Dicloro-5-metil-N-[1-(1,3-tiazol-2-il)piperidin-4-il]-1H-pirrol-2-carboxamida

Se disolvió 3,4-dicloro-5-metil-*N*-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 1**; 1 g, 3.2 mmol) en NMP (10ml). Se agregó bromotiazol (2.65 g; 16 mmol) seguido por la adición de *N,N*-diisopropiletilamina (2.75 ml, 16 mmol).

Empleando un Smith Microwave Synthesizer, la mezcla se sometió a microondas unimodal a 150 °C por un total de 3 h. La mezcla se diluyó con EtOAc y se lavó bien con agua, $NaHCO_3$, solución salina. La fase orgánica se lavó sobre Na_2SO_4 y se concentró al vacío para producir el compuesto del título como un sólido marrón (692 mg).

MS (ES) MH^+: 361 para $C_{14}H_{16}Cl_2N_4OS$

^1H NMR δ: 1.78 (m, 2H); 1.98 (m, 2H); 2.26 (s, 3H); 3.28 (m, 2H); 3.95 (m, 2H); 4.12 (m, 1H); 6.93 (d, 1H); 7.22 (s, 1H); 7.31 (d, 1H); 12.10 (s, 1H).

Ejemplo 330: 1-(6-Cloro-4-cianopiridin-2-il)piperidin-4-il-4-bromo-5-metil-1H-Pirrol-2-carboxilato

El compuesto del título se preparó en forma análoga al **Ejemplo 308** a partir de 2-cloro-6-(4-hidroxipiperidin-1-il)isonicotinonitrilo (**Intermedio 26**) y 4-bromo-5-metil-1H-pirrol-2-ácido carboxílico (**Intermedio 18**).

MS (ES)M+H: 425 para $C_{17}H_{16}BrClN_4O$

Ejemplo 331: Metil 2-(4-{[5-metil-1H-pirrol-2-il)carbonil]amino} piperidin-1-il)-6-cloroisonicotinato

El compuesto del título se preparó en forma análoga al **Ejemplo 18** comenzando a partir de 5-metil-1H-pirrol-2-ácido carboxílico (**Intermedio 29**) y metil 2-(4-aminopiperidin-1-il)-6-cloroisonicotinato sal de clorhidrato (**Intermedio 93**).

MS (ES, M+H): 376 para $C_{18}H_{21}ClN_4O_3$

Ejemplo 332: 2-Cloro-6-(4-{[(5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1il)ácido isonicotínico

El compuesto del título se preparó en forma análoga al **Ejemplo 44** comenzando a partir de metil 2-(4-{[5-metil-1*H*-pirrol-2-il)carbonil]amino} piperidin-1-il)-6-cloroisonicotinato (**Ejemplo 331**).

MS (ES, M+H): 362 para $C_{17}H_{19}ClN_4O_3$

Ejemplo 333: Metil 2-cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol -2-il)carbonil]amino}piperidin-1-il)isonicotinato

El compuesto del título se preparó en forma análoga al **Ejemplo 18** comenzando a partir de 3,4-dicloro-5-metil-1*H*-pirrol-2-ácido carboxílico (**Intermedio 3**) y metil 2-(4-aminopiperidin-1-il)-6-cloroisonicotinato sal de clorhidrato (**Intermedio 93**).

MS (ES, M+H): 445,447 para $C_{18}H_{19}Cl_3N_4O_3$

Ejemplo 334: Metil 2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino}piperidin-1-il)-6-(metilsulfinil) isonicotinato

El compuesto del título se preparó en forma análoga al **Ejemplo 6** comenzando a partir de 3,4-dicloro-5-metil-*N*-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 1**) y metil 2-cloro-6-(metilsulfinil) isonicotinato (**Intermedio 84**).

MS (ES, M+H): 473,471 para $C_{19}H_{22}Cl_2N_4O_4S$

Ejemplo 335: 6-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)-2-pirrolidin-1-ilpirimidina-4-ácido carboxílico

El compuesto del título se sintetizó mediante un método análogo al del **Intermedio 3** comenzando a partir de metil 6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-2-pirrolidin-1-ilpirimidina-4-carboxilato (**Ejemplo 316**).

MS (ES): 465.3 (M-H) para $C_{20}H_{24}Cl_2N_6O_3$

^{1}H NMR δ: 1.5 (q, 2H); 1.86 (br s, 4H); 2.11 (s, 3H); 3.21 (t, 2H); 3.49 (br s, 4H); 3.6-4.5 (m, 6H); 6.84 (s, 1H); 7.16 (d, 1H); 11.93 (s, 1H).

Ejemplo 336: Etil 2-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-1,3-tiazol-4-carboxilato

El compuesto del título se preparó en forma análoga al **Ejemplo 320** a partir de 3,4-dicloro-5-metil-*N*-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 1**) y etil 2-bromo-1,3-tiazol-4-carboxilato (disponible en el comercio).

MS (ES) M+H: 431,433 para $C_{17}H_{20}Cl_2N_4O_3S$

Ejemplo 337: 3,4-Dicloro-*N*-(1-(4-ciano-1,3-tiazol-2-il) piperidin-4-il]-5-metil-1*H*-pirrol-2-carboxamida

El compuesto del título se preparó como se describe para el **Ejemplo 321** a partir de 3,4-dicloro-5-metil-*N*-piperidin-4-il-1*H*-pirrol-2-clorhidrato de carboxamida (**Intermedio 1**) y 2-bromo- 1,3-tiazol-4-carbonitrilo (preparado como se describe en *J. Am. Chem. Soc.* **1952**, 74, 5799).

MS (ES) (M+H): 384 para $C_{15}H_{15}Cl_2N_5OS$

^{1}H NMR δ: 1.69-1.77 (m, 2H); 1.98 (dd, 2H); 2.24 (s, 3H); 3.42 (m, 2H); 3.97 (d, 2H); 4.10 - 4.16 (m, 1H); 7.34 - 7.36 (d, 1H); 8.09 (s, 1H); 12.03 (s, 1H).

Ejemplo 338: 4-Bromo-*N*-[1-(4-cianopiridin-2-il) piperidin-4-il]-5-metil-1*H*-pirrol-2-carboxamida

El compuesto del título se preparó en forma análoga al **Ejemplo 18** a partir de 3,4-dicloro-5-metil-1*H*-pirrol-2-ácido carboxílico (**Intermedio 3**) y 2-(4-aminopiperidin-1-il) isonicotinonitrilo sal de clorhidrato (**Intermedio 208**).

MS (ES): 412 (M+H) para $C_{17}H_{16}Cl_3N_5O$

Ejemplo 339: Etil 4-[(*tert*-butilamino)carbonil]-2-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-1,3-tiazol-5-carboxilato

Ejemplo 340: 5-Tiazol ácido carboxílico, 4-ciano-2-[4-[[(3,4-dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino]-1-piperidinil]-, etiléster

Una solución de etil 2-{4-[(*tert*-butoxicarbonil)amino]piperidin-1-il}-4-ciano-1,3-tiazol-5-carboxilato (**Intermedio 223**) (1.9 g) y 15 ml TFA en 20 ml DCM se revolvió a temperatura ambiente durante la noche. El solvente se extrajo y el residuo se absorbió en DCM y se lavó con Na_2CO_3 acuoso y solución salina. El secado ($MgSO_4$) y la extracción del solvente produjeron 920 mg de un aceite marrón oscuro. A una solución de 880 mg (3.1 mmol) del aceite y diisopropiletilamina (0.7ml, 3.8 mmol) se agregó 3,4-dicloro-5-metil-1*H*-pirrol-2-carbonilo cloruro (**Intermedio 224**) (800 mg, 3.8mmol) y la mezcla se revolvió a temperatura ambiente durante la noche. Se agregó más 3,4-dicloro-5-metil-1*H*-pirrol-2-carbonilo cloruro (100 mg) y se continuó revolviendo durante 2 horas. La mezcla se diluyó con EtOAc y se lavó con agua y solución salina. El secado ($MgSO_4$) y la extracción del solvente produjeron un aceite el cual se sometió a cromatografía sobre gel de sílice (DCM seguido por gradiente de elución a MeOH al 5% en DCM). Durante la desprotección de TFA, se observó una reacción del isobutileno con el grupo nitrilo - la mezcla se continuó. El material principal se aisló y se sometió a cromatografía HPLC de fase inversa (45-65% gradiente de CH_3CN en agua con TFA al 0.1 %). Se aislaron dos materiales. El primer compuesto levigado fue el **Ejemplo 339**:

MS (ES): 530.1 $(M+H)^{+1}$, 528.2 $(M-H)^{-1}$

^{1}H NMR δ: 1.22 (t, *J*=7. 06Hz, 2H); 1.32 (s, 9H); 1.63 (s, 2H); 1.91 (s, 3H); 2.18 (s, 3H); 3.34 (s, 2H); 4.1 (m, 1H); 3.90 (s, 2H); 4.18 (q, *J*=7.16Hz, 2H); 7.30 (d, *J*=7.54Hz, 1H); 8.01 (s, 1H); 11.99 (s, 1H).

El segundo compuesto levigado fue el **Ejemplo 340**:

MS (ES): 456.0 $(M+H)^{+1}$, 454.1 $(M-H)^{-1}$

^{1}H NMR δ: 1.28 (t, *J*=7.06Hz, 3H); 1.55-1.75 (m, 2H); 1.82-2.02 (m, 2H); 2.18 (s, 3H); 3.33-3.52 (m, 2H); 3.85-4.02 (m, 2H); 4.04 (s, 1H); 4.30 (q, *J*=7. 10Hz, 2H); 7.29 (d, *J*=7.72Hz, 1H); 11.80 - 12.17 (m, 1H).

Ejemplo 341: 4-Ciano-2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino}piperidin-1-il)-1,3-tiazol-5-ácido carboxílico

Se calentó una solución de etil 4-[(*tert*-butilamino)carbonil]-2-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-1,3-tiazol-5-carboxilato (**Ejemplo 340**; 140 mg, 0.31 mmol) y 2 N LiOH en agua (0.93 ml, 1.86 mmol) en 6 ml 1:1 THF: MeOH a 80 °C durante 30 min en un reactor de microondas. Se agregó 1 N HCl (1.86ml) y la mezcla se diluyó con agua. El material precipitado se filtró y se enjuagó bien con agua. El secado del producto precipitado al vacío produjo 105 mg de producto.

MS (ES): 428.0 (M+H)

^{1}H NMR δ: 1.67 (s, 1H); 1.80-2.04 (m, 2H); 2.18 (s, 3H); 3.33 (s, 2H); 3.89 (s, 2H); 4.06 (d, *J*=5.09Hz, 1H); 7.30 (s, 1H); 12.03 (s, 1H); 13.92 (s, 1H).

Ejemplo 342: 4-[(*tert*-Butilamino)carbonil]-2-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-1,3-tiazol-5-ácido carboxílico

Se calentó una solución de 5-tiazol ácido carboxílico, 4-ciano-2-[4-[[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino]-1-piperidinil]-, etiléster (**Ejemplo 339**; 186 mg, 0.35 mmol) y 2 N LiOH en agua (0.35 ml, 0.7 mmol) en 6 ml MeOH a 80 °C durante 30 min en un reactor de microondas. Se agregó 1 N HCl (0.7ml) y la mezcla se diluyó con agua.

El material precipitado se filtró, se enjuagó bien con agua y se secó al vacío para producir 164 mg de producto.

MS (ES): 502.1 (M+H)

^{1}H NMR δ: 1.20-1.57 (m, 9H); 1.66 (s, 2H); 1.90 (s, 2H); 2.18 (s, 3H); 3.34 (s, 2H); 4.00 (s, 3H); 7.31 (d, *J*=7.72Hz, 1H); 12.01 (s, 1H); 16.06 (s, 1H).

Ejemplos 343-346

Los siguientes ejemplos se prepararon por medio del procedimiento del **Ejemplo 223** a partir de los materiales de partida indicados.

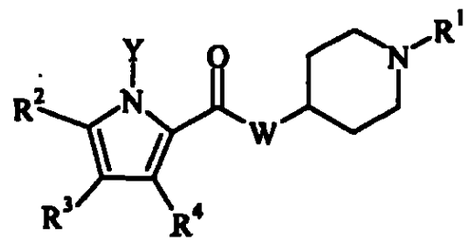
Ex.	R	^{1}H NMR δ	M+1	MP

Ex.	R	'H NMR δ	M+1	MP
343	2-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino} piperidin-1-il)-4-metil-1,3-tiazol-5-ácido carboxílico	1.62 (q, 2H); 1.89 (d, 2H); 2.16 (s, 3H); 2.91 (t, 2H); 3.55 (s, 3H); 3.69 (d, 2H); 3.87-4.04 (m, 1H); 7.26 (d, 1H); 11.95 (s, 1H).	417	Etil 2-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il) carbonil]amino} piperidin-1-il-4-metil-1,3-tiazol-5-carboxilato **(Ejemplo 218)**
344	3-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)ácido benzoico	1.65 (q, 2H); 1.89 (d, 2H); 2.16 (s, 3H); 2.91 (t, 2H); 3.70 (d, 2H); 3.83-4.04 (m, 1H); 7.17-7.27 (m, 2H); 7.27-7.40 (m, 2H); 7.45 (s, 1H); 11.94 (s, 1H).	396	Metil 3-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino} piperidin-1-il) benzoato **(Ejemplo 211)**
345	3-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)-5-morfolin-4-il ácido benzoico	1.63-1.85 (q, 2H); 1.90-2.06 (m, 2H); 2.13 (s, 3H); 3.05-3.23 (m, 6H); 3.59 (d, 2H); 3.71 (bs, 4H); 3.89-4.02 (m, 1H); 6.94 (s, 1H); 7.13(s, 1H); 7.19 (s, 1H).	481	Metil 3-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino} piperidin-1-il)-5-morfolin-4-ilbenzoato **(Ejemplo 216)**

Ex.	R	'H NMR δ	M+1	MP
346	3-(4-{[(3,4-Dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)-5-(4-metilpiperazin-1-il)ácido benzoico	1.51-1.73 (m, 2H); 1.80-1.97 (m, 2H); 2.14 (s, 3H); 2.53 (s, 4H); 2.81 (s, 3H); 2.87-3.01 (m, 3H); 3.04-3.24 (m, 2H); 3.39-3.56 (m, 2H); 3.65 (d, 2H); 6.76 (s, 1H); 6.94 (s, 1H); 7.04 (s, 1H).	495	Metil 3-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il) carbonil]amino} piperidin-1-il)-5-(4-metilpiperazin-1-il)benzoato **(Ejemplo 217)**

Reivindicaciones

1. Un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo:



(I)

donde:

W es O o NR^5;

Y es hidrógeno;

R^1 se selecciona entre R^1a, R^1b, R^1c, R^1d, R^1e y R^1f;

R^1a es un anillo heterocíclico saturado, parcialmente insaturado o insaturado de 4 a 7 miembros que contiene 1, 2, 3 o 4 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga enlaces O-O o S-S), donde un grupo $-CH_2-$ se puede reemplazar opcionalmente por un -C(O)-, un anillo de átomos de sulfuro opcionalmente se puede oxidar para formar el S-óxido (s) y un anillo de átomos de nitrógeno opcionalmente se puede oxidar para formar el N-óxido y donde el citado anillo se puede sustituir opcionalmente por 1, 2 o 3 radicales seleccionados independientemente entre: nitro, ciano, sulfo, formilo, hidroxiiminometilo, (2-6C)alquenilo, (2-6C)alquinilo, -CO(1-6C)alquilo, -COO(1-6C)alquilo (opcionalmente sustituido por -COO(1-6C)alquilo), trifluorometilo, $-CONR^6R^7$, $-OCONR^6R^7$, $-N(R^7)COR^6$, $-CONHCH(CO_2R^7)R^6$, halo, hidroxi, carboxi, (1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, halo, ciano, nitro, -COO(1-6C)alquilo, -OCO((1-4C)alquilo, (1-6C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, hidroxi(1-4C)alcoxi-, (2-4C)alqueniloxi, trifluorometilo, $-CONR^6R^7$, carboxi, -NHC(O)O(1-4C)alquilo, $-OCONR^6R^7$, -C(=NOH)(1-4C)alquilo, $-C(=NOH)NR^6R^7$, $-NHC(=NH)NR^6R^7$, $-NHC(O)NR^6R^7$, -NHC(O)(1-4C)alquilo, -

NHC(O)heterociclilo, -NHC(O)arilo, -NHS(O)p(1-4C)alquilo, -S(O)p(1-4C)alquilo, -S(O)pNR^{6}R^7, -NHSO$_2$R^6, -NR^{6}R^7 y heterociclilo], (3-6C) cicloalquilo (opcionalmente sustituido por 1 o 2 radicales seleccionados entre (1-6C)alquilo y los radicales opcionales descritos para (1-6C)alquilo arriba), -O(1-6C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), -S(O)p(1-4C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), heterociclilo, arilo, -NHC(O)O(1-4C)alquilo, -C(=NOR^7)(1-4C)alquilo, -C(=NOR^7)NR^{6}R^7, -S(O)pNR^{6}R^7, -S(O)p(1-4C)alquilCONHR^7, -NR^{7}S(O)pNR^{6}R^7, -NR^{7}S(O)p(1-4C)alquilo, -NR^{7}S(O)p-arilo, -C(O)NHS(O)p(1-4C)alquilo, -C(O)NHS(O)p-arilo, -NR^{6}R^7, -CH$_2$CH(CO$_2$R^6)OH, -(1-4C)alquilCH(NR^{6}R^7) CO$_2$R^6 y -(1-4C)alquilCH(NR^{6}R^7)CO(NR^{6}R^7); donde cualquier grupo arilo o heterociclilo en cualquiera de los anteriores valores para los radicales en R^{1}a puede sustituirse opcionalmente por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, hidroxi, (1-4C)alcoxi, halo, ciano, nitro, carboxi, hidroxi(1-4C)alquil-, (1-4C)alquil(1-4C)alquil-, halo(1-4C)alquil-, difluorometilo, trifluorometilo, trifluorometoxi, formilo, -CO(1-4C)alquilo -COO(1-4C)alquilo, -C(O)NH$_2$, -C(O)NH(1-4C)alquilo, -C(O)N[di(1-4C)alquilo], -S(O)$_2$NH$_2$, -S(O)$_2$NH(1-4C)alquilo y -S(O)$_2$N[di(1-4C)alquilo];

R^{1}b es un anillo bicíclico heterocíclico de 8-10 miembros que contiene 1, 2, 3 o 4 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga enlaces O-O o S-S), donde un grupo -CH$_2$- se puede reemplazar opcionalmente por un -C(O)-, un anillo de átomos de sulfuro opcionalmente se puede oxidar para formar el S-óxido (s) y un anillo de átomos de nitrógeno opcionalmente se puede oxidar para formar el N-óxido y donde el citado anillo se puede sustituir opcionalmente por 1, 2 o 3 radicales seleccionados independientemente entre los radicales enumerados para R^{1}a arriba;

R^{1}c es un anillo fenilo, sustituido por 1, 2 o 3 radicales seleccionados independientemente entre los radicales enumerados para R^{1}a arriba;

R^1d se selecciona entre -CH_2R^1a, -C(O)R^1a, -OR^1a, S(O)qR^1a (donde q es 1 o 2);

R^1e se selecciona entre -CH_2R^1b, -C(O)R^1b, -OR^1b, S(O)qR^1b (donde q es 1 o 2);

R^1f se selecciona entre -CH_2R^1c, -C(O)R^1c -OR^1c, S(O)qR^1c (donde q es 1 o 2);

R^2 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, (2-4C)alquenilo, (2-4C)alquinilo, halo, ciano, fluorometilo, difluorometilo y trifluorometilo;

R^3 se selecciona entre hidrógeno, (1-4C)alquilo, ciclopropilo, (2-4C)alquenilo, (2-4C)alquinilo, halo, hidroxi, ciano, fluorometilo, difluorometilo trifluorometilo, -CO(1-6C)alquilo y (1-6C)alcoxi;

R^4 se selecciona entre hidrógeno, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, nitro, hidroxi, halo, ciano, (3-6C)cicloalquilo, -(1-6C)alquil(3-6C) cicloalquilo, halo(1-4C)alquil-, difluorometilo, trifluorometilo, -CO(1-6C)alquilo y (1-6C)alcoxi;

R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-4C)alquenilo, (3-6C)cicloalquilo, -(1-4C)alquilC(O)O(1-4C)alquilo, hidroxi, amino, -NH(1-4C)alquilo, - N[di(1-4C)alquilo], (1-4C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi(1-4C)alcoxi, (1-4C)alcoxi(1-4C)alquil-, (1-4C)alquiltio(1-4C)alquil-, hidroxi(1-4C)alquil-, -(1-4C)alquilNH_2, -(1-4C)alquilNH(1-4C)alquilo, -(1-4C)alquilN[di(1-4C)alquilo] y -(1-4C)alquilheterociclilo;

R^7 se selecciona independientemente en cada caso entre hidrógeno y (1-6C)alquilo;

o R^6 y R^7 pueden junto con el nitrógeno al cual están adheridos formar un anillo heterociclilo de 5 o 6 miembros, opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, hidroxi, (1-4C)alcoxi, halo, ciano, nitro, carboxi, hidroxi(1-4C)alquil-, (1-4C)alcoxi (1-4C)alquil-, halo (1-4C)alquil-, difluorometilo, trifluorometilo, trifluorometoxi, formilo, -CO(1-4C)alquilo, -COO(1-4C)alquilo, -C(O)NH_2, -C(O)NH(1-4C)alquilo, -

C(O)N[di(1-4C)alquilo], $-S(O)_2NH_2$, $-S(O)_2NH$(1-4C)alquilo, $-S(O)_2N$[di(1-4C)alquil] y -S(O)p(1-4C)alquilo;
R^5 se selecciona entre hidrógeno y (1-4C)alquilo;
p es (independientemente en cada caso) 0, 1 o 2.

2. Un compuesto de fórmula (1) o una sal farmacéuticamente aceptable del mismo como se reivindica en la reivindicación 1 donde W es O.

3. Un compuesto de fórmula (1) o una sal farmacéuticamente aceptable del mismo como se reivindica en la reivindicación 1 donde W es NR^5.

4. Un compuesto de fórmula (1) o una sal farmacéuticamente aceptable del mismo como se reivindica en una cualquiera de las reivindicaciones 1-3 donde R^1 se selecciona entre R^1a, R^1b, R^1c y R^1d; donde.

R^1a es un anillo heterocíclico saturado, parcialmente insaturado o insaturado de 5 o 6 miembros que contiene 1, 2, 3 o 4 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga enlaces O-O o S-S), donde un grupo $-CH_2-$ se puede reemplazar opcionalmente por un -C(O)-, un anillo de átomos de sulfuro opcionalmente se puede oxidar para formar el S-óxido(s) y un anillo de átomos de nitrógeno opcionalmente se puede oxidar para formar el N-óxido y donde el citado anillo se puede sustituir opcionalmente por 1, 2 o 3 radicales seleccionados independientemente entre:
nitro, ciano, sulfo, formilo, hidroxiiminometilo, (2-6C)alquenilo, -CO(1-6C)alquilo, -COO(1-6C)alquilo trifluorometilo, $-CONR^6R^7$, $-N(R^7)COR^6$, halo, hidroxi, carboxi, (1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, -OCO(1-4C)alquilo, (1-6C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, hidroxi(1-4C)alcoxi, (2-4C)alqueniloxi, -NHC(O)O(1-4C)alquilo, $-NHC(=NH)NR^6R^7$, $-NHC(O)NR^6R^7$, -NHC(O)(1-4C)alquilo, -NHC(O)heterociclilo, -NHC(O)arilo, -NHS(O)p(1-4C)alquilo, -S(O)p(1-4C)alquilo, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$ y heterociclilo], (3-6C)cicloalquilo, -O(1-6C)alquilo

(opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba) -S(O)p(1-4C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), heterociclilo, -NHC(O)O(1-4C)alquilo, -C(=NOR^7)(1-4C)alquilo, -C(=NOR^7)NR^{6}R^7, -S(O)p(1-4C)alquilCONHR^7, -C(O)NHS(O)p(1-4C)alquilo y -NR^{6}R^7, donde cualquier grupo arilo o heterociclilo en cualquiera de los anteriores valores para los radicales en R^{1}a puede sustituirse opcionalmente por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo y carboxi;

R^{1}b es un anillo bicíclico heterocíclico de 10 miembros que contiene 1, 2 o 4 heteroátomos seleccionados independientemente entre S y N (siempre que dicho anillo no contenga enlaces S-S), donde un grupo -CH_2- se puede reemplazar opcionalmente por un -C(O)- y donde el citado anillo se puede sustituir opcionalmente por 1, 2 o 3 radicales seleccionados independientemente entre los radicales enumerados para R^{1}a arriba;

R^{1}c es un anillo fenilo, sustituido por 1, 2 o 3 radicales seleccionados independientemente entre los radicales enumerados para R^{1}a arriba;

R^{1}d se selecciona entre -CH_2R^{1}a y -C(O)R^{1}a.

5. Un compuesto de fórmula (1) o una sal farmacéuticamente aceptable del mismo como se reivindica en una cualquiera de las reivindicaciones 1-4 donde R^2 se selecciona entre (1-4C)alquilo, halo y ciano.

6. Un compuesto de fórmula (1) o una sal farmacéuticamente aceptable del mismo como se reivindica en una cualquiera de las reivindicaciones 1-5 donde R^3 se selecciona entre hidrógeno, (1-4C)alquilo, halo, ciano y -CO(1-6C)alquilo.

7. Un compuesto de fórmula (1) o una sal farmacéuticamente aceptable del mismo como se reivindica en una cualquiera de las reivindicaciones 1-6 donde R^4 se selecciona entre hidrógeno, (1-4C)alquilo, halo y ciano.

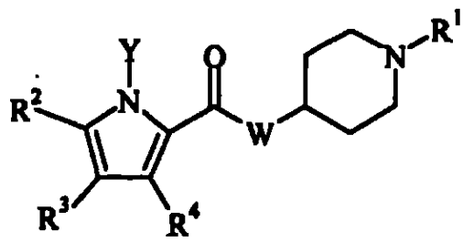
8. Un compuesto de fórmula (1) o una sal farmacéuticamente aceptable del mismo como se reivindica en una cualquiera de las reivindicaciones 1-7 donde:

R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-4C)alquenilo, (3-6C)cicloalquilo, -(1-4C)alquilC(O)O(1-4C)alquilo, hidroxi, amino, -N[di(1-4C)alquilo], (1-4C)alcoxi y -(1-4C)alquilheterociclilo;

R^7 se selecciona independientemente en cada caso entre hidrógeno y (1-6C)alquilo;

o R^6 y R^7 pueden junto con el nitrógeno al cual están adheridos formar un anillo heterociclilo de 5 o 6 miembros, opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo.

9. Un compuesto de fórmula (1) o una sal farmacéuticamente aceptable del mismo:



(1)

donde:

R^1 se selecciona entre R^1a, R^1b, R^1c y R^1d; donde

R^1a es piridinilo, *N*-oxopiridinilo, pirimidinilo, tiazolilo, tiadiazolilo, tetrazolilo, imidazolilo, triazinilo, pirrolidinilo, tienilo, furanilo, oxadiazolilo, isoxazolilo, oxazolilo o pirrolilo, donde el citado R^1a se puede sustituir opcionalmente por 1, 2 o 3 radicales seleccionados independientemente entre:

nitro, ciano, sulfo, formilo, hidroxiiminometilo, (2-6C)alquenilo, -CO(1-6C)alquilo, -COO(1-6C)alquilo trifluorometilo, $-CONR^6R^7$, $-N(R^7)COR^6$, halo, hidroxi, carboxi, (1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, -OCO(1-

4C)alquilo, (1-6C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, hidroxi(1-4C)alcoxi, (2-4C)alqueniloxi, -NHC(O)O(1-4C)alquilo, -NHC(=NH)NR^6R^7, -NHC(O)NR^6R^7, -NHC(O)(1-4C)alquilo, -NHC(O)tetrahidrofuranilo, -NHC(O)fenilo, -NHS(O)p(1-4C)alquilo, -S(O)p(1-4C)alquilo, -S(O)pNR^6R^7, -$NHSO_2R^6$, -NR^6R^7, morfolino, 1,3-dioxo-1,3-dihidro-2H-isoindolilo y 1,3-dioxolanil], ciclopropilo, -O(1-6C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), -S(O)p(1-4C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), tetrazolilo, 2-oxo-1,3,4-oxadiazolilo, 1,2,4-oxadiazolilo, morfolino, piperazinilo, pirrolidinilo, -NHC(O)O(1-4C)alquilo, -C(=NOR^7)(1-4C)alquilo, -C(=NOR^7)NR^6R^7, -S(O)p(1-4C)alquilCONHR^7, -C(O)NHS(O)p(1-4C)alquilo y -NR^6R^7;

donde cualquier fenilo, tetrahidrofuranilo, morfolino, 1,3-dioxo-1,3-dihidro-2H-isoindolilo, 1,3-dioxolanilo, tetrazolilo, 2-oxo-1,3,4-oxadiazolilo, 1,2,4-oxadiazolilo, morfolino, piperazinilo, pirrolidinilo, en cualquiera de los anteriores valores para los radicales en R^1a puede sustituirse opcionalmente por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo y carboxi;

R^1b es R^1b es quinolinilo, purinilo, benzotiazolilo, indolilo, 4-oxoquinolinilo, 2,7-naftiridinilo o quinazolinilo y donde el citado R^1b se puede sustituir opcionalmente por 1, 2 o 3 radicales seleccionados independientemente entre los radicales enumerados para R^1a arriba;

R^1c es un anillo fenilo, sustituido por 1, 2 o 3 radicales seleccionados independientemente entre los radicales enumerados para R^1a arriba;

R^1d se selecciona entre -CH_2R^1a y -C(O)R^1a;

R^2 se selecciona entre metilo, etilo, isopropilo, cloro y ciano;

R^3 se selecciona entre hidrógeno, metilo, etilo, cloro, bromo, ciano y -COMe;

R^4 se selecciona entre hidrógeno, cloro, metilo, etilo y ciano;

R^5 es hidrógeno o metilo;

R^6 se selecciona independientemente en cada caso entre hidrógeno, (1-4C)alquilo, (3-4C)alquenilo, ciclopropilo, -(1-4C)alquilC(O)O(1-

4C)alquilo, hidroxi, amino, -N[di(1-4C)alquilo], (1-4C)alcoxi y -(1-4C)alquilmorfolino;

R^7 se selecciona independientemente en cada caso entre hidrógeno y (1-4C)alquilo;

o R^6 y R^7 pueden junto con el nitrógeno al cual están adheridos formar piperazinilo o morfolino opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo;

p es (independientemente en cada caso) 0, 1 o 2.

10. Un compuesto de fórmula (1) o una sal farmacéuticamente aceptable del mismo seleccionado entre:

2-cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino} piperidin-1-il)-*N*-metoxipirimidina-4-carboxamida;

2-cloro-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino} piperidin-1-il)isonicotinamida;

1-[4-(aminocarbonil)-6-cloro-2-piridinil]-4-piperidinilo 4-bromo-5-metil-1H-pirrol-2-carboxilato;

1-{4-[amino(hidroxiimino)metil]-6-cloro-2-piridinil}-4-piperidinilo 3,4-dicloro-5-metil-1H-pirrol-2-carboxilato;

2-butoxi-6-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino} piperidin-1-il)ácido isonicotínico;

2-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-6-(2-metoxietoxi)ácido isonicotínico;

2-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino}piperidin-1-il)-*N*-metoxi-6-(metilsulfonil)isonicotinamida;

2-(butiltio)-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil] amino}piperidin-1-il)pirimidina-4-ácido carboxílico;

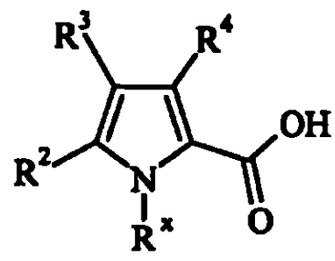
2-(*tert*-butiltio)-6-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonilo amino}piperidin-1-il)pirimidina-4-ácido carboxílico;

2-*tert*-butil-6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino} piperidin-1-il)pirimidina-4-ácido carboxílico;

4-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)quinolina-2-ácido carboxílico;
2-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-1,3-tiazol-5-ácido carboxílico;
2-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-1,3-tiazol-4-ácido carboxílico;
6-cloro-4-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino} piperidin-1-il)quinolina-2-ácido carboxílico;
5-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino}piperidin-1-il)-*N*-metoxinicotinamida;
6-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)piridina-2-ácido carboxílico;
4-[(*tert*-butilamino)carbonil]-2-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-1,3-tiazol-5-ácido carboxílico;
2-(4-{[(3,4-dicloro-5-metil-1*H*-pirrol-2-il)carbonil]amino}piperidin-1-il)-4-metil-1,3-tiazol-5-ácido carboxílico; y
3-(4-{[(3,4-dicloro-5-metil-1H-pirrol-2-il)carbonil]amino}piperidin-1-il) ácido benzoico.

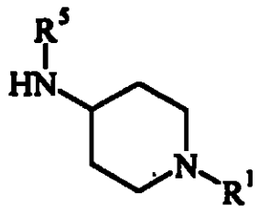
11. Un proceso para preparar un compuesto de fórmula (1) o una sal farmacéuticamente aceptable del mismo, proceso este (donde los grupos variables son, salvo si se especifica en contrario, como se define en la reivindicación 1) que comprende:

a) para compuestos de fórmula (1) donde W es NR^5; hacer reaccionar un ácido de fórmula (2a):



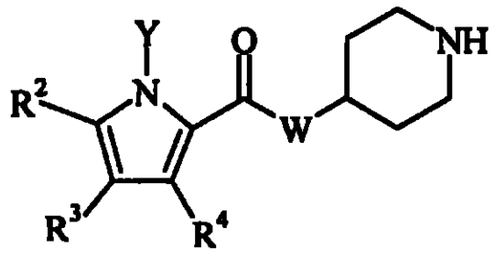
(2a)

(donde R^x es hidrógeno o un grupo de protección apropiado) o un derivado activado del mismo; con una amina de fórmula (3a); o



(3a)

b) hacer reaccionar un compuesto de fórmula (4a):



(4a)

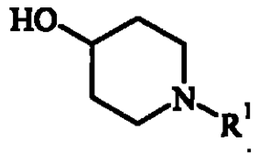
con un compuesto de fórmula (5a):

$X\text{-}R^1$

(5a)

donde X es un grupo desplazable;

c) para compuestos de fórmula (1) donde W es O; hacer reaccionar un ácido de fórmula (2a) o un derivado activado del mismo, con un alcohol de fórmula (6a); o



(6a)

y posteriormente, de ser necesario:

i) convertir un compuesto de fórmula (1) en otro compuesto de fórmula (1);

ii) extraer cualquier grupo de protección;

iii) formar una sal farmacéuticamente aceptable.

12. Un compuesto de fórmula (1), o una sal farmacéuticamente aceptable

del mismo, como se reivindica en una cualquiera de las reivindicaciones 1-10, para su utilización en un método para el tratamiento del cuerpo humano o animal mediante terapia.

13. Un método para producir un efecto antibacterial en un animal de sangre caliente, como el hombre, que requiera el citado tratamiento, que comprende administrar al citado animal una cantidad efectiva de un compuesto de fórmula (1), o una sal farmacéuticamente aceptable del mismo como se reivindica en una cualquiera de las reivindicaciones 1-10.

14. Un método para la inhibición de la ADN girasa bacterial en un animal de sangre caliente, como un ser humano, que requiera el citado tratamiento que comprende administrar al citado animal una cantidad efectiva de un compuesto de fórmula (1) o una sal farmacéuticamente aceptable del mismo como se reivindica en una cualquiera de las reivindicaciones 1-10.

15. Un método para tratar una infección bacterial en un animal de sangre caliente, como un ser humano, que requiera el citado tratamiento que comprende administrar al citado animal una cantidad efectiva de un compuesto de fórmula (1) o una sal farmacéuticamente aceptable del mismo como se reivindica en una cualquiera de las reivindicaciones 1-10.

16. Un compuesto de fórmula (1) o una sal farmacéuticamente aceptable del mismo como se reivindica en una cualquiera de las reivindicaciones 1-10 para su utilización como un medicamento.

17. La utilización de un compuesto de fórmula (1), o una sal farmacéuticamente aceptable del mismo como se reivindica en una cualquiera de las reivindicaciones 1-10 en la manufactura de un medicamento para su utilización en la producción de un efecto antibacterial en un animal de sangre caliente como un ser humano.

18. La utilización de un compuesto de fórmula (1), o una sal farmacéuticamente aceptable del mismo como se reivindica en una cualquiera de las reivindicaciones 1-10 en la manufactura de un medicamento para su utilización en la inhibición de ADN girasa bacterial en un animal de sangre caliente como un ser humano.

19. La utilización de un compuesto de fórmula (1), o una sal farmacéuticamente aceptable del mismo como se reivindica en una cualquiera de las reivindicaciones 1-10 en la manufactura de un medicamento para su utilización en el tratamiento de una infección bacterial en un animal de sangre caliente como un ser humano.

20. Un compuesto de fórmula (1), o una sal farmacéuticamente aceptable del mismo como se reivindica en una cualquiera de las reivindicaciones 1-10 para su utilización en la producción de un efecto antibacterial en un animal de sangre caliente como un ser humano.

21. Un compuesto de fórmula (1), o una sal farmacéuticamente aceptable del mismo como se reivindica en una cualquiera de las reivindicaciones 1-10 para su utilización en la inhibición de ADN girasa bacterial en un animal de sangre caliente como un ser humano.

22. Un compuesto de fórmula (1), o una sal farmacéuticamente aceptable del mismo como se reivindica en una cualquiera de las reivindicaciones 1-10 para su utilización en el tratamiento de una infección bacterial en un animal de sangre caliente como un ser humano.

23. Una composición farmacéutica que comprende un compuesto de fórmula (1) o una sal farmacéuticamente aceptable del mismo como se reivindica en una cualquiera de las reivindicaciones 1-10 y un diluyente o excipiente farmacéuticamente aceptable.

24. Una composición farmacéutica que comprende un compuesto de fórmula (1) o una sal farmacéuticamente aceptable del mismo como se reivindica en una cualquiera de las reivindicaciones 1-10, en asocio con un diluyente o excipiente farmacéuticamente aceptable para su utilización en la producción de un efecto antibacterial en un animal de sangre caliente, como un ser humano.

25. Una composición farmacéutica que comprende un compuesto de fórmula (1) o una sal farmacéuticamente aceptable del mismo como se reivindica en una cualquiera de las reivindicaciones 1-10, en asocio con un diluyente o excipiente farmacéuticamente aceptable para su utilización en la inhibición de ADN girasa bacterial en un animal de sangre caliente, como un ser humano.

26. Una composición farmacéutica que comprende un compuesto de fórmula (1) o una sal farmacéuticamente aceptable del mismo como se reivindica en una cualquiera de las reivindicaciones 1-10, en asocio con un diluyente o excipiente farmacéuticamente aceptable para su utilización en el tratamiento de una infección bacterial en un animal de sangre caliente, como un ser humano.

PCT REQUEST

Duplicate of Original

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	

0-4	Form PCT/RO/101 PCT Request	
0-4-1	Prepared Using	PCT-SAFE [EASY mode] Version 3.50 (Build 0002.162)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United Kingdom Patent Office (RO/GB)
0-7	Applicant's or agent's file reference	101212-1 WO
I	Title of Invention	CHEMICAL COMPOUNDS
II	Applicant	
II-1	This person is	applicant only
II-2	Applicant for	AP: (BW GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW); EA: (AM AZ BY KG KZ MD RU TJ TM); EP: (AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PL PT RO SE SI SK TR); OA: (BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG); AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH& LI CN CO CR CU CZ DE DK DM DZ EC EE EG 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 MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
II-4	Name	ASTRAZENECA AB
II-5	Address	Sodertalje SE-151 85 Sweden
II-6	State of nationality	SE
II-7	State of residence	SE
II-8	Telephone No.	+44 1625 230148
II-9	Facsimile No.	+46 8553 28820

III-1	Applicant and/or Inventor	
III-1-1	This person is	applicant only
III-1-2	Applicant for	MG
III-1-4	Name	ASTRAZENECA UK LIMITED
III-1-5	Address	15 Stanhope Gate London Greater London W1K 1LN United Kingdom
III-1-6	State of nationality	GB
III-1-7	State of residence	GB
III-2	Applicant and/or Inventor	
III-2-1	This person is	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	BREEZE, Alexander, Louis
III-2-5	Address	AstraZeneca R&D Alderley Alderley Park Macclesfield Cheshire SK10 4TG United Kingdom
III-2-6	State of nationality	GB
III-2-7	State of residence	GB
III-3	Applicant and/or Inventor	
III-3-1	This person is	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	GREEN, Oluyinka, Morenike
III-3-5	Address	AstraZeneca R&D Boston 35 Gatehouse Drive Waltham, Massachusetts 02451 United States of America
III-3-6	State of nationality	US
III-3-7	State of residence	US

III-4	Applicant and/or Inventor	
III-4-1	This person is	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	HULL, Kenneth, Gregory
III-4-5	Address	AstraZeneca R&D Boston 35 Gatehouse Drive Waltham, Massachusetts 02451 United States of America
III-4-6	State of nationality	US
III-4-7	State of residence	US
III-5	Applicant and/or Inventor	
III-5-1	This person is	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	NI, Haihong
III-5-5	Address	AstraZeneca R&D Boston 35 Gatehouse Drive Waltham, Massachusetts 02451 United States of America
III-5-6	State of nationality	US
III-5-7	State of residence	US
III-6	Applicant and/or Inventor	
III-6-1	This person is	applicant and inventor
III-6-2	Applicant for	US only
III-6-4	Name (LAST, First)	HAUCK, Sheila, Irene
III-6-5	Address	AstraZeneca R&D Boston 35 Gatehouse Drive Waltham, Massachusetts 02451 United States of America
III-6-6	State of nationality	US
III-6-7	State of residence	US
III-7	Applicant and/or Inventor	
III-7-1	This person is	applicant and inventor
III-7-2	Applicant for	US only
III-7-4	Name (LAST, First)	MULLEN, George, Byron
III-7-5	Address	AstraZeneca R&D Boston 35 Gatehouse Drive Waltham, Massachusetts 02451 United States of America
III-7-6	State of nationality	US
III-7-7	State of residence	US

III-8	Applicant and/or inventor	
III-8-1	This person is	applicant and inventor
III-8-2	Applicant for	US only
III-8-4	Name (LAST, First)	HALES, Neil, James
III-8-5	Address	AstraZeneca R&D Alderley Alderley Park Macclesfield Cheshire SK10 4TG United Kingdom
III-8-6	State of nationality	GB
III-8-7	State of residence	GB
III-9	Applicant and/or inventor	
III-9-1	This person is	applicant and inventor
III-9-2	Applicant for	US only
III-9-4	Name (LAST, First)	TIMMS, David
III-9-5	Address	AstraZeneca R&D Alderley Alderley Park Macclesfield Cheshire Sk10 4TG United Kingdom
III-9-6	State of nationality	GB
III-9-7	State of residence	GB
IV-1	Agent or common representative; or address for correspondence	
	The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name	ASTRAZENECA
IV-1-2	Address	Global Intellectual Property SE-151 85 Sodertalje Sweden
IV-1-3	Telephone No.	+44 1625 230148
IV-1-4	Facsimile No.	+46 8553 28820
V	DESIGNATIONS	
V-1	The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.	

VI-1	Priority claim of earlier national application		
VI-1-1	Filing date	13 September 2003 (13.09.2003)	
VI-1-2	Number	0321509.2	
VI-1-3	Country	GB	
VI-2	Priority claim of earlier national application		
VI-2-1	Filing date	12 May 2004 (12.05.2004)	
VI-2-2	Number	0410527.6	
VI-2-3	Country	GB	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	6	✓
IX-2	Description	235	-
IX-3	Claims	11	-
IX-4	Abstract	1	✓
IX-5	Drawings	0	-
IX-7	TOTAL	253	
	Accompanying Items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-10	Original general power of attorney	✓	-
IX-13	Priority document(s)	Item(s) VI-1 VI-2	-
IX-17	PCT-SAFE physical media	-	✓
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	

X-1	Signature of applicant, agent or common representative	
X-1-1	Name	ASTRAZENECA
X-1-2	Name of signatory	BILL, Kevin
X-1-3	Capacity	Agent
X-2	Signature of applicant, agent or common representative	
X-2-1	Name (LAST, First)	
X-2-2	Name of signatory	
X-2-3	Capacity	

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

AS: 100681
1/2

440

I, KENNETH GREENWOOD, Notary Public of the Town of Egham in Surrey, duly admitted and sworn, practising in the said Town,

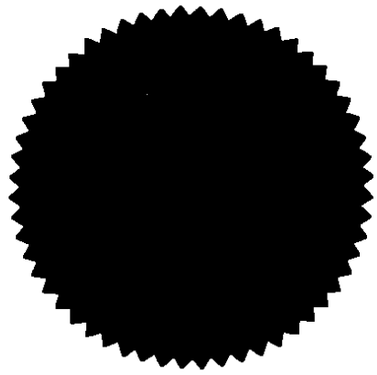
DO HEREBY CERTIFY AND ATTEST:

THAT the signatures set and subscribed at the foot of the hereunto annexed document marked "K.G.A." signed by me and dated are genuine.

ASSIGNMENT signed by, MORENIKE OLUYINKA GREEN, HAIHONG NI, BYRON GEORGE MULLEN, GREGORY KENNETH HULL and IRENE SHEILA HAUCK.

IN TESTIMONY WHEREOF I have hereunto set my hand and affixed my Seal of Office in the Town of Egham aforesaid, this 22nd day of February Two Thousand and Six

HORNE ENGALL AND FREEMAN
NOTARY PUBLIC
MY COMMISSION IS PERMANENT



254962

441

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 — George Andrew Lewis
   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

Certified/Attesté

5. at London/à Londres

6. the/le 24 February 2006

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 **G942164**

9. Stamp:
   timbre:

10. Signature: [redacted]

N. DONKOR

FOREIGN AND COMMONWEALTH OFFICE LONDON

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

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ASSIGNMENT

TRASPASO

The undersigned,

abajo firmado

GREEN, Oluyinka, Morenike; HULL, Kenneth, Gregory ; NI, Haihong; HAUCK, Sheila, Irene and MULLEN, George, Byron

domiciled in
AstraZeneca R&D Boston, 35 Gatehouse Drive, Waltham, MA 02451, United States

domiciliado en

hereby state under oath to be the sole and true inventor of

declara bajo juramento ser único y verdadero inventor de.

PYRROL DERIVATIVES WITH ANTIBACTERIAL ACTIVITY

state as well that assign, without reservations or limitation, in favor of

Declara asimismo que cede y transfiere sin reserva ni limitación, a favor de la sociedad

AstraZeneca AB

a corporation organized and existing under the laws of Sweden

organizada y existente de conformidad con la leyes de

domiciled in

domiciliada en

SE-151 85 Södertälje, Sweden

all rights inherent to said invention, and that the above mentioned corporation hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia.

Todos los derechos inherentes a dicha invención y que la citada sociedad queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

GREEN, Oluyinka, Morenike

HULL, Kenneth, Gregory

NI, Haihong

HAUCK, Sheila, Irene

MULLEN, George, Byron

TRADUCCION AL ESPAÑOL del Documento de Cesión a **AstraZeneca AB** firmado por los Cedentes y el Cesionario.

YO, KENNETH GREENWOOD, Notario Público del pueblo de Egham en Surrey, debidamente admitido y jurado, practicando en dicho pueblo,

POR LA PRESENTE CERTIFICO Y DOY TESTIMONIO:

QUE las firmas puestas y suscritas al pie del documento anexo a éste marcadas "K.G.A." firmado y fechado por mi son genuinas.

CESIÓN firmada por, MORENIKE OLUYINKA GREEN, HAIHONG NI, BYRON GEORGE MULLEN, GREGORY KENNETH HULL, and IRENE SHEILA HAUCK

EN TESTIMONIO DE LO CUAL he puesto mi firma y fijado mi sello de oficina en el antes dicho pueblo de Egham, este 22 de febrero de dos mil seis.

HORNE ENGALL Y FREEMAN
NOTARIO PUBLICO
MI COMISIÓN ES PERMANENTE

444

APOSTILLA

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

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte

   Este documento público

2. ha sido firmado por **George Andrew Lewis**
3. Actuando en capacidad de **Notario Público**
4. lleva el sello/timbre de **Dicho Notario Público**

Certificado

5. en Londres 6. el **24 de febrero de 2006**
7. por el Secretario Principal de Estado de Su Majestad para Relaciones Extranjeras y de la Mancomunidad
8. No. **G942164**
9. Sello/Timbre 10. Firma: **N. Donkor**

Por el Secretario de Estado

Si este documento ha de ser utilizado en un país el cual no es parte de la Convención de La Haya del 5 de octubre de 1961, debe ser presentado ante la sección consular de la misión que representa ese país. Una apostilla o certificado de legalización solo confirma que la firma, sello o timbre en el documento es genuino. No significa que los contenidos del documento estén correctos o que la Oficina Extranjera y de la Mancomunidad apruebe sus contenidos.

AB: 100681
2/2

101212-1P CO

445

ASSIGNMENT

The undersigned,

BREEZE, Alexander, Louis; HALES, Neil, James and TIMMS, David

domiciled in
AstraZeneca R&D Alderley, Alderley Park,
Macclesfield, Cheshire, SK10 4TG, United Kingdom

hereby state under oath to be the sole and true inventor of

PYRROL DERIVATIVES WITH ANTIBACTERIAL ACTIVITY

state as well that assign, without reservations or limitation, in favor of

AstraZeneca AB

a corporation organized and existing under the laws of

Sweden

domiciled in

SE-151 85 Södertälje, Sweden

all rights inherent to said invention, and that the above mentioned corporation hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia.

.....
BREEZE, Alexander, Louis

.....
TIMMS, David

TRASPAS

abajo firmado

domiciliado en

declara bajo juramento ser único y verdadero inventor de.

Declara asimismo que cede y transfiere sin reserva ni limitación, a favor de la sociedad

organizada y existente de conformidad con la leves de

domiciliada en

Todos los derechos inherentes a dicha invención y que la citada sociedad queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

Neil James Hales
.....
HALES, Neil, James

EXECUTION
Certified Verified and Authenticated
In The Town Of Egham In Surrey
This 6th Day Of May 2008

KENNETH GREENWOOD
NOTARY PUBLIC
HORNE ENGALL AND FREEMAN

253001.

445

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 — **Kenneth Greenwood**
   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 **07 February 2006**

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 **G925312**

9. Stamp:
   timbre:

10. Signature: **J. Thethy**

FOREIGN AND COMMONWEALTH OFFICE LONDON

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. An apostille or legalisation certificate only confirms that the signature, seal or stamp on the document is genuine. It does not mean that the contents of the document are correct or that the Foreign & Commonwealth Office approves of the contents.

TRADUCCION AL ESPAÑOL del Documento de Cesión a **AstraZeneca AB** firmado por los Cedentes y el Cesionario.

En el documento de cesión hay un sello que dice:
EJECUCION
Certificado Verificado y Autenticado
En el pueblo de Egham en Surrey
Este 6 de febrero de 2006

KENNETH GREENWOOD
NOTARIO PUBLICO
HORNE ENGALL Y FREEMAN

APOSTILLA
(Convención de La Haya del 5 de octubre de 1961)
REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
   Este documento público
2. ha sido firmado por **Kenneth Greenwood**
3. Actuando en capacidad de **Notario Público**
4. lleva el sello/timbre de **Dicho Notario Público**

Certificado

5. en Londres 6. el **07 de febrero de 2006**
7. por el Secretario Principal de Estado de Su Majestad para Relaciones Extranjeras y de la Mancomunidad
8. No. **G925312**
9. Sello/Timbre 10. Firma: **J. Thethy**

Por el Secretario de Estado

Si este documento ha de ser utilizado en un país el cual no es parte de la Convención de La Haya del 5 de octubre de 1961, debe ser presentado ante la sección consular de la misión que representa ese país. Una apostilla o certificado de legalización solo confirma que la firma, sello o timbre en el documento es genuino. No significa que los contenidos del documento estén correctos o que la Oficina Extranjera y de la Mancomunidad apruebe sus contenidos.

448

Brigard & Castro

BOGOTA - COLOMBIA

PODER

Yo (nosotros)

domiciliado(s) en

Nombro(amos) a: **RAMIRO CASTRO DUQUE y/o JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S.**
de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales y enseñas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

A este efecto, lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeren conducentes al resguardo de mis (nuestros intereses), con todas las demás facultades legales necesarias.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistir, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: **RAMIRO CASTRO DUQUE y/o JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S.**
domiciliado(s) en la Carrera 7 No. 16-56 Piso 9, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

Otorgado y firmado en

hoy de de 200_

Firma

Nombre
Cargo

POWER OF ATTORNEY

I (We) ASTRAZENECA AB

domiciled in SE-151 Sodertalje, Sweden

Hereby appoint **RAMIRO CASTRO DUQUE and/or JUAN PABLO CADENA SARMIENTO and/or BEATRIZ JARAMILLO S.**
of Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetables varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or explotation of licenses, action of unfair competition; penal demands, actions of indemnities for damages: claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures: and in other actions or similar proceedings.

To that effect they are hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotes and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kind of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

This power includes the faculty to ratify or confirm desist, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. At the same time I (We) hereby appoint **RAMIRO CASTRO DUQUE and/or JUAN PABLO CADENA SARMIENTO and/or BEATRIZ JARAMILLO S.**
domiciled in Carrera 7 No. 16-56, Piso 9, my (our) attorney(s) in fact, with powers to receive notifications and to designate judicial and extrajudicial attorneys.

Granted and signed in Macclesfield, Cheshire, England 18th day of July 2003

Signature

Name KEVIN BELL

Title Director, IP Services

En la Notaría Cuarenta ... 02 FEB. 2004 ... NOTARIO CUARENTA (E) ... Bogotá, D.C., Colombia

CERTIFICADO NOTARIAL (SOCIEDAD)

Hoy de de
personalmente compareció ante mí

a quien conozco, y de quien me consta que firmó el anterior documento, debidamente juramentado declaró y dijo que él es

de

Sociedad legalmente constituida para un período de duración que aún no ha terminado; que el declarante está autorizado por dicha compañía para conferir este poder; que el sello estampado por él al pie de tal poder, en nombre y representación de la expresada compañía, es el sello oficial de ella; y que el objeto para el cual se confiere este instrumento está comprendido dentro del de la sociedad.

El suscrito Notario hace constar que tuvo a la vista las pruebas de la existencia de la sociedad.

Estado de
con fecha

y que quien confiere el presente poder es su representante.

Notario Público (sello)

NOTARIAL CERTIFICATE (CORPORATION)

On this 18th day of July 2003 of
personally appeared before me
KEVIN BILL
to me known, and known to me to be the person who signed the foregoing instrument who being by me duly sworn did depose and say that he (she) is the
ATTORNEY
of
ASTRAZENECA AB

Which is legally constituted for a term not yet expired, that deponent is authorized by said Company to confer this Power of Attorney: that the seal affixed hereunto by the deponent in the name and on behalf of said Corporation is the corporate seal thereof; and that purpose for which this instrument is granted included within the corporate purpose of company.

The undersigned Notary Public attests that he has seen the documents that prove the existence of the company.

State of Sweden
under date of 1st January 2003

and that he (she) who grants the present power of attorney is its Representative.

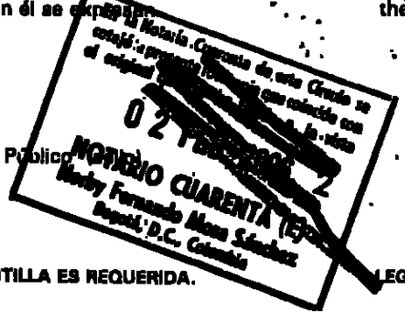
Notary Public (Seal)

CERTIFICADO NOTARIAL PERSONA NATURAL

Hoy de de , compareció(eron)
ante mí

a quien (es) conozco y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede y quien(es) declara(n) que otorgan el mismo para los fines y propósitos que en él se expresan.

Notario Público



NOTARIAL CERTIFICATE NATURAL PERSON

On this day of of
personally appeared before me

who is(are) known to me and who I attest executed the foregoing document and he (they) declared he (they) grant(s) the document for the uses and purposes therein expressed.

Notary Public (Seal)

LEGALIZACION POR APOSTILLA ES REQUERIDA.

LEGALIZATION BY APOSTILLE IS REQUIRED.

451 449

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 — J B Hodgson
   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

   Certified/*Attesté*

5. at London/*à Londres*
6. the/*le* 17 February 2004

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* **G348987**

9. Stamp:
   timbre.

10. Signature: *J. Ireland*

FOREIGN AND COMMONWEALTH OFFICE LONDON

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.

02 FEB. 20
NOTARIO CUARENTA (E)

452 450

TRADUCCIÓN SIMPLE AL ESPAÑOL del la Apostilla que vienen junto con el Certificado Notarial (Sociedad) y el Poder concedido por ASTRAZENECA AB, domiciliada en SE - 151 Sodertalje, Suecia a Ramiro Castro Duque y/o Juan Pablo Cadena Sarmiento y/o Beatriz Jaramillo S, domiciliados en la Carrera 7 #16-56, P. 9, Bogotá D.C., Colombia.

AUTENTICACIÓN

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

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

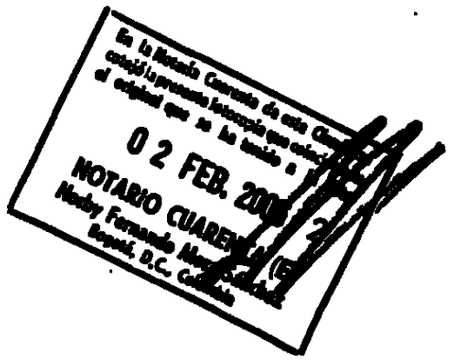
1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
2. Este documento público
   ha sido firmado por **J. B. Hodgson**
3. actuando en capacidad de **Notario Público**
4. lleva el sello de: **Dicho Notario Público**

CERTIFICADO

5. en Londres **6. el 17 de Febrero de 2004**
7. por El secretario de Estado Principal de Su Majestad para Asuntos Exteriores y de la Comunidad
8. No. **G348987**
9. Sello 10. Firma

J. Ireland (Firma)

Si este documento va a ser utilizado en un país que no es parte de la Convención de La Haya del 5 de Octubre de 1961, debe ser presentado a la sección consular de la misión que representa a ese país.



451

GAVIRI A 453

REPÚBLICA DE COLOMBIA

ORGANIZACION ELECTORAL
REGISTRADURÍA NACIONAL DEL ESTADO CIVIL

REGISTRO CIVIL DE DEFUNCIÓN

Indicativo Serial 5562241

Datos de la oficina de registro

Clase de oficina: Registraduría | Notaría X | Consulado | Corregimiento | Insp. de Policía | Código 9795

País - Departamento - Municipio - Corregimiento o/o Inspección de Policía

COLOMBIA CUNDINAMARCA BOGOTA D. C NOTARIA 32.

Datos del inscrito

Apellidos y nombres completos

CASTRO DUQUE RAMIRO

Documento de identificación (Clase y número)	Sexo (en Letras)
C.C. No. 170322 DE BOGOTA	MASCULINO

Datos de la defunción

Lugar de la Defunción: País - Departamento - Municipio - Corregimiento o/o Inspección de Policía

COLOMBIA CUNDINAMARCA BOGOTA D.C.

Fecha de la defunción	Hora	Número de certificado de defunción
Año 2004 Mes 10 Día 30	04:10 PM	A- 2094375.

Presunción de muerte

Juzgado que profiera la sentencia	Fecha de la sentencia
-------------------	Año Mes Día

Documento presentado	Nombre y cargo del funcionario
Autorización judicial [ ] Certificado Médico [X]	ANDRES DIAZ CAMPOS.- R. M. No. 79982662

Datos del denunciante

Apellidos y nombres completos

EDGAR DAVID REGINO H.

Documentos de identificación (Clase y número)	Firma
C.C. No. 15.030.154 DE LORICA/ CORDOBA	[firma]

Primer testigo

Apellidos y nombres completos

Documentos de identificación (Clase y número)	Firma
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Segundo testigo

Apellidos y nombres completos

Documentos de identificación (Clase y número)	Firma
-------------------	------------

Fecha de inscripción	Nombre y firma del funcionario que autoriza
Año 2004 Mes 11 Día 02	BLANCA LUCIA ... RESTREPO NOTARIA ...

ESPACIO PARA NOTAS

PADRES: ALFONSO CASTRO
MERCEDES DUQUE.

ORIGINAL PARA LA OFICINA DE REGISTRO

NOTARIA 32
DEL CIRCULO DE SANTA FE DE BOGOTA, D.C.

Germán Eleázar Moreno L.
Notario

COMO SECRETARIO DELEGADO DE LA NOTARIA TREINTA Y DOS (32) DEL CIRCULO DE BOGOTA

CERTIFICO QUE:

La presente acta es fiel copia del original tomada del registro civil de defunciones serial indicativo número: 5T62249

que expido en la ciudad de Bogotá D.C., hoy: 05 NOV. 2004

NELSON FLOREZ G.
SECRETARIO DELEGADO

NOTARIA 32 DEL CIRCULO DE BOGOTA D.C.
NELSON FLOREZ G.
SECRETARIO DELEGADO PARA COPIAS
DECRETO 1334 DE 1999

452

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Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL TRAMITE

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

Firma Responsable: _____

Fecha: _____

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

(21) N° de solicitud: 06-34461
(22) Fecha de solicitud:

30Prioridad (31) No. Prioridad 32) Fecha (33) País
0321509.2 13-09-2003 GB
0410527.6 12-05-2004 GB

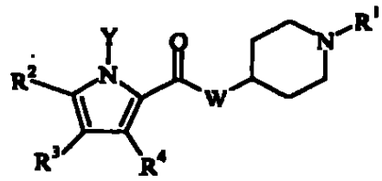
(51) Int Cl: C07D401/13, 417/14, A61K31/454, A61P31/04.
(71)Solicitante(s) ASTRAZENECA AB
(72) Inventor(es) Alexander Louis BREEZE, Oluyinka Morenike GREEN, Kenneth Gregory HULL, Haihong NI, Sheila Irene HAUCK, George Byron MULLEN, Neil James HALES, David TIMMS
(74) Agente: JUAN PABLO CADENA SARMIENTO

(85) Fecha inicio fase nacional: 13-04-2006
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 10-09-2004
No. de solicitud PCT/GB2005/026149

(87) Publicación internacional
Fecha: 24-03-2005
N° publicación: WO 2005/026149 A1

(54) Título: DERIVADOS DE PIRROL CON ACTIVIDAD ANTIBACTERIANA

Reivindicación(es): 1. Un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo:



(I)

donde:
W es O o NR^5;
Y es hidrógeno;
R^1 se selecciona entre R^1a, R^1b, R^1c, R^1d, R^1e y R^1f;
R^1a es un anillo heterocíclico saturado, parcialmente insaturado o insaturado de 4 a 7 miembros que contiene 1, 2, 3 o 4 heteroátomos seleccionados independientemente entre O, S y N (siempre que dicho anillo no contenga enlaces O-O o S-S), donde un grupo $-CH_2-$ se puede reemplazar opcionalmente por un -C(O)-, un anillo de átomos de sulfuro opcionalmente se puede oxidar para formar el S-óxido (s) y un anillo de átomos de nitrógeno opcionalmente se puede oxidar para formar el N-óxido y donde el citado anillo se puede sustituir opcionalmente por 1, 2 o 3 radicales seleccionados independientemente entre: nitro, ciano, sulfo, formilo, hidroxiiminometilo, (2-6C)alquenilo, (2-6C)alquinilo, -CO(1-6C)alquilo, -COO(1-6C)alquilo (opcionalmente sustituido por -COO(1-6C)alquilo), trifluorometilo, $-CONR^6R^7$, $-OCONR^6R^7$, $-N(R^7)COR^6$, $-CONHCH(CO_2R^7)R^6$, halo, hidroxi, carboxi, (1-6C)alquilo [opcionalmente sustituido por 1 o 2 radicales seleccionados independientemente entre hidroxi, halo, ciano, nitro, -COO(1-6C)alquilo, -OCO((1-4C)alquilo, (1-6C)alcoxi, (1-4C)alcoxi(1-4C)alcoxi, hidroxi(1-4C)alcoxi-, (2-4C)alqueniloxi, trifluorometilo, $-CONR^6R^7$, carboxi, -NHC(O)O(1-4C)alquilo, $-OCONR^6R^7$, $-C(=NOH)(1-4C)$alquilo, $-C(=NOH)NR^6R^7$, $-NHC(=NH)NR^6R^7$, $-NHC(O)NR^6R^7$, -NHC(O)(1-4C)alquilo, - NHC(O)heterociclilo, -NHC(O)arilo, -NHS(O)p(1-4C)alquilo, -S(O)p(1-4C)alquilo, $-S(O)pNR^6R^7$, $-NHSO_2R^6$, $-NR^6R^7$ y heterociclilo], (3-6C) cicloalquilo (opcionalmente sustituido por 1 o 2 radicales seleccionados entre (1-6C)alquilo y los radicales opcionales descritos para (1-6C)alquilo arriba), -O(1-6C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), -S(O)p(1-4C)alquilo (opcionalmente sustituido por 1 o 2 radicales como se describió para (1-6C)alquilo arriba), heterociclilo, arilo, -NHC(O)O(1-4C)alquilo, $-C(=NOR^7)(1-4C)$alquilo, $-C(=NOR^7)NR^6R^7$, $-S(O)pNR^6R^7$, -S(O)p(1-4C)alquilCONHR^7, $-NR^7S(O)pNR^6R^7$, $-NR^7S(O)p(1-4C)$alquilo, $-NR^7S(O)p$-arilo, -C(O)NHS(O)p(1-4C)alquilo, -C(O)NHS(O)p-arilo, $-NR^6R^7$, $-CH_2CH(CO_2R^6)OH$, $-(1-4C)$alquilCH(NR^6R^7) CO_2R^6 y $-(1-4C)$alquilCH(NR^6R^7)CO(NR^6R^7); donde cualquier grupo arilo o heterociclilo en cualquiera de los anteriores valores para los radicales en R^1a puede sustituirse opcionalmente por 1 o 2 radicales seleccionados independientemente entre (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, hidroxi, (1-4C)alcoxi, halo, ciano, nitro, carboxi, hidroxi(1-4C)alquil-, (1-4C)alquil(1-4C)alquil-, halo(1-4C)alquil-, difluorometilo, trifluorometilo, trifluorometoxi, formilo, -CO(1-4C)alquilo -COO(1-4C)alquilo, $-C(O)NH_2$, -C(O)NH(1-4C)alquilo, -C(O)N[di(1-4C)alquilo], $-S(O)_2NH_2$, $-S(O)_2NH(1-4C)$alquilo y $-S(O)_2N$[di(1-4C)alquilo]...

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REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
CADENA SARMIENTO JUAN PABLO
Apoderado(a) y/o Representante de
ASTRAZENECA AB

REFERENCIA	Radicación No.	06 34461
	Solicitud internacional	GB2004/003874
	Fecha inicio fase nacional	13/04/2006
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	8043

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:

1. Debe aclarar el nombre del inventor por cuanto difiere en la publicación internacional y en el petororio presentado.

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 Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha
jramos 28 JUL. 2006